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The Alkaloids of *Hunteria eburnea* Pichon. II. The Quaternary Bases

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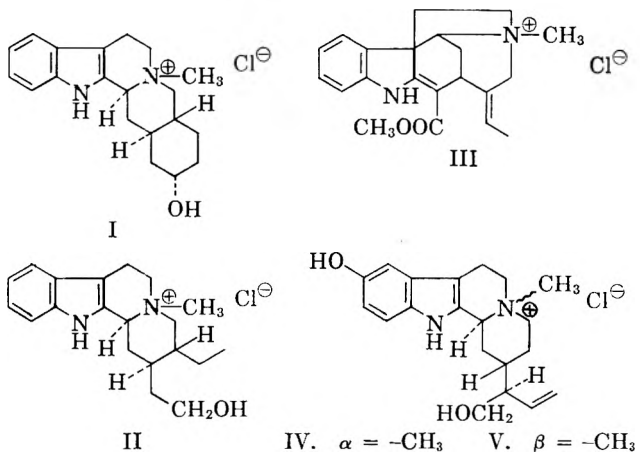
The isolation of one tertiary and thirteen quaternary alkaloids from *Hunteria eburnea* is described. Three of these are identified as yohimbol methochloride (I), dihydrocorynantheol methochloride (II), and akuammicine methochloride (III). The first example of a new class of alkaloids is given which occurs in the form of its diastereoisomeric quaternary N_b salts, hunterburnine α- and β-methochlorides (IV and V). The structure of a third 5-hydroxyindole, huntrabrine methochloride (VI), is proposed from degradative work.

As part of a program to identify the hypotensive principles of *Hunteria eburnea* Pichon,[1,2] we have isolated nine inactive or weakly effective tertiary bases.[3a,b] Further work showed that methanolic extracts of the bark from which the majority of the tertiary bases had been removed with methylene chloride contained most of the activity. This extract again was separated into water insoluble residual tertiary bases and water soluble quaternary bases, the latter possessing most of the activity.[4] The quaternary alkaloids were removed from the water at pH 5 as their insoluble picrates which for subsequent work were transformed into the chloride salts. In all, fourteen crystalline alkaloids were separated from this mixture by processes (see Experimental and Fig. 1) which had as their end chromatography on cellulose powder.[5]

Six of these alkaloids were isolated in quantities insufficient for complete or accurate characterization and are referred to by the suffixes F, H, I, J, K, and N.[6]

Yohimbol methochloride (I),[7] dihydrocorynantheol methochloride (II),[8,9] and akuammicine methochloride (III) were recognized, and the structures of the 5-hydroxyindoles hunterburnine α- and β-methochlorides (IV and V, respectively)[10-12] were elucidated by the X-ray crystallographic technique. The absolute stereochemistry depicted for the latter two alkaloids is based



upon biogenetic considerations[13] and the validity of the C_{15} rule[14] for these molecules. In agreement with Katritzky's findings,[15] the chemical shift attributed to the quaternary methyl of the *cis*-quinolizidine (IV) is found at lower field (δ = 3.47) than in the case of *trans*-

(1) Raymond-Hamet, *Compt. rend.*, **240**, 1470 (1955); A. Engelhardt and H. Gelbrecht, *Naturwissenschaften*, **45**, 547 (1958); A. Engelhardt and H. Gelbrecht, *Arzneimittel Forsch.*, **11**, 414 (1961).

(2) The activity referred to throughout this paper means the blood pressure lowering response observed in anesthetized dogs by Drs. A. J. Plummer and W. A. Barrett of our pharmacology department.

(3) (a) Unpublished work from these laboratories; (b) For structures of four of the tertiary bases see M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960).

(4) The weak hypotensive activity found in the residual tertiary bases could be enhanced by quaternization, however, no crystalline compounds were isolable even after extensive processing.

(5) The isolation of the alkaloids of calabash curare is a classical example of complex mixtures of quaternary alkaloids being separated by cellulose powder chromatography; H. Schmid, J. Kebrle, and P. Karrer, *Helv. Chim. Acta*, **35**, 1864 (1952).

(6) The possibility that some of these compounds were different crystalline forms of already isolated material was not investigated. In one case another unknown was identified as hunterburnine β-methochloride by seeding a methanolic solution of the former with crystals of the latter.

(7) B. Witkop, *Ann.*, **554**, 83 (1943).

(8) C. Vamvacas, W. v. Philipsborn, E. Schlittler, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **40**, 1793 (1957).

(9) Dihydrocorynantheol has now been isolated from *Aspidosperma* species; B. Gilbert, L. D. Antonaccio, and C. Djerassi, *J. Org. Chem.*, **27**, 4702 (1962).

(10) J. D. M. Asher, J. Monteath Robertson, G. A. Sim, M. F. Bartlett, R. Sklar, and W. I. Taylor, *Proc. Chem. Soc.*, 72 (1962).

(11) C. C. Scott, G. A. Sim, and J. Monteath Robertson, *ibid.*, 355 (1962).

(12) The tertiary base hunterburnine has yet to be recognized and isolated.

(13) E. Schlittler and W. I. Taylor, *Experientia*, **16**, 244 (1960).

(14) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474, 6535 (1959).

(15) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

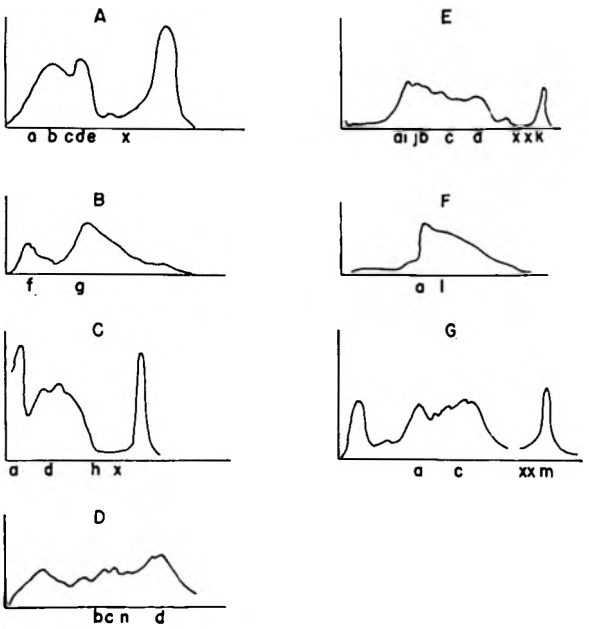
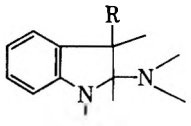


Fig. 1.—Diagrammatic eluate patterns of chromatograms A–G. The weights of alkaloids eluted are plotted as a function of the volume of eluent (see Table I for actual weights and volumes used), with the alkaloids isolated at: a, huntracine chloride; b, yohimbol methochloride; c, hunterburnine β-methochloride; d, huntrabrine methochloride; e, hunterburnine α-methochloride; f, hunteria alkaloid-F; g, akuammicine methochloride; h, hunteria alkaloid-H; i, hunteria alkaloid-I; j, hunteria alkaloid-J; k, hunteria alkaloid-K; l, dihydrocorynantheol methochloride; m, hunteramine; n, hunteria alkaloid-N; X, solvent change.

(V) (δ = 3.31).[16] Although this is the first recognized example of the occurrence in nature[17] of such N_b diastereoisomers, we predict that this will be found to be quite common in quaternary bases where the possibility exists,[18] and, since they have been found together, it suggests that the biological methylation step may parallel the specificity of the analogous laboratory operation.

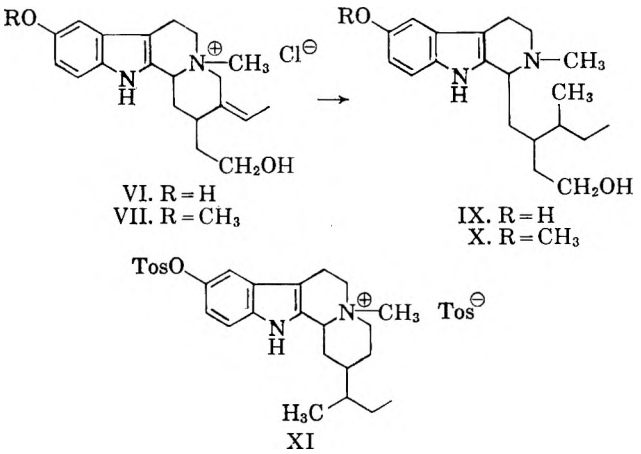
A third 5-hydroxyindole, huntrabine methochloride (VI), was available in sufficient amounts for degradative work (*vide infra*). Of the remaining two alkaloids, hunteramine (possibly $C_{26}H_{34}N_2O_{10}$) was a water soluble tertiary base. The final one, hunteracine chloride ($C_{20}H_{25}N_2OCl$), has a chromophore similar to echitamine, suggesting the partial structure VIII.



VIII

There was no methoxyl or N-methyl group (confirmed by p.m.r. spectroscopy)[19]; the compound was unaffected under acetylation conditions and had a reducible double bond shown to be an ethylidine by p.m.r. spectroscopy. Sublimation of the quaternary hydroxide gave a crystalline tertiary pseudoindoxyl along with a water soluble quaternary compound with the same chromophore as the starting material. Upon attempted pyrolysis or selenium dehydrogenation, hunteracine chloride was recovered unchanged. Lack of material precluded substantiation of these intriguing results, in which R in VIII may be hydroxyl.

Huntrabrine methochloride, $C_{20}H_{27}N_2O_2Cl$, in agreement with its proposed structure VI, gave on acetylation a mixture of O-mono-, O,O-di-, and O,O,N-triacetates. The p.m.r. spectrum[19] of the alkaloid revealed the presence of an ethylidene, a quaternary N-methyl, and confirmed the distribution of protons on the aromatic nucleus. Reaction with either diazomethane or dimethyl sulfate gave the phenolic methyl ether (VII). Upon hydrogenation, either huntrabrine methochloride or the methyl ether underwent a facile Emde degradation yielding the tertiary bases (IX and X), respectively. The Emde product (IX) upon



VI. R = H
VII. R = CH_3

IX. R = H
X. R = CH_3

XI

tosylation gave a phenolic O-tosyl quaternary tosylate (XI)[20] which was converted readily to the phenolic-O-tosyl quaternary chloride (XI. tosyl$^-$ = Cl$^-$), and which upon selenium dehydrogenation afforded a product with a sempervirine-like ultraviolet absorption spectrum as well as a 2-pyridyl indole. The Emde base (IX) itself upon dehydrogenation also gave products with 2-pyridylindole ultraviolet absorption spectra which we suggest is the result of a cyclization under the reaction conditions.[21]

Interestingly, none of the quaternary bases so far isolated are quaternary salts of the known co-occurring tertiary bases. In fact, the quaternary alkaloids whose structures were determined were derived from yohimbinoid precursors, whereas the tertiary bases[3b] belong to the *aspidosperma-eburnea* type. Whether this means that the quaternary compounds are not derived from their immediate tertiary precursors is a question which cannot be settled from our work, but may be answerable if suitable studies with labeled compounds were carried out.

Experimental

The melting points were taken in evacuated capillaries and are uncorrected. Unless noted otherwise, analytical samples were routinely dried at 80–100° for 12–24 hr. *in vacuo*, the ultraviolet

(16) The spectra were run on the Varian Model A-60 spectrometer in trifluoroacetic acid by Misses N. Cahoon and J. A. Siragusa using tetramethylsilane as a reference.

(17) The epimeric methiodides of yohimban have been reported in the literature; B. Witkop, *J. Am. Chem. Soc.*, **71**, 2559 (1949); B. Witkop and S. M. Goodwin, *ibid.*, **75**, 3371 (1953).

(18) The difficulty which we have experienced in the isolation of the pure quaternary bases from the crude mixture may be due to the presence of further examples of this type of isomerism.

(19) Run by Dr. A. F. Zürcher in deuterium oxide with tetramethylsilane as standard.

(20) This is more facile that the analogous quaternization of dihydrocorynantheol; E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **80**, 3484 (1958); ref. 14.

(21) Cyclizations during dehydrogenation reactions are known; for example, the dehydrogenation of melinonine B (ref. 8).

TABLE I

SUMMARY OF THE CHROMATOGRAPHIC RESULTS

Chromatogram	Column size, cm.	Solvent	Vol., l.	Added[a] wt., g.	Eluted wt., g.	Alkaloids isolated[b]
A	15 × 40	Water–acetone (8%)	15	26	14	a (1.05 g.), b (0.41 g.), c (0.12 g.), d (0.30 g.), e (1.41 g.)
		Water–acetone (20%)	9		10	.....
B	9.5 × 40	Ethyl Acetate–acetone–water (50:45:17)	3	3.9	3.7	f (0.34 g.), g (0.11 g.)
C	15 × 40	Water–acetone (10%)	15	33	21	a (0.20 g.), d (5.10 g.), h (0.20 g.)
		Water–acetone (20%)	14		9	.....
D[c]	8 × 110	Water–acetone (8%)	16	4.5	4.2	b (0.09 g.), c (0.009 g.), d (0.65 g.), n (0.033 g.)
E	8 × 110	Water–acetone (10%)	15	5	3.4	a (0.01 g.), b (0.01 g.), c (0.08 g.), d (0.10 g.), i (0.02 g.), j (0.02 g.)
		Water–acetone (15%)	4		0.1	.....
		Water–acetone (20%)	4		.1	k (0.014 g.)
F[d]	8 × 110	Water–acetone (10%)	8	6.4	5.0	a (0.28 g.), l (0.15 g.)
G	10 × 40	Water–acetone (8%)	8	3.5	2.5	a (0.02 g.), c (0.08 g.)
		Water–acetone (15%)	1.5		0.17	.....
		Water–acetone (20%)	4		.70	m (0.20 g.)

[a] See Experimental section for description of material used. [b] Letters correspond to names of alkaloids shown in Fig. 1. [c] Rechromatography of the mother liquors of huntrabrine methochloride. [d] Rechromatography of the first peak of chromatogram A.

absorption spectra were run in ethanol and expressed as mμ (ε), and the infrared absorption spectra were run in Nujol.

Isolation of the Alkaloids. Extraction of the Bark.—The root and stem bark which had previously been extracted with methylene chloride were reprocessed with recycling methanol at 40°, yielding 8 kg. of extractables from 60 kg. of bark.[22] A portion (300 g.) was dissolved in 10% acetic acid, filtered, and shaken with three portions of methylene chloride which removed 3.4 g. of material. The pH was brought to 8–9 with lithium hydroxide, generating a precipitate (112 g.) which was removed by filtration.

The filtrate was extracted with methylene chloride, brought to pH 6 (acetic acid), and all traces of methylene chloride were removed by bubbling nitrogen through the solution. This procedure led to a filterable precipitate (40 g.) upon addition of lithium picrate solution (30 g. of picric acid in 300 ml. of water with sufficient added lithium hydroxide to give a clear solution). The picrate salts were converted to the chloride salts by stirring with Amberlite IRA 400 (Cl^-) (360 g.) in acetone–methanol–water (900 ml., 6:2:1) for 18 hr. yielding the crude chloride salts (16.5 g.) after lyophilization (chromatogram A).

A portion of the filtrate of the picrate precipitation was evaporated to a small volume *in vacuo*. The precipitate was washed with water and converted to its chloride salts [Amberlite IRA 400 (Cl^-)]. After removing inorganic salts by partial precipitation from methanol, the chlorides (24 g.) were precipitated by addition of acetone and shaken with Darco decolorizing charcoal (*ca.* 50 g.) in hot water. The material (3.5 g.) adsorbed on the charcoal was eluted with hot methanol and used in chromatogram G.

A sample of the crude chloride salts (40 g.), used for chromatogram A, was dissolved in water and extracted continuously with methylene chloride for 24 hr., yielding 1.9 g. of residue. After a second extraction with methylene chloride for 4 days, a further 1.4 g. was extracted which was combined with similar material (2.5 g.) and used in chromatogram B. The aqueous phase of this extraction was heated on a steam bath with Darco decolorizing charcoal (35 g.), filtered and concentrated *in vacuo*, and finally freeze dried (yield 33 g., chromatogram C). Material (5 g.) was eluted from the charcoal with hot methanol (chromatogram E).

Chromatography.—The following solvent systems for chromatography on paper strips gave separations of the crude chloride mixture: methyl ethyl ketone–methanol–water (12:4:1), *t*-butyl alcohol–benzene–water (3.1:1:2), ethyl acetate–*t*-butyl alcohol–water (4:2:1), *t*-butyl alcohol–toluene–water (3.1:1:1). Upon application of these systems to columns, little separation was achieved. The completely homogeneous system acetone–water and later ethylacetate–acetone–water which gave poor separations on paper because of streaking were the solvents of choice for the columns.

(22) Carried out by J. Drew and L. Blodgett in pilot plant equipment.

Preparation of the Cellulose Columns.—A glass column (120 cm. by 8 cm.) was half-filled with acetone. A flat bed for the cellulose was made of glass wool and Berkshire sand. Cellulose powder (Whatman ashless standard grade, *ca.* 2 kg.) was placed in a vacuum desiccator, covered with acetone, and the air removed by repeated suction.[23] A portion (*ca.* 400 ml.) of this slurry was poured into the column, stirred to break up lumps, allowed to settle, and compressed tightly with a tamping rod using leverage. Repetition of this procedure resulted in a column 110 cm. long, which upon washing with 8% water–acetone caused the cellulose to expand, the top few segments rising slightly in the column. After washing with 8-hydroxyquinoline (1 g.) and testing the uniformity of the packing with Calco oil red or blue H 1700 (American Cyanamid Co., Boundbrook, New Jersey), the column was ready for use. The sample was placed on the column in water–acetone (usually 13% water) and immediately the chosen eluent added and the flow rate adjusted to 3–6 ml./min. All chromatograms were carried out at 25 ± 0.5°, streaking being pronounced whenever the temperature fluctuated. The elution pattern of a number of the chromatograms are shown in Fig. 1 and the results are summarized in Table I.

Hunteracine Chloride.—A sample from chromatogram A was recrystallized from ethanol for analysis, m.p. 343–344° dec., $[\alpha]_D$ −91° (27.5% H_2O–MeOH); λ_{max} 234 (7900), 291 (2200); λ_{min} 218 (4200), 256 (200), with no shift observed in acid or base.

Anal. Calcd. for $C_{20}H_{25}N_2OCl$: C, 69.60; H, 7.30; N, 8.12; Cl, 10.28; CCH_3, 4.06. Found: C, 69.87; H, 7.47; N, 8.17; Cl, 10.94; OCH_3, 0.0; CCH_3, 6.9.

Hydrogenation of Hunteracine Chloride.—Hunteracine chloride (19 mg.) in water (1.4 ml.) was hydrogenated in the presence of prereduced platinum catalyst with the uptake stopping at 1 mole equivalent. After filtration and evaporation, the residue crystallized from methanol–acetone, m.p. >320°.

Anal. Calcd. for $C_{20}H_{27}N_2OCl \cdot H_2O$: C, 65.81; H, 8.01. Found: C, 66.38; H, 7.83.

Hofmann Degradation of Hunteracine Chloride.—Hunteracine chloride (200 mg.) was converted to the methohydroxide with Amberlite CG 45 (OH) in methanol (10 ml.). After concentration the hydroxide (210 mg.) was sublimed at 150–180° under high vacuum yielding a sublimate (190 mg.) purified by chromatography on alumina. The methylene chloride eluate furnished a residue (20 mg.) crystallized from methanol–ether and recrystallized from benzene–ethyl acetate yielding a product (8 mg.), m.p. 183–185°; λ_{max} ($\epsilon^{1\%}_{1\,cm}$) 231 (900), 390 (120); λ_{sh} 250 (240), 263 (130), 343 (37); λ_{min} 285–295 (15) showing no change in acid or base.

Anal. Found: C, 75.59; H, 8.18.

The 10 and 20% methanol–methylene chloride eluates of the above chromatogram gave a residue crystallizing from ethanol–

(23) This is a modification of a procedure recommended by S. Gardell, *Acta Chem. Scand.* **11**, 668 (1957).

ethyl acetate to afford a neutral compound (20 mg.), m.p. 159–160°; λ_{max} ($\epsilon^{1\%}_{1cm}$) 234 (250), 290 (70); λ_{min} 219 (140), 256 (10).

Anal. Found: C, 65.98; H, 7.31; N, 10.99.

Yohimbol Methochloride.—A sample from chromatogram A was crystallized from acetone–water for analysis, m.p. 264–265°.

Anal. Calcd. for $C_{20}H_{27}N_2OCl \cdot {}^1/_2H_2O$: C, 67.47; H, 7.93; N, 7.87. Found: C, 67.40; H, 8.16; N, 7.52.

Yohimbol from Yohimbol Methochloride.—Yohimbol methochloride (100 mg.) after drying at 100° *in vacuo* was heated in two 50-mg. portions at 340° under high vacuum. The sublimate was dissolved in methylene chloride and washed with dilute sodium carbonate. Evaporation yielded a solid (62 mg.) purified by chromatography on alumina with the 0.5% methanol–methylene chloride eluate affording yohimbol (55 mg.), m.p. 249–251°, from methanol–water; $[\alpha]_D$ −49° (methanol). It was found to be identical in all respects with yohimbol prepared from epiyohimbol by the route given below.

Yohimbol from Epiyohimbol.—Epiyohimbol (1.9 g.), mesyl chloride (1.1 mole equivalents), and pyridine (10 ml.) were allowed to stand overnight at 0°. The crystals were removed by filtration, taken up in water, made basic with sodium hydroxide, extracted with methylene chloride, which was dried and evaporated, and the mesylate was crystallized from methanol–methylene chloride (m.p. 180°, yield 1.3 g.).

The mesylate (430 mg.) was heated overnight on a steam bath with acetic acid (10 ml.) and sodium acetate (450 mg.). Upon diluting with water, making basic (sodium hydroxide), extracting with methylene chloride, and evaporating, the residue was chromatographed on alumina yielding a yohimbene (290 mg.) from the methylene chloride eluate, m.p. 215–216°, from methanol–water; $[\alpha]_D$ −180° (ethanol).

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97. Found: C, 81.94; H, 8.03. From the 2% methanol–methylene chloride eluate yohimbol O-acetate (43 mg.) crystallized from methanol–water, m.p. 251°. It was sublimed for analysis.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74. Found: C, 74.7; H, 7.9.

Alkaline hydrolysis of the acetate furnished yohimbol,[24] m.p. 251–253°, $[\alpha]_D$ −38° (methanol).

Yohimbol Methochloride from Yohimbol.—The above prepared yohimbol was quaternized with methyl chloride in a sealed tube at 100°, yielding yohimbol methochloride, m.p. 263° dec., $[\alpha]_D$ +53° (methanol).[25]

Dihydrocorynantheol Methochloride.—A sample from chromatogram F was recrystallized from ethanol for analysis, m.p. 296–297°, $[\alpha]_D$ +101°, and was identical in all respects with an authentic sample.[26]

Anal. Calcd. for $C_{20}H_{29}N_2OCl$: C, 68.85; H, 8.36; N, 8.01. Found: C, 68.51; H, 8.40; N, 7.78.

Hunteramine.—This water-soluble base was recrystallized twice from ethanol, m.p. 206–208°, pK_a' 4.6; λ_{max} ($\epsilon^{1\%}_{1cm}$) 221 (800), 271 (150), 278 (150); λ_{sh} 282 (140), 289 (120); λ_{min} 253 (120), 276 (150), 287 (103); ν_{max} 3350–3170, 1160, 1075, 745 cm.$^{-1}$.

Anal. Found: C, 58.60; H, 6.73; N, 5.31.

Akuammicine Methochloride. (a).—A sample from chromatogram B was recrystallized from methanol and then from *t*-butyl alcohol for analysis, m.p. 271–272°, $[\alpha]_D$ −567° (3:1 methanol–water).

Anal. Calcd. for $C_{21}H_{25}N_2O_2Cl$: C, 67.62; H, 6.76; N, 7.51; Cl, 9.51. Found: C, 67.56; H, 6.76; N, 7.77; Cl, 10.79.

(b).—Akuammicine[27] (20 mg.) was heated with excess methyl chloride in methanol in a sealed tube for 4.5 hr. at 100°. The product crystallized from ethanol–water, m.p. 265–276° dec., was identical to the compound isolated previously.

Hunterburnine α-Methochloride.—For analysis it was recrystallized four times from water, m.p. 335°, λ^{EtOH}_{max} 273 (8700), 300 (4300); λ_{sh} 311 (3700); λ_{min} 244 (6500), 294 (3700).

Anal. Calcd. for $C_{20}H_{27}N_2O_2Cl$: C, 66.17; H, 7.50; N, 7.72. Found: C, 66.10; H, 7.53; N, 7.76; NCH_3, 3.83.

A sample of hunterburnine α-methochloride was converted into the iodide with Amberlite CG 45 (I) in aqueous methanol. The product, crystallized from water, melted at 294–295°.

Hunterburnine β-Methochloride.—The salt was crystallized from acetone–water, m.p. 307–308°, $[\alpha]_D$ +105° (27.5% water–methanol).

Anal. Calcd. for $C_{20}H_{27}N_2O_2Cl$: C, 66.17; H, 7.50; N, 7.72. Found: C, 66.31; H, 7.58; N, 7.61.

Hunterburnine β-Methiodide.—A sample of the methochloride was filtered through a column of Amberlite CG 45 (I) in methanol, and the product from the eluate was crystallized from ethanol–ethyl acetate, m.p. 277–280°.

Anal. Calcd. for $C_{20}H_{27}N_2O_2I$: C, 52.86; H, 5.99. Found: C, 52.87; H, 6.04.

Huntrabrine Methochloride.—This alkaloid was recrystallized from ethanol–water for analysis, m.p. 285–287°, $[\alpha]_D$ +54° (water), λ^{EtOH}_{max} 271 (8800), 300 (4300); λ_{sh} 310 (3800); ν_{max} 3120, 1220, 1135, 1031, 923, 913, 839, 814 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{27}N_2O_2Cl$: C, 66.31; H, 7.58; N, 7.61. Found: C, 65.88; H, 7.77; N, 7.81; CCH_3, 4.24.

The alkaloid took up one mole equivalent upon hydrogenation in water using Adam's catalyst and gave acetaldehyde (characterized as its dinitrophenylhydrazone derivative) upon ozonolysis. Methylation using either diazomethane or dimethyl sulfate gave the same amorphous O-methyl ether.

Acetylation of Huntrabrine Methochloride.—Huntrabrine methochloride (31 mg.) in acetic anhydride (0.5 ml.) and pyridine (1 ml.) was heated *in vacuo* for 4 hr. After concentration, the residue was crystallized from methanol–acetone to furnish the O,N-diacetate; melting commenced at 160° (evolution of water) and was complete at 195°; when inserted at 170° it softened slightly and melted at 200°; ν_{max} 1740 (weak shoulder at 1760), 1700 cm.$^{-1}$; λ_{max} 239–41 (17,100), 287 (5350), 299 (4150); λ_{sh} 230 (15,200), 265 (10,600), 292 (5060).

Anal. Calcd. for $C_{24}H_{31}N_2O_4Cl \cdot H_2O$: C, 61.99; H, 7.15. Found: C, 61.47; H, 7.09.

Emde Reduction of Huntrabrine Methochloride.—Huntrabrine methochloride (500 mg.) in 80% aqueous ethanol (50 ml.) was added to platinum oxide catalyst (100 mg.) prereduced in 95% ethanol (25 ml.), and stirred in a hydrogen atmosphere. The uptake of hydrogen was complete (67 ml., 2 mole equivalents) in 2 hr. After removal of the catalyst and evaporation, the residue (504 mg.) in methylene chloride was washed with dilute sodium bicarbonate and potassium hydroxide, dried, and evaporated to dryness. The crude Emde product (380 mg.) was sublimed in high vacuum at 190–220° for analysis, pK_a' 6.94.

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.35; H, 9.09; N, 8.55.

On chromatography the Emde product was eluted with 2% methanol–methylene chloride. It also gave an amorphous monoacetate ester ($\nu_{C=O}$ 1738 cm.$^{-1}$) with acetic anhydride in pyridine.

Tosylation of the Emde Product.—The Emde product (360 mg.) was treated with *p*-tosyl chloride (500 mg.) in pyridine (5 ml.) at 0° for 4 days. Upon evaporating to dryness under reduced pressure (bath temperature 30–40°), the residue (860 mg.) crystallized from acetone–ether to furnish the quaternary phenolic O-tosyl tosylate (180 mg.), m.p. 281–282°, λ_{max} 223 (60,000), 273 (8200), 282 (8100), 291 (6200); λ_{min} 247 (5600), 278 (8000), 290 (6100).

Anal. Calcd. for $C_{34}H_{42}N_2O_6S_2$: C, 63.91; H, 6.63; N, 4.38. Found: C, 64.03; H, 6.65; N, 4.08.

The ditosyl derivative upon refluxing in collidine for 1 hr. was recovered unaltered.

The quaternary salt was filtered through Amberlite CG 45 (Cl^-) in methanol to give the crystalline phenolic O-tosyl quaternary chloride, m.p. 225–226° (m.m.p. with the starting material was 225–245°).

Anal. Calcd. for $C_{27}H_{35}N_2O_3SCl$: Cl, 7.0. Found: Cl, 6.1.

Selenium Dehydrogenation of the Ditosylate.—The above ditosylate (120 mg.) and selenium (1.1 g.) were heated at 365°

(24) Yohimbol, along with epiyohimbol, has previously been prepared by the Meerwein-Pondorff-Verley reduction of yohimbone (ref. 7); A. Le Hir and R. Goutarel, *Bull. soc. chim. France*, 1023 (1953); but this was unsatisfactory in our hands, the epi compound being the major product. In agreement with E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958), and in contrast to Z. J. Vejdelek and R. Macek, *Chem. Listy*, **52**, 2140 (1958), we find that sodium borohydride reduction of yohimbone gives the epi alcohol as the sole product.

(25) The rotation found for the yohimbol methochloride from *H. eburnea* was −16° (27.5% water–methanol), indicating that this compound was contaminated with a trace of a highly levorotatory substance, perhaps akuammicine methochloride ($[\alpha]_D$ −567°). It is also possible that the rotations of other alkaloids which we describe may be influenced in a similar fashion.

(26) Prepared from corynanetheine furnished by Dr. M.-M. Janot, according to published procedures [M.-M. Janot and R. Goutarel, *Bull soc. chim. France*, 588 (1951)].

(27) Kindly supplied by G. F. Smith, Manchester, England.

for 8 min. in a sealed evacuated tube. The contents were dissolved in methylene chloride and chromatographed on alumina.

The methylene chloride eluate gave a fraction (15 mg.) with ultraviolet (λ_{max} 330; 2-pyridylindole), and the 1% methanol in methylene chloride eluate afforded a sempervirine-like substance (2 mg.), $\lambda_{max}^{neutral}$ 385, 340, 286; λ_{max}^{base} 354, 286.

Emde Reduction of Phenolic O-Methylhuntrabrine Chloride.—The crude methyl ether (600 mg.) was dissolved in 80% ethanol (40 ml.), added to prereduced platinum oxide (200 mg.) in alcohol (25 ml.), and stirred in a hydrogen atmosphere for 18 hr. After removal of the catalyst and evaporation, the residue (600 mg.) was shaken with dilute potassium hydroxide and methylene chloride, yielding the crude Emde base (290 mg.) to the organic phase. Chromatography on basic alumina gave from the benzene–ether (2:1) eluate the Emde base (230 mg.) which gave crystals (150 mg.) from ether–hexane, m.p. 107–108°.

Anal. Calcd. for $C_{21}H_{32}N_2O_2$: C, 73.21; H, 9.36; N, 8.13. Found: C, 73.24; H, 9.50; N, 8.06.

Partially Characterized Bases.—All the following bases described contained halide as determined by precipitation with silver nitrate, and the ultraviolet absorption spectra are recorded as λ ($\epsilon_{1\text{ cm}}^{1\%}$).

Alkaloid-F.—It was recrystallized from *t*-butyl alcohol–water (20:1), m.p. 242–243°, λ_{max} 222 (860), 275 (230); λ_{sh} 283 (200), 292 (150); λ_{min} 246 (75); ν_{max} 3460, 3410, 1737, 1211 and 750 cm.$^{-1}$.

Anal. Found: C, 64.70; H, 6.81.

Alkaloid-H.—This yellow compound crystallized from ethanol–ethyl acetate, m.p. 300°; $\lambda_{max}^{EtOH\text{ or acid}}$ 312–315 (420), 403 (630); λ_{sh} 245 (341); λ_{min} 274 (126), 345 (189); λ_{max}^{base} 227–232 (590), 323 (370), 418–423 (460); λ_{min} 283 (150), 360 (240); ν_{max} 3535, 3175, 1640, 1573, 1203, 1062, 853 and 810 cm.$^{-1}$.

Alkaloid-I.—Crystallized from ethanol, it had m.p. 278–280°, λ_{max} 219 (1200), 273 (240), 279 (250), 289 (210); λ_{min} 240 (60), 276 (240), 286 (180) with no change in base; ν_{max} 3300, 3150, 750 cm.$^{-1}$.

Alkaloid-J.—A sample crystallized from ethanol had m.p. 291–293°, λ_{max} 272 (230), 279 (230), 289 (200); λ_{min} 240 (51), 276 (220), 286 (160) with no shift in acid or base; ν_{max} 3437, 3149, 1631, 1245, 1050, 752 cm.$^{-1}$.

Alkaloid-K.—It was obtained crystalline from ethanol, m.p. 207–208°; λ_{max} 222 (840), 272 (150), 279 (150), 289 (120); λ_{min} 253 (120), 277 (140), 287 (110).

Alkaloid-N.—It was crystallized from ethanol, m.p. 263–266°, λ_{max} 266 (210), 270 (220), 277 (210), 280 (160); λ_{sh} 280 (210), 310 (20); λ_{min} 240 (56), 274 (210), 285 (140), with no shift in acid or base; ν_{max} 3330, 3140, 1308, 1226, 1110, 1076, 1060, 1048, 903, 758, 740 cm.$^{-1}$.

Acknowledgment.—We wish to express our appreciation to Dr. E. Schlittler for his constant interest and encouragement, to Mr. L. Dorfman and his staff for the analytical and spectral work, and to Dr. M. J. Allen and his staff for the potentiometric microtitrations.

Reactions of Metal Chelates. V.[1,2] Substitution of Metal Acetylacetonates with Friedel-Crafts Acylating Reagents and Sulfur Electrophiles

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The inert trisacetylacetonates of chromium(III), cobalt(III), and rhodium(III) have been acylated with acid chlorides in the presence of Lewis acids. Mono-, di-, and triacyl chelates have been characterized. Thiocyanogen, sulfur dichloride, and arenesulfenyl chlorides substitute the chelate rings without catalysis. The reactions of a chelate sulfenyl chloride have been studied.

During a general study of reactions of coordinated ligands we have sought to demonstrate quasi-aromatic chemical properties of metal acetylacetonates.[1-10] Electrophilic substitution at the central carbon of these chelate rings has been illustrated with a variety of reagents. Through such reactions iodo,[5] bromo,[5,11] chloro,[5] thiocyanato,[1,12] nitro,[4] acetyl,[4] formyl,[8] chloromethyl,[13] and aminomethyl[13] groups have been substituted directly into the relatively inert trisacetylacetonates of rhodium(III), chromium(III), and cobalt(III).

Since the Friedel and Crafts synthesis of aryl ketones is one of the best-known classical aromatic reactions it was of interest to see if this method could be applied to the acylation of stable metal chelate rings. Furthermore, in certain cases it seemed possible to prepare the anticipated products independently by chelation of triacylamethanes.

The first attempted acylations of chromium(III) acetylacetonate failed, largely because of acid-catalyzed degradation of the chelate ring. Although chromium acetylacetonate is fairly stable in the presence of aluminum chloride, treatment of this chelate with a mixture of aluminum chloride and acetyl chloride led to extensive decomposition. Less powerful acids such as stannic chloride and zinc chloride were not effective in catalyzing this reaction. A mixture of pyridine and acetic anhydride or acetyl chloride also failed to react with this chelate. However, the acetylation was successful when chromium acetylacetonate was allowed to react with acetic anhydride and boron trifluoride etherate in methylene chloride. Under these conditions a complex mixture of acetylated chelates was formed. Careful recrystallization afforded a sample which seemed to be pure triacetylated chelate A.[4]

(1) Previous paper, J. P. Collman, R. P. Blair, R. L. Marshall, and L. Slade, *Inorg. Chem.*, in press.

(2) (a) This research was supported by a grant from the Petroleum Research Fund, administered by the American Chemical Society and by the Office of Army Research grant number DA-ORD-[D]-31124-G185. Grateful acknowledgment is made to the donors of these funds. (b) Part of this work was abstracted from the Ph.D. dissertation of R. L. Marshall, University of North Carolina, 1962.

(3) Petroleum Research Fund Fellow.

(4) J. P. Collman, R. A. Moss, S. D. Goldby, and W. S. Trahanovsky, *Chem. Ind.* (London), 1213 (1960).

(5) J. P. Collman, R. A. Moss, H Maltz, and C. C. Heindel, *J. Am. Chem. Soc.*, **83**, 531 (1961).

(6) J. P. Collman and E. T. Kittleman, *ibid.*, **83**, 3529 (1961).

(7) J. P. Collman, R. P. Blair, A. L. Slade, and R. L. Marshall, *Chem. Ind.* (London), 141 (1961).

(8) J. P. Collman, R. L. Marshall, W. L. Young, III, and S. D. Goldby, *Inorg. Chem.*, **1**, 704 (1962).

(9) J. P. Collman and E. T. Kittleman, *ibid.*, **1**, 499 (1962).

(10) J. P. Collman, R. L. Marshall, and W. L. Young, III, *Chem. Ind.* (London), 1380 (1962).

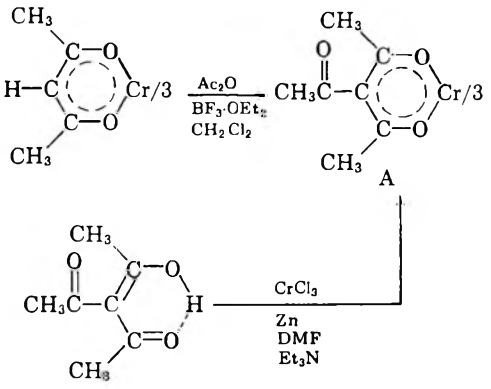
(11) R. W. Kluiber, *J. Am. Chem. Soc.*, **82**, 4839 (1960).

(12) R. W. Kluiber, *ibid.*, **83**, 3030 (1961).

(13) J. P. Collman, R. L. Marshall, and R. H. Barker, unpublished results.

Later experiments showed that this sample was contaminated with mono- and diacetylated chromium chelates.

Another apparently pure triacetylated chromium chelate was prepared by treating chromium(III) acetate hydrate with pure triacetylmethane in hot dimethylacetamide. This chelate and the purified Friedel–Crafts product had nearly identical infrared spectra and melting points. However, it was later found that hydrolysis of the ligand during the chelation reaction gave rise to an impure product. Later, when a completely nonaqueous chelation technique had been developed,[6,8] an authentic sample of the pure triacetylated chelate A was prepared from anhydrous chromium(III) chloride, zinc dust, dimethylformamide, and triethylamine. The pure triacetylated chelate A had a slightly different infrared spectrum than the Friedel–Crafts product. Careful chromatography of the Friedel–Crafts product then demonstrated that it was contaminated with partially acetylated chelates. Attempts to purify further the acetylation product and to isolate mono- and diacetylated chromium chelates were successful. Chromatography of this mixture under a variety of conditions did not effect a clean separation.

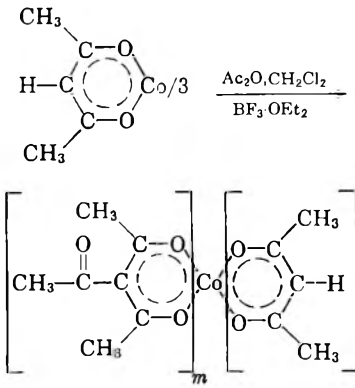


Dryden[14] had reported earlier that infrared spectra of unsubstituted metal acetylacetonates exhibit a doublet at 1580 and 1520 cm.$^{-1}$ whereas 3-substituted acetylacetonates show only a singlet in this region (about 1560 cm.$^{-1}$). A second band in the 1500–1600-cm.$^{-1}$ region in the spectrum of our Friedel–Crafts product was at first[4] thought to be a violation of Dryden's rule, but the lower frequency band (1520 cm.$^{-1}$) is now known to come from the mono- and diacetylated impurities. We have since found Dryden's rule to be valid for a large number of substituted metal acetylacetonates, and at this date are aware of no exception to this rule. Additional studies of the infrared spectra of mixed-ring metal acetylacetonates show that the vibrations of the three rings are independent of each other above 700 cm.$^{-1}$.[13]

Another infrared band characteristic of unsubstituted acetylacetonate chelate rings is the weak (–H) in-plane bending mode at 1195 cm.$^{-1}$. The absence of this band is good evidence of complete substitution of all chelate rings.[15,16]

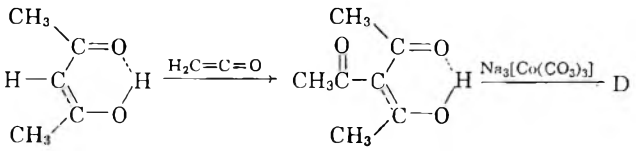
(14) R. P. Dryden and A. Winston, *J. Phys. Chem.*, **62**, 635 (1958).
(15) K. Nakamoto, P. J. McCarthy, and A. E. Martell, *J. Am. Chem. Soc.*, **83**, 1272 (1961).
(16) C. Djoidjevic, J. Lewis, and R. S. Nyholm, *Chem. Ind.* (London), 122 (1959).

The Friedel–Crafts acetylation of cobalt(III) acetylacetonate gave more clear-cut results. Under the same conditions used for the chromium chelate, the cobalt compound yielded a mixture of four chelates which were readily separated by chromatography or alumina. Cobalt acetylacetonate and the mono-, di-, and triacetylated cobalt acetylacetonates (B, C, and D) were eluted from the column in that order.



B, $m = 1, n = 2$
C, $m = 2, n = 1$
D, $m = 3, n = 0$

The structures of the acetylated chelates were assigned on the basis of their infrared spectra, proton magnetic resonance spectra, and elemental analyses. Furthermore, the triacetylated chelate D was prepared independently by reaction of triacetylmethane with $Na_3[Co(CO_3)_3]$.



Comparison of the infrared spectra of the mono- and diacetylated cobalt chelates, B and C, showed only the anticipated differences in peak intensities. Each spectrum exhibited an uncoordinated ketone band at 1680 cm.$^{-1}$, two strong peaks from 1500–1600 cm.$^{-1}$, and a small band at 1195 cm.$^{-1}$. By contrast, the spectrum of the pure triacetylated cobalt chelate D showed in addition to a strong band at 1680 cm.$^{-1}$ only a single peak in the 1500–1600-cm.$^{-1}$ region (1555 cm.$^{-1}$) and no absorption near 1195 cm.$^{-1}$. This spectrum was identical with that of the pure triacetylated chromium chelate A, prepared from the pure ligand under anhydrous conditions.

The nuclear magnetic resonance spectra of the diamagnetic mono-, di-, and triacetylated cobalt(III) chelates (B, C, and D) provided additional evidence for the assigned structures. A benzene solution of monoacetylated chelate, B, exhibited signals at 4.65, 7.91, 8.02, and 8.07 (doublet) τ with relative intensities of 2:6:3:12. Comparison with the parent acetylacetonate which has peaks at 8.10 and 4.65 τ in the ratio 6:1 showed that the 8.02 peak is caused by the uncoordinated acetyl group, whereas the doublet at 8.07 τ must be due to the methyl groups on the two unsubstituted chelate rings. The doublet is caused by the different chemical environment of the methyl groups on each of these rings arising from differential anisotropy of the neighboring rings.[10] The peak at 7.91 is then

assigned to the methyl groups on the single acetylated chelate ring.

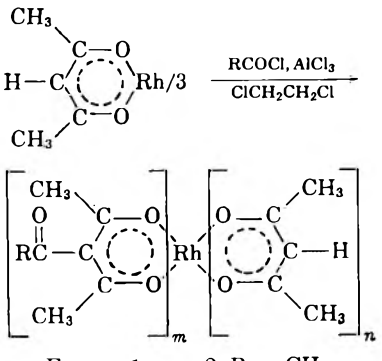
The spectrum of the diacetylated chelate, C, exhibited peaks at 4.40, 7.93 (doublet), 8.03, and 8.09 τ with intensities of 1:12:6:6, respectively. This is exactly the spectrum anticipated by comparison with the monoacetyl spectrum.

It is noteworthy that in chloroform these two spectra are the same except that the peak caused by the uncoordinated acetyl groups is the lowest field methyl signal. This might arise from some type of unsymmetrical solvation in one of the two solvents.

A solution of triacetylated chelate D in benzene exhibited two single peaks at 7.98 and 8.04 τ in the ratio of 2:1. These signals are easily assigned to the methyl groups on the chelate ring and the uncoordinated acetyl methyls.

Since Friedel–Crafts acylation of chromium and cobalt acetylacetonates under the same conditions affords mostly a triacetylated chromium chelate and little or no starting material, but very little triacetylated coblat chelate and a relatively large amount of starting material, it would seem that chromium acetylacetonate is more reactive than cobalt acetylacetonate. Extensive degradation during the work-up and chromatography steps introduces some uncertainty into this argument. However, the acetylation of rhodium acetylacetonate illustrates a clear-cut decrease in reactivity of this chelate ring.

Acetylation of rhodium(III) acetylacetonate proved to be much more difficult than that of the chromium(III) and cobalt(III) chelates. Under the same conditions which had been successful with the other metals (boron trifluoride–acetic anhydride for thirty-minute reaction at room temperature), rhodium(III) acetylacetonate failed to react. Treatment of the rhodium chelate with a large excess of this acetylating agent at 40° for five hours afforded a 19% yield of monoacetylated chelate E and 50% recovered starting material. Fortunately, this loss in reactivity of rhodium complexes parallels in increased resistance to acid degradation of these chelate rings. It was, therefore, possible to employ acid chlorides and aluminum chloride to acylate rhodium acetylacetonate. Under such conditions the mono- and diacetylated rhodium chelates, E and F, were obtained along with substantial quantities of recovered starting material. The mixtures were separated by chromatography and the diamagnetic mono- and diacetylated chelates, E and F, identified by their n.m.r. spectra. Except for changes in chemical shift values the n.m.r. spectra of E and F exactly paralleled those of the analogous cobalt chelates B and C. The infrared spectra were also very similar.



E, $m = 1, n = 2$, R = CH_3
F, $m = 2, n = 1$, R = CH_3
G, $m = 3, n = 0$, R = CH_3
H, $m = 1, n = 2$, R = C_6H_5
I, $m = 2, n = 1$, R = C_6H_5
J, $m = 1, n = 2$, R = C_9H_7

The symmetrical triacetylated rhodium chelate A was not obtained from this reaction even under more vigorous conditions.

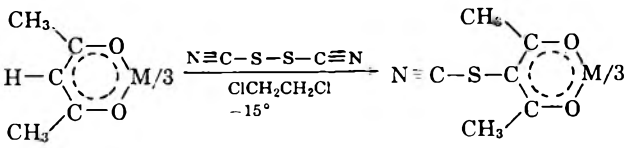
Attempted acetylation of rhodium acetylacetonate with acetic anhydride and polyphosphoric acid at room temperature was unsuccessful and reaction at 60° led to extensive decomposition of the chelate. It was noted that rhodium acetylacetonate is almost completely insoluble in polyphosphoric acid in contrast to cold concentrated sulfuric acid, in which the chelate can be dissolved without decomposition.

Treatment of chromium and cobalt acetylacetonates with other acylation reagents such as propionyl chloride, propionic anhydride, butyryl chloride, butyric anhydride, benzoyl chloride, and *p*-nitrobenzoyl chloride in the presence of aluminum chloride or boron trifluoride etherate resulted in extensive chelate degradation. Small amounts of acylated chelates isolated from these reactions were not tractable in our hands. It seems likely that increased bulk in the acylating agent sterically inhibits the Friedel–Crafts reaction so that competing ring degradation dominates. However, benzoyl chloride and butyryl chloride were used successfully to substitute rhodium(III) acetylacetonate in the same manner as the acetylation of the rhodium chelate. Monobenzoylated, dibenzoylated, and monobutyrylated rhodium chelates, H, I, and J, were prepared in this way.

Friedel–Crafts reactions of rhodium acetylacetonate with diphenylcarbamyl chloride or ethyl chlorocarbonate in the presence of aluminum chloride were not successful. Attempted alkylations of rhodium acetylacetonate with benzyl chloride using boron trifluoride or aluminum chloride were also unsuccessful. Attempts to introduce allyl groups into chromium acetylacetonate failed.

Kluiber[12] had reported earlier that sulfur electrophiles can be conveniently introduced into metal acetylacetonate rings. He described the preparation of the trissulfenyl chlorides and thiocyanates of cobalt(III) and chromium(III) acetylacetonates and the conversion of the chromium trissulfenyl chloride into the tristhiocyanate derivative. The trifunctionality of the chromium sulfenyl chloride made a study of its reactions difficult.

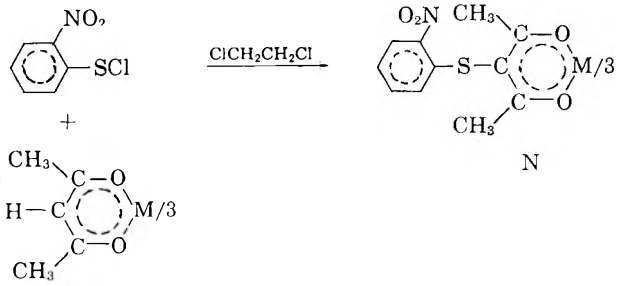
We have also studied the introduction of sulfur electrophiles into metal acetylacetonate chelate rings. Thus treatments of rhodium(III), cobalt(III), and chromium(III) acetylacetonates with thiocyanogen gives high yields of the tristhiocyanato chelates, K, L, and M. The diamagnetic rhodium and cobalt chelates show only one signal in their proton resonance spectra.



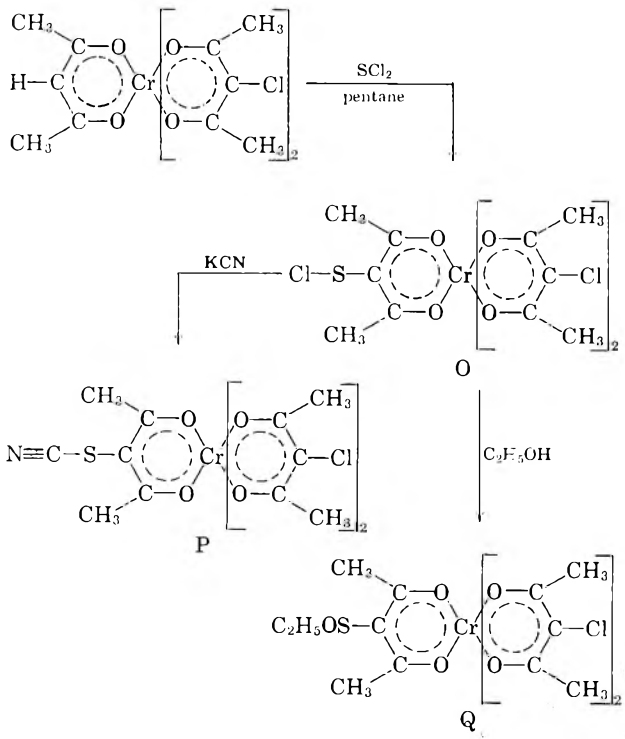
K, M = Rh
L, M = Co
M, M = Cr

The infrared spectra of these chelates exhibit the anticipated nitrile peak at 2150 cm.$^{-1}$, a single peak in the 1500–1600-cm.$^{-1}$ region (1555 cm.$^{-1}$) and no absorption at 1195 cm.$^{-1}$.

In a similar manner, arenesulfenyl chlorides were also found to substitute these chelate rings. No catalysis was required for these reactions. The aryl sulfide chelates N formed very stable 1:1 solvates with benzene, a common phenomenon in acetylacetonate chemistry.[11,12,17] These sulfides were surprisingly resistant to oxidation and failed to react with 30% hydrogen peroxide. Attempts to prepare a chelate sulfone by treatment of rhodium(III) acetylacetonate with benzenesulfonyl chloride and aluminum chloride failed.



In order to avoid the complications attending the reactions of trissulfenyl chlorides it seemed desirable to prepare a mono-functional chelate sulfenyl chloride. This was done by treating dichlorinated chromium acetylacetonate with sulfur dichloride. The dichloro chlorosulfenyl chelate, O, was then allowed to react with cyanide ion to form the dichloro thiocyanato chelate P. In a similar way, reaction of the sulfenyl chloride with dry ethanol afforded ethyl sulfenate Q.



Use of partially halogenated metal acetylacetonates to introduce only one reactive functional group into chelate rings and, therefore, avoid the complications of trifunctionality deserves more comment. Although such a scheme is often necessary when one wishes to study the reactions of functional groups on chelate rings, unexpected complications may arise. The chloro groups in dichlorinated chromium acetylacetonate are subject to electrophilic cleavage from the chelate rings.[18] Thus the mixed-ring chelates may be contaminated and require tedious purification. Use of blocking groups such as nitro which cannot be cleaved by electrophiles results in strong deactivation of the remaining unsubstituted ring.[13] These problems currently are being studied in attempts to prepare linear polymers with a chelate ring backbone.

Experimental

All melting points were taken on a Kofler hot stage apparatus fitted with a polarizing microscope and are not corrected. Infrared spectra were recorded on a Perkin-Elmer Infracord fitted with sodium chloride optics and with a Perkin-Elmer Model 421 double grating spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60 spectrometer at 60 Mc. using tetramethylsilane as an internal standard. Chemical shifts are reported in τ values and relative intensities are given in parentheses.

Acetylation of Tris(2,4-pentanediono)rhodium(III) Using Acetic Anhydride and Boron Trifluoride.—To a stirred solution of rhodium(III) acetylacetonate[19] (500 mg., 1.25 mmoles) in 100 ml. of pure methylene chloride was added 770 mg. (7.5 mmoles, 0.71 ml.) of freshly distilled acetic anhydride and 1.06 g. (7.5 mmoles, 0.91 ml.) of freshly distilled boron trifluoride etherate. The reaction mixture was heated at reflux under nitrogen for 5 hr.

The reaction mixture was poured into 250 ml. of water and ice containing enough sodium carbonate to neutralize the acidic by-products and stirred rapidly. The separated methylene chloride phase was extracted twice more with small portions of pure water, dried with calcium chloride, and evaporated to yield a light yellow, amorphous powder.

The crude mixture of chelates was dissolved in benzene and purified by chromatography using a 12 × 1 in. column of Merck alumina and benzene as an eluent. Three bands were collected over a long period. The first band, which was recovered from the solvent by flash evaporation on a rotating Rinco evaporator and then recrystallized from benzene–heptane, weighed 250 mg., m.p. 260–263°. An infrared spectrum and a mixture melting point showed this band to be recovered rhodium acetylacetonate, m.p. 260–261°; infrared (KBr), 1565, 1515, 1380, 1268, 1200, 1020, 935 cm.$^{-1}$; ultraviolet (ethanol), λ_{max} 258 mμ (ϵ 9040), 317 (10,700); n.m.r. (CCl_4), 7.89 (6), 4.65 τ (1).

The second band afforded 105 mg. (19%) of pure (3-acetyl-2,4-pentanediono)-bis(2,4-pentanediono)rhodium(III), m.p. 252–253°; infrared (KBr), 1675, 1550, 1360, 1265, 1240, 1200, 1060, 1025, 935 cm.$^{-1}$; ultraviolet (ethanol), λ_{max} 258 mμ (ϵ 12,750), 317 (10,200). The n.m.r. spectrum of this acetylated chelate was consistent with the assigned structure: ($CHCl_3$), 7.85 (6), 7.84 (6), 7.82 (6), 7.55 (3), 4.46 (2) τ; (CCl_4), 7.89, 7.87, 7.85, 7.62, 4.63 τ.

Anal. Calcd. for $C_{17}H_{24}O_7Rh$: C, 46.17; H, 5.24. Found: C, 46.32; H, 5.32.

The third band afforded 12 mg. of an intractable chelate. An infrared spectrum of this substance indicated a more intense uncoordinated carbonyl absorption than possessed by the monoacetylated product.

An acetylation reaction attempted at the boiling point of 1,2-dichloroethane (83°) for 1 hr. resulted in major decomposition of the chelate system and less than 10% recovery of starting material. No acetylated products were detected.

Acetylation of Tris(2,4-pentanediono)rhodium(III) using Acetyl Chloride and Aluminum Chloride.—To a stirred suspension of 2.0 g. (15 mmoles) of sublimed, anhydrous aluminum chloride in 50 ml. of pure 1,2-dichloroethane under a nitrogen atmosphere was added 1.18 g. (15 mmoles, 1.07 ml.) of freshly distilled acetyl

(17) J. F. Steinbeck and J. H. Burns, *J. Am. Chem. Soc.*, **80**, 1839 (1958).

(18) J. P. Collman, W. L. Young, III, R. H. Barker, and M. Yamada, 142nd National Meeting of American Chemical Society, Organic Division, Atlantic City, N. J., September, 1962; Abstract of papers, p. 40-Q.

(19) F. P. Dwyer and A. M. Sargeson, *J. Am. Chem. Soc.*, **75**, 984 (1953).

chloride. The resulting solution was cooled to −20° with a methanol–ice bath. To this mixture was added over a 10-min. period a solution of 1.00 g. (2.5 mmoles) of rhodium(III) acetylacetonate in 20 ml. of 1,2-dichloroethane. The solution was stirred for an additional 20 min. during which time the temperature rose to −15°. The reaction mixture was poured into 200 ml. of ice and water containing 15 ml. of concentrated hydrochloric acid and stirred vigorously. The aqueous layer became slightly yellow indicating some decomposition of the chelate system. The organic phase was extracted once more with water, dried over potassium carbonate, and filtered. The crude mixture of chelates was recovered by solvent evaporation.

Chromatographic purification of the crude product in the usual way afforded three chelates. The first band afforded 300 mg. of recovered rhodium acetylacetonate The second band yielded 350 mg. of (3-acetyl-2,4-pentanediono)bis(2,4-pentanediono)rhodium-(III), m.p. 252–254°. The identity of this monoacetylation product was confirmed by comparing its infrared spectrum and nuclear magnetic resonance spectrum with those of a sample of the material obtained previously.

The third band afforded 110 mg. of yellow crystals, m.p. 259–261 dec. The infrared spectrum, nuclear magnetic resonance spectrum, and elemental analysis indicate that this compound is (2,4-pentanediono)bis(3-acetyl-2,4-pentanediono)rhodium(III), the diacetylated chelate: infrared (KBr), 1700, 1685, 1560, 1520, 1420, 1350, 1275, 1240, 1200, 1055, 1020, 950, 925 cm.$^{-1}$; ultraviolet (ethanol), λ_{max} 259 mμ (ε 12,050), 317 (7360); n.m.r. ($CHCl_3$), 7.84 (6), 7.82 (6), 7.80 (6), 7.55 (6), 4.46 (1) τ; (CCl_4), 7.86, 7.85, 7.80, 7.61, 4.63 τ.

Anal. Calcd. for $C_{19}N_{23}O_8Rh$: C, 47.12; H, 5.20. Found: C, 47.33; H, 5.23.

This reaction afforded a 33% recovery of starting material, a 32% yield of monoacetylated product, and a 13% yield of diacetylated product. Repetition of this experiment using acetyl chloride in place of 1,2-dichloroethane as solvent yielded 40% starting material, 18% monoacetyl, and 10% diacetyl chelate.

Butyrylation of Tris(2,4-pentanediono)rhodium(III).—Treatment of 1.0 g. of rhodium acetylacetonate with 2.0 g. of aluminum chloride and 1.6 g. of *n*-butyryl chloride in 75 ml. of 1,2-dichloroethane under the same conditions described before yielded 67% recovered starting material and 100 mg. (8.5%) of (3-butyryl-2,4-pentanediono)bis(2,4-pentanediono)rhodium(III); m.p. 185–187; infrared (KBr), 1680, 1560, 1520, 1370, 1270, 1205, 1020, and 930 cm.$^{-1}$; ultraviolet (ethanol), λ_{max} 260 mμ (ε 8020), 317 (6980); n.m.r. ($CHCl_3$), 9.05 triplet (3), multiplet 8.70–8.15 (2), 7.88 (6), 7.87 (6), 7.85 (6), 7.36 triplet (2), 4.47 (2) τ.

Anal. Calcd. for $C_{19}H_{27}O_7Rh$: C, 48.52; H, 5.79. Found: C, 48.43; H, 5.93.

An additional 10 mg. of an impure acylated chelate was obtained from the third band, but attempts to purify this crude product failed.

Benzoylation of Tris(2,4-pentanediono)rhodium(III).—Treatment of 1.0 g. of rhodium acetylacetonate with 2.00 g. of aluminum chloride and 4.22 g. (30 mmoles, 3.5 ml.) of freshly distilled benzoyl chloride in 80 ml. of 1,2-dichloroethane under the same conditions for 1 hr. afforded 330 mg. (33%) of starting material, 120 mg. of monobenzoylated chelate and 40 mg. of dibenzoylated chelate.

The monobenzoyl compound, (3-benzoyl-2,4-pentanediono)-bis(2,4-pentanediono)rhodium(III), 150 mg. (11%), m.p. 231–232°, was the second band eluted from the column with benzene. The spectral characteristics and elemental analysis of this compound confirm the assigned structure: infrared (KBr), 1660, 1560, 1515, 1370, 1282, 1267, 1245, 1195, 1133, 892 cm.$^{-1}$; ultraviolet ($CHCl_3$), λ_{max} 316 mμ (ε 8550); n.m.r., 7.97 (6), 7.82 (6), 7.75 (6), 4.43 (2), 1.65–2.5 (5) τ.

Anal. Calcd. for $C_{22}H_{23}O_7Rh$: C, 52.39; H, 5.00. Found: C, 52.78; H, 5.00.

The dibenzoylated chelate, (2,4-pentanediono)bis(3-benzoyl-2,4-pentanediono)rhodium(III), 40 mg. (4%), m.p. 205–208°, was removed from the column by extruding the third band and extracting with boiling benzene–methanol. The spectral characteristics and analyses of this chelate confirm the assigned structure: infrared (KBr), 1660, 1555, 1515, 1360, 1280, 1245, 1133, and 890 cm.$^{-1}$; ultraviolet ($CHCl_3$), λ_{max} 311 mμ (ε 5620); n.m.r. ($CHCl_3$), 7.94 (6), 7.86 (6), 7.72 (6), 4.50–4.40 (1), 1.65–3.65 (10) τ.

Anal. Calcd. for $C_{29}H_{29}O_7Rh$: C, 57.24; H, 4.80. Found: C, 57.60; H, 4.95.

Preparation of Triacetylmethane.—Ketene was generated from reagent acetone in a cracking apparatus[20] and was passed for 3 hr. into 200 g. of acetylacetone. The orange liquid was evaporated at 70° to an orange oil by a rotatory evaporator, then vacuum distilled at 27 mm. The third fraction (b.p. 108–112°) was redistilled at 30 mm. to give 105.9 g. (28.5%) of a faintly yellow oil (b.p. 111–113°) which was shown to be pure by vapor phase chromatography and identified as triacetylmethane by its physical properties, infrared spectrum, and chelation with copper(II) acetate.

Preparation of Bis(3-acetyl-2,4-pentanediono)copper(II).—To 2 ml. of triacetylmethane in 1 ml. of ethanol was added 4 ml. of saturated copper(II) acetate solution. The solution turned immediately dark blue. After stirring at room temperature for 25 min., small crystals of blue bis(3-acetyl-2,4-pentanediono)-copper(II) were obtained. Yield: 0.35 g., m.p. 207–207.5°; infrared (KBr), 1685, 1582, 1450, 1400, 1350, 1239, 1055 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}O_6Cu$: C, 48.66; H, 5.25. Found: C, 48.44; H, 5.55.

Preparation of Tris(3-acetyl-2,4-pentanediono)chromium(III) from Triacetylmethane. A.—An intimate mixture of 0.5 g. of anhydrous chromium trichloride and 0.5 g. of zinc dust was added to 5 ml. of dimethylformamide. An exothermic reaction ensued and a green solution was formed. To this solution was added 8 ml. (8.6 g., 60 mmoles) of triacetylmethane, 3.16 g. (20 mmoles of anhydrous chromium(III) chloride, and 0.3 g. of zinc dust. To the green mixture was added dropwise 8.3 ml. (6.0 g., 60 mmoles) of triethylamine. The exothermic reaction was kept at about 60° by stirring the mixture through an external water bath. The purple mixture was stirred for an additional 1.5 hr. and then poured into 300 ml. of water. The purple precipitate was collected on a filter, washed with water, sucked dry, and then dissolved in methylene chloride and filtered. The organic phase was dried over magnesium sulfate and evaporated to a purple solid. Recrystallization from benzene–heptane afforded purple crystals, m.p. 195–197°, 5.87 g. The mother liquor afforded an additional 0.47 g.; total yield 6.34 g. (66.7%). Another recrystallization afforded an analytical sample, m.p. 197–198°. A test chromatographic column showed only a single chelate. The infrared spectrum and elemental analyses indicated that the product was pure tris(3-acetyl-2,4-pentanediono)-chromium(III): infrared (KBr), 1687, 1560, 1450, 1420, 1360, 1242, 1055 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}O_9Cr$: C, 53.05; H, 5.69. Found: C, 53.28; H, 5.88.

B.—To a stirred suspension of 0.83 g. of chromium(III) acetate hydrate in 10 ml. of dimethylacetamide was added 1.42 g. of triacetylmethane. The mixture was heated to 80° or 16 hr. and then combined with 50 ml. of water. The resulting solution was extracted with two 50-ml. portions of chloroform. The chloroform extracts were combined, washed with two 100-ml. portions of water, and then dried over calcium sulfate. The solvent was removed and the purple oil was crystallized from ethanol. Two recrystallizations from ethanol yielded 0.14 g. (8.6%) of the triacetylated chromium(III) chelate as a purple powder, m.p. 197–199°. The infrared spectrum of this chelate indicated the presence of a small amount of unsubstituted chelate rings.

C.—To a solution of 0.37 g. of tris(tetrahydrofuran)trichlorochromium(III) and 0.43 g. of triacetylmethane in 25 ml. of 1:1 acetone–water was added 0.3 g. of triethylamine. The mixture was stirred for an hour and the resulting purple solution was then extracted with 20 ml. of methylene chloride. The solution was dried, the solvent removed, and the purple residue crystallized from benzene–heptane. The resulting powder was further purified by chromatography on alumina. The yield of triacetylated chromium(III) acetylacetonate was 0.19 g. (25%), m.p. 196–198°. The infrared spectrum of this product indicated the presence of a small amount of unsubstituted chelate rings.

Acetylation of Chromium(III) Acetylacetonate.—To a solution of 10 g. of chromium acetylacetonate and 10.5 g. of freshly distilled acetic anhydride in 50 ml. of anhydrous methylene chloride under nitrogen was added 10 ml. of pure boronitrifluoride etherate. The deep purple solution was stirred at room temperature for 30 min. and then shaken vigorously with cold aqueous potassium acetate. The organic phase was dried, filtered, and the solvent removed. The purple oil was poured into ethanol, and the resulting violet crystals were collected and then recrystallized from ethanol. The crude purple powder, 5.7 g. (52%), melted at

(20) J. W. Williams and C. D. Hurd, *J. Org. Chem.*, **5**, 122 (1940).

192–194°. Two more recrystallizations from ethanol afforded an analytical sample of tris(3-acetyl-2,4-pentanediono)chromium(III), m.p. 198–200°. The infrared spectrum of this sample indicated a small amount of partially acetylated chelate was present.

Anal. Calcd. for $C_{21}H_{27}O_9Cr$: C, 53.05; H, 5.69. Found: C, 53.03; H, 6.10.

Acetylation of Cobalt(III) Acetylacetonate.—To a solution of 10 g. of cobalt(III) acetylacetonate and 10.5 g. of acetic anhydride in 50 ml. of anhydrous methylene chloride was added 10 ml. of freshly distilled boron trifluoride etherate. The deep green solution was stirred for 30 min. and then decomposed with cold potassium acetate solution. The organic phase was separated, dried, and evaporated to dryness. The crude green powder was taken up in benzene and purified by chromatography on a 52 × 6 cm. column of alumina. Elution was begun with benzene and completed with methylene chloride–benzene. Four green bands were collected and each crystalline product was recrystallized from ethanol.

The first band afforded 0.15 g. of cobalt(III) acetylacetonate, identified by mixture melting point with an authentic sample and its infrared spectrum.

The second band yielded 0.57 g. of (3-acetyl-2,4-pentanediono)bis(2,4-pentanediono)cobalt(III), m.p. 185–186°; infrared (KBr), 1675, 1565, 1517, 1370, 1279, 1245, 1191, and 1057 cm.$^{-1}$. The proton magnetic resonance spectrum of the monoacetylated chelate showed signals at 8.08 (6), 8.06 (6), 8.02 (3), 7.91 (6), and 4.20 (2) τ in benzene.

Anal. Calcd. for $C_{17}H_{23}O_7Co$: C, 51.27; H, 5.78. Found: C, 51.26; H, 5.83.

The third band afforded 0.68 g. of (2,4-pentanediono)bis(3-acetyl-2,4-pentanediono)cobalt(III), m.p. 184–185°. A mixture melting point with the monoacetylated chelate was 180–182°. The infrared and n.m.r. spectra and elemental analysis confirmed the structure of the diacetylated chelate: infrared (KBr), 1678, 1560, 1518, 1390, 1360, 1241, 1191, and 1057 cm.$^{-1}$; n.m.r., 8.09 (6), 8.03 (6), 7.94 (6), 7.92 (6), and 4.70 (1) τ in benzene.

Anal. Calcd. for $C_{19}H_{25}O_8Co$: C, 51.83; H, 5.68. Found: C, 51.44; H, 5.75.

The fourth band yielded only an oily green solid. This chelate was further purified by chromatography on Florisil, using methylene chloride–2-propanol as an eluent. Recrystallization from ethanol gave 0.08 g. of tris(3-acetyl-2,4-pentanediono)cobalt(III) as green needles, m.p. 169–170°; infrared (KBr), 1689, 1561, 1311, 1246, and 1059 cm.$^{-1}$, no 1191-cm.$^{-1}$ band; n.m.r., 8.04 (1) and 7.98 (2) τ in benzene.

Anal. Calcd. for $C_{21}H_{27}O_9Co$: C, 52.28; H, 5.64. Found: C, 52.27; H, 5.92.

Preparation of Tris(3-acetyl-2,4-pentanediono)cobalt(III) by Chelation of Triacetylmethane: A. With Cobaltous Carbonate and Hydrogen Peroxide.—To a suspension of 0.50 g. of cobaltous carbonate in 3.58 g. of triacetylmethane was added slowly with vigorous stirring 12 ml. of 10% hydrogen peroxide. After stirring 20 min. at 50°, the green solution was diluted with 100 ml. of water and extracted with three 35-ml. portions of chloroform. The extracts were combined and dried over anhydrous magnesium sulfate. Upon removal of the solvent, a green oil resulted which was purified by chromatography on alumina. Three green bands were separated, collected, and crystallized from benzene–heptane. The first band (0.245 g.) was identical in melting point and infrared spectrum to (3-acetyl-2,4-pentanediono)bis-(2,4-pentanediono)cobalt(III). The infrared spectrum and melting point identified the solid from the second band (0.265 g.) as (2,4-pentanediono)bis(3-acetyl-2,4-pentanediono)cobalt(III). The third band gave a modest yield (0.165 g.) of a compound identical in melting point to tris(3-acetyl-2,4-pentanediono)cobalt(III). The infrared spectrum of this compound, however, revealed the presence of a slight impurity of the diacetylated chelate. Further purification of this band by alumina chromatography gave pure tris(3-acetyl-2,4-pentanediono)cobalt(III), m.p. 169–170°.

B. With Sodium Tricarbonatocobalt(III) 3-Hydrate.—To a suspension of 0.89 g. of sodium tricarbonatocobalt(III) trihydrate in 10 ml. of 1:1 acetone–water was added with stirring at 50° 1.56 g. of triacetylmethane. After 45 min., the black-green suspension was extracted with two 25-ml. portions of chloroform. The green extract was washed with 50 ml. of water, dried over anhydrous magnesium sulfate, and evaporated to a bright green oil. The oil upon crystallization from benzene–heptane gave 0.18 g. (11.4%) of crude tris(3-acetyl-2,4-pentanediono)cobalt(III). Purification of this material by Florisil chromatography afforded 0.10 g. of pure tris(3-acetyl-2,4-pentanediono)cobalt(III) identical in melting point and infrared spectrum to an authentic sample obtained from the Friedel–Crafts acetylation. The chromatography also revealed traces of mono- and diacetylated cobalt(III) acetylacetonates.

Treatment of Chromium(III) and Cobalt(III) Acetylacetonates with Ketene. Into a solution of 5.0 g. of chromium acetylacetonate in a solution of 50 ml. of xylene, 25 ml. of toluene, and 25 ml. of benzene was bubbled through a vigorous stream of gaseous ketene for 2 hr. The chelate was recovered by evaporation of the solvent and chromatography in the usual manner. A mixture melting point of this product with an authentic sample of chromium(III) acetylacetonate was not depressed. Only the starting material was detected in the work-up. A similar experiment using cobalt(III) acetylacetonate also yielded only the starting material.

Treatment of Rhodium(III) Acetylacetonate with Diphenylcarbamyl Chloride.—To a stirred suspension of 533 mg. (4 mmoles) of anhydrous aluminum chloride in 35 ml. of dichloroethane was added 928 mg. of diphenylcarbamyl chloride. The resulting suspension was cooled to 0°. To this mixture was added dropwise 400 mg. of rhodium acetylacetonate in 15 ml. of dichloroethane. The reaction was allowed to stir for 1 hr. at room temperature. The usual work-up afforded 365 mg. of recovered rhodium acetylacetonate.

A similar experiment with ethyl chlorocarbonate gave the same results.

Treatment of Tris(3-phenylthio-2,4-pentanediono)rhodium(III) with Hydrogen Peroxide.—A solution of 100 mg. of the sulfide chelate, 20 ml. of acetic acid, and 10 ml. of 30% hydrogen peroxide was stirred at room temperature for 30 min. The usual work-up afforded only the starting material. A repetition of this experiment at a higher reaction temperature resulted in nearly total decomposition of the chelate system; however, the recovered chelate had not been oxidized.

Treatment of Rhodium(III) Acetylacetonate with Benzyl Chloride under Friedel–Crafts Conditions.—To a stirred mixture of 800 mg. (6 mmoles) of anhydrous aluminum chloride and 400 mg. (1 mmole) of rhodium acetylacetonate in 50 ml. of 1,2-dichloroethane was added dropwise 840 mg. (6 mmoles) of freshly distilled benzyl chloride in 10 ml. of 1,2-dichloroethane. The mixture was stirred under nitrogen for 30 min. and then decomposed with dilute hydrochloric acid and worked up in the usual manner. The starting material was recovered in high yield. Little decomposition was noticed and no other chelates were detected—even by chromatography.

Similar experiments with boron trifluoride etherate and varying conditions gave the same result.

Tris(3-thiocyanato-2,4-pentanediono)chromium(III).—Lead thiocyanate was prepared by dropwise addition of an aqueous solution of sodium thiocyanate to a rapidly stirred solution of lead nitrate. The insoluble salt was collected by suction filtration and washed several times with ice–water and finally with anhydrous ether. The salt was stored in a vacuum desiccator over phosphorus pentoxide in the dark.

Thiocyanogen was prepared by dropwise addition of a solution of 10.5 g. (0.066 mole, 3.37 ml.) of bromine in 20 ml. of 1,2-dichloroethane to a vigorously stirred suspension of 21.4 g. (0.066 mole) of anhydrous lead thiocyanate in 80 ml. of 1,2-dichloroethane cooled to −15°. The red bromine color was allowed to disappear before each successive addition of bromine. The mixture of thiocyanogen and lead bromide was stirred for 5 min. after the bromine addition was completed.

The solid lead bromide was allowed to settle and the colorless thiocyanogen solution was filtered into a stirred solution of 7.0 g. (0.02 mole) of chromium(III) acetylacetonate in 50 ml. of 1,2-dichloroethane cooled to −15°. The mixture was stirred for 2 hr. at −15° and then allowed to come to room temperature and react for an additional hour. The reaction mixture was extracted two times with water. The organic phase was dried with calcium chloride, filtered, and evaporated to dryness. The red powder was recrystallized from 95% ethanol to yield 7.85 g. of pure tris(3-thiocyanato-2,4-pentanediono)chromium(III), m.p. 191–192°; a second crop of 2.10 g., m.p. 190–192°, was obtained by concentration of the mother liquor. The total yield was 9.95 g. (95.6%); infrared (KBr), 2150, 1555, 1405, 1360, 1330, 1175, 1060, and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{18}O_6N_3S_3Cr$: C, 41.53; H, 3.49; N, 8.07; S, 18.48. Found: C, 41.56; H, 3.56; N, 7.78; S, 17.81.

Tris(3-thiocyanato-2,4-pentanediono)cobalt(III).—Under the same conditions used for the analogous chromium complex the green crystalline tris(3-thiocyanato-2,4-pentanediono)cobalt(III) was formed in 76% yield, m.p. 166–167° dec.; infrared (KBr), same as chromium complex; ultraviolet ($CHCl_3$), λ_{max} 300 mμ (ε 13,750); n.m.r. (CCl_4), 7.30 τ.

Anal. Calcd. for $C_{18}H_{18}O_6N_3S_3Co$: C, 40.98; H, 3.44; N, 7.97; S, 18.24. Found: C, 40.34; H, 3.92; N, 7.98; S, 18.43.

Tris(3-thiocyanato-2,4-pentanediono)rhodium(III).—Under the same conditions used for the analogous chromium complex the yellow crystalline trithiocyanatorhodium chelate was prepared in 98% yield, m.p. 214–215°; infrared (KBr), 2150, 1550, 1365, 1331, 1055, 1025, 918 cm.$^{-1}$; ultraviolet ($CHCl_3$), λ_{max} 310 mμ (ε 65,500); n.m.r. ($CHCl_3$), 7.30 τ.

Anal. Calcd. for $C_{18}H_{18}O_6N_3S_3Rh$: C, 37.90; H, 3.18; N, 7.35. Found: C, 37.74; H, 3.42; N, 7.83, 7.06.

Tris(3-phenylthio-2,4-pentanediono)chromium(III).—To a stirred solution of 3.40 g. (0.01 mole) of chromium(III) acetylacetonate in 50 ml. of 1,2-dichloroethane was added dropwise a solution of 5.8 g. (0.04 mole) of freshly prepared benzenesulfenyl chloride in 25 ml. of 1,2-dichloroethane. The temperature quickly rose to 40° and local boiling was observed. The reaction was stirred at room temperature for 30 min. The mixture was extracted with dilute aqueous sodium carbonate. The green aqueous layer indicated some decomposition had taken place. The organic layer was separated, dried over potassium carbonate, filtered, and evaporated to dryness. The grey-purple, amorphous residue was recrystallized from 80% ethanol to yield 2.0 g. (32.7%) of crystalline tris(3-phenylthio-2,4-pentanediono)-chromium(III), m.p. 90–100°. An analytical sample was prepared by two more recrystallizations from ethanol–water, m.p. 104–105°; infrared (KBr), 1550, 1470, 1410, 1360, 1330, 1070, 1025, 920 cm.$^{-1}$; ultraviolet ($CHCl_3$), λ_{max} 326 mμ (ε 14,400).

Anal. Calcd. for $C_{33}H_{33}O_6S_3Cr$: C, 58.82; H, 4.94; S, 14.27. Found: C, 58.57; H, 5.21; S, 13.14.

Tris(3-*o*-nitrophenylthio-2,4-pentanediono)cobalt(III).—To a stirred solution of 3.51 g. (0.01 mole) of cobalt acetylacetonate in 50 ml. of 1,2-dichloroethane cooled to 0° was added dropwise a solution of 7.55 g. (0.04 mole) of *o*-nitrobenzenesulfenyl chloride in 50 ml. of 1,2-dichloroethane at such a rate that the temperature did not rise above 5°. The mixture was stirred for an additional 30 min. at 0–5°.

The organic phase was extracted four times with water. The fourth aqueous wash was neutral to litmus. The organic phase was dried over potassium carbonate, filtered, and evaporated to a dark, viscous oil. The oil was taken up in hot benzene, treated with activated charcoal, filtered, and then diluted with an equal volume of hot heptane. Slow cooling of this solution afforded brown crystals which were collected and air dried. The first crop weighed 6.20 g., m.p. 211–212° dec., and a second crop of 1.0 g. was obtained by concentrating the mother liquor (total yield 80.7% calculated for benzene solvate); infrared (KBr), 1590, 1565, 1550, 1515, 1410, 1360, 1335, 1300, 1100, 1072, 1038, 845 cm.$^{-1}$; ultraviolet ($CHCl_3$), λ_{max} 370 mμ (ε 23,700); n.m.r. (CCl_4), 7.46 (18), 2.71 (18) τ (broad). The infrared n.m.r. and elemental analysis of this substance indicate that it is a monobenzene solvate. It is remarkable that treatment at 100° and 0.1 mm. for 24 hr. failed to remove the benzene.

Anal. Calcd. for $C_{33}H_{30}O_{12}N_3S_3Co \cdot C_6H_6$: C, 52.50; H, 4.06; N, 4.70. Found: C, 51.71; H, 4.06; N, 4.85.

Tris(3-*o*-nitrophenylthio-2,4-pentanediono)chromium(III).—Under the same conditions as the cobalt analog this chromium chelate was prepared in 80% yield, m.p. 251–252°. Again the spectral properties and elemental analysis indicate a monobenzene solvate; infrared (KBr), 1583, 1565, 1550, 1512, 1410, 1360, 1445, 1300, 1240, 1070, 1035, 1015, 915, 845 cm.$^{-1}$; ultraviolet ($CHCl_3$), λ_{max} 367 mμ (ε 21,300).

Anal. Calcd. for $C_{33}H_{30}O_{12}N_3S_3Cr \cdot C_6H_6$: C, 52.81; H, 4.09; N, 4.74; S, 10.84. Found: C, 51.92, 52.73; H, 4.10, 4.17; N, 4.74, 5.09; S, 10.29.

Tris(3-*o*-nitrophenylthio-2,4-pentanediono)rhodium(III).—In a manner similar to that described before the rhodium thioether was prepared in 70% yield, m.p. 261–263°; infrared (KBr), 1588, 1565, 1540, 1515, 1450, 1410, 1360, 1335, 1300, 1245, 1100, 1065, 1035, 915, 845 cm.$^{-1}$; ultraviolet ($CHCl_3$), λ_{max} 268 mμ (ε 16,500), 369 (14,300); n.m.r. (CCl_4), 7.46, 2.71 τ (broad). Again the thioether was a very stable monobenzene solvate.

Anal. Calcd. for $C_{33}H_{30}O_{12}N_3S_3Rh \cdot C_6H_6$: C, 49.95; H, 3.87; N, 4.48. Found: C, 50.39; H, 4.02; N, 4.55.

Reaction of Sulfur Dichloride with Dichlorinated Chromium(III) Acetylacetonate.—To a suspension of 6.0 g. (14.3 mmoles) of (2,4-pentanediono)bis(3-chloro-2,4-pentanediono)chromium(III) in 50 ml. of pure pentane was added 3.2 ml. (49 mmoles) of freshly distilled sulfur dichloride. The mixture was stirred for 12 hr., and then the solid product was collected and washed several times with pure pentane. Recrystallization from benzene–heptane afforded 4.5 g. of (3-chlorothio-2,4-pentanediono)-bis(3-chloro-2,4-pentanediono)chromium(III), tan crystals, m.p. 153, 153.5°; infrared (KBr), 1550, 1450, 1410, 1360, 1335, 1290, 1040, 1020, 980, 920, and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{18}Cl_3O_6SCr$: C, 37.20; H, 3.72; S, 6.62; Cl, 22.0C. Found: C, 37.74; H, 3.75; S, 6.29; Cl, 21.72.

Treatment of Chelate Sulfenyl Chloride with Cyanide.—To a solution of 1.00 g. (2 mmoles) of (3-chlorothio-2,4-pentanediono)-bis(3-chloro-2,4-pentanediono)chromium(III) in 20 ml. of benzene was added 0.26 g. (4 mmoles) of potassium cyanide and the mixture was stirred for 1 hr. The mixture was filtered and the filtrate was evaporated. The brown powder was taken up in benzene and purified by chromatography on Florisil (deactivated by addition of 10% water). The first band was collected, the solvent evaporated, and the product recrystallized from benzene–heptane, 405 mg., tan needles, m.p. 198–199°. The infrared spectrum was almost identical with that of the starting material.

Anal. Calcd. for $C_{16}H_{18}Cl_2O_6NSCr$: C, 40.43; H, 3.81; N, 2.94; S, 6.74; Cl, 14.91. Found: C, 40.21; H, 3.99; N, 2.69; S, 6.46; Cl, 14.60.

Reaction of Chelate Sulfenyl Chloride with Ethanol.—To a solution of 1.00 g. (2 mmoles) of (3-chlorothio-2,4-pentanediono)-bis(3-chloro-2,4-pentanediono)chromium in 20 ml. of benzene was added 0.184 g. (4 mmoles) of absolute ethanol and 0.216 g. (2 mmoles) of triethylamine. The solution was stirred for 1.5 hr., filtered, and the solvent was removed. The residue was purified by chromatography on Florisil (deactivated by 10% water) using benzene as the eluent. The first band afforded (3-ethoxysulfenyl-2,4-pentanediono)bis(3-chloro-2,4-pentanediono)chromium(III) after recrystallization from benzene–heptane, m.p. 245–246°, 56 mg.; infrared (KBr), 1550, 1480, 1440, 1375, 1355, 1320, 1160, 1075, 1050, 1025, 925, 690 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{23}Cl_2O_7SCr$: C, 41.30; H, 4.69; S, 6.48; Cl, 14.34. Found: C, 41.26; H, 4.19; S, 6.49; Cl, 15.11

The Mechanism of the Prins Reaction. III. The Acetolysis of Arenesulfonates of *anti*-3-Oxabicyclo[3.3.1]nonan-9-ol and *trans*-6-Hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane[1]

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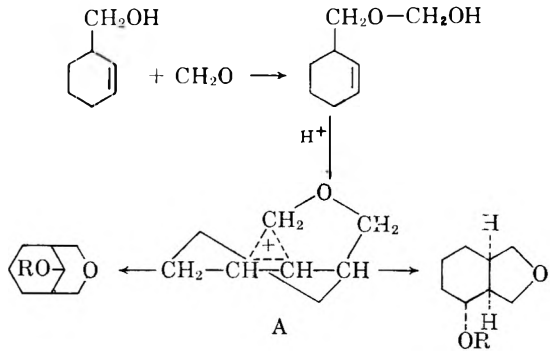
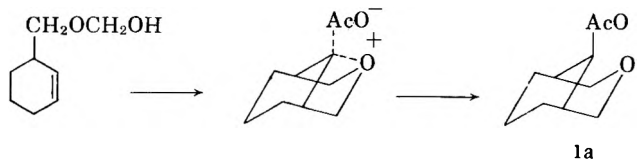
The acetolysis of arenesulfonates of both *anti*-3-oxabicyclo[3.3.1]nonan-9-ol and *trans*-6-hydroxy-*cis*-3-oxabicyclo [4.3.0]nonane gives the same products although in different yields. The acetates of the parent alcohols are formed in the same ratio in both cases. It is suggested that the formation of the bicyclic alcohols, **1** and **2**, in the Prins reaction of cyclohexene and the solvolysis of their arenesulfonates proceeds by way of the nonclassical bridged ion A.

A recent study of the saponification products from the sulfuric acid-catalyzed reaction of cyclohexene and formaldehyde in acetic acid solution revealed the presence of a previously unreported compound, *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane.[2] It was suggested[2] that both this new alcohol and a previously reported isomer, *anti*-3-oxbicyclo[3.3.1]nonan-9-ol,[3] are formed from a single carbonium ion intermediate, A, derived from 3-hydroxymethylcyclohexene *via* the hemiformal. It was established earlier that the acetate of 3-hydroxymethylcyclohexene is among the products of the Prins reaction of cyclohexene.[3]



1. R = H
1a. R = Ac
2. R = H
2a. R = Ac

Blomquist and Wolinsky[3] have offered a mechanism for the formation of the acetate of *anti*-3-oxabicyclo-[3.3.1]nonan-9-ol involving a four-membered oxonium ion derived from the hemiformal of 3-hydroxymethylcyclohexene.



1a

Since both mechanisms assume that the bicyclic acetates, **1a** and **2a**, are formed from 3-hydroxymethylcyclohexene, we first examined the reaction of 3-hydroxymethylcyclohexene under the conditions of the Prins reaction used in previous studies.[2,3] The acetate of 3-oxabicyclo[3.3.1]nonan-9-ol, **1a**, was obtained in 22% yield, the acetate of *trans*-6-hydroxy-*cis*-3-bicyclo[4.3.0]nonane was obtained in 8% yield and the bicyclic olefin, *cis*-3-oxabicyclo[4.3.0]-6-nonene, was isolated in 40% yield. In addition, there was formed a quantity of unidentified high boiling material. The yields were determined by vapor phase chromatography of the distilled reaction products and the compounds were identified by comparison of their retention times and infrared spectra with those of authentic samples. A portion of the products was saponified and the alcohols were identified similarly by vapor phase chromatography and infrared spectroscopy. This evidence provides firm support for the assumption that the bicyclic acetates, **1a** and **2a**, arise from 3-hydroxymethylcyclohexene.

We have undertaken an investigation of the acetolysis of arenesulfonates of 3-oxabicyclo[3.3.1]nonan-9-ol and *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane to obtain evidence regarding the mechanism of their formation in the Prins reaction. It was anticipated that the solvolysis would proceed through the intermediate or intermediates involved in their formation and this would be discernible in the nature and distribution of the solvolysis products. The results of the solvolysis studies are summarized in Table I. The values in parenthesis refer to the corresponding alcohols in the case of the substitution products. The discrepancies in the analyses before and after saponification are undoubtedly caused by the difficulty of extracting the alcohols from aqueous solution.

The products from the solvolyses were examined by vapor phase chromatography and infrared spectroscopy. A control experiment indicated that the acetate–olefin mixture was stable under the reaction conditions but some of the olefin was lost in the isolation procedure. The reproducibility of the vapor phase chromatographic analysis was about ±2%. We did not find conditions for separating the *cis*- and *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonanes (**2a** and **3a**) or their acetates by vapor phase chromatography. The analysis was carried out for both the acetates and the alcohols by comparing the infrared spectra of the mixtures isolated by vapor phase chromatography with mixtures of known composition. In all cases the infrared spectra of the product *anti*-3-oxabicyclo[3.3.1]-nonan-9-ol and its acetate were identical with those of authentic samples. The *anti*-3-oxabicyclo[3.3.1]nonan-9-ol and *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]-nonane (containing *ca.* 10% of the all *cis*-isomer) obtained from the solvolysis of the tosylate of *anti*-3-oxabicyclo[3.3.1]nonan-9-ol were characterized as crystalline derivatives identical in all respect with authentic samples. The acetolysis of arenesulfonates of both alcohols produced some unidentified material with the longest retention time on vapor phase chromatography.

(1) Supported by the Petroleum Research Fund of the American Chemical Society, grant no. 915-A4.

(2) L. J. Dolby, *J. Org. Chem.*, **27**, 2971 (1962).

(3) A. T. Blomquist and J. Wolinsky, *J. Am. Chem. Soc.*, **79**, 6025 (1957).

TABLE I

PRODUCTS OF ACETOLYSIS[a] OF ARENESULFONATES OF *anti*-3-OXABICYCLO[3.3.1]NONAN-9-OL AND *trans*-6-HYDROXY-*cis*-3-OXABICYCLO-[4.3.0]NONANE

Arenesulfonate	*cis*-3-Oxabicyclo-[4.3.0]-6-nonene,[b] %	*anti*-9-Acetoxy-3-oxabicyelo[3.3.1]-nonane, 1a, %	*trans*-6-Acetoxy-*cis*-3-oxabicyclo-[4.3.0]nonane, 2a, %	*cis*-6-Acetoxy-*cis*-3-oxabicyclo-[4.3.0]nonane, 3a. %	Unidentified, %
Tosylate of 1	53	20	20	2	5
	(71)	(14)	(12)	(1)	(2)
p-Nitrobenzenesulfonate of 1	55	17	19	2	8
p-Nitrobenzenesulfonate of 2[c]	43	11	12	18	16
	(70)	(8)	(7)	(10)	(6)

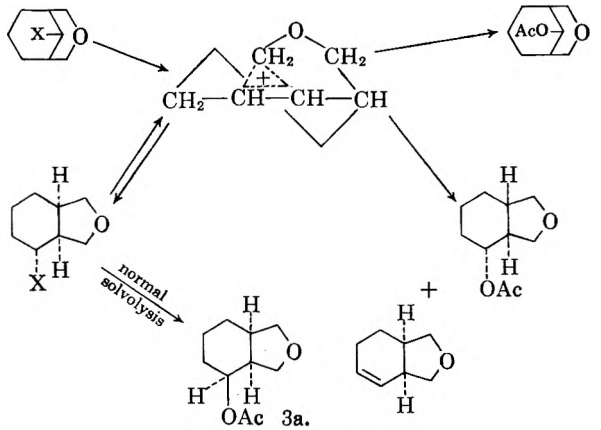
[a] All solvolyses were carried out in 0.2 *M* sodium acetate in reagent grade acetic acid at about 100°. [b] The olefin was contaminated with small amounts of materials (<5%) with almost identical retention times on vapor phase chromatography. [c] A second small-scale run gave a similar product distribution except that there was less unidentified material found.

The infrared spectrum of this material suggests a saturated acetate structure.

A sample of *cis*-3-oxabicyclo[4.3.0]-6-nonene was prepared by the phosphoric acid-catalyzed dehydration of 3-oxabicyclo[3.3.1]nonan-9-ol (1). The physical properties of the olefin prepared in the present investigation are in good agreement with those of the material isolated previously from the Prins reaction of cyclohexene.[3] Additional evidence for the position of the double bond was obtained from the proton magnetic resonance spectrum.[4] The spectrum shows three areas of absorption: peaks in the region 3.3–4.3 τ values corresponding to two protons, peaks in the region of 5.4–6.4 τ values corresponding to four protons, and peaks in the range of 6.7–8.2 τ values corresponding to six protons. The spectrum was not analyzed in detail, but the absorption at 3.3–4.3 τ provides good evidence for two vinyl protons consistent with the *cis*-3-oxabicyclo[4.3.0]-6-nonene structure. The peaks at 5.4–6.4 τ are ascribed to protons adjacent to the oxygen of the tetrahydrofuran ring.[5]

Interestingly, the acid-catalyzed dehydration of the 3-oxabicyclo[3.3.1]nonan-9-ol produced some formaldehyde, isolated as the 2,4-dinitrophenylhydrazone. The formaldehyde probably is liberated by essentially the reverse of the reaction leading to the formation of the bicyclic alcohol.

The product distributions from the acetolyses of the arensulfonates of the isomeric alcohols lead us to propose the following reaction scheme.



X = Arenesulfonate

The product studies indicate that the 6-acetoxy-*cis*-3-oxabicyclo[4.3.0]nonane obtained from the solvolysis of the *p*-nitrobenzenesulfonate of *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane contains about 60% of the all *cis* isomer, the product of normal solvolysis with inversion. The relatively large fraction (40%) of retention of configuration in this material is not the result of a normal solvolysis. For example, the substitution products from the methanolysis of *trans*-2-methylcyclohexyl tosylate show 86% inversion, 8% retention of configuration, and 6% rearrangement product, 1-methyl-1-methoxycyclohexane.[6]

It is interesting that acetolysis of arenesulfonates of *anti*-3-oxabicyclo-[3.3.1]nonan-9-ol also produces some *cis*-6-acetoxy-*cis*-3-oxabicyclo[4.3.0]nonane. We suggest that this product arises by isomerization of the arenesulfonate of the *anti*-3-oxabicyclo[3.3.1]nonan-9-ol *via* the bridged ion A to the 3-oxabicyclo[4.3.0]nonane arenesulfonate followed by normal solvolysis. It is not clear whether the olefin is formed from the bridged ion A or a normal solvolytic pathway.

It is significant that the same products are formed from arenesulfonates of both bicyclic alcohols, **1** and **2**. However, the most important piece of evidence for the intervention of the common intermediate, A, is that the acetates of retained configuration, **1a** and **2a**, were formed in the same ratio, within experimental error, in both cases.

It should be pointed out that the results can be accommodated by replacing intermediate A with a pair of rapidly equilibrating classical carbonium ions.

Either hypothesis readily accounts for the formation of the same products from arenesulfonates of both alcohols and is consistent with the large fraction of retention of configuration found in both cases.

Experimental[7]

The Sulfuric Acid-Catalyzed Reaction of 3-Hydroxymethylcyclohexene and Formaldehyde in Acetic Acid Solution.[8]—

(4) The proton magnetic resonance spectrum was determined in carbon tetrachloride solution with a Varian HR-60 operating at 60 mc.

(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 55.

(6) W. Hückel, R. Bross, O. Fechtig, H. Feltkamp, S. Geiger, M. Hanack, M. Heinzel, A. Hübele, J. Kurz, M. Maier, D. Maucher, G. Näher, R. Neidlein, and R. B. Rashingkar, *Ann.*, **624**, 208 (1959).

(7) All melting points and boiling points are uncorrected; distillations were carried out using a 65-cm. modified Podbielniak tantalum spiral column. Microanalyses are by Pascher and Pascher Microanalytical Laboratory, Bonn, Germany. Infrared spectra were determined with a Beckman IR-7 infrared spectrophotometer.

(8) The authors are indebted to Mr. David R. Rosencrantz for carrying out this reaction.

To a stirred solution of 1.83 g. of paraformaldehyde, 5 ml. of glacial acetic acid, and 1 drop of concentrated sulfuric acid at 50° was added slowly a solution of 5.0 g. of 3-hydroxymethylcyclohexanol and 5 ml. of acetic acid. The resulting solution was heated at 70° for 2 hr. with stirring. The reaction mixture was diluted with water, neutralized with sodium carbonate, and extracted with chloroform. Fractional distillation of the product afforded 6.11 g. of material collected in three fractions. The first fraction, 2.20 g. (*ca.* 40%), b.p. 50–83° (13 mm.), $n^{25}D$ 1.4675, was predominantly *cis*-3-oxabicyclo[4.3.0]-6-nonene, identified from its retention time on vapor phase chromatography and the infrared spectrum of a sample purified by vapor phase chromatography. The second fraction, 2.45 g., b.p. 98–125° (13 mm.), $n^{25}D$ 1.4850, was found by vapor phase chromatography and infrared spectroscopy to be a mixture of the acetates of 3-oxabicyclo[4.3.0]nonane (**2a**) in the ratio of 3:1. The yield of the acetate of 3-oxabicyclo[3.3.1]nonan-9-ol is 22% and the yield of the acetate of *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane is 8%. The third fraction, 1.36 g., b.p. 110–130° (0.25 mm.), $n^{25}D$ 1.4928, did not contain any of the compounds previously identified and was not investigated further.

A 1.0-g. sample of the second fraction was saponified with methanolic sodium hydroxide. The reaction mixture was diluted with water and extracted with chloroform. The chloroform was distilled and the residue was subjected to vapor phase chromatography. Both 3-oxabicyclo[3.3.1]nonan-9-ol and *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane were identified by their retention times and the infrared spectra of collected samples.

***cis*-3-Oxabicyclo[4.3.0]-6-nonene.**—A 14.0-g. sample of 3-oxabicyclo[3.3.1]nonan-9-ol and 2.0 ml. of 85% phosphoric acid were distilled at atmospheric pressure to yield crude *cis*-3-oxabicyclo[4.3.0]-6-nonene, b.p. 150–190°. The crude product was taken up in ether, washed with water, and dried over potassium carbonate. Fractionation of the residue yielded 7.0 g. (57%) of *cis*-2-oxabicyclo[4.3.0]-6-nonene, b.p. 79–82° (20 mm.), $n^{25}D$ 1.4871 [lit.[3] b.p. 83–84° (35 mm.), $n^{25}D$ 1.4876].

The aqueous wash was treated with 2,4-dinitrophenylhydrazine solution. The precipitate, 0.1706 g. (1%), was identified as formaldehyde 2,4-dinitrophenylhydrazone, m.p. 166–167°, undepressed upon mixture with an authentic sample. The infrared spectrum was also identical with that of authentic formaldehyde 2,4-dinitrophenylhydrazone.

***trans*-6-Acetoxy-*cis*-3-oxabicyclo[4.3.0]nonane.**—A small sample of *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane was acetylated with acetic anhydride and a drop of perchloric acid. The crude acetate was purified by vapor phase chromatography as described previously. The analytical sample showed $n^{25}D$ 1.4709.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.18; H, 8.64.

***cis*-6-Acetoxy-*cis*-3-oxabicyclo[4.3.0]nonane** was prepared from *cis*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane as described for *trans*-6-acetoxy-*cis*-3-oxabicyclo[4.3.0]nonane and showed the same refractive index, $n^{25}D$ 1.4709, and retention time on vapor phase chromatography.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.99; H, 8.76.

Acetolysis of the Tosylate of 3-Oxabicyclo[3.3.1]nonan-9-ol.—The tosylate of 3-oxabicyclo[3.3.1]nonan-9-ol, m.p. 103–104° (lit.[3] m.p. 105–106°), was prepared by treating the alcohol with *p*-toluenesulfonylchloride in pyridine solution. A 13.950-g. sample of the tosylate, 300 ml. of reagent grade acetic acid, and 5.00 g. of sodium acetate were placed in a round-bottomed flask and heated on the steam bath for 24 hr. The cooled mixture was diluted with 900 ml. of water and the acetic acid was neutralized with solid sodium carbonate. The reaction mixture was extracted five times with ether and the combined extracts were washed with water then dried over sodium sulfate. The ether was flash distilled and the residue was examined by vapor phase chromatography using a 5-ft. column of 20% Carbowax 20M on firebrick at 200°. The vapor phase chromatogram showed four main peaks with retention times of 5 min., 15 min., 23 min., and 27 min. The retention times of the first three compounds corresponded to the retention times of authentic samples of *cis*-3-oxabicyclo[4.3.0]-6-nonene and the acetates of 3-oxabicyclo[3.3.1]nonan-9-ol and *trans*-6-hydroxybicyclo[4.3.0]-nonane. The fourth peak was unidentified. Samples of each peak effluent were collected from several runs. The infrared spectra of the first two components eluted were identical with those of authentic samples of *cis*-3-oxabicyclo[4.3.0]-6-nonene and *anti*-9-acetoxy-3-oxabicyclo[3.3.1]nonane, respectively. The third peak proved to be a mixture of *cis*- and *trans*-6-acetoxy-*cis*-3-oxabicyclo[4.3.0]nonane which by infrared analysis was found to contain 10% of the all *cis* isomer.

It was assumed that the area under each peak is directly proportional to the mole fraction of that component in the mixture and the yield of each compound is recorded in Table I.

The remainder of the reaction products was dissolved in a solution of 50 ml. of methanol, 20 ml. of water, and 5 g. of sodium hydroxide and stored overnight. The solution was diluted with water and continuously extracted with ether. The ether was distilled and the residue was examined by vapor phase chromatography, using a 5-ft. column of 20% Carbowax 20M on firebrick at 200°. The vapor phase chromatogram showed four peaks with retention times of 5 min., 28 min., 37 min., and 41 min. The retention times of the first three peaks eluted are identical with the retention times of *cis*-3-oxabicyclo[4.3.0]-6-nonene, 3-oxabicyclo[3.3.1]nonan-9-ol and 6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane, respectively. The fourth peak at a longer retention time was not identified. Samples of the first three components were collected from multiple injections and the infrared spectra of the first two were identical with those of *cis*-3-oxabicyclo[4.3.0]-6-nonene and *anti*-3-oxabicyclo[4.3.1]nonan-9-ol, respectively. The third component was found by infrared analysis to be *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane containing 10% of the all *cis* isomer.

A sample of the *anti*-3-oxabicyclo[3.3.1]nonan-9-ol collected by vapor phase chromatography was converted to the tosylate which was identical in all respects with an authentic sample.

A sample of the *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane similarly was converted to the *p*-nitrobenzenesulfonate which was identical with an authentic sample.[2]

Acetolysis of the *p*-Nitrobenzenesulfonate of *anti*-3-Oxabicyclo[3.3.1]nonan-9-ol.—The *p*-nitrobenzenesulfonate of *anti*-3-oxabicyclo[3.3.1]nonan-9-ol was prepared in the usual manner and crystallized from benzene–petroleum ether. The analytical sample melted at 133–135°.

Anal. Calcd. for $C_{14}H_{17}NO_6S$: C, 51.36; H, 5.23; N, 4.27. Found: C, 50.96; H, 5.10; N, 4.33.

The acetolysis of a sample of the *p*-nitrobenzenesulfonate was carried out as described for the acetolysis of the tosylate and the product mixture was analyzed by vapor phase chromatography and infrared spectroscopy. The product distribution is recorded in Table I.

Acetolysis of the *p*-Nitrobenzenesulfonate of *trans*-6-Hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane.—A 5.4-g. sample of the *p*-nitrobenzenesulfonate[2] was solvolyzed and the products were analyzed as described for the solvolysis of the tosylate of *anti*-3-oxabicyclo[3.3.1]nonan-9-ol. The product distribution is recorded in Table I. A sample of the unidentified component was obtained by vapor phase chromatography and its infrared spectrum showed peaks at 1735 cm.$^{-1}$ and 1250 cm.$^{-1}$ ascribed to an acetate group. There was no absorption near 1600 cm.$^{-1}$ which could be attributed to a double bond.

The crude reaction mixture was saponified and examined by vapor phase chromatography and infrared spectroscopy as previously described. These results are recorded in Table I.

A second run gave similar results except that the amount of unidentified product was somewhat less.

Control Experiments on the Stability of the Products and the Isolation Procedure.—A mixture of *cis*-3-oxabicyclo[4.3.0]-non-6-ene and the acetates of *anti*-3-oxabicyclo[3.3.1]nonan-9-ol and *trans*-6-hydroxy[4.3.0]nonane was prepared and analyzed by vapor phase chromatography. It was found to contain 43% of the olefin, 19% of the acetate of *anti*-3-oxabicyclo[3.3.1]nonan-9-ol, and 38% of the acetate of *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane. The mixture was dissolved in 0.1 *M* sodium acetate in acetic acid. A portion of the solution was worked up immediately and analyzed by vapor phase chromatography. The crude material was found to consist of 37% of the olefin, 22% of the acetate of *anti*-3-oxabicyclo[3.3.1]nonan-9-ol, and 41% of the acetate of *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane. The remainder of the acetic acid solution of the mixture was heated on the steam bath for 24 hr. and worked up. The mixture was found to contain 36% of the olefin, 22% of the acetate of *anti*-3-oxabicyclo[3.3.1]nonan-9-ol, and 42% of the acetate of *trans*-6-hydroxy-*cis*-3-oxabicyclo[4.3.0]nonane.

The Reaction of Enamines of Cyclic Ketones with Dimethyl Acetylenedicarboxylate[1]

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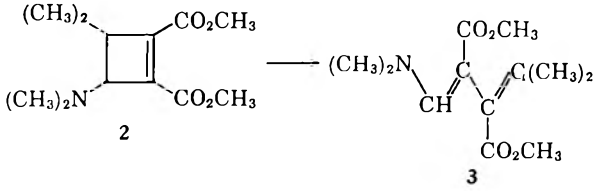
Received January 3, 1963

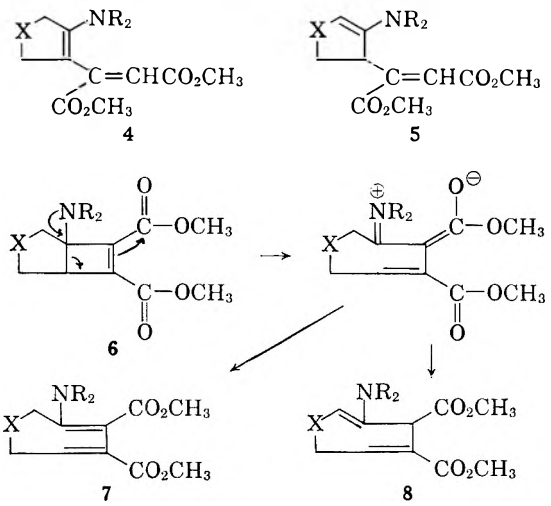
Enamines of cyclic ketones react with dimethyl acetylenedicarboxylate to yield an intermediate cyclobutene adduct which undergoes rearrangement under the conditions of the reaction with expansion of the carbocyclic ring by two carbon atoms. Hydrolysis of these products yields the corresponding keto dicarboxylic esters.

The reaction of enamines of cyclic ketones with electrophilic olefins produces an adduct which, on hydrolysis, affords the substituted ketone corresponding to the Michael addition product of the ketone and the electrophilic olefin.[2] 1-(N-Morpholino)cyclohexene and methyl acrylate, for example, produce an adduct which is converted to methyl 3-(2-oxocyclohexyl)propionate by hydrolysis in dilute acid. Brannock[3] has shown, however, that enamines derived from aldehydes react with electrophilic olefins by a cycloaddition mechanism to produce the corresponding cyclobutane derivatives. Dimethyl maleate and N,N-dimethylisobutenylamine, for example, react to form diethyl 4 - dimethylamino - 3,3 - dimethyl - 1,2 - cyclobutanedicarboxylate. The cycloaddition reaction of enamines derived from aldehydes has also been shown to occur with ketenes,[4] and with aliphatic sulfonyl chlorides[5] or acid chlorides[6] in the presence of tertiary amine. Enamines derived from cyclic ketones similarly undergo cycloaddition reactions with benzyne,[7] ketene,[6] and with aliphatic sulfonyl halides in the presence of tertiary amine.[5a] Dimethyl acetylenedicarboxylate (1) adds to N,N-dimethylisobutenylamine to produce the intermediate adduct 2 which undergoes ring opening to 3.[3a]



2 3

In view of these results the reaction of 1 with enamines derived from cyclic ketones appeared of interest since the ring opening of the cycloaddition product, should the reaction proceed in this manner, would lead to a novel method for the expansion of a carbocyclic ring by two carbon atoms. The enamines (9–14) listed in Table I reacted with 1 in toluene to produce a 1:1 adduct in all cases which were studied. The possible structures considered for these adducts were as follows: either of the tautomeric Michael-type addition products (4 and 5), the cycloaddition product (6), and either of the dienamine structures (7 and 8) resulting from ring opening of 6.[8] The product from



4 5 6 7 8

enamines 9–13 are assigned structures 15–19 corresponding to structure 7, whereas the product from enamine 14 is assigned structure 20 corresponding to the rearranged structure 8. The reaction appears, therefore, to yield the cyclobutene adduct (6) which is unstable to the conditions of the reaction and undergoes rearrangement to 7 or 8. The pyrrolidine enamines gave substantially better yields of adduct than did the morpholine enamines in the two cases where comparisons were made. The structure of 15 is established as follows: the n.m.r. spectrum shows absorption for one vinyl proton at 7.00 p.p.m. (see Table I) as a triplet (J = 7 c.p.s.). This clearly eliminates a Michael-type addition product (4 or 5) in which the long-range coupling of such a proton on the β-carbon of an α,β-unsaturated carbomethoxy system would be less than 3 c.p.s. and a cycloaddition product (6) in which there would be no vinyl proton absorption. Furthermore, the absence of any vinyl proton absorption at higher field eliminates structures of the type 5 and 8 in which the vinyl proton on the β-carbon of the enamine system would show absorption at 4–5 p.p.m. Structure 15 is in agreement with this vinyl absorption. Similar arguments may be applied to the products assigned structures 16–19 (see Table I). The product from 14, however, must be assigned structure 20 rather than the alternative con-

(1) This research has been supported by National Science Foundation, grant no. G-21443.

(2) (a) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5128 (1956); (b) G. Stork, Abstracts of the 16th National Organic Symposium of the American Chemical Society, Seattle, Wash., June, 1959, p. 44; (c) L. Birkofer and C. Barnikel, *Chem. Ber.*, **91**, 1996 (1958).

(3) (a) K. C. Brannock, Enamine Symposium, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961; (b) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(4) (a) G. Opitz, H. Adolph, M. Kleemann, and F. Zimmermann, *Angew. Chem.*, **73**, 654 (1961); (b) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **26**, 4775 (1961); (c) G. A. Berchtold, G. R. Harvey, and G. E. Wilson, Jr., *ibid.*, **26**, 4776 (1961).

(5) (a) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **84**, 313 (1962); (b) G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962); (c) G. Opitz and H. Adolph, *Angew. Chem., Intern. Ed.*, **1**, 113 (1962).

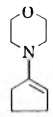
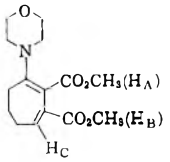
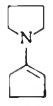
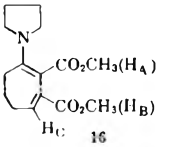
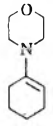
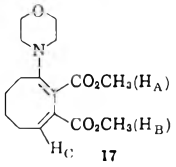
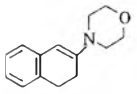
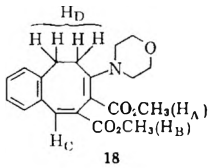
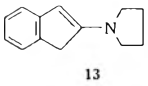
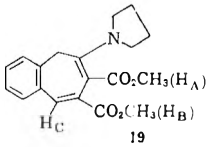
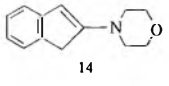
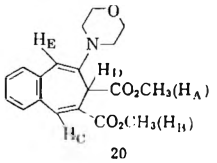
(6) (a) G. Opitz, M. Kleemann, and F. Zimmermann, *Angew. Chem.*, **74**, 32 (1962); (b) G. Opitz, M. Kleemann, and F. Zimmermann, *Angew. Chem., Intern. Ed.*, **1**, 51 (1962).

(7) M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).

(8) Whether isomers 5 and 8 would be formed directly or would be formed by tautomerism of 4 and 7, respectively, cannot be determined. That the position of the enamine double bond is sensitive to steric effects in β-substituted enamines derived from cyclic ketones has been demonstrated previously; see, for example (a) G. A. Berchtold, *J. Org. Chem.*, **26**, 3043 (1961), (b) ref. 2b.

TABLE I

REARRANGED CYCLOADDITION PRODUCTS AND NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA

Enamine	Rearrangement product	N.m.r. data: Proton	Chemical shift, p.p.m.	J, c.p.s.
 9	 15	H_A	3.63[a]	
		H_B	3.73[a]	
		H_C	7.00[b]	7
 10	 16	H_A	3.58[a]	
		H_B	3.70[a]	
		H_C	6.88[b]	7
 11	 17	H_A	3.62[a]	
		H_B	3.70[a]	
		H_C	6.68[c]	7.5 and 9
 12	 18	H_A	3.57[a]	
		H_B	3.80[a]	
		H_C	7.65[a]	
		H_D	2.98[d]	
		Ar–H	7.17[a]	
 13	 19	H_A	3.65[a]	
		H_B	3.85[a]	
		H_C	7.58[a]	
		Ar–H	7.1–7.5[e]	
 14	 20	H_A	3.30[a]	
		H_B	3.88[a]	
		H_C	8.02[d]	
		H_D	5.22[d]	
		H_E	5.88[f]	2
		Ar–H	7.0–7.6[e]	

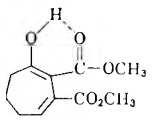
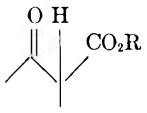
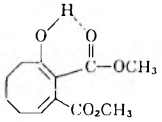
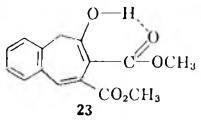
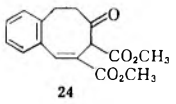
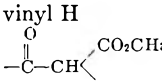
[a] Singlet. [b] Triplet. [c] Quadruplet. [d] Broad singlet. [e] Complex multiplet. [f] Doublet.

jugated structure corresponding to **19** on the basis of the resonance absorption of H_D and H_E at 5.22 and 5.88 p.p.m., respectively, with $J_{H_D - H_E} \simeq 2$ c.p.s. Structure **19** shows no absorption in this region but does show unresolved absorption in the region of 3–4.5 p.p.m. due to the methylene group of the cycloheptatriene ring and the methylene groups on the nitrogen atom of the pyrrolidine ring. In further agreement with this structure the methyl resonance of the carbomethoxy group on the saturated carbon atom of **20** has shifted to higher field as a result of shielding due to the diamagnetic field from the interatomic current of the benzene ring. This shielding effect of the aromatic nucleus allows assignment of the proton absorption of the methoxy groups of **19** and **20** as indicated in Table I. The infrared and ultraviolet spectra of these adducts are also in agreement with the proposed structures and are listed in the Experimental section.

Mild acid hydrolysis of the enamine functionality of adducts **15**–**20** produced the corresponding keto dicarboxylic esters **21**–**24** listed in Table II along with the n.m.r. spectral data for these products. The n.m.r. spectrum of **21** shows the enolic hydrogen absorption at 12.54 p.p.m. and the tertiary proton absorption of the keto form at 5.73 p.p.m. Integration of these two absorptions indicates that **21** exists in the enol form to the extent of approximately 60–70% under the conditions in which the spectrum was recorded. The spectrum of **22** shows no indication of the keto form, the enolic hydrogen absorption occurring at 12.58 p.p.m. Product **23** likewise appears to exist entirely as the enolic tautomer, the enolic hydroxyl absorption occurring at 12.55 p.p.m. The spectrum of **24**, however, indicates the product exists entirely in the keto form, since the resonance absorption of the tertiary proton alpha to the keto group, a carbomethoxy group, and the olefinic bond appears at 4.78 p.p.m. and is split into a doublet ($J \simeq 2$ c.p.s.) by long-range coupling with the vinyl proton which absorbs at 7.95 p.p.m. The rest of the n.m.r. spectral data listed in Table II further substantiate the proposed structures. It should be noted that the hydrolysis product from the Michael-type addition products **4** and **5** would give no β-dicarbonyl system and, therefore, would not show the low field

TABLE II

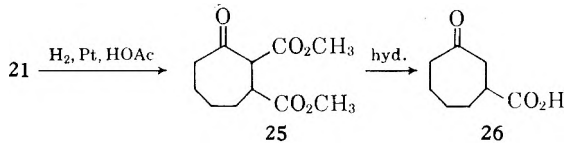
HYDROLYSIS PRODUCTS AND NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA

Adduct hydrolyzed	Hydrolysis product	N.m.r. data: Proton	Chemical shift, p.p.m.	J, c.p.s.
15 or 16	 21	enolic H	12.54[a]	
		vinyl H	7.05[b]	8
		$2CH_3$—O—	3.73[a]	
			5.73[c]	
17	 22	enolic H	12.58[a]	
		vinyl H	6.90[d]	7 and 9
		$2CH_3$—O—	3.72[a]	
19 or 20	 23	enolic H	12.55[a]	
		vinyl H	7.78[a]	
		$2CH_3$—O—	3.70,[a] 3.83[a]	
		—CH_2—	3.33[a]	
		Ar—H	7.30[e]	
18	 24	vinyl H	7.95[f]	1
			4.78[f]	1
		$2CH_3$—O—	3.70,[a] 3.87[a]	
		Ar—CH_2—CH_2—CO—	2.6–3.4[e]	
		Ar—H	7.27[a]	

[a] Singlet. [b] Triplet. [c] Broad singlet. [d] Quadruplet. [e] Complex multiplet. [f] Doublet.

resonance absorption for the hydrogen-bonded enolic proton in the region of 12.5 p.p.m. The infrared and ultraviolet spectra of these hydrolysis products further support the assigned structures and are listed in the Experimental section. The hydrolysis products **21**–**24** all gave a deep violet color with ferric chloride in aqueous ethanol.

To establish further the structures of these reaction products, **21** was hydrogenated over platinum in acetic acid to **25** which was hydrolyzedand monode carboxylated to 3-carboxycycloheptanone (**26**) the infrared spectrum of which was identical to that of a sample prepared by Michael addition of hydrogen cyanide to 2-cycloheptenone and hydrolysis of the resulting 3-cyanocycloheptanone.



Experimental[9]

General Procedure for the Reaction of 1 with Enamines.—A solution of the enamine in anhydrous toluene under a nitrogen atmosphere was cooled to 0–5° in an ice bath. Compound **1** was added slowly with stirring at such a rate that the temperature never rose above 50°. When all of **1** had been added, the mixture was heated under gentle reflux for 12 hr. The mixture was cooled and the product was precipitated by the addition of excess ethyl ether. The product was then recrystallized from acetone to constant melting point.

1-(N-Morpholino)-2,3-dicarbomethoxy-1,3-cycloheptadiene (15).—This product was obtained in 48% yield from 16.2 g. (0.0774 mole) of **1** and 11.0 g. (0.0774 mole) of **9**[2c] in 40 ml. of toluene, m.p. 167–168°; $\lambda_{max}^{CH_3OH}$ 334 mμ (ε 9760); ν^{CHCl_3} 1715–1680 (s), 1610 (m), and 1540 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 60.98; H, 7.17; N, 4.75. Found: C, 60.89; H, 6.94; N, 4.65.

1-(N-Pyrrolidino)-2,3-dicarbomethoxy-1,3-cycloheptadiene (16).—This product was obtained in 71% yield from 10.7 g. (0.0835 mole) of **10**[10] and 11.8 g. (0.0835 mole) of **1** in 50 ml. of toluene, m.p. 145–146°; $\lambda_{max}^{CH_3OH}$ 304 mμ (ε 11,130), 324 mμ (ε 11,030); ν^{CHCl_3} 1171 (s), 1675 (s), 1605 (m), and 1532 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.52; H, 7.53; N, 5.02. Found: C, 64.33; H, 7.33; N, 4.91.

1-(N-Morpholino)-2,3-dicarbomethoxy-1,3-cyclooctadiene (17).—This product was obtained in 42% yield from 4.25 g. (0.030 mole) of **1** and 5.00 g. (0.030 mole) of **11**[11] in 10 ml. of toluene, m.p. 210–211°; $\lambda_{max}^{CH_3OH}$ 327 mμ (ε 10,940); ν^{CHCl_3} 1720–1680 (s), 1618 (m), and 1540 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{23}NO_5$: C, 62.11; H, 7.61; N, 4.54. Found: C, 62.55; H, 7.50; N, 4.53.

1,2-Benzo-4,5-dicarbomethoxy-6-(N-morpholino)-1,3,5-cyclooctatriene (18).—This product was obtained in 30% yield from 14.2 g. (0.0660 mole) of **12** and 9.40 g. (0.0060 mole) of **1** in 20 ml. of toluene as yellow crystals, m.p. 133–134°; $\lambda_{max}^{CH_3OH}$ 256 mμ (ε 8850) 312 mμ (ε 7640); ν^{CHCl_3} 1706–1690 (s), 1616 (m), 1598 (w), 1545 (s), and 1495 (w) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.22; H, 6.41; N, 3.92. Found: C, 67.01; H, 6.35; N, 3.80.

1,2-Benzo-4,5-dicarbomethoxy-6-(N-morpholino)-1,3,5-cycloheptatriene (19).—This product was obtained in 78% yield from 34.0 g. (0.183 mole) of **13**[12] and 26.0 g. (0.183 mole) of **1** in 50 ml. of toluene as yellow crystals, m.p. 159–160°; $\lambda_{max}^{CH_3OH}$ 255 mμ (ε 18,530), 287 mμ (ε 8460), 318 mμ (ε 9490), and 362 mμ (ε 7840); ν^{CHCl_3} 1710–1675 (s), 1588 (w), 1560 (m), 1530 (s), and 1485 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.72; H, 6.42; N, 4.28. Found: C, 69.93; H, 6.30; N, 4.45.

3,4-Benzo-6,7-dicarbomethoxy-1-(N-morpholino)-1,3,5-cycloheptatriene (20).—This product was obtained in 30% yield from 8.81 g. (0.0437 mole) of **14**[12] and 6.70 g. (0.0437 mole) of **1** in 20 ml. of toluene as yellow crystals, m.p. 170–171°; $\lambda_{max}^{CH_3OH}$ 265 mμ (ε 41,150), 293 mμ (ε 9620), and 375 mμ (ε 2520); ν^{CHCl_3} 1730–1695 (s), 1635 (s), 1613 (s), 1545 (m), and 1483 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.12; N, 4.08. Found: C, 66.34; H, 6.18; N, 3.95.

(9) Melting points are corrected and boiling points are uncorrected.

(10) E. Bergmann and R. Ikan, *J. Am. Chem. Soc.*, **78**, 1482 (1956).

(11) S. Hünig, E. Benzing, and E. Lücke, *Chem. Ber.*, **90**, 2833 (1957).

(12) A. T. Blomquist and E. Moriconi, *J. Org. Chem.*, **26**, 3751 (1961).

Procedure for the Hydrolysis of Adducts 15–20.—Each of the adducts (1.00 g.) was dissolved in 5.0 ml. of methanol and 1.0 ml. of concentrated hydrochloric acid and heated on a steam bath to reflux. Water (2–5 ml.) was added and the solution was heated on a steam bath for 10 min. The solution was allowed to cool and precipitation was induced by scratching the wall of the flask. The product was collected by suction filtration, washed thoroughly with 2:1 aqueous methanol, and recrystallized from aqueous methanol to obtain the analytically pure hydrolysis product.

2,3-Dicarbomethoxy-3-cycloheptenone (21).—This product was obtained in 89–92% yield from the hydrolysis of **15** or **16**, m.p. 63.5–64.0°; $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 8030); ν^{CHCl_3} 1712 (s), 1650 (s), 1600 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.37; H, 6.24. Found: C, 58.66; H, 6.24.

2,3-Dicarbomethoxy-3-cyclooctenone (22).—This product was obtained in 86% yield from the hydrolysis of **17**, m.p. 75.4–76.3°; $\lambda_{max}^{CH_3OH}$ 256 mμ (ε 9880); ν^{CHCl_3} 1720 (s), 1662 (s), 1653 (s), 1618 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.70. Found: C, 59.83; H, 6.53.

5,6-Benzo-2,3-dicarbomethoxy-3,5-cycloheptadienone (23).—This product was obtained in 90% yield from the hydrolysis of **19** or **20**, m.p. 103–104°; $\lambda_{max}^{CH_3OH}$ 244 mμ (ε 18,400); 287 mμ (ε 7610); ν^{CHCl_3} 1715 (s), 1654 (s), 1595 (s), 1490 (w) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.11. Found: C, 65.57; H, 5.17.

5,6-Benzo-2,3-dicarbomethoxy-2,5-cyclo̊ctadienone (24).—This product was obtained in 87% yield from the hydrolysis of **18**, m.p. 103–104°; $\lambda_{max}^{CH_3OH}$ 266 mμ (ε 9420); ν^{CHCl_3} 1740 (s), 1710 (s), 1655 (s), 1615 (m), 1493 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.67; H, 5.55. Found: C, 66.91; H, 5.63.

2,3-Dicarbomethoxycycloheptanone (25).—A solution of **21** (9.60 g., 43 mmoles) in 10 ml. of glacial acetic acid was stirred hydrogen at atmospheric pressure and room temperature with prereduced catalyst prepared from 96 mg. of platinum oxide. In 4 hr. 43 mmoles of hydrogen had been absorbed. The solvent was removed by distillation and the residue was distilled to obtain 3.8 g. (40%) of **25**, b.p. 134–138° at 0.65 mm., $n^{26}D$ 1.4785; ν^{CHCl_3} 1730 (s), 1705 (s), 1640 (w), 1610 (w) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.90; H, 7.02. Found: C, 57.72; H, 6.96.

3-Carboxycycloheptanone (26).—(a) **Preparation from 25.**—Compound **25** (3.98 g., 0.0174 mole) was added to 10 ml. of a solution containing 29% potassium hydroxide in methanol and the mixture was refluxed for 6 hr. The methanol was evaporated and the residue was extracted once with chloroform. Acidification of the residue with hydrochloric acid effected spontaneous decarboxylation. The acid solution was extracted with three 20-ml. portions of ether. The ether extracts were dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the residue distilled at 200° at 0.65 mm. Crystallization was induced from a 1:1 mixture of benzene–cyclohexane to give 1.66 g. (61%) of a colorless crystalling product, m.p. 40–41°; ν^{CHCl_3} 2920 (s), 1700 (s), 1550 (m) cm.$^{-1}$.

Preparation from Cycloheptenone.—A solution of 2- and 3-cycloheptenone[13] (4.25 g., 0.0385 mole) and 2 ml. of glacial acetic acid in 27 ml. of 95% ethanol was cooled in an ice bath with stirring while a solution of 7.15 g. of potassium cyanide in 13 ml. of water was added over a period of 35 min. The mixture was stirred in an ice bath for 8 hr. after the addition was complete. A saturated sodium chloride solution (75 ml.) was added and the product was extracted with three 50-ml. portions of ether. The combined extracts were washed with 75 ml. of saturated sodium chloride solution, dried over sodium sulfate, and the ether removed under reduced pressure. Distillation gave 1.9 g. (38%) of nitrile, b.p. 131–134° at 10 mm. Hydrolysis of 0.765 g. (5.6 mmoles) of nitrile was effected by refluxing in 10 ml. of 20% methanolic potassium hydroxide for 12 hr. The reaction mixture was extracted with chloroform, acidified with hydrochloric acid, extracted with three 10-ml. portions of ether, and dried over anhydrous sodium sulfate. The ether was evaporated and the residue distilled in a Hickman still to obtain 0.250 g. (28%) of 3-carboxycycloheptanone, the infrared spectrum of which was identical to the sample prepared by the hydrolysis and monodecarboxylation of **25**.

(13) R. Belcher, W. Hoyle, and T. West, *J. Chem. Soc.*, 2743 (1958).

Enamine Chemistry. I. Reactions with Nonactivated Terminal Acetylenic Compounds[1]

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Received January 3, 1963

The addition, preferably catalyzed by copper(I) chloride, of a variety of nonactivated terminal acetylenic compounds to the double bonds of enamines derived from isobutyraldehyde and butyraldehyde is described.

The reaction between acetylenic compounds and secondary amines is well known, and it has been postulated that this reaction proceeds *via* an enamine intermediate (I)[2] which then reacts with more of the acetylenic compound to give the adduct (II).

$$RC{\equiv}CH + HNR_2 \longrightarrow \underset{\text{I}}{[RCH{=}CHNR_2]}$$

$$[RCH{=}CHNR_2] + RC{\equiv}CH \longrightarrow RC{\equiv}CCHCH_2R \quad (NR_2) \quad \text{II}$$

We have found that nonactivated terminal acetylenic compounds (those with no electron-withdrawing group adjacent to the acetylenic linkage) do indeed react with enamines to give products (III) arising from

$$RC{\equiv}CH + HC(NR_2){=}CR_2 \longrightarrow RC{\equiv}CCHCHR_2 \quad (NR_2) \quad \text{III}$$

the addition of the acetylenic compounds to the double bonds of the enamines.

To effect the uncatalyzed addition of acetylenic compounds to enamines, prolonged heating was necessary. However, with the addition of a catalytic amount of copper(I) chloride, the reaction time was greatly decreased and, in some cases, the reaction proceeded exothermically and spontaneously.

The structure of the adduct (IV) from ethynylbenzene and N,N-dimethylisobutenylamine was based on its conversion to 4-methyl-2-pentenophenone (V).

The structures of the other adducts were assigned by analogy.

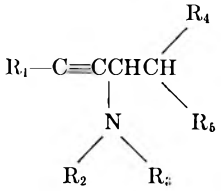
Table I is a list of products obtained during this investigation from the reaction of various enamines with terminal acetylenic compounds.

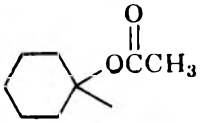
(1) A portion of the material in this paper was presented at the Enamine Chemistry Symposium, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(2) W. Reppe, *Ann. Chem.*, **596**, 12 (1955); J. D. Rose and R. A. Gale, *J. Chem. Soc.*, **792** (1949); C. W. Kruse and R. F. Kleinschmidt, *J. Am. Chem. Soc.*, **83**, 216 (1961).

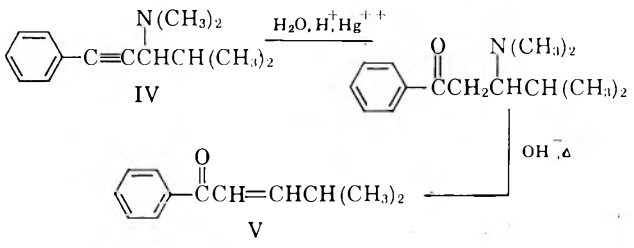
TABLE I

ADDITION PRODUCTS OF ENAMINES AND TERMINAL ACETYLENIC COMPOUNDS



Structure	R_1	R_2	R_3	R_4	R_5	B.p., °C. (mm.)	$n^{20}D$	Yield, %	Method[a]	Anal. Calcd.	Anal. Found
VI	H	CH_3	CH_3	CH_3	CH_3	68–69 (100–109)	...	21	A	N, 11.2	N, 11.4
VII	$(CH_3)_2CHCH(N(CH_3)_2)$—	CH_3	CH_3	CH_3	CH_3	106 (9)	1.4575	47	A	N, 12.5	N, 12.5
VIII	C_6H_5	$R_2 + R_3 =$		CH_3	CH_3	118–124 (1.5)	1.5393	64	B	C, 84.6 H, 9.6	C, 84.3 H, 9.3
	C_4H_9	CH_3	CH_3	CH_3	CH_3	45–50 (0.5)	1.4453	76	C	C, 79.5 H, 12.8	C, 79.8 H, 12.7
	C_4H_9	$R_2 + R_3 =$		CH_3	CH_3	67–77 (0.5–1.5)	1.4688	72	C	C, 81.4 H, 12.3	C, 81.7 H, 12.0
	C_4H_9	$R_2 + R_3 =$		H	C_2H_5	75–77 (0.5)	1.4708	77	C	C, 81.4 H, 12.3	C, 81.2 H, 11.9
	C_6H_5	CH_3	CH_3	CH_3	CH_3	70–75 (*ca.* 0.5)	1.5258	86	C	C, 83.5 H, 9.5	C, 83.8 H 9.7
	CH_3COOCH_2—	CH_3	CH_3	CH_3	CH_3	57–60 (*ca.* 0.5)	1.4523	79	C	C, 67.0 H, 9.7	C, 67.3 H, 9.9
	$CH_3COOC(CH_3)_2$—	CH_3	CH_3	CH_3	CH_3	45–53 (0.5–1)	1.4451	75	C	C, 69.3 H, 10.3	C, 69.4 H, 10.3
IX	$CH_3COOC(CH_3)(CH_2CH_3)$—	CH_3	CH_3	CH_3	CH_3	60–65 (*ca.* 0.5)	1.4477	89	C	C, 70.3 H, 10.5	C, 70.2 H, 10.6
	$CH_3COOC(CH_3)(CH_2CH(CH_3)_2)$—	CH_3	CH_3	CH_3	CH_3	68–74 (*ca.* 0.5)	1.4498	88	C	C, 71.9 H, 10.9	C, 72.3 H, 11.2
		CH_3	CH_3	CH_3	CH_3	83–89 (*ca.* 0.5)	1.4714	89	C	C, 72.4 H, 10.3	C, 72.8 H, 10.3
X	$HOC(CH_3)_2$—	CH_3	CH_3	CH_3	CH_3	58–67 (1–1.5)	1.4570	76	D	C, 72.1 H, 11.6	C, 71.9 H, 11.3

[a] For a detailed example of each method, see Experimental.



Experimental[3]

Materials.—N,N-Dimethylisobutylamine was prepared as previously described.[4] 1-Isobutenylpiperidine was prepared as described by Benzing[5] and 1-butenylpiperidine was prepared by the method of Mannich.[6]

The following examples illustrate the methods of preparation used in this investigation.

1-Isopropyl-N,N-dimethyl-2-propynylamine (VI) and N,N,N′,N′,2,7-Hexamethyl-4-octyne-3,6-diamine (VII). Method A.—A mixture of N,N-dimethylisobutenylamine (99 g., 1 mole), copper(I) chloride (0.5 g.), and benzene (125 ml.) was heated to 100° in an autoclave under 7 atm. of nitrogen pressure. Acetylene was added until the pressure was 14 atm. As the reaction proceeded, the pressure dropped to 7 atm. and more acetylene was added until the pressure was again 14 atm. This was repeated until the pressure remained constant. After the mixture was cooled to room temperature, the catalyst was removed by

(3) Boiling points and melting points are uncorrected. Melting points were determined using a Fisher-Johns melting point apparatus.

(4) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).

(5) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

(6) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

filtration, and the benzene was removed by distillation to a base temperature of 155° at 200 mm. The distillation was continued to give, after removal of an intermediate fraction, 26.2 g. (21%) of 1-isopropyl-N,N-dimethyl-2-propynylamine, b.p. 68–69° at 100–109 mm.

The distillation was continued and, after collection of an intermediate fraction, there was obtained 53 g. (47%) of N,N,N′,N′,-2,7-hexamethyl-4-octyne-3,6-diamine, b.p. 106° at 9 mm., $n^{20}D$ 1.4575.

1-(1-Isopropyl-3-phenyl-2-propyn-3-yl)piperidine (VIII). Method B.—Ethylnylbenzene (27 g., 0.26 mole) and 1-isobutenylpiperidine (40 g., 0.29 mole) were combined and heated at 145–150° for 15 hr. Distillation of the reaction mixture through a 6-in. Vigreux column gave, after removal of 15 g. of forerun, 40.5 g. (64%) of 1-(1-isopropyl-3-phenyl-2-propyn-3-yl)piperidine, b.p. 118–124° at 1.5 mm., n^{20}n 1.5393.

6-Dimethylamino-3,7-dimethyl-4-octyn-3-yl Acetate (IX). Method C.—N,N-Dimethylisobutenylamine (200 g., 2.02 moles) and copper(I) chloride (3 g.) were placed in a three-necked reaction flask equipped with a mechanical stirrer, thermometer, and dropping funnel. The stirrer was started and 3-methyl-1-pentyn-3-yl acetate (280 g., 2 moles) was added dropwise. An exothermic reaction occurred and the temperature of the mixture was maintained at 40–45° by intermittent cooling. The mixture was stirred for 2 hr. after the addition was completed and the catalyst was then removed by filtration. Distillation of the reaction mixture through a 6-in. Vigreux column gave, after removal of a 15-g. forerun, 428 g. (89%) of 6-dimethylamino-3,7-dimethyl-4-octyn-3-yl acetate, b.p. 60–65° at *ca.* 0.5 mm., $n^{20}D$ 1.4477.

5-Dimethylamino-2,6-dimethyl-3-heptyn-2-ol (X). Method D.—N,N-Dimethylisobutenyl amine (50 g., 0.5 mole), copper(I) chloride (3 g.), and hydroquinone (0.1 g.), were placed in a three-necked reaction flask and heated to reflux (86°). The mixture was stirred while 2-methyl-3-butyn-2-ol (42 g., 0.5 mole) was added dropwise. The mixture was heated during the addition and the temperature rose to 110° and refluxing ceased. The temperature was kept at 110° for 10 min. The mixture was then cooled to room temperature, filtered, and distilled through a 6-in. Vigreux column to give, after removal of a 1-g. forerun, 70 g. (76%) of 5-dimethylamino-2,6-dimethyl 3-heptyn-2-ol, b.p. 58–67° at 1–1.5 mm., $n^{20}D$ 1.4570.

Transformation of 1-Isopropyl-N,N-dimethyl-3-phenyl-2-propynylamine (IV) to 4-Methyl-2-pentenophenone (V).—To a solution of 60 ml. of concentrated sulfuric acid and 15 ml. of water was added 1-isopropyl-N,N-dimethyl-3-phenyl-2-propynylamine (27 g., 0.137 mole). To this mixture was added mercury(II) sulfate (1 g.). The resulting mixture was heated on the steam bath for 4 hr. and then poured onto ice and extracted once with ether (200 ml.). Evaporation of the ethereal extract on the steam bath gave less than 1 g. of residue. The remaining aqueous layer was made basic with sodium hydroxide (12 g., 0.3 mole) and extracted once with ether (400 ml.). Evaporation of the ether on the steam bath to 75° gave 26.5 g. of residue. The residue was combined with 10% sodium hydroxide solution (10 ml.), water (10 ml.), and ethyl alcohol (75 ml.) and was heated on the steam bath for 5.5 hr. During this time dimethylamine was evolved. After the mixture was chilled, a solid separated which was collected, washed with aqueous ethyl alcohol, and dried to give 9.5 g. (41%) of 4-methyl-2-pentenophenone, m.p. 142–143° (reported[7] m.p. 139–140°).

(7) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).

Enamine Chemistry. II. Reactions with Acetylenedicarboxylates[1]

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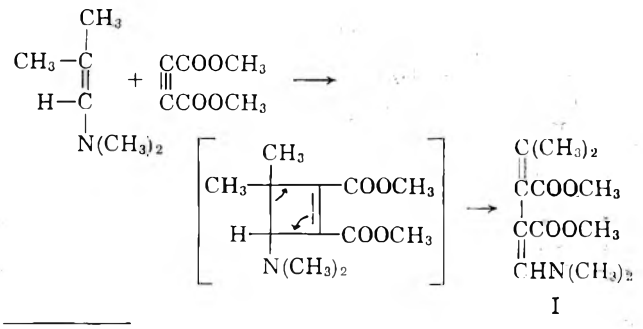
The reaction of a variety of enamines with acetylenedicarboxylates was studied. The reaction products are those derived from the cyclobutene rearrangement of cycloaddition adducts initially formed. In the case of enamines derived from alicyclic ketones, the net result of the reaction is a ring enlargement in which two carbon atoms are inserted into the ring. Some further transformations of the reaction products are described.

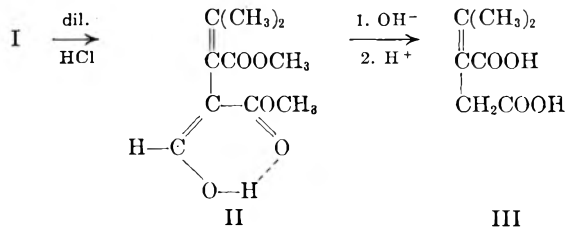
The cycloaddition of electrophilic olefins to enamines, leading to cyclobutanes, has been reported.[2] The reactions of a variety of enamines derived from acyclic aldehydes and ketones and cyclic ketones with both acetylenedicarboxylates and propiolates have now been investigated. The reactions involving acetylenedicarboxylates proved to be more straightforward and will be discussed in this paper.

The reaction of enamines derived from butyraldehyde, isobutyraldehyde, and 3-pentanone with acetylenedicarboxylates gives products derived from ring opening of the expected cyclobutene intermediates. The reaction sequence is shown for N,N-dimethylisobutenylamine and dimethyl acetylenedicarboxylate.



I

The enamine function of the product (I) was hydrolyzed with dilute acid to give the hydroxymethylene ester (II) which in turn was cleaved by aqueous alkali to give teraconic acid (III).



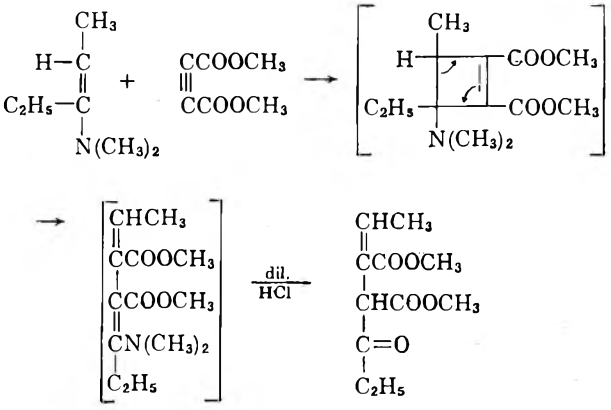
II III

Similar transformations were carried out with the product derived from butyraldehyde, whereas the product derived from 3-pentanone was converted directly to the keto diester (IV) without the isolation of intermediates.

A similar reaction of enamines derived from cyclic ketones with acetylenedicarboxylates, the net result of

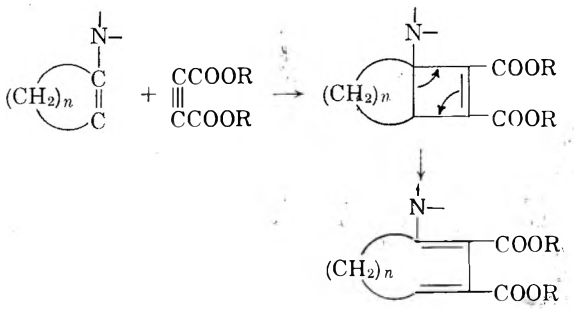
(1) A portion of the material in this paper was presented at the Enamine Chemistry Symposium, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(2) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).



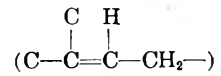
IV

which would be a ring enlargement with insertion of two carbons in the ring, appeared especially attractive to us.



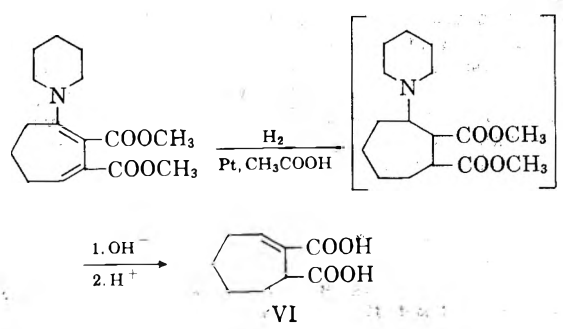
V

This sequence occurred smoothly with enamines derived from cyclopentanone, cycloheptanone, cyclooctanone, and cyclododecanone, that is, when n = 3, 5, 6, or 10. The structures of the five adducts were assigned, in part, on the basis of their hydrolysis to the corresponding unsaturated keto esters, and, in part, on the basis of their n.m.r. spectra, which showed a single olefinic proton as a triplet.



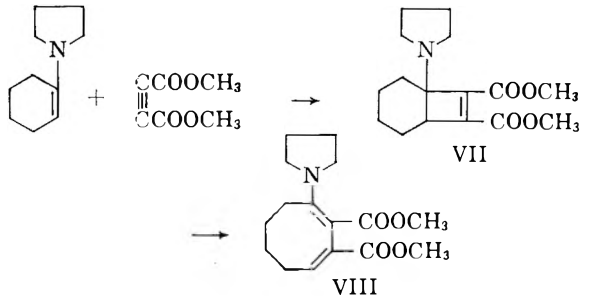
In addition, all of the adducts showed very similar infrared absorptions in the C=O and C=C range [maxima at 5.75–5.80 μ, 5.95–6.0 μ, 6.1–6.3 μ (weak), and 6.45–6.5μ].

The adduct (V) derived from cyclopentanone (n = 3), was further converted by hydrogenation and digestion of the crude product with aqueous alkali to 2-cycloheptene-1,2-dicarboxylic acid (VI). On hydrogenation, VI gave the known *cis*-1,2-cycloheptanedicarboxylic acid which was isomerized to the known *trans*-1,2-cycloheptanedicarboxylic acid by heating it with dilute sulfuric acid.

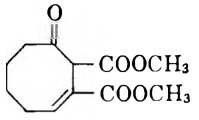


VI

Reaction of the pyrrolidine enamine of cyclohexanone with dimethyl acetylenedicarboxylate gave a heat-sensitive solid in good yield to which we have assigned the bicyclooctene structure (VII). No vinyl protons



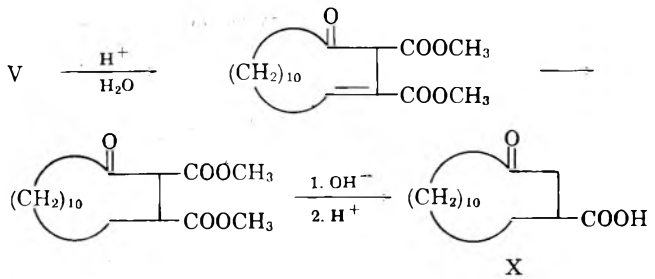
were indicated in the n.m.r. spectrum of VII and its infrared spectrum was compatible with the proposed structure. The compound undergoes considerable decomposition on melting (77–81°) or on attempted recrystallization from hexane. It could be recrystallized from ether, however. After heating VII for eighteen hours on a steam bath, the ring enlargement product (VIII) was obtained in 11% yield. In another case, VIII was obtained fortuitously in 33% yield when VII was subjected to an unsuccessful series of transformations. A significant amount of rearrangement of VII occurs when it is treated with dilute acid since the keto ester (IX) was obtained in 21% yield after this treatment; hydrolysis of VIII under similar conditions gave IX in 53% yield.



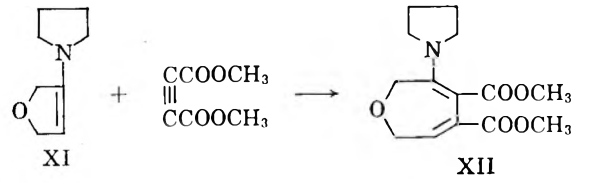
IX

We believe that the reluctance of VII to undergo the cyclobutene rearrangement may be due to the 6/4 ring fusion forcing the cyclobutene ring into nonplanarity, and thus making the rearrangement less favorable. The nature of the thermal decomposition products of VII, other than VIII, has not been determined.

The product derived from cyclododecanone (V. n = 10) was converted by hydrolysis, hydrogenation, saponification, and decarboxylation to 3-oxocyclotetradecanecarboxylic acid (X).



In one case, the heterocyclic enamine (XI) obtained from dihydro-3(2*H*)-furanone gave the ring enlargement product (XII) in poor yield.



Experimental[3]

Materials.—1-Ethyl-N,N-dimethylpropenylamine was prepared by a slight modification of the method of Stork and Landesman.[4] The methiodide salt of the N-methylimine of 3-pentanone was treated with a twofold excess of triethylamine in benzene. After the mixture had stood at room temperature for 24 hr., it was filtered and the filtrate was distilled to give 1-ethyl-N,N-dimethylpropenylamine, b.p. 127–128° (atm. pressure), $n^{20}D$ 1.4479, in 46% yield.

Anal. Calcd. for $C_7H_{15}N$: C, 74.2; H, 13.3. Found: C, 73.9; H, 13.2.

1-(1-Cyclododecenyl)pyrrolidine was prepared by refluxing, for 3 days, a mixture of cyclododecanone (182 g., 1 mole), pyrrolidine (213 g., 3 moles), 0.25 g. of *p*-toluenesulfonic acid, 200 ml. of xylene, and 25 ml. of hexane under a column topped with a Dean–Stark trap. After distillation, the enamine, b.p. 120–125° at 0.4–0.5 mm., $n^{20}D$ 1.5237, was obtained in 77% yield.

Anal. Calcd. for $C_{16}H_{29}N$: C, 83.1; H, 10.9. Found: C, 82.9; H, 10.8.

1-(2,5-Dihydro-3-furyl)pyrrolidine.—Dihydro-3(2*H*)-furanone[5] (36.5 g., 0.4 mole) was added to a slurry of 5 g. of anhydrous potassium carbonate in pyrrolidine (28.4 g., 0.4 mole) at 0° and the mixture was allowed to stand for 3 hr. at 0°. It was then filtered and the filtrate was distilled to give 18 g. (32%) of 1-(2,5-dihydro-3-furyl)pyrrolidine, b.p. 55–59° at 0.2 mm., $n^{20}D$ 1.5148. This enamine was quite sensitive to heat and much of it was lost during distillation. For most purposes, the crude material can be used without distillation. The alternative structure, 1-(4,5-dihydro-3-furyl)pyrrolidine, was excluded on the basis of the n.m.r. spectrum (determined at 40 Mc. with a Varian Associates 4300B instrument) which showed an olefinic proton singlet (as does 2,5-dihydrofuran) at 4 p.p.m. (relative to tetramethylsilane) and a single absorption for the two methylene groups at 4.7 p.p.m. In the alternative structure, the absorptions due to the two methylene groups would be expected to be resolved.

Anal. Calcd. for $C_8H_{13}NO$: N, 10.0. Found: N, 9.8.

1-(1-Cyclooctenyl)piperidine, b.p. 87–88° at 1 mm., $n^{20}D$ 1.5164, was prepared in 72% yield by the method of Kuehne.[6]

Anal. Calcd. for $C_{13}H_{23}N$: N, 7.3. Found: N, 7.1.

N,N-Dimethylisobutenylamine,[7] 1-butenylpiperidine,[8] and the pyrrolidine enamines of cyclopentanone, cyclohexanone, and cycloheptanone[6] were prepared as described in the literature.

Dimethyl 2-Dimethylaminomethylene-3-isopropylidenesuccinate.—N,N-Dimethylisobutenylamine (45.5 g., 0.46 mole) was added dropwise to dimethyl acetylenedicarboxylate (65.3 g., 0.46 mole) in 50 ml. of ether with cooling to keep the temperature at 25–30°. The mixture was allowed to reflux spontaneously (about 1 hr.) and was then heated at reflux for 0.5 hr. On distillation, there was obtained 54.2 g. (49%) of crude dimethyl 2-dimethylaminomethylene-3-isopropylidenesuccinate, b.p. 119–121° at 0.55 mm., which crystallized, m.p. 65–75°. A sample for analysis, recrystallized from hexane, melted at 83.5–84.5°.

Anal. Calcd. for $C_{12}H_{19}NO_4$: C, 59.3; H, 7.9; N, 5.8. Found: C, 59.7; H, 7.8; N, 5.6.

Dimethyl 2-Formyl-3-isopropylidenesuccinate.—Dimethyl 2-dimethylaminomethylene-3-isopropylidenesuccinate (16 g., 0.066 mole) was added to a solution of 25 ml. of concentrated hydrochloric acid in 175 ml. of water and warmed gently on the steam bath until solution was complete. The mixture rapidly became turbid and an oil layer separated. The mixture was allowed to stand 1 hr. and was then extracted with ether. Distillation of the extract gave 9 g. (64%) of dimethyl 2-formyl-3-isopropylidene succinate, b.p. 93–96° at 0.8 mm., $n^{20}D$ 1.4909 (supercooled), which crystallized, m.p. 56–58°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.1; H, 6.6. Found: C, 55.8; H, 6.6.

This material gave an intense violet color with iron(III) chloride solution and its infrared spectrum showed that it was, for the most part, the enol or hydroxymethylene form.[9] This material did not give a solid 2,4-dinitrophenylhydrazone.

Diethyl 2-Dimethylaminomethylene-3-isopropylidenesuccinate.—Diethyl acetylenedicarboxylate (170 g., 1.0 mole) was added dropwise to N,N-dimethylisobutenylamine (120 g., 1.2 moles) in 150 ml. of ether over a 2-hr. period, at such a rate that the mixture was maintained at reflux (44–46°). The temperature was allowed to decrease slowly to room temperature over the next hour and the mixture stood overnight. It was then distilled to remove excess N,N-dimethylisobutenylamine by heating it to 65° at 2 mm. When cooled, the entire residue (270 g.; theoretical yield, 269 g.) crystallized.

The product was treated with Darco and recrystallized from hexane to give 197 g. (73%) of diethyl 2-dimethylaminomethylene-3-isopropylidenesuccinate, m.p. 57–58°. A sample for analysis, recrystallized from hexane, melted at 59°.

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.4; H, 8.6; N, 5.2. Found: C, 62.3; H, 8.5; N, 5.1.

This material did not give a solid 2,4-dinitrophenylhydrazone.

Diethyl 2-Formyl-3-isopropylidenesuccinate.—Diethyl 2-dimethylaminomethylene-3-isopropylidenesuccinate (100 g., 0.37 mole) was dissolved in a solution of 150 ml. of concentrated hydrochloric acid in 850 ml. of water. An oil layer separated after a short time. The mixture was allowed to stand, with occasional shaking, for 1 hr. and was then extracted with ether. Distillation of the ether layer gave 64 g. (70%) of diethyl 2-formyl-3-isopropylidenesuccinate, b.p. 110–112° at 3 mm.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.5; H, 7.5. Found: C, 59.6; H, 7.6.

This product gave an intense violet color with iron(III) chloride solution and its infrared spectrum showed that it was, for the most part, the enol form. It did not give a solid 2,4-dinitrophenylhydrazone, but did give a semicarbazone, m.p. 144–146°.

Anal. Calcd. for $C_{13}H_{21}N_3O_5$: C, 52.2; H, 7.1. Found: C, 52.1; H, 7.2.

Teraconic Acid.—Diethyl 2-formyl-3-isopropylidenesuccinate (30 g., 0.124 mole) was refluxed with 20 g. of sodium hydroxide in 75 ml. of water for 3 hr. The solution was acidified with concentrated hydrochloric acid, cooled, and filtered to give 19 g. (97%) of crude teraconic acid, m.p. 168–171° dec. A sample for analysis, recrystallized from water, melted at 174° dec.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.2; H, 6.3; neut. equiv., 79.08. Found: C, 53.2; H, 6.4; neut. equiv., 78.8.

An authentic sample of teraconic acid prepared by the method of Kloetzel[10] melted at 174° and showed no depression of the melting point when admixed with the teraconic acid obtained previously.

Dimethyl 2-Piperidinomethylene-3-propylidenesuccinate.—Dimethyl acetylenedicarboxylate (14 g., 0.1 mole) was added dropwise with stirring to 1-(1-butenyl)piperidine (14 g., 0.1 mole) in ether (25 ml.) at such a rate that gentle refluxing of the ether was maintained. Distillation of the mixture through a 3-in. Vigreux column gave, after removal of ether and a 4-g. forerun, 14 g. (50%) of dimethyl 2-piperidinomethylene-3-propylidenesuccinate, b.p. 150–156° at 1.5 mm., $n^{20}D$ 1.5354.

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2. Found: C, 63.9; H, 8.1.

Dimethyl 2-Formyl-3-propylidenesuccinate.—Dimethyl 2-piperidinomethylene-3-propylidenesuccinate (11 g., 0.04 mole) was dissolved in a solution of concentrated hydrochloric acid (16 ml.) in water (90 ml.). The mixture was allowed to stand, with occasional shaking, for 1.5 hr. and was then extracted with ether and the etheral extract was distilled to give 4 g. (48%) of dimethyl 2-formyl-3-propylidenesuccinate, b.p. 93–96° at 1 mm., $n^{20}D$ 1.4833.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.0; H, 6.6. Found: C, 55.8; H, 6.7.

2-Propylidenesuccinic Acid.—Dimethyl 2-formyl-3-propylidenesuccinate (3 g., 0.014 mole) was refluxed wth a solution of sodium hydroxide (2.5 g., 0.063 mole) in water (20 ml.) for 1.5 hr. The resulting solution was acidified with concentrated hydrochloric acid and extracted with ether. Evaporation of the ether on a steam bath gave 1.7 g. (77%) of crude 2-propylidenesuccinic acid. A small sample, recrystallized from water, melted at 166–167° (reported[10] m.p. 163–166°).

Dimethyl 2-Ethylidene-1-propionylsuccinate.—To a solution of 1-ethyl-N,N-dimethylpropenylamine (28.3 g., 0.25 mole) in

(3) Melting points are uncorrected and were determined using a Fisher-Johns melting point apparatus.
(4) H. K. Landesman, P.D. thesis, Columbia University, 1956.
(5) H. Wynberg, *J. Am. Chem. Soc.*, **80**, 364 (1958).
(6) M. E. Kuehne, *ibid.*, **81**, 5400 (1959).
(7) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).
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(9) W. J. Croxall and J. O. Van Hook, *J. Am. Chem. Soc.*, **72**, 803 (1950)
(10) M. C. Kloetzel, *ibid.*, **70**, 3571 (1948).

ether (100 ml.) was added, over 1 hr., dimethyl acetylenedicarboxylate (35.5 g., 0.25 mole). The temperature of the reaction mixture was maintained below 35° by intermittent cooling. After the reaction mixture had stood for 2 hr., the ether was evaporated on a steam bath and the residual oil was dissolved in a solution of concentrated hydrochloric acid (30 ml.) and water (150 ml.). The mixture stood for 18 hr.; the oil which had separated was removed by extraction with ether. Distillation of the etheral extract gave, after removal of ether, 50.8 g. (89%) of dimethyl 2-ethylidene-1-propionylsuccinate, b.p. 102–104° at 1.2 mm., $n^{20}D$ 1.4743. The infrared spectrum was consistent with the assigned structure.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.8; H, 7.1. Found: C, 58.0; H, 7.0.

Dimethyl 3-(1-Pyrrolidinyl)-2,7-cycloheptadiene-1,2-dicarboxylate.—Dimethyl acetylenedicarboxylate (28.4 g., 0.2 mole) was added, over 10 min., to 1-(1-cyclopentenyl)pyrrolidine (30.2 g., 0.22 mole) in ether (150 ml.) with cooling to keep the temperature at 25–35°. The mixture was allowed to stand for 0.5 hr. and the ether was removed by evaporation on a steam bath. On cooling, the residue crystallized. Recrystallization of the product from a hexane–benzene mixture gave 39.8 g. (71%) of dimethyl 3-(1-pyrrolidinyl)-2,7-cycloheptadiene-1,2-dicarboxylate, m.p. 147–148°.

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.6. Found: C, 64.9; H, 7.8.

Dimethyl 7-Oxo-2-cycloheptene-1,2-dicarboxylate.—Dimethyl-3-(1-pyrrolidinyl)-2,7-cycloheptadiene-1,2-dicarboxylate (11.5 g., 0.041 mole) was dissolved in a solution of concentrated hydrochloric acid (10 ml.) and water (40 ml.). After the mixture had stood for 15 hr., the oil layer which had separated was removed by extraction with ether. Distillation of the etheral extract gave, after removal of ether, 4.6 g. (49%) of dimethyl 7-oxo-2-cycloheptene-1,2-dicarboxylate, b.p. 101–106° at 0.4–0.5 mm. This compound crystallized on standing and melted at 55–57°. Its n.m.r. spectrum showed that it was, for the most part, the enol form.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.4; H, 6.2. Found: C, 58.5; H, 6.5.

2-Cycloheptene-1,2-dicarboxylic Acid.—Dimethyl 3-(1-pyrrolidinyl)-2,7-cycloheptadiene-1,2-dicarboxylate (42 g., 0.15 mole) was dissolved in acetic acid (350 ml.) and hydrogenated at 40 p.s.i. at room temperature, using 0.5 g. of platinum(IV) oxide as a catalyst, until hydrogen absorption had stopped. The catalyst was removed by filtration and most of the acetic acid was removed by distillation under reduced pressure. The residue was treated with excess aqueous 20% sodium hydroxide in methanol, and heated on a steam bath for 2 hr. The solution was acidified with concentrated hydrochloric acid and was extracted three times with ether. Evaporation of the combined etheral extracts gave 7 g. (25%) of 2-cycloheptene-1,2-dicarboxylic acid. A sample, recrystallized from water, melted at 168–170°. N.m.r. spectrum showed one olefinic proton absorption as a triplet.

Anal. Calcd. for $C_9H_{12}O_4$ C, 58.7; H, 6.6; neut. equiv., 92.1. Found: C, 58.5; H, 6.5; neut. equiv., 92.2.

2-Cycloheptene-1,2-dicarboxylic acid was obtained in 73% yield from a similar hydrogenation using 0.25 mole of dimethyl 3-(1-pyrrolidinyl)-2,7-cycloheptadiene-1,2-dicarboxylate, 500 ml. of acetic acid, and 2 g. of platinum(IV) oxide. Treatment was then the same as that used previously.

***cis*-1,2-Cycloheptanedicarboxylic Acid.**—2-Cycloheptene-1,2-dicarboxylic acid (15 g., 0.082 mole) was dissolved in a solution of water (100 ml.) and sodium hydroxide (6.6 g., 0.165 mole) and hydrogenated at 125° and 1500 p.s.i., using 5 g. of Raney nickel as a catalyst. The catalyst was removed by filtration and the filtrate was evaporated on a steam bath to one-third the original volume. The solution was acidified with concentrated hydrochloric acid and filtered to give 12 g. of *cis*-1,2-cycloheptanedicarboxylic acid. Extraction of the filtrate with ether and evaporation of the etheral extract gave an additional 2.5 g. of product. The yield was 95%. A sample for analysis, recrystallized from toluene, melted at 130–131° (reported[11] m.p. 133–135°).

The infrared spectrum of the acid was identical with that of a sample of authentic *cis*-1,2-cycloheptanedicarboxylic acid.[12]

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.0; H, 7.6. Found: C, 58.0; H, 7.5.

***trans*-1,2-Cycloheptanedicarboxylic Acid.**—*cis*-1,2-Cycloheptanedicarboxylic acid (5 g., 0.027 mole) was combined with 25 ml. of a 30% (by volume) solution of concentrated sulfuric acid in water and heated for 12 hr. in a bomb at 150°. The mixture was cooled and filtered to give 4 g. (80%) of *trans*-1,2-cycloheptanedicarboxylic acid. A sample, recrystallized three times from acetonitrile, melted at 156–157° (reported m.p. 157–158.5°,[11] 145–147[13]). A stable hemihydrate, m.p. 160–161°, has been reported[14] but was not encountered by us. The infrared spectrum of our material was identical with that of a sample supplied by Dr. R. A. Raphael.[15] We found the melting point of this sample to be 155–156°. On one occasion, we obtained a small amount of the *trans*-1,2-cycloheptanedicarboxylic acid, which melted at 115–120°. This may have been due to polymorphism, since the optically active *trans* acid has been reported to melt at 115–116°.[11]

Dimethyl 1-(1-Pyrrolidinyl)bicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate.—Dimethyl acetylenedicarboxylate (28.4 g., 0.2 mole) was added over 10 min. to 1-(1-cyclohexenyl)pyrrolidine (30.2 g., 0.2 mole) in 150 ml. of ether with cooling to keep the temperature at 25–35°. Toward the end of the addition a crystalline precipitate appeared. The mixture was allowed to stand for 10 min. and 150 ml. of pentane was added. The mixture was chilled and filtered to give 41 g. (70%) of dimethyl 1-(1-pyrrolidinyl)bicyclo[4.2.0]-oct-7-ene-7,8-dicarboxylate, m.p. 77–81°. This compound is thermally unstable and undergoes considerable change on melting or on attempted recrystallization from hexane. It could, however, be recrystallized from ether.

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.5; H, 7.9. Found: C, 65.6; H, 7.9.

Dimethyl 3-(1-Pyrrolidinyl)-2,8-cyclooctadiene-1,2-dicarboxylate.—Dimethyl 1-(1-pyrrolidinyl)bicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate (37 g., 0.126 mole) was heated on a steam bath for 18 hr. The material was cooled, and ether (100 ml.) was added. It was then chilled and filtered to give 4 g. (11%) of dimethyl 3-(1-pyrrolidinyl)-2,8-cyclooctadiene-1,2-dicarboxylate, m.p. 138–140°. After recrystallization of the product from ether, the melting point was 141–142°.

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.5; H, 7.9. Found: C, 65.5; H, 7.9.

Dimethyl 3-(1-pyrrolidinyl)-2,8-cyclooctadiene-1,2-dicarboxylate was obtained fortuitously in 33% yield from dimethyl 1-(1-pyrrolidinyl)bicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate when the latter compound was subjected to an unsuccessful series of transformations.

On standing, the bicyclooctene undergoes a significant amount of rearrangement, as shown by the fact that a 21% yield of dimethyl 8-oxo-2-cyclooctene-1,2-dicarboxylate was obtained from treatment of the bicyclooctene with dilute hydrochloric acid.

Dimethyl 8-Oxo-2-cyclooctene-1,2-dicarboxylate.—Dimethyl 3-(1-pyrrolidinyl)-2,8-cyclooctadiene-1,2-dicarboxylate (4 g., 0.017 mole) was dissolved in 25 ml. of 10% hydrochloric acid solution and allowed to stand for 24 hr. at room temperature. The oil which had separated was extracted with ether and the ether was evaporated on a steam bath, leaving 1.75 g. (53%) of dimethyl 8-oxo-2-cyclooctene-1,2-dicarboxylate, which crystallized on standing. A sample for analysis, recrystallized from hexane, melted at 74–75°. The n.m.r. spectrum showed that it was, for the most part, the enol form.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.0; H, 6.7. Found: C, 59.8; H, 6.7.

Dimethyl 3-(1-Pyrrolidinyl)-2,9-cyclononadiene-1,2-dicarboxylate.—To a solution of 1-(1-cycloheptenyl)pyrrolidine (3.3 g., 0.02 mole) in ether (25 ml.) was added, over 5 min., dimethyl acetylenedicarboxylate (2.8 g., 0.02 mole) with cooling to keep the temperature at 30–35°. The reaction mixture was allowed to stand at room temperature for 0.5 hr. and then cooled to 10°. After filtration, 3.9 g. of dimethyl 3-(1-pyrrolidinyl)-2,9-cyclononadiene-1,2-dicarboxylate, m.p. 109.5–110.5°, was obtained. Evaporation of the filtrate and addition of pentane gave an additional 1.8 g. of the same product. The combined yield was 93%.

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(15) We are indebted to Dr. R. A. Raphael, University of Glasgow, for supplying us with a sample of *trans*-1,2-cycloheptanedicarboxylic acid.

Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.4; H, 8.2. Found: C, 66.7; H, 8.4.

Diethyl 3-Piperidino-2,10-cyclodecadiene-1,2-dicarboxylate.—1-(1-Cyclooctenyl)piperidine (3.86 g., 0.02 mole) and diethyl acetylenedicarboxylate (3.40 g., 0.02 mole) were allowed to react in ether as described in the preceding example. There was obtained 4.4 g. (60%) of diethyl 3-piperidino-2,10-cyclodecadiene-1,2-dicarboxylate, m.p. 91–92°.

Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.4; H, 9.2. Found: C, 69.5; H, 9.2.

Dimethyl 3-Pyrrolidinyl-2,14-cyclotetradecadiene-1,2-dicarboxylate.—To 1-(1-cyclododecenyl)pyrrolidine (8.5 g., 0.036 mole) in 25 ml. of ether was added, portionwise, dimethyl acetylenedicarboxylate (5.15 g., 0.036 mole) with cooling to keep the temperature at 30–35°. The ether was removed on a steam bath and the residue was crystallized from pentane to give 12.35 g. (90.5%) of crude dimethyl 3-pyrrolidinyl-2,14-cyclotetradecadiene-1,2-dicarboxylate. A sample for analysis, recrystallized from ether, melted at 94–95°.

Anal. Calcd. for $C_{22}H_{35}NO_4$: D, 70.0; H, 9.3. Found: C, 69.9; H, 9.1.

Hydrolysis of dimethyl 3-pyrrolidinyl-2,14-cyclotetradecadiene-1,2-dicarboxylate with dilute hydrochloric acid gave dimethyl 14-oxo-2-cyclotetradecene-1,2-dicarboxylate, m.p. 73–74° (recrystallized from ether), in 83% yield.

Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.6; H, 8.7. Found: C, 66.6; H, 8.8.

Hydrogenation of dimethyl 14-oxo-2-cyclotetradecene-1,2-dicarboxylate in methanol over 5% palladium on alumina at room temperature and 3 atm. gave dimethyl 3-oxocyclotetradecane-1,2-dicarboxylate, m.p. 93° (recrystallized from methanol), in 84% yield.

Anal. Calcd. for $C_{18}H_{30}O_5$: C, 66.2; H, 9.3. Found: C, 66.3; H, 9.3.

Treatment of dimethyl 3-oxocyclotetradecane-1,2-dicarboxylate (32.6 g., 0.1 mole) with a solution of 15 g. of sodium hydroxide in 250 ml. of methanol and 250 ml. of water at reflux for 5 hr., followed by acidification with concentrated hydrochloric acid, gave 21.5 g. (85%) of 3-oxocyclotetradecanecarboxylic acid, m.p. 142.5–143.5° (recrystallized from toluene).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.8; H, 10.3. Found: C, 70.6; H, 10.5.

Dimethyl 2,7-Dihydro-3-pyrrolidinyl-4,5-oxepindicarboxylate.—Dimethyl acetylenedicarboxylate (15.2 g., 0.107 mole) was added portionwise to 1-(2,5-dihydro-3-furyl)pyrrolidine (14.9 g., 0.107 mole) in 75 ml. of ether with cooling to maintain the temperature at 25–30°. The mixture was allowed to stand overnight and the ether was removed on a steam bath. After addition of more ether and chilling, 5 g. (17%) of dimethyl 2,7-dihydro-3-pyrrolidinyl-4,5-oxepindicarboxylate was obtained. A sample for analysis, recrystallized from a benzene–hexane mixture, melted at 162–163°.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.6. Found: C, 59.9; H, 6.7.

Ketenes I. Cycloaddition of Ketene and Dialkylketenes to Enamines

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The cycloaddition of dialkylketenes to enamines derived from secondary aldehydes takes place readily to form 3-dialkylamino-2,2,4,4-tetraalkylcyclobutanones. When the cycloaddition involves enamines containing a β-hydrogen and/or ketene, the enolizable cyclobutanones are unstable and are isomerized thermally to dialkylaminovinyl ketones. A number of cyclobutanones and their rearrangement and reduction products are described.

Ketenes add to a number of olefinic compounds to form cyclobutane derivatives.[1] Ketene[2] and diphenylketene[3] have been studied more than any other member of the series; cycloadditions of dialkylketenes with olefinic compounds have been reported only for dimethylketene with ethyl vinyl ether[4] and cyclopentadiene.[4,5] In a study of the scope of the cycloaddition reactions of dialkylketenes, we observed the particularly facile addition of dimethylketene to enamines. This reaction, noted independently by other workers,[6,7] was reported briefly in a Communication.[8] The present paper is a more detailed account of our work.

Stable cyclobutanone derivatives were obtained by addition of dialkylketenes to enamines lacking any β-hydrogen atoms. Dimethylketene and N,N-dimethylisobutenylamine, mixed in isopropyl acetate at room temperature, reacted to give 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone (I) in 64% yield. The structure of I was consistent with infrared and n.m.r. spectral data, and was confirmed by quaternization with methyl tosylate and alkaline degradation to 2,2,4-trimethyl-3-pentenoic acid (II).

The cycloaddition reaction was carried out with several dialkylketenes and a variety of enamines derived

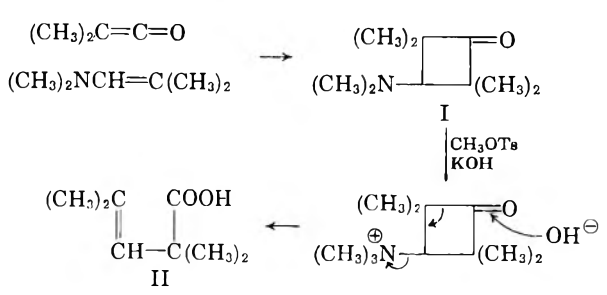

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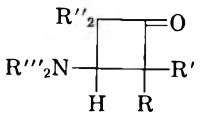
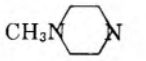
TABLE I

DIALKYLAMINOCYCLOBUTANONES



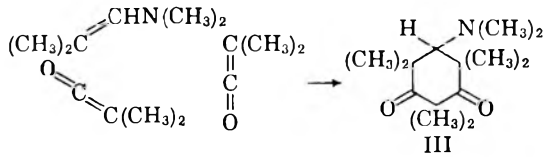
R[a]	R'[a]	R''	R'''$_2$N	B.p., °C. (mm.)	n^{20}D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	CH_3	CH_3	$(CH_3)_2N$	83–85 (24)	1.4439	71.1	71.3	11.2	11.2	8.3	8.1
CH_3	CH_3	CH_3		95–97 (4.2)	1.4705	74.5	74.3	11.0	11.2	6.7	6.5
CH_3	CH_3	CH_3		58–59.5[b]		68.3	68.3	10.0	10.0	6.6	6.6
CH_3	CH_3	CH_3		256 dec.[c]		72.0	72.1	10.2	10.2	8.4	8.3
CH_3	CH_3	CH_3		105–107 (3)[d]		69.7	70.2	10.7	10.8	12.5	12.4
CH_3	C_2H_5	CH_3		101–103 (1.3)	1.4736	69.4	69.6	10.2	10.4	6.2	6.3
C_2H_5	C_2H_5	CH_3	$(CH_3)_2N$	95–98 (8)	1.4585	73.1	72.9	11.7	11.8	7.1	7.0
C_2H_5	C_2H_5	CH_3		101–104 (0.7)[d]	1.4794	70.3	69.9	10.5	10.5	5.9	5.9
C_2H_5	C_2H_5	C_2H_5	$(CH_3)_2N$	112 (5)	1.4662	74.7	74.1	12.0	11.6	6.2	5.9
C_2H_5	C_2H_5	C_2H_5		130–132 (1.5)[d]		77.0	76.7	11.7	11.7	5.3	5.0
C_2H_5	C_4H_9	CH_3	$(CH_3)_2N$	94 (2)	1.4592	74.7	74.9	12.0	12.5	6.2	6.1
$-(CH_2)_5-$		CH_3		81–82.5[e]		77.1	77.1	10.8	11.0	5.6	5.4

[a] Substituents on original dialkylketene. [b] Melting point (from pentane). [c] Bis adduct, melting point (from toluene). [d] Solidified on standing. [e] Melting point (from ethyl alcohol).

from secondary aldehydes and secondary amines; the products are listed in Table I. In general, the reaction was more sluggish with enamines from higher aldehydes, and higher dialkylketenes also exhibited less reactivity. The effect of substituents on the nitrogen atom of the enamine was less obvious. *N*-Isobutenyl derivatives of dimethylamine, piperidine, and morpholine all reacted rapidly, but the corresponding derivative of *N*-methylaniline was relatively inert.

The order of addition of the reactants was important to obtain optimum yields. Best results were obtained by addition of the dialkylketene to a solution of the enamine. In the cycloaddition of dimethylketene and *N*,*N*-dimethylisobutenylamine, either simultaneous or inverse addition led to large amounts of dimethylketene polymer. This polymer had the poly(enol ester) structure described by Natta[9] and by Hasek.[10]

When highly polar solvents were used, the rate of the cycloaddition reaction was increased, as evidenced by a more exothermic reaction. In addition to the 1:1 adduct, appreciable quantities of 2:1 and 3:1 dialkylketene–enamine adducts were formed. Cycloaddition of equimolar quantities of dimethylketene and *N*,*N*-dimethylisobutenylamine in acetonitrile gave 24% of I, 32% of a 2:1 adduct, and 9% of a 3:1 adduct. The 2:1 adduct was identified as 5-dimethylamino-2,2,4,4,6,6-hexamethyl-1,3-cyclohexanedione (III); the assignment was based on infrared and n.m.r. spectra, and on the reduction of III with lithium aluminum hydride to a glycol. Some 2:1 adducts are listed in Table II; work on the 3:1 adducts is incomplete.



III

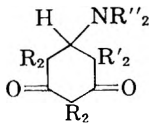
The 3-dialkylamino-2,2,4,4-tetraalkylcyclobutanones were reduced to the corresponding carbinols by metal hydrides and by catalytic hydrogenation. Sodium borohydride served adequately when the ring substituents were methyl groups, but lithium aluminum hydride gave better yields when the cyclobutanone contained larger alkyl groups. The reduction of I by sodium borohydride gave one isomer of 3-dimethylamino-2,2,4,4-tetramethylcyclobutanol (IV), m.p. 70–72°, in 92% yield, but catalytic hydrogenation over a ruthenium catalyst gave a mixture of this isomer and a higher melting one, m.p. 129–130°. The n.m.r. spectrum of the lower melting isomer contained a single peak for the ring methyl groups, whereas the spectrum of the higher melting isomer contained two such peaks. Apparently the magnetic anisotropies of the hydroxy and dimethylamino groups in IV are equivalent, and the chemical shifts of the methyl groups on the cyclo-

(9) (a) G. Natta, G. Mazzanti, G. Pregaglia, M. Binaghi, and M. Peraldo, *J. Am. Chem. Soc.*, **82**, 4743 (1960); (b) G. Natta, G. Mazzanti, G. Pregaglia, and M. Binaghi, *Makromol. Chem.*, **44**, 537 (1961).

(10) R. H. Hasek, R. D. Clark, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **27**, 60 (1962).

TABLE II

DIALKYLAMINOCYCLOHEXANEDIONES

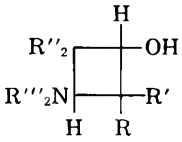


R[a]	R′	R″₂N	B.p., °C. (mm.)	$n^{20}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	CH_3	$(CH_3)_2N$	132–134 (4)	1.4948	70.4	70.7	10.5	10.8	5.8	5.8
CH_3	CH_3		134–136 (1.2)	1.5090	73.2	73.0	10.4	10.4	5.0	4.9
C_2H_5	CH_3	$(CH_3)_2N$	130–133 (0.8)	1.4950	73.2	72.7	11.2	11.0	4.8	4.9

[a] Substituents on original dialkylketene.

TABLE III

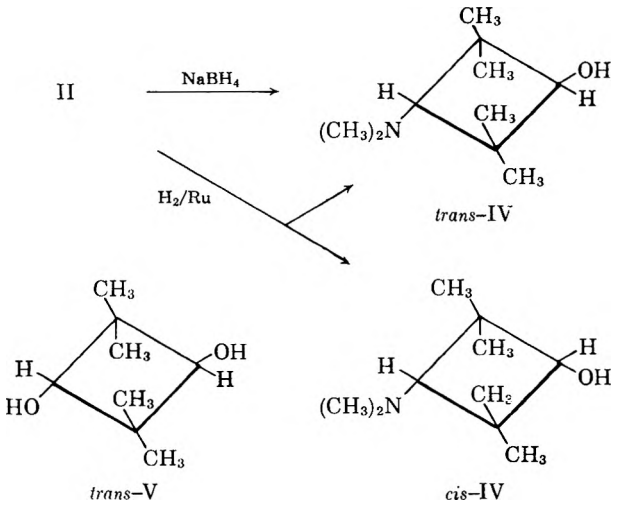
DIALKYLAMINOCYCLOBUTANOLS



R	R′	R″	R‴₂N	Reducing agent[a]	M.p., °C.[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	H	CH_3	$(CH_3)_2N$	A[c]	58–60	67.1	66.8	11.9	12.1	9.8	9.7
H	C_2H_5	H		A[c]	98[d]	72.1	72.2	11.5	11.7	7.7	7.6
H	C_2H_5	CH_3	$(CH_3)_2N$	A[c]	87–89[e]	74.0	74.2	11.8	11.8	6.6	6.8
CH_3	CH_3	CH_3	$(CH_3)_2N$	B, C	70–72[f]	70.3	70.3	12.3	12.5	8.2	8.1
CH_3	CH_3	CH_3	$(CH_3)_2N$	C	129–130[g]	70.3	70.4	12.3	12.7	8.2	8.1
CH_3	CH_3	CH_3		B	92–94	74.0	73.8	11.8	11.6	6.6	6.5
CH_3	CH_3	CH_3		A	100.5–103	67.7	67.7	10.8	10.8	6.6	6.5
C_2H_5	C_2H_5	CH_3	$(CH_3)_2N$	B	74–75	72.4	72.3	12.6	12.6	7.0	6.8
C_2H_5	C_2H_5	C_2H_5	$(CH_3)_2N$	A	75–78	74.0	74.2	12.8	13.0	6.2	6.4
C_2H_5	C_4H_9	CH_3	$(CH_3)_2N$	A	100–101[h]	74.3	73.9	12.4	12.7	6.2	6.1
$-(CH_2)_5-$		CH_3		B	141–142[i]	76.6	76.5	11.5	11.3	5.6	5.2

[a] A = $LiAlH_4$; B = $NaBH_4$; C = catalytic hydrogenation. [b] Recrystallized from hexane. [c] From unstable cycloadduct, which was not isolated. [d] Boiling point (0.8 mm.). [e] Boiling point (0.5 mm.). [f] *trans* Isomer. [g] *cis* Isomer. [h] Boiling point (1.3 mm.). [i] Recrystallized from benzene–hexane mixture.

butane nucleus are the same as those measured for the *cis* and *trans* isomers of 2,2,4,4-tetramethyl-1,3-cyclobutanediol (V).[11] The configurations of the isomers of



IV thus correspond to those of the glycol V; the lower melting isomer is *trans* and the higher melting one is *cis*.

A number of 3-dialkylaminocyclobutanols prepared by hydride reduction are listed in Table III. Many were obtained as crystalline compounds with fairly sharp melting points. Each solid product probably was a single isomer, but data were insufficient for assignment of configuration.

The cycloaddition reaction was extended to ketene and to enamines containing β-hydrogen atoms. The enolizable cyclobutanones obtained from these reactants were unstable and underwent ring opening to form aminovinyl ketones. Ketene and *N*,*N*-dimethylisobutenylamine, for example, reacted readily at 0° and a 93% yield of distilled product was obtained. This 1:1 adduct was not a cyclobutanone but the acyclic compound, 1-dimethylamino-4-methyl-1-penten-3-one (VI). The structure was assigned from infrared and n.m.r. spectra, and confirmed by an alternate synthesis;

(11) R. H. Hasek, E. U. Elam, J. C. Martin, and R. G. Nations, *J. Org. Chem.*, **26**, 700 (1961).

TABLE IV

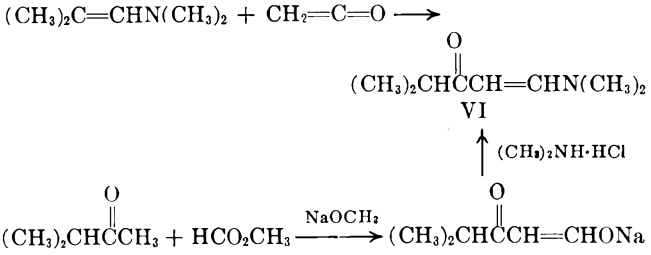
AMINOVINYL KETONES

$R_2NCH{=}CR'CCHR''_2$ (O)

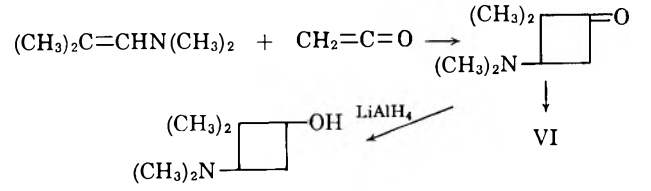
R_2N	R′	R″	B.p., °C. (mm.)	$n^{20}D$	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %[a]— Calcd.	Found
$(CH_3)_2N$	H	CH_3	105–107 (2)	1.5301	68.0	68.0	10.6	10.9	9.9	9.7
	H	CH_3	133 (1.7)	1.5485	72.9	72.9	10.5	10.2	7.7	7.9
	H	CH_3	137 (1.3)	1.5518	65.6	66.1	9.3	9.4	7.7	7.6
$C_6H_5NCH_3$	H	CH_3	121–127 (0.6)	1.6074	76.9	76.7	8.4	8.2	6.8	6.7
$(CNCH_2CH_2)_2N$	H	CH_3	158–159[b]		65.7	65.4	7.8	7.9	19.2	18.9
$(C_6H_5CH_2)_2N$	H	CH_3	100–105 (0.002)[c]		82.0	81.9	7.9	7.9	4.8	4.7
	H	CH_3	253–254[d]		69.0	68.8	9.4	9.3	10.1	10.3
$(CH_3)_2N$	H	C_2H_5	100–103 (0.7)	1.5235	71.0	70.8	11.2	11.4	8.3	8.0
	C_2H_5	CH_3	119–121 (0.6)	1.5424	74.6	74.3	11.0	10.9	6.7	6.6

[a] Spurious values for nitrogen were obtained by the Kjeldahl procedure; recorded values are by Dumas method. [b] Melting point (from ethyl alcohol). [c] Solidified on standing. [d] Bis adduct, melting point (from aqueous ethyl alcohol).

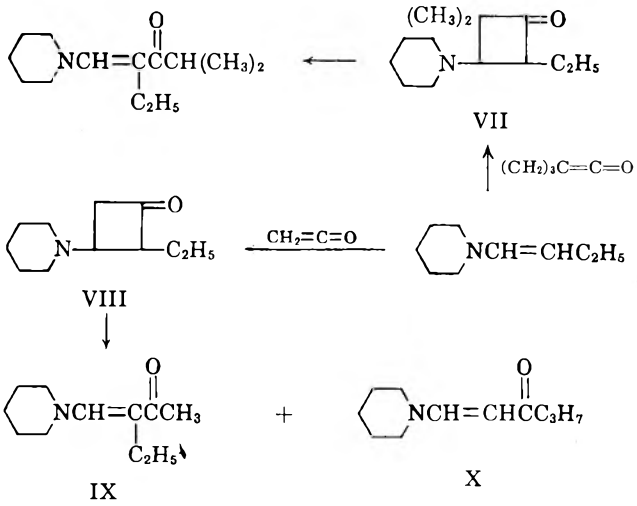
3-methyl-2-butanone and methyl formate were condensed to the sodium salt of 1-hydroxy-4-methyl-1-penten-3-one, which reacted with dimethylamine hydrochloride to give VI.[12]



The structure of VI, with the ketene moiety in the center of the molecule, indicated a cycloaddition mechanism followed by a ring cleavage. Infrared spectra confirmed this view, for the cold reaction product exhibited an absorption at 5.63 μ characteristic of cyclobutanones, which disappeared as the product was warmed.[13] Addition of lithium aluminum hydride to the cold reaction product converted the unstable cycloadduct to 3-dimethylamino-2,2-dimethylcyclobutanol.



All enolizable cyclobutanones prepared by other combinations of ketenes and enamines rearranged during distillation to aminovinyl ketones. The cycloadducts of dialkylketenes with enamines containing a β-hydrogen atom behaved in this manner. Dimethylketene and 1-(1-butenyl)piperidine in hexane solution at −20° gave 2-ethyl-4,4-dimethyl-3-piperidinocyclobutanone (VII), which rearranged during distillation to 2-ethyl-4-methyl-1-piperidino-1-penten-3-one. The cycloaddition and ketene and 1-(1-butenyl)piperidine gave 2-ethyl-3-piperidinocyclobutanone (VIII), which could undergo two modes of rearrangement to give a mixture of 2-ethyl-1-piperidino-1-buten-3-one (IX) and 1-piperidino-1-hexen-3-one (X). This mixture was not resolved by distillation, but the n.m.r. spectrum indicated a 1:2 ratio of IX to X.



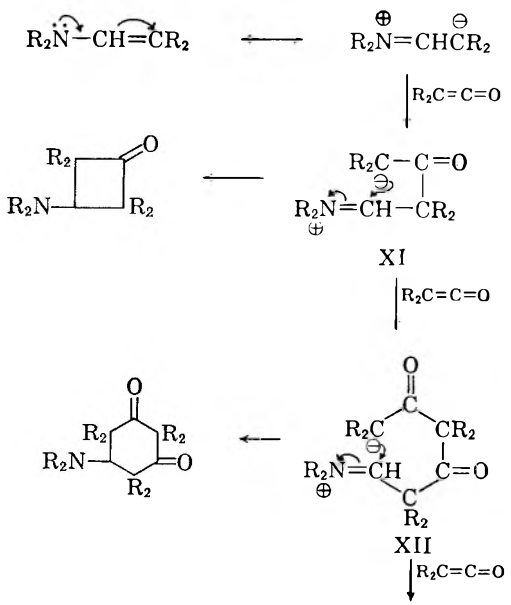
The aminovinyl ketones prepared through the cycloaddition and rearrangement reactions are listed in Table IV. It is noteworthy that *N*-isobutenyl-*N*-methylaniline, which failed to react with dimethylketene, added to ketene. No 2:1 adducts of ketene and enamines were isolated from reactions carried out in polar solvents.

The mechanism of cyclobutanone formation from ketenes and olefins has not been ascertained; structures are compatible with a diradical mechanism or with an ionic process involving nucleophilic attack by the olefin. The ease of cycloaddition of ketenes to the strongly nucleophilic enamines supports the latter ionic mechanism. This is bolstered by the effect of polarity of

(12) E. Benary, *Ber.*, **63**, 1573 (1930).

(13) Other workers isolated some unstable ketene–enamine adducts and noted their rearrangement to the aminovinyl ketones.[6,7]

the solvent on the rate of reaction, and by the formation of by-products ranging from 2:1 adducts to ketene polymers. Stabilization of the charge separation in the ionic intermediates (XI and XII) might be expected to facilitate further addition of the ketene and the subsequent formation of the higher adducts.



Experimental

The enamines used in these experiments were prepared from aldehydes and secondary amines.[14-16] Two enamines not previously reported were prepared: 1-methyl-4-isobutenylpiperazine, b.p. 38–40° (1 mm.), $n^{20}D$ 1.4718, and *N,N*-dibenzylisobutenylamine, b.p. 110–114° (0.8 mm.), $n^{20}D$ 1.5591. Ketene was obtained from an industrial production unit, and dialkylketenes were prepared by pyrolysis of corresponding anhydrides.[17]

3-Dimethylamino-2,2,4,4-tetramethylcyclobutanone (I).—Over a period of 15 min., 70 g. (1.0 mole) of dimethylketene was added to a stirred solution of 99 g. (1.0 mole) of *N,N*-dimethylisobutenylamine in 400 ml. of isopropyl acetate under a nitrogen atmosphere. The reaction temperature slowly rose to 45°, but was then held at 25–30° by a water bath. The reaction solution was stirred for 6 hr. and then distilled through a 12-in. packed column to give some unchanged enamine, tetramethyl-1,3-cyclobutanedione, and 108 g. (64%) of 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone, b.p. 83–85° (24 mm.), $n^{20}D$ 1.4439.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 71.1; H, 11.2; N, 8.2. Found: C, 71.3; H, 11.2; N, 8.1. Infrared maxima (smear[18]: 3.6 [$N(CH_3)_2$], 5.62 μ (cyclobutanone). N.m.r. spectrum (neat)[19]: −87 [$N(CH_3)_2$ and CH], −51 and −44 c.p.s. (CH_3 groups).

Quaternization and Hydrolysis of I.—A solution of 84 g. (0.5 mole) of 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone and 93 g. (0.5 mole) of methyl tosylate was heated overnight on a steam bath. When a solution of 56 g. (1.0 mole) of potassium hydroxide in 200 ml. of water was added to the solid product at room temperature, the mixture became quite hot and trimethylamine evolved. The solution was heated on a steam bath for 6 hr., then cooled, and extracted with ether. The aqueous layer was acidified by the slow addition of concentrated hydrochloric acid. The organic layer which separated was taken up in ether, washed with water, and dried over anhydrous magnesium sulfate. Distillation through a 10-in. packed column gave 43.2 g. (71%) of 2,2,4-trimethyl-3-pentenoic acid (II), b.p. 86° (2 mm.), $n^{20}D$ 1.4472.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.6; H, 9.9; neut. equiv., 142. Found: C, 67.6; H, 10.1; neut. equiv., 142. Infrared maxima (smear): 3.87, 3.9 (OH), 5.87 (COOH), 10.6 (OH deformation), 12.22 μ (C=CH). N.m.r. (neat): −490 (COOH), −208 (C=CH), −64 and −67 [$(CH_3)_2C$=CH], −52 c.p.s. [$C(CH_3)_2$]. With a warm sample and higher resolution, the peak at −208 c.p.s. was resolved into seven peaks and the doublet at −64 and −67 c.p.s. into two sets of doublets with the same coupling constant. This pattern, from spin–spin interaction of the methyl groups and the olefinic proton, is characteristic of the grouping $(CH_3)_2C$=CH—.

***trans*-3-Dimethylamino-2,2,4,4-tetramethylcyclobutanol (IV).**—A solution of 3.8 g. (0.1 mole) of sodium borohydride in 25 ml. of water was added slowly to a stirred solution of 50 g. (0.3 mole) of 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone (I) in 75 ml. of ethyl alcohol. The temperature of the exothermic reaction was kept at 25–30° by a water bath. The mixture was stirred for 1 hr. after addition was complete, then heated in an evaporating dish on the steam bath until most of the ethyl alcohol was removed. The residue was extracted with 300 ml. of ether, and the ether layer was separated, washed with water, and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 46.8 g. (92%) of *trans*-3-dimethylamino-2,2,4,4-tetramethylcyclobutanol (IV), m.p. 69–72°. An analytical sample was prepared by dissolving some IV in warm hexane and chilling the solution in Dry Ice. Rapid filtration of the solid gave a sample, m.p. 70–72°.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.2; H, 12.3; N, 8.2; neut. equiv., 171. Found: C, 70.3; H, 12.5; N, 8.1; neut. equiv., 171.8. Infrared maxima (KBr pellet): 3.12 (OH), 3.53, 3.59 μ [$N(CH_3)_2$]. N.m.r. spectrum (saturated chloroform solution): −155 (OH), −130 (O—CH), −84 [$N(CH_3)_2$], −63 (N—CH), −41 c.p.s. (CH_3 groups).

The *N*-phenylurethane was prepared from IV and phenyl isocyanate, with *N,N,N',N'*-tetramethyl-1,3-butanediamine used as a catalyst. The derivative, recrystallized twice from hexane, melted at 134.5–135.5°.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.4; H, 9.0; N, 9.7. Found: C, 70.4; H, 9.0; N, 9.7.

***cis*-3-Dimethylamino-2,2,4,4-tetramethylcyclobutanol (IV).**—A solution of 100 g. of 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone in 500 ml. of isooctane was hydrogenated in a stainless steel rocking autoclave over 30 g. of 5% ruthenium on powdered carbon at 100° and 3000 p.s.i. for 4 hr. The catalyst was removed by filtration and washed with 300 ml. of methanol. Analysis of the combined filtrates by vapor phase chromatography showed no starting material was present. The filtrate was distilled through a 6-in. Vigreux column to a base temperature of 150°. The residue solidified on cooling and was recrystallized from hexane to give 32.0 g. of crude *cis*-IV, m.p. 124.5–128.5°. Another recrystallization from hexane raised the melting point to 129–130°.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.2; H, 12.3; N, 8.2. Found: C, 70.4; H, 12.7; N, 8.1. Infrared maxima (KBr pellet): 3.15 (OH), 3.55 and 3.62 μ [$N(CH_3)_2$]. N.m.r. spectrum (20% solution in chloroform): −41 and −49 (CH_3), −78 (N—CH), −83 [$N(CH_3)_2$], −113 (OH), −134 c.p.s. (O—CH). The picrate, recrystallized from ethyl alcohol, melted at 238–239°.

Anal. Calcd. for $C_{16}H_{24}N_4O_3$: C, 48.0; H, 6.0; N, 14.0. Found: C, 48.0; H, 6.1; N, 13.6.

Evaporation of the filtrate yielded 53.7 g. of solid material consisting mostly of *trans*-IV.

5-Dimethylamino-2,2,4,4,6,6-hexamethyl-1,3-cyclohexanedione (III).—Over a period of 30 min., 210 g. (3.0 moles) of dimethylketene was added to a stirred solution of 297 g. (3.0 moles) of *N,N*-dimethylisobutenylamine in 700 ml. of acetonitrile. The temperature of the exothermic reaction was kept at 30–40° by an ice bath. Stirring was continued for several hours at room temperature, and the solvent then was evaporated on a steam bath. The residue (374.3 g.) was taken up in dilute hydrochloric acid and extracted with ether. The aqueous residue was made alkaline with sodium hydroxide, and the organic layer which separated was taken up in ether and dried over an-

(14) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

(15) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(16) G. Opitz, H. Hellman, and H. W. Schubert, *Ann.*, **623**, 112 (1959).

(17) R. H. Hasek and E. U. Elam (to Eastman Kodak Co.), Canadian Patent 618,772 (1961).

(18) Infrared spectra were determined on a Baird AB2 instrument. Significant maxima are reported in microns (μ).

(19) N.m.r. spectra were obtained with a Varian V4300B spectrometer at 40 Mc. Unless otherwise noted, spectra are quoted in cycles per second (c.p.s.) relative to tetramethylsilane as an internal standard.

hydrous magnesium sulfate. Distillation through a 12-in. packed column gave 123 g. of 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone (I) and 115.1 g. (32%) of 5-dimethylamino-2,2,4,4,6,6-hexamethyl-1,3-cyclohexanedione (III), b.p. 132–134° (4 mm.), $n^{20}D$ 1.4948.

Anal. Calcd. for $C_{14}H_{25}NO_2$ (III): mol. wt., 239. Found: mol. wt., (ebullioscopic in benzene), 244. Infrared maxima (smear): 3.61 [$N(CH_3)_2$], 5.75 μ (C=O). N.m.r. spectrum (50% solution in benzene): −98 [$N(CH_3)_2$], −94 (N—CH), −68 [—$COC(CH_3)_2CO$—], −52 and −47 c.p.s. (CH_3 groups). With dilution of the sample, the peak at −68 c.p.s. separated into a doublet.

The black residue from the distillation was extracted with 200 ml. of hot acetone. Evaporation of the acetone left 27.5 g. of solid residue, which was recrystallized from ethyl alcohol and then from toluene to give 19.4 g., m.p. 168–169°. Elemental analysis and molecular weight determination indicated that this compound was an adduct of three molecules of dimethylketene and one molecule of *N,N*-dimethylisobutenylamine.

Anal. Calcd. for $C_{18}H_{31}NO_3$: C, 69.9; H, 10.1; N, 4.6; mol. wt., 309. Found: C, 70.1; H, 10.5; N, 4.6; mol. wt. (ebullioscopic in benzene), 318. Infrared maxima (mineral oil mull): 3.5, 3.6 [$N(CH_3)_2$], 5.74 μ (C=O).

2,2,4,4,6,6-Hexamethyl-5-piperidino-1,3-cyclohexanedione.—Dimethylketene (280 g., 4.0 moles) was added to a stirred solution of 280 g. (2.0 moles) of *N*-isobutenylpiperidine in 500 ml. of dimethylformamide. The exothermic reaction was kept at 40–50° by an ice bath. The reaction mixture was stirred for 6 hr. and then distilled through a 10-in. packed column to give 104.3 g. (25%) of 2,2,4,4-tetramethyl-3-piperidinocyclobutanone and 180.4 g. (31%) of 2,2,4,4,6,6-hexamethyl-5-piperidino-1,3-cyclohexanedione, b.p. 134–136° (1.2 mm.), $n^{20}D$ 1.5090.

Anal. Calcd. for $C_{17}H_{29}NO_2$: mol. wt., 279. Found: mol. wt. (ebullioscopic in benzene), 280. Infrared maxima (smear): 3.55, 3.62 ($C_5H_{10}N$), 5.76 μ (C=O).

A solid product which precipitated in the still during the above distillation was removed by filtration and recrystallized from toluene to give 51.3 g. of a 3:1 adduct, m.p. 216.5–217.5°.

Anal. Calcd. for $C_{21}H_{35}NO_3$: C, 72.2; H, 10.0; mol. wt., 349. Found: C, 72.0; H, 10.2; mol. wt. (ebullioscopic in benzene), 345. Infrared maxima (mineral oil mull): 3.55 ($C_5H_{10}N$), 5.78 μ (C=O).

2,2,4,4,6,6-Hexamethyl-5-piperidino-1,3-cyclohexanediol.—A solution of 50 g. (0.185 mole) of 2,2,4,4,6,6-hexamethyl-5-piperidino-1,3-cyclohexanedione in 100 ml. of tetrahydrofuran was added slowly to a stirred solution of 11.4 g. (0.3 mole) of lithium aluminum hydride in 200 ml. of tetrahydrofuran at 10–20°. The solution was refluxed for 1 hr., cooled, and 12 ml. of water, 9 ml. of 20% sodium hydroxide solution, and 38 ml. of water were added successively. The mixture was filtered and the solid was washed with several portions of tetrahydrofuran. Evaporation of the filtrate left 49.4 g. (97%) of crude product, m.p. 208–211°. Recrystallization from toluene gave 36.3 g. (72%) of 2,2,4,4,6,6-hexamethyl-5-piperidino-1,3-cyclohexanediol, m.p. 212–213°.

Anal. Calcd. for $C_{17}H_{33}NO_2$: C, 72.1; H, 11.7; N, 5.0. Found: C, 71.9; H, 11.5; N, 4.9. Infrared maxima (mineral oil mull): 2.98 (OH), 3.65 μ [$N(CH_3)_2$].

5-Dimethylamino-2,2,4,4,6,6-hexamethyl-1,3-cyclohexanediol.—By the same procedure, 5-dimethylamino-2,2,4,4,6,6-hexamethyl-1,3-cyclohexanedione (III) was reduced with lithium aluminum hydride to the corresponding glycol, m.p. 208–210°.

Anal. Calcd. for $C_{14}H_{29}NO_2$: C, 69.2; H, 11.9; N, 5.8. Found: C, 68.8; H, 12.0; N, 5.6. Infrared maxima (mineral oil mull): 3.01 (OH), 3.6 μ [$N(CH_3)_2$].

2-Butyl-3-dimethylamino-2-ethyl-4,4-dimethylcyclobutanol.—A solution of 70 g. (0.31 mole) of 2-butyl-3-dimethylamino-2-ethyl-4,4-dimethylcyclobutanone in 100 ml. of ether was added slowly to a stirred suspension of 8.8 g. (0.23 mole) of lithium aluminum hydride in 200 ml. of ether. The temperature was maintained at 10–15° by an ice bath. After the addition was complete, the mixture was stirred for 1 hr. at room temperature. A small amount of ethyl acetate was added to destroy the excess lithium aluminum hydride, followed by slow addition of 9 ml. of water, 7 ml. of 20% sodium hydroxide solution, and 27 ml. of water. An ice bath was used for cooling during these additions. The white solid that formed was removed by filtration and washed with several portions of ether. The combined ether layers were dried over anhydrous magnesium sulfate and distilled through a 12-in. packed column to give 59 g. (84%) of 2-butyl-3-dimethylamino-2-ethyl-4,4-dimethylcyclobutanol, b.p. 99–102° (1.3 mm.), $n^{20}D$ 1.4804. Infrared maxima (smear): 3.12 (OH), 3.55, 3.61 μ [$N(CH_3)_2$].

1-Dimethylamino-4-methyl-1-penten-3-one (VI).—Gaseous ketene was passed into a rapidly stirred solution of 316 g. (3.2 moles) of *N,N*-dimethylisobutenylamine in 300 ml. of ethyl ether to a weight increase of 147 g. (3.5 moles). The exothermic reaction was kept at 20–30° by intermittent use of an ice bath. The reaction solution was stirred at room temperature for an additional hour and distilled through a 12-in. packed column to give 409.6 g. (93%) of 1-dimethylamino-4-methyl-1-penten-3-one, b.p. 105–107° (2 mm.), $n^{20}D$ 1.5301.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.0; H, 10.6; N, 9.9. Found: C, 68.0; H, 10.9; N, 9.7. Infrared maxima: 6.05, 6.25, 6.38 μ (N—C=C—C=O).

1-Dimethylamino-2,2-dimethylcyclobutanol.—Ketene was passed into a rapidly stirred solution of 99 g. (1 mole) of *N,N*-dimethylisobutenylamine in 400 ml. of ethyl ether at −15 to −20° to a weight increase of 42 g. (1 mole). The cold reaction mixture was stirred for 1 hr. and then was added slowly to a stirred suspension of 28.4 g. (0.75 mole) of lithium aluminum hydride in 500 ml. of ethyl ether at 15–25°. Stirring was continued for 2 hr. after the addition. Excess lithium aluminum hydride was destroyed by the addition of ethyl acetate, followed by successive additions of 28 ml. of water, 21 ml. of 20% sodium hydroxide solution, and 115 ml. of water. The white solid was removed by filtration and washed several times with ether. Distillation of the combined filtrates through an 8-in. Vigreux column gave 118.2 g. (83%) of 1-dimethylamino-2,2-dimethylcyclobutanol, b.p. 88–91° (7 mm.), which solidified on cooling. An analytical sample recrystallized from hexane melted at 58–60°. Infrared maxima: 3.0 (OH), 3.56 and 3.62 μ [$N(CH_3)_2$].

1,1′-(1,4-Piperazinediyl)bis[4-methyl-1-penten-3-one].—A solution of 194 g. (1.0 mole) of 1,4-diisobutenylpiperazine in 400 ml. of ethyl ether was cooled in an ice bath and stirred rapidly as ketene was added to a weight increase of 84 g. (2.0 moles). A large amount of solid precipitated. The entire reaction mixture was evaporated on a steam bath to 256 g. of solid residue, which was recrystallized from aqueous ethyl alcohol to give 201.7 g. (73%) of 1,1′-(1,4-piperazinediyl)bis[4-methyl-1-penten-3-one], m.p. 253–254°.

2-Ethyl-4-methyl-1-piperidino-1-penten-3-one (XI).—Seventy grams (1.0 mole) of dimethylketene was added to a stirred solution of 139 g. (1.0 mole) of 1-(1-butenyl)piperidine in 400 ml. of ether under a nitrogen atmosphere over 15 min. The reaction mixture was stirred for 30 min. after the addition and then distilled through a 10-in. packed column to give 172 g. (82%) of 2-ethyl-4-methyl-1-piperidino-1-penten-3-one (XI), b.p. 119–121° (0.6 mm.), $n^{20}D$ 1.5424.

2-Ethyl-4,4-dimethyl-3-piperidinocyclobutanone (VII) and 2-Ethyl-4,4-dimethyl-3-piperidinocyclobutanol.—Thirty-five grams (0.5 mole) of dimethylketene was added to a stirred solution of 69.5 g. (0.5 mole) of 1-(1-butenyl)piperidine in 200 ml. of ether at −20° to 0°. An infrared spectrum, taken an hour after addition was complete, showed a strong absorption at 5.65 μ, indicative of the cycloadduct, 2-ethyl-4,4-dimethyl-3-piperidinocyclobutanone. The cold solution was added slowly to a stirred suspension of 14.2 g. (0.375 mole) of lithium aluminum hydride in 250 ml. of ether at 10–20°. After addition was complete, stirring was continued for 1 hr. at room temperature; 14 ml. of water was added carefully, with cooling, followed by 10 ml. of 20% sodium hydroxide solution and 50 ml. of water. The solid that formed was removed by filtration and washed with several portions of ether. The combined filtrates were distilled through a 10-in. packed column to give 71.2 g. (68%) of 2-ethyl-4,4-dimethyl-3-piperidinocyclobutanol, b.p. 87–89° (0.5 mm.), $n^{20}D$ 1.4870.

2-Ethyl-3-piperidinocyclobutanone (VIII) and 2-Ethyl-3-piperidinocyclobutanol.—Ketene was passed into a stirred solution of 69.5 g. (0.5 mole) of 1-(1-butenyl)piperidine in 200 ml. of ether at −20° to a weight increase of 25.5 g. (0.6 mole). The reaction solution was stirred at −20° for 1 hr. after the addition. An infrared spectrum of the solution showed an absorption at 5.65 μ, characteristic of a cyclobutanone (VIII). The cold solution was added slowly to a stirred suspension of 14.2 g. (0.375 mole) of lithium aluminum hydride in 250 ml. of ether at 15–25°. After addition was complete, stirring was continued for 1 hr. at room temperature, and 14 ml. of water was added carefully, with cooling, followed by 10 ml. of 20% sodium hydroxide solution and 49 ml. of water. The solid that formed was removed by

filtration and washed with several portions of ether. The combined filtrates were distilled through a 10-in. packed column to give 65.1 g. (71%) of 2-ethyl-3-piperidinocyclobutanol, b.p. 98° (0.8 mm.), $n^{20}D$ 1.4930.

The rearrangement of VIII to a mixture of 2-ethyl-1-piperidino-1-buten-3-one and 1-piperidino-1-hexen-3-one was followed by infrared spectra. A small sample of the ether solution of VIII described previously was allowed to stand for a few days at room temperature. Periodic examination by infrared spectroscopy showed a gradual disappearance of the band at 5.65 μ and a corresponding appearance of bands at 6.05, 6.25, and 6.38 μ.

2-Ethyl-1-piperidino-1-buten-3-one (IX) and 1-Piperidino-1-hexen-3-one (X).—Ketene was added to a stirred solution of 139 g. (1 mole) of 1-(1-butenyl)piperidine in 400 ml. of benzene to a weight increase of 42 g. (1 mole). Frequent cooling was required to maintain the reaction temperature at 10 to 25°. The solution was stirred for 1 hr. after the addition, and then distilled through a 10-in. packed column to give 109.2 g. (60%) of a mixture of IX and X, b.p. 137° (0.3 mm.), $n^{22}D$ 1.5544.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.9; H, 10.5; N, 7.8. Found: C, 72.7; H, 10.5; N, 7.7. N.m.r. spectrum (50% solution in CCl_4): IX, singlet at −301 (C=CH—N), broad peaks at −150 and −85 ($C_5H_{10}N$), −100 (CH_3C=O), −108 (CH_2), −60 c.p.s. (CH_3); X, doublets centered at −308 and −216 (CH=CH—N), broad peaks at −150 and −85 ($C_5H_{10}N$), −108 (CH_2C=O), −85 (CH_2), −60 c.p.s. (CH_3). Relative areas of peaks corresponding to C=CH—N protons indicated the ratio of IX to X was approximately 1:2.

Acknowledgment.—We wish to thank Mr. P. G. Gott for the preparation of some compounds involved in this work, Mr. A. L. Thompson for interpretation of infrared spectra, Dr. Wilson Goodlett for interpretation of n.m.r. spectra, and Dr. K. C. Brannock for many helpful discussions.

An Unusual Fragmentation–Rearrangement under Acyloin Reaction Conditions[1,2c]

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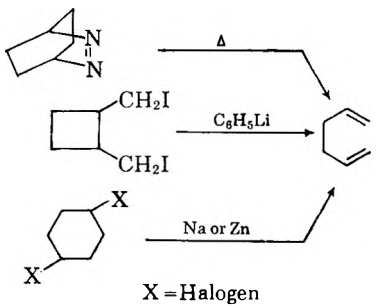
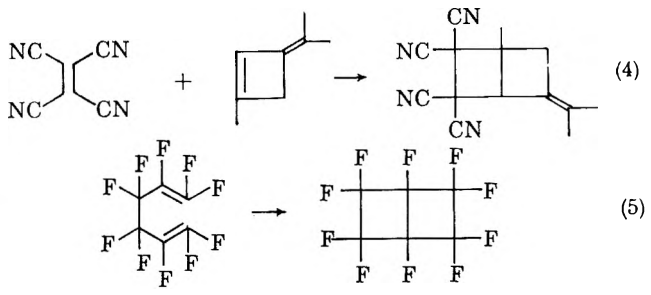
Attempted acyloin ring closure on *cis*-1,2-dicarbethoxycyclobutane leads, by an apparent fragmentation reaction, to 2-carbethoxycyclopentanone.

The bicyclo[2.2.0]hexane skeleton has eluded most attempts toward its synthesis.[3] The result of many previous investigations has been a fragmentation reaction[3c] as the following examples indicate.



(1)[3a] (2)[3b] (3)[3c]

Only unusual reagents or combinations of reagents, *e.g.*, tetracyanoethylene and 1-methyl-3-isopropylidenecyclobutene,[4] the isomerization of perfluoro-1,5-hexadiene,[5] or photochemical reactions[6] have been successful in producing the bicyclo[2.2.0]hexane system. In fact, the first example of "Dewar benzene," a bicyclo[2.2.0]hexadiene, has been produced by a photochemical reaction.[7]



(4) (5)

Cope and Herrick,[8] in their synthesis of bicyclo[4.2.0]octane-7-ol-8-one from 1,2-dicarbethoxycyclohexane, demonstrated that the acyloin reaction can produce a four-membered ring. Because the generally accepted mechanism for the acyloin reaction involves the dimerization of intermediate radical ions[9] and because the fragmentation reactions known to us when this work was started involved purely ionic intermediates[3c,10] it was felt that bicyclo[2.2.0]hexane-2-ol-3-one might be prepared simply from 1,2-dicarbethoxycyclobutane following the example of Cope and Herrick.

When this reaction was conducted in liquid ammonia,[11] the major product (40%) was 2-carbethoxycyclopentanone, identical in all respects with an authen-

(1) This paper was presented before the Division of Organic Chemistry at the 143rd National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2)(a) To whom inquiries concerning this communication should be addressed; (b) Participant in the National Science Foundation supported Research Participation for College Teachers program in the Summer of 1962. (c) NOTE ADDED IN PROOF.—After this paper was accepted, we learned, by personal communication, that the observations reported here had been made independently (*and prior to our work*) by Dr. H. Ogura and Dr. J. Meinwald at Cornell University. Dr. P. G. Gassman at Ohio State University has also independently observed this rearrangement.

(3) (a) S. G. Cohen and R. Zand, *J. Am. Chem. Soc.*, **84**, 586 (1962); (b) R. Criegee and K. Matterstock, unpublished results quoted by E. Vogel, *Angew. Chem.*, **72**, 4 (1960); (c) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).

(4) J. K. Williams, *J. Am. Chem. Soc.*, **81**, 4013 (1959).

(5) A. H. Fainberg and W. T. Miller, *ibid.*, **79**, 4170 (1957).

(6) (a) S. Cremer and R. Srinivasan, *Tetrahedron Letters*, No. **21**, 24 (1960); (b) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **81**, 4060 (1959).

(7) E. E. van Tamelen and S. P. Pappas, *ibid.*, **84**, 3789 (1962).

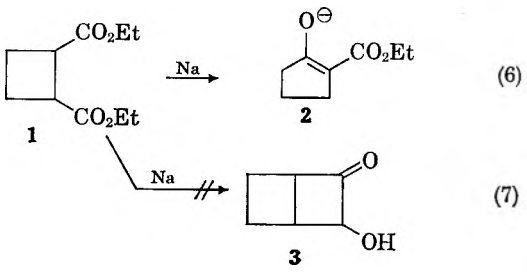
(8) A. C. Cope and E. C. Herrick, *ibid.*, **72**, 983 (1950).

(9) S. M. McElvain, "Organic Reactions," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 256.

(10) C. A. Grob, *Experentia*, **13/3**, 126 (1957).

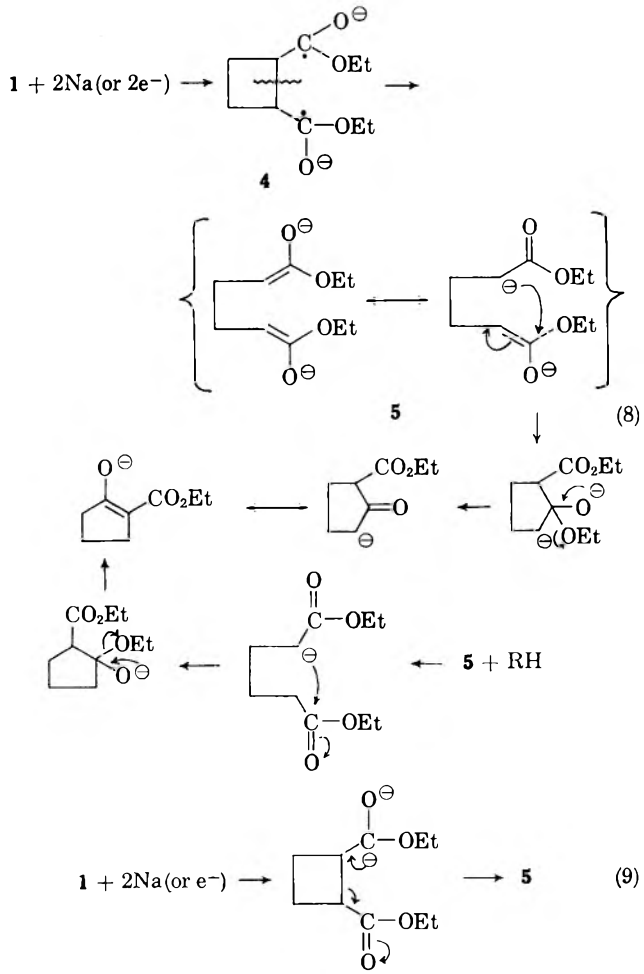
(11) *Cf.*, J. C. Sheehan, R. A. Coderre, and P. A. Cruickshank, *J. Am. Chem. Soc.*, **75**, 6231 (1953).

tic sample.[12] When toluene was the solvent, the yield of keto ester was only 9–20%. In both solvents, particularly toluene, other, unidentified, substances were produced in varying amounts. There was no evidence for acyloin products.[2c]

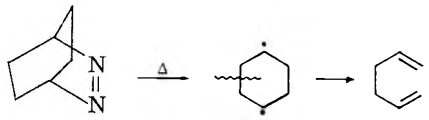


Sheehan has shown that sodium dispersion in toluene will produce adipoin from adipic ester.[13] We find that under the liquid ammonia conditions adipoin also is produced, but in lower yield than in the toluene reaction.

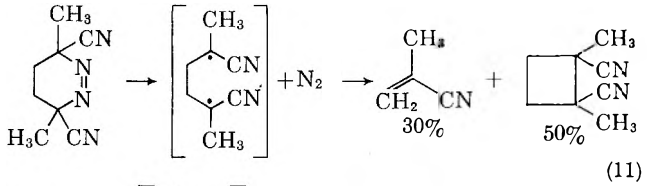
Two general mechanisms seem possible. In the first, a diradical intermediate, **4**, homolyzes to produce the fragmentation product, a bisenolate, **5**, of diethyl adipate. The enolate may react directly to produce an anion of 2-carbethoxycyclopentanone or it may abstract a proton from either the solvent or an unreacted molecule of ester to produce the monoenolate of adipic ester which subsequently undergoes the Dieckmann reaction in the usual way. The second mechanism involves the rearrangement of a 1,2-dianion to give **5**.

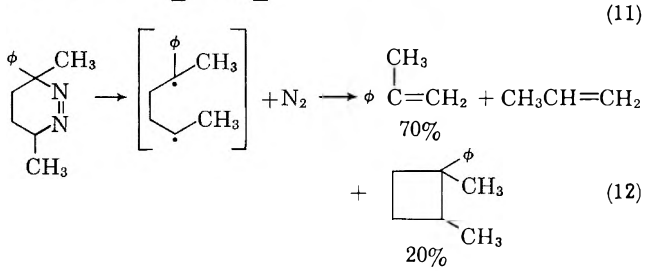


It does not seem possible at this time to choose between these alternatives. The dianion mechanism has been proposed in the past,[14] in modified form, to explain the results obtained in acyloin reactions. Recent work of Hauser[15] shows the plausibility of the 1,2-dianion. On the other hand, the formation of 1,5-hexadiene from 2,3-diazabicyclo[2.2.0]oct-2-ene[3a] follows a free radical path.[16]



Fragmentations have been observed in other decompositions of azo compounds.[17]





Experimental

cis-**1,2-Dicarbethoxycyclobutane.**—This starting ester was prepared by Fischer esterification of *cis*-1,2-cyclobutane dicarboxylic acid anhydride.[18]

Acyloin Reactions in Liquid Ammonia.[11]—The reactions were carried out under dry, oxygen-free nitrogen in a three-neck flask fitted with a dropping funnel, Dry Ice condenser, and a Trubore stirrer and insulated by a heating mantle. In a typical reaction, sodium, 4.65 g. (0.20 g.-atom), was added to 1.0 l. of liquid ammonia and 100 ml. of anhydrous ether. Ten grams (0.05 mole) of the diester in 400 ml. of anhydrous ether was added over 5 hr. Anhydrous ether, 200 ml., was added and the ammonia and ether evaporated under a stream of nitrogen over 24 hr. To the reaction mixture, which was a light creamy paste, was added a further 200 ml. of ether and this also was evaporated. The procedure was repeated (two to three times) until the exit gas was no longer basic to wet litmus. This left a yellow paste which was worked up by adding 250 ml. of ether and then (rapidly) excess dilute 3–5% hydrochloric acid solution while the flask and contents were cooled in an ice bath. The ether layer was separated, dried over anhydrous magnesium sulfate, evaporated, and the residue was distilled at 3.0 mm., b.p. 81–84°. The yield of 2-carbethoxycyclopentanone was 40–42%, $n^{25}D$ 1.4484–1.4488; semicarbazone, m.p. 141–144°. The infrared spectrum was

(12) P. S. Pinkney, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 116.

(13) J. C. Sheehan, R. C. O'Neill, and M. A. White, *J. Am. Chem. Soc.*, **72**, 3376 (1950).

(14) (a) H. Scheibler and F. Emden, *Ann.*, **434**, 265 (1923); (b) F. F. Blicke, *J. Am. Chem. Soc.*, **47**, 229 (1925).

(15) (a) C. R. Hauser, T. M. Harris, and T. G. Ledford, *ibid.*, **81**, 4099 (1959); (b) W. G. Kofron, W. R. Dunnavant, and C. R. Hauser, *J. Org. Chem.*, **27**, 2737 (1962).

(16) It may be, however, that the bicyclo-(2.2.0)-hexane *was* formed from the diradical, **7**, but, that at the high temperature of pyrolysis, it rearranged.[6a]

(17) (a) C. G. Overberger, G. Kesslin, and N. R. Byrd, *J. Org. Chem.*, **27**, 1568 (1962); (b) C. G. Overberger and G. Kesslin *ibid.*, **27**, 3898 (1962).

(18) E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schlatter, *J. Am. Chem. Soc.*, **64**, 2696 (1942).

identical with an authentic sample prepared in 65% yield according to the method of Pinkney,[12] $n^{25}D$ 1.4491, b.p. 75–84° at 2.9 mm.; semicarbazone, m.p. 141–144°; m.m.p. with "acyloin" product, 141–144°.

In one reaction starting with 29.25 g. of diester there was obtained 10.2 g. (41%) of keto ester, 1.22 g. of a liquid, b.p. 86–95° at 0.01–0.02 mm., $n^{25}D$ 1.4557, and 1.1 g. of a yellow liquid, b.p. 120–133° at 0.01 mm., $n^{25}D$ 1.4681. Both of these liquids had infrared spectra indicative of ketones, but no further attempts have been made to characterize them.

Acyloin Reaction in Toluene.—Into a 2-l., three-neck flask, fitted with a Hershberg dropping funnel, Trubore stirrer, and condenser was distilled 650 ml. of toluene (from calcium hydride), under dry, oxygen-free nitrogen. The toluene was brought to a boil and sodium, 5.95 g. (0.259 g.-atom), was added. With vigorous stirring (not high speed) the diester, 12.80 g. (0.064 mole) in 210 ml. of dry toluene, was added over 1.5 hr. The solution turned yellow within 10 min. The reaction mixture was cooled to 0° and then 14.7 ml. of glacial acetic acid was added. The presence of unchanged sodium was noted, and it was destroyed by stirring, under nitrogen, with 30 ml. of dry ethanol. The reaction mixture was quite red at this point. The solvent was evaporated under reduced pressure and the residue was filtered. The organic layer was washed repeatedly with 5% sodium bicarbonate solution, then with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and distilled to give 2.05 g. (20.5%) of 2-carbethoxycyclopentanone, $n^{25}D$ 1.4484, b.p. 60–66° at 0.9 mm. In a similar, subsequent run the yield was only 8.7%.

Adipoin.—Under the conditions for acyloin reactions in liquid ammonia described previously, there was obtained 0.60 g. (8.3%) of adipoin, b.p. 71–72.5° at 7.0 mm., $n^{25}D$ 1.4658, from 12.8 g. of diethyl adipate. The adipoin readily solidified. No keto ester was obtained.

Elimination Reactions of α-Halogenated Ketones. XI.[1a] Kinetic and Product Studies of Amine-Promoted Elimination from 2-Bromo-2-benzyl-4,4-dimethyl-1-tetralone in Benzene

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Received July 16, 1962

Dehydrobromination of 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone (I) by piperidine or morpholine in dilute benzene solution at elevated temperatures has been found to give largely 2-benzal-4,4-dimethyl-1-tetralone (II) accompanied by lesser amounts of 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (III). The kinetics suggest that a substitution reaction initially accompanies elimination but the intermediate formed in the substitution subsequently undergoes an elimination reaction to yield the α,β-unsaturated ketones.

Amine-promoted elimination from 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone (I) in the absence of solvent or in a variety of solvents[2] previously has been shown to yield a mixture of two α,β-unsaturated ketones: 2-benzal-4,4-dimethyl-1-tetralone (II) by exocylic elimination and 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (III) by endocyclic elimination. This first investigation[2] and also subsequent investigations[3–6] involving various elimination promoting reagents all led to largely or completely endocyclic elimination.

In this investigation it has been found that elimination as promoted by piperidine or preferably by morpholine in dilute benzene solution at elevated temperatures leads to high yields of the exocyclic isomer II.

During the initial stages of reaction in both the piperidine- and the morpholine-promoted elimination, the second-order rate coeffficients for amine neutralization were about 50% greater in value than the second-order rate coefficients for bromide ion production. It follows that during the initial stages of reaction, amine is being consumed faster than the rate at which bromide ions are being produced. It is known that the two amines are stable in benzene[7] and further during amine-promoted elimination from 4-biphenylyl 1-bromocyclohexyl ketone in benzene, the values for the two sets of second-order rate coefficients were identical in value.[7]

It follows that the nonidentity of values results from interaction of the amine with either the reactant bromotetralone I, other than to produce the α,β-unsaturated ketones, or alternatively the α,β-unsaturated ketones are first formed and then a relatively rapid addition of amine occurs with establishment of an equilibrium between the α,β-unsaturated ketones and the 1:4 addition product; elimination–addition reactions of this nature previously have been observed.[8] An explanation in terms of 1:4 addition is, however, invalidated by the absence of any addition product when the reaction is completed; also the extent of subsequent addition would be dependent upon the concentration of amine and would not be consistently about 50% of the extent of bromide production. At 100% bromide ion formation it is found that only an equivalent quantity of amine has been consumed; for example, a solution 0.0200 *M* in bromotetralone I and 0.0400 *M* in piperidine had reacted to 98% after 138 hr. at 90.6° and remaining was 44% of the initial piperidine concentration.

Since the additional consumption of amine cannot be explained in terms of elimination–addition it follows that substitution must initially accompany the elimination. If these substitution products are in themselves unstable then over longer periods of time, they subsequently can undergo elimination reaction to yield the isolated α,β-unsaturated ketones. Both elimination and substitution lead to the formation of one molecule of amine hydrobromide but in the substitution reaction

(1) (a) For paper X in this series see D. N. Kevill, G. A. Coppens, and N. H. Cromwell, *J. Org. Chem.*, **28**, 567 (1963); (b) to whom communications concerning this article should be addressed.

(2) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 901 (1958).

(3) N. H. Cromwell, R. P. Ayer, and P. W. Foster, *ibid.*, **82**, 130 (1960).

(4) D. N. Kevill and N. H. Cromwell, *ibid.*, **83**, 3812 (1961).

(5) D. N. Kevill and N. H. Cromwell, *ibid.*, **83**, 3815 (1961).

(6) G. Coppens, D. N. Kevill, and N. H. Cromwell, *J. Org. Chem.*, **27**, 3299 (1962).

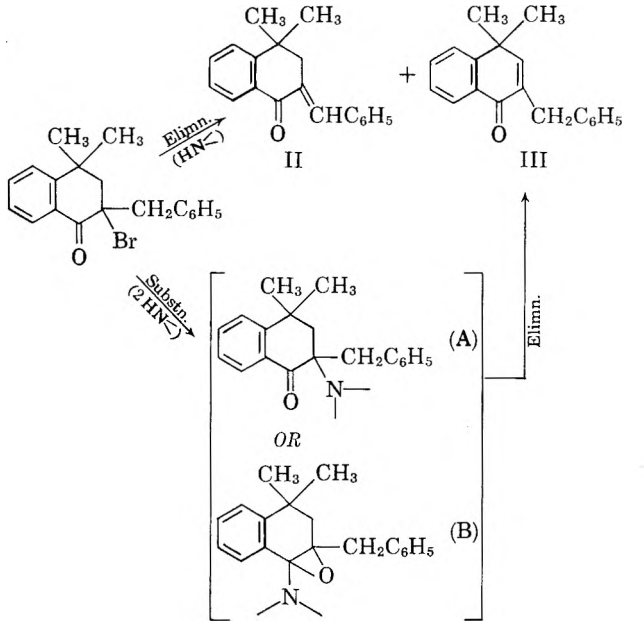
(7) D. N. Kevill, P. H. Hess, P. W. Foster, and N. H. Cromwell, *J. Am. Chem. Soc.*, **84**, 983 (1962).

(8) N. H. Cromwell and P. H. Hess, *ibid.*, **83**, 1237 (1961).

a further amine molecule is consumed. This second molecule is regenerated in the subsequent elimination reaction.

One possible path of substitution–elimination would involve direct substitution to give the α-aminotetralone A and then subsequent elimination to yield the isolated α,β-unsaturated ketones. Arguing against this reaction path is the known stability of tertiary α-amino ketones under the reaction conditions; for example, α-piperidino-*p*-phenylisobutyrophenone was recovered unchanged after refluxing in benzene for 24 hr. with a mixture of piperidine and piperidine hydrobromide.[8]

Another, and we think more probable, explanation incorporates into the reaction scheme the formation of an unstable epoxyamine B which subsequently decomposes to the isolated elimination products. Unstable intermediates of this type have recently been postulated for the closely related reactions of α-bromoketones with primary amines.[9]



The ratio of exocyclic to endocyclic elimination has been determined from an analysis of both the ultraviolet and proton magnetic resonance spectra of the reaction products. The ratio has been shown (Table V) to be dependent upon the nature of the amine but to be independent of both amine concentration (within the range 0.04–0.16 *M*) and temperature (within the range 60–90°). Analysis of either the ultraviolet or proton magnetic resonance spectra led to identical per cent compositions and, since the ultraviolet technique measures the percentage of II in the total product while the proton magnetic resonance technique measures the percentage of II relative to the sum of II and III, the identity of the values confirms that at 100% reaction of bromotetralone I the product consists only of a mixture of II and III.

Kinetics Results[10]

Stability of Reactants in Benzene.—Morpholine and piperidine have previously been shown to be stable in benzene.[7] A solution 0.0327 *M* in bromotetralone I was found not to produce any bromide ions during a period of 22 days at 90.6°.

Kinetics of the Piperidine-Promoted Elimination from α-Bromotetralone I in Benzene.—The kinetics of the piperidine-promoted elimination have been followed both by determination of the rate of piperidine neutralization and by determination of the rate of bromide ion formation. It was found that the rate of piperidine neutralization was under identical reaction conditions somewhat greater than the rate of bromide ion formation. During each individual run no drift could be detected in the integrated values for the second-order coefficients, either for piperidine neutralization or for bromide ion production, over at least 50% of stoichiometrically possible reaction.

TABLE I

MEAN VALUES FOR THE SECOND-ORDER RATE COEFFICIENT FOR PIPERIDINE NEUTRALIZATION, $k_2^{(H+)}$, IN THE REACTION OF 2-BROMO-2-BENZYL-4,4-DIMETHYL-1-TETRALONE (I) WITH PIPERIDINE IN BENZENE[a]

t, °C.	[Bromotetralone]	[Piperidine]	$10^4 k_2^{(H+)}$ (l. moles^{-1} sec.$^{-1}$)
61.0	0.0400	0.0100	1.16
61.0	.0395	.0400	1.06
75.0	.0400	.00500	2.7
75.0	.0395	.0200	3.0
75.0	.0400	.0400	2.8
90.6	.0400	.00500	6.4
90.6	.0100	.0100	6.7
90.6	.0400	.0100	6.9
90.6	.0395	.0200	7.5
90.6	.0395	.0400	6.8

[a] $k_2^{(H+)} = Ae^{-E/RT}$; $A = 10^{5.8}$ l. moles^{-1} sec.$^{-1}$; $E = 15.0$ kcal./mole.

TABLE II

MEAN VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS FOR BROMIDE ION PRODUCTION, $k_2^{(Br^-)}$, IN THE REACTION OF 2-BROMO-2-BENZYL-4,4-DIMETHYL-1-TETRALONE (I) WITH PIPERIDINE IN BENZENE[a]

t, °C.	[Bromotetralone]	[Piperidine]	$10^4 k_2^{(Br^-)}$ (l. moles^{-1} sec.$^{-1}$)
60.0	0.0327	0.0371	0.65
60.0	.0327	.0532	0.65
60.0	.0327	.0788	0.65
75.0	.0400	.0400	1.9[b]
90.6	.0100	.0100	4.3[b]
90.6	.0327	.0194	4.2
90.6	.0488	.0408	4.5
90.6	.0327	.0448	4.3
90.6	.0327	.0851	4.1
105.0	.0109	.0248	9.3
105.0	.0243	.0382	9.1
105.0	.0396	.0492	10.1

[a] $k_2^{(Br^-)} = Ae^{-E/RT}$; $A = 10^{5.6}$ l. moles^{-1} sec.$^{-1}$; $E = 15.0$ kcal./mole. [b] Followed by potentiometric titration.

Kinetics of Morpholine-Promoted Elimination from α-Bromotetralone I in Benzene.—The kinetic pattern was similar to that for piperidine promoted elimination except in that a slight fall off in the integrated values for the second-order rate coefficient for bromide ion

(9)(a) C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963); (b) see also, A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 901 (1958).

(10) The concentrations reported within this paper are not corrected for expansion of the solvent from room temperature to reaction temperature. Other entities quoted which are concentration dependent are similarly uncorrected.

TABLE III

INITIAL VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS FOR MORPHOLINE NEUTRALIZATION, $k_2^{(H+)}$, AND FOR THE SECOND-ORDER RATE COEFFICIENTS FOR BROMIDE ION PRODUCTION, $k_2^{(Br-)}$, IN THE REACTION OF 2-BROMO-2-BENZYL-4,4-DIMETHYL-1-TETRALONE (I) WITH MORPHOLINE IN BENZENE[a]

t, °C.	[Bromotetralone]	[Morpholine]	$10^5k_2^{(Br-)}$ (l. moles^{-1} sec.$^{-1}$)	$10^5k_2^{(H+)}$ (l. moles^{-1} sec.$^{-1}$)
61.0	0.0400	0.0400	1.16	...
61.0	.0800	.1600	1.07	...
75.0	.0400	.0400	3.20	...
75.0	.0400	.0800	3.10	...
90.6	.0400	.0200	8.30	12.0
90.6	.0400	.0400	9.40	11.9
90.6	.0400	.0800	9.40	...
90.6	.0800	.1600	9.30	...

[a] $k_2^{(Br^-)} = Ae^{-E/RT}$; $A = 10^{6.3}$ l. moles^{-1} sec.$^{-1}$; $E = 17.2$ kcal./mole.

production with increasing extent of reaction was observed and initial values were obtained by extrapolation to zero extent of reaction.

Kinetic Techniques.—All runs were carried out by the sealed bulb technique. The kinetic methods already have been described. All measurements of amine neutralization were performed by titration in acetone against standard methanolic hydrogen chloride solution using Lacmoid as indicator.[5] In all instances of morpholine-promoted elimination and in two instances indicated in Table II, of piperidine-promoted reaction, the extent of bromide ion formation was determined by potentiometric titration.[5] For piperidine-promoted reaction, unless otherwise stated in Table II, the extent of bromide ion formation was followed by Volhard titration.

Several illustrative runs are given. The integrated values for the second-order rate coefficients, k_2 (l. moles^{-1} sec.$^{-1}$), are calculated with respect to the bromotetralone I and to the amine.

(A) Temperature, 60.0°; 4.52-ml. aliquots at 24°; [bromotetralone]: 0.0327 *M*; [piperidine]: 0.0532 *M*; Volhard titration; excess 0.00817 *M* $AgNO_3$ added; titers in ml. of 0.0105 *M* KCNS.

Time (min):	0	1040	2510	3170	3880	4380	5730	6760
Vol. $AgNO_3$:	10.00	10.00	10.00	10.00	10.00	20.00	20.00	20.00
Titer:	7.42	4.80	2.40	1.65	0.85	8.15	6.95	6.40
$10^4k_2^{(Br-)}$:	...	0.69	0.66	0.64	0.65	0.64	0.66	0.64

Mean $k_2^{(Br^-)}$ is 0.65 × 10^{-4} l. moles^{-1} sec.$^{-1}$.

(B) Temperature, 61.0°; 5.05-ml. aliquots at 24°; [bromotetralone]: 0.0395 *M*; [piperidine]: 0.0400 *M*; titers are in ml. of 0.0525 *M* HCl.

Time (min):	0	1200	1500	1780	2690	3344	4254
Titer:	3.71	2.86	2.72	2.57	2.22	2.07	1.86
$10^4k_2^{(H+)}$:	..	1.07	1.05	1.08	1.08	1.03	1.02

Mean $k_2^{(H+)}$ is 1.06 × 10^{-4} l. moles^{-1} sec.$^{-1}$.

(C) Temperature, 75.0°; 5.05-ml. aliquots at 24°; [bromotetralone]: 0.0400 *M*; [morpholine]: 0.0400 *M*; potentiometric titration; titers are in ml. of 0.0100 *M* $AgNO_3$.

Time, (min):	0	240	1340	1750	2620	2870	4190
Titer:	0.20	0.55	1.96	2.41	3.10	3.33	4.22
$10^5k_2^{(Br-)}$:	..	3.1	3.0	3.0	2.7	2.7	2.5

Initial $k_2^{(Br^-)}$ (by extrapolation) is 3.2 × 10^{-5} l. moles^{-1} sec.$^{-1}$.

(D) Temperature, 90.6°; 5.05-ml. aliquots at 24°; [bromotetralone]: 0.0400 *M*; [morpholine]: 0.0400 *M*; titers are in ml. of 0.0525 *M* HCl.

Time, (min):	0	102	194	250	354	510	1400
Titer:	3.42	3.33	3.26	3.22	3.15	3.01	2.51
$10^5k_2^{(H+)}$:	..	12.4	11.8	11.6	11.3	12.4	12.1

Mean $k_2^{(H+)}$ is 11.9 × 10^{-5} l. moles^{-1} sec.$^{-1}$.

Product Studies[11]

A solution 0.0400 *M* in bromotetralone I and 0.0800 *M* in piperidine maintained at 90.6° for 90 hr. was found by titration in the usual manner to have 46% of the initial piperidine concentration remaining and 97% of possible bromide ion formation developed. After 138 hr. at 90.6° the respective values were 44% and 98%.

A series of studies upon the reaction product was carried out varying the concentration of piperidine or morpholine and the reaction temperature. The reaction product is known to be a mixture of the endocyclic and exocyclic α,β-unsaturated ketones.[2]

In each determination, one ampoule of 30 ml. and two of 5 ml. of reaction mixture were maintained at the constant temperature. The 5-ml. ampoules were analyzed for extent of reaction by titration of the bromide ion produced. When titration indicated complete, or very near complete, reaction then the 30-ml. ampoule was removed, precipitated amine hydrobromide was filtered off, and the filtrate evaporated to dryness. The residue was taken up in ether and the ether solution washed several times with water and then evaporated to dryness to give the crude product. The crude product was dried and the ultraviolet and proton magnetic resonance spectra were then determined without further purification. It was feared that attempts at further purification would alter the ratio between the *endo* and *exo* isomers and invalidate the spectral determinations.

Ultraviolet Spectra.—The concentration of the exocyclic α,β-unsaturated ketone II was easily determined by a consideration of the ultraviolet spectrum of the reaction product in the region 300–360 mμ, where it absorbs strongly while the endocyclic α,β-unsaturated ketone III has virtually no absorption (Table IV).

TABLE IV

TABULATION OF ABSORPTION COEFFICIENT (ϵ) AGAINST WAVE LENGTH (λ) FOR THE ULTRAVIOLET ABSORPTION SPECTRA IN SOLVENT METHANOL OF 2-BENZYL-4,4-DIMETHYL-1-KETO-1,4-DIHYDRONAPHTHALENE (III) AND 2-BENZAL-4,4-DIMETHYL-1-TETRALONE (II)

λ, mμ	3100	3200	3300	3400	3500	3600
ϵ, III	900	200	0	0	0	0
ϵ, II	12,800	12,000	9900	6600	3400	1700

By an analysis of the ultraviolet spectrum at the six tabulated wave lengths a mean value for the per cent of *exo* isomer in the reaction product was established. The values obtained are summarized in Table V.

Proton Magnetic Resonance Spectra.—The exocyclic α,β-unsaturated ketone II shows six methyl protons at 8.72 τ, two methylene protons at 7.12 and 7.08 τ, and nine aromatic protons, plus one vinyl proton, in the region 1.8 to 3.0 τ, with the vinyl proton at 2.18 τ and the aromatic proton β to the carbonyl group at 1.97 τ.

The endocyclic α,β-unsaturated ketone III shows

(11) Ultraviolet absorption spectra were determined with a Cary Model 11-MS recording spectrophotometer using reagent grade methanol solutions. Infrared spectra were measured with a Perkin-Elmer Model 21 double beam recording instrument employing sodium chloride optics and matched sodium chloride cells with carbon tetrachloride solutions. Proton magnetic resonance spectra were determined with a Varian A-60 instrument using carbon tetrachloride solutions containing a trace of tetramethylsilane for internal calibration.

TABLE V

YIELDS OF α,β-UNSATURATED KETONE AFTER REACTION OF 0.0400 *M* 2-BROMO-2-BENZYL-4,4-DIMETHYL-1-TETRALONE (I) WITH PIPERIDINE OR MORPHOLINE IN BENZENE AT VARIOUS TEMPERATURES AND THE PER CENTS OF EXOCYCLIC ISOMER IN THE REACTION PRODUCTS AS DETERMINED BY ULTRAVIOLET AND PROTON MAGNETIC RESONANCE SPECTRA

t, °C.	Amine	[Amine]	Reaction time, days	% Reaction[a]	% Yield	% *Exo* isomer	
						Ultraviolet	p.m.r.
61.0	$C_5H_{11}N$	0.0800	11	96	95	62	63
75.0	$C_5H_{11}N$	.0400	14	80	98[b]	62[c]	
75.0	$C_5H_{11}N$	.0800	11	97	94	55	63
75.0	$C_5H_{11}N$[d]	.160	5	100	95	58	64
90.6	$C_5H_{11}N$	.0800	8	100	98	68	63
61.0	C_4H_9ON	.160	24	91	86[b]	76[c]	
75.0	C_4H_9ON[d]	.160	23	95	97	80	75
90.6	C_4H_9ON	.160	8	98	98	76	77
90.6	C_4H_9ON	.160	8	98	100	73	77

[a] As determined by titration of bromide ion. [b] Contaminated with unreacted bromotetralone I; positive Beilstein test. [c] Absorption values corrected for small concentration of unreacted bromotetralone I. [d] Infrared spectrum of reaction product also determined.

six methyl protons at 8.62 τ, two methylene protons at 6.32 τ, one vinyl proton at 3.60 τ, and nine aromatic protons in the region 1.8 to 3.0 τ, with the aromatic proton β to the carbonyl group at 1.87 τ.

Since the markedly different displacements of the methylene protons in the two compounds occur in regions where the other compound does not interfere, the integration over these areas within a mixture of the two α,β-unsaturated ketones gives a direct measure of the relative proportions of II and III. The values obtained for the various reaction products are summarized in Table V.

Infrared Spectra.—Although infrared spectroscopy affords only a semiquantitative means of analyzing the reaction product the validity of the quantitative analysis of the reaction product as carried out by ultraviolet and proton magnetic resonance spectroscopy was in two instances supported by consideration of the infrared spectrum of the reaction product. The two examples chosen are indicated in Table V.

The pure endocyclic isomer has $\gamma_{c=o}$ 1662/100 and the pure exocyclic isomer has $\gamma_{c=o}$ 1673/94.[2] In the piperidine-promoted elimination example the proton magnetic resonance spectrum indicates 64% exocyclic isomer and the infrared spectrum is found to have two distinct carbonyl peaks, $\gamma_{c=o}$ 1662/83 due to the endocyclic isomer and $\gamma_{c=o}$ 1675/81 due to the exocyclic isomer. The absorption intensities are of the order of magnitude which would be predicted for 64% *exo* isomer. In the morpholine-promoted elimination example the proton magnetic resonance spectrum indicates 75% exocyclic isomer and the infrared spectrum shows only one distinct peak, $\gamma_{c=o}$ 1675/84 due to the exocyclic isomer and a slight shoulder, $\gamma_{c=o}$ 1666/77 due to the 25% of endocyclic isomer present.

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Comparison of 9-Phenylfluorenyl and Triphenylmethyl in the Decomposition of Azo Compounds[1a,b]

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p-Nitrophenylazo-, *o*-nitrophenylazo-, and 2,4-dinitrophenylazo derivatives of 9-phenylfluorene and triphenylmethane have been prepared and the kinetics of their decomposition in toluene has been studied. In each case the phenylfluorenyl derivative decomposed more rapidly than the corresponding triphenylmethyl derivative, and with lower activation energy. This is ascribed to and cited as evidence for the greater resonance stabilization of phenylfluorenyl as compared with triphenylmethyl radical. The partially compensating energies and entropies of activation are discussed. The relevance of these results to the dissociation of the related hexaarylethanes is discussed. Attempts to prepare azo compounds as sources of 9-fluorenyl radical, for comparison with diphenylmethyl, are described.

Bis(9-phenylfluorenyl) (I) one of the products formed by disproportionation[2] of triphenylmethyl radical in light is more stable than hexaphenylethane, and is not dissociated noticeably into free radicals at room temperature, but does dissociate reversibly at slightly higher temperature.[3] Of the factors affecting such dissociations, two important ones are[4] (1) resonance stabilization of the radicals which are formed, and (2) steric interactions, both those within each half, favoring a trigonal trivalent central carbon, and those between the two halves which may hinder their close approach and the formation of a strong central bond.

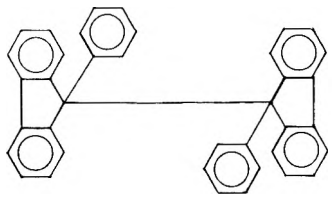
The greater stability of bis(9-phenylfluorenyl) was first attributed to the smaller resonance energy of the

(1) (a) We are pleased to acknowledge generous support of this work by the National Science Foundation, grants G4244 and 14049; (b) taken in part from a dissertation submitted by Fredric Cohen in partial fulfillment of the requirements for the Ph.D. degree in chemistry, Brandeis University.

(2) J. Schmidlin and A. Garcia-Banus, *Ber.*, **45**, 1344 (1912).

(3) H. E. Bent and J. E. Cline, *J. Am. Chem. Soc.*, **58**, 1624 (1936).

(4) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 382 ff.



I

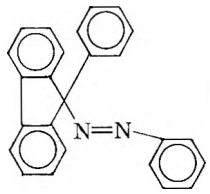
9-phenylfluorenyl radical,[5] a view supported by early valence bond calculations.[6] However, the heat of its reaction with oxygen[3] indicated that the decreased dissociation was due to a stronger central bond, presumably due to smaller steric interactions, and molecular orbital calculations,[6,7] indicated greater resonance stabilization of fluorenyl and 9-phenylfluorenyl radicals as compared with diphenylmethyl and triphenylmethyl radicals. The phenyl rings in triphenylmethyl radical cannot all become coplanar, and they may be oriented like the blades of a propeller[8,9] or only one or two may contribute to the resonance energy. The radical then does not have as great resonance stabilization as it would have if it were planar.[5,9] The planar structure of the fluorene system makes it possible for 9-phenylfluorenyl radical to be more nearly planar and it may well have greater resonance stabilization. The planar structure of the fluorene molecule itself gives it enhanced resonance energy as compared with the related molecules, diphenylmethane and biphenyl[10]; any increase in the resonance stabilization of the fluorene-derived radicals must be greater than the increase in the resonance stabilization of the corresponding fluorene-containing molecules if this property is to contribute to enhanced ease of formation of the radicals.

The greater methyl affinity of 6-phenyldibenzofulvene than that of triphenylethylene[11] and the greater reactivity of dibenzofulvene toward methacrylate radical as compared with 1,1-diphenylethylene[12] have been attributed to the resonance stabilization of fluorenyl radical being greater than that of diphenylmethyl. Steric factors may affect the rates of these additions in favor of the fluorene-derived compounds.

In azo compounds, R—N=N—R′, separation of the two potential radicals by the nitrogen makes steric interaction between them less important. Steric effects as such within the group R might favor decomposition of triphenylmethyl derivatives over corresponding 9-phenylfluorenyl compounds. Possible greater resonance stabilization of the 9-phenylfluorenyl radical would favor decomposition of its azo derivatives since the ease of decomposition of such compounds is markedly affected by the stability of the resulting radicals.[13] It seemed of interest to attempt to incorporate the fluorenyl and phenylfluorenyl groups into some azo compounds and to compare the kinetics of their decomposition with those of analogous diphenylmethyl and triphenylmethyl compounds.

(5) L. C. Pauling and G. W. Wheland, *J. Chem. Phys.*, **1**, 362 (1933).
(6) Ref. 4, p. 384, Table 7.3.
(7) A. Streitwieser, Jr., "Molecular Orbital Theory," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 394.
(8) H. O. Pritchard and F. H. Sumner, *J. Chem. Soc.*, 1041 (1955).
(9) M. Szwarc, *Discussions Faraday Soc.*, **2**, 42 (1947).
(10) Ref. 4, p. 98.
(11) M. Szwarc and F. Leavitt, *J. Am. Chem. Soc.*, **78**, 3590 (1956).
(12) J. L. Kice and F. Taymoorian, *ibid.*, **81**, 3403 (1959).
(13) (a) S. G. Cohen and C. H. Wang, *ibid.*, **77**, 2457 (1955); (b) **77**, 3628 (1955).

Preparation of Compounds.—In one set of experiments some derivatives of phenylazo-9-phenylfluorene (II) were prepared for comparison with the corresponding derivatives of phenylazotriphenylmethane. In these syntheses, displacement reactions of the substituted phenylhydrazines with triphenylmethyl chloride proceeded well, but displacements on 9-phenyl-9-chlorofluorene were less satisfactory, and 9-phenyl-9-bromofluorene was used instead; this observation is consistent with the lower capacity of the phenylfluorenyl halides to ionize.[14] The hydrazo compounds formed by these displacements were oxidized to the azo compounds by treatment with amyl nitrite in ether in the presence of acetyl chloride. Attempts to prepare the parent compound, phenylazo-9-phenylfluorene (II), and *p*-bromo-

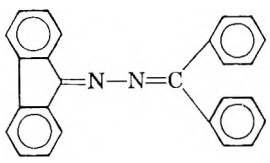


II

phenyl- and *m*-nitrophenylazo-9-phenylfluorene were unsuccessful. The displacement steps apparently proceeded satisfatcorily but decomposition occurred during either the purification of the easily oxidized hydrazo compounds or during the oxidation step. The phenylazotriphenylmethanes as a class decompose slightly above room temperature[15] and this provided evidence of a negative nature, that the 9-phenylfluorenylazo analog are less stable and that the 9-phenylfluorenyl radical may be more stable than triphenylmethyl. We were able to prepare *p*-nitrophenyl-, *o*-nitrophenyl-, and 2,4 dinitrophenylazo-9-phenylfluorenes. *p*-Nitrophenylazotriphenylmethane,[16] *o*-nitrophenylazotriphenylmethane,[16] and 2,4-dinitrophenylazotriphenylmethane were prepared for comparison.

In another set of experiments, attempts were made to prepare azobis-9-fluorene for comparison with azobisdiphenylmethane.[13a] Catalytic hydrogenation of the very insoluble fluorenone–azine failed, leading under mild conditions to recovered azine, and under more vigorous conditions to hydrogenolysis and formation of fluorene. Attempted preparation of 9-fluorenylhydrazine also failed, treatment of fluorenonehydrazone with lithium aluminum hydride leading to recovered hydrazone, while treatment with hydrogen and platinum in ethanol–hydrochloric acid leading to the azine.

We failed also in attempts to prepare the related unsymmetrical azo compound containing one fluorenyl and one diphenylmethyl radical, 9-fluorenylazodiphenylmethane. The mixed azine III, m.p. 102–104°,



was prepared from benzophenone hydrazone and fluorenone. It had the correct analysis and different

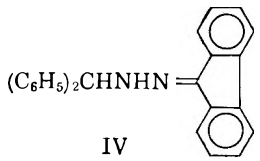
(14) K. Ziegler and H. Wolschitt, *Ann.*, **479**, 90 (1930).
(15) S. G. Cohen and C. H. Wang, *J. Am. Chem. Soc.*, **75**, 5504 (1953).
(16) M. Gomberg and A. Campbell, *ibid.*, **20**, 783 (1898).

TABLE I

DECOMPOSITION OF SUBSTITUTED (X)-PHENYLAZOTRIPHENYLMETHANES AND (X)-PHENYLAZO-9-PHENYLFLUORENES IN TOLUENE

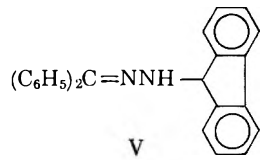
(X)	T, °C. ±0.03	$k_1 \times 10^4$/sec. Individual	Average	E_a, kcal./mole	$A \times 10^{-15}$	$\Delta S \pm$ cal./mole/deg.
		A. Phenylazotriphenylmethanes				
H	45.45	0.868, 0.849				
		0.845, 0.829	0.848 ± 0.011	29.3 ± 0.3	11	14
	55.55	3.51, 3.51				
		3.51	3.51			
p-NO_2	64.94	2.53, 2.64				
		2.58	2.58 ± 0.04	29.4 ± .4	2.6	11
	75.06	9.25, 9.14				
		9.18	9.19 ± .04			
o-NO_2	64.94	1.45, 1.47				
		1.46	1.46 ± .01	29.6 ± .5	2.0	10
	75.06	5.26, 5.11				
		5.37, 5.30	5.26 ± .08			
2,4-di-NO_2	75.06	1.90, 1.92				
		1.87	1.90 ± .02	29.3 ± .4	0.46	8
	84.98	6.11, 6.11				
		6.18	6.13 ± .03			
		B. Phenylazo-9-phenylfluorene				
p-NO_2	45.45	2.03, 2.11				
		2.04	2.06 ± .02	26.7 ± .3	0.43	8
	55.55	7.56, 7.44				
		7.53	7.53 ± .02			
o-NO_2	45.45	1.01, 1.01	1.01	26.8 ± .3	0.24	7
	55.55	3.76, 3.67				
		3.69	3.71 ± .04			
2,4-di-NO_2	55.55	2.04, 2.07				
		2.07	2.06 ± .01	28.5 ± .3	1.8	11
	64.94	6.91, 6.87				
		6.99	6.92 ± .04			

properties from those of the two symmetrical azines. Hydrogenation in ethanol over platinum oxide led to absorption of only one mole of hydrogen and formation in high yield of a light yellow compound which did not decompose when heated to 200°. This compound appeared to be fluorenone diphenylmethylhydrazone (IV),



IV

m.p. 107–109°. Hydrogenation of the azine in acetic acid under slightly more vigorous conditions led to a product which appeared to be the crude hydrazo compound. It decomposed with gas evolution in a melting point capillary, and changed on standing, and from it was obtained a stable compound, which was white and thermally stable and appeared to be the isomeric hydrazone benzophenonefluorenylhydrazone (V) with



V

m.p. 153–156°. There was some evidence that the desired azo compound, tautomeric with both IV and V, was formed by autoxidation of the hydrazo compound, but attempted purification converted it in part to the hydrazone V, a common difficulty in the preparation of azo compounds of this type. The cyclopentadieneimine character of IV may make it less stable than V.

Kinetic Studies.—Decomposition of the azo compounds was carried out in dilute (0.01 *M*) solution in toluene and followed by measurement of evolved nitrogen. New equipment, described in the Experimental section, was designed for increased accuracy and to minimize errors which may have occurred in earlier work. The reaction vessel was fitted with an effective internal stirrer to avoid supersaturation and the volume measuring system allowed continuous observation of volume change at atmospheric pressure. The decompositions showed first-order kinetics and linear plots of $\ln V_\infty/(V_\infty - Vt)$ may be drawn. Rate constants were calculated by the Guggenheim procedure[17] by the method of least squares, activation energies and *A* factors, and entropies of activation in the usual way. Generally three or more decompositions were carried out for each of the seven compounds at two temperatures. The results are summarized in Table I.

These data indicated that, in this group of azo compounds, those which lead to the 9-phenylfluorenyl radical decompose at 65° about ten times as fast as those which lead to triphenylmethyl, and the latter must be heated about 20° higher to achieve the same rate of decomposition as the former. If this relationship should apply also to the unsubstituted phenylazo-9-phenylfluorene, it would decompose in solution at room temperature. Its preparation and study would present some problems, reflected in our failure to obtain it. In these decompositions, steric effects—other

(17) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

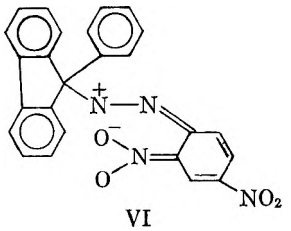
than their possible effects on resonance stabilization of radicals—would favor decomposition of the triphenylmethyl derivatives and we conclude that these greater rates of decomposition of the 9-phenylfluorenyl derivatives are due to the greater resonance stabilization of 9-phenylfluorenyl radical as compared with triphenylmethyl, and that these kinetic measurements provide experimental evidence for this. The dissociation of hexaphenylethane is greater than that of bis(9-phenylfluorenyl) I because of steric interactions which prevent formation of as strong a central bond in the former.

9-Phenylfluorene is more acidic than triphenylmethane,[18] its anion being more stable than triphenylmethide, while the 9-phenylfluorenyl cation is formed far less readily from either the carbinol[18b] or the chloride[14] than is the triphenylmethyl cation. Simple resonance considerations might indicate enhanced stabilization of both the anion and the cation by the fused planar ring system in the derivative of fluorene, while molecular orbital considerations[18b,19] would indicate that the cyclopentadienide aromatic character of the phenylfluorene system favors formation of the anion, and acidity, and makes more difficult removal of the electron pair and formation of the cation. It appears that both the planarity of the fluorene system and its cyclopentadienyl radical[19] character may contribute to the enhanced stability of phenylfluorenyl radical as compared with triphenylmethyl.

The phenylazotriphenylmethanes decompose more slowly essentially because of a higher activation energy for the decomposition. The decomposition of the four compounds in this set now are found to have essentially the same activation energy, 29.4 kcal./mole, higher than the 27 kcal. which we reported[15] earlier for two of these compounds, and which had also been reported[20] by D. H. Hey, *et al.*, for the unsubstituted compound. The present results seem to be the most reliable. The *p*-nitrophenyl and *o*-nitrophenyl compounds in the phenylfluorene series show a lower activation energy, 26.7 kcal./mole, and the difference, 2.7 kcal., may be a measure of the effect of the higher resonance energy of the phenylfluorenyl radical in facilitating rupture of the triarylmethyl–nitrogen bond. The *A* factors and entropies of activation are considerably less favorable for these two compounds than for the corresponding phenylazotriphenylmethanes and the more favorable energy of activation must more than compensate for this to lead to the observed more rapid rates. The greater resonance stabilization of the 9-phenylfluorenyl radical may impose a more restricted geometry on it, leading to a partially compensating entropy effect. Similar conditions may be involved in many situations in which partially compensating energy and entropy effects are observed, leading to the necessary minimum in the free energy of activation.

The effect of the nitro substituents on the rates is similar in the two series: *p*-NO_2 > *o*-NO_2 > 2,4-di-NO_2, with the relative rates in the triphenylmethyl set, 4.8:2.8:1.0, and in the 9-phenylfluorenyl set, 3.7:1.8:1.0. Except for the 2,4-dinitrophenylazo-9-phenylfluorene, variations in rate within each set appear to be due to variations in the *A* factors or entropies of activation and not to the energy of activation. In compounds of these types, in which the triarylmethyl–azo linkage is likely to be much weaker than the phenyl–azo link, the transition state for the decomposition may involve very marked rupture of the weaker bond leading to the triarylmethyl radical, and only slight rupture of the phenyl–nitrogen bond. The activation energy, in this situation may depend largely on the strength of the weaker bond. The extent of rupture of the stronger bond, while not contributing much to the stabilization energy of the transition state may contribute to its "looseness," to the extent of its two-body or three-body nature and thus to the entropy of activation. The greater the three-body character, the more favorable the entropy will be.[13b,21] The effect of the nitro-substituents may be to strengthen the phenyl–azo links either by introducing some double bond character to this bond or by polarization of the azo group, reducing the three-body character of the transition state and leading to less favorable entropy.

The 2,4-dinitrophenylazo-9-phenylfluorene alone has its rate of decomposition more rapid than the triphenylmethyl analog both because of a slightly more favorable energy and a more favorable entropy of activation. This molecule may have stabilization of the initial state as by contribution of a form of type VI, which also might be possible for the *o*-nitro compound in



VI

this set. Stabilization and restricted geometry of the initial state may lead to the less favorable energy and more favorable entropy of activation as compared with the other phenylfluorenyl compounds.

Ultraviolet and visible absorption spectra were obtained for the seven azo compounds in toluene, and for some of them in hexane and in ethanol. The *o*-nitrophenylazo-9-phenylfluorene was insufficiently soluble in the latter two solvents. In toluene, the spectrum of 2,4-dinitrophenylazotriphenylmethane seemed to resemble that of its *p*-nitro analog, while the spectrum of 2,4-dinitrophenylazo-9-phenylfluorene resembled that of its *o*-nitro analog.

Experimental[22]

A solution of 80 g. of (0.44 mole) of fluorenone (Eastman Kodak Co., m.p. 82–84°) in 600 ml. of anhydrous ether was added in 4.5 hr. to 240 ml. of 3 *M* phenylmagnesium bromide (Arapahoe). The mixture was refluxed for 1 hr., cooled, and filtered; the precipitate was washed with ether and added to a solution of 15 ml. of sulfuric acid in 500 ml. of water. The new precipitate was crystallized from ethanol, **9-phenyl-9-hydroxyfluorene**,[23] 108 g. (0.42 mole), 95% yield, m.p. 108–110°; reported[23] m.p. 109°.

(18) (a) J. B. Conant and G. W. Wheland, *J. Am. Chem. Soc.*, **54**, 1212 (1932); (b) G. W. Wheland, ref. 4, pp. 347, 365.

(19) A. Streitwieser, Jr., ref. 7, pp. 269–274.

(20) G. L. Davies, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 4397 (1956).

(21) C. Steel, *J. Chem. Phys.*, **31**, 899 (1959); S. G. Cohen, R. Zand, and C. Steel, *J. Am. Chem. Soc.*, **83**, 2895 (1961).

(22) Melting points are uncorrected. Elementary analyses are by Dr. S. M. Nagy and Dr. W. C. Fitz.

(23) F. Ullmann and R. Von Wurstemberger, *Ber.*, **37**, 73 (1904).

The phenylfluorenol, 50 g. (0.19 mole), was treated with 230 ml. of acetyl chloride at room temperature over night, concentrated, triturated, and washed with petroleum ether, leading to **9-phenyl-9-chlorofluorene**, 28 g. (0.10 mole), 53% yield, m.p. 79–80°; reported[24] m.p. 78–79°.

The phenylfluorenol, 40 g. (0.15 mole), was treated similarly with 100 g. of acetyl bromide, leading to **9-phenyl-9-bromofluorene**, 44 g. (0.14 mole), 89% yield, m.p. 101.5–103°; reported[24] m.p. 99°.

***p*-Nitrophenylazo-9-phenylfluorene**.—A solution of 9-phenyl-9-bromofluorene, 4.0 g. (0.012 mole), and *p*-nitrophenylhydrazine, 5.0 g. (0.033 mole, Eastman Kodak Co.), in 100 ml. of dioxane was stirred for 1 hr. at room temperature, filtered to remove *p*-nitrophenylhydrazine hydrobromide, concentrated to 30 ml., filtered again, diluted with 30 ml. of methanol, treated with water until turbid, and refrigerated, leading to **N-9-phenylfluorenyl-N′-*p*-nitrophenylhydrazine**, 3.2 g. (0.0081 mole), 65% yield, m.p. 190–192 dec.

Anal. Calcd. for $C_{25}H_{19}N_3O_2$: N, 10.68. Found: N, 10.30.

The hydrazo compound, 5.0 g., was suspended in 200 ml. of ether and treated with 12.5 ml. of amyl nitrite and 6.5 ml. of acetyl chloride at room temperature for 1 hr. The solvent was evaporated and the residue was treated with methanol, leading to the azo compound, 3.5 g., 70% yield, m.p. 115.5° dec.

Anal. Calcd. for $C_{25}H_{17}N_3O_2$: C, 76.71; H, 4.38; N, 10.74. Found: C, 76.9; H, 4.1; N, 10.92.

***p*-Nitrophenylazotriphenylmethane**.—Triphenylmethyl chloride, 13 g. (0.046 mole, Eastman Kodak Co., m.p. 109–111°), and *p*-nitrophenylhydrazine, 10 g. (0.070 mole), were boiled under reflux for 1.5 hr. in 400 ml. of ether. The precipitate was filtered and washed with hot methylene chloride, the filtrates were combined, concentrated, and treated with methanol, leading to **N-triphenylmethyl-N′-*p*-nitrophenylhydrazine**, 12 g. (0.032 mole), 66% yield, m.p. 189–191° dec.; reported,[20] 170°.

The hydrazo compound, above, 4.0 g. (0.010 mole), was stirred for 0.5 hr. at room temperature with 8 ml. of amyl nitrite and 3 ml. of acetyl chloride in 400 ml. of ether. The solution was concentrated and cooled, crystals were collected and recrystallized from methylene chloride–petroleum ether, leading to the azo compound, 3.7 g., 94% yield, m.p. 119° dec.; reported[16] m.p. 118.5°.

***o*-Nitrophenylazo-9-phenylfluorene**.—*o*-Nitroaniline, 10 g. (0.072 mole, Eastman Kodak Co., m.p. 71–72°) was diazotized and reduced with sodium sulfite, leading to *o*-nitrophenylhydrazine, 4.5 g. (0.029 mole), 41% yield, m.p. 90–92.5° from ethanol, reported[25] m.p. 92–93°.

A solution of 4.3 g. (0.013 mole) of 9-phenyl-9-bromofluorene and 2 g. (0.013 mole) of *o*-nitrophenylhydrazine in 300 ml. of ether was boiled under reflux fr 6 hr., cooled, filtered, and concentrated. The residue was crystallized from methanol, leading to N-9-phenylfluorenyl-N′-*o*-nitrophenylhydrazine, 1.4 g. (0.0036 mole), 27% yield, m.p. 199° dec.

Anal. Calcd. for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.0; H, 4.9; N, 10.12.

The hydrazo compound, 1.0 g., in 300 ml. of ether, was treated with 5 ml. of amyl nitrite and 0.7 ml. of acetyl chloride at room temperature for 3 hr., concentrated, and crystallized from methylene chloride, leading to the azo compound, 0.72 g., 72% yield, m.p. 115° dec.

Anal. Calcd. for $C_{25}H_{17}N_3O_2$: C, 76.71; H, 4.38; N, 10.74. Found: C, 76.52; H, 4.26; N, 10.49.

***o*-Nitrophenylazotriphenylmethane**—*o*-Nitrophenylhydrazine, 5.0 g. (0.033 mole), and triphenylmethyl chloride, 4.5 g. (0.106 mole), were boiled under reflux in 200 ml. of ether for 1.5 hr. The precipitate was filtered and washed with hot methylene chloride, the washings were combined with the filtrate, concentrated, and treated with methanol leading to N-triphenylmethyl-N′-*o*-nitrophenylhydrazine, 5.5 g. (0.014 mole), 84% yield, m.p. 166–168° dec., reported[16] m.p. 168°.

The hydrazo compound, 5.0 g. was stirred with 17 ml. of amyl nitrite and 4 ml. of acetyl chloride in 400 ml. of ether for 2 hr. at room temperature. The solution was concentrated, the azo compound was collected and crystallized from methylene chloride–petroleum ether, 4.3 g., 86% yield, m.p. 121.5° dec., reported[16] m.p. 116°.

2,4-Dinitrophenylazo-9-phenylfluorene.—9-Phenyl-9-bromofluorene, 5.0 g. (0.016 mole), was stirred for 40 min. at 65° with 6.0 g. (0.030 mole, Matheson, m.p. 196–198°) of 2,4-dinitrophenylhydrazine in 100 ml. of dioxane. The mixture was filtered and the filtrate was concentrated *in vacuo*, cooled, and filtered leading to orange crystals of the hydrazine, 6.4 g. (0.015 mole, 94% yield), m.p. 207 dec., reported[26] m.p. 233–234°.

Anal. Calcd. for $C_{25}H_{18}N_4O_4$: C, 68.50; H, 4.11; N, 12.77. Found: C, 68.45; H, 4.75; N, 13.08.

A suspension of this hydrazine, 3.2 g. in 400 ml. of ether, was stirred for 2 hr. at room temperature with 8 ml. of amyl nitrite and 4 ml. of acetyl chloride. The solution was evaporated *in vacuo* at room temperature until crystals appeared, cooled, and filtered leading to the orange azo compound, 3.0 g., 94% yield, m.p. 129° dec.

Anal. Calcd. for $C_{25}H_{16}N_4O_4$: C, 68.81, H 3.69; N, 12.83. Found: C, 68.95; H, 4.09; N, 12.65.

2,4-Dinitrophenylazotriphenylmethane.—A solution of 8.0 g. (0.029 mole) of triphenylmethyl chloride and 12.0 g. (0.061 mole) of 2,4-dinitrophenylhydrazine in 300 ml. of dioxane was warmed at 70° for 1 hr., filtered, and concentrated *in vacuo*, leading to **N-triphenylmethyl-N′-2,4-dinitrophenylhydrazine**, 11.3 g. (0.025 mole), 85% yield, m.p. 185–188° dec. from acetone; reported[26] 193–194°.

Anal. Calcd. for $C_{25}H_{20}N_4O_4$: C, 68.17; H, 4.58; N, 12.72. Found: C, 68.45; H, 4.75; N, 13.08.

The hydrazo compound, 2.5 g., was treated with 5 ml. of amyl nitrite and 2.5 ml. of acetyl chloride in 400 ml. of ether for 2 hr. at room temperature, concentrated *in vacuo*, cooled, and filtered. The solid was washed with ethanol and crystallized from ethyl acetate at −80°, leading to the azo compound, 2.1 g., 60% yield, m.p. 133–135° dec.

Anal. Calcd. for $C_{25}H_{18}N_4O_4$: C, 68.48; H, 4.14; N, 12.78. Found: C, 68.10; H, 4.21; N, 13.08.

Fluorenone Hydrazone.—Treatment of 36 g. (0.20 mole) of fluorenone (Matheson, m.p. 83–84°) with 10 g. of 64% hydrazine (Eastman Kodak Co.) in 200 ml. of ethanol and 10 ml. of acetic acid under reflux for 20 min., led to the hydrazone, 34 g. (0.175 mole), 88% yield, m.p. 148–149° from ethanol; reported[27] m.p. 149°.

Fluorenone azine was formed by treatment of 10 g. (0.052 mole) of the hydrazone in 200 ml. of ethanol with 3 ml. of concentrated sulfuric acid at 60° for 3 hr., 7.5 g. (0.021 mole), 81% yield, m.p. 264–265° from *m*-xylene; reported[28] m.p. 265°.

A solution of 3.4 g. of the azine in 300 ml. of tetrahydrofuran and 6 ml. of concentrated hydrochloric acid was hydrogenated over platinum oxide at 50° leading to recovery of 2.0 g. (59%) of the azine and a trace of yellow solid melting at 70–80°. Hydrogenation of 2.0 g. (0.0056 mole) of the azine in 300 ml. of acetic acid at 100° over platinum oxide led to fluorene, 0.40 g. (0.0024 mole), 21% yield, m.p. and m.m.p. 114–116°.

Fluorenone–Benzophenone Azine.—A solution of 14 g. (0.071 mole) of benzophenone hydrazone, m.p. 96°, and 12 g. (0.067 mole) of fluorenone in 150 ml. of absolute ethanol containing a few drops of acetic acid was heated to 70°, cooled slowly, and concentrated, leading to the mixed azine, deep yellow crystals, 16.5 g. (0.046 mole), 69% yield, m.p. 102–104°; reported[29] m.p. 121°.

Anal. Calcd. for $C_{26}H_{18}N_2$: C, 87.12; H, 5.06. Found: C, 87.52; H, 5.18.

The azine, 6.0 g. (0.017 mole), in 600 ml. of ethanol was hydrogenated over platinum oxide at one atmosphere, 400 cc. of hydrogen being absorbed in 5 hr., the reaction stopping. The solution was filtered, 50 ml. of water was added, and the solution was cooled overnight leading to a yellow solid, m.p. 107–109°, 5.2 g. (0.014 mole), 86% yield.

Anal. Calcd. for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59. Found: C, 86.22; H, 5.10.

The azine, 7.5 g. (0.021 mole), in 300 ml. of acetic acid was hydrogenated over platinum oxide at 35°, 30 p.s.i., filtered, and evaporated, leading to a crude solid residue which melted at 85–102° and decomposed at about 115°. This turned to a yellow gum when stored in a refrigerator. This was washed with cold acetone leaving a white residue, 2.0 g., 28% yield, m.p. 153–156° from ethanol.

Anal. Calcd. for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59. Found: C, 86.25; H, 5.63.

(24) A. Kliegl, *Ber.*, **38**, 284 (1905).
(25) E. Fischer, *Ann.*, **190**, 71 (1877).
(26) S. Patai and S. Dayagi, *J. Org. Chem.*, **23**, 2014 (1958).
(27) H. Wieland and A. Roseen, *Ann.*, **381**, 231 (1911).
(28) T. Curtius and K. Kof, *J. prakt. Chem.*, [2] **86**, 130 (1912).
(29) J. Guenzet, *Bull. soc. chim. France*, 1012 (1961).

From the acetone washings was obtained 0.60 g. more of this compound, total yield 37%, and a yellow solid, 0.70 g., 10% yield, melting 102–104°, decomposing at 110°. Crystallization from warm alcohol converted it to the white compound, m.p. *ca.* 150°.

Kinetic Studies.—The reaction vessel was a 100-ml. flask, essentially filled with toluene, immersed in an oil bath, the temperature of which was controlled to ±0.03. The gas-outlet tube was in part insulated and the temperature in the remainder and in the gas burette was controlled to within ±0.10° by circulating liquid from a second thermostat. The flask was evacuated several times and flushed with a stream of nitrogen, saturating the solvent. While nitrogen was flowing, the sample, about 1 mmole, in a Teflon holder, was placed in a neck of the flask, supported by an iron bar. The flask was sealed, lowered into the bath, and equilibrated, only the sample being above the bath level. An internal paddle stirrer coupled to an alnico magnet located in a submerged neck of the flask was rotated rapidly by a magnet placed above the bath. After equilibration, the support was withdrawn from under the sample by a magnet, the azo compound dissolved quickly, and nitrogen began to evolve. A sensitive manometer activated the gas volume measuring system. The manometer was a small Pyrex U-tube containing water, one arm connected to the gas-outlet tube, the other having one fixed and one movable contact in a Teflon bushing which was adjusted to a point slightly above the water level when the system was at atmospheric pressure. The effective diameters of the two arms of the manometer were different so that change in liquid level in the contact arm was sensitive to change in pressure. Contact activated a relay which started a motor and screw device which pulled on the plunger of a syringe which drew liquid from the gas buret maintaining the system at atmospheric pressure. The gas buret was read easily at frequent intervals.

Absorption spectra of the azo compounds were determined on a Perkin-Elmer Model 202 visible-ultraviolet spectrophotometer. For each of the compounds there is listed the solvent, absorption maxima, and log of the extenction coefficients. Phenylazotriphenylmethane: toluene, 284 mμ, 4.0; 424, 1.5; hexane, 267, 4.0; 272, 4.0; 421 2.3. *o*-Nitrophenylazotriphenylmethane: toluene, 283 mμ, 3.9; 424, 2.6; hexane, 267, 4.2; 273, 4.2; 425, 2.6. *p*-Nitrophenylazotriphenylmethane: toluene, 287 mμ, 4.0; 441, 2.5; hexane, 267, 4.2; 282, 4.2; 440, 2.7. 2,4-Dinitrophenylazotriphenylmethane: toluene, 284 mμ, 4.0; 439, 2.7; hexane, 267, 3.9; 273, 3.9; 442, 2.3. *o*-Nitrophenylazo-9-phenylfluorene: toluene, 285 mμ, 4.0; 406, shoulder, 2.5. *p*-Nitrophenylazo-9-phenylfluorene: toluene, 285 mμ, 4.5; 424, shoulder, 2.5; hexane, 267, 4.6; 273, 4.6; 429, 2.5; ethanol, 211, 5.0; 277, 4.8; 412, shoulder, 2.8. 2,4-Dinitrophenylazo-9-phenylfluorene: toluene 285 mμ, 4.3; 406, 2.8; hexane, 266, 4.3; 272, 4.3; ethanol, 209, 4.9; 275, 4.5; 412, shoulder, 2.8.

Some Reactions of Diazomethane with Carbon Dioxide and Ammonia in Aqueous Solution

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Carbon dioxide was allowed to react with diazomethane, prepared by alkaline hydrolysis of N-methyl-N-nitroso-N′-nitroguanidine. The different products were separated by gas chromatography, collected separately, and identified as dimethyl carbonate, methyl carbamate, N-methyl methyl carbamate, and N-dimethyl methyl carbamate. Methyl carbamate and its N-methyl derivatives were formed because of the presence of ammonia in the ethereal solution of diazomethane. Dimethyl carbonate, methyl carbamate, N-methyl methyl carbamate, and N-dimethyl methyl carbamate were found to be the products of the reaction between ammonia, carbon dioxide, and diazomethane, in aqueous solution. A mechanism for the formation of methyl carbamate and its N-methyl derivatives from ammonia, carbon dioxide, and diazomethane in the presence of water is proposed.

Diazomethane has been used in our laboratory in the search for unstable intermediates in the carboxylation reaction of photosynthesis—*i.e.*, the carboxylation of ribulose-1,5-diphosphate to give phosphoglyceric acid, the first stable product in the carbon reduction cycle of photosynthesis. It usually was prepared by alkaline hydrolysis of N-methyl-N-nitroso-N′-nitroguanidine.[2] In all the experiments with diazomethane ^{14}C-bicarbonate was present in the reaction mixture. It is known that the product of the reaction of bicarbonate with diazomethane is dimethyl carbonate. However, by the use of paper and vapor phase chromatography for the separation of the products of the reaction of ^{14}C-bicarbonate and diazomethane, three other ^{14}C-labeled compounds were found in addition to dimethyl carbonate. These were identified as methyl carbamate, N-methyl methyl carbamate, and N-dimethyl methyl carbamate. The carbamate nitrogen atom was found to have its origin in ammonia present in the solution inadvertently at first (as a by-product of the hydrolysis of the nitroguanidine) and later deliberately added. The mechanism of the formation of the methyl carbamates has been investigated.

Experimental

Preparation of Diazomethane.—An ethereal solution of diazomethane was prepared either by alkaline hydrolysis of N-methyl-N-nitroso-N′-nitroguanidine as described by McKay,[2] or from N-methyl-N-nitroso-*p*-toluenesulfonamide (Diazald) as described by Backer and de Boer.[3] Both compounds were obtained from Aldrich Chemical Co.

Reaction of $H^{14}CO_3^-$ with Diazomethane.—A 0.50-ml. solution of $H^{14}CO_3^-$ (1.98 mc./ml.; 0.06 *M*) was mixed with an ethereal solution of diazomethane until the yellow color persisted. The reaction mixture was left at room temperature for a few hours, and overnight in the deep freeze (−16°). The solution was concentrated under a current of air at 5° and the different radioactive components of the mixture were separated by gas chromatography in conjunction with a proportional counter.[4–7]

(1) (a) Abstracted from a thesis submitted by George A. Akoyunoglou, August, 1962, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of California, Berkeley; (b) partially supported by the Greek State Scholarship Foundation; (c) Ames Research Center, National Aeronautics and Space Administration, Moffett Field, Calif.; (d) The preparation of this paper was sponsored by the U. S. Atomic Energy Commission.

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(3) H. J. Backer and Th. J. de Boer, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **54B**, 191 (1951); *Chem. Abstr.*, **46**, 1961 (1952).

(4) I. M. Whittemore, University of California Radiation Laboratory Quarterly Report, UCRL-9408, p. 49, September, 1960.

(5) G. Akoyunoglou, thesis, University of California, Berkeley, UCRL-10352, August, 1962.

(6) R. Wolfgang and F. S. Rowland, *Anal. Chem.*, **30**, 903 (1958).

(7) R. Wolfgang and C. F. McKay, *Nucleonics*, **16**, No. 10, 69 (1958).

Reaction of Gaseous Carbon Dioxide with Diazomethane.—Gaseous carbon dioxide (100%) was bubbled through an inlet tube into the ethereal solution of diazomethane at 2° until the solution became colorless. The flask containing the ethereal solution of diazomethane had also a small amount of water (2.5 ml.). The inlet tube was dipped below the surface of the water layer. The solution was concentrated at 5° under a current of air, and the different components of the reaction mixture were separated by vapor phase chromatography and collected separately.

Vapor Phase Chromatography.—A Wilkens standard gas chromatograph, Model A90, connected with a Brown recorder and a 10-ft. EGS (ethyleneglycol polyester of succinic acid) column, were used for the separation and identification of the different compounds. A collector, in conjunction with the chromatography unit, was used to collect the different compounds separately. The collector was cooled by a Dry Ice–acetone bath or by liquid nitrogen.

Preparation of Methyl Carbamate (Methylurethan).—Methyl carbamate was prepared from methyl chlorocarbonate and ammonia as described by Hartman and Brethen.[8] The methyl chlorocarbonate (carbomethoxychloride) was prepared by the procedure described by Bergmann and Zervas for the preparation of carbobenzoxychloride.[9] The phosgene, necessary for the preparation of methyl chlorocarbonate, was prepared by the procedure described by Vogel.[10]

Anal. Calcd. for $C_2H_5O_2N$: C, 32.00; H, 6.66; N, 18.66; O, 42.66. Found: C, 31.79; H, 6.58; N, 17.95.

Preparation of N-Methyl Methyl Carbamate.—N-Methyl methyl carbamate was prepared from dimethyl carbonate and methylamine as described by Delepine and Schving.[11]

Anal. Calcd. for $C_3H_7O_2N$: C, 40.45; H, 7.86; N, 15.73; O, 35.95. Found: C, 40.57; H, 7.94; N, 15.60.

Preparation of N-Dimethyl Methyl Carbamate.—N-Dimethyl methyl carbamate was prepared from dimethyl carbonate and dimethylamine as described by Delepine and Schving.[11]

Anal. Calcd for $C_4H_9O_2N$: C, 46.60; H, 8.74; N, 13.59, O, 31.07. Found: C, 46.85; H, 8.52; N, 13.17.

Results

Vapor phase chromatography in conjunction with a proportional counter was used for the separation of the different radioactive products of the ^{14}C-bicarbonate and diazomethane[12] reaction. It was found that the mixture consisted of five radioactive compounds as shown in Fig. 1. These were identified as carbon dioxide, dimethyl carbonate (DMC), N-dimethyl methyl carbamate (III), N-methyl methyl carbamate (NMMCR), and methyl carbamate (MCR).

Gas and paper chromatography of the untreated aqueous solution of $NaH^{14}CO_3$ showed that there were no radioactive impurities present, and that the bicarbonate was the precursor of all (four) compounds which were formed by action of diazomethane on $NaH^{14}CO_3$.

The same compounds were formed when gaseous carbon dioxide ($C^{12}O_2$) reacted with diazomethane in solution, as is shown in Fig. 2 and 3.

Identification of the Products.—For the identification of the products, larger amounts (nonradioactive) were prepared from gaseous carbon dioxide and diazomethane. The components of the reaction mixture were separated and purified by gas chromatography and collected separately.

The identification of them was based on:

(1) The analysis for C, H, N, O, and determination of molecular weight; (2) the study of the mass and infra-

(8) W. W. Hartman and M. R. Brethen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 278.

(9) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(10) A. I. Vogel, "Textbook of Practical Organic Chemistry," Longmans Green, New York, N. Y., 1956, p. 185.

(11) M. Delepine and F. Schving, *Soc. chim. France*, **7**, 894 (1910).

(12) If it is not otherwise stated, the ethereal solution of diazomethane was prepared by alkaline hydrolysis of N-methyl-N-nitroso-N′-nitroguanidine.

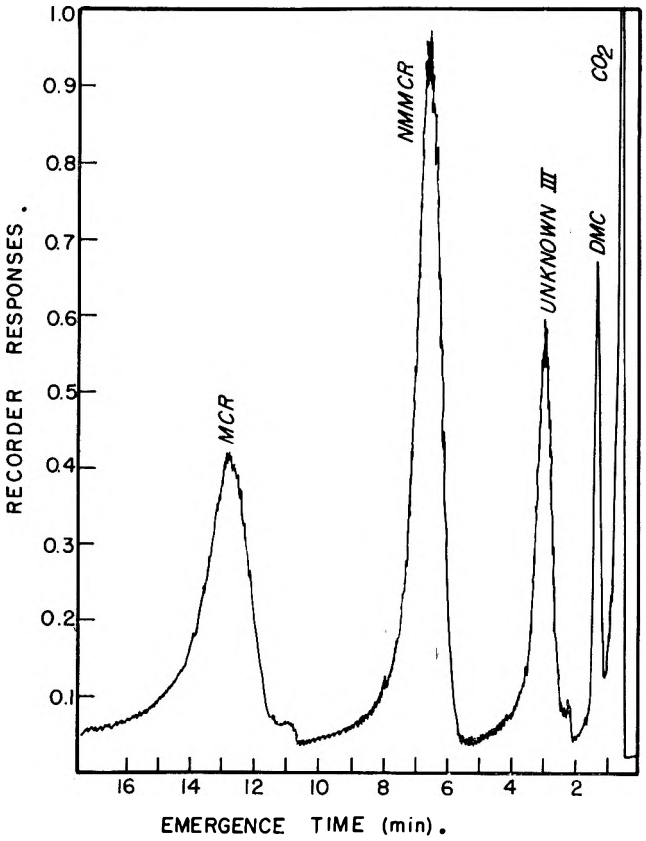


Fig. 1.—Gas chromatogram of the radioactive mixture of the products of the reaction $NaH^{14}CO_3$ with diazomethane prepared from N-methyl-N-nitroso-N′-nitroguanidine. The recorder response is proportioned to radioactivity. DMC is dimethyl carbonate; unknown III is N-dimethyl methyl carbamate; NMMCR is N-methyl methyl carbamate; and MCR is methyl carbamate.

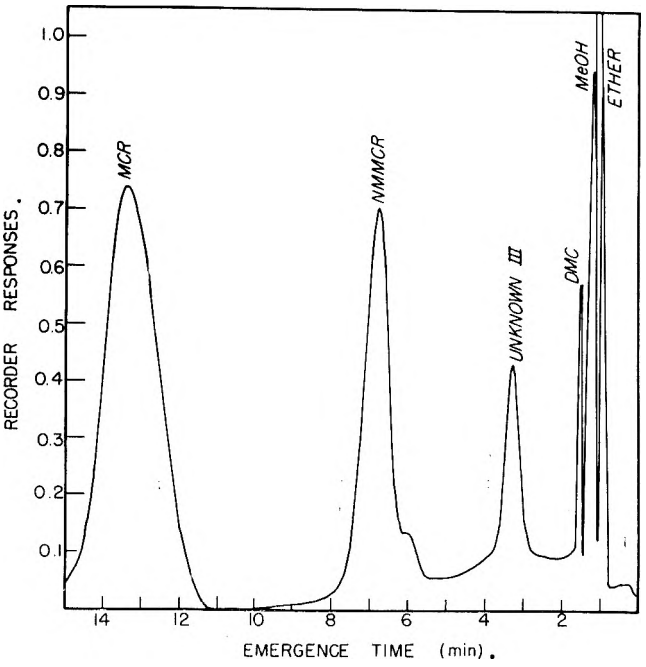


Fig. 2.—Gas chromatogram of the nonradioactive mixture of the products of the reaction of carbon dioxide with diazomethane prepared from N-methyl-N-nitroso-N′-nitroguanidine. The recorder response is proportional to the mass of material. DMC is dimethyl carbonate; unknown III is N-dimethyl methyl carbamate; NMMCR is N-methyl methyl carbamate; and MCR is methyl carbamate.

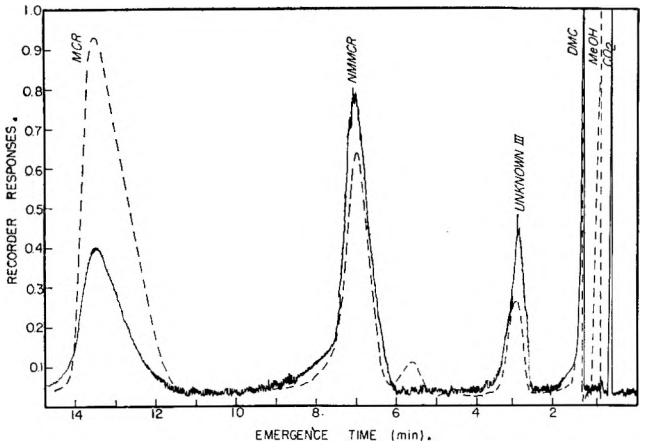


Fig. 3.—Gas cochromatogram of the radioactive mixture of the p oducts of the reaction $NaH^{14}CO_3 + CH_2N_2$, and the nonradioactive products of the reaction $CO_2 + CH_2N_2$. Diazomethane was prepared from N-methyl-N-nitroso-N'-nitroguanidine. Solid line is the radioactivity recording; dotted line is the mass recording. DMC is dimethyl carbonate; unknown III is N-dimethyl methyl carbamate; NMMCR is N-methyl methyl carbamate; and MCR is methyl carbamate.

red spectra, and their comparison with the mass and infrared spectra of authentic marker compounds; and (3) the cochromatography of the unknown compounds or their hydroxamate derivatives with authentic marker compounds (*e.g.*, Fig. 3).

Gas cochromatography of the radioactive products, which were collected separately, with authentic dimethyl carbonate, N-dimethyl methyl carbamate, N-methyl methyl carbamate, and methyl carbamate, respectively, showed in each case an exact coincidence of the radioactivity with the mass peaks.

Analysis of the products for C, H, N, and O content and determination of molecular weight are shown in Table I.

TABLE I

Analysis for	% C	% H	% N	Mol. wt.
Found for DMC	39.81	6.72	...	88.0
Calcd. for $C_3H_6O_3$	40.00	6.66	...	90.0
Found for NDMMCR	46.48	8.86	13.25	109.0
Calcd. for $C_4H_9NO_2$	46.60	8.74	13.59	103.0
Found for NMMCR	40.63	7.82	15.49	84.0
Calcd. for $C_3H_7NO_2$	40.45	7.86	15.73	89.0
Found for MCR	31.61	6.71	17.75	74.0
Calcd. for $C_2H_5NO_2$	32.00	6.66	18.66	75.0

The comparison of the mass spectra of the products with the mass spectra of dimethyl carbonate, N-dimethyl methyl carbamate, N-methyl methyl carbamate, and methyl carbamate, respectively, showed an exact coincidence in the place and number of peaks and in the relative abundance of each peak. Identification of the products was finally confirmed by the identity of their infrared spectra with that of authentic dimethyl carbonate, N-dimethyl methyl carbamate, N-methyl methyl carbamate, and methyl carbamate, respectively. The relative yield of each product is approximately 40% dimethyl carbonate, 35% methyl carbamate, 20% N-methyl methyl carbamate, and 5% N-dimethyl methyl carbamate.

Discussion

The appearance of compounds containing only one nitrogen atom as a result of a reaction of diazomethane was so unusual as to prompt us to seek some other source for that nitrogen atom than diazomethane itself. This was established by demonstrating the absence of carbamates in reactions of diazomethane prepared from N-methyl-N-nitroso-*p*-toluenesulfonamide, and suggested as the source of the single atom of nitrogen a by-product of the N-nitroso-N-methyl-N'-nitroguanidine hydrolysis. This was easily demonstrated to be free ammonia. The presence of ammonia can be accounted for by the alkaline hydrolysis of the imide group of N-methyl-N-nitroso-N'-nitroguanidine. The hydrolysis can take place before or after the formation of diazomethane. In the first case N-methyl-N-nitroso-N'-nitrourea is formed according to the reaction

$$CH_3N(NO)C(NH)NHNO_2 + H_2O \xrightarrow{HO^-} CH_3N(NO)CONHNO_2 + NH_3$$

which is further hydrolyzed to yield diazomethane. In the second case, diazomethane is formed first, and the residue is further hydrolyzed to give ammonia.

Mechanism of the Reaction.—Presumably dimethyl carbonate was formed by the action of diazomethane on carbonic acid (reaction of diazomethane with acidic hydrogen) according to Arndt,[13] Eistert,[14] or Roberts[15] mechanisms. Methyl carbamate was formed by the action of diazomethane on ammonium carbamate, which is present in a mixture of carbon dioxide and ammonia. Three hypotheses were considered to account for the formation of N-methyl methyl carbamate and N-dimethyl methyl carbamate from ammonia, carbon dioxide, and diazomethane.

(a) Methyl carbamate may be formed first, which then reacts with diazomethane to give its N-methyl derivatives.

(b) Diazomethane may react with ammonia to give methylamine and dimethylamine, which form the salts of N-methyl carbamic acid and N-dimethyl carbamic acid in the presence of carbon dioxide. The acids may be further methylated by the action of diazomethane to yield the corresponding methyl esters.

(c) The carbamic acid, present in a mixture of ammonia and carbon dioxide, may react with diazomethane to form its N-methyl derivatives (N-methyl carbamic acid and N-dimethyl carbamic acid), and the products are further methylated to yield the corresponding methyl esters.

The first (a) hypothesis is not correct, because: (1) continued action of diazomethane on the reaction mixture did not show an increase in the amount of NMMCR and NDMMCR, as would be the case if they were formed by methylation of methyl carbamate; (2) action of diazomethane on ^{14}C-MCR, or unlabeled MCR, showed no formation of any N-methyl derivative.

The second (b) hypothesis also is not correct because: (1) the same relative amount of each product was

(13) F. G. Arndt, "Organic Analysis," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1953, p. 221.

(14) B. Eistert, *Angew. Chem.*, **54**, 99 (1941); translated and revised by F. W. Spangler in "Newer Methods of Preparative Organic Chemistry," 1st Ed., Interscience Publishers, Inc., New York, N. Y., 1948, pp. 513–570.

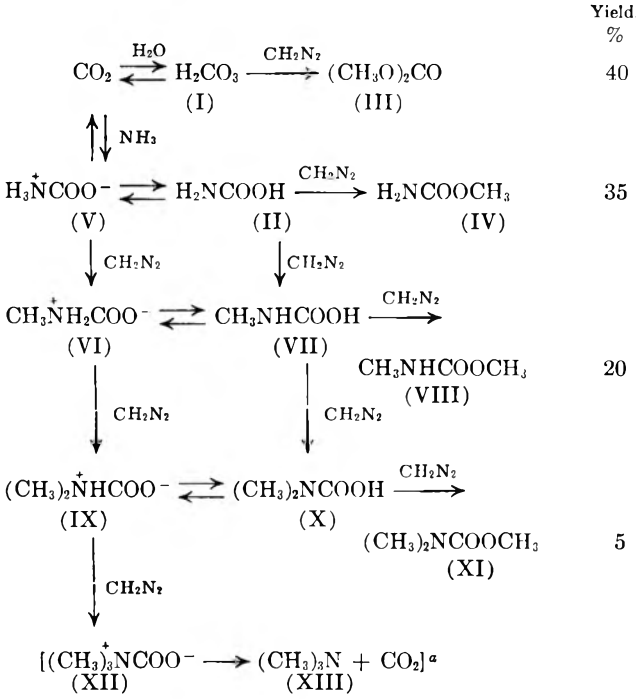
(15) G. D. Roberts, W. Watamore, and R. E. McMahon, *J. Am. Chem. Soc.*, **73**, 760 (1951).

formed when either a new or an old preparation of diazomethane was used; (2) all attempts to prepare methyl derivatives of ammonia by the action of diazomethane on gaseous ammonia, or aqueous ammoniacal solution or solutions of ammonium salts were unsuccessful.

Table II shows the proposed mechanism for the formation of the products of the reaction of ammonia, carbon dioxide, and diazomethane in the presence of water, and the different reactions that may take place, according to the third hypothesis.

TABLE II

MECHANISM OF THE REACTION OF DIAZOMETHANE WITH AN AQUEOUS SOLUTION OF A MIXTURE OF CARBON DIOXIDE AND AMMONIA



[a] It is not known if trimethylamine is really formed because no attempts were made to detect it.

Carbon dioxide reacts either with water to form carbonic acid (I) or with ammonia to give carbamic acid (II). Compound I with diazomethane gives dimethyl carbonate (III). Compound II is in equilibrium with compound V, its zwitterion. Diazomethane reacts with compounds II and V to give methyl carbamate (IV) and N-methyl carbamic acid (VII) or the N-methyl derivative of the zwitterion (VI), respectively. Compound VI is in equilibrium with compound VII, and diazomethane reacts with both of them to give N-methyl methyl carbamate (VIII) and N-dimethyl carbamic acid (X) or compound IX, respectively, and so on. It is not known whether diazomethane reacts with compound IX to give the betaine (XII), which, being unstable, would give trimethylamine (XIII) and carbon dioxide, because no attempts were made to detect trimethylamine. If trimethylamine is formed, the yield would be very low, as can be seen from the low yield of its precursors.

The mechanism of the methylation of the various intermediates (Table II) with diazomethane is probably similar to the mechanism proposed by Arndt[13] or Roberts[15] for the methylation of compounds containing acidic hydrogen.

The proposed mechanism finds support in the observation by Kuhn and Ruelius[16] that extended action of diazomethane on the aqueous solution of an amino acid produced, as final product, the corresponding betaine. Some intermediates (*e.g.*, the methyl ester of the amino acid) were present in the case when the reaction was allowed to proceed for a short time only. Because of the basicity of the amino group, and the presence of water, a self-hydrolysis of the methyl esters occurred, reforming the free acids, thus permitting the quantitative transformation of the amino acid to betaine. In the case of the carbamates the methyl ester of carbamic acid, and methyl esters of the N-methyl derivatives of carbamic acid (compounds IV, VIII, and XI) once formed, cannot be self-hydrolyzed, even in the presence of water, because the amide group is not so strong a basic group as the amino group of amino acids. Therefore, a mixture of all these compounds is the final product of the above reaction.

Summary

Carbon dioxide was allowed to react with diazomethane, prepared by alkaline hydrolysis of N-methyl-N-nitroso-N′-nitroguanidine. The different products were separated by gas chromatography, collected separately, and identified as dimethyl carbonate, methyl carbamate, N-methyl methyl carbamate, and N-dimethyl methyl carbamate. Methyl carbamate and its N-methyl derivatives were formed because of the presence of ammonia in the ethereal solution of diazomethane.

Dimethyl carbonate, methyl carbamate, N-methyl methyl carbamate, and N-dimethyl methyl carbamate were found to be the products of the reaction between ammonia, carbon dioxide, and diazomethane, in aqueous solution. A mechanism for the formation of methyl carbamate and its N-methyl derivatives from ammonia, carbon dioxide, and diazomethane in the presence of water is proposed.

It is thus to be expected that any experiments designed to trap unstable products formed from radioactive carbon dioxide in the presence of any enzyme protein will lead to the appearance of large amounts of carbon dioxide fixed as methyl carbamate on the free amino groups of the protein as well as any amino acid which may be present. In fact, such observations have been made with carboxydismutase.[5]

(16) R. Kuhn and H. W. Ruelius, *Ber.*, **83**, 420 (1950).

Syntheses of 1,3-Diazaphenothiazines.[1] I.

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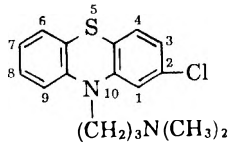
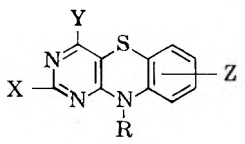
Excellent yields of 2,4-diamino-1,3-diazaphenothiazine have been obtained by the reaction of 2,4-disubstituted 5-bromo-6-chloropyrimidines with *o*-mercaptoaniline under either acidic or basic conditions. Using basic conditions, it was possible to isolate a stable intermediate, the 6-*o*-aminophenylmercaptopyrimidine, which subsequently could be made to rearrange and cyclize. Under acid conditions the identical diazaphenothiazine was obtained directly from the reactants.

The chemical structure of the well known tranquillizer drug, chlorpromazine, I, has been modified extensively by numerous workers. Most of the earlier variations



I

involved changes in the structure of the side chain at position 10 and in the substituent at position 2. More recently a number of investigators have modified the chlorpromazine structure by the introduction of another heteroatom, nitrogen, in the positions 1,[2] 2,[3] 3,[4] and 4[5] of the phenothiazine ring to give monoazaphenothiazines. It seemed worthwhile to attempt to prepare some analogous diazaphenothiazines,[6] such as II.



II

X and/or Y = H, alkyl, OH, NH_2, N(R_1)(R_2), halogen, etc.
Z = H, halogen, etc.
R = H, alkyl, ω-aminoalkyl, etc.

Of several routes considered by us for the syntheses of diazaphenothiazines, those described in this paper are the first successfully completed. These syntheses were accomplished by the reaction of *o*-mercaptoaniline with suitably substituted 5-bromo-6-chloropyrimidines.[7]

Figure 1 shows two alternative routes used for the preparation of 2,4-diamino-5-bromo-6-chloropyrimidine VI. Replacement of the hydroxy group of 2,4-diamino-6-hydroxypyrimidine, III, by chlorine with phosphorus oxychloride gave 2,4-diamino-6-chloropyrimidine, IV, which was then brominated in the 5 position to give VI. This bromination was done in aqueous methanol keeping the solution near neutrality by the addition of sodium bicarbonate, in order to neutralize the hydrobromic acid liberated in the reaction, which otherwise might promote hydrolysis of the 6-chlorine. Compound VI was also obtained by bromination of III in the 5-position, to give V, in which the 6-hydroxy group was then replaced by chlorine using phosphorus oxychloride. Employing essentially the same procedure, except bubbling chlorine gas into the solution, 2,4-diamino-5,6-dichloropyrimidine was also prepared.

As shown in Fig 2, the chlorobromopyrimidine (VI) reacted with *o*-mercaptoaniline under two different sets of conditions to give the desired 1,3-diazaphenothiazine, IX.

The success of these syntheses, as planned, depended on several features of reactivity peculiar to pyrimidine derivatives. The reactivity for nucleophilic replacement reactions of halogens in the 2-, 4-, or 6-positions of pyrimidines is well known, while halogen in the 5-position is relatively inert.[8] Furthermore, Banks[9] showed that the reaction of aromatic amines with such chloropyrimidines was greatly accelerated by the use of acid catalysts.

While the mercapto group of *o*-mercaptoaniline is more nucleophilic than the amino group, it was hoped that use of the acid-catalyzed procedure of Banks[9] (see upper route of Fig. 2) would both favor the replacement of the 6-chlorine of the pyrimidine, VI, by the anilino nitrogen, and also possibly minimize attack by the sulfur. If the 6-(*o*-mercaptoanilino)pyrimidine intermediate, VII (shown in brackets in Fig. 2), were formed, it seemed almost certain that it could be cyclized readily to the diazaphenothiazine IX (Fig. 2). The cyclization perhaps would require the use of a weak base catalyst to generate the even more nucleophilic mercaptide anion to react with the relatively inert 5-bromo group. In the intermediate shown, VII, it seemed that the combination of the high nucleophilicity of the sulfur and the favorable steric arrangement within the molecule, should ensure the success of the reaction. Interestingly, under the Banks-type reaction conditions, the diazaphenothiazine, IX, was obtained directly from the acid

(1) Presented at the Metropolitan Regional Meeting, American Chemical Society, New York, N. Y., January, 1962.

(2) (a) W. A. Schuler and H. Klebe, German Patent 964,050 (1957); U. S. Patent 2,974,139 (1961); *Ann.*, **653**, 172 (1962); (b) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, **80**, 1651 (1958); (c) A. v. Schlichtegroll, *Arzeneimittel Forsch.*, **7**, 237 (1957); **8**, 489 (1958).

(3) (a) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958); (b) P. N. Craig, M. Gordon, J. J. Lafferty, B. Lester, M. Pavloff, and L. Zirkle, *ibid.*, **25**, 944 (1960).

(4) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).

(5) T. Takahashi and E. Yoshii, *Pharm. Bull.* (Tokyo), **2**, 382 (1954); *Chem. Abstr.*, **50**, 13032e (1956).

(6) Independent syntheses of compounds containing this ring system have also been reported: (a) A. Westermann, O. Bub, and L. Suranyi, D.R. Patent 1,110,651 (1961); *Chem. Abstr.*, **56**, 2461a (1962); (b) B. Roth, L. Schloemer, and G. H. Hitchings, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(7) Several such bromochloropyrimidines had been made and used in an earlier investigation from these laboratories: A. P. Phillips and A. Maggiolo, *J. Am. Chem. Soc.*, **74**, 3922 (1952); *cf.* also C. C. Price, N. J. Leonard, and R. H. Reitsema; *ibid.*, **68**, 766 (1946); E. Ochiai and Y. Ito, *J. Pharm. Soc. Japan*, **57**, 579 (1937); *Chem. Abstr.*, **31**, 6238[6] (1937).

(8) Although 5-halogenopyrimidines have usually been found to be inert in displacement reactions, when activated by the presence of one or more C=O groups in the 4- and 2-position as in 5-bromouracil [A. P. Phillips, *J. Am. Chem. Soc.*, **73**, 1061 (1951)] and 5-bromoisocytosine [A. P. Phillips, *ibid.*, **75**, 4092 (1953)], replacement of the bromo by amines has been accomplished.

(9) C. K. Banks, *ibid.*, **66**, 1131 (1944).

reaction mixture in yields of 70–90% after about two hours of warming.

Similarly, 2,4-diamino-5,6-dichloropyrimidine reacted with *o*-mercaptoaniline under acid-catalyzed conditions to give IX in excellent yield. Under identical conditions of acid catalysis 2,4-diamino-5-bromo-6-chloropyrimidine reacted with aniline to give 2,4-diamino-5-bromo-6-anilinopyrimidine in excellent yield.

When the chlorobromopyrimidine, VI, and *o*-mercaptoaniline were combined in ethanol solution containing an excess of triethylamine, a nearly quantitative yield of the sulfide intermediate, VIII, 2,4-diamino-5-bromo-6-*o*-aminophenylmercaptopyrimidine, was obtained rapidly after a brief period of heating. The basic reaction conditions were used in this case in order to favor the displacement of the 6-chloro by the mercaptide anion. In the intermediate, VIII, presumably the same steric relationship, favorable for cyclization, exists as in the postulated isomeric intermediate, VII. Because of the lower nucleophilicity of the anilino nitrogen *no easy displacement* of the inert 5-bromo by it should be anticipated. As expected, VIII was easily isolable, and was stable to handling, to recrystallization, and to heating to its melting point.

The ultraviolet spectrum obtained from VIII was substantially in agreement with that of 2,4-diamino-5-bromo-6-phenylmercaptopyrimidine. This was prepared from 2,4-diamino-5-bromo-6-chloropyrimidine and thiophenol in a solution of ethanol containing triethylamine. The ultraviolet spectrum of VIII differed significantly from that of the diazophenothiazine product IX, and from that of 2,4-diamino-5-bromo-6-anilinopyrimidine (see Experimental).

Using triethylamine as a solvent 2,4-diamino-6-chloropyrimidine reacted with *o*-mercaptoaniline to form 2,4-diamino-6-(*o*-aminophenylmercapto)pyrimidine as expected.

The stable sulfide intermediate, VIII, was transformed rapidly, cleanly, and nearly quantitatively, by warming for a short period (ten to twenty minutes) in alcoholic hydrogen chloride, into the same diazaphenothiazine, IX, obtained previously. This transformation most probably involves a Smiles-type[10,11] rearrangement. A reasonable but tentative representation of the mode of acid-catalyzed Smiles-type rearrangement involved here is outlined in Fig. 3.

In acid solution, protonization of the pyrimidine ring at the 1-nitrogen should activate the 6-position for an initial intramolecular attack of the sulfide bond by the anilino nitrogen. Subsequently, a nearly synchronous rupture of sulfide bond at the 6-position of the pyrimidine should place the newly formed and highly nucleophilic sulfide anion in a favorable steric position such that rotation, around the newly formed carbon–nitrogen bond, would allow the mercaptide ion to attack the carbon–bromine bond at the adjacent 5-position. In the cyclic five-membered transition state hypothesized the two rings would appear in a spiro-type arrangement of two planes at right angles.

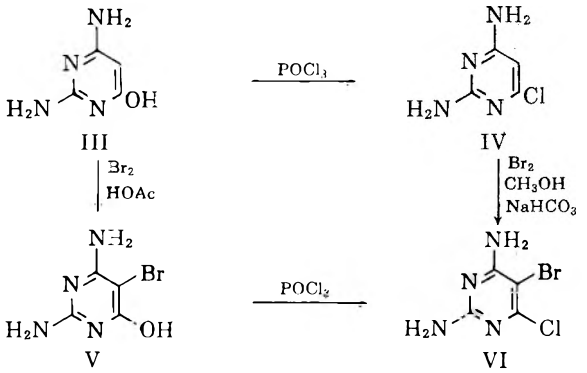


Figure 1

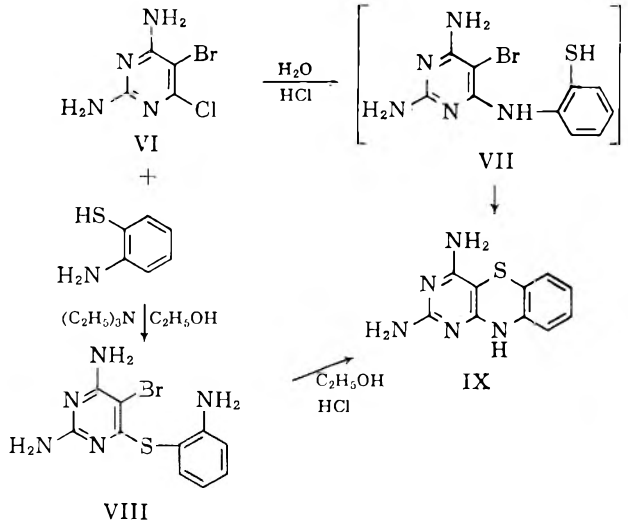


Figure 2

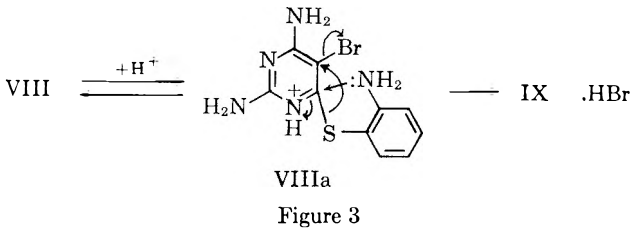


Figure 3

Experimental[12]

2,4-Diamino-5-bromo-6-chloropyrimidine (Compound VI).—To a rapidly stirred solution of a mixture of 15 g. (0.1 mole) of 2,4-diamino-6-chloropyrimidine (m.p. 202°) and 10 g. of sodium bicarbonate in 300 ml. of 50% aqueous methanol, was added dropwise a solution of 16 g. of bromine in 50 ml. of methanol over 30 min. After half the amount of bromine had been added, 5 g. of additional solid sodium bicarbonate was added to the reaction mixture. It was stirred for a total of 1.5 hr. The flocculent precipitate which separated was filtered off and washed with water. The product, 14 g. (62% yield), was crystallized from boiling water, m.p. 217°.

Anal. Calcd. for $C_4H_4BrClN_4$: C, 21.5; H, 1.8; N, 25.0. Found: C, 21.3; H, 1.6; N, 25.3.

Ultraviolet spectra: at pH 1: λ_{max} 300, ϵ 5480, λ_{min} 270, ϵ 1400; at pH 11: λ_{max} 296, ϵ 6750, λ_{min} 265, ϵ 1170.

2,4-Diamino-5,6-dichloropyrimidine.—The previous procedure was used except the pH was maintained at 6–6.5 by the addition of an aqueous methanolic solution of sodium bicarbonate and the chlorine gas was bubbled through the solution. The product, obtained in 50% yield, was crystallized twice from 20% methanol–water solution, m.p. 218°.[13]

(10) While the Smiles rearrangement of benzenoid compounds is usually accomplished in basic media, it is quite reasonable that this sort of migration in the pyrimidine series should be facilitated by acid catalysis, just as is the bimolecular displacement of the 6-chlorine by aniline.

(11) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).

(12) All melting points are uncorrected. All ultraviolet spectra in 50% aqueous methanol.

(13) S. J. Childress and R. L. McKee, *J. Am. Chem. Soc.*, **72**, 4271 (1950), reported m.p. 218°. This was a by-product in 11% yield.

Anal. Calcd. for $C_4H_4Cl_2N_4$: C, 26.8; H, 2.2; N, 31.3. Found: C, 26.8; H, 2.2; N, 30.8.

Ultraviolet spectra: at pH 1: λ_{max} 297, ϵ 6440, λ_{min} 265, ϵ 2480; at pH 11: λ_{max} 295, ϵ 7700, λ_{min} 265, ϵ 2200.

2,4-Diamino-5-bromo-6-phenylmercaptopyrimidine.—This was a model compound prepared to compare its spectral data with those of compound VIII.

A mixture of 2.3 g. (0.01 mole) of 2,4-diamino-5-bromo-6-chloropyrimidine and 1.1 g. (0.01 mole) of thiophenol in 50 ml. of ethanol containing 4 ml. of triethylamine was refluxed for 2 hr. The product was recrystallized successively from aqueous ethanol, aqueous methanol, and finally from an ethyl acetate–hexane mixture whereupon 1.5 g., m.p. 183–185°, was obtained.

Anal. Calcd. for $C_{10}H_9BrN_4S \cdot H_2O$: C, 38.1; H, 3.5. Found: C, 38.3; H, 3.3.

Ultraviolet spectra: at pH 1: λ_{max} 312, ϵ 15,300, λ_{min} 270, ϵ 5680; at pH 11: λ_{max} 301, ϵ 13,510, λ_{min} 270, ϵ 5620.

2,4-Diamino-5-bromo-6-anilinopyrimidine.—This was a model compound prepared to contrast with the spectral data of compounds VIII and IX.

A mixture of 0.01 mole of 2,4-diamino-5-bromo-6-chloropyrimidine and 1.5 g. of aniline hydrochloride in 50 ml. of water was heated at 100° for 3 hr. It was left at room temperature overnight when 1.5 g. of water-insoluble material separated. The aqueous filtrate was made basic with ammonia to pH 10. The basic product, after repeated crystallization from acetone, weighed 1 g., m.p. 208–209°.

Anal. Calcd. for $C_{10}H_{10}BrN_5$: C, 42.9; H, 3.6; N, 25.0. Found: C, 42.8; H, 3.6; N, 25.2.

Ultraviolet spectra: at pH 1: λ_{max} 295, ϵ 21,400, λ_{min} 270, ϵ 7800; at pH 11: λ_{max} 292, ϵ 21,700, λ_{min} 270, ϵ 9800.

2,4-Diamino-5-bromo-6-(*o*-aminophenylmercapto)pyrimidine (Compound VIII).—To a solution of 1.5 g. (0.012 mole) of *o*-mercaptoaniline in 80 ml. of ethanol containing 4 ml. of triethylamine was added 2.3 g. (0.01 mole) of 2,4-diamino-5-bromo-6-chloropyrimidine. The mixture was heated for 2 hr. on the water bath. Ethanol and excess triethylamine were removed by evaporation *in vacuo*. The residue was washed successively with ether and water to remove any triethylamine hydrochloride. The product, 2.7 g. (90%), crystallized as fluffy white crystals from methanol, m.p. 175–176°.

Anal. Calcd. for $C_{10}H_{10}BrN_5S$: C, 38.4; H, 3.2; N, 22.4. Found: C, 38.6; H, 3.0; N, 22.5.

Ultraviolet spectra: at pH 1: λ_{max} 312, ϵ 14,350, λ_{min} 275, ϵ 4140; at pH 11: λ_{max} 303, ϵ 14,200, λ_{min} 270, ϵ 3,280.

2,4-Diamino-5-chloro-6-(*o*-aminophenylmercapto)pyrimidine.—A solution of 1.8 g. of 2,4-diamino-5,6-dichloropyrimidine and 1.3 g. of *o*-mercaptoaniline in 70 ml. of triethylamine was refluxed for 45 min. An oily layer separated. The solvent was decanted and the oily product solidified on scratching to a waxy mass. It was washed successively with additional triethylamine and water. Recrystallization from acetone gave 2.8 g., m.p. 175–176°.

Anal. Calcd. for $C_{10}H_{10}ClN_5S$: C, 44.9; H, 3.7; N, 26.2. Found: C, 45.0; H, 3.6; N, 25.8.

2,4-Diamino-6-(*o*-aminophenylmercapto)pyrimidine.—This was prepared by the same procedure as that used for compound VIII from 10 g. of 2,4-diamino-6-chloropyrimidine and 9 g. of *o*-mercaptoaniline in 100 ml. of triethylamine solution containing 15 ml. of ethanol. On repeated crystallization from methanol there was obtained 7.5 g. of needles, m.p. 221–222°.

Anal. Calcd. for $C_{10}H_{11}N_5S$: C, 51.5; H, 4.7; N, 30.0. Found: C, 51.7; H, 4.9; N, 29.9.

Ultraviolet spectra: at pH 1: λ_{max} 287, ϵ 12,000, λ_{min} 265, ϵ 7240; at pH 11: λ_{max} 287, ϵ 11,300, λ_{min} 265, ϵ 5500.

2,4-Diamino-1,3-diazaphenothiazine (Compound IX). Method A.—A solution of 2.3 g. (0.01 mole) of 2,4-diamino-5-bromo-6-chloropyrimidine and 1.5 g. (0.012 mole) of *o*-mercaptoaniline in 100 ml. of water containing a few drops of concentrated hydrochloric acid[14] was heated for 2 hr. on a water bath. A clear yellow solution resulted within 15–20 min. On cooling a turbidity (disulfide) appeared. The solution was filtered and the product was precipitated from the clear filtrate by the addition of ammonia to pH 8–10. Recrystallization from acetone gave 2.1 g. (90%) of yellow crystals, m.p. 255–256°.

Anal. Calcd. for $C_{10}H_9N_5S$: C, 52.0; H, 3.9; N, 30.3; S, 13.8. Found: C, 52.2; H, 4.3; N, 30.3; S, 13.8.

Ultraviolet spectra: at pH 1: λ_{max} 268, ϵ 29,940, λ_{max} 295, ϵ 6600, λ_{min} 291, ϵ 6580; at pH 11: λ_{max} 255, ϵ 30,000, λ_{max} 293, ϵ 5940, λ_{min} 277, ϵ 4130.

The **hydrochloride** salt of the base was obtained by the addition of ethanolic hydrogen chloride to the acetone solution of 1 g. of this base. After recrystallization from methanol–ether mixtures, it melted at 336–337° dec.

Anal. for $C_{10}H_9N_5S \cdot HCl$: C, 44.8; H, 3.6; N, 26.2. Found: C, 45.0; H, 3.8; N, 25.6.

Compound IX was also obtained readily using 2,4-diamino-5,6-dichloropyrimidine with *o*-mercaptoaniline under the conditions of method A. When liberated as the base and recrystallized from acetone it melted at 255–256°.

Method B.—To a suspension of 7 g. (0.023 mole) of 2,4-diamino-5-bromo-6-(*o*-aminophenylmercapto)pyrimidine in 100 ml. of ethanol was added excess ethanolic hydrogen chloride to pH 1–2. After heating on a water bath for 10–20 min. the original white precipitate dissolved to give first a clear deep yellow solution after which a deep yellow precipitate separated. The product, m.p. 335–337° dec., was obtained in 95% yield. The mixture melting point with the hydrochloride, obtained by method A, was undepressed. The spectral and analytical data were identical.

This hydrochloride when neutralized afforded a base identical with that described previously.

Alternatively, when a clear solution of 1 g. of 2,4-diamino-5-chloro-6-(*o*-aminophenylmercapto)pyrimidine in 20 ml. of methanolic hydrogen chloride was warmed in a water bath for 1 hr., a precipitate appeared. It was worked up as before whereupon recrystallization from methanol–ether mixtures gave the product, m.p. 335–337°. The mixture melting point with the product from method B above was undepressed.

Acknowledgment.—The authors wish to thank Ronald E. Brooks for his assistance in the early part of this project.

(14) Alternatively, the hydrochloride salt of *o*-mercaptoaniline could be used without any additional acid.

Thiadiazoles. II. Formation of 4-Amino-1,2,5-thiadiazole-3-carboxylic Acid and Its Derivatives by Ring-Cleavage of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one[1,2]

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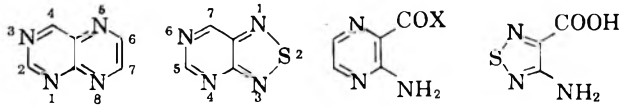
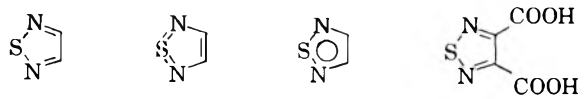
Basic reagents cleave the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII) under mild conditions. The products of these reactions are derivatives of the recently described 1,2,5-thiadiazole ring. These reactions, which afford 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV) and its derivatives, comprise a new method for the synthesis of 1,2,5-thiadiazoles. The mode of ring-opening and the properties of the thiadiazoles are discussed.

The isoelectronic relationship between the pteridine ring (I) and the [1,2,5]thiadiazolo[3,4-*d*]pyrimidine ring (II) was shown to be manifested in similarities in a number of properties of derivatives of these two ring systems.[2] Under basic conditions, certain pteridines suffer cleavage of the pyrimidine ring, giving rise thereby to derivatives of 3-aminopyrazinoic acid (IIIa).[3,4] Confirmation[2] of the predicted resemblance of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines and pteridines indicated that 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV) and its derivatives would be formed by the action of basic reagents on [1,2,5]thiadiazolo[3,4-*d*]pyrimidines. Ring-opening reactions of 4-quinazolones[5] provided a further precedent for this projected transformation.

Until recent years, the 1,2,5-thiadiazole ring (Va–c) was known only in compounds, such as the 2,1,3-benzothiadiazoles, in which it is fused to another ring system.[6,7] The first monocyclic 1,2,5-thiadiazoles[8] were obtained by oxidation of 2,1,3-benzothiadiazoles.[9–11] A study by Khaletskiĭ, Pesin, and Chou[9] of the effect of oxidizing agents on 2,1,3-benzothiadiazoles led to the isolation of 1,2,5-thiadiazole-3,4-dicarboxylic acid (VI), its 1,1-dioxide, and the semicarbazone of 1,2,5-thiadiazole-3,4-dicarboxaldehyde. The oxidation of 2,1,3-benzothiadiazoles to 1,2,5-thiadiazole-3,4-dicarboxylic acid (VI), the conversion of this compound to various carboxylic acid derivatives, and the obtaining of 1,2,5-thiadiazole-3-carboxylic acid and its derivatives *via* decarboxylation of VI have been reported by Carmack, Weinstock, and Shew[7,10] and by Sekikawa.[11] In addition, the former investigators have prepared the parent compound 1,2,5-thiadiazole (V).



I II IIIa. X = OH IIIb. X = NH_2 IV



Va Vb Vc VI

Reaction of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII) with ethanolic ammonia at 80° gave a compound with the composition of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII). 4-Amino-1,2,5-thiadiazole-3-carboxylic acid (IV) was isolated after treatment of VII with aqueous potassium hydroxide, and the hydrazide (IX) of this acid was obtained in 95% yield by treating VII with hydrazine. The compounds represented by structures[12] IV, VIII, and IX are the products expected by analogy with ring-cleavage reactions of pteridines[4] and other fused-ring heterocycles.[5] Confirmation of the structure of the amino carboxamide (VIII) was obtained by reclosing the pyrimidine ring, to VII, with ethyl orthoformate containing a catalytic amount of *p*-toluenesulfonic acid. The amino acid (IV) was related structurally to the carboxamide VIII by alkaline hydrolysis of the latter compound to IV.

Two products were isolated from the reaction of VII with refluxing butylamine: one of these was 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide (X), isolated in 45% yield; the second product proved to be 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII), isolated in 37% yield. Similarly, anhydrous methylamine gave a

(1) This investigation was supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, contract no. SA-43-ph-1740.

(2) Part I: Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2154 (1962).

(3) For example: (a) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945); (b) J. H. Mowat, J. H. Boothe, B. L. Hutchings, E. L. R. Stokstad, C. W. Waller, R. B. Angier, J. Semb, D. B. Cosulich, and Y. Subba Row, *ibid.*, **70**, 14 (1948); (c) E. C. Taylor, Jr., *ibid.*, **74**, 1651 (1952); (d) E. C. Taylor, Jr., *ibid.*, **74**, 2380 (1952); (e) E. C. Taylor, Jr., J. A. Carbon, and D. R. Hoff, *ibid.*, **75**, 1904 (1953); (f) E. C. Taylor, O. Vogl, and P. K. Loeffler, *ibid.*, **81**, 2479 (1959); (g) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952); (h) A. Albert, *ibid.*, 2690 (1955); (i) A. Albert, D. J. Brown, and H. C. S. Wood, *ibid.*, 2066 (1956); (j) D. J. Brown and N. W. Jacobsen, *ibid.*, 1978 (1960); (k) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **26**, 2364 (1961); (l) W. V. Curran and R. B. Angier, *ibid.*, **27**, 1366 (1962).

(4) E. C. Taylor, Jr., "Chemistry and Biology of Pteridines, Ciba Foundation Symposium," G. E. W. Wolstenholme and M. P. Cameron, Ed., Little, Brown and Co., Boston, Mass., 1954, pp. 2–34.

(5) (a) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 341 (1946); (b) N. J. Leonard, W. V. Ruyle, and L. C. Bannister, *ibid.*, **13**, 617 (1948); (c) N. J. Leonard and W. V. Ruyle, *ibid.*, **13**, 903 (1948).

(6) L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Vol. 4, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1952 pp. 205–211.

(7) W. R. Sherman, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, pp. 579–586.

(8) However, a fused-ring derivative in which the thiadiazole ring has aliphatic substituents, derived from the bornane skeleton, had been claimed earlier: D. C. Sen, *J. Indian Chem. Soc.*, **15**, 537 (1938). Other than this claim, only three 1,2,5-thiadiazoles[6] had been reported in the periodical literature prior to the initiation of our work.

(9) (a) A. M. Khaletskiĭ, V. G. Pesin, and T. Chou, *Dokl. Akad. Nauk SSSR*, **114**, 811 (1957); *Chem. Abstr.*, **52**, 4605i (1958); (b) V. G. Pesin, A. M. Khaletskiĭ, and T. Chou, *Zh. Obshch. Khim.*, **28**, 2089 (1958); see English translation, *J. Gen. Chem. USSR*, **28**, 2126 (1958), Consultants Bureau, Inc., New York, N. Y.

(10) (a) M. Carmack, L. M. Weinstock, and D. Shew, Abstracts of Papers, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959, p. 37P; (b) M. Carmack, D. Shew, and L. M. Weinstock, U. S. Patent 2,980,687 (April 18, 1961); *Chem. Abstr.*, **55**, 21147h (1961); U. S. Patents 2,990,408 and 2,990,409 (June 27, 1961); *Chem. Abstr.*, **56**, 4775 (1962).

(11) I. Sekikawa, *Bull. Chem. Soc. Japan*, **33**, 1229 (1960).

(12) Although structures Vb and Vc may be more nearly in accord with evidence[13] that 1,2,5-thiadiazole is aromatic, structure Va is used for the sake of simplicity throughout this discussion.

(13) R. A. Bonham and F. A. Momany, *J. Am. Chem. Soc.*, **83**, 4475 (1961).

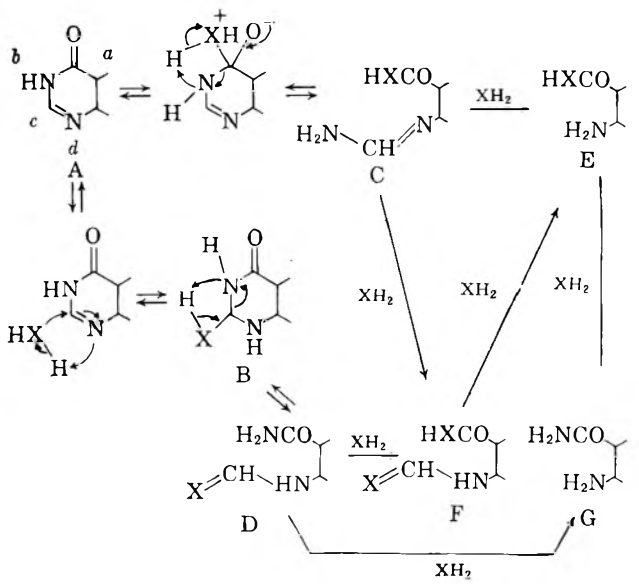
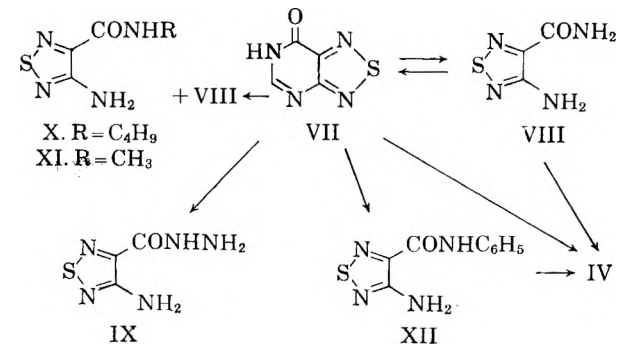


Fig. 1.—X = RN, O, HN, NH_2N. *a* = position 7 of VII or 4 of 4-pteridinones. *c* = position 5 of VII or 2 of 4-pteridinones.

crude product that was predominantly the *N*-methyl amide (XI), but paper chromatography revealed the presence of some 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII). The pure *N*-methyl amide was obtained in 41% yield, and a small amount of the unsubstituted amide (VIII) was also isolated.

Treatment of VII with aniline in the presence of a small quantity of hydrochloric acid gave 4-amino-1,2,5-thiadiazole-3-carboxanilide (XII). Under comparable conditions, ring-opening was not effected either by anhydrous aniline or by aniline containing a small amount of water. The carboxanilide has also been isolated when the preparation of VII from 5,6-diaminopyrimidin-4(3*H*)-one sulfate has been conducted on a large scale. Aniline, formed in the reaction from *N*-sulfinylaniline, must have reacted with VII through the intervention of protons, originating from the pyrimidine sulfate, and water added during the isolation. The formation of XII during the preparation of VII has not been observed when the pyrimidine free base was used as the starting material and the product isolated without adding water. In the reaction of VII with the weak base aniline, it seems likely that equilibria established between VII and ring-opened intermediates are overwhelmingly in favor of VII and that the addition of aqueous acid shifts the equilibria by hydrolyzing a ring-opened intermediate to XII. The carboxanilide was hydrolyzed by aqueous base to 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV).



Basic cleavage of the pyrimidine ring of quinazolines,[5] purines[14] (especially *N*-substituted purines), *v*-triazolo-[4,5-*d*]pyrimidines,[15] and other heterocyclic systems, besides the pteridines, is known; and rearrangement and amine-exchange reactions of such fused heterocycles and of pyrimidines have been explained by postulating opening and reclosure of the pyrimidine ring.[5,14,16] Ring-opening of VII is, however, more appropriately compared with ring-opening of its electronic analogs, the 4-pteridinones. The 1,2,5-thiadiazoles were formed from VII under milder conditions than those reported[3b,4] for the cleavage of 4-pteridinones not substituted on the ring-nitrogen atoms. For example, aqueous base cleaved VII within one-half hour at 100° and in less than three hours at 50°, whereas several hours of refluxing were required for the cleavage of 4-pteridinone.[3i] (*N*-substituted 4-pteridinones are more easily cleaved than are those without substituents on the ring-nitrogen atoms.[3d,3i])

The isolation of 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV) from the alkaline cleavage of VII under mild conditions suggests superficially that initial attack occurred at position 7. On the other hand, it is difficult to see how 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) could be formed by initial attack of butylamine or methylamine at position 7. In Fig. 1 the transformations depicted with partial structures A–G, representing VII or 4-pteridinones and 1,2,5-thiadiazoles or pyrazines, show pathways by which the terminal products E and G (*e.g.*, IV and VIII–XII) may be formed by initial attack of the nucleophilic agent at either position 5 (*c* of A) or position 7 (*a* of A), the later stages (E, F, G) resulting from hydrolysis or amine-exchange reactions of formamidine and amide groups. Evidence for reaction at *c* or at both *a* and *c* is available from the pteridine series.[17]

Alkaline hydrolysis, mentioned previously, of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) to the carboxylic acid IV was conducted under the same conditions used to prepare IV from VII. This reaction not only related the amide and the acid structurally, but also demonstrated that the amide might have been an intermediate[19] in the formation of IV from VII. In order to determine whether 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) might be a precursor of the *N*-alkyl amides (X and XI), an amide-exchange reaction was attempted by treating VIII with butylamine under the conditions used in the reaction of butylamine with VII.

(14) E. Shaw, *J. Org. Chem.*, **27**, 883 (1962), and references cited therein; G. B. Elion, *ibid.*, **27**, 2478 (1962); E. Fischer, *Ber.*, **31**, 3266 (1898).

(15) L. L. Bennett, Jr., and H. T. Baker, *J. Org. Chem.*, **22**, 707 (1957); J. S. Webb and A. S. Tomcufcik, U. S. Patent 2,714,110 (July 26, 1955).

(16) D. J. Brown, *Nature*, **189**, 828 (1961); E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

(17) Although the formation of 3-aminopyrazinoic acids and *N*-substituted 3-aminopyrazinamides from 4-pteridinones also suggests reaction at *a*, this obvious interpretation was contradicted by Taylor's finding[4] that ring-opening of a 4-pteridinone by isopropylamine, which gave the *N*-isopropyl amide at 200°, gave the unsubstituted amide at a lower temperature (150°). The formation of both 3-amino-*N*-methylpyrazinamide and 3-aminopyrazinoic acid from 3-methyl-4(3*H*)-pteridinone under conditions that did not hydrolyze the amide to the acid was cited by Wood[18] as evidence for ring-opening at both *a* and *c*. More recently, Curran and Angier[3k] have obtained *N*-substituted 3-formamidopyrazinamides by basic cleavage of 3-substituted 4-pteridinones and, though they do not rule out two modes of fission, favor one mode, namely, reaction at *c*. *Cf.* E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Am. Chem. Soc.*, **82**, 6058 (1960); **83**, 2786 (1961).

(18) H. C. S. Wood, pp. 35–42 of reference cited in footnote 4; *cf.* ref. 3i.

(19) Both 3-aminopyrazinamide (IIIb) and 3-aminopyrazinoic acid (IIIa) have been obtained[3b] from an alkaline hydrolysis of 4-pteridinone.

TABLE I

PHYSICAL PROPERTIES OF 1,2,5-THIADIAZOLES

Compound	pH	Ultraviolet data[a] λ_{max} in mμ ($\epsilon \times 10^{-3}$)[b]	Infrared data[c] $\bar{\nu}$ in cm.$^{-1}$ 1700–1400-cm.$^{-1}$ region	900–650-cm.$^{-1}$ region	Paper chromatographic data[d] R_f values A	B	C	D	Color of fluorescence[e]
VIII	1	214 (10.9), 326 (6.2)	1700s, 1605s	865ms, 850ms	0.68	0.79	0.73	0.59	BL
	7	213 (11.0), 326 (6.2)	1510w, 1470s	800ms, 730w					BS
	13	326 (6.2)	1400ms	680s					
	1 *N* HCl	213 (10.6), 325 (6.1)							
	5.4 *N* HCl	216 (9.5), 263 (2.3), 326 (5.2)							
	6 *N* HCl[i]	263 (4.0), 323 (4.3)							
XI	1	326 (7.0)	1665s, 1605s	860ms, 810ms	.79	.86	.81	.70	BL
	7	325 (7.0)	1550s, 1500w	790w, 750w					BS
	13	326 (7.0)	1445ms 1400mw						
X	1	213 (11.4), 326 (7.4)	1655s, 1600s	855ms, 820ms	.90	.93	.89	.73	BL
	7	213 (11.4), 326 (7.4)	1535s, 1500w	795w, 750ms					BS
	13	326 (7.4)	1460sh., 1450ms 1420m, 1400w	705w, 650m					
IX	1	215 (11.1), 331 (7.0)	1665ms, 1600s	895m, 855ms	.84	...	...	.62	BL
	7	212 (11.0), 326 (7.4)	1555ms, 1500w	815m, 760m					BS
	13	325 (10.0)	1445m	670mw					
XII	1	232 (11.2), 280 (3.7), 336 (10.3)	1675s, 1605s 1540s, 1490mw	900mw, 855m 840m, 800m	.88	.93	.86	...	VL VS
	7	232 (11.3), 280 (3.8), 336 (10.2)	1450s, 1435sh 1400w	790mw, 755s 690m					
	13	230 (sh), 330 (10.0)							
IV	1	328 (6.3)	1690s, 1600s	850ms, 810ms	.13	.76	.47	.79	BL or VL[f]
	7	316 (6.7)	1515mw, 1465s	710s					VS
	13	316 (6.7)							
K salt of IV			1620s, 1510m 1445m	880w, 860m 825m, 810m 755m					
3-Amino-pyrazinamide (IIIb)	1	241 (12.1), 352 (6.8)	1690s, 1610s	900m, 850m					
	7	246 (11.5), 350 (6.4)[g]	1555ms, 1520w	815ms, 770mw					
	13	245 (12.8), 350 (6.4)	1440ms	740m, 650m					
	1 *N* HCl[h]	241 (12.6), 352–353 (7.1)							
	6 *N* HCl[h]	242 (12.6), 354 (7.1)							

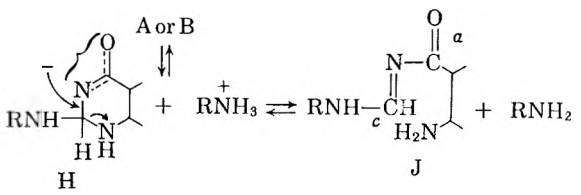
[a] Only VIII, IX, and X in neutral and acidic solutions were examined in the region 220–210 mμ. Spectra of 1 *N* and 6 *N* hydrochloric acid solutions were determined by dissolving specimens directly in these solvents, determining the spectra within 5 min., and redetermining the spectra 10 min. later as a test of stability. [b] A slight shoulder appears at 225–230 mμ in all of the thiadiazole spectra except those of IV at pH 7 and 13, that of VIII in 6 *N* HCl, and those of XII, in which a plateau or maximum is present at 230–232 mμ. [c] s = strong, m = medium, w = weak. [d] Solvent systems A, B, C, D are defined in ref. 26. [e] BL = Blue fluorescence in long wave length light (365 mμ), BS = blue fluorescence in short wave length light (254 mμ), VL and VS have the same meaning for violet fluorescence. [f] Violet in solvent D. [g] Data at pH 7 in agreement with data of Albert[3h] at pH 6. [h] In over-all shape, the differences among the three curves produced by the acidic solutions are much less than the difference between the spectra given by the neutral and the 0.1 *N* hydrochloric acid solutions. [i] Not determined in the region 220–210 mμ

The pure amide VIII was recovered in 90% yield. The reaction G → E (X = RN) is, therefore, not essential in the formation of the *N*-alkyl amides (X and XI).[20] Failure of the transamidation may be interpreted as evidence for separate and simultaneous attack at both *a* and *c*, but this evidence is not unequivocal for at least two reasons. First, the *N*-alkyl amides might be formed by the route B → D → F → E (X = RN), the transamidation occurring prior to the liberation of the amino group. The finding of Curran and Angier[3k] that 3-formamidopyrazinamides are more easily hydrolyzed than 3-aminopyrazinamides is consistent with this possibility and also provides a possible explanation for the results of Wood.[17] Secondly, attack at *c* could lead to fission of the *c*–*d* bond and generate an intermediate from which both VIII and the *N*-alkyl amides might be formed.[21]

(20) This conversion may have occurred to some extent during the reaction of methylamine with VII since the latter reaction was allowed to proceed for a longer period of time than the reaction with butylamine.

Some of the physical properties of the 1,2,5-thiadiazoles are summarized in Table I. The ultraviolet spectra of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) at pH 1, 7, and 13 are identical. The *N*-methyl (XI) and *N*-butyl (X) amides likewise give identical spectra at these three pH values, and the spectra of all

(21) In basic solution, A should be present partly or entirely, depending on the basic strength of the medium, as the anion. Species H may be formed from the anion of A or by ionization of B (Fig. 1). The acylformamidine (J) should react at the carbonyl carbon atom (*a*), this course



giving the *N*-alkylamides (X and XI). The amide VIII may be formed simultaneously by attack at the formamidine carbon atom (*c*) or by the amidine-exchange reaction D → G (Fig. 1), if initial attack at *c* of A were to give both D and J.

three amides, as well as that of the acid hydrazide (IX) at pH 7, are essentially the same except for slight differences in intensity. The spectrum of 4-amino-1,2,5-thiadiazole-3-carboxamide in 1 *N* hydrochloric acid is also unchanged. All of these spectra display an absorption maximum at 326 mμ. When the spectra of the amide (VIII), the *N*-butyl amide (X), and the acid hydrazide (IX) at pH 1 and 7 were examined between 220 and 210 mμ, a maximum was found near 214 mμ.

The constancy of the spectra of VIII, X, and XI within a broad range of pH values suggests that the neutral molecules are present in the acidic solutions and that these amino carboxamides, therefore, are very weak bases. This evidence is supported by the failure of VIII to form an isolable hydrochloride with anhydrous hydrogen chloride in ethanol. However, the presence of both the cation and the neutral molecule of VIII in strong hydrochloric acid (5.4–6*N*) is indicated by decreased intensity of the ultraviolet maxima at 326 mμ and 214 mμ and by the appearance of a maximum at 263 mμ. In comparison, 3-aminopyrazinamide (IIIb), the pyrazine analog[22] of VIII, must be present chiefly as the cation in 0.1 *N* hydrochloric acid since its spectrum in this solution differs slightly, but palpably, from the spectra given by neutral and alkaline solutions and undergoes little additional change as the acidity is increased to 1 *N* and 6 *N* hydrochloric acid. By utilizing generalizations[24] for protonation of π-deficient heterocycles, these data may be interpreted further. The slight change in the spectrum of 3-aminopyrazinamide (IIIb) in acidic solution suggests protonation on a ring-nitrogen atom,[25] whereas the large change represented by the appearance of a maximum at 263 mμ in the spectrum of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) in strong acid suggests protonation on the amino-nitrogen atom. The spectra of VIII and the pyrazine derivative (IIIb) are otherwise similar in appearance, but the maxima of the thiadiazole derivative (VIII) are displaced hypsochromically by approximately 25 and 32 mμ, respectively, from the long and short wave length maxima of the pyrazine analog in neutral solution. The absorption maximum (316 mμ) of the amino acid (IV) at pH 7 shows a similar hypsochromic shift with respect to that reported[3h] (340 mμ) for 3-aminopyrazinoic acid at pH 6.

The infrared spectra of all of the 1,2,5-thiadiazoles have bands of medium or medium–strong intensity at 860–850 cm.$^{-1}$ and 820–800 cm.$^{-1}$, as does 3-aminopyrazinamide; a strong band, presumably due to NH_2-deformation vibrations, at 1610–1600 cm.$^{-1}$; the expected bands in the 3-μ and 6-μ regions corresponding to N—H and C=O stretching vibrations; and, except for IV and VIII, a band at 1555–1535 cm.$^{-1}$ in the region of secondary amide II bands.

Experimental[26]

4-Amino-1,2,5-thiadiazole-3-carboxamide (VIII).—A mixture of 308 mg. of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII), 15 ml. of absolute ethanol, and 15 ml. of liquid ammonia was heated in a 50-ml. stainless steel bomb at 80° for 18 hr. (On a larger scale the proportion of starting material was increased almost fourfold.) The reaction solution was removed from the chilled bomb and concentrated *in vacuo* at room temperature to approximately 5 ml. The crystalline precipitate (m.p. 164–166°) amounted to 197 mg. after it had been washed with ethanol (2 ml.) and dried *in vacuo* at 56°; a second crop (m.p. 168–169°), which was obtained by evaporating the solvent *in vacuo* from the filtrate and recrystallizing the residue from ethanol–hexane, raised the yield of crude product to 82%. Recrystallization from ethanol–hexane (1:1) or sublimation (*e.g.*, at 0.15–0.2 mm. and 100–105°) gave pure VIII; yields, 61–66%; m.p. 170–171°.

Anal. Calcd. for $C_3H_4N_4OS$: C, 24.99; H, 2.80; N, 38.87; S, 22.24. Found: C, 25.27; H, 2.67; N, 39.03; S, 22.35.

No precipitate was formed when a large excess of dry hydrogen chloride was passed into an ethanol solution of VIII. The free base was recovered (97%) by concentrating the solution *in vacuo*.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid (IV). a. From VII.—A solution of 462 mg. (3.0 mmoles) of [1,2,5]thiadiazolo-[3,4-*d*]pyrimidin-7(6*H*)-one (VII) in 10 ml. of 1.2 *N* aqueous potassium hydroxide was heated at the reflux temperature for 30 min., filtered, and acidified to pH 1.6 with 6 *N* hydrochloric acid. The crystalline precipitate that formed at pH 3–1.6 melted at 220° and depressed the melting point of the starting material; yield, 282 mg. (65%). The product was recrystallized from water; m.p. 220–221° (with sublimation); recovery, 80%.

Anal. Calcd. for $C_3H_3N_3O_2S$: C, 24.83; H, 2.09; N, 28.95; S, 22.09. Found: C, 24.86; H, 2.07; N, 29.01; S, 22.05.

b. From 4-Amino-1,2,5-thiadiazole-3-carboxamide.—A mixture of 288 mg. (2 mmoles) of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII), 10 ml. of 2 *N* aqueous potassium hydroxide, and 10 ml. of ethanol was heated at the reflux temperature for 30 min. Acidification of the reaction mixture to pH 1.2 with 6 *N* hydrochloric acid and concentration of the acidified mixture afforded 210 mg. (72%) of a white crystalline solid (m.p., 220–222° subl.) that produced infrared and ultraviolet absorption spectra identical with those of 4-amino-1,2,5-thiadiazole-3-carboxylic acid obtained from VII.

c. From 4-Amino-1,2,5-thiadiazole-3-carboxanilide (XII).—A solution of 42.5 g. of XII, 1 l. of absolute ethanol, and 400 ml. of 4 *N* aqueous potassium hydroxide was heated at the reflux temperature for 2.5 hr. The potassium salt separated from the cold reaction mixture in 94% yield (33.19 g.), and a portion was recrystallized from water–ethanol; m.p. 338–340° dec. (Al block).

Anal. Calcd. for $C_3H_2N_3OSK$: C, 19.67; H, 1.10; N, 22.93; S, 17.50. Found: C, 19.73; H, 1.38; N, 23.09; S, 17.3.

The remainder of the potassium salt (31.4 g.) was dissolved in 500 ml. of warm water, and the solution was filtered and acidified with 6 *N* hydrochloric acid. The white crystalline product, consisting of a first crop of 20.36 g. (82%) and a second crop of 1.8 g. (7%), was identified by melting point (221°) and by infrared and ultraviolet spectra as 4-amino-1,2,5-thiadiazole-3-carboxylic acid.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid Hydrazide (IX).—A solution of 462 mg. of VII in 27 ml. of anhydrous hydrazine was heated at 95–100° for 105 min. and then evaporated to dryness *in vacuo*. The residue was triturated with 5 ml. of ethanol and with 10 ml. of hexane and dried *in vacuo* over phosphorus pentoxide; yield, 452 mg. (95%); m.p. 202–204° dec. (oil bath). Recrystallization from water gave yellow needles that melted at 206°.

(22) The isoelectronic relationship of the 1,2,5-thiadiazole ring and the pyrazine ring has been noted by Carmack[10a] and by Koutecky.[23]

(23) R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.*, **26**, 156 (1961).

(24) A. Albert, "Heterocyclic Chemistry," The Athlone Press, University of London, 1959, pp. 49, 302.

(25) *Cf.* G. W. H. Cheeseman, *J. Chem. Soc.*, 242 (1960), for protonation of 2-aminopyrazines.

(26) Unless otherwise noted, melting points were determined with a Kofler Heizbank melting point apparatus and are corrected. Infrared spectra were determined with samples in pressed potassium bromide disks and with a Perkin-Elmer Model 221G spectrophotometer with the sodium chloride prism–grating interchange. Ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer. Solutions for ultraviolet determinations were prepared by dissolving the sample in water or ethanol and diluting 5-ml. aliquot portions to 50 ml. with 0.1 *N* hydrochloric acid, pH 7 phosphate buffer, and 0.1 *N* sodium hydroxide. Spectra given by these solutions of a compound are considered to be its spectra at pH 1, 7, and 13. Paper chromatography was performed by the descending technique on Whatman no. 1 paper in the following solvent systems: (A) butanol saturated with water, (B) butanol–acetic acid–water (5:2:3 by volume), (C) 2-propanol–water–concentrated aqueous ammonia (70:25:5 by volume), and (D) acetate buffer (pH 6.7). Spots were detected with two ultraviolet lamps that emit light principally at 365 and 254 mμ.

Anal. Calcd. for $C_3H_5N_5OS$: C, 22.63; H, 3.17; N, 44.00; S, 20.13. Found: C, 22.75; H, 3.27; N, 43.73; S, 20.31.

Reaction of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one with Butylamine.—A solution of 2.31 g. of VII (m.p. 234° dec., 98% pure by ultraviolet absorption) and 35 ml. of dry, redistilled butylamine was heated at the reflux temperature for 3 hr. and then concentrated *in vacuo* to a sirup. The residue was slurried with a mixture of ethanol (3 ml.) and hexane (10 ml.). A white crystalline solid that formed in the slurry was separated by filtration and washed with 6 ml. of hexane. This fraction was chromatographically homogeneous and was shown by melting point (169–170°, not depressed by VIII), infrared spectrum, and paper chromatographic characteristics to be **4-amino-1,2,5-thiadiazole-3-carboxamide (VIII)**; yield, 800 mg. (37%).

The filtrate combined with the washings deposited 1.34 g. (45%) of chromatographically homogeneous **4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide (X)** (m.p., 79–80°). An analytical sample was obtained as white needles by recrystallization from hexane; m.p. 82–84°.

Anal. Calcd. for $C_7H_{12}N_4OS$: C, 41.98; H, 6.04; N, 27.98; S, 16.01. Found: C, 42.21; H, 5.77; N, 27.79; S, 15.83.

4-Amino-N-methyl-1,2,5-thiadiazole-3-carboxamide (XI).—The conditions for the reaction of VII with anhydrous methylamine were identical with those employed in the preparation of VIII. Evaporation of the volatile components from the reaction mixture and sublimation of the residue at 90° and 0.2 mm. gave a white sublimate, in 70% yield calculated as XI, that melted at 122–124°. Paper chromatography showed the presence of two components: the preponderant component was identical with pure XI obtained subsequently; the minor, more slowly moving spot had the same R_f values in four solvent systems as 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII). Recrystallization of the sublimate from water gave white needles; m.p. 136–137°; yield from VII, 41%.

Anal. Calcd. for $C_4H_6N_4OS$: C, 30.37; H, 3.82; N, 35.42; S, 20.27. Found: C, 30.39; H, 3.78; N, 35.58; S, 20.20.

4-Amino-1,2,5-thiadiazole-3-carboxamide (VIII) was isolated in 10% yield from a larger reaction by extracting XI from the total reaction residue with hexane in a Soxhlet extractor.

4-Amino-1,2,5-thiadiazole-3-carboxanilide (XII).—A mixture consisting of 308 mg. (2 mmoles) of VII, 10 ml. of aniline, and 0.2 ml. of 12 *N* hydrochloric acid was heated at 100° for 4.5 hr. The ultraviolet spectrum at pH 1 of an aliquot removed after 3 hr. of heating showed that ring-opening was essentially complete. Concentration of the reaction mixture *in vacuo* left an orange oil that solidified when 20% ethanol was added. The crystalline product (m.p. 137–140°) was filtered from the cold mixture, washed with 10% ethanol, and dried *in vacuo* at 78°; yield, 274 mg. (62%). Beige crystals obtained by recrystallization from 60% ethanol melted at 141°.

Anal. Calcd. for $C_9H_8N_4OS$: C, 49.08; H, 3.66; N, 25.44; S, 14.56. Found: C, 48.91; H, 3.72; N, 25.13; S, 14.7.

An experiment identical with the one described before except for the omission of hydrochloric acid was performed simultaneously. Ultraviolet spectra at pH 1 of aliquots removed after 3 hr. and 5.5 hr. of heating were essentially identical with the spectrum of the starting material (VII). Additional heating up to 70 hr. caused slow deterioration of the reaction mixture, although ultraviolet absorption characteristic of VII was still observable after 22 hr. No evidence for the formation of XII could be gleaned from the ultraviolet examination of the reaction mixture.

A third experiment that was identical with the first except for the addition of 0.2 ml. of water instead of hydrochloric acid showed that the starting material was practically unaffected up to 25 hr. after heating was begun. Continued heating caused the long wave length maximum to shift toward longer wave lengths, but after several days it was still about 15 mμ from that of XII.

The carboxanilide (XII) was also isolated from certain reactions carried out to prepare VII on a large scale (see subsequent description).

Cyclization of 4-Amino-1,2,5-thiadiazole-3-carboxamide (VIII) to [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII).—A mixture of 288 mg. of 4-amino-1,2,5-thiadiazole-3-carboxamide, 20 ml. of triethyl orthoformate, and a crystal of *p*-toluenesulfonic acid monohydrate was heated at the reflux temperature for 3 days. Ten milliliters of triethyl orthoformate was added to the heterogeneous mixture, and heating was continued for 4 days. A small amount of suspended white solid (19 mg.; m.p. 230–250° dec.) was removed by filtration, and the filtrate was evaporated to dryness. The yellow crystalline residue was triturated with 1:1 hexane–ethanol, separated by filtration, and dried *in vacuo* at 65° for 2 hr.; wt., 160 mg. (52% yield); m.p. 229–232° dec. (oil bath) (lit.[2] m.p. 234°). Ultraviolet spectra at pH 1, 7, and 13 and the infrared spectrum were identical with those of [1,2,5]-thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.

Attempted Transamidation of 4-Amino-1,2,5-thiadiazole-3-carboxamide.—A mixture of 288 mg. of VIII and 10 ml. of dry, redistilled butylamine was heated at the reflux temperature for 3 hr. and then concentrated *in vacuo* to dryness. The crystalline residue was slurried with a mixture of ethanol (3 ml.) and hexane (10 ml.) and was then collected by filtration; wt., 258 mg. (90% recovery); m.p. 172°. The infrared spectrum and paper chromatograms of this material showed that it was pure VIII. A small fraction (13 mg., m.p. 162–166°) obtained from the filtrate was shown by paper chromatography to be VIII contaminated with small amounts of impurities, one of which may have been the *N*-butyl amide (X).

[1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII).—Although VII was prepared[2] on a small scale from *N*-sulfinylaniline and either 5,6-diaminopyrimidin-4(3*H*)-one free base or its sulfate, large-scale reactions utilizing the sulfate afforded large amounts of 4-amino-1,2,5-thiadiazole-3-carboxanilide (XII) as well as VII. The isolation procedure included the evaporation of pyridine from the reaction mixture followed by the addition and re-evaporation of water to aid in the removal of traces of pyridine and aniline (formed in the reaction from *N*-sulfinylaniline). Under the catalytic influence of protons originating from the pyrimidine sulfate, aniline may have reacted with VII during the prolonged evaporation of pyridine from the large reaction mixtures, or water added during the isolation may have participated in the ring-opening of VII. The following steps carried out in accordance with the general procedure[2] for the preparation of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines constitute an improved procedure for preparing VII from the pyrimidine free base.

A mixture of 30 ml. of *N*-sulfinylaniline, 300 ml. of anhydrous pyridine, and 11.0 g. of 5,6-diaminopyrimidin-4(3*H*)-one free base (obtained by dissolving 17.5 g. of the sulfate in 900 ml. of boiling water, neutralizing the hot solution with 6 *N* ammonia, and recrystallizing the cream colored crystals from water) was heated at the reflux temperature for 1.75 hr., cooled, stirred with activated carbon, concentrated *in vacuo* to about 150 ml., and chilled (−12°). The white crystalline precipitate was washed with benzene; wt., 9.56 g. (71%); m.p. 234° dec. A second portion of 1.48 g. (11%) was obtained by recrystallizing, from water, second and third crops (total crude yield, 93%) obtained by diluting the filtrate from crop 1 with water and benzene. Both crop 1 and the second portion had ultraviolet maxima and extinction coefficients essentially identical with those of the analytical sample.[2]

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Preparation and Reactions of 1-(Nitroguanyl)aziridines

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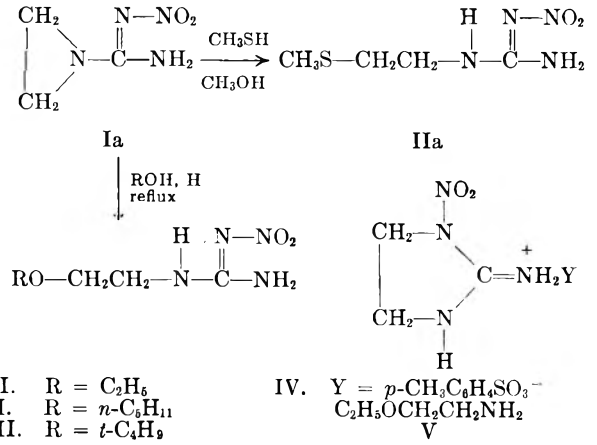
The formation of two 1-(nitroguanyl)aziridines was achieved by the reaction of 2-methyl-1-nitro-2-thiopseudourea with ethyleneimine and 2-methylaziridine. Cleavage of these aziridines in acidic media produced linear alkylnitroguanidines. The cyanobromination of 1-(nitroguanyl)aziridine (Ia) gave 3-cyano-2-imino-1-nitroimidazolidine (VIII) and 2-amino-1-nitroimidazolidinium bromide (IX) in good yields.

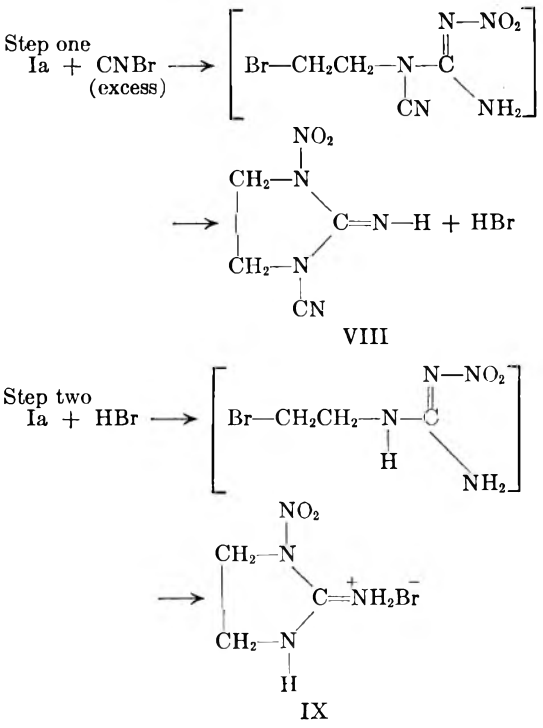
Amines react readily with 2-methyl-1-nitro-2-thiopseudourea to produce linear[1] and cyclic[2] guanidines. We have found that the reaction of ethylenimine and 2-methylaziridine with 2-methyl-1-nitro-2-thiopseudourea in a mixture of ether and methanol results in the formation of 1-(nitroguanyl)aziridine (Ia) and 2-methyl-1-(nitroguanyl)aziridine (Ib) in 80% and 53% yields, respectively. These compounds are white crystalline solids and are stable at room temperature in the absence of light, atmospheric carbon dioxide, and water vapor. On the other hand, the reaction of ethylenimine and 2-methyl-1-nitro-2-thiopseudourea in methanol alone gave only a low yield of 2-(methylthio)ethylnitroguanidine (IIa).

The ethanolysis of 1-(nitroguanyl)aziridine (Ia) with absolute ethanol and *p*-toluenesulfonic acid formed 1-(2-ethoxyethyl)-3-nitroguanidine (III) and 2-amino-1-nitroimidazolidine *p*-toluenesulfonate (IV). 2-Ethoxyethylamine (V) synthesized from 2-ethoxyethyl bromide[3] *via* the Gabriel method gave with 2-methyl-1-nitro-2-thiopseudourea a derivative whose properties were identical with III. The nitrate salt of 2-amino-1-nitroimidazolidine[4] was converted to IV by its reaction with *p*-toluenesulfonic acid. The alcoholysis reaction was extended to 1-pentanol and 2-methyl-2-propanol which gave the corresponding 1-(2-alkoxyethyl)-3-nitroguanidines (VI and VII). This appears to be a general method for the syntheses of 1-(2-alkoxyethyl)-3-nitroguanidines. The cleavage of Ia in methylene chloride solution with nitric, hydrochloric, and hydrobromic acids produced the corresponding 2-substituted ethylnitroguanidines. In Scheme I are summarized the general reactions of 1-(nitroguanyl)aziridine.



SCHEME I

The cyanobromination[5] of 1-(nitroguanyl)aziridine (Ia) in boiling benzene probably proceeds through a linear intermediate N-(2-bromoethyl)-N-cyano-nitroguanidine which cyclizes by an internal SN2 mechanism[6] to form VIII in 43% yield. The hydrogen bromide liberated in the first step cleaves Ia to form 2-bromoethyl-3-nitroguanidine which rapidly cyclizes to IX in 41% yield.



Under the cyanobromination conditions previously stated, 1-(nitroguanyl)aziridine-d_2 produced 3-cyano-2-imino-d_1-1-nitroimidazolidine (VIII*) and 2-amino-d_2-1-nitroimidazolidinium-d_1 bromide (IX*). The identity of VIII* and IX* was established by their infrared curves.

The ultraviolet absorption spectra[7,8] of the 1-(nitroguanyl)aziridines in ethanol show them to have nitrimino structures with principal absorption maxima 2700–2720 Å. All of the substituted ethylnitroguanidines had absorption curves similar to ethylnitroguanidine with maxima 2650–2740 Å. Compounds VIII and

(1) L. Fishbein and J. A. Gallaghan, *J. Am. Chem. Soc.*, **76**, 1877 (1954).
(2) L. S. Hafner and Robert Evans, *ibid.*, **79**, 3783 (1957).
(3) G. C. Harrison and H. Diehl, *Org. Syn.*, **23**, 32 (1943).
(4) A. F. McKay and J. E. Milks, *J. Am. Chem. Soc.*, **72**, 1616 (1950).
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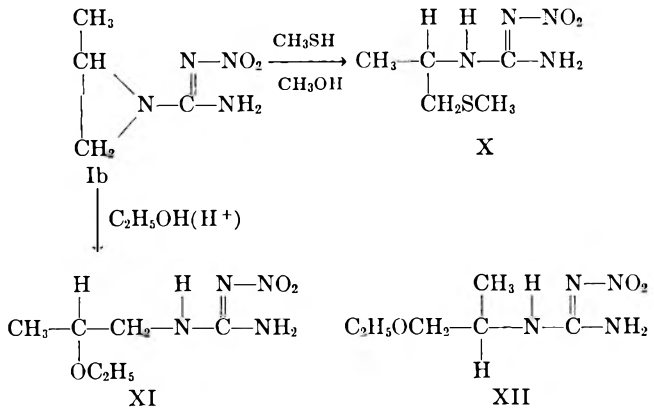
(6) C. Boyars, W. F. Sager, and S. Skolnik, *J. Am. Chem. Soc.*, **78**, 4590 (1956).
(7) A. F. McKay, J. P. Picard, and P. E. Brunet, *Can. J. Chem.*, **79**, 746 (1951).
(8) W. D. Kumler and P. P. T. Sah, *J. Org. Chem.*, **18**, 669 (1953), reported the principal absorption maxima of nitroguanidines at 2300–2400 Å. (nitroamino) and 2650–2740 Å. (nitrimino), respectively.

IX have nitramino structures with maxima at 2380 Å. and 2440 Å., respectively.

The infrared spectra of compounds II–XII were consistent with the proposed structures. The symmetric ν (NO_2) was located in the 1293–1270-cm.$^{-1}$ region in these compounds. The asymmetric nitro group frequencies of the 1-(nitroguanyl)aziridines (Ia, Ib), 1535 cm.$^{-1}$ and 1527 cm.$^{-1}$, respectively, are in agreement with Bellamy's[9] findings for polynitramines rather than Kumler's[10] assignments for nitroguanidine derivatives.

The principal acidic cleavage products of 2-methyl-1-(nitroguanyl)aziridine (Ib) were dependent upon the strength of the acid's conjugate base. With the strong conjugate base methyl mercaptide, 1-(methylthio)-2-propylnitroguanidine (X), m.p. 79–80°, was isolated and its structure established by an independent synthesis. In the reaction with the weak conjugate base *p*-toluenesulfonate, 2-ethoxy-1-propylnitroguanidine (XI), m.p. 155–156°, was formed instead of the isomeric 1-ethoxy-2-propylnitroguanidine (XII), m.p. 88–89°. The structures of XI and XII were established by independent syntheses. The proposed structures of the derivatives of Ib are indicated in Scheme II.



SCHEME II

Experimental

The melting points were determined on a micro Kofler hot stage. The infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer with sodium chloride or calcium fluoride optics as Nujol mulls or potassium bromide pellets. The ultraviolet spectra were recorded on a Beckman DK–2 spectrophotometer or a Beckman DU in 1-cm. silica cells.

1-(Nitroguanyl)aziridine (Ia).—Ethylenimine (6.4 g., 0.148 mole) was added to a mixture of 75 ml. of absolute ether and 75 ml. of absolute methanol. Twenty grams (0.148 mole) of 2-methyl-1-nitro-2-thiopseudourea was added, and the temperature rose from 20° to 38° with the rapid evolution of methyl mercaptan. After 15 min., 50 ml. of ether and 30 ml. of methanol were added, and the temperature was raised to 50° within a half hour. The mixture was cooled to 30° and evaporated to dryness in a stream of dry air. The solid was stirred in 150 ml. of ether and filtered. The ether extract evaporated to a gummy residue and was discarded.

The crystalline residue was dissolved in 250 ml. of absolute methanol and filtered. Upon cooling and concentration, 15.5 g. (80.2%) of 1-(nitroguanyl)aziridine (m.p. 124–126°) was obtained. An analytical sample, m.p. 129–130°, was obtained by repeated crystallization from methanol.

Anal. Calcd. for $C_3H_6N_4O_2$: C, 27.69; H, 4.60; N, 43.07. Found: C, 27.98; H, 4.60; N, 42.53. Ultraviolet spectrum in isopropyl Alcohol: λ_{max} 2710 Å., log ϵ 4.20; ν_{max} (KBr) 1625 (s), 1535 (s) cm.$^{-1}$.

2-Methyl-1-(nitroguanyl)aziridine (Ib).—To a mixture of absolute ether (200 ml.) and absolute methanol (40 ml.) was added freshly distilled 2-methylaziridine (Interchemical Corp., 5.7 g. 0.1 mole) and 2-methyl-1-nitro-2-thiopseudourea (13.5 g., 0.1 mole). The temperature was maintained at 25–27° by a water bath until a homogeneous solution occurred (1.5–2 hr.). The solution was evaporated to 20 ml. by a stream of dry air, 200 ml. of ether was added, and the mixture was evaporated to dryness. Twelve grams of 2-methyl-1-(nitroguanyl)aziridine (m.p. 102–104°, 83% yield) was isolated. Upon recrystallization from ethanol and methylene chloride a crystalline solid was obtained whose m.p. was 109–110°.

Anal. Calcd. for $C_4H_8N_4O_2$: C, 33.33; H, 5.63; N, 38.88. Found: C, 33.47; H, 5.94; N, 38.63. Ultraviolet spectrum in isopropyl alcohol: λ_{max} 2720 Å., log ϵ 4.21; ν_{max} (KBr) 1614 (s), 1527 (s) cm.$^{-1}$.

2-(Methylthio)ethylnitroguanidine (IIa). A.—From an equimolar quantity of ethylenimine and 2-methyl-1-nitro-2-thiopseudourea in absolute methanol at room temperature (21 hr.), white crystals of IIa were obtained. Recrystallization from methanol and water gave 18.2% of product; m.p. 115–116°; ν_{max} (KBr) 1645 (s), 1594 (s), 1535 (m, broad) 1297 (s) cm.$^{-1}$.

Anal. Calcd. for $C_4H_{10}N_4O_2S$: C, 26.96; H, 5.66; N, 31.44. Found: C, 27.44; H, 5.77; N, 31.17.

B.—A solution of 1-(nitroguanyl)aziridine (Ia) (0.417 g. 0.0032 mole) in 25 ml. of absolute ethanol was saturated with methyl mercaptan at 20° (1 hr.). The reaction flask was stoppered and allowed to stand 18 hr. at 23°. The mixture was evaporated to dryness and the residue recrystallized from ethanol and methanol–ether. The product weighed 0.301 g. (53% yield) and melted at 115–116°. A mixture melting point with a sample of material obtained from the reaction of 2-methyl-1-nitro-2-thiopseudourea with 2-(methylthio)ethylamine was not depressed.

C.—The reaction of 2-(methylthio)ethyl amine with 2-methyl-1-nitro-2-thiopseudourea. The 2-(methylthio)ethyl amine was prepared by the reaction of methyl mercaptan with ethylenimine.[11] To 2.00 g. (0.0219 mole) of the amine in 25 ml. of absolute ether and 25 ml. of absolute ethanol was added 3 g. (0.0222 mole) of finely ground 2-methyl-1-nitro-2-thiopseudourea. The reaction was allowed to stand overnight. After recrystallization from a mixture of ether and methanol, 2.89 g. (73% yield, m.p. 115–116°) of material was obtained which did not depress the melting point of the product from method A.

***p*-Toluenesulfonate of 2-Amino-1-nitroimidazolidine (IV).**—To 1-(nitroguanyl)aziridine (Ia, 1.0 g., 0.0768 mole) dissolved in 100 ml. of hot absolute ethanol was added *p*-toluenesulfonic acid (0.1 g., 0.0005 mole). The mixture was then refluxed for 4.5 hr. and allowed to stand 74 hr. at room temperature. An amorphous precipitate was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml. of absolute methanol. A crystalline precipitate (0.052 g., m.p. 182–184°) was formed by the addition of 75 ml. of ether and and storage overnight at 0°. After recrystallization from absolute ethanol, the compound melted at 183–185°. A mixture melting point with an authentic sample of the compound prepared from the nitrate salt of 2-amino-1-nitroimidazolidine and *p*-toluenesulfonic acid was not depressed. The yield based on the *p*-toluenesulfonic acid was 29.6%.

Anal. Calcd. for $C_{10}H_{14}N_4O_5S$: C, 39.73; H, 4.67; N, 18.54. Found: C, 39.70; H, 5.03; N, 18.52.

1-(2-Ethoxyethyl)-3-nitroguanidine (III).—Upon evaporation the filtrate from IV gave 0.634 g. of 1-(2-ethoxyethyl)-3-nitroguanidine (m.p. 83.5–84.5°, 47% yield); ν_{max} (KBr) 1645 (vs), 1600 (vs), 1552 (m), 1272 (vs) cm.$^{-1}$.

Anal. Calcd. for $C_5H_{12}N_4O_3$: C, 34.08; H, 6.87; N, 31.81. Found: C, 34.16; H, 6.57; N, 31.76.

The reaction of 2-ethoxyethylamine (V) with 2-methyl-1-nitro-2-thiopseudourea also gave III. A mixture melting point was not depressed.

2-Ethoxyethylamine (V).—A sample of 2-ethoxyethyl bromide was converted to N-(2-ethoxyethyl)phthalimide in 57% yield. A pure sample of this compound obtained from a mixture of ether and low-boiling petroleum ether melted at 39–40°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.76; H, 6.65; N, 6.18.

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen and Co. Ltd., London, 1958, p. 302.

(10) W. D. Kumler, *J. Am. Chem. Soc.*, **76**, 814–816 (1954).

(11) T. Wieland, E. F. Moller, and C. Dieckleman, *Chem. Ber.*, **85**, 1635 (1952).

The 2-ethoxyethylamine was obtained in 50% yield by hydrazinolysis of the N-(2-ethoxyethyl)phthalimide.

1-[2-(1-Pentoxyethyl)]-3-nitroguanidine (VI).—To 100 ml. of freshly distilled 1-pentanol was added *p*-toluenesulfonic acid (0.1 g.) and Ia (2.6 g., 0.02 mole). The mixture was refluxed for 6 hr. and the excess 1-pentanol was removed by distillation under diminished pressure. The residue recrystallized from ethanol, methylene chloride, and finally distilled water melted sharply at 92°; ν_{max} (KBr), 1653 (vs), 1605 (s), 1542 (m, broad), 1287 (s) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{18}N_4O_3$: C, 44.02; H, 8.31; N, 25.66. Found: C, 43.70; H, 7.88; N, 25.74.

2-(*t*-Butoxy)ethylnitroguanidine (VII).—A mixture of 2-methyl-2-propanol (150 ml., freshly distilled), 1-(nitroguanyl)aziridine (Ia) (1.04 g., 0.08 mole), and *p*-toluenesulfonic acid (0.1 g.) was refluxed for 18 hr. The excess alcohol was removed by distillation under reduced pressure and the residue recrystallized from ethanol to yield crude 2-(*t*-butoxy)ethylnitroguanidine (VII). An analytical sample (m.p. 150–151°) was obtained after repeated recrystallization from ethanol.

Anal. Calcd. for $C_7H_{16}N_4O_3$: C, 41.17; H, 7.89; N, 27.44. Found: C, 40.60; H, 7.33; N, 26.30, 26.70.

3-Cyano-2-imino-1-nitroimidazolidine (VIII) and 2-Amino-1-nitroimidazolidinium Bromide (IX).—When 1-(nitroguanyl)aziridine (Ia) (4 g., 0.03 mole), cyanogen bromide (6 g., 0.057 mole), and dry benzene (200 ml.) were refluxed with vigorous stirring for 110 min., VIII, m.p. 139°, was formed in 43% yield and IX, m.p. 183–185° (lit. 179.5–180°, ref. 4), was formed in 41% yield.

Anal. Calcd. for $C_4H_5N_5O_2$ (VIII): C, 30.97; H, 3.25; N, 45.15. Found: C, 30.90; H, 3.23; N, 45.21; λ_{max} 2380 Å. (ϵ 748) alcohol. ν_{max} (Nujol) 3408–3300 (2 bands, s), 2240 (s), 1707 (s), 1682 (s), 1548 (s) cm.$^{-1}$; deuterated: 2563 (m), 2470 (m), 2242 (s), 1688 (s), 1544 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_3H_7BrN_4O_2$ (IX): C, 17.07; H, 3.34; Br, 37.87; N, 26.55. Found: C, 17.35; H, 3.42; Br, 37.17; N, 26.84.

Infrared spectrum: ν_{max} (Nujol) 1707–1708 (s), 1683 (s), 1548 (s) cm.$^{-1}$.

Deuteration of 1-(Nitroguanyl)aziridine (Ia), 3-Cyano-2-imino-1-nitroimidazolidine (VIII) and 2-Amino-1-nitroimidazolidinium Bromide (IX).—Analytically pure samples of Ia, VIII, and IX (500 mg. or 1 g.) and 5–10 ml. of 99.5% deuterium oxide were heated at 50–55° (2–18 hr.) in 60-ml. stoppered cylindrical tubes. The samples were evaporated to dryness on a vacuum line and mulls of the deuterated solids prepared in the usual manner.

1-(Methylthio)-2-propylamine.—Equimolar quantities of methyl mercaptan and 2-methylaziridine in excess methanol were kept at −78° for 4 hr. and allowed to warm to room temperature overnight. The mixture was dried for several days over anhydrous sodium sulfate and fractionally distilled. An analytical fraction (16.8 g., 53%; b.p. 155–156°, $n^{20}D$ 1.4832) was collected. Mylius[12] reported that the picrate of the isomeric 2-(methylthio)-1-propylamine melted at 133–134°.

Anal. Calcd. for $C_4H_{11}NS$: C, 45.72; H, 10.48; N, 13.33. Found: C, 45.15; H, 10.43; N, 13.53.

Picrate.—*Anal.* Calcd. for $C_{10}H_{14}N_4O_7S$: C, 35.93; H, 4.19; N, 16.77. Found: C, 35.18; H, 4.24; N, 16.94; m.p. of picrate 150–151°.

1-(Methylthio)-2-propylnitroguanidine (X). A.—The condensation of 1-(methylthio)-2-propylamine (5 g., 0.048 mole) with 2-methyl-1-nitro-2-thiopseudourea (6.8 g., 0.05 mole) gave 5.3 g. of 1-(methylthio)-2-propylnitroguanidine (X) in 54% yield. Crystallization from methylene chloride gave an analytical sample, m.p. 79–80°.

Anal. Calcd. for $C_5H_{12}N_4O_2S$: C, 31.28; H, 6.29; N, 29.15. Found: C, 31.49; H, 5.97; N, 29.30.

B.—A solution of 5 g. of methyl mercaptan in 20 ml. of methyl alcohol was added to 1.44 g. (0.01 mole) of 2-methyl-1-(nitroguanyl)aziridine (Ib) at −24°. After 4 hr. the mixture was allowed to warm to room temperature and stand overnight. The mixture was evaporated to dryness and extracted with benzene. The benzene extract was concentrated, and the solid was identical to 1-(methylthio)-2-propylnitroguanidine prepared in A.

2-(Ethoxy)-1-propylnitroguanidine (XI). A.—A mixture of 2-methyl-1-(nitroguanyl)aziridine (1.44 g., 0.01 mole), 100 ml. of absolute ethanol, and 0.18 g. of *p*-toluenesulfonic acid was refluxed for 5 hr. One and nine-tenth grams of light brown, gummy residue, m.p. 120–145°, was obtained by air evaporation to dryness. After several recrystallizations from ethanol, 0.457 g. (24% yield) of white solid, m.p. 155–156°, was obtained.

Anal. Calcd. for $C_6H_{14}N_4O_3$: C, 37.88; H, 7.42; N, 29.46. Found: C, 38.00; H, 7.28; N, 29.50.

B.—To ethanol (50 ml.) were added 2-ethoxy-1-propylamine (2.0 g., 0.02 mole, b.p. 118°[13], $n^{23}D$ 1.4101) and 2-methyl-1-nitro-2-thiopseudourea (2.7 g., 0.02 mole). The mixture was refluxed for 3 hr. and evaporated to dryness by a water aspirator. After trituration with ether and recrystallization from ethanol the product was identical with 2-ethoxy-1-propyl-3-nitroguanidine (XI) prepared by method A.

1-Ethoxy-2-propylnitroguanidine (XII).—To 1.103 g. (0.0107 mole) of 1-ethoxy-2-propylamine[14] ($n^{20}D$ 1.4079, b.p. 116°; picrate m.p. 132°) was added 20 ml. of ether–ethanol (1:1).

Anal. Calcd. for $C_{11}H_{16}N_4O_8$: C, 39.76; H, 4.85; N, 16.86. Found: C, 39.74; H, 4.22; N, 16.71.

After solution had occurred, 1.44 g. (0.0107 mole) of 2-methyl-1-nitro-2-thiopseudourea and 100 ml. of ether were added. The reaction mixture was stirred 19 hr. and evaporated to dryness; 1.5 g. of 1-ethoxy-2-propylnitroguanidine (m.p. 80–82°; crude yield, 63%) was obtained. After recrystallization from water, the m.p. was 88–89°.

Anal. Calcd. for $C_6H_{14}N_4O_3$: C, 37.88; H, 7.42; N, 29.46. Found: C, 38.16; H, 7.93; N, 29.34.

Acknowledgment.—We wish to thank Mrs. P. Wheeler and Miss A. Richardson for the microanalyses. Also, we wish to thank Drs. G. B. Wilmot and A. S. Tompa for help in interpretation of infrared spectra.

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Small Charged Rings. III. Heterocyclic Ring Expansion through Aziridinium Salts[1-3]

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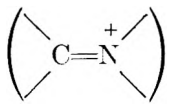
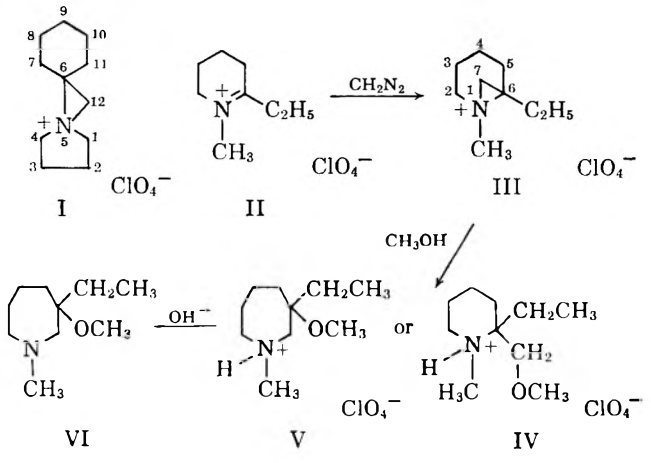
The generality of aziridinium ring synthesis by the addition of diazomethane to the $\backslash C{=}\overset{+}{N}/$ grouping has been demonstrated in representative mono-, bi-, and tricyclic systems. Alcoholysis and hydrolysis of aziridinium salts in these systems lead effectively to heterocyclic ring enlargement and provide a new route to cyclic β-alkoxy- and β-hydroxyamino compounds. Examples are presented for the expansion of a six-membered ring through an aziridinium salt to a seven-membered ring (II → III → VI), a 1-azabicyclo[4.4.0]decane to a substituted 1-azabicyclo[4.4.1]undecane system (IX → X → XII), and a 2-azabicyclo[4.4.0]decane to a substituted 3-azabicyclo[5.4.0]undecane system (XV → XVI → XVIII). We found it possible to provide steric limitation to this ring enlargement reaction. Thus, the tetracyclic aziridinium compound XX resulting from the addition of diazomethane to $\Delta^{1(6)}$-tetrahydrojulolidinium perchlorate (XIX) underwent solvolysis at the less substituted aziridinium-ring carbon atom. Reconstitution of aziridinium perchlorates has been shown to be possible by treatment of substituted β-bromoalkyl-3°-amines with silver perchlorate.

The finding[1,4] that an aziridinium salt such as 5-azoniadispiro[4.0.5.1]dodecane perchlorate[5] (2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate) (I) can be made simply and in high yield by the nucleophilic attack of diazomethane on the corresponding ternary iminium perchlorate encouraged us to extend this new method of synthesis to other representative aziridinium salts. Thus, we have added diazomethane successfully to the ternary iminium grouping



contained in monocyclic, bicyclic, and tricyclic systems. Moreover, the solvolysis of the aziridinium salt I in methanol to give a product having methoxyl attached to the more highly substituted carbon of the three-membered ring, namely N - (1 - methoxycyclohexylmethyl)pyrrolidine,[1,4] suggested that this reaction might be employed for heterocyclic ring expansion if the original $\backslash C{=}\overset{+}{N}/$ function were endocyclic.



The first preparation of 5-azoniadispiro[4.0.5.1]-dodecane perchlorate (I) from N-cyclohexylidenepyrrolidinium perchlorate had been run in methanol–ether at low temperature.[1,4] In order to avoid the initial employment of a hydroxylic solvent and to extend the usefulness of the diazomethane reaction other solvent–ether pairs were tried for the preparation of I. It was found that combinations of N-cyclohexylidenepyrrolidinium perchlorate in methylene chloride, dimethylformamide, or acetonitrile with diazomethane in ether at 0° were satisfactory and that methylene chloride gave the best results. The first model endocyclic iminium system employed was 2-ethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate (II),[6,7] $C_8H_{16}ClNO_4$, made *via* the mercuric acetate oxidation of 2-ethyl-1-methylpiperidine. When compound II in methylene chloride was treated with diazomethane in ether at 0° a new product was formed in 87% yield which had the correct analysis for $C_9H_{18}ClNO_4$, corresponding to the addition of a methylene group to the original compound. The structure 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]-heptane perchlorate (III), which was favored by analogy with I and by the absence of infrared absorption maxima corresponding to $-\overset{+}{N}-H$ and $\backslash C{=}\overset{+}{N}/$, was secured by the n.m.r. spectrum in deuteriochloroform. The signal at lowest field, τ value 6.33,[8] appeared as an unsymmetrical triplet and integrated for two protons, consistent with an assignment to the hydrogens on C-2 (III), next to N^+, as in models previously provided.[1,8] The integrated singlet at 6.79, which indicated three protons and was assignable to $-\overset{+}{N}-CH_3$ as in the models tetramethylammonium perchlorate (6.84) and 1,1-dimethylpyrrolidinium perchlorate (6.85),[1] was actually superimposed upon the

(1) For the second article in the series, see N. J. Leonard and K. Jann *J. Am. Chem. Soc.*, **84**, 4806 (1962).

(2) This investigation was supported by a research grant (USPHS-RG5829) from the National Institutes of Health, U. S. Public Health Service, to whom we acknowledge our thanks.

(3) Presented at the Seventeenth National Organic Chemistry Symposium of the American Chemical Society, June, 1961, Bloomington, Ind.; see Abstracts, pp. 1-10.

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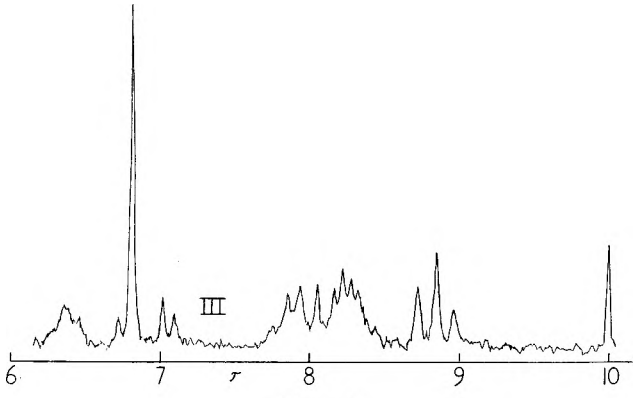


Figure 1

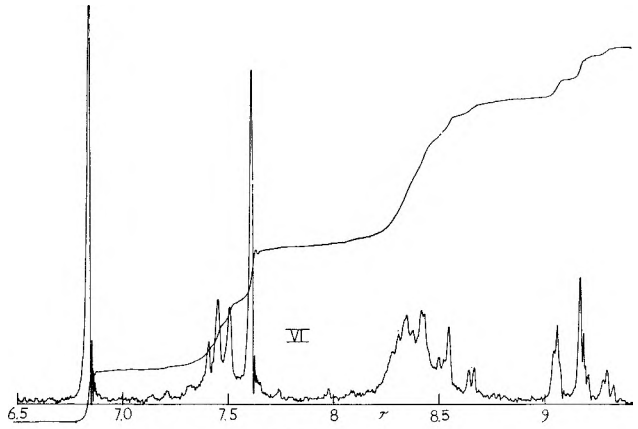
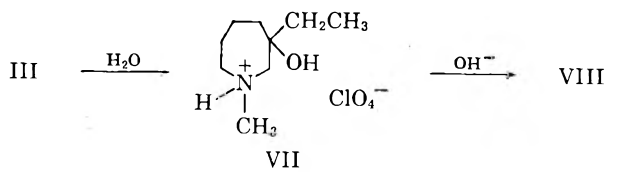


Figure 2

second line of four in a doublet system, AB (Fig. 1), with $J_{AB} = 5.0 \pm 0.5$ c.p.s., $\delta_B - \delta_A = 16.8$ c.p.s., or chemical shifts of 6.75 and 7.03. For reference, the $\overset{+}{N}$–CH_2 (aziridinium ring) singlet signal was reported at 7.02 for I in liquid sulfur dioxide and at 6.98 for 5-azoniadispiro[4.0.5.1.]dodecane fluoborate (I, BF_4^- in place of ClO_4^-) in deuteriochloroform.[1] (See Experimental for further values.) Compound III, unlike I, is asymmetric and the aziridinium ring protons are structurally nonidentical, magnetically nonequivalent, and hence display an AB type of n.m.r. spectrum. Even in structures less fixed, examples have been provided where a chemical shift is observed between *gem*-methylenic protons which are conformationally distinct.[9-11] The rest of the n.m.r. spectrum of III includes signals at 7.83, 7.93, 8.04, 8.15, 8.21, 8.27, and 8.31 integrating for eight protons—six ring protons plus two protons of CH_2–CH_3—and a triplet at 8.84 ($J = 8.0 \pm 0.5$ c.p.s.), not completely symmetrical, integrating for three protons, corresponding to the methyl group in CH_2CH_3.

The methanolysis of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate (III) was complete within two hours at reflux temperature, and the major product was isolated in pure form, $C_{10}H_{22}ClNO_5$, m.p. 111–111.5°, in 90% yield. Analysis showed the presence of a methoxyl group and the infrared spectrum showed the presence of an $\overset{+}{N}$–H group. The expected product of solvolytic ring cleavage of III would be 3-ethyl-3-methoxy-1-methyl-1-azacycloheptane perchlorate (V) based on analogy with the methanolysis product of I[1] and with the direction of the ring opening of 1-(3′-aminopropyl)-2,2-dimethylethylenimine with picric acid in methanol observed by Tarbell and Noble,[12] but the alternative structure, 2-ethyl-2-methoxymethyl-1-methylpiperidine perchlorate (IV), could not be ruled out. The n.m.r. spectrum of the salt in deuteriochloroform did not offer clear distinction between the two alternative structures, since the broad low-field absorption integrating for four protons could correspond to either CH_2–$\overset{+}{N}$(H)–CH_2 (V) or to CH_2–$\overset{+}{N}$(H)— plus CH_2–O (IV). The common structural features of either salt structure were confirmed by τ values in the n.m.r. spectrum at 6.72 (singlet, 3 protons, O–CH_3); 6.97, 6.88 (doublet, 3 protons, $\overset{+}{N}$H–CH_3); 7.9–8.7 (broad-6 ring protons, 2 protons in CH_2CH_3); 9.12 (triplet, 3 protons, CH_2–CH_3). The spectrum of the liberated base (Fig. 2) was definitive since the CH_2–N signals, unlike those of $\overset{+}{N}$–CH_2, did not interfere with the signal of CH_3–O. There was no signal at lower field than that for CH_3–O (τ value 6.84),[8] indicating the absence of the CH_2–O required for formulation as the base corresponding to IV and, therefore, establishing the structure of the amine as 3-ethyl-3-methoxy-1-methyl-1-azacycloheptane (VI) and the salt as V. The ring-enlargement route offers synthetic utility for arriving at compounds like VI which would be difficulty accessible by other means. Hydrolysis of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate (III) led to 3-ethyl-3-hydroxyl-1-methyl-1-azacycloheptane perchlorate (VII), which exhibited infrared maxima corresponding to O—H and $\overset{+}{N}$—H stretching and an n.m.r. spectrum similar to that of V in its common features. Treatment with base yielded 3-ethyl-3-hydroxyl-1-methyl-1-azacycloheptane (VIII), the structural assignment of which was made possible by the n.m.r. spectrum. Similarities to the spectrum of VI



were noted plus the absence of any low-field signal corresponding to CH_2OH[13] which would be present in the product of alternative ring cleavage, at the aziridinium $\overset{+}{N}$—CH_2 bond in III. An n.m.r. spectral verification of structural assignments V and VI, VII and VIII was possible by running as a check an SN2 type of ring opening by treatment of III with sodium methoxide

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(13) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 55.

and sodium hydroxide and observing that the products showed $C\underline{H}_2OCH_3$ at τ value 6.63 (base corresponding to IV) and $C\underline{H}_2OH$ at 6.68, respectively.

In the bicyclic series, $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (IX)[14] was converted to 1-azoniatricyclo[4.4.1.0]undecane perchlorate (X) in 90% yield by treatment with diazomethane. The structural assignment was based on the absence of $>\overset{+}{N}-H$ and $>C=\overset{+}{N}<$ stretching bands in the infrared spectrum and on the presence of the singlet signal (2 protons) at a τ value of 6.83 in the n.m.r. spectrum. The appearance of this unsplit signal at higher field than that for $C\underline{H}_2-\overset{+}{N}$ in five- and six-membered ring models[1] is indicative of proton attachment to a three-membered ring, $>C\underline{H}-\overset{+}{N}<$.[1,8] Each of the equivalent protons on C-11 extends over a six-membered ring. The other four protons adjacent to $\overset{+}{N}$, in the system $CH_2C\underline{H}_2\overset{+}{N}C\underline{H}_2CH_2$ were detectable as a triplet at a τ value of 6.38. If methanol were to react with X predominantly in an SN1 manner, it would provide a direct conversion route from a bicyclo[4.4.0]decane ring system (IX) to a bicyclo[4.4.1]undecane system (XI). Methanolysis of 1-azoniatricyclo[4.4.1.0]undecane perchlorate (X) did indeed produce 6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate (XI) in 81% yield, as judged by microanalysis, infrared and n.m.r. spectra of the salt, and confirmed through the n.m.r. spectrum of the base (XII) by applying the principles which have been cited above. There was no signal at lower field than 6.83, where a singlet assignable to the O–CH_3 group appeared. Instead, a singlet corresponding to two protons was found at 6.88 corresponding to the bridging $>C-C\underline{H}_2-N$. Hydrolysis of X at steam-bath temperature during six hours also resulted in aziridinium ring opening (93% yield) with substitution on the more substituted carbon. After treatment with base, 6-hydroxy-1-azabicyclo[4.4.1]undecane (XIII) was obtained, and the structure was determined by comparative examination of the n.m.r. spectra (see Experimental). Double ring expansion thus has been realized in the over-all conversion of IX to both XII and XIII.

Hydrogenolysis of the aziridinium ring present in 1-azoniatricyclo[4.4.1.0]undecane perchlorate (X) proceeded, by contrast, with cleavage of the less hindered C–N bond of the three-membered ring, as would be suggested by previous experience.[1,15,16] The hydrogenation of X in the presence of platinum oxide was rapid and could be carried out in acetone solution. The perchlorate of the saturated product was converted to the base, which was identified as 6-methyl-1-azabicyclo[4.4.0]decane[5] (or 10-methylquinolizidine) (XIV)[14] by direct comparison with authentic material.

Another bicyclic system investigated was 1-methyl-$\Delta^{1(9)}$-octahydroquinolinium perchlorate (XV), which is readily available by the lithium–*n*-propylamine reduction of 1-methyltetrahydroquinoline to the enamine mixture, followed by neutralization with perchloric acid to give the ternary iminium salt.[17] Reaction of XV with diazomethane proceeded rapidly and in high yield. The infrared spectrum of the major product, $C_{11}H_{20}ClNO_4$, m.p. 129–129.5°, was devoid of maxima corresponding to $>\overset{+}{N}-H$ and $>C=\overset{+}{N}<$ functions and exhibited an n.m.r. spectrum (Fig. 3) indicative of the structure 1-methyl-1-azoniatricyclo[8.1.0.0^{5,10}]undecane perchlorate (XVI). In the spectrum the singlet at τ value 6.81 was assignable to $C\underline{H}_3-N$,[1] as in III, and the pair of doublets at τ = 6.66 and 7.09 with a coupling constant J = 5.0 ± 0.5 c.p.s., were indicative of the two aziridinium ring protons (AB) in the unsymmetrical molecule.[9–11]

Turning to the chemistry of 1-methyl-1-azoniatricyclo[8.1.0.0.^{5,10}]undecane (XVI), methanolysis yielded (86% over-all from XV) a product with properties consistent for 1-methoxy-3-methyl-3-azabicyclo[5.4.0]-undecane perchlorate (XVII). Establishment of structure was possible by liberation of the free base, C_{12}-$H_{23}NO$, which in the n.m.r. spectrum exhibited no signal at lower field than the O–CH_3 signal (τ value 6.83; N–CH_3 signal at 7.75) and therefore did not possess a $C\underline{H}_2OCH_3$ grouping. This synthesis of 1-methoxy-3-methyl-3-azabicyclo[5.4.0]undecane (XVIII) represents an efficient single ring expansion from a bicyclo[4.4.0]decane (XV) to a bicyclo[5.4.0]-undecane system. In another example, ethanolysis of XVI yielded as a major product 1-ethoxy-3-methyl-3-azabicyclo[5.4.0]undecane by analogy with XVII.

The diazomethane attack on the $>C=\overset{+}{N}<$ group in a tricyclic system is exemplified with $\Delta^{1(6)}$-tetrahydrojulolidinium perchlorate (XIX). The structure of the aziridinium product, $C_{13}H_{22}ClNO_4$, m.p. 150–151° dec., was established by the usual analytical and spectral

(14) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).

(15) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *ibid.*, **68**, 140 (1946).

(16) J. V. Karabinos and K. T. Serijan, *ibid.*, **67**, 1856 (1945).

(17) N. J. Leonard, C. K. Steinhardt, and C. Lee, *J. Org. Chem.*, **27**, 4027 (1962).

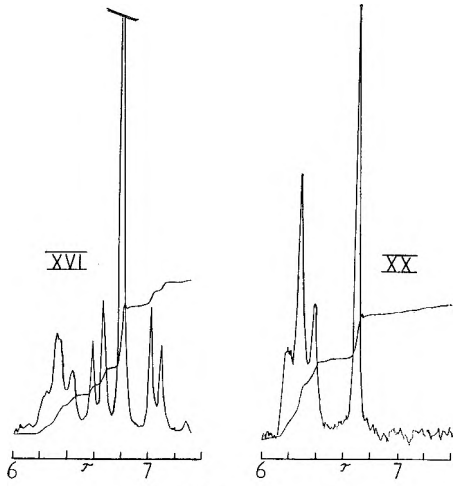
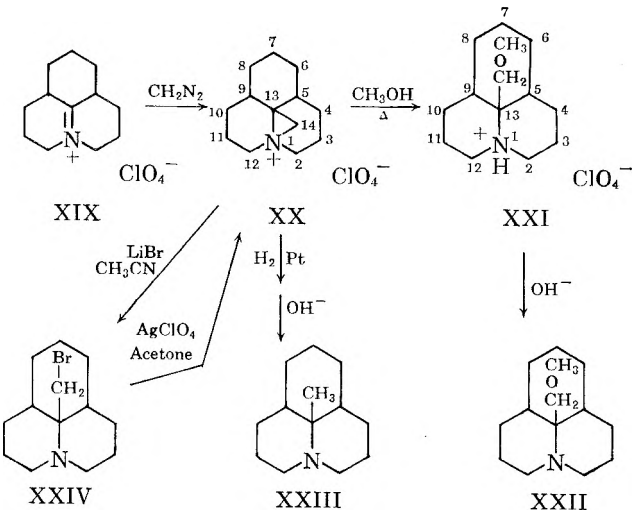


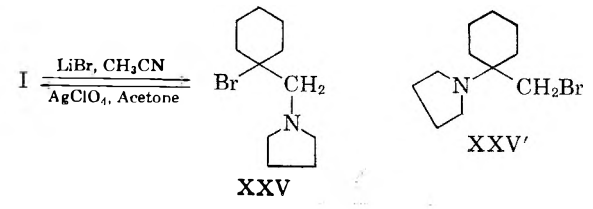
Figure 3



criteria as 1-azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane perchlorate (XX). In contrast to XVI and in similarity with X, the two methylenic protons in the aziridinium ring (CH_2–N) are equivalent, and a singlet was observed at a τ value of 6.70 in the n.m.r. spectrum (Fig. 3). Methanolysis of XX proceeded slowly to yield (89%) a new product, $C_{14}H_{26}ClNO_5$, which indicated by its composition that it contained the added elements of methanol. The —N—H group was identified in this perchlorate salt by the infrared maximum at 3125 cm.$^{-1}$, and the grouping N^+—C—CH_2—O—CH_3 was shown—in contradistinction to the alternative N^+—CH_2—C—O—CH_3 grouping—by the clear *singlets* in the n.m.r. spectrum (in methylene chloride) at τ values of 6.09 and 6.55 (1.97/3.03 protons by integration). The structure 13-methoxymethyl-1-azatricyclo[7.3.1.0.^{5,13}]tridecane perchlorate XXI was, therefore, assignable to the methanolysis product of XX. For the base which was liberated from the perchlorate the lowest-field signals in the n.m.r. spectrum were two singlets at τ values (carbon tetrachloride) 6.24 and 6.75 integrating for 2 and 3 protons, respectively. The grouping CH_2—O—CH_3 was, therefore, present in the base, of structure 13-methoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXII), and the sharp melting point of this compound, 79.5–80°, along with the spectral data, suggested that a single isomer had been produced from the precursor XX of m.p. 150–151° dec. It is apparent that opening of the aziridinium ring in the tetracyclic system XX has occurred in a manner different from that observed in the methanolysis of I, III, X, and XVI. The tertiary aziridinium carbon (13) in XX is sufficiently hindered, or the tetracyclic molecule is constrained so that the linkage N_1–C_{13} is not readily broken, with the result that the methoxy group becomes attached to the primary aziridinium carbon by solvolysis or displacement. A limitation to the ring-enlargement reaction, therefore, is realized in structure XX.

The hydrogenation of 1-azoniatetracyclo[7.3.2.0.^{1,13}-0^{5,13}]tetradecane perchlorate (XX) in acetone using platinum oxide produced (93%) 13-methyl-1-azatricyclo[7.3.1.0.^{5,13}]tridecane perchlorate, the structure of which was assigned on the basis of infrared and n.m.r. spectra and from which the base, 13-methyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXIII), m.p. 31–32°, was liberated. Indication of the C-methyl group in XXIII which had been introduced was obtained from the singlet n.m.r. signal at τ value 8.96. The treatment of XX with lithium bromide in acetonitrile solution using anhydrous reagents and extraction continuously with pentane afforded (95%) a bromine-containing base, $C_{13}H_{22}BrN$, m.p. 110–112°. The CH_2Br grouping was indicated by the singlet signal at lowest field (6.19) in the n.m.r. spectrum in benzene solution. The same compound was made by treating $\Delta^{1(6)}$-tetrahydrojulolidinium bromide (XIX, Br^- in place of ClO_4^-) with diazomethane. Assignment of the structure as 13-bromomethyl-1-azatricyclo[7.3.1.0^{5,13}]-tridecane (XXIV) was confirmed by conversion to the perchlorate salt, which likewise showed a *singlet* at 5.87 in the n.m.r. spectrum in acetonitrile solution consistent for two protons in the grouping NH^+—C—CH_2Br, but not in the alternative structural grouping NH^+—CH_2—C—Br. The *resynthesis* of the aziridinium perchlorate XX was achieved by treating 13-bromomethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXIV) with silver perchlorate in acetone solution.

In order to compare the behavior of 5-azoniadispiro[4.0.5.1]dodecane perchlorate (I) with lithium bromide in acetonitrile to that of XX, the former was submitted to the same reaction and isolation procedure. It yielded a product which exhibited a singlet proton signal in the n.m.r. spectrum in benzene solution at 7.08. On the basis of the known methoxy compounds corresponding to XXV and XXV′ (OCH_3 in place of Br),[1] which showed τ_{CH_2} at 7.62 and 6.65, respectively,



and on the relative deshielding of methylene protons by β- and by α-Br and OCH_3 substituents,[18] the observed τ_{CH_2} value of 7.08 falls within the range calculated for XXV but not for XXV′. In confirmation of the assigned structure, N - (1 - bromocyclohexylmethyl)-pyrrolidine (XXV), the perchlorate salt, m.p. 165–166° dec., exhibited a doublet at 6.24 in deuteriochloroform, or 6.29 in acetonitrile, $J = 5.0 \pm 0.5$ c.p.s., consistent with splitting of the methylene protons by the proton on nitrogen in the conjugate acid ($C\underline{H}_2$-$\overset{+}{N}$H), plus broad absorption near 2.3 which was probably the signal corresponding to the nitrogen proton. When the salt was dissolved in heavy water, lyophilized, and redissolved in deuteriochloroform, the n.m.r. spectrum was similar to that of the original except that a singlet at 6.24 replaced the doublet and there was no absorption in the $\tau = 2.3$ region. The observed spectral changes should not be exhibited by the perchlorate of the base XXV′. Finally, the reconversion of N-(1-bromocyclohexylmethyl)pyrrolidine (XXV) to the aziridinium salt, 5-azoniadispiro[4.0.5.1]dodecane perchlorate (I), was effected by treatment of XXV with silver perchlorate in acetone while maintaining the reaction mixture cold.

Experimental[19]

Preparation of 5-Azoniadispiro[4.0.5.1]dodecane Perchlorate (2,2-Pentamethylene-1,1-tetramethyleneaziridinium Perchlorate) (I) in Methylene Chloride.—A solution of 5.0 g. (19.8 mmoles) of N-cyclohexylidenepyrrolidinium perchlorate[1] in 200 ml. of dry methylene chloride maintained at 0° was treated with diazomethane in ether[20] until the yellow color of the diazomethane persisted. Nitrogen was evolved during the addition. On standing for 3 hr. at 0° a colorless crystalline solid separated, 4.90 g. (93%), m.p. 130.0–131.5°. An additional 0.30 g. separated on addition of ether. Recrystallization from 2-propanol–ether raised the melting point to 132–133°. The perchlorate obtained was identical with an authentic sample prepared previously.[1]

In Dimethylformamide.—A solution of 3.0 g. (11.9 mmoles) of N-cyclohexylidenepyrrolidinium perchlorate in 100 ml. of dimethylformamide maintained at 0° was treated with diazomethane in ether until the yellow color of diazomethane persisted. Nitrogen was evolved as rapidly as the diazomethane was added. The solvent was removed on a rotary evaporator after standing at 0° for a few minutes. When ether was added to the remaining colorless oil, the oil solidified. Recrystallization from acetone–ether gave 1.96 g. (62%) of a perchlorate, m.p. 130–131°, which on further recrystallization was identical with the sample described previously.

In Acetonitrile.—A solution of 3.0 g. (11.9 mmoles) of N-cyclohexylidenepyrrolidinium perchlorate in 50 ml. of acetonitrile maintained at 0° was treated with diazomethane in ether. The product, isolated as above, was recrystallized from acetone–ether yielding 2.75 g. (87%) of colorless crystals, m.p. 134–135°, identical with the best sample of 5-azoniadispiro[4.0.5.1]dodecane perchlorate.

The typifying proton signal in the n.m.r. spectrum for this compound and the introduced aziridinium $C\underline{H}_2$-$\overset{+}{N}$ grouping was previously reported, on two different instruments,[1] as a singlet at τ value 7.02 in liquid sulfur dioxide and at 6.98 in deuteriochloroform for the corresponding fluoborate salt. On the Varian Associates Model A-60 spectrometer we have more recently obtained values of 6.88 for compound I in $CDCl_3$, 6.91 for I in $CDCl_3$–CH_2Cl_2, and 6.93 for I (BF_4^- in place of ClO_4^-) in $CDCl_3$.

6-Ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (III).—A solution of 4.0 g. (17.7 mmoles) of 2-ethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate (II)[6,7] in 50 ml. of dry methylene chloride at 0° was treated with diazomethane in ether prepared from 5.0 g. of N-nitrosomethylurea. The solution was stirred for 20 min., then allowed to warm to room temperature. The solid residue obtained on removal of the solvent on a rotary evaporator was recrystallized from 2-propanol–ether yielding 3.85 g. (87%) of a colorless perchlorate, m.p. 137–138°; no infrared maxima corresponding to $\geq\overset{+}{N}$—H and $>C{=}\overset{+}{N}<$; n.m.r. signals occur at τ values ($CDCl_3$): 6.33,[21] 6.70, 6.79 (doublet and singlet overlaid at 6.79); 7.00, 7.08 (doublet); 7.83, 7.93, 8.04, 8.15, 8.21, 8.27, 8.31; 8.84 (center of triplet, $J = 8.0 \pm 0.5$ c.p.s.) (see Fig. 1).

Anal. Calcd. for $C_9H_{18}ClNO_4$: C, 45.09; H, 7.56; N, 5.84. Found: C, 44.89; H, 7.51; N, 5.76.

Methanolysis of 6-Ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (III).—A solution of 1.20 g. (4.81 mmoles) of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate in 20 ml. of absolute methanol was refluxed for 2 hr. The colorless solid obtained on removal of the methanol *in vacuo* was recrystallized from 2-propanol–ether yielding 1.22 g. (90%) of **3-ethyl-3-methoxy-1-methyl-1-azacycloheptane perchlorate** (V), m.p. 111.0–111.5°; ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($\geq\overset{+}{N}$—H); n.m.r. signals at τ ($CDCl_3$): 6.30, 6.40, 6.53, 6.83, 7.05 (broad, 4 protons); 6.72 (singlet, 3 protons, O-$C\underline{H}_3$); 6.97, 6.88 (doublet, 3 protons, $\overset{+}{N}$H-$C\underline{H}_3$); 7.9–8.7 (broad, 8 protons–6 ring protons, 2 $C\underline{H}_2$-CH_3 protons); 9.12 (triplet, $J = 7.2 \pm 0.5$ c.p.s., not completely symmetrical, 3 protons, CH_2-$C\underline{H}_3$).

Anal. Calcd. for $C_{10}H_{22}ClNO_5$: C, 44.20; H, 8.10; N, 5.15; OCH_3, 11.42. Found: C, 43.97; H, 7.98; N, 5.21; OCH_3, 11.28.

An aqueous solution of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give **3-ethyl-3-methoxy-1-methyl-1-azacycloheptane (VI)** as a colorless liquid; n.m.r. signals (Fig. 2) at τ ($CDCl_3$): 6.83 (singlet, 3 protons, O-$C\underline{H}_3$); 7.3–7.8 (4 protons, $C\underline{H}_2NC\underline{H}_2$); 7.62 (singlet, 3 protons, N-$C\underline{H}_3$); 8.17–8.75 (6 ring protons and 2 protons in $C\underline{H}_2$-CH_3); 9.17 (unsym. triplet, $J = 7.5 \pm 0.5$ c.p.s., 3 protons, CH_2-$C\underline{H}_3$).

Hydrolysis of 6-Ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (III).—A sample of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate liquified and then later solidified when allowed to stand in a humid atmosphere for several months. Recrystallization from 2-propanol–ether at −40° gave a colorless solid, m.p. 85.5–86.5°; ν_{max}^{Nujol} 3453 (O-H), 3090 cm.$^{-1}$ ($\geq\overset{+}{N}$—H); n.m.r. signals at τ ($CDCl_3$ + CH_2Cl_2): 6.30, 6.44, 6.51, 6.64, 6.72 plus a doublet at 6.88, 6.98, $J = 5.5 \pm 0.5$ c.p.s. ($\overset{+}{N}$H-$C\underline{H}_3$) (total 8 protons); 8.27,[21] 8.43, 8.55 (8 protons); 9.06 (triplet, unsymmetrical, $J = 7.0 \pm 0.5$ c.p.s., 3 protons, CH_2-$C\underline{H}_3$). Addition of acetic acid did not allow the assignment of the O-H proton but did show that the doublet at 6.88, 6.98 was due to $\overset{+}{N}$H-$C\underline{H}_3$ because the doublet became a singlet at 6.96, identifying the compound as **3-ethyl-3-hydroxy-1-methyl-1-azacycloheptane perchlorate** (VII).

Anal. Calcd. for $C_9H_{20}ClNO_5$: C, 41.95; H, 7.82; N, 5.84. Found: C, 41.78; H, 7.69; N, 5.63.

An aqueous solution of 0.300 g. (1.26 mmoles) of the perchlorate was treated with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give 0.143 g. (79%) of **3-ethyl-3-hydroxy-1-**

(18) Ref. 13, pp. 53 and 59.

(19) All melting points are corrected, boiling points are uncorrected. We are indebted to Mr. Josef Nemeth, Miss Jane Liu, Mr. Gary D. Callahan, and Miss Mary Ann Weatherford for the microanalyses. We also wish to thank Mr. Dick H. Johnson, Mr. Oliver W. Norton, and Miss Gail Gregory for determining the n.m.r. spectra at 60 Mc. with a Varian Associates Model V-4300B spectrometer equipped with a superstabilizer, or with a Varian Associates Model A-60 spectrometer. The chemical shifts were determined using tetramethylsilane as an internal standard ($\tau = 10$), obtaining side bands by the application of an audio-frequency signal from an external source. The infrared spectra were determined using a Perkin-Elmer automatic recording infrared spectrophotometer Model 21.

(20) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(21) Center of unresolved multiplet.

methyl-1-azacycloheptane (VIII) as a colorless liquid. The n.m.r. spectrum showed signals at τ values ($CDCl_3$): 5.29 (O-H); 7.26, 7.47, 7.72 (4 protons, CH_2NCH_2 plus 2 ring protons); 7.58 (3 protons, N-CH_3); 8.41 (4 ring protons); 8.55 (2 protons, J = 7.0 ± 0.5 c.p.s., CH_2-CH_3, superimposed on the 4 protons centered on 8.41); 9.10 (triplet, unsym., J = 7.0 ± 0.5 c.p.s., CH_2-CH_3). The ethyl group showed long range splitting both in the methylene and the methyl, $J \approx 0.7$ c.p.s. The signal at 5.29 was shifted to 4.19 by the addition of a trace of acetic acid.

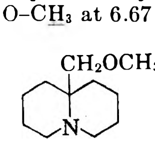
1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 10.0 g. (42.1 mmoles) of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (IX)[14] in 400 ml. of anhydrous methylene chloride maintained at 0° was treated with diazomethane in ether. The diazomethane was added in five portions over a 30-min. period, and the solution was stirred for an additional 0.5 hr. at 0°. The solvent was removed on a rotary evaporator leaving a colorless oil which slowly crystallized when washed with ether and cooled to −60°. The colorless perchlorate, 9.6 g. (90%), m.p. 142–144°, showed no infrared maxima corresponding to $\gt\overset{+}{N}$—H and $\gt C{=}\overset{+}{N}\lt$. The n.m.r. spectrum (simplified) showed signals at τ ($CDCl_3$): 6.38 (triplet, 4 protons, J = 6.0 ± 0.5 c.p.s., CH_2-CH_2—$\overset{+}{N}$—CH_2CH_2); 6.83 (singlet, 2 protons, aziridinium CH_2–$\overset{+}{N}$); 7.85 (triplet, 4 protons, J = 6.2 ± 0.5 c.p.s.); 8.22, 8.27, 8.32 (total of 8 protons).

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21; N, 5.58. Found: C, 47.39; H, 7.29; N, 5.53.

Methanolysis of 1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 2.0 g. (8.42 mmoles) of 1-azoniatricyclo-[4.4.1.0]undecane perchlorate in 5 ml. of anhydrous methanol was refluxed for 2 hr. To the warm solution ether was added to turbidity. The solid which separated from the solution after standing at 0° overnight was recrystallized from 2-propanol–ether yielding 1.99 g. (81%), m.p. 136–137°; ν_{max}^{Nujol} 3100 cm.$^{-1}$ ($\gt\overset{+}{N}$—H), of product, colorless plates, identified (later in text also) as **6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate (XI)**; n.m.r. signals occur at τ ($CDCl_3$): 6.43–6.64 (total of 6 protons—including 6.43, 6.48, most probably the bridging CH_2—$\overset{+}{N}$(H)— split by the proton on nitrogen: if so, J = 3.0 c.p.s.; plus 6.56, 6.64); 6.79 (singlet, 3 protons, O-CH_3); 8.12 (unresolved multiplet equal to 12 protons).

Anal. Calcd. for $C_{11}H_{22}ClNO_5$: C, 46.56; H, 7.82; N, 4.94; OCH_3, 10.94. Found: C, 46.60; H, 7.78; N, 5.01; OCH_3, 10.56.

An aqueous solution of 0.154 g. (0.543 mmole) of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give 0.082 g. (82%) of **6-methoxy-1-azabicyclo[4.4.1]undecane (XII)** as a colorless oil, n.m.r. signals at τ ($CDCl_3$): 6.83 (singlet, 3 protons, O-CH_3); 6.88 (singlet, 2 protons, bridging CH_2-N); 7.08 (multiplet, having the outline of a triplet further split, 4 protons, CH_2CH_2-N-CH_2CH_2; 8.32, 8.42 (unresolved multiplets, 12 protons). For comparison, a sample of 6-methoxymethyl-1-azabicyclo[4.4.0]decane (XXVI)[22] had n.m.r. signals for O-CH_3 at 6.67 and for CH_2-O at 6.39.



XXVI

Hydrolysis of 1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 1.0 g. (4.21 mmoles) of 1-azoniatricyclo-[4.4.1.0]undecane perchlorate in 10 ml. of water was heated on a steam bath for 6 hr. The water was removed on a rotary evaporator and the remaining colorless oil was washed with ether until the oil solidified. Recrystallization from 2-propanol–ether gave 1.00 g. (93%) of a colorless solid, m.p. 98–99°; ν_{max}^{Nujol} 3410 cm.$^{-1}$ (O-H), 3060 cm.$^{-1}$ ($\gt\overset{+}{N}$—H); n.m.r. signals observed at τ (CH_2Cl_2): 6.15 (1 proton, O-H, assigned on the basis that $\gt\overset{+}{N}$—H is not usually observed); 6.41 (apparent singlet, 2 protons, bridging CH_2-$\overset{+}{N}$); 6.4–6.8 (complex multiplet, 4 protons, CH_2-$CH_2\overset{+}{N}CH_2CH_2$); 8.13 (complex multiplet, 12 protons).

Anal. Calcd. for $C_{10}H_{20}ClNO_5$: C, 44.54; H, 7.47; N, 5.20. Found: C, 44.60; H, 7.60; N, 5.42.

An aqueous solution of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give a solid, **6-hydroxy-1-azabicyclo[4.4.1]undecane (XIII)**, m.p. 94–96°. Sublimation raised the melting point to 97–99°; $\nu_{max}^{CCl_4}$ 3580, 3350 cm.$^{-1}$; n.m.r. signals at τ ($CDCl_3$): 6.90 (singlet, 2 protons, bridging CH_2-N); 7.07 (multiplet, 4 protons, CH_2-CH_2-N-CH_2CH_2); 7.60 (singlet, 1 proton, O-H, since signal moved to lower field when a trace of acetic acid was added); 8.30, 8.37 (unresolved multiplet, 12 protons). For comparison, an impure (containing XIII) sample of 6-hydroxymethyl-1-azabicyclo[4.4.0]decane (XXVI, but OH in place of OCH_3) had an n.m.r. signal at 6.43 plus differences in the 8.2–8.6 region.

Catalytic Reduction of 1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 1.0 g. (4.21 mmoles) of 1-azoniatricyclo[4.4.1.0]undecane perchlorate in 100 ml. of anhydrous acetone was hydrogenated at 35 p.s.i. in the presence of 0.5 g. of platinum oxide. Filtration of the reduction mixture followed by removal of the solvent on a rotary evaporator yielded a slightly colored oil. The oil was dissolved in ethanol, treated with decolorizing carbon, and cooled. An oil separated which slowly crystallized on further cooling. The crystalline solid was recrystallized from 2-propanol–ether yielding 0.758 g. (75%) of a perchlorate, m.p. 161–163°; $\nu_{max}^{CHCl_3}$ 3020 cm.$^{-1}$ ($\gt\overset{+}{N}$—H); n.m.r. signals at τ ($CDCl_3$): 6.80, 6.87, 6.95 (4 protons, CH_2-$\overset{+}{N}$-CH_2); 8.20 (12 protons); 8.57 (sharp singlet, 3 protons, C-CH_3), identical, within experimental errors of the Varian A-60, with the n.m.r. spectrum of authentic **6-methyl-1-azabicyclo[4.4.0]decane perchlorate** (10-methylquinolizidine[14] perchlorate). In the 2600–2900-cm.$^{-1}$ region of the infrared spectrum,[23,24] as determined in chloroform solution (0.20 M) using a Perkin-Elmer Model 237 spectrophotometer, were observed maxima at 2945 cm.$^{-1}$ (ϵ 197), 2870 (88), 2795 (77), 2655 (23), and 2610 (22).

Anal. Calcd. for $C_{10}H_{20}ClNO_4$: C, 47.34; H, 7.95; N, 5.52. Found: C, 47.13; H, 8.04; N, 5.38.

An aqueous solution 0.140 g. (0.552 mmole) of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether removed on a rotary evaporator to give 0.063 g. (87%) of **6-methyl-1-azabicyclo[4.4.0]decane (XIV)** as a colorless oil; n.m.r. signals at τ ($CDCl_3$): 7.49, 7.57, 7.75, 7.83 (4 protons, CH_2-N-CH_2); 8.50[21] (multiplet with peaks at 8.45, 8.50, 8.05, 8.08, 8.14, 8.17, 8.19, 12 protons); 9.07 (singlet, 3 protons, $\gt$C—CH_3). The infrared spectrum in 0.20 M carbon tetrachloride as determined using a Perkin-Elmer Model 237 spectrophotometer exhibited maxima as follows[23,24]: 2970 cm.$^{-1}$ (ϵ 102), 2925 (490), 2880 (sh) (122), 2860 (133), 2790 (130), 2745 (88), 2670 (32). An authentic sample of 6-methyl-1-azabicyclo[4.4.0]decane (10-methylquinolizidine)[14] was prepared according to the method previously used in this laboratory, and the samples proved to be identical by comparison of infrared and n.m.r. spectra and the infrared and n.m.r. spectra of their perchlorates. The melting points of mixtures of the perchlorates and of the picrates were not depressed.

1-Methyl-1-azoniatricyclo[8.1.0.0^{5,10}]undecane Perchlorate (XVI).—A solution of 1.5 g. (6 mmoles) of 1-methyl-$\Delta^{1(9)}$-octahydroquinolinium perchlorate (XV)[17] in 175 ml. of methylene chloride was treated with an ethereal solution of diazomethane at 25°. The reaction was nearly instantaneous as evidenced by im-

(22) J. V. Paukstelis, unpublished work.

(23) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

(24) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

mediate decolorization of the diazomethane and nitrogen evolution. Addition of ethereal diazomethane was halted after a yellow color persisted in the reaction mixture. The solution was allowed to stand overnight, solvent was removed under reduced pressure in a rotary evaporator, and oily needles were obtained, recrystallized from diethyl ketone, m.p. 129–129.5° (depends on rate of heating; values of 118° to 131° have been recorded on the same sample), yield 1.43 g. (90%); no infrared maxima corresponding to $-\overset{+}{N}-H$ or $C=\overset{+}{N}$; n.m.r. τ values ($CDCl_3$): 6.32,[21] 6.66 (τ for doublet, $J = 5.0 \pm 0.5$ c.p.s.), 6.81 (3 protons, $C\underline{H}_3-\overset{+}{N}$), 7.09 ($\tau$ for doublet, $J = 5.0 \pm 0.5$ c.p.s.), 8.25 (broad)[21] (Fig. 3).

Anal. Calcd. for $C_{11}H_{20}ClNO_4$: C, 49.72; H, 7.59; H, 5.27. Found: C, 49.82; H, 7.67; N, 5.28.

Methanolysis of 1-Methyl-1-azoniatricyclo[8.1.0.0^{5,10}]undecane Perchlorate (XVI).—The crude crystalline product obtained as described above by addition of diazomethane to 1.5 g. of 1-methyl-$\Delta^{1(9)}$-octahydroquinolinium perchlorate was heated under reflux with methanol for 45 min. The solution was concentrated and the major product was precipitated with ether to yield 1.52 g. (86% over-all) of **1-methoxy-3-methyl-3-azabicyclo[5.4.0]undecane perchlorate (XVII)**, colorless plates, m.p. 163–163.5°; ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($-\overset{+}{N}-H$); n.m.r. τ values ($CDCl_3$): *ca.* 2.0[21] (1 proton, $\overset{+}{N}H$); 5.6–7.6 (broad); 6.66 (singlet, 3 protons, O–$C\underline{H}_3$); 6.95 (τ for doublet, $J = 5.4 \pm 0.5$ c.p.s. $C\underline{H}_3-\overset{+}{N}H$); 8.07, 8.40 (complex multiplet).

Anal. Calcd. for $C_{12}H_{24}ClNO_5$: C, 48.40; H, 8.12; N, 4.70; OCH_3, 10.42. Found: C, 48.57; H, 8.14; N, 4.75; OCH_3, 10.52.

The salt was made basic with aqueous sodium hydroxide and extracted with ether. The ether was evaporated leaving 0.96 g. (96%) of colorless oil which was distilled under reduced pressure in a Hickman still. Gas–liquid chromatography showed a single peak. N.m.r. analysis (neat) showed no signal at lower field than the O–$C\underline{H}_3$ signal (τ value 6.83); an N–$C\underline{H}_3$ signal at 7.75, and complex absorption at higher field, consistent with the structural assignment **1-methoxy-3-methyl-3-azabicyclo[5.4.0]undecane (XVIII)** to the major product.

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.19; H, 11.89; N, 7.17.

Ethanolysis of 1-Methyl-1-azoniatricyclo[8.1.0.0^{5,10}]undecane Perchlorate (XVI).—Ethanolysis of the same aziridinium perchlorate was achieved by refluxing in ethanol overnight. Upon addition of ether colorless plates separated, m.p. 174–175°, ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($-\overset{+}{N}-H$); n.m.r. τ values ($CDCl_3$): *ca.* 2.0[21] ($\overset{+}{N}H$); 6.46 (quartet, $J = 7.0 \pm 0.5$ c.p.s., O–$C\underline{H}_2CH_3$); 5.6–7.4 (broad); 6.94 (τ for doublet, $J = 5.4 \pm 0.5$ c.p.s., $C\underline{H}_3-\overset{+}{N}H$); 7.5–9.0 (broad); 8.71 (triplet, $J = 6.9 \pm 0.5$ c.p.s., O–CH_2–$C\underline{H}_3$). This major product was assigned the structure analogous to XVII, **1-ethoxy-3-methyl-3-azabicyclo[5.4.0]undecane perchlorate.**

Anal. Calcd. for $C_{13}H_{26}ClNO_5$: C, 50.07; H, 8.41; N, 4.49. Found: C, 50.15; H, 8.65; N, 4.44.

1-Azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane Perchlorate (XX).—$\Delta^{1(6)}$-Tetrahydrojulolidinium perchlorate (XIX), made by the method of Leonard, Steinhardt, and Lee,[17,25] appeared to be a single chemical individual according to the usual criteria. Only a single infrared absorption band was observed corresponding to $C=\overset{+}{N}$ stretch at 1680 cm.$^{-1}$ (chloroform) on the Perkin-Elmer Model 237 spectrophotometer. However, since the band was unsymmetrical and since the properties of the two isomers of XIX might be very similar, it cannot be guaranteed that the major substance was free of stereoisomeric contamination. The perchlorate was treated with diazomethane in methanol–ether at 0°, and the product, **1-azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane perchlorate (XX)**, was isolated by concentrating the methanol–ether solution to one quarter of its initial volume and cooling to −40°. It was recrystallized from acetone, colorless needles, m.p. 150–151° dec., yield 72%; no infrared maxima corresponding to $-\overset{+}{N}-H$ or $C=\overset{+}{N}$; n.m.r. τ values ($CDCl_3$): 6.20, 6.30, 6.40, and extending to higher field; 6.70 (singlet, 2 protons, aziridinium $C\underline{H}_2-N^+$); 8.21[21] (broad) (Fig. 3).

Anal. Calcd. for $C_{13}H_{22}ClNO_4$: C, 53.51; H, 7.61; N, 4.81. Found: C, 53.49; H, 7.44; N, 4.80.

This product appears to be a single isomer judged by the sharpness of its melting point and by spectral criteria.

Methanolysis of 1-Azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane Perchlorate (XX).—A solution of 0.78 g. (2.7 mmoles) of 1-azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane perchlorate (XX) was heated under reflux in absolute methanol for 21 hr., protected from moisture by a drying tube. Upon cooling, the methanol solution deposited 0.773 g. (89% yield) of colorless prisms, identified (see discussion) as **13-methoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane perchlorate (XXI)**, m.p. 226–227°; ν_{max}^{KBr} 3125 cm.$^{-1}$ ($-\overset{+}{N}-H$); selected n.m.r. τ values (CH_2Cl_2): 6.09 (singlet, 1.97 protons, $C\underline{H}_2$–O–CH_3); 6.55 (singlet, 3.03 protons—as integrated—CH_2–O–$C\underline{H}_3$).

Anal. Calcd. for $C_{14}H_{26}ClNO_5$: C, 51.92; H, 8.09; N, 4.33. Found: C, 51.96; H, 8.06; N, 4.45.

13-Methoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXII).—A sample of 0.773 g. (2.39 mmoles) of 13-methoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane perchlorate was made basic with aqueous sodium hydroxide and extracted with ether. The ether extracts were dried and concentrated. Upon cooling the ether solution deposited colorless prisms, 0.40 g. (75% yield), m.p. 79.5–80°; n.m.r. τ values (in CCl_4): on the Varian 4300 B: 6.31 (singlet), 6.70 (singlet), and complex signals near 7.57, 8.20, and 8.76. The base reacts slowly with carbon tetrachloride. N.m.r. τ values (in benzene) were observed on the Varian A-60 at: 6.24 (2 protons, $C\underline{H}_2$–O); 6.75 (3 protons, O–$C\underline{H}_3$); complex absorption 7.3–8.9 (20 protons). In the infrared spectrum, maxima were observed (10% CCl_4) at 2915, 2865, 2807, 2775, 2688 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.31; H, 11.42; N, 6.15.

Catalytic Reduction of 1-Azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane Perchlorate (XX).—A solution of 3.0 g. (10.3 mmoles) of 1-azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane perchlorate in 150 ml. of reagent grade acetone to which had been added 1.0 g. of platinum oxide was hydrogenated at 3 atm. for 7.5 hr. The filtered acetone solution was concentrated *in vacuo* and ether was added. Colorless needles separated, m.p. 256–257° dec., yield 2.82 g. (93%), identified as **13-methyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane perchlorate (XXIII)**; ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($-\overset{+}{N}-H$); n.m.r. τ values ($CDCl_3$): 6.76[21] ($C\underline{H}_2\overset{+}{N}HC\underline{H}_2$), 7.77–8.25–8.60 (broad); 8.39 ($\overset{+}{N}-\underset{|}{C}-C\underline{H}_3$).

Anal. Calcd. for $C_{13}H_{24}ClNO_4$: C, 53.15; H, 8.23; N, 4.77. Found: C, 53.01; H, 8.33; N, 4.77.

13-Methyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXIII).—The perchlorate described above was made basic with aqueous sodium hydroxide and extracted with ether. The dried ether solution was evaporated, and the solid residue was recrystallized from pentane, m.p. 31–32°, 95% recovery from the perchlorate; $\nu_{max}^{CCl_4}$ 2900, 2850, 2795, 2770, 2675 cm.$^{-1}$, with intensities comparable to those observed for XXII; n.m.r. τ values (CCl_4 or C_6H_6): 8.96 (CH_3) and complex absorption for ring protons.

Anal. Calcd. for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.25. Found: C, 80.70; H, 12.05; N, 7.48.

13-Bromomethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXIV).—A solution of 4.0 g. (46 mmoles) of anhydrous lithium bromide in 70 ml. of dry acetonitrile was prepared by stirring *ca.* 10 min. and the solution was filtered to remove a slight turbidity. To the filtrate was added 2.58 g. (8.7 mmoles) of 1-azoniatetracyclo[7.3-2.0.^{1,13}0^{5,13}]tetradecane perchlorate (XX), and the mixture was extracted continuously with olefin-free pentane for 18 hr. The pentane extracts were filtered and the filtrate was evaporated to dryness to afford 2.26 g. (95% yield) of colorless prisms, m.p. 110–112°; n.m.r. τ values (benzene): 6.19 (singlet for $C\underline{H}_2Br$), 7.5–9.2 (complex absorption of ring protons).

Anal. Calcd. for $C_{13}H_{22}BrN$: C, 57.35; H, 8.15; N, 5.14. Found: C, 57.51; H, 8.39; N, 5.24.

(25) *Cf.* also F. Bohlmann and C. Arndt, *Chem. Ber.*, **91**, 2167 (1958).

The same compound was made starting with $\Delta^{1(6)}$-tetrahydrojulolidinium bromide (XIX, Br^- in place of ClO_4^-) made by adding anhydrous hydrogen bromide to an ethereal solution of 0.976 g. (5.5 mmoles) of tetrahydrojulolidine[17] until no more salt precipitated. The colorless hydrobromide was washed with ether, dissolved in methylene chloride and treated with excess diazomethane in ether. After standing overnight the solution was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from 2-propanol, the crystals were dissolved in ether, the ethereal solution was filtered, and the ether was evaporated. The crystals gave a positive Beilstein test and an immediate precipitate upon addition of silver perchlorate in acetone. Infrared maxima were observed (10% CCl_4) at 2925, 2863, 2810, 2778, and 2690 cm.$^{-1}$. The band at 2863 cm.$^{-1}$ was more intense than the comparable band for XXI and XXIII.

The **perchlorate** of 13-bromomethyl-1-azatricyclo[7.3.1.$0^{5,13}$]-tridecane (XXIV) was formed in ether using 1:1 aqueous perchloric acid–ethanol. The precipitate (92% yield) was washed with ether, m.p. 263–265° dec.; ν_{max}^{Nujol} *ca.* 3100 cm.$^{-1}$ ($-\overset{+}{N}-H$) (Infracord); n.m.r. τ value (CH_3CN): 5.87 (singlet).

Anal. Calcd. for $C_{13}H_{23}BrClNO_4$: C, 41.89; H, 6.22; N, 3.76. Found: C, 42.31; H, 6.06; N, 3.68.

Treatment of 0.232 g. (0.85 mmole) of 13-bromomethyl-1-azatricyclo[7.3.1.$0^{5,13}$]tridecane (XXIV) in acetone with an acetone solution of 0.219 g. (0.98 mmole) of silver perchlorate monohydrate yielded silver bromide, which was separated by filtration. The filtrate was evaporated to dryness *in vacuo* on a rotary evaporator leaving 0.216 g. (87%) of crude product which was recrystallized from ethyl methyl ketone. Colorless needles, m.p. 150–151° dec., 0.097 g. (39%), were obtained which did not depress the melting point of **1-azoniatetracyclo[7.3.2.0.$^{1,13}0^{5,13}$] tetradecane perchlorate (XX)** previously prepared.

N-(1-Bromocyclohexylmethyl)pyrrolidine (XXV).—A solution of 3.0 g. (34.6 mmoles) of dry lithium bromide in 70 ml. of anhydrous acetonitrile was filtered to remove a trace of residue. To the clear solution 2.0 g. (7.55 mmoles) of 5-azoniadispiro-[4.0.5.1]dodecane perchlorate (I) was added, and the resulting solution was extracted continuously with pentane overnight. The pentane extracts were evaporated to dryness leaving 1.42 g. (77% yield) of free base, $n^{24}D$ 1.5150. This material was distilled, 73–75° (0.02 mm.), to give 0.93 g. of clear distillate, $n^{24}D$ 1.5156, together with 0.157 g. of pot residue, crude m.p. 190–208°. The nature of this residue was not determined. Several attempts were made to obtain a satisfactory analysis on the free base; however, despite repeated distillation, each analysis gave a high per cent of carbon, indiating that dehydrobromination had occurred. Each distillation was accompanied by salt formation, and each time the clear distillate turned turbid after standing a short time. N.m.r. τ values were observed (neat) at: 7.05 (singlet), 7.28 (multiplet), and broad complex absorption near 8.30, in a ratio of areas of 2:4:14; (benzene): 7.08 (singlet, 2 protons), 7.35 (complex multiplet, 4 protons), ring protons at higher field.

Addition of 1:1 perchloric acid–ethanol to an ethereal solution of the free base afforded the **perchlorate,** colorless plates, m.p. 165–166° dec. The perchlorate was recrystallized from isopropyl alcohol, m.p. now 162.5–163° dec.; ν_{max}^{Nujol} 3100 cm.$^{-1}$ ($-\overset{+}{N}-H$); n.m.r. τ values ($CDCl_3$): *ca.* 2.3 ($\overset{+}{N}H$); 6.24 (doublet, J = 5.0 ± 0.5 c.p.s.) plus complex signals both sides of doublet (total of 6 protons); complex absorption at high field (14 protons).

Anal. Calcd. for $C_{11}H_{21}BrClNO_4$: C, 38.10; H, 6.11; N, 4.04. Found: C, 38.09; H, 6.02; N, 3.90.

A solution of 1.6 g. of N-(1-bromocyclohexylmethyl)pyrrolidine in benzene was filtered to remove some crystals which had formed and evaporated *in vacuo*. The residue was dissolved in 50 ml. of acetone and to this solution at −33° was added an acetone solution of 1.4 g. of silver perchlorate. An immediate precipitate of silver bromide formed and the temperature rose to −5°. The silver bromide was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved quickly in absolute ethanol; the solution was filtered and cooled in a Dry Ice–isopropyl alcohol bath. The colorless needles were removed by filtration and washed with ether to afford 0.70 g. (40%) of I, m.p. 127–128.5°; m.m.p. with authentic 5-azoniadispiro-[4.0.5.1]dodecane perchlorate, 131.5–132°; authentic I, m.p. 132–133°. The infrared spectrum of the compound was identical with that of pure I except for very weak bands at 3400 cm.$^{-1}$ and 1700 cm.$^{-1}$.

1-N-Pyrrolidylcyclohexanemethanol.—This compound, previously described,[1] showed n.m.r. signals (CH_2Cl_2) at τ values 6.45 (2 protons), 6.95 (1 proton, OH), 7.35 (4), 8.29 (4), 8.50 (10). The chemical shift of the hydroxyl hydrogen was assigned by addition of a small amount of acetic acid.

Polynucleotides. I. Synthesis of Uridylyl-(3′ → 5′)-uridine and Uridylyl-(3′ → 5′)-6-azauridine

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2′,5′-Di-*O*-trityluridine serves as a convenient starting point for the synthesis of phosphate dinucleosides containing uridine. This compound was readily phosphorylated with cyanoethylphosphate and, after removal of the cyanoethyl group, the resultant blocked nucleotide was used to phosphorylate 2′,3′-isopropylideneuridine and 2,3′-isopropylidene-6-azauridine. After removal of blocking groups, the compounds listed in the title were isolated in good yield from ion-exchange columns.

The synthesis of (3′ → 5′) linked diribonucleoside phosphates by present techniques requires extensive use of multiple blocking groups.[1,2] The major problem in these syntheses arises from the need for a suitably blocked derivative of a nucleoside with a free 3′ hydroxyl group. Blocking requirements alternatively may be minimized by synthesizing diribonucleoside phosphates consisting of mixed (2′ → 5′) and (3′ → 5′) linked isomers.[3] The mixed isomers in most cases can be separated by ion exchange chromatography. Both these synthetic approaches are applicable to general synthesis in this field; however, there may be special cases where opportune use of a particular compound can avoid many of the intermediate steps. Such a case is exemplified by 2′,5′-di-*O*-trityluridine which is readily synthesized and makes a useful starting point for synthesis of diribonucleoside phosphates containing uridine.

Tritylation of uridine with an excess of trityl chloride gives a product containing two trityl groups. This compound, first synthesized by Levene,[4] was identified

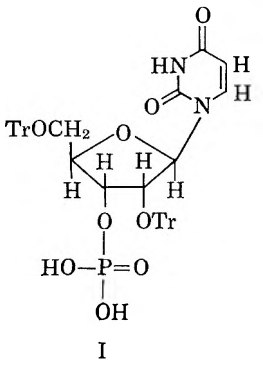
(1) M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).

(2) D. H. Rammler and H. G. Khorana, *ibid.*, **84**, 3112 (1962).

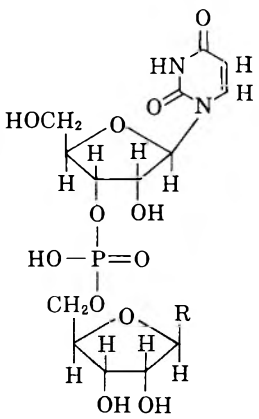
(3) A. M. Michelson, *J. Chem. Soc.*, 3655 (1959).

(4) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **105**, 419 (1934).

by Fox[5] as 2′,5′-di-*O*-trityluridine. Proof of structure rests on the fact that when the free hydroxyl at position-3′ is inverted, only the xylose derivative is obtained. 2′,5′-Di-*O*-trityluridine was phosphorylated readily with cyanoethyl phosphate[6] to produce 2′,5′-ditrityluridine-3′ cyanoethyl phosphate which upon removal of the cyanoethyl group by alkaline treatment produced compound I. The product as obtained from the reaction mixture was contaminated with salts and organic material. It was purified by partition chromatography on a column of Celite according to the general method of Hall.[7] Compound I represents a key intermediate and would be expected to react with a number of suitably protected nucleosides which contain an open 5′ position. Two such syntheses are presented here. Reaction of I with the 2′,3′-isopropylidene derivatives of uridine and 6-azauridine afforded, after removal of blocking groups with 80% acetic acid, uridylyl-(3′ → 5′)-uridine (II), and uridylyl-(3′ → 5′)-6-azauridine (III), respectively.



I



II. R = uracil
III. R = 6-azauracil

Uridylyl-(3′ → 5′)-uridine at this stage was obtained in a yield of 33% when the ratio of nucleoside intermediate to nucleotide intermediate was 2:1. This result compares with a yield of 50% reported for this dinucleoside phosphate when the 2′ position of the nucleotide intermediate was blocked with a dihydropyranyl group.[1] The bulkier trityl group thus appears to reduce the yield at the phosphorylation step but this is more than offset by a considerable reduction in number of steps in the over-all synthesis. The yield can be increased to 44% by using a 5:1 ratio of nucleoside intermediate to nucleotide intermediate. Uridylyl-(3′ → 5′)-uridine was readily purified by chromatography on a column of DEAE-cellulose using a buffer of triethylammonium carbonate (pH 8.6). It was obtained as the triethylammonium salt, analytically pure, in a yield of 29% based on compound I.

Uridylyl-(3′ → 5′)-6-azauridine was also purified on a DEAE-cellulose column and was isolated as the chromatographically homogeneous triethylammonium salt. Great care had to be exercised in the final isolation due to lability of this product. For example an aqueous solution of the free acid standing at room temperature decomposed within twelve hours to uridylic acid and 6-azauridine in contrast to uridylyl-(3′ → 5′)-uridine which can stand several days under these conditions without decomposing. An aqueous solution of the neutral salt which stood at room temperature for one day showed considerable amount of free nucleoside. The synthesis of compound III by another method has been reported[8] but authors of this paper did not suggest that the product so obtained was particularly labile.

Both products were degraded to uridine-3′ phosphate and nucleoside by ribonuclease, with about 1% of each product being resistant to the action of the enzyme which indicates slight contamination with the 2′ → 5′ isomer. This result agrees with that of Smith and co-workers[1] who found that treatment of such reaction products with acetic acid resulted in a small amount of isomerization. The fact that these dinucleoside phosphates were hydrolyzed with ribonuclease constitutes independent proof that the starting material in these syntheses is indeed 2′,5′-ditrityluridine.

2′,5′-Ditrityluridine-3′ phosphate offers a convenient starting point for the preparation of diribonucleoside phosphates containing a uridine residue and the procedure reported in this paper is suitable for scaling up to larger quantities.

Experimental

Preparation of 2′,5′-Di-*O*-trityluridine-3′ Phosphate.—To a solution of 5 g. (6.86 mmoles) of 2′,5′-di-*O*-trityluridine[5] in 75 cc. of anhydrous pyridine was added (13.72 mmoles) of cyanoethyl phosphate.[6] The mixture was concentrated to a sirup on a rotary evaporator (*in vacuo*) and again dissolved in 75 cc. of pyridine and evaporated (repeated three times). After dissolving the resulting gum in 100 cc. of anhydrous pyridine, 10 g. of dicyclohexylcarbodiimide (DCC) was added and the mixture was shaken a few minutes to effect solution. The mixture was tightly stoppered and allowed to stand at room temperature for 3 days after which water was added and the reaction mixture was allowed to stand at room temperature overnight. Insoluble dicyclohexylurea was removed by filtration. Concentration of the filtrate yielded more of the urea. The final filtrate was evaporated to dryness and the residue was washed several times with anhydrous ether to remove any remaining DCC and dicyclohexylurea. The slightly colored material was placed in a flask and 125 cc. of 1 *N* sodium hydroxide was added and, after refluxing the mixture for 40 min., it was filtered and the filtrate concentrated to dryness. The entire product mixture was dissolved in water and the pH was adjusted to 9.0 with IR-120 resin (H^+). It was necessary to add ethanol occasionally to the mixture because of its tendency to gel. After removal of the resin and other solid particles by filtration, the filtrate was lyophilized. The product was purified by partition chromatography on a Celite column according to the following general method of Hall.[7] The lyophilized material was dissolved in 15 cc. of the lower phase of a *n*-butyl alcohol–water (3:1) solvent mixture and mixed with 30 g. of Celite-545 which was then packed on top of a previously packed Celite column (130 g., 1 in. × 36 in.). The upper phase of the *n*-butyl alcohol–water solvent mixture was passed through the column at a rate of 175 cc./hr. The product began to come off the column immediately after the solvent front had appeared and elution was complete when 700 cc. of solvent had passed through. Upon concentration of this fraction a solid precipitated which was collected and air dried (4.51 g., 73%). Paper chromatography in solvent A showed a single spot (R_f 0.86).

Anal. Calcd. for $C_{47}H_{39}O_9PNa_2 \cdot 3H_2O$: C, 62.40; H, 4.98; N, 3.09; P, 3.41. Found: C, 62.55; H, 5.00; N, 3.22; P, 3.11.

Uridine-3′ Phosphate.—2′,5′-Di-*O*-trityluridine-3′ phosphate (sodium salt 0.5 g.) was dissolved in a minimum amount of water and filtered to remove the suspended particles. After addition of 24 cc. of 80% acetic acid, the solution was heated at 100° for 1.5 hr. The solution was cooled and filtered to remove triphenylcarbinol, after which the filtrate was concentrated to dryness and excess acid was removed by azeotroping with

(5) N. C. Yung and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).
(6) G. M. Tener, *ibid.*, **83**, 159 (1961).
(7) R. H. Hall, *J. Biol. Chem.*, **237**, 2282 (1962).
(8) J. Smrt and F. Sorm, *Collection Czech. Chem. Commun.*, **27**, 73 (1962).

water and ethanol. The remaining solid material was dissolved in a minimum amount of water, and two volumes of ethanol were added. After cooling the solution in an ice bath for 30 min., fine crystalline needles began to come out of solution. Uridine-3′ phosphate (disodium salt) was collected by filtration and dried over phosphorus pentoxide in a desiccator (yield 230 mg., 95%).

Anal. Calcd. for $C_9H_{11}O_9N_2PNa_2 \cdot 3H_2O$: C, 25.60; H, 4.04; N, 6.64; P, 7.34. Found: C, 25.42; H, 4.04; N, 6.57; P, 7.27.

Preparation of 2′,3′-Isopropylidene-6-azauridine.—This method is based on that of Hampton.[9] Five grams (20.3 mmoles) of 6-azauridine and 6.3 g. (20.3 mmoles) of di-*p*-nitrophenol phosphate were dissolved in 200 cc. of acetone containing 20.8 g. (200 mmoles) of 2,2-dimethoxypropane. The mixture was shaken for 30 min. on a mechanical shaker at which time a clear solution had resulted. After standing at room temperature for 4.5 hr., 24 g. of acetone washed Dowex-2 resin (OH^-) was added and the mixture was shaken for several minutes until the solution was neutral. After filtering, a clear solution was obtained which contained only one ultraviolet absorbing spot upon paper chromatography in systems A and B. The solution was lyophilized and the residue upon shaking with anhydrous ether became a dry powder (wt. 5.2 g., yield 85%) which gave the correct analysis.

Anal. Calcd. for $C_{11}H_{15}O_8N_3$: C, 46.31; H, 5.33; N, 14.73. Found: C, 46.25; H, 5.37; N, 14.47.

Synthesis of Uridylyl-(3′→5′)-Uridine.—The sodium salt of 2′-5′-di-*O*-trityluridine-3′ phosphate (90.6 mg., 0.1 mmole) was dissolved in a small quantity of water. This was passed through a short column of Dowex-50 (pyridinium form). The column was washed with a few milliliters of water and the combined filtrates were lyophilized. 2′,3′-Isopropylideneuridine (0.2 mmole) dissolved in 2 cc. of anhydrous pyridine was added and the mixture was concentrated to a gum on a flash evaporator. Evaporation with pyridine was repeated three times in order to render it completely anhydrous. In order to protect the mixture from the atmospheric moisture, dry nitrogen was released into the evaporator after each evaporation. After dissolving the resulting gum in 4 cc. of anhydrous pyridine, DCC (4 mmoles) was added, after which the reaction flask was flushed with dry nitrogen and tightly stoppered. The mixture was allowed to stand at room temperature for 3 days at which time more DCC (2 mmoles) was added and the mixture was allowed to stand at room temperature for two additional days. On the fifth day, water (8 cc.) was added and after remaining at room temperature for 24 hr. the reaction mixture was concentrated to dryness. Excess pyridine was removed by azeotroping with water then ethanol and the resulting solid product mixture was treated with 80% acetic acid (40 cc.) for 30 min. at 100°. The acid solution was cooled and filtered to remove dicyclohexylurea and triphenylcarbinol. Concentration of the filtrate yielded a gummy material which was evaporated repeatedly with water to remove excess acetic acid. The product was dissolved in the minimum amount of water, a small portion of which was applied to Whatman no. 3MM paper (acid washed). Development of the chromatogram in solvent I, indicated three bands, corresponding to uridylic acid, uridylyl-(3′→5′)-uridine, and uridine, respectively. Quantitative elution of the dinucleoside phosphate band indicated a yield of 33% at this point. Increased yields were obtained by using a larger ratio of 2′,3′-isopropylideneuridine to 2′,5′-di-*O*-trityluridine-3′ phosphate as shown.

Nucleoside : nucleotide	Yield, %
2:1	33
5:1	44
10:1	50

Isolation of Uridylyl-(3′→5′)-uridine by Ion Exchange Chromatography.—DEAE-Cellulose resin was suspended in an excess of water and stirred for several minutes. After allowing the material to stand for a while, the water was decanted, after which the washing procedure was repeated until the wash water became clear. The cellulose was washed with 1 l. of 0.5 *N* sodium hydroxide and then washed with more water until it was free of base, after which it was suspended in 0.1 *M* ammonium carbonate (pH 8.6) and packed, under pressure (4 lb.), in a 1 × 24 cm. column. One liter of the above ammonium carbonate solution was passed through the column, followed by 1 l. of a 0.01 *M* ammonium carbonate solution (pH 8.6). Finally, the column was washed with 1 l. of a 0.01 *M* triethylammonium carbonate solution (pH 8.6). The pH of a solution containing the reaction mixture was adjusted to 8.6 with ammonium hydroxide and the solution run into the column. A linear gradient with respect to triethylammonium carbonate at pH 8.6 (0.01 *M* → 0.1 *M*, total volume 2 l.) was applied to the column at a flow rate of 24 cc. per hour. All operations were conducted at 4°. Uridylyl-(3′→5′)-uridine appeared in the fraction of the effluent between 910 cc. and 1200 cc. This fraction was lyophilized and the residue was dissolved in water and relyophilized. This process was repeated a total of four times after which 20 mg. of product (29% based on compound I) was obtained as the triethylammonium salt.

Anal. Calcd. for $C_{24}H_{38}O_{14}N_5P \cdot 2H_2O$: C, 41.9; H, 6.15; P, 4.49; N, 10.2. Found: C, 41.85; H, 6.49; P, 3.51; N, 9.98.

Uridylyl-(3′→5′)-6-azauridine.—Synthetic procedure was the same as that preceeding 0.2—mmole of nucleoside and 0.1 of nucleotide being used. The product was purified on a DEAE-cellulose column described previously with a slight modification because direct lyophilization of the column effluent resulted in some hydrolysis of the product. Dowex-50 (H^+) was added carefully to the collected effluent until a pH 7.5 was reached, after which it was lyophilized. The residue weighed 22 mg. and moved as a single spot upon chromatography in solvent systems A and B and upon electrophoresis at pH 3.0. It was 95% pure, estimated spectrophotometrically which means a final yield of 31% based on compound I. Ribonuclease hydrolyzes this product to one equivalent each of uridylic acid and 6-azauridine.

Ribonuclease Treatment.—One milligram of the dinucleoside phosphate was dissolved in 0.5 cc. of water and the pH was adjusted to 7.5. Magnesium sulfate (5 λ of 1 *M* solution), and 0.1 mg. of crystalline ribonuclease were added. After 6 hr. at room temperature the entire sample was streaked on Whatman 3MM paper which was developed in solvent B. The quantitative elution and spectrophotometric analysis showed that each

TABLE I

Compound	R_f value, Solvent A	R_f value, Solvent B
Uridine	0.62	0.44
6-Azauridine	.59	.47
2′,3′-Isopropylideneuridine	.81	.77
2′,3′-Isopropylidene-6-azauridine	.79	.78
Uridine-3′ phosphate	.50	.09
Uridylyl-(3′ → 5′)-uridine	.39	.15
Uridylyl-(3′ → 5′)-6-azauridine	.29	.16

TABLE II

Compound	Distance moved toward anode, cm.
6-Azuridino	2.6
Uridine	2.3
Uridylyl-(3′ → 5′)-uridine	18.5
Uridylyl-(3′ → 5′)-6-azauridine	23.2
Uridine-3′ phosphate	24.5

TABLE III

SPECTROPHOTOMETRIC DATA

Compound	pH	Max	E_{max}
Uridine-3′ phosphate	2.0	262	10.0
	11.5	261	7.0
Uridylyl-(3′ → 5′)-uridine	2.0	260	19.2
	9.0	260	17.6
Uridylyl-(3′ → 5′)-6-azauridine	2.0	259	16.3
	10.0	254	12.7
2′,3′-Isopropylidene-6-azauridine	6.3	258	6.5
	11.5	254	7.4
2′,5′-Di-*O*-trityluridine-3′-phosphate	6.3	260	7.2
	10.5	260	6.2

(9) A. Hampton, *J. Am. Chem. Soc.*, **83**, 3640 (1961).

dinucleoside phosphate had produced one equivalent each of nucleoside and uridylic acid. A residue (1.3%) of each dinucleoside phosphate still remained.

Paper Chromatography.—Solvent A: isopropyl alcohol–1% aqueous ammonium sulfate (2:1). Solvent B: isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2). (See Table I.)

Paper Electrophoresis.—Electrophoresis was conducted in a Gilson Electrophorator for 1 hr., using a buffer of 0.01 *M* ammonium formate (pH 3.0) with a voltage gradient of 100 volts per cm. (See Tables II and III.)

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Pteridine Chemistry. X. Methylation Studies. III. Steric Effects of Phenyl Groups at C-6 and C-7[1]

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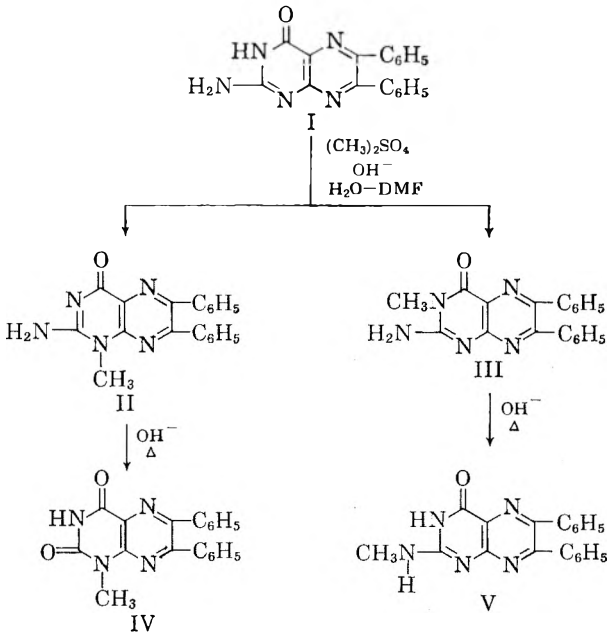
The methylation of 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III) with dimethyl sulfate in dimethylformamide–acetic acid occurred predominantly at N-1 and only slightly at N-8 to give the 2-imino-1,3-dimethyl derivative VII (63% yield) and the 2-imino-3,8-dimethyl derivative VIII (10% yield). Contrastingly, when the C-7 substituent was hydrogen rather than phenyl, *i.e.*, 2-amino-3-methyl-6-phenyl-4(3*H*)-pteridinone (XIIa), the relative amounts of N-1 and N-8 methylated products (XIIIa and XIVa) were reversed. However, when the C-6 substituent was hydrogen, *i.e.*, 2-amino-3-methyl-7-phenyl-4(3*H*)-pteridinone (XIIb), methylation occurred only at N-1. The varying yields of 8-methyl derivatives are ascribed to steric effects. Additional related methylations also are discussed.

The nature of the products obtained from the methylation of 2-amino-4-hydroxypteridines has been found to be dependent not only upon the conditions of the reaction[2a] but also upon the substituents located at positions 6 and 7 of the pteridine ring. Thus, 2-amino-4-hydroxypteridine-6-carboxylic acid treated with dimethyl sulfate in an aqueous alkaline solution at pH 8–11.5 gave a 30% yield of a crude mixture of the 1-methyl and 3-methyl derivatives and a 25–30% yield of the 3,8-dimethyl derivative. The isomeric 2-amino-4-hydroxypteridine-7-carboxylic acid, however, gave only the 1-methyl and 3-methyl derivatives.[1]

In order to continue the study of the effect of substituents upon this methylation reaction 2-amino-4-hydroxy-6,7-diphenylpteridine (I) was treated with dimethyl sulfate in a water–dimethylformamide[2b] solution at pH 8–11.5. There was isolated from this reaction the 1-methyl derivative II (52% yield) and the 3-methyl derivative III (10% yield). (A very small amount of the 3,8-dimethyl derivative VIII was detected by paper chromatography but was not isolated.) The comparatively high yield of the 1-methyl isomer II in this reaction is somewhat different from the results of the previous methylation studies[2a,3] where any preponderance of one isomer over the other was, in each case, in favor of the 3-methyl derivative.

The structures of the 3-methyl III and 1-methyl II derivatives were proved by well established methods.[2a,4] The 3-methyl derivative III upon treatment with 1.0 *N* sodium hydroxide rearranged to the 2-methylamino derivative V while the 1-methyl derivative II under the same conditions was hydrolyzed to the 1-methyl-2,4-pteridinedione IV. Furthermore, the 3-methyl III and 1-methyl II compounds also were synthesized unequivocally by the reactions of benzil with 3-methyl-2,5,6-triamino-4(3*H*)-pyrimidinone[4] and 1-methyl-2,5,-6-triamino-4(1*H*)-pyrimidinone,[4,5] respectively.



A previous report[1] also has shown that 2-amino-3-methyl-4-pteridinones can be methylated in nonbasic solvents and that the substituents in the pyrazine ring again have some influence upon the course of the reaction. Thus the methylation of the 3-methyl derivative of 2-amino-4-hydroxypteridine-6-carboxylic acid with dimethyl sulfate in a boiling dimethylformamide–acetic acid solution gave, as the only major product, the 3,8-dimethyl derivative. In contrast, the isomeric 7-carboxylic acid derivative under the same conditions gave no detectable dimethyl derivative.[1]

In the present investigation 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III) when treated with

(1) Presented in part at the IIIrd International Pteridine Symposium, Stuttgart, Germany, September 12–15, 1962.

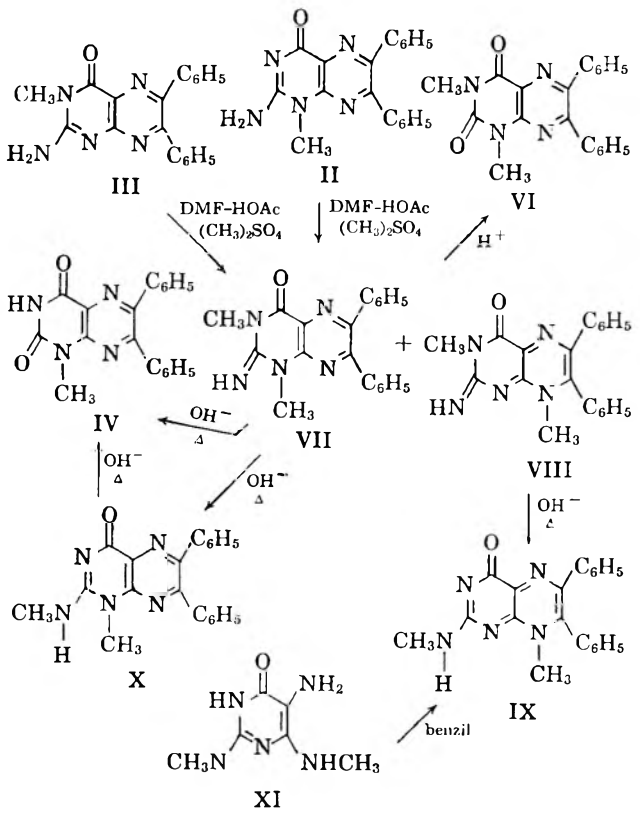
(2) (a) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **27**, 892 (1962). (b) The use of dimethylformamide was necessitated by the low solubility of the 6,7-diphenyl derivative I in water.

(3) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **26**, 2129 (1961).

(4) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958).

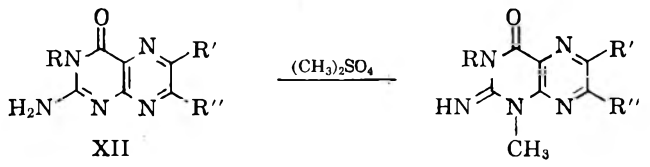
(5) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *ibid.*, **73**, 2864 (1951).

excess dimethyl sulfate in a hot dimethylformamide solution did give the 3,8-dimethyl derivative VIII in 10% yield. However, the main product was an isomeric dimethyl derivative obtained in 63% yield. This was shown to be the 2-imino-1,3-dimethyl derivative VII by the following reactions. The 1-methyl derivative II, methylated under the same conditions used for the 3-methyl derivative III, gave the same dimethyl derivative VII. Assuming no rearrangement had occurred this proved the 1,3-dimethyl structure VII. Mild alkaline treatment of VII gave the expected[1,4] isomeric 2-methylamino-1-methyl derivative X, while longer hydrolysis gave the same 1-methyl-2,4-pteridinedione IV which had been obtained by alkaline hydrolysis of the 2-amino-1-methyl derivative II. The structure of the 3,8-dimethyl derivative VIII, which was indicated by its ultraviolet absorption spectra, was proved by alkaline rearrangement to the isomeric 2-methylamino-8-methyl derivative IX which was independently synthesized from benzil and 5-amino-2,6-bis(methylamino)-4(3*H*)-pyrimidinone XI. [During the course of this study it was noted that the 2-imino-1,3-dimethyl derivative VII was hydrolyzed to 1,3-dimethyl-6,7-diphenyl-2,4(1*H*,3*H*)-pteridinedione (VI) by prolonged heating in a Methyl Cellosolve–hydrochloric acid solution.]

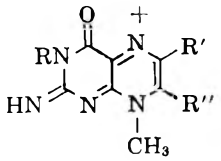


Isolation of 2-imino-1,3-dimethyl derivative VII from the methylation of III was quite unexpected since no such compound had been obtained from similar reactions with the 6- and 7-carboxylic acid derivatives of 2-amino-4-hydroxypteridine. Apparently the N-1 position in the 3-methyl-6,7-diphenyl derivative III is more subject to electrophilic attack by the alkylating agent than is the case with the corresponding 6- and 7-carboxylic acid derivatives.[1] This correlates well with the comparatively high yield of the 1-methyl isomer II obtained upon methylation of 2-amino-4-hydroxy-6,7-diphenylpteridine (I). It would also appear, however, that the presence of either a phenyl group or a carboxylic acid group in position 7 sterically hinders the methylation at N-8. In order to further elucidate this postulated steric effect the methylation studies were continued with the 6- and 7-monophenyl derivatives of 2-amino-3-methyl-4-pteridinone.

With dimethylformamide–acetic acid–dimethyl sulfate as the reaction solvent (100°) 2-amino-3-methyl-6-phenyl-4(3*H*)-pteridinone XIIa gave the 2-imino-3,8-dimethyl derivative XIVa in a 63% yield and the 2-imino-1,3-dimethyl derivative XIIIa in only a 13% yield. On the other hand, 2-amino-3-methyl-7-phenyl-4(3*H*)-pteridinone XIIb gave a 41% yield of the 2-imino-1,3-dimethyl derivative XIIIb while none of the 2-imino-3,8-dimethyl derivative was formed. (8-Methyl derivatives of these phenylpteridines possess a strong yellow-green fluorescence readily detectable on paper chromatograms.)



a series: R = CH_3; R′ = C_6H_5; R″ = H
b series: R = CH_3; R′ = H; R″ = C_6H_5
c series: R = H; R′ = C_6H_5; R″ = H
d series: R = H; R′ = H; R″ C_6H_5



Results obtained with the three phenylpteridines (III, XIIa, and XIIb) are best explained by assuming that a phenyl group in position 7 of the pteridine sterically hinders alkylation at N-8.[6] Even the production of a 10% yield of a 3,8-dimethyl derivative from the methylation of 2-amino-3-methyl-6,7-diphenyl-4-(3*H*)-pteridinone (III) compared with complete absence of any 8-methyl derivative in the methylation of the corresponding 7-phenylpteridine XIIb can be explained. Models show that in a 6,7-diphenylpteridine the two phenyl rings are not free to rotate and cannot be coplanar with the pteridine ring whereas in a 7-phenylpteridine with no substituent in position 6 the phenyl ring is free to rotate. Thus, in the latter case, approach of the alkylating agent to N-8 is more effectively hindered than in the 6,7-diphenyl series. In accordance with this postulated steric effect it was noted that the methylation of the 6-phenylpteridine XIIa proceeds at a faster rate than does the methylation of the 7-phenylpteridine XIIb.

Although the reactions were more complex and the yields were not satisfactory, similar steric effects were noted when the parent 2-amino-4-hydroxypteridines were methylated. With dimethylformamide–acetic acid–dimethyl sulfate at 100° 2-amino-4-hydroxy-7-phenylpteridine (XIId) gave the 1,3-dimethyl deriva-

(6) An alternative possibility is that these results might be explained by electron-donating or withdrawing effects of the phenyl groups. This was discounted when it was found that a consideration of the published p*K* values[7] for pyridine and its 2-, 3- and 4-phenyl derivatives would lead one to predict results exactly the opposite of those found in this investigation.

(7) A. R. Katritsky and J. M. Lagowski, "Heterocyclic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 56.

tive XIIIb in a 12% yield. This was the only isolated product and no 8-methyl derivative was detected. Considerable decomposition occurred. 2-Amino-4-hydroxy-6,7-diphenylpteridine (I) under these conditions gave a complex mixture with no predominant product. The 1-methyl derivative II was the only product isolated (10% yield), but chromatography showed the presence of the 3-methyl III and 1,3-dimethyl VII derivatives as well as a small amount of an 8-methyl derivative. On the other hand, 2-amino-4-hydroxy-6-phenylpteridine (XIIc) gave as the principal product the 8-monomethyl derivative XIVc in a 40% yield. Chromatography demonstrated the presence, in smaller amounts, of the 1-methyl and, presumably, the 3-methyl derivatives. A very small amount of the 1,3-dimethyl derivative XIIIa was also isolated. This last reaction is another example[1,8] where a neutral form of a 2-amino-4-hydroxypteridine is preferentially alkylated in the pyrazine ring at N-8. However, the other reactions demonstrate that this preferential alkylation occurs only in the absence of bulky substituents at position 7.

Experimental[9]

All of the compounds reported here as well as most of the reaction mixtures were examined by paper chromatography using the descending technique on Whatman no. 1 paper.

All evaporations were carried out under reduced pressure.

Methylation of 2-Amino-4-hydroxy-6,7-diphenylpteridine (I). A.—A mixture of 3.15 g. (10 mmoles) of 2-amino-4-hydroxy-6,7-diphenylpteridine, 50 ml. of water, 50 ml. of dimethylformamide (DMF), and 20 ml. of 1.0 *N* sodium hydroxide was stirred with a magnetic stirrer to produce almost complete solution. One milliliter (10.7 mmoles) of dimethyl sulfate (DMS) was added. Stirring was continued and at intervals the indicated materials were added as follows: 30 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS; 60 min., 5 ml. of 1.0 *N* NaOH and 0.9 ml. of DMS; 90 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS; 120 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS; 150 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS. After an additional hour of stirring the pH was *ca.* 6. The mixture was cooled and the crystalline product was collected; yield 3.0 g. (the filtrate showed the presence of a small amount of the 3,8-dimethyl derivative which was not isolated).

This product (3.0 g.) was dissolved in 170 ml. of hot DMF, which was treated with charcoal, filtered, and allowed to stand at room temperature overnight. The crystalline product was collected; yield 1.7 g. (52%); m.p. 322–325°. This was chromatographically pure 2-amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II).

For analyses a portion (1.5 g.) of this product was crystallized first from 90 ml. of DMF and then from 35 ml. of 2-methoxyethanol; yield 0.50 g.; m.p. 327–329°; $\lambda_{max}^{CH_3OH}$ 268 mμ (ε 20,800), 362 mμ (ε 16,800); $\lambda_{max}^{0.1\,N\,HCl}$ 220–230 mμ (ε 24,300), 280 mμ (ε 14,100), 363 mμ (ε 14,800). The only paper chromatographic solvent system found to separate the 1-methyl II and the 3-methyl III derivatives was isopropyl alcohol–1.0 *N* NH_4OH (7:3) in which II had R_f 0.85 (deep blue) and III had R_f 0.90 (light blue).

Anal. Calcd. for $C_{19}H_{15}N_5O$(329): C, 69.3; H, 4.6; N, 21.2. Found: C, 68.8; H, 5.0; N, 21.2.

The filtrate from the 1.7 g. of 1-methyl derivative II was evaporated to 10 ml., after which 40 ml. of 0.5 *N* hydrochloric acid was added. This was heated on a steam bath, then cooled to room temperature, and the product was collected; yield 0.65 g. (paper chromatography indicated this to be a mixture of starting material and the 3-methyl derivative III). The filtrate was cooled overnight to give a crystalline product; yield 0.35 g. (10%). A solution of 250 mg. of this material in 10 ml. of DMF was heated to 100° and diluted with 25 ml. of water containing 0.5 ml. of pyridine; yield of crystalline product, 200 mg.; m.p. 347–350°. Infrared spectra, mixture melting point, and paper chromatography in two systems showed this to be identical with an authentic sample of 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III).

B.—A mixture of 600 mg. (1.97 mmoles) of 2-amino-4-hydroxy-6,7-diphenylpteridine (I), 20 ml. of dimethylformamide (DMF), 2.0 ml. of acetic acid, and 3.0 ml. of dimethyl sulfate was heated to boiling for 10 min. An additional 1.5 ml. of dimethyl sulfate was added and the solution heated to boiling for 5 min. The solution was treated with charcoal, filtered, and evaporated to a sirup. The sirup was dissolved in 40 ml. of water, made alkaline with sodium carbonate, and cooled; yield 690 mg.

A 600-mg. portion of this product was crystallized from 7 ml. of DMF using charcoal to clarify it; yield 75 mg. A recrystallization from 4 ml. of 2-methoxyethanol gave 40 mg. of product; m.p. 325–327°. This was shown to be identical with an authentic sample of the 1-methyl derivative II (mixture melting point and infrared absorption spectra).

Paper chromatography showed that the initial crude product contained at least three other products. They were not obtained in a pure state.

2-Amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II). A.—This was first prepared by the methylation of 2-amino-4-hydroxy-6,7-diphenylpteridine (I) as described previously and was shown to be identical with the product described under B (infrared absorption spectra, mixture melting point, and paper chromatography).

B.—A mixture of 155 mg. (10 mmoles) of 2,5,6-triamino-1-methyl-4(1*H*)-pyrimidinone, 230 mg. (1.1 mmoles) of benzil, 4.0 ml. of water, and 3 drops of acetic acid was heated to reflux for 1.5 hr. The mixture was cooled and the product was collected; yield 200 mg. (61%). This was crystallized from 15 ml. of DMF; yield 130 mg.; m.p. 325–328°. A sample was recrystallized from 2-methoxyethanol for infrared spectral determinations. Characterization of this compound is described under A above and under methylation of I.

2-Amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III). A.—A solution containing 14.3 g. (75 mmoles) of 2,5,6-triamino-3-methyl-4(3*H*)-pyrimidinone hydrochloride, 13.8 g. (168 mmoles) of sodium acetate, and a trace of sodium hydrosulfite in 230 ml. of warm water was added to a second solution of 16.9 g. (80 mmoles) of benzil in 400 ml. of hot ethanol. The mixture was heated to reflux for 90 min. and cooled overnight; yield 21.8 g. (89%); m.p. 348–351°.

A sample (300 mg.) was recrystallized from a solution of 15 ml. of dimethylformamide and 10 ml. of water; yield 230 mg.; no change in melting point; R_f 0.30 (3% NH_4Cl) (blue), 0.57 (0.1 *N* HCl) (blue); $\lambda_{max}^{pH\ 7.0\ and\ 9.2}$ 291 mμ (ε 23,000), 377 mμ (ε 12,800); $\lambda_{max}^{0.1\,N\,HCl}$ 230 mμ (ε 30,900), 280 mμ (ε 14,500), 362 mμ (ε 15,500).

Anal. Calcd. for $C_{19}H_{15}N_5O$ (329): C, 69.3; H, 4.6; N, 21.2. Found: C, 68.9; H, 4.7; N, 21.5.

B.—This compound III was also one of the products isolated from the methylation of 2-amino-4-hydroxy-6,7-diphenylpteridine (I) as described previously.

Methylation of 2-Amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III).—A mixture of 14.0 g. (42.5 mmoles) of III, 500 ml. of dimethylformamide (DMF), 50 ml. of acetic acid, and 22.5 ml. (240 mmoles) of dimethyl sulfate was heated on a steam bath for 5 hr. with six 22.5-ml. portions of dimethyl sulfate being added at regular intervals. The solution was evaporated to about 125 ml. and diluted to a volume of 1 l. with warm water. This was treated with charcoal, warmed briefly on the steam bath, filtered, and cooled to 20°. Solid sodium carbonate was added slowly with stirring to pH *ca.* 9. The mixture was cooled overnight and the product collected; yield 15 g. This was slurried in 150 ml. of absolute ethanol and warmed on a steam bath. The amorphous solid dissolved and a crystalline product separated. The mixture was cooled and the product was collected; yield 9.3 g. (63%); m.p. 239–242°. Paper chromatography indicated this material to be essentially pure. However, it was recrystallized from 125 ml. of 2-methoxyethanol; yield 8.0 g. (55%) of a cream colored product subsequently shown to be 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII); m.p. 241–242°; R_f 0.65 (3% NH_4Cl), 0.70 (0.1 *N* HCl) (deep blue); $\lambda_{max}^{pH\ 7.0}$ 266 mμ (ε 18,500), 290 mμ (ε 17,100) (sh), 378 mμ (ε 13,400); $\lambda_{max}^{0.1\,N\,NaOH}$ 268 mμ (ε 18,500), 290 mμ (ε 15,800) (sh 378 mμ (ε 13,300); $\lambda_{max}^{0.1\,N\,HCl}$ 232 mμ (ε 31,500), 280 mμ (ε 15,400), 363 mμ (ε 16,100).

(8) D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 869 (1961).

(9) All melting points were taken in a Mel-temp melting point apparatus using a thermometer calibrated for 3-in. immersion.

Anal. Calcd. for $C_{20}H_{17}N_5O$ (343): C, 70.0; H, 5.0; N, 20.4. Found: C, 70.3; H, 5.2; N, 20.6.

The ethanolic filtrate from the 9.3 g. of the 1,3-dimethyl derivative VII was evaporated to dryness. The residue was slurried in 40 ml. of water and sodium bicarbonate was added to pH 7.5. The mixture was cooled and the solid was collected; yield 3.6 g. This solid was dissolved in a solution of 12 ml. of water and 0.7 ml. of concentrated hydrochloric acid, which was then treated with charcoal and filtered. The filtrate was diluted first with 10 ml. of concentrated hydrochloric acid and then with 25 ml. of ethanol. This was cooled overnight, the mixture was agitated and rubbed, cooled several more hours, and the product was collected; yield 0.3 g. of product, primarily starting material, which was discarded. The filtrate was evaporated to dryness several times with the aid of ethanol, 70 ml. of ethanol was finally added, and the mixture was heated to boiling and filtered; yield 310 mg. (this was primarily the 3,8-dimethyl derivative VIII but it was less pure than the next crop). The filtrate, when cooled, gave a nicely crystalline yellow product; yield 1.4 g. (9.6%) of 2-imino-3,8-dimethyl-6,7-diphenyl-2,8-dihydro-4(3*H*)-pteridinone (VIII) as its hydrochloride; m.p. 238–240°. Since paper chromatography indicated that this contained small amounts of impurities, it was suspended in 28 ml. of 1.0 *N* hydrochloric acid which was heated to boiling, treated with charcoal, and filtered. The filtrate upon cooling deposited yellow crystals; yield 0.95 g. (6.5%); m.p. 241–243°; R_f 0.78 (3% NH_4Cl) (yellow-green becoming blue when fumed with ammonia); $\lambda_{max}^{0.1\ N\ NaOH}$ 247 mμ (ε 26,600), 283 mμ (ε 9,100) (sh), 358 mμ (ε 13,300); $\lambda_{max}^{0.1\ N\ HCl}$ 273 mμ (ε 17,500), 295 mμ (ε 16,400), 428 mμ (ε 14,400).

Anal. Calcd. for $C_{20}H_{17}N_5O \cdot HCl$ (380): C, 63.3; H, 4.8; N, 18.4; Cl, 9.4. Found: C, 63.2; H, 4.9; N, 18.3; Cl, 9.8.

Methylation of 2-Amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II).—A mixture of 600 mg. (1.8 mmoles) of II, 40 ml. of dimethylformamide (DMF), 3.0 ml. of acetic acid, and 1 ml. of dimethyl sulfate was heated on a steam bath for 8 hr. Four 1-ml. portions of dimethyl sulfate were added at regular intervals. The solution was evaporated to a small volume and diluted to 90 ml. with water. This was warmed a short time, treated with charcoal, and filtered. The filtrate was brought to pH 9 with sodium carbonate and cooled; yield 500 mg.

The solid was dissolved in 10 ml. of hot ethanol, filtered from a little solid, and cooled overnight; yield of crystalline product 210 mg.; m.p. 236–240°. This was similar to the crude main product obtained from the methylation of the 3-methyl derivative III.

Recrystallization of this material from ethanol gave a product identical with 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII) originally obtained by the methylation of the 3-methyl derivative III (mixture melting point and infrared spectra).

1-Methyl-6,7-diphenyl-2,4(1*H*,3*H*)-pteridinedione (IV).[10] **A.**—A solution of 300 mg. (0.9 mmole) of 2-amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II) in 10 ml. of 2-methoxyethanol and 20 ml. of 1.0 *N* sodium hydroxide was heated on a steam bath for 30 min. The hot solution was acidified with 2 ml. of acetic acid and cooled overnight; yield 240 mg. This was recrystallized first from 20 ml. of 50% 2-methoxyethanol and a second time from 3 ml. of 2-methoxy-ethanol; yield 130 mg.; m.p. 277–279° (lit.[10] 263–264) R_f 0.35 (0.1 *N* HCl) (blue); $\lambda_{max}^{0.1\ N\ NaOH}$ 267 mμ (ε 18,500), 367 mμ (ε 14,500); $\lambda_{max}^{0.1\ N\ HCl}$ 278 mμ (ε 14,900), 365 mμ (ε 13,500).

Anal. Calcd. for $C_{19}H_{14}N_4O_2$(330): C, 69.2; H, 4.2; N, 17.0. Found: C, 69.3; H, 4.4; N, 17.2.

B.—A 300-mg. sample (0.87 mmole) of 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII) was hydrolyzed and purified in exactly the same manner as described in preceding method A; final yield 100 mg.; m.p. 277–279°. This was shown to be identical with the product obtained before through the use of infrared spectra, mixture melting point, and paper chromatography.

2-Methylamino-4-hydroxy-6,7-diphenylpteridine (V).—A solution of 100 mg. (0.3 mmole) of 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III) in 5 ml. of 2-methoxyethanol and 10 ml. of 1.0 *N* sodium hydroxide was heated 2 hr. on a steam bath, then treated with charcoal, and filtered. The hot filtrate was added to a hot solution of 12 ml. of 1.0 *N* hydrochloric acid and cooled; yield was 85 mg. of crystalline product; m.p. 359–361°; R_f 0.44 (0.1 *N* HCl) (blue); $\lambda_{max}^{pH\ 9.2}$ 282 mμ (ε 22,400), 386 mμ (ε 12,500); $\lambda_{max}^{pH\ 7.0}$ 296 mμ (ε 22,400), 377 mμ (ε 11,500); $\lambda_{max}^{0.1\ N\ HCl}$ 232 mμ (ε 26,000), 283 mμ (ε 13,800), 363 mμ (ε 13,700).

Anal. Calcd. for $C_{19}H_{15}N_5O$ (329): C, 69.3; H, 4.6; N, 21.2. Found: C, 69.2; H, 4.7; N, 20.9.

2-Methylamino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (X).—A solution of 300 mg. (0.88 mmole) of 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII) in 5 ml. of boiling 2-methoxyethanol was diluted with 10 ml. of 1.0 *N* sodium hydroxide. This was heated on a steam bath for 2 min. followed immediately by acidification with 1 ml. of concentrated hydrochloric acid. The solution was diluted with 20 ml. of hot water, then neutralized to pH 7.5 with sodium bicarbonate and cooled; yield 280 mg. This was crystallized from 10 ml. of 2-methoxyethanol; yield 200 mg. (67%); m.p. 304–306°; R_f 0.35 (3% NH_4Cl) (deep blue); $\lambda_{max}^{pH\ 7.0}$ 269 mμ (ε 20,200), 367 mμ (ε 16,300); $\lambda_{max}^{0.1\ N\ HCl}$ 280 mμ (ε 14,700); 365 mμ (ε 14,600).

Anal. Calcd. for $C_{20}H_{17}N_5O$ (343): C, 70.0; H, 5.0; N, 20.4. Found: C, 69.6; H, 5.2; N, 20.2.

2-Methylamino-8-methyl-6,7-diphenyl-4(8*H*)-pteridinone (IX).

A.—A solution of 100 mg. of 2-imino-3,8-dimethyl-6,7-diphenyl-2,8-dihydro-4(3*H*)-pteridinone hydrochloride (VIII·HCl) in 5 ml. of 2-methoxyethanol and 5 ml. of 1.0 *N* sodium hydroxide was heated on a steam bath for 5 min. The hot solution was acidified with 1 ml. of concentrated hydrochloric acid and a yellow crystalline product separated. The mixture was cooled and the product was collected; yield 65 mg. The infrared spectrum and paper chromatographic behavior of this product showed it to be identical with an authentic sample of IX·HCl prepared as described under B.

B.[11]—2,4-Bismethylamino-5-amino-6-hydroxypyrimidine (0.50 g., 3.0 mmoles) (XI) was dissolved in 5 ml. of hot water containing a pinch of sodium hydrosulfite. A solution of 0.75 g. (3.6 mmoles) of benzil in 10 ml. of warm ethanol was added and the mixture was heated to reflux for 2 hr. The reaction mixture was then evaporated and the residue taken up in 80 ml. of hot ethanol. Addition of 5.0 ml. of concentrated hydrochloric acid gave crystals; yield 0.70 g. (61%); m.p. 350–357° with previous browning and wetting; R_f 0.73 (yellow-green fluorescence) in 3% ammonium chloride. This material (600 mg.) was dissolved in 50 ml. of boiling water, treated with charcoal, and filtered. The filtrate was reheated to boiling and 25 ml. of concentrated hydrochloric acid was added to give crystals almost immediately; yield 330 mg.; $\lambda_{max}^{0.1\ N\ HCl}$ 285 mμ (ε 11,600) (sh); 300 mμ (ε 12,500), 430 mμ (ε 9,500); $\lambda_{max}^{0.1\ N\ NaOH}$ 252 mμ (ε 9,600), 287 mμ (ε 7,000) (sh), 375 mμ (ε 7,600); $\lambda_{max}^{pH\ 7.0}$ 289 mμ (ε 14,600), 437 mμ (ε 8,400).

Anal. Calcd. for $C_{20}H_{17}N_5O \cdot HCl$ (380): C, 63.3; H, 4.8; N, 18.4. Found: C, 63.3; H, 4.9; N, 18.5.

1,3-Dimethyl-6,7-diphenyl-2,4(1*H*,3*H*)-pteridinedione[12] (VI).—A solution of 500 mg. (1.45 mmoles) of 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII), 100 ml. of 2-methoxyethanol, and 2.5 ml. of concentrated hydrochloric acid was heated to reflux for 46 hr. with 2-ml. portions of concentrated hydrochloric acid being added after 4, 10, 16, and 22 hr. The solution was evaporated to dryness and the crystalline residue was slurried in 25 ml. of hot methanol and cooled; yield 440 mg. (88%); m.p. 229–231°. This was recrystallized from 6 ml. of 2-methoxyethanol; yield 380 mg. (76%); m.p. 231–232° (lit.[12] m.p. 226–227°); R_f 0.3 (0.1 *N* HCl); $\lambda_{max}^{pH\ 7.0}$ 226 mμ (ε 25,000), 276 mμ (ε 14,800), 363 mμ (ε 14,100).

Anal. Calcd. for $C_{20}H_{16}N_4O_2$ (344): C, 69.8; H, 4.7; N, 16.3. Found: C, 69.8; H, 4.7; N, 16.0.

Methylation of 2-amino-3-methyl-7-phenyl-4(3*H*)-pteridinone[13] XIIb.—A mixture of 5.0 g. (19.8 mmoles) of XIIb, 250 ml. of dimethylformamide, 25 ml. of acetic acid, and 9 ml. of dimethyl sulfate was heated on a steam bath for 4 hr. with 9-ml. portions of dimethyl sulfate being added after 30 min. and 2.5 hr. The solution was evaporated to a sirup which was dissolved in 200 ml. of water. This was heated on a steam bath for 15 min., treated with charcoal, filtered, and cooled; yield of crystalline product, 2.4 g. (fraction A).

The filtrate was adjusted to pH 3 with sodium carbonate, treated with charcoal and filtered. The filtrate was adjusted to pH 9 with sodium carbonate and cooled two days; yield 2.4 g. (fraction B).

(10) G. Henseke and H. G. Patswaldt, *Chem. Ber.*, **89**, 2909 (1956).

(11) This reaction was carried out by W. V. Curran.

(12) F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 2798 (1954).

(13) R. B. Angier, *J. Org. Chem.*, **28**, 1398 (1963).

Fraction A was dissolved in 60 ml. of hot water, treated with charcoal, and filtered. The hot solution was acidified with 6 ml. of concentrated hydrochloric acid and cooled to give a crystalline product; yield 1.9 g. (fraction C). Paper chromatography indicated this to be essentially pure 1,3-dimethyl derivative XIIIb.

Fraction B was suspended in 40 ml. of boiling water and acidified to pH 2 with concentrated hydrochloric acid. This was filtered hot and the solid was discarded. The filtrate was clarified with charcoal, acidified with 5 ml. of concentrated hydrochloric acid, and cooled; yield 0.75 g. This purification was repeated; yield 0.6 g. (fraction D).

Fractions C and D were combined to give 2.5 g. (41%) of XIIIb as a hydrochloride.

For analyses a portion (140 mg.) of this product was dissolved in 30 ml. of hot water containing a drop of concentrated hydrochloric acid. This was heated to 85° and neutralized with a solution of sodium acetate and cooled; yield, 90 mg. of 2-imino-1,3-dimethyl-7-phenyl-1,2-dihydro-4(3*H*)-pteridinone XIIIb; m.p. 290–292°; R_f 0.53 (3% NH_4Cl) (purple); $\lambda_{max}^{pH\ 7.0}$ 214 mμ (ε 22,200), 235 mμ (ε 22,900), 262 mμ (ε 15,000), 367 mμ (ε 16,000); $\lambda_{max}^{0.1\ N\ HCl}$ 229 mμ (ε 25,800), 348 mμ (ε 23,200).

Anal. Calcd. for $C_{14}H_{13}N_5O$ (267): C, 62.9; H, 4.9; N, 26.2. Found: C, 62.7; H, 4.7; N, 26.1.

At no time did chromatography indicate the presence of any 8-methyl derivatives.

Methylation of 2-Amino-4-hydroxy-7-phenylpteridine[13] (XIId).—A mixture of 2.4 g. (10 mmoles) of XIId, 125 ml. of dimethylformamide, 12 ml. of acetic acid, and 4.5 ml. of dimethyl sulfate was heated on a steam bath for 5 hr. with 4.5-ml. portions of dimethyl sulfate being added after 2 and 3.5 hr. heating. The dark solution was evaporated to a sirup which was dissolved in 100 ml. of water and heated 10 min. on a steam bath. This was treated with charcoal, filtered, cooled, and adjusted to pH 3 with sodium carbonate. The material (a few mg.) which separated was removed by filtration. The filtrate was adjusted to pH 9 with sodium carbonate and cooled overnight; yield 1.3 g. of dark material. Although paper chromatography indicated the presence of the 1,3-dimethyl derivative XIIIb, this crop was not successfully purified.

The filtrate, upon further cooling, deposited 320 mg. of product. This filtrate was extracted with three 60-ml. portions of chloroform which were dried over magnesium sulfate and evaporated to a sirup. This was slurried in 20 ml. of hot ethanol and cooled; yield of crystalline product, 180 mg.

These last two fractions were combined (500 mg.), suspended in 15 ml. of hot water, and treated with 6 drops of concentrated hydrochloric acid. This was heated to boiling, clarified with charcoal, treated with 1.6 ml. of concentrated hydrochloric acid, and cooled; yield, 380 mg. (12.5%) of the hydrochloride of 2-imino-1,3-dimethyl-7-phenyl-1,2-dihydro-4(3*H*)-pteridinone XIIIb. It was shown to be identical with the product obtained by the methylation of XIIb described previously. This was the only pure product isolated from this reaction and no 8-methyl derivative was detected.

Methylation of 2-Amino-3-methyl-6-phenyl-4(3*H*)-pteridinone[13] (XIIa).—A solution of 3.1 g. (12.2 mmoles) of XIIa, 120 ml. of dimethylformamide, 12 ml. of acetic acid, and 6 ml. of dimethyl sulfate was heated on a steam bath for 1 hr. The solution was evaporated to a sirup which was dissolved in 85 ml. of water and heated 10 min. on a steam bath. This was brought to pH 3 with sodium bicarbonate, cooled, treated with charcoal, and filtered to remove cloudiness. The filtrate was adjusted to pH 10 with sodium carbonate and cooled well. The product was collected and dried; yield 2.8 g. (86%).

A suspension of this material in 65 ml. of absolute ethanol was heated to boiling, then cooled several hours. The crystalline product was collected; yield 430 mg. (13%); m.p. 249–251° (slight residue). Chromatography indicated that this was fairly pure 1,3-dimethyl derivative XIIIa. It was recrystallized from 9 ml. of 2-methoxyethanol; pale yellow platelets; yield, 320 mg. (10%) of 2-imino-1,3-dimethyl-6-phenyl-1,2-dihydro-4(3*H*)-pteridinone (XIIIa); m.p. 251–253°; R_f 0.70 (0.1 *N* HCl) (purple); $\lambda_{max}^{pH\ 7.0}$ 288 mμ (ε 18,700), 370 mμ (ε 8000); $\lambda_{max}^{0.1\ N\ HCl}$ 279 mμ (ε 20,800), 351 mμ (ε 9800).

Anal. Calcd. for $C_{14}H_{13}N_5O$ (267): C, 62.9; H, 4.9; N, 26.2. Found: C, 63.1 H, 5.0; N, 26.4.

The ethanol filtrate from the 430 mg. of XIIIa above was cooled overnight and the resulting hazy solution was filtered. The filtrate was treated with 2.0 ml. of concentrated hydrochloric acid to give, immediately, a yellow crystalline product. The mixture was cooled several hours and the product was collected; yield 2.4 g. (63%). Chromatography showed this to be fairly pure 3,8-dimethyl derivative XIVa.

For analyses a sample (270 mg.) of XIVa was dissolved in 10 ml. of water containing a drop of concentrated hydrochloric acid. The hot solution was treated with charcoal, filtered, and acidified, while hot, with 2 ml. of concentrated hydrochloric acid. The product crystallized in diamond shaped crystals; yield 210 mg.; R_f 0.65 (0.1 *N* HCl) (yellow-green becoming blue when fumed with ammonia), 0.60 (3% NH_4Cl); $\lambda_{max}^{0.1\ N\ NaOH}$ 242 mμ (ε 17,400), 292 mμ (ε 8800), 360 mμ (ε 17,900); $\lambda_{max}^{0.1\ N\ HCl}$ 275 mμ (ε 18,200), 305 mμ (ε 25,600), 425 mμ (ε 12,200).

Anal. Calcd. for $C_{14}H_{13}N_5O\cdot HCl$ (304): C, 55.3; H, 4.6; N, 23.0; Cl, 11.7. Found: C, 55.5; H, 5.1; N, 22.8; Cl, 11.8.

Slow evaporation of the filtrate from the 2.4 g. of XIVa while being dried by suction on the filter, gave 120 mg. of a crystalline product different from XIIIa or XIVa. This appears to be an 8-methyl derivative but its exact structure is unknown.

Methylation of 2-Amino-4-hydroxy-6-phenylpteridine[13] (XIIc).—A mixture of 1.4 g. (5.8 mmoles) of XIIc, 80 ml. of dimethylformamide, 7.0 ml. of acetic acid, and 2.5 ml. of dimethyl sulfate was heated on a steam bath for 4 hr. with 2.5-ml. portions of dimethyl sulfate being added after 1 hr. and 2.5 hr. The solution was evaporated to a sirup and diluted to a volume of 125 ml. with water. This was heated 10 min., treated with charcoal, filtered, and brought to pH 8 with sodium carbonate; yield of solid, 1.2 g. (Extraction of the filtrate with chloroform gave 60 mg. of material which was identical with the 1,3-dimethyl derivative XIIIc.)

This solid (1.2 g.) was extracted twice with 20-ml. portions of warm chloroform and the extracts were discarded. The remaining solid (0.95 g.) was dissolved in 40 ml. of hot 0.1 *N* hydrochloric acid, treated with charcoal, and filtered. The hot filtrate was diluted with 10 ml. of concentrated hydrochloric acid and cooled; yield of crystalline product 0.7 g. (41%); chromatography indicated the presence of some impurities but ultraviolet absorption spectra indicated a purity of 90–95% 2-amino-8-methyl-6-phenyl-4(8*H*)-pteridinone (XIVc) as its hydrochloride. This was crystallized two more times in the manner described before; yield 0.30 g. (19%); R_f 0.55 (0.1 *N* HCl) (yellow-green), 0.35 (3% NH_4Cl) (yellow-green); $\lambda_{max}^{0.1\ N\ NaOH}$ 248 mμ (ε 15,600), 285 mμ (plateau) (ε 5800), 367 mμ (ε 18,300); $\lambda_{max}^{pH\ 7.0-9.2}$ 289 mμ (ε 29,600), 430 mμ (ε 11,000); $\lambda_{max}^{0.1\ N\ HCl}$ 270 mμ (plateau) (ε 12,400), 304 mμ (ε 28,000), 425 mμ (ε 12,000).

Anal. Calcd. for $C_{13}H_{11}N_5O\cdot HCl\cdot {}^1/_2H_2O$ (299): C, 52.2; H, 4.4; N, 23.4; Cl, 11.9. Found: C, 52.3; H, 4.2; N, 23.6; Cl, 12.0.

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The Darzens Condensation. II. Reaction of Chloroacetamides with Aromatic Aldehydes

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N,N-Dialkyl-α-chloroacetamides undergo the Darzens condensation at relatively low temperatures with aromatic aldehydes to give *cis*- and *trans*-epoxyamides in essentially equal amounts. In the presence of potassium *t*-butoxide the sterically favored *trans*-epoxide does not undergo epimerization whereas the *cis* isomer epimerizes at relatively high temperature. The Darzens condensation with amides is viewed as proceeding *via* a slow irreversible aldolization followed by a rapid cyclization step. The configurational assignment of the isomeric epoxy amides is confirmed by n.m.r. spectra and by an unambiguous synthesis of the *trans*-epoxyamides. The reliability of n.m.r. in the quantitative determination of a mixture of *cis*–*trans*-epoxides is demonstrated. Infrared data of the *cis*–*trans*-epoxyamides are also reported.

In continuing our studies on the Darzens condensation,[1] we undertook the investigation of the reaction of N,N-disubstituted α-chloroacetamides with aromatic aldehydes. Although a few reactions with amides were reported previously,[2] their stereochemical products were not isolated or identified. Of particular interest to us were the observations that only *trans*-epoxides were formed from benzaldehyde and ethyl chloroacetate[3] or chloroacetone[4] under normal Darzens conditions. However, Linstead[5] reported the formation of the *cis*-epoxide from benzaldehyde and methyl α-chloroacetate and, recently, Field[6] also reported the probable formation of the *cis*-epoxide from benzaldehyde and ethyl chloroacetate.

Normally the Darzens condensation leads to a mixture of *cis*- and *trans*-epoxy diastereoisomers. However, depending on the reaction conditions either or both isomers can be isolated. The kinetically (or sterically) favored *trans*-epoxide (carbonyl group *trans* to substituent in 3-position) is initially formed but on prolonged contact with the basic media, epimerization[7,8] occurs with the crystallization of the less soluble *cis* isomer.[7,9]

Several investigators have dealt with the stereochemistry of the Darzens condensation. Ballester and Perez-Blanco[10a] have demonstrated that the base-catalyzed condensation of *m*-nitrobenzaldehyde and 2,4,6-trimethoxyphenacyl chloride affords the two isomeric chlorohydrins and each of these under usual Darzens condensation conditions gives the same, and only one, epoxy isomer. This isomer is also the sole product in Darzens condensation from the same reactants. Ballester and Bartlett[10b] indicated that the aldolization step in the Darzens condensation from benzaldehyde and the phenacyl chloride is irreversible. Zimmerman and Ahramjian[11] also have noted that each of the diastereoisomers of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate under Darzens conditions, affords only one epoxide. However, in contrast to Ballester,[10b] they concluded that the Darzens condensation proceeds *via* an initial rapidly reversible aldolization–dealdolization prequilibrium followed by a rate-limiting and stereochemically controlled cyclization. As a consequence of overlap control, that epoxide is formed in which the carbonyl group occupies an unhindered position with respect to the 3-phenyl group in the transition state.

We have reported previously[1] that acetophenone and N,N-diethyl-α-chloroacetamide under Darzens conditions gave both *cis*- and *trans*-epoxides in about equal amounts. However, in contrast to the reaction of ethyl chloroacetate[3] or methyl chloroacetate[5] with benzaldehyde, N,N-diethyl-α-chloroacetamide and N,N-diallyl-α-chloroacetamide with benzaldehyde each gave a mixture of the *cis* and *trans* diastereoisomers in essentially equal amounts. Similar results were also obtained for substituted aromatic aldehydes with N,N-diethyl-α-chloroacetamide (Table I). One would expect as a consequence of overlap control in the transition state[11] that 2,6-dichlorobenzaldehyde would provide a system where the *trans* isomer might predominate. This, however, under Darzens conditions gave a mixture of the *cis*- and *trans*-epoxyamides in equal quantities. The formation of the *cis*-epoxyamide could result from the base-catalyzed epimerization of the *trans*-epoxyamide in the reaction medium. However, this interpretation is rejected in that equal quantities of both isomers were obtained in all cases and the *trans*-epoxyamide is not epimerized even under more drastic conditions (Table V).

Our first attempt in the investigation of the configuration of the isomers obtained in Darzens condensation was the synthesis of *trans*-Ia through the known stereospecific epoxidation of *trans*-IIa with peracid.[12] Unfortunately, *trans*-IIa did not give any epoxidation product with monoperphthalic acid. The *trans* bromo-

(1) A. J. Speziale and H. W. Frazier, *J. Org. Chem.*, **26**, 3176 (1961).

(2) M. S. Newman and B. J. Bagerlein, *Org. Reactions*, **5**, 438 (1949).

(3) (a) H. O. House, J. W. Baker, and D. A. Madden, *J. Am. Chem. Soc.*, **80**, 6386 (1958); (b) H. O. House and J. W. Baker, *ibid.*, **80**, 6389 (1958).

(4) H. Kwart and L. G. Kirk, *J. Org. Chem.*, **32**, 116 (1957).

(5) (a) R. P. Linstead, L. N. Owen, and R. F. Webb, *J. Chem. Soc.*, 1218 (1953). (b) There is some doubt as to the stereochemical homogeneity of the methyl 3-phenylglycidate prepared by these workers. The glycidate distilled over a 10° range and the elemental analysis for carbon was 3% lower than the calcd. value. Our work on the Darzens condensation from benzaldehyde and methyl α-chloroacetate clearly indicate a mixture of *cis*- and *trans*-glycidates.

(6) L. Field and C. G. Carlile, *J. Org. Chem.*, **26**, 3170 (1961).

(7) N. H. Cromwell and R. A. Setterquist, *J. Am. Chem. Soc.*, **76**, 5752 (1954).

(8) H. O. House and R. S. Ro, *ibid.*, **80**, 2428 (1958).

(9) (a) H. Jorlander, *Ber.*, **50**, 1457 (1917); (b) S. Bodforss, *ibid.*, **51**, 192 (1918); (c) J. H. Berson, *J. Am. Chem. Soc.*, **74**, 5175 (1952); *Chem. Ind.* (London), 814 (1957); (d) H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *J. Am. Chem. Soc.*, **75**, 96 (1953); (e) H. H. Wasserman and H. E. Aubrey, *ibid.*, **77**, 590 (1955); (f) H. Dahm and L. Loewe, *Chimia*, **11**, 98 (1951); (g) recently N. H. Cromwell, F. H. Schumacher, and J. L. Adelfang [*J. Am. Chem. Soc.*, **83**, 974 (1961)] have shown that when sufficient solvent is used *cis*-2-nitro chalcone oxide undergoes base-catalyzed epimerization to form the thermodynamically stable *trans* isomer.

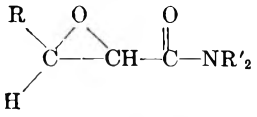
(10) (a) M. Ballester and D. Perez-Blanco, *J. Org. Chem.*, **23**, 652 (1958); (b) M. Ballester and P. D. Bartlett, *J. Am. Chem. Soc.*, **75**, 2042 (1953).

(11) H. E. Zimmerman and L. E. Ahramjian, *ibid.*, **82**, 5459 (1960), also references to other work.

(12) (a) S. Winstein and R. B. Henderson in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 1; (b) D. Swern, *Chem. Rev.*, **45**, 30 (1949); (c) D. Swern, *Org. Reactions*, **7**, 378 (1953).

TABLE I

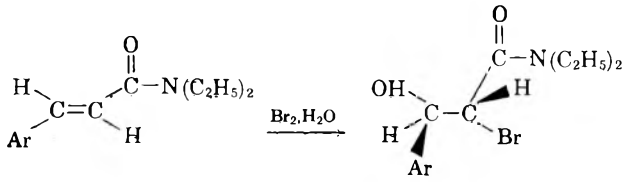
cis- AND *trans*-N,N-DIALKYLGLYCIDAMIDES



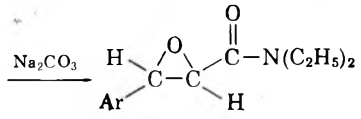
I

			cis			*trans*		
I	R	R′	Yield, %	M.p. or b.p., °C.	$n^{25}D$	Yield, %	M.p. or b.p., °C.	$n^{25}D$
a	Phenyl	C_2H_5	35.4	52.4–53.0		31.8	88.0–88.4	
b	2,6-Dichlorophenyl	C_2H_5	26.0	112–113		35.5		1.5505
c	2,4-Dichlorophenyl	C_2H_5	21.4	98–100		24	142–147 (0.14 mm.)	1.5523
d	*m*-Nitrophenyl	C_2H_5	36.7		1.5452	34.5	122.4–123.0	
e	Phenyl	$CH_2CH{=}CH_2$	43.0	88.6–90		43.0	147–150 (0.2 mm.)	1.5448

acetoxylation[13] of a *trans* olefin with N-bromosuccinimide–acetic acid followed by ring closure to give a *trans*-epoxide with base was also unsuccessful for *trans*-IIa. Only tarry material was obtained. However, conclusive evidence for the configurational assignment of the isomeric epoxyamides was obtained from an unambiguous synthesis of *trans*-Ia,b from *trans*-IIa,b, on the basis of the known *trans* addition of hypohalous acid to α,β-unsaturated carbonyl compounds followed by intramolecular S_N2 displacement at the halogen-bearing carbon atom.[14]



trans-IIa,b *erythro*-IIIa,b



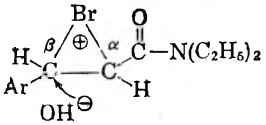
trans-Ia,b

a. Ar = phenyl
b. Ar = 2,6-dichlorophenyl

Thus, *trans*-IIa,b gave *erythro*-bromohydrin IIIa,b which, followed by treatment with base, gave *trans*-epoxyamides Ia,b. The identity of this *trans*-Ia to the high melting solid (m.p. 88.0–88.4°) and *trans*-Ib to the oil ($n^{25}D$: 1.5505) from the Darzens condensation was demonstrated by mixture melting point determination (for Ia), n.m.r. spectrum[15] (Tables II–IV), and transparency in their infrared spectrum. The assignment of configuration for Ia and Ib was further investigated by an alternate synthesis.

(13) A. Jovtscheff, *Ber.*, **93**, 2048 (1960).

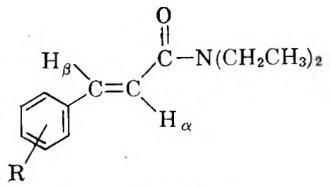
(14) The bromohydrins IIIa,b are assigned the α-bromo-β-hydroxy structures since attack of hydroxide ion on the bromonium ion intermediate would be expected to occur on the β-carbon atom because a lower electron density would be expected on that carbon atom than on the α-carbon atom and the positive character at reaction site would be more stabilized by the phenyl group (β-carbon) than by the carbonyl group (α-carbon). See (a) A. Feldstein and C. A. Vander Werf, *J. Am. Chem. Soc.*, **76**, 1626 (1954); (b) H. O. House and R. L. Wasson, *ibid.*, **78**, 4394 (1956); (c) N. H. Cromwell and R. E. Bambury, *J. Org. Chem.*, **26**, 997 (1961).



(15) C. A. Relly and J. D. Swalen, *J. Chem. Phys.*, **32**, 1378 (1960).

TABLE II

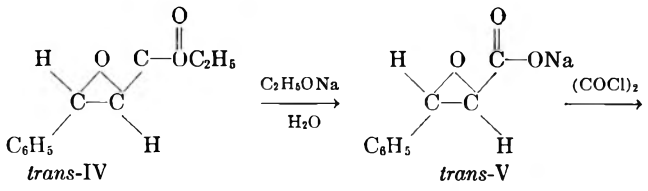
CHEMICAL SHIFTS[a] AND SPIN–SPIN COUPLING CONSTANTS OF CINNAMAMIDES



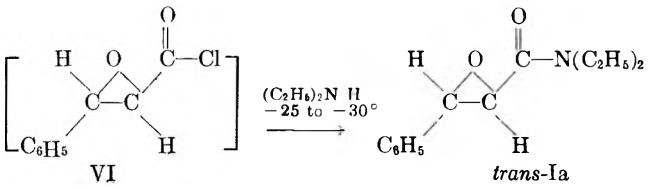
trans-II

	Chemical shifts, τ						
Compound R	CH_3 triplet	CH_2 quartet	H_α doublet	H_β doublet	Coupling constants, c.p.s. J_{CH_3}	J_{CH_2}	$J_{H_\alpha H_\beta}$[b]
H	8.78	6.50	3.18	2.25	7.5	7.5	16.0
2,6-Dichloro	8.85	6.66	3.31	2.60	7.5	7.5	15.5

[a] N.m.r. spectra were measured at 60 Mc./sec. on a modified Varian Model A-60 spectrometer. The samples contained tetramethylsilane (TMS) as internal reference. [b] 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. 238.



trans-IV *trans*-V



VI *trans*-Ia

Ethyl 3-phenylglycidate (IV) which has been assigned the *trans* configuration[16] was converted by the sequence (IV→Ia) to *trans*-N,N-diethyl-3-phenylglycidamide (m.p. 88.0–88.4°) in 62% yield. Although the epimerization of epoxides by base is well known,[7,8] IV did not epimerize upon treatment with sodium ethoxide. This is supported by n.m.r. data of V whose coupling constant for α,β-hydrogens (2.0 c.p.s.) is the same as that observed for IV.[16]

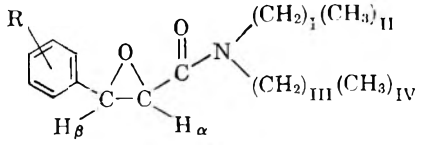
Cis-hydroxylation[17] of *trans*-IIa,b with neutral permanganate gave *threo*-VIIa (m.p. 72°) and *threo*-VIIb (m.p. 113–114°), respectively. Treatment of the high

(16) The configuration of (IV) was assigned by House, *et al.*, as *trans* (see ref. 3). This was further confirmed by n.m.r. spectrum in our laboratory. The coupling constant for α,β hydrogens is found to be 2.0 c.p.s. and is in full agreement with known data (see ref. 15).

(17) J. Boeseken, *Rec. trav. chim.*, **47**, 683 (1928).

TABLE III

CHEMICAL SHIFTS[a] AND SPIN–SPIN COUPLING CONSTANTS OF *cis*-N,N-DIETHYLGLYCIDAMIDES FROM DARZENS CONDENSATION

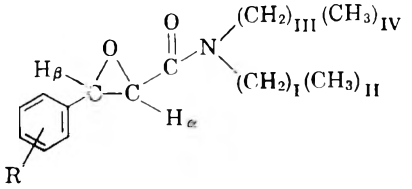


Compound R	Chemical shifts, τ: $(CH_3)_{II}$ triplet	$(CH_3)_{IV}$ triplet	Δδ, c.p.s.	$(CH_2)_I$ quartet	$(CH_2)_{III}$ quartet	Δδ c.p.s.	Hα doublet	Hβ doublet	Coupling constants, c.p.s.: J_{CH_3}	J_{CH_2}	$J_{H_\alpha H_\beta}$[15]
H	9.24	8.97	16.2	6.88	6.72	9.6	6.13	5.75	7.2	7.2	5.0
2,6-Dichloro-	9.03	8.70	19.8	6.80	6.34	12.0	5.97	5.76	7.2	7.2	5.0
2,4-Dichloro	9.22	8.86	21.6	7.00	6.68	19.2	6.13	5.64	7.2	7.2	5.0
m-Nitro	9.20	8.84	21.6	6.80	6.60	12.0	5.95	5.55	7.2	7.2	5.0
N,N-Diallyl 3-phenylglycidamide							6.10	5.72			5.0

[a] N.m.r. spectra were measured at 60 Mc./sec. on a modified Varian Model A-60 spectrometer. The samples contained tetramethylsilane as internal reference.

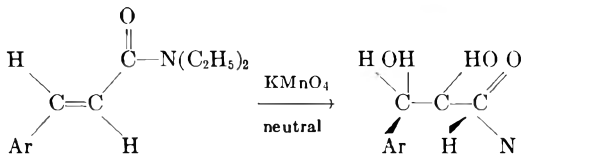
TABLE IV

CHEMICAL SHIFTS[a] AND SPIN–SPIN COUPLING CONSTANTS OF *trans*-N,N-DIETHYLGLYCIDAMIDES FROM DARZENS CONDENSATION



Compound R	Chemical shifts, τ: $(CH_3)_{II}$ triplet	$(CH_3)_{IV}$ triplet	Δδ, c.p.s.	$(CH_2)_I$ quartet	$(CH_2)_{III}$ quartet	Δδ, c.p.s.	Hα doublet	Hβ doublet	Coupling constants, c.p.s.: J_{CH_3}	J_{CH_2}	$J_{H_\alpha H_\beta}$[15]
H	8.84	8.80	2.4	6.55		0	6.43	5.94	7.2	7.2	2.0
H[b]	8.85	8.80	3.0	6.56		0	6.43	5.94	7.2	7.2	2.0
2,6-Dichloro	8.88	8.76	7.2	6.66		0	6.34	5.92	7.2	7.2	2.0
2,6-Dichloro[b]	8.80	8.68	7.2	6.50		0	6.15	5.65	7.2	7.2	2.0
2,4-Dichloro	8.93	8.82	6.6	6.71		0	6.60	5.93	7.2	7.2	2.0
m-Nitro	8.80	8.73	4.2	6.58	6.50	4.8	6.35	5.76	7.2	7.2	2.0
N,N-Diallyl 3-phenylglycidate							6.40	6.03			2.0

[a] N.m.r. spectra were measured at 60 Mc./sec. on a modified Varian model A-60 spectrometer. The samples contained tetramethylsilane as internal reference. [b] From bromohydrin method.



IIa,b

VIIa, m.p. 72°
VIIb, m.p. 113–114°

Higher melting isomeric epoxy amide of Ia (m.p. 88.0–88.4) $\xrightarrow[\text{dioxane}]{H_2SO_4}$ VIII *erythro*-diol, m.p. 58–59°

cis-trans-Ib $\xrightarrow[\text{dioxane}]{H_2SO_4}$ IX *erythro*-diol, m.p. 148–149° + *cis*-Ib, m.p. 112–113°

melting isomeric epoxy amide of Ia with sulfuric acid in aqueous dioxane afforded a diol VIII (m.p. 58–59°). Since VIII is different from *threo*-VIIa, the configuration for VIII can be assigned as *erythro* which would be derived from the ring opening of *trans*-Ia, (m.p. 88.0–88.4°) with inversion of configuration.[18] Consequently the low melting solid (m.p. 52.4–53.0°) from the Darzens condensation of benzaldehyde and N,N-diethyl-α-chloroacetamide is *cis*-Ia. Similarly when *cis–trans* mixture of Ib was treated with sulfuric acid in aqueous dioxane at 45–50°, there was isolated a diol IX (m.p. 148–149°) and a solid (m.p. 112–113°) which was identical in its infrared spectrum with that isolated from *cis-trans*-Ib from Darzens condensation. The mixed melting point showed no depression. By following the same reasoning for the assignment of *trans*-Ia from VIII, the diol IX is assigned as *erythro* which would be derived from the ring opening of *trans*-Ib (oil, $n^{25}D$: 1.5505). Consequently the solid Ib (m.p. 112–113°) is the *cis* isomer. The resistance to ring opening of the *cis*-epoxyamide Ib in acid media was also observed for other *cis*-epoxyamides and this interesting finding is under further investigation.

Since *trans*-IV did not undergo epimerization upon treatment with base, alkaline epimerization of the *cis*-epoxide was undertaken. Each of the isomeric N,N-diallyl 3-phenylglycidamides was dissolved in *t*-butyl alcohol in the presence of catalytic amount of potassium *t*-butoxide. The results of these experiments, as shown in Table V, indicated that the sterically favored *trans*-epoxide does not undergo epimerization whereas the *cis*-epoxide epimerizes to the *trans* isomer to the extent of 31.8% (calculated from n.m.r. spectrum). Furthermore the extent of epimerization does not change upon further heating. To indicate that epimerization

(18) The ring opening of epoxides in acid media is expected to proceed by an Sn2 mechanism with the inversion of configuration [R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959)], although ring openings with retention of configuration are also reported. [See (a) R. Kuhn and F. Ebel, *Ber.*, **58**, 919 (1925); (b) J. Boeseken, *Rec. trav. chim.*, **41**, 199 (1922); (c) H. H. Wasserman and N. E. Aubrey, *J. Am. Chem. Soc.*, **78**, 1726 (1956).]

TABLE V

EPIMERIZATION OF *cis*- AND *trans*-N,N-DIALLYL-3-PHENYLGLYCIDAMIDE IN PRESENCE OF POTASSIUM *t*-BUTOXIDE[a]

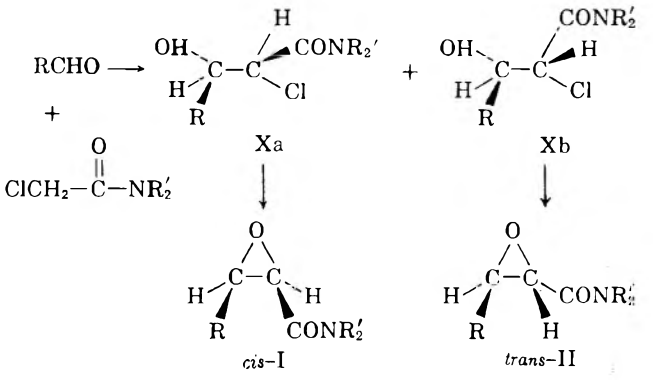
	After standing at room temperature for 6 days		After 2 hr. at 60°		After 25 hr. at 60°	
	trans	*cis*	*trans*	*cis*	*trans*	*cis*
trans	100	0	100	0	100	0
cis	0	100	32	68	32	68
cis[b]	...	...	...	..	...	100

[a] Yields were calculated from n.m.r. spectrum. [b] Without potassium *t*-butoxide.

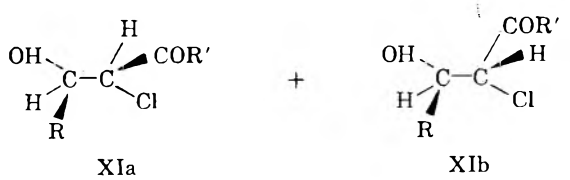
did not result from heat alone, the *cis* isomer was recovered unchanged after fifteen hours at 60°.

In general the Darzens condensation should give diastereoisomeric halohydrin intermediates in essentially equal quantities. The ratios and stereochemistry of the epoxides derived from these halohydrins are determined by epimerization of the chlorohydrin anions and/or epoxides, or, as reported in one instance, the reversibility of the aldolization step.[11]

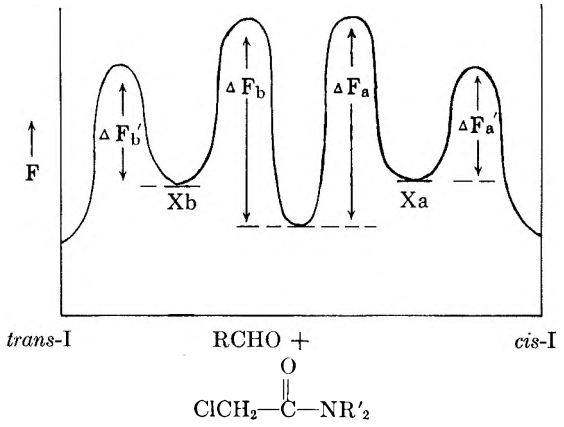
Since our epimerization conditions were more drastic than those in the Darzens condensation and the *trans*-epoxides did not isomerize to the *cis*, the formation of *cis*- and *trans*-epoxyamides in the Darzens condensation undoubtedly arise from ring closure of the diastereoisomeric chlorohydrins Xa and Xb.



The epimerization of the chlorohydrins (leading to only one epoxide) would be controlled by the acidity of the α-hydrogen atom. Since the α-hydrogen of an amide is less acidic than the α-hydrogen of an ester[19] and probably also of a ketone, epimerization of the chlorohydrin Xa to the less sterically hindered Xb *via* base-catalyzed enolization did not occur. Consequently both *cis*- and *trans*-epoxyamides were produced from the cyclization of Xa and Xb despite the fact that the formation of the *cis* isomer was derived from the unfavored conformer Xa. In the condensation of aromatic aldehydes with ethyl chloroacetate,[3] phenacyl chloride,[9e] chloroacetone,[4] and 2,4,6-trimethoxyphenacyl chloride,[10a] the diastereoisomeric chlorohydrins XIa and XIb were presumably formed. However, due to the greater acidity of their α-hydrogens as compared to Xa and Xb, epimerization of the chlorohydrin to the less sterically hindered conformer XIb took place and hence the *trans* isomer was the sole or major product.



In contrast to the reversible aldolization–dealdolization prequilibrium reported by Zimmerman and Ahramjiam,[11] the formation of the aldolization products Xa and Xb (from α-chloroacetamides and aromatic aldehydes) must be the rate controlling step followed by a rapid cyclization to the isomeric epoxides. The free energy of aldolization ΔF_a and ΔF_b (to form Xa and Xb) must be greater than their respective free energies of cyclization $\Delta F_a'$ and $\Delta F_b'$.



The n.m.r. spectra for *cis*- and *trans*-epoxyamides were analyzed in detail (Tables III and IV). The coupling constant for α-β hydrogen ($JH_\alpha H_\beta$) in the *cis*-epoxyamides is 5.0 c.p.s. and for the *trans* isomer ($J_{H_\alpha H_\beta}$) 2.0 c.p.s. These are in agreement with published data[15] for simple epoxides. The n.m.r. spectra for the *cis* isomers showed two nonequivalent methyl and methylene groups with a difference of chemical shift ranging from 16.2–21.6 c.p.s. for methyl and 9.6–19.2 c.p.s. for the methylene group. The nonequivalency of the ethyl groups is clearly due to the restricted rotation about the CN bond at room temperature.[20] Consequently their environments, particularly with regard to the 3-aryl group, are different. Although rotation about CN bond is still restricted in the corresponding *trans* isomer, the nonequivalency of these groups with respect to the 3-aryl group is reduced due to the greater distance. The difference in chemical shift is, therefore, diminished. Thus, for the olefinic compounds (Table II) the distances between the alkyl amido groups and 3-aryl group are sufficiently far apart that no difference in chemical shift is observed. The assignment of $(CH_2)_I$ and $(CH_2)_{II}$ at higher field than $(CH_2)_{III}$ and $(CH_2)_{IV}$ (for *cis*- and *trans*-epoxyamides) is based on the assumption that the average environment of the former is nearer the 3-aryl group. Hence the shielding effect of the phenyl ring should be greater. The assignment of the α-hydrogen at a higher field than that of the β is based on previous n.m.r. spectra of ethyl α-bromocinnamate and ethyl cinnamate.[19] In these two compounds the α-hydrogen is at higher field than the β.

The reliability of n.m.r. spectra in quantitative determination of *cis*-*trans*-epoxyamides is demonstrated as follows. An authentic mixture of 49.1% of *cis*-Ia

(19) A. J. Speziale and C. C. Tung, *J. Org. Chem.*, **28**, 1353 (1963).

(20) The n.m.r. spectra of *cis*-Ia at 85° exhibited only one triplet for two methyl groups and one quartet for two methylene groups.

and 50.9% of *trans*-Ia showed 51% of *cis*-Ia and 49% of *trans*-Ia, respectively, by measuring the area of one doublet, $J_{H_\alpha H_\beta}$ = 5.0 c.p.s. (H_β) for *cis*-Ia and another doublet, $J_{H_\alpha H_\beta}$ = 2.0 c.p.s. (H_β) for *trans*-Ia. Also, the *cis–trans* mixture of Ia before chromatographic separation from Darzens condensation (m.p. 43–47°) was found to consist of 50% *cis* and 50% *trans* by the same method of n.m.r. analysis. The isolated yields were 52.7% *cis* and 47.3% *trans* (actual yield is 35.4% *cis* and 31.8% *trans*). Thus, n.m.r. spectra serve as a very convenient means to determine the per cent of *cis*- and *trans*-epoxyamides from Darzens condensation without involving the tedious process of separation. For example, reaction of 0.20 mole each of *o*-methylbenzaldehyde, N,N-diethyl-α-chloroacetamide under Darzens conditions gave 31.6 g. of distilled liquid, b.p. 140–145°, (0.72 mm.), and 6.5 g. of liquid boiling at 145–149° (0.72 mm). Both products gave correct elemental analysis for the desired epoxyamide. However, n.m.r. spectrum of the oil, b.p. 145–149° (0.72 mm.), indicated only one pair of doublets with a coupling constant of 2.0 c.p.s. for the *trans*-epoxyamide whereas the spectrum of the oil, b.p. 140–145° (0.72 mm.), revealed two pairs of doublets with coupling constants of 5.0 c.p.s. (*cis*) for one pair and 2.0 c.p.s. (*trans*) for the other. The area of the doublet with a coupling constant 5.0 c.p.s. (*cis*) and that of the other doublet with a coupling constant 2.0 c.p.s. (*trans*) was found to be 53.7% and 46.3%, respectively. Thus, we concluded that the products from Darzens condensation contain 55.5% of *trans*- and 44.5% of *cis*-epoxyamide in a total yield of 82.0%. Similarly, the 3,4-dichlorobenzaldehyde and N,N-diethyl-α-chloroacetamide gave a product which distilled at 170–180° (0.2 mm.) in 69.2% yield. It gave correct elemental analysis for the desired epoxy amide and from its n.m.r. spectrum, the product consisted of 50–50 *cis*- and *trans*-epoxyamide, respectively.

The infrared data for *cis*- and *trans*-epoxyamides are shown in Table V. These have characteristic bands attributable to the epoxy group in the 8-, 11-, and 12-μ region.[1] In general, the *cis* isomers showed absorption at 12-μ region whereas this band was absent in the corresponding *trans* isomer. The n.m.r. data, therefore, serves to corroborate the diagnostic importance of the 12-μ band for the *cis* isomer and its absence for the *trans* isomer.

Experimental

***cis–trans*-N,N-Diethyl 3-phenylglycidamide (Ia).**—A solution of potassium *t*-butoxide (16 g., 0.41 g.-atom of potassium and 400 ml. of *t*-butyl alcohol, dried by distilling from sodium) was added to a mixture of 42.4 g. (0.40 mole) of benzaldehyde and 59.8 g. (0.40 mole) of N,N-diethyl-α-chloroacetamide under an atmosphere of nitrogen at 5–10° during 1.5 hr. The mixture was stirred at 10° for 1 hr. and the alcohol was removed at 50° (40 mm.). The residue was treated with 300 ml. of ether and sufficient water to dissolve the potassium chloride. (Potentiometric titration: 0.40 mole Cl^-.) The ether layer was removed, washed with saturated sodium chloride solution, dried with magnesium sulfate, and evaporated to dryness. The crude viscous oil (87.1 g., 99.5% yield) was treated with 150 ml. of ether and 300 ml. of hexane and cooled to 0–5°. The white crystals were filtered, wt. 77 g.; 88.4% yield, m.p. 43–47°. Ten grams of this material was fractionally crystallized from hexane. The less soluble fractions (3.6 g., 31.8% yield) melted at 88.8–90°, was identified as the *trans* isomer and the more soluble fractions (4.0 g., 35.4 yield) melted at 52.4–53°, was identified as *cis* isomer.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found (*trans*): C, 71.27; H, 7.77; N, 6.52. Found (*cis*): C, 71.27; H, 7.92; N, 6.32.

***cis–trans*-N,N-Diethyl-3-(2,6-dichlorophenyl)glycidamide (Ib).**—This glycidamide was prepared from a solution of 35.0 g. (0.20 mole) of 2,6-dichlorobenzaldehyde (Chemical Procurement Laboratories, Inc., College Point, N. Y.), 29.9 g. (0.20 mole) of the chloroacetamide in 100 ml. of ether and 0.20 mole of potassium *t*-butoxide in 250 ml. of *t*-butyl alcohol as described before. The crude epoxyamide, 57.8 g. (theory, $n^{25}D$ 1.5505) was distilled at 165–175° (0.15 mm.); 36.5 g. (63.4% yield, $n^{25}D$ 1.5536).

Anal. Calcd. for $C_{13}H_{15}Cl_2NO_2$: N, 4.86; Cl, 24.60. Found: N, 4.89; Cl, 25.08.

Seven and two-tenths grams of this distilled epoxyamide was chromatographed on alumina. The first six fractions on elution with benzene–hexane mixture afforded 4.0 g. (35.5% yield) of an oil (*trans*) $n^{25}D$ 1.5505. Further elution with benzene afforded 3.0 g. (26.0% yield) of solid (*cis*) m.p. 112–113° after recrystallization from hexane.

Anal. Calcd. for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.25; N, 4.86; Cl, 24.61. Found (*cis* solid): C, 53.72; H, 5.28; N, 4.96; Cl, 24.82. Found (*trans* oil): C, 54.16; H, 5.51; N, 5.03; Cl, 24.57.

***cis–trans*-N,N-Diethyl-3-(2,4-dichlorophenyl)glycidamide (Ic).**—The glycidamide was prepared from a solution of 35.0 g. (0.20 mole) of 2,4-dichlorobenzaldehyde, 29.9 g. (0.20 mole) of the chloroacetamide in 100 ml. of ether and 0.20 mole of potassium *t*-butoxide in 250 ml. of *t*-butyl alcohol as described in the previous experiment. The crude epoxyamide was obtained in 99.4% yield. Upon recrystallization from hexane it gave a colorless solid (*cis*), m.p. 98–100°, wt. 12.3 g. (21.4% yield). The solvent was removed under vacuum and the residue was distilled to obtain the *trans* isomer, b.p. 142–147° (0.12 mm.), 13.8 g. (23.9% yield).

Anal. Calcd. for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.25; N, 4.86; Cl, 24.61. Found (*cis*): C, 53.94; H, 5.24; N, 4.80; Cl, 24.50. Found (*trans*): C, 54.55; H, 5.05; N, 5.14; Cl, 24.63.

***cis–trans*-N,N-Diethyl-3-(*m*-nitrophenyl)glycidamide (Id).**—From 22.5 g. (0.15 mole) of *m*-nitrobenzaldehyde, 22.5 g. (0.15 mole) of chloroacetamide in 200 ml. of ether, and 0.15 mole of potassium *t*-butoxide in 150 ml. of *t*-butyl alcohol, there was obtained 27.9 g. of crude glycidamide. Recrystallization from methanol gave 7.9 g. of colorless solid, m.p. 122.4–123°. On further evaporation of the mother liquor, an additional 5.8 g. of same material was obtained. Total weight of solid was 13.7 g. (*trans*), 34.5% yield. The filtrate was evaporated to dryness and chromatographed and eluted with 20–80% chloroform–ether solvent, 14.6 g. of an oil (*cis*), 36.7% yield, $n^{25}D$ 1.5452, was obtained.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.10; H, 6.05; N, 10.58. Found (*cis*): C, 59.05; H, 6.22; N, 10.89. Found (*trans*): C, 58.88; H, 6.04; N, 10.24.

***cist–trans*-N,N-Diallyl-3-phenylglycidamide (Ie).**—The Darzens condensation was carried out as described for the diethyl analog (Ia). The crude epoxy amide was recrystallized from ether–hexane mixture. There was obtained 31.6 g. (43.0% yield) of solid, *cis*, m.p. 86–87° and 41.2 g. (56.4%) of oil, *trans*, $n^{25}D$ 1.5376–1.5428, from concentration of the mother liquors. The solid, recrystallized from ethyl acetate–hexane, melted at 88.6–90°. The oil was distilled, b.p. 147–150° (0.2 mm.), $n^{25}D$ 1.5448; 31.2 g., (43% yield).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.05; N, 5.79 Found (*trans*, oil): C, 74.66; H, 7.55; N, 6.20. Found (*cis*, solid): C, 74.51; H, 7.33; N, 5.97.

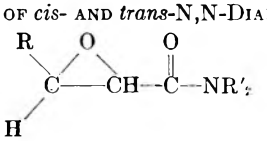
***cis–trans*-N,N-Diethyl-3-*o*-tolyl-glycidamide.**—The Darzens condensation from 0.20 mole of *o*-methylbenzaldehyde and N,N-diethyl-α-chloroacetamide as described for Ia gave 46.1 g. (98.7% yield) of crude product. Distillation gave the following two fractions; b.p. 140–145° (0.72 mm.), wt. 31.6 g. (contains 53.7% *cis* and 46.3% *trans* from n.m.r. spectrum), b.p. 145–149° (0.72 mm.), wt. 6.5 g. (pure *trans* from n.m.r. spectrum). Total yield was 82.0% with 44.5% *cis* and 55.5% *trans* isomer.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.20; H, 8.21; N, 6.00. Found (*trans*): C, 71.95; H, 8.09; N, 6.24. Found (*cis trans*): C, 71.98; H, 8.26; N, 6.09.

***cis–trans*-N,N-Diethyl-3(3,4-dichlorophenyl)glycidamide.**—Treatment of 0.20 mole of 2,4-dichlorobenzaldehyde with N,N-diethyl-α-chloroacetamide under Darzens conditions afforded

TABLE VI

INFRARED SPECTRA[a] OF *cis*- AND *trans*-N,N-DIALKYLGLYCIDAMIDES



			Absorption wave length (μ)				
				Epoxide			
R	R′	Isomer	C=O	8.0-μ region	11.0-μ region	12.0-μ region	Other region
C_6H_5	CH_2CH_3	*cis*	6.00 (s)	7.92 (s); 8.19 (m)	10.94 (s); 11.10 (m)	12.03 (m)	6.75 (s); 6.83 (s); 8.72 (m); 9.09 (m); 9.71 (w); 10.50 (w); 10.71 (w)
C_6H_5	CH_2CH_3	*trans*	6.00 (s)	7.93 (s); 8.20 (m)	10.95 (w); 11.13 (m)		6.73 (s); 6.82 (s); 8.75 (s); 9.11 (m); 9.75 (w); 10.50 (w); 11.65 (w)
2,6-$Cl_2C_6H_3$	CH_2CH_3	*cis*	6.02 (s)	7.95 (m)	10.85 (m); 11.10 (w); 11.20 (w)	11.90 (m)	3.37 (m); 6.40 (m); 6.82 (m); 6.97 (s); 7.25 (m); 7.67 (w); 8.75 (m); 9.17 (m); 10.50 (w)
2,6-$Cl_2C_6H_3$	CH_2CH_3	*trans*	6.06 (s)	7.95 (m)	11.00 (m); 11.55 (w)		3.40 (m); 6.40 (m); 6.98 (s); 8.75 (m); 9.15 (m); 10.55 (w)
2,4-$Cl_2C_6H_3$	CH_2CH_3	*cis*	6.05 (s)	7.92	10.86 (m); 11.00 (m)	11.89 (s); 12.20 (m)	3.36 (s); 6.76 (s); 6.83 (s); 10.50 (m) 11.54 (m)
2,4-$Cl_2C_6H_3$	CH_2CH_3	*trans*	6.05 (s)	7.90 (m)	11.00 (m); 11.40 (m)		3.32 (m); 6.81 (s); 7.20 (m); 8.70 (m); 9.05 (m); 10.50 (w)
m-$NO_2C_6H_4$	CH_2CH_3	*cis*	6.10 (s)	7.90 (m); 8.21 (m)	10.99 (m); 11.40 (m)	12.00 (m); 12.30 (m)	3.35 (m); 6.60 (s); 7.40 (s); 8.71 (m); 9.10 (m); 9.25 (m); 10.45 (m); 13.20 (s); 13.50 (s)
m-$NO_2C_6H_4$	CH_2CH_3	*trans*	6.12 (s)	7.90 (m); 8.25 (m)	10.99 (w); 11.35 (m); 11.75 (m)		3.40 (s); 6.60 (s); 7.40 (s); 8.70 (m); 9.10 (m); 9.25 (m); 10.45 (m); 12.75 (m); 13.65 (m)
C_6H_5	$CH_2CH{=}CH_2$	*cis*	5.96 (s)	7.80 (m); 8.18 (s)	10.80 (s); 10.91 (m)		3.25 (w); 3.35 (w); 3.43 (w); 6.95 (s); 7.04 (s); 8.38 (m); 9.01 (w); 10.07 (s)
C_6H_5	$CH_2CH{=}CH_2$	*trans*	6.00 (s)	7.80 (m); 8.15 (s)	10.80 (s)	11.96 (w); 12.28 (w)	3.25 (w); 3.35 (w); 3.43 (w); 7.08 (s); 8.87 (m); 10.07 (m)
o-$CH_3C_6H_4$	CH_2CH_3	*trans*	6.05 (s)	7.93 (s)	11.11 (m)		3.36 (s); 6.73 (s); 6.82 (s)

[a] All spectra in 3% chloroform.

39.7 g. (69.2% yield), $n^{25}D$ 1.5538, of *cis*–*trans*-epoxyamide, b.p. 170–180° (0.2 mm.). Attempts at purification by crystallization from solvents were unsuccessful. Its composition, by n.m.r. was shown to be a mixture of equal amounts of *cis* and *trans* isomers.

Anal. Calcd. for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.24; N, 4.86; Cl, 24.60. Found: C, 54.18; H, 5.52; N, 4.84; Cl, 24.60.

trans-**N,N-Diethyl-3-phenylglycidamide (Ia) (Authentic).** (a) **From *erythro*-N,N-Diethyl-α-bromo-β-phenyl-β-hydroxypropioamide (IIIa).**—To a stirred solution containing 32.0 g. (0.20 mole) of bromine in 250 ml. of 9% sulfuric acid at 0° was added dropwise a solution of 33.0 g. (0.20 mole) of silver nitrate in 80 ml. of water until the solution was just decolorized. To the above stirred solution at 0°, 20.3 g. (0.10 mole) of *trans*-N,N-diethylcinnamide (IIa)[19] in 500 ml. of dioxane was added dropwise over a period of 1.5 hr. The reaction mixture was allowed to warm to room temperature and heated at 50° for 10 min. The reaction mixture was filtered to remove silver bromide (40.8 g., theory) and the filtrate was poured into 2 l. of water. The product was extracted with ether, washed with cold water and dried over anhydrous magnesium sulfate. The solvent was evaporated to dryness to give 30.1 g. (50.0% yield) of oil which solidified on cooling. An analytical sample crystallized from hexane–benzene and recrystallized from cyclohexane gave colorless solid (IIIa), m.p. 137.2–138°.

Anal. Calcd. for $C_{13}H_{18}BrNO_2$: C, 52.10; H, 6.04; Br, 26.65; N, 4.67. Found: C, 52.18; H, 6.12; Br, 27.00; N, 4.69.

A mixture of 3.47 g. (0.0115 mole) of IIIa and 9.10 g. (0.0865 mole) of sodium carbonate in 80 ml. of water was heated to reflux for 1 hr. After cooling the reaction mixture to room temperature, the oily product was extracted with two 100-ml. portions of ether, washed with water and dried over anhydrous magnesium sulfate. The ether was removed *in vacuo*, there was obtained 2.33 g. (92.5% yield) of colorless oil, which solidified on standing. This solid has identical n.m.r. (Table IV) and infrared spectrum (Table VI) with the high melting solid Ia obtained from Darzens condensation. Mixture melting point showed no depression.

(b) **From Ethyl *trans*-3-Phenylglycidate (IV).**—To a solution of sodium ethoxide in ethanol at 0–5° (3.1 g., 0.1355 g.-atom of sodium and 70 ml. of absolute ethanol), there was added 25.6 g. (0.1355 mole) of ethyl *trans*-3-phenylglycidate (IV)[21] in 0.5 hr. The clear yellow solution was treated dropwise at 0–5° with 2.17 g. (0.1355 mole) of water. The sodium salt precipitated immediately. The mixture was filtered after stirring 0.5 hr. and then dried at 100° to obtain 20.8 g., (83% yield) of sodium *trans*-3-phenylglycidate[3a] (V). A small amount was recrystallized from ethanol and the samples did not differ in their infrared spectra: 6.15 μ (carbonyl) and 8.00, 11.24, 12.17 μ (epoxide).

A suspension of 20.8 g. (0.112 mole) of sodium *trans*-3-phenylglycidate (V) in 100 ml. of dry benzene and 5 drops of pyridine was cooled to 0–5° and treated with 18.9 g. (0.15 mole) of oxalyl chloride in 50 ml. of benzene during the course of 1 hr. The mixture was stirred for 0.5 hr. at 0–5° and the benzene removed *in vacuo* below 15°. A fresh 100 ml. of dry benzene was added and then distilled *in vacuo* below 15°. The crude epoxy acid chloride was dissolved in ether, cooled to −25 to −30°, and treated with 16.4 g. (0.224 mole) of diethylamine in 50 ml. of ether during 0.75 hr. The mixture was stirred for 1 hr. at −20°, allowed to warm to −10°, and treated with 20 ml. of water. The ether layer was removed immediately and, while drying with magnesium sulfate, the solvent was removed *in vacuo* below 0°. Fresh ether was added and again removed *in vacuo* to dryness at 0°. The crude epoxyamide was recrystallized from hexane; wt. 13.6 g., m.p. 84–87°. A mixture melting point with the *trans*-epoxyamide (m.p. 88.0–88.4°) isolated from the Darzens condensation was not depressed and the two spectra were superimposable.

Hexane other liquor was concentrated to dryness *in vacuo*. The oil (6.2 g.) was chromatographed on alumina. There was isolated 1.6 g. of the *trans*-epoxyamide (total yield: 15.2 g., 62%), several other fractions which showed OH and COOH absorption in the infrared and 1.9 g. of oil (last fraction) which showed weak OH band and may have contained a small amount of the *cis*-epoxyamide by infrared analysis.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: (84–87°) C, 70.91; H, 8.11; N, 6.43.

***trans*-N,N-Diethyl-3-(2,6-dichlorophenyl)glycidamide (Ib) (Authentic).** (a) **From *erythro*-N,N-Diethyl-α-bromo-β-(2,6-dichlorophenyl)-β-hydroxypropioamide (IIIb).**—The procedure for the preparation of IIIa afforded a crude product in 90.8% yield which was recrystallized from hexane–benzene to give 12.0 g. (65.3% yield) of colorless solid, m.p. 156–157°.

Anal. Calcd. for $C_{13}H_{16}Br\,Cl_2NO_2$: C, 42.30; H, 4.37; Br, 21.69; Cl, 19.20; N, 3.79. Found: C, 42.50; H, 4.32; Br, 21.17; Cl, 18.97; N, 3.77.

The same procedure for the treatment of IIIa with base was employed. From 3.0 g. (0.00814 mole) of IIIb and 6.4 g. (0.061 mole) of sodium carbonate in 70 ml. of water, there was obtained 2.22 g. (94.8% yield), $n^{25}D$ 1.5478 of crude *trans*-Ib. The crude product was chromatographed on alumina and eluted with benzene–chloroform to give 2.2 g. (94.0% yield) of *trans*-Ib, $n^{25}D$ 1.5455.

Anal. Calcd. for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.25; N, 4.86; Cl, 24.61. Found: C, 54.25; H, 5.21; N, 5.00; Cl, 24.93.

This *trans*-Ib has identical n.m.r. spectrum (Table IV) and infrared spectrum (Table VI) with the liquid, $n^{25}D$ 1.5505, obtained from Darzens condensation.

***threo*-N,N-Diethyl-2,3-dihydroxy-3-phenylpropionamide (VIIa).**—The procedure employed by Boeseken[17] was followed. A solution of 20.3 g. (0.1 mole) of *trans*-N,N-diethylcinnamide (IIa) m.p. 71–72°, in 1 l. of ethanol was cooled to −40°. A solution of 18.0 g. (0.12 mole) of potassium permanganate and 20.0 g. (0.08 mole) of magnesium sulfate heptahydrate in 600 ml. of water was then added at −40° in 5 hr. The cooling bath was removed and the reaction mixture allowed to stir to room temperature. It was filtered and evaporated to one-third its original volume and then extracted with ether. Evaporation of the ether left 15.5 g. (65.4% yield) of oil. The infrared spectrum and analysis indicated this material to be a mixture of unreacted amide and diol. The oil was chromatographed on alumina. Elution with benzene afforded 5.4 g. (26.5% recovery) of starting amide, m.p. 71–72°. Elution with 95 and 80% ethanol gave 5.8 g. of oil (24.5% yield; 33% conv.) $n^{25}D$ 1.5320–1.5305. Several recrystallizations of the oil from hexane afforded a white solid (4.4 g.) m.p. 72°. It depressed the melting point of starting cinnamamide.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90; OH, 14.33. Found: C, 65.94; H, 7.41; N, 6.15; OH, 14.52. Infrared spectrum showed absorption at 2.80, 2.90 and 9.45 μ (hydroxy) and at 6.15 μ (amide).

***threo*-N,N-Diethyl 3-(2,6-dichlorophenyl)-2,3-dihydroxypropionamide (VIIb).**—A solution of 13.6 g. (0.05 mole) of *trans*-N,N-diethyl-2,6-dichlorophenylcinnamide (IIb) in 500 ml. of ethanol was cooled to −40° and treated with a solution of 9.0 g. (0.06 mole) of potassium permanganate and 10.0 g. (0.04 mole) of magnesium sulfate heptahydrate during 5 hr. The mixture was allowed to warm to room temperature, filtered, and the filtrate reduced in volume and extracted with ether. The ether solution was evaporated to dryness to give 12.3 g. (80.4% yield) of crude solid. This was recrystallized from benzene–hexane to give the *threo*-diol, wt. 5.5 g. (36% yield) m.p. 112–113°. Recrystallization from hexane afforded pure diol amide, m.p. 113–114°. A mixture melting point with authentic *cis*-epoxy amide (m.p. 112–113°) was depressed. Infrared spectrum showed absorption at 2.84, 2.95 and 9.23 μ (OH) and 6.10 μ (amide). Bands at 11.77 and 12.23 μ characteristic for the epoxy amide were absent.

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3$: C, 50.99; H, 5.60; Cl, 23.16; N, 4.58; OH, 11.10. Found: C, 50.71; H, 5.67; Cl, 23.51; N, 4.66; OH, 11.47. The benzene–hexane mother liquors after removal of the *threo*-diol were evaporated to dryness to give 5.1 g. of unidentified oil, $n^{25}D$ 1.5674. No OH absorption was present in its infrared spectrum.

***erythro*-N,N-Diethyl-2,3-dihydro-3-phenylpropionamide (VIII).**—A solution of 5.0 g. (0.023 mole) of high melting isomer of N,N-diethyl-3-phenylglycidamide (m.p. 87–88°) in 50 ml. of acetone and 100 ml. of 30% sulfuric acid was heated at 40–45° for 2 hr. It was poured into water, extracted with ether and the ether solution dried and evaporated. There remained 4.0 g., 74% yield, of oil; $n^{22}D$ 1.5320. This was chromatographed on alumina and eluted with ethanol–ether mixture. The eluent afforded a solid which was recrystallized from hexane, m.p. 58–59°.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90; OH, 14.33. Found: C, 65.72; H, 7.88: N, 6.43; OH, 14.13. Infrared spectrum showed absorptions identical with that of *threo* isomer VIIa.

***erythro*-N,N-Diethyl-3-(2,6-dichlorophenyl)-2,3-dihydroxypropionamide (IX).**—A solution of 9.0 g. (0.315 mole) of *cis–trans*-N,N-diethyl-3-(2,6-dichlorophenyl)glycidamide (Ib) ($n^{25}D$ 1.5536) in 75 ml. of acetone, 75 ml. of water and 15 ml. of concentrated sulfuric acid was heated at 45–50° for 28 hr. and allowed to stand at room temperature for 3 days. The acetone was removed and the mixture extracted with ether, washed with bicarbonate, dried, and evaporated. There remained an oil, wt. 8.1 g. (90% yield) $n^{22}D$ 1.5542. It was chromatographed on alumina and eluted with benzene and ethanol–hexane mixture. The benzene eluents afforded unchanged *cis*-epoxyamide, m.p. 112–113°; 3.4 g. (38% recovery). The ethanol–hexane eluent afforded 3.0 g. (34.5%) of the diol, m.p. 146–147°. Its melting point was was raised to 148–149° after recrystallization from hexane.

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3$: C, 50.99; H, 5.60; Cl, 23.16; N, 4.58; OH, 11.10. Found: C, 51.38; H, 5.99; Cl, 23.26; N, 4.59; OH, 11.00. Infrared spectrum showed absorptions at 2.95 μ (hydroxy) and 6.12 μ (amide).

Attempted Epimerization of *trans*-N,N-Diallyl-3-phenylglycidamide with Potassium *t*-Butoxide in *t*-Butyl Alcohol.—A solution of 18.4 g. of *trans*-epoxyamide, 0.2 g. of potassium *t*-butoxide in 55 ml. of *t*-butyl alcohol was allowed to stand at room temperature for 6 days and followed by heating at 60° for 2 hr. The solvent was evaporated to dryness *in vacuo* to give an oil which was pure unchanged *trans*-epoxyamide by n.m.r. The sample remained unchanged after it was redissolved in 55 ml. of *t*-butyl alcohol and heated at 60° for 13 hr.

Epimerization of *cis*-N,N-Diallyl-3-phenylglycidamide. (a) **Potassium *t*-Butoxide in *t*-Butyl Alcohol.**—A solution of 9.2 g. of *cis*-epoxyamide, 0.1 g. of potassium *t*-butoxide in 185 ml. of *t*-butyl alcohol was treated as described previously. The results are tabulated in Table V.

(b) **In the Absence of Potassium *t*-Butoxide.**—A solution of 1.5 g. of *cis*-epoxyamide in 50 ml. of *t*-butyl alcohol was heated at 60° for 15 hr. After removal of the solvent, 1.5 g. of *cis*-epoxy-

(21) Sample was prepared according to the method of W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953). For assignment of configuration, see ref. 16.

amide, m.p. 88.6–90° was recovered. Its n.m.r. spectrum was identical to the starting *cis* isomer.

***trans*-N,N-Diethyl-2,6-dichlorophenylcinnamide (IIb).**—A solution containing 16.5 g. (0.076 mole) of 2,6-dichlorocinnamic acid[22] (m.p. 193.7–194.2°) and 18.0 g. (0.152 mole) of thionyl chloride in 100 ml. of benzene was heated to reflux for 1 hr. The solvent was evaporated to dryness to give a colorless solid, m.p. 68–69°. The yield was 17.2 g. (96.3% yield). One recrystallization from hexane crystals, m.p. 69.2–70.1°.

Anal. Calcd. for $C_9H_5Cl_3O$: Cl, 42.25. Found: Cl, 42.68.

To a stirred solution of 16.0 g. (0.068 mole) of 2,6-dichlorocinnamoyl chloride in 120 ml. of ether was added 12.5 g. (0.17 mole) of diethylamine over a period of 10 min. Stirring at room temperature was continued for 1 hr. The diethylamine hydrochloride salt (7.8 g., theory) was removed and the filtrate was evaporated *in vacuo* to dryness to yield 17.8 g. of light brown viscous oil. The distilled product, b.p. 170–171° (0.5 mm.), $n^{25}D$ 1.5791, was obtained in 15.2 g. (82.2% yield). The compound was identified as *trans* from n.m.r. spectrum (Table II).

Anal. Calcd. for $C_{13}H_{15}Cl_2NO$: Cl, 26.05; N, 5.15. Found: Cl, 26.02; N, 4.64.

Attempted Epoxidation of *trans*-IIa with Monoperphthalic Acid.—The procedure of Wheeler[23] was followed. A solution of 610 ml. of an ether solution containing 0.44 mole of monoperphthalic acid[24] and 14.0 g. (0.07 mole) of *trans*-N,N-diethylcinnamamide (IIa) was allowed to stand at 5° for 35 days. Water was added to destroy the peracid and the filtered solution was evaporated to dryness *in vacuo*. The residue was extracted with chloroform and chloroform extract was washed with aqueous sodium bicarbonate solution. After being dried over anhydrous magnesium sulfate, solvent was removed to give 12.1 g. (86.5% recovery) of starting *trans*-cinnamamide (IIa), m.p. 70–71°.

Attempted Bromoacetoxylation of *trans*-IIa with N-Bromosuccinimide–Acetic Acid.—The procedure of Jovtscheff[13] was followed. A solution of 10.0 g. (0.05 mole) of *trans*-N,N-diethylcinnamide (IIa) an 18.0 g. (0.10 mole) of N-bromosuccinimide in 500 ml. of glacial acetic acid was stirred at room temperature in a dark flask for a period of 1.5 hr. The reaction mixture was poured into 500 ml. of water containing 30 g. of potassium iodide and the liberated iodine was destroyed by aqueous sodium thiosulfate. The mixture after being extracted with ether, dried over anhydrous magnesium sulfate, evaporated to dryness *in vacuo* gave a dark brown tarry material. Attempts to purify this material by crystallization and chromatography were unsuccessful.

(22) F. Böck, G. Lock and K. Schmidt, *Monatsh.*, **64**, 399 (1934).

(23) K. W. Wheeler, M. G. Van Campen, Jr., and R. S. Shelton, *J. Org. Chem.*, **25**, 1021 (1960).

(24) H. Böhme, *Org. Syn.*, **20**, 70 (1940).

Reaction of Amides and Esters of α,β-Dibromopropionic Acids with Triphenylphosphine

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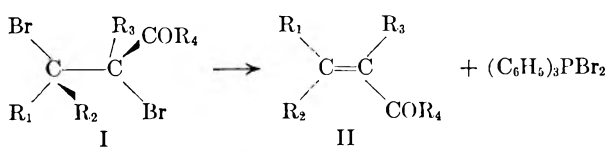
The debromination of the dibromides derived from ethyl methacrylate, methyl acrylate, and N,N-diethyl 3,3-dimethylacrylamide with triphenylphosphine is reported. However, 2,3-dibromopropionamide with triphenylphosphine underwent displacement of the α-bromine atom and dehydrohalogenation to produce the ylid (VI).

In connection with our work on the debromination of *erythro*-N,N-diethylcinnamamide dibromide with bases,[1] the reaction of amides and esters of α,β-dibromopropionic acid with triphenylphosphine was undertaken. Abramov and Ilyina[2] in their investigation of the mechanism of the Arbuzov rearrangement of methyl α,β-dibromopropionate with tributylphosphite, reported a small quantity of by-product whose constants agreed with those of methyl acrylate. Very recently, Dershowitz and Proskauer[3] reported the debromination of dibromides of cinnamic acid, chalcone and *trans*-dibenzoylethylene with one mole equivalent of trialkylphosphite. They also stated that diphosphonates were formed when two mole equivalents of trialkylphosphite were employed.

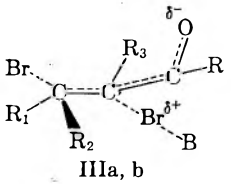
We have found that ethyl methacrylate dibromide (Ia) and methyl acrylate dibromide (Ib) with one mole equivalent of triphenylphosphine gave theoretical yields of triphenylphosphine dibromide and 49.5% yield of ethyl methacrylate (IIa) and 64.0% yield of methyl acrylate (IIb), respectively, were obtained.



I II

a. $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = OC_2H_5$
b. $R_1 = R_2 = R_3 = H$; $R_4 = OCH_3$
c. $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4 = N(C_2H_5)_2$

When two mole equivalents of triphenylphosphine were employed, the debromination of Ia,b to IIa,b proceeded with the recovery of one mole equivalent of the unchanged triphenylphosphine. The elimination of bromine can be reasonably explained[1] *via* a favored *trans*-coplanar transition state IIIa,b in which the incipient negative charge on the α-carbon atom can be stabilized by resonance with the carbonyl group.



IIIa, b

Dehydrobromination of Ib or SN2 displacement of the α or β-bromine atoms of Ia,b by triphenylphosphine was not observed. The elimination of hydrogen bromide from Ib would involve the unfavored conformer Ib′.[4]

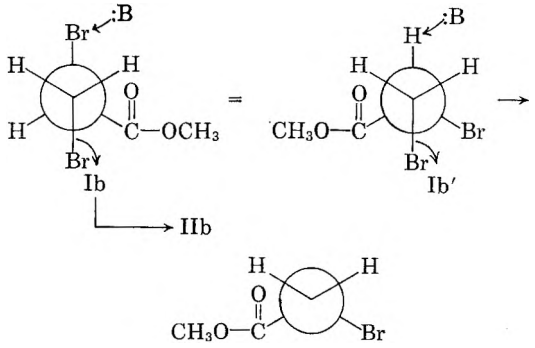
The reaction of N,N-diethyl 3,3-dimethylacrylamide dibromide (Ic) with triphenylphosphine was also found to give the debrominated product IIc. However, reaction of acrylamide dibromide IV with two moles of triphenylphosphine gave a product $C_{21}H_{19}BrNOP$ in 85% yield and triphenylphosphonium bromide in 90% yield. The product was water soluble and its aqueous

(1) A. J. Speziale and C. C. Tung, *J. Org. Chem.*, **28**, 1323 (1963).

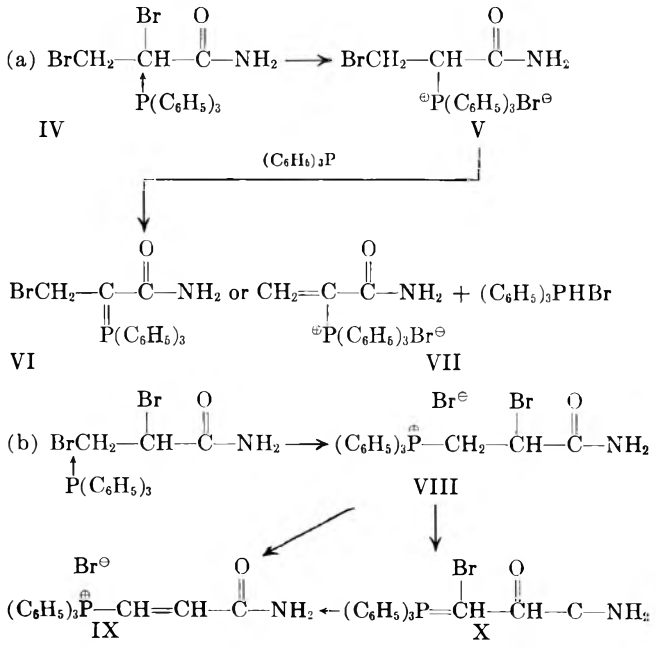
(2) V. S. Abramov and N. A. Ilyina, *J. Gen. Chem., USSR* (Eng. Trans.), **26**, 2245 (1956).

(3) S. Dershowitz and S. Proskauer, *J. Org. Chem.*, **26**, 3595 (1961).

(4) The difference of 33 kcal./g.-bond between C–Br and C–H would favor C–Br bond breaking.

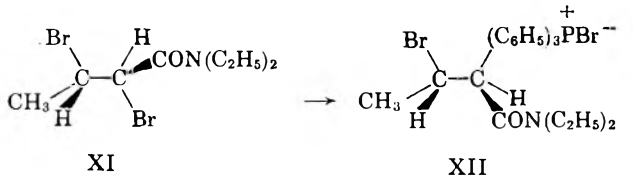


solution gave an equivalent of ionic bromide. Two paths can be formulated for the reaction of IV with triphenylphosphine. These involve an S_N2 displacement of one of the bromine atoms together with the elimination of hydrogen bromide. Path a would involve the displacement of the α-bromine atom by triphenylphosphine with subsequent removal of hydrogen bromide by the second mole of phosphine to produce either VI or VII. Path b would involve the less likely displacement of the β-bromine atom with the formation of a mixture of the *cis–trans* isomers IX or the bromo ylid X. There were no bands attributable to a carbon–carbon double bond in the infrared spectrum of the product. Further, n.m.r. spectrum[5] of the product indicated no olefinic protons but showed a clean doublet for $-CH_2-$ protons resulting from spin–spin coupling with phosphorus. Therefore, the $C_{21}H_{19}BrNOP$ compound has the ylid structure VI.



The reaction of *erythro*-N,N-diethyl 3-methylacrylamide dibromide (XI) with two mole equivalents of triphenylphosphine gave the phosphonium bromide XII as the only identified product. The failure of XII to eliminate hydrogen bromide as did V may indicate

(5) Spectra were measured at 60 Mc./sec. on a modified Varian Mode A-60 spectrometer in dimethyl sulfoxide solution with tetramethylsilane as an internal reference. Chemical shifts observed are: for acrylamide (IV) amide protons (wide band) at τ 2.6 and olefinic protons (multiplet) at τ 3.7–4.5 in an intensity ratio of 2:3; for VI ring protons (doublet) at τ 1.8, amide protons (wide band) at τ 2.6 and β-methylene protons at τ 6.0 (doublet with a coupling constant of 8.0 c.p.s.) in an intensity ratio of 15:2:2.



that the α-hydrogen atom in XII is less acidic than that of V.

Experimental

Reaction of Ethyl Methacrylate Dibromide (Ia) with Triphenylphosphine.—To a solution of 15.80 g. (0.060 mole) of triphenylphosphine in 85 ml. of ether was added 16.44 g. (0.06 mole) of ethyl methacrylate dibromide. Solid material precipitated immediately and the reaction mixture was heated to reflux temperature for 3 hr. The product, distilled at 40–41°, 68 ml., was found both from infrared analysis and vapor phase chromatography to contain 5% of ethyl methacrylate (3.4 g., 50% yield). The residue 25.2 g. (theory) was identified as triphenylphosphine dibromide by infrared analysis and by its conversion to triphenylphosphine oxide.

When the reaction was carried out in benzene solution at room temperature for 3 hr., same results were obtained.

Reaction of Methyl Acrylate Dibromide (Ib) with Triphenylphosphine.—The reaction was carried out under conditions described for Ia. From 14.75 g. (0.060 mole) of methyl acrylate dibromide and 15.80 g. (0.060 mole) of triphenylphosphine was obtained 3.3 g. (64.0% yield) of methyl acrylate and 25.1 g. (98% yield) of triphenylphosphine dibromide.

Reaction of N,N-Diethyl 3,3-Dimethylacrylamide Dibromide (Ic) with Triphenylphosphine.—To a stirred solution of 26.2 g. (0.10 mole) of triphenylphosphine in 130 ml. of benzene was added 15.75 g. (0.05 mole) of N,N-diethyl 1,2-dibromo-2-methyl butyramide in 20 ml. of benzene. Solid was precipitated immediately and the temperature of reaction rose from 24° to 30°. The reaction was heated at reflux temperature for 3 hr. After cooling to room temperature, the triphenylphosphine dibromide was collected by filtration and dried immediately *in vacuo*. The weight of dried triphenylphosphine dibromide was 20.5 g. (97%) and was converted to triphenylphosphine oxide in quantitative yield. The benzene filtrate was evaporated to dryness and the residue distilled *in vacuo* to give 6.51 g. (84%) of N,N-diethyl 2,2-dimethylacrylamide and 13.07 g. (0.05 mole) of unchanged triphenylphosphine.

When the reaction was carried out at room temperature, the same results were obtained.

Reaction of Acrylamide Dibromide (IV) with Triphenylphosphine.—To a stirred solution of 11.6 g. (0.05 mole) of acrylamide dibromide in 70 ml. of dioxane at 24° was added dropwise a solution of 26.2 g. (0.10 mole) of triphenylphosphine in 80 ml. of dioxane over a period of 1 hr. The temperature of the reaction mixture was maintained at 20–25° by external cooling and stirring continued for an additional 3 hr. The colorless solid was collected by filtration and dried *in vacuo*. One crystallization from chloroform–hexane mixture gave 17.6 g. (85% yield) of colorless solid VI, m.p. 241–242°. The compound was soluble in water and gave a positive test for ionic bromide.

Anal. Calcd. for $C_{21}H_{19}BrNOP$: C, 61.30; H, 4.65; N, 3.40; P, 7.54; Br, 19.45; mol. wt., 412. Found: C, 60.68; H, 4.70; N, 3.31; P, 7.58; Br, 19.48; mol. wt., 424.

The dioxane filtrate was evaporated to dryness to give 18.4 g. of a viscous light yellow liquid which upon treatment with water gave 12.70 g., 90% yield (0.046 mole) of triphenylphosphine oxide. The formation of the triphenylphosphine oxide resulted from the reaction of triphenylphosphine hydrobromide with glycolaldehyde which was an impurity in the dioxane used. When the dioxane used in this experiment was evaporated to dryness, a viscous colorless syrup was obtained which had infrared absorption at 3550 $cm.^{-1}$ (—OH) and 1725 $cm.^{-1}$ (—C=O). Treatment of this syrup with alcoholic 2,4-dinitrophenylhydrazine gave the deep yellow glyoxal bis(2,4-dinitrophenylhydrazone), m.p. 285–87°.[6]

(6) T. Banks, C. Vaughan, and L. M. Marshall, *Anal. Chem.*, **27**, 1348 (1955). Reported m.p. for glyoxal bis(2,4-dinitrophenylhydrazone) is 290–300°.

Reaction of Triphenylphosphine Hydrobromide with Crude Dioxane.—A suspension of 10.0 g. (0.0292 mole) of triphenylphosphine hydrobromide in 250 ml. of crude dioxane was stirred at room temperature for 2 hr. The unchanged triphenylphosphine hydrobromide (6.1 g.) was removed by filtration and the filtrate was evaporated to dryness to give 5.9 g. of viscous liquid. The viscous liquid, upon stirring with water, gave 3.01 g. (96% yield based on the used triphenylphosphine hydrobromide) of triphenylphosphine oxide, m.p. 155–56°.

Reaction of N,N-Diethyl 3-Methylacrylamide Dibromide (XI) with Triphenylphosphine.—A solution containing 30.1 g. (0.10 mole) of XI and 52.4 g. (0.20 mole) of triphenylphosphine in 470 ml. of anhydrous acetone was stirred at room temperature for 12 hr. The solid material, 6.1 g., was collected by filtration. The filtrate was evaporated under reduced pressure to about 250 ml. and additional 11.5 g. of solid was collected. The combined solid after recrystallization from chloroform–ether gave an unidentified colorless solid, m.p. 149–150°, with the following analysis: C, 66.30; H, 5.19; P, 9.65; Br, 11.95. This solid, upon treatment with water, gave triphenylphosphine oxide. The acetone filtrate was evaporated to dryness and the residue recrystallized from acetone–ether. There was obtained 27.6 g. of a colorless solid, m.p. 97–98°. The elemental analysis indicated the compound to be the monohydrate of XII. The yield was 47%.

Anal. Calcd. for $C_{26}H_{32}Br_2NO_2P \cdot H_2O$: C, 53.70; H, 5.50; N, 2.41; Br, 27.50; P, 5.34; mol. wt., 581. Found: C, 53.58; H, 5.45; N, 2.42; Br, 27.05; P, 5.29; mol. wt., 606.

The Preparation of 14β,21-Epoxy Steroids

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The 14β,21-epoxy steroidal moiety has been synthesized by a basic displacement cyclization reaction of a C-20-methoxyimino derivative of a 14β-hydroxy-21-methanesulfonyloxy-20-ketopregnane. Mineral acid hydrolysis removed the C-20 protective grouping to provide the desired 14β,21-epoxy-20-ketopregnane. 14β,21-Epoxy-14β-pregn-4-ene-3,20-dione has been prepared by a multi-stage synthesis from digitoxigenin acetate.

This laboratory[1] has been concerned for some time in the preparation of epoxy steroids, more particularly in the ether formed by attachment of the C-21 hydroxymethyl grouping to the various positions on the steroid D ring. In this connection we became interested in the suggestion of Tschesche and Buschauer[2] that a 14β,21-epoxy moiety constituted a part of the structure of diginigenin.[3] This paper describes a synthetic pathway to the 14β,21-epoxy-20-ketone grouping.

An appropriate starting material for this investigation was selected from the cardiac aglycones which contain a 14β-hydroxyl group. Accordingly, digitoxigenin acetate was ozonized by the procedure of Oliveto and coworkers[4] to give the desired 3β-acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I). The latter was evidently less contaminated with 17-iso compound than the preparation described by Meyer and Reichstein.[6]

Since cyclizing reactions that might be utilized to prepare a 14β,21-epoxide from I would involve basic conditions, it was considered desirable to protect the base sensitive ketol grouping in I by preparing a C-20 carbonyl derivative which would withstand these conditions. The first consideration was given to the ethylene ketal grouping because of its well known base stability properties. Since it is also evident that the 14β-hydroxyl group is quite acid sensitive, various methods of ketalization were attempted. While it was possible to produce a 20-ketal by any of several methods, it was not possible to maintain the 14β-hydroxyl function. In every case dehydration occurred to give 3β-acetoxy-20-ethylenedioxypregn-14-en-21-ol (II). That the unsaturation was at position 14:15 and not the alternatively possible 8:14 position was determined by ultraviolet absorption measurements in the 190–225-mμ region and also by a proton magnetic resonance spectrum of II. As pointed out by Bladon, Henbest, and Wood[7a] and later expanded by Ellington and Meakins[7b] it is possible in the ultraviolet spectrum to distinguish by the shape of the curves[8] between a doubly exocyclic tetrasubstituted ethylenic linkage as in a $\Delta^{8(14)}$-compound and an exocyclic trisubstituted double bond as in a Δ^{14}-compound. The n.m.r. spectrum of II clearly showed the vinyl proton at C-15, thereby eliminating any consideration of a $\Delta^{8(14)}$-compound. The ketal II was hydrolyzed in acid to afford 3β-acetoxy-21-hydroxypregn-14-en-20-one (III), which also revealed a vinyl proton in the n.m.r. spectrum.

The 20-carbonyl group of I was protected successfully by reaction with methoxyamine hydrochloride in the presence of potassium acetate without concomitant destruction of the 14β-hydroxyl function. The resultant methoxyimino[9] derivative IVa was an uncrystallizable glass which, however, could be smoothly converted into the crystalline 3β-acetoxy-21-methanesulfonyloxy-20-methoxyimino-14β-pregnan-14β-ol (IVb). The desired displacement cyclization and simultaneous deacetylation was then readily achieved by treatment of the mesylate IVb with potassium hydroxide in methanol. The methoxyimino group of the cyclic product Va was

(1) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955); W. S. Allen and S. Bernstein, *ibid.*, **78**, 3223 (1956).

(2) R. Tschesche and G. Buschauer, *Ann.*, **603**, 59 (1957).

(3) C. W. Schoppee, R. Lack, and A. V. Robertson, *J. Chem. Soc.*, 3610 (1962), have disclosed that the structure of diginigenin is 12α,20α-epoxy-3β-hydroxy-14β,17α-pregn-5-ene-11,15-dione.

(4) E. P. Oliveto, L. Weber, C. G. Finckenor, M. M. Pechet, and E. B. Herschberg, *J. Am. Chem. Soc.*, **81**, 2831 (1959), have described an ozonolysis procedure which eliminates the bicarbonate[5] treatment of the intermediate 21-glyoxylic ester.

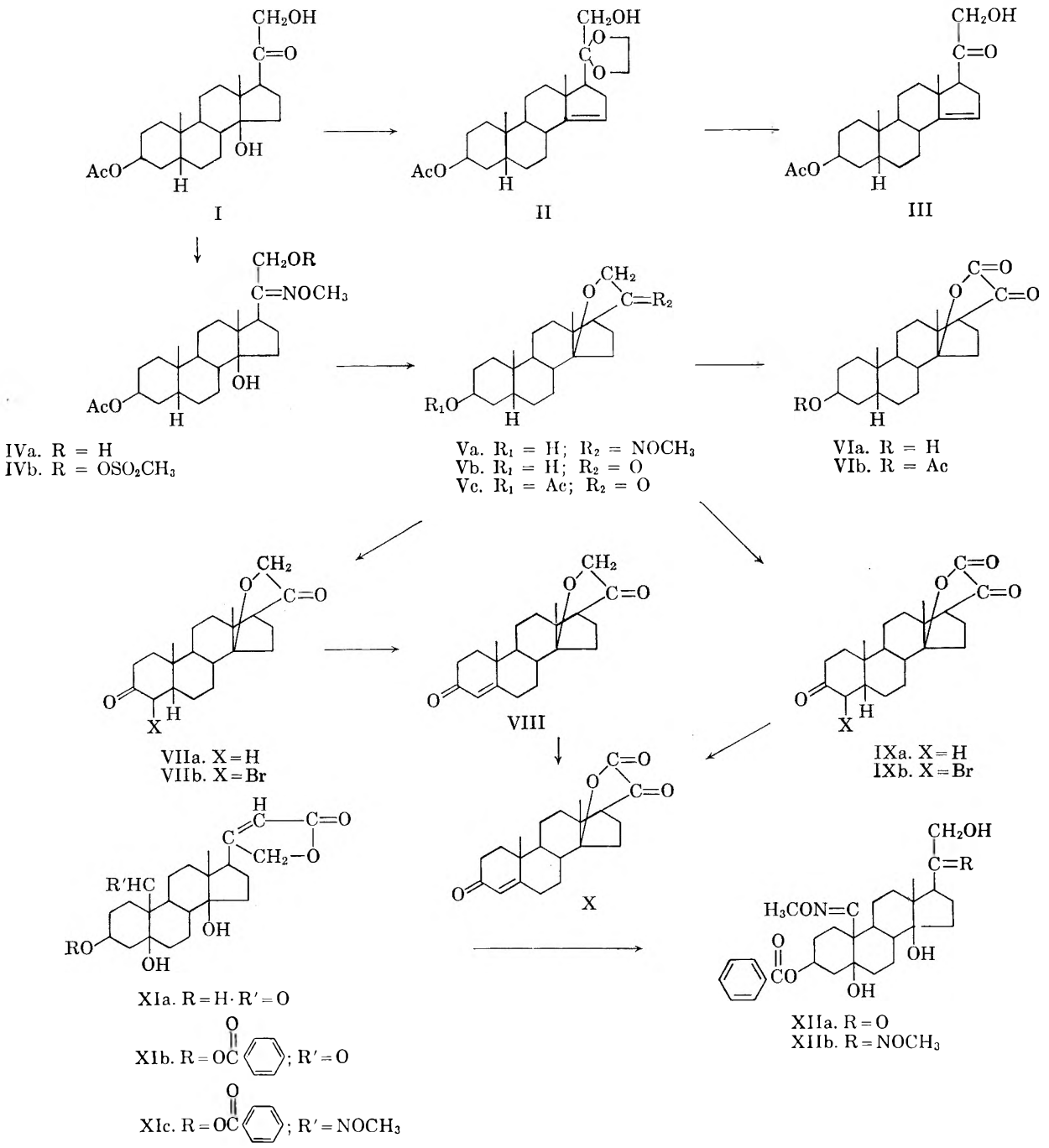
(5) C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1576 (1952), have shown that bicarbonate hydrolysis invites considerable isomerization at C-17 in this type of compound.

(6) K. Meyer and T. Reichstein, *Helv. Chim. Acta*, **30**, 1508 (1947).

(7) (a) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2739 (1952); (b) P. S. Ellington and G. D. Meakins, *ibid.*, 697 (1960).

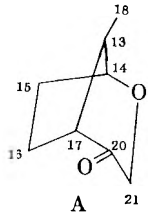
(8) Subsequent papers considering techniques to determine the exact maximum of an isolated double bond in the ultraviolet absorption spectrum have led to considerable discussion. *Cf.*, D. W. Turner, *ibid.*, 30 (1959); K. Stich, G. Rotzler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1480 (1959); Ref. 7b; J. H. Chapman and A. C. Parker, *J. Chem. Soc.*, 2075 (1961); T. H. Applewhite and R. A. Micheli, *J. Org. Chem.*, **27**, 345 (1962); R. Bühler and T. Reichstein, *Helv. Chim. Acta*, **45**, 389 (1962).

(9) The bismethoxyimino derivatives of certain corticoids have been described[10a] and a patent application[10b] describing the use of this protective grouping has been printed.



cleaved by mineral acid hydrolysis[10] to yield the desired 3β-hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb).

The new ring system locked together with the steroidal D ring forms a 2-oxabicyclo[3.2.1]octane system A



(steroid numbering shown) which has been known for many years.[11] In this particular case Dreiding models suggest strongly that the six-membered oxygen containing ring preferably would exist in a chair form since in a boat conformation there would be extreme steric interaction of one hydrogen of the C-21 methylene grouping and the C-18 angular methyl group. It is not apparent why the infrared absorption spectrum of Vb reveals a peak as high as 1730 cm.$^{-1}$ for the C-20 carbonyl function. No examples of a system such as A containing infrared data could be found. However, the infrared absorption peak of bicyclo[3.2.1]octan-2-one at 1717[12a] cm.$^{-1}$ and that of 5,8,8-trimethylbicyclo-[3.2.1]octan-2-one (homoepicamphor)[12b] at 1716 cm.$^{-1}$, the models of which indicate no significant strain differences from an oxygen containing system such as A, show that the bicyclo system as such does not necessarily account for the high absorption band of Vb.

(10) (a) S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 4614 (1958); (b) A. G. Long and S. Eardley, Union of South Africa Patent Application 595,054 (December 3, 1959).

(11) C. Harries and H. Neresheimer, *Ber.*, **39**, 2846 (1906).

(12) (a) R. Zbinden and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **82**, 1215 (1960); (b) H. Fabre, B. Marinier, and J-C. Richer, *Can. J. Chem.*, **34**, 1329 (1956).

The n.m.r. spectrum of Vb and that of its 3-acetate derivative Vc was instructive since the signal due to the C-21-methylene grouping was revealed to be that of an AB system in which the two hydrogen are nonequivalent to about the same degree as in the 21-acetoxy-20-one moiety mentioned by Shoolery and Rogers.[13] For the particular case of Vb the J_{AB} is about 17 c.p.s. and the calculated chemical shifts for the two hydrogens are at 3.96 and 4.15 p.p.m. Also of interest is the fact that the n.m.r. spectra of all the 14β,21-epoxides revealed only one signal for the combined C-18 and C-19 methyl hydrogens. These were at 0.97, 1.00, and 1.01 p.p.m., respectively, for compounds Va, Vb, and Vc.

In order to provide further proof for the 14β,21-epoxy-structure, the acetate derivative Vc was oxidized with chromic acid in acetic acid to give 3β-acetoxy-14β-hydroxy-20-keto-14β-pregnan-21-oic acid 21,14-lactone (VIb). The latter compound has been prepared by other investigators[14] utilizing different pathways. Also within our own laboratory the lactone VIb has been obtained in poor yield by adaptation of a method[15] used previously on another cardenolide. Direct comparison of our preparations with an authentic sample[14a,16] revealed the absolute identity of these preparations.

Finally it was considered advantageous to prepare the Δ^4-3-one analogs of the 14β,21-epoxides. Accordingly, the 3β-ol Vb was treated with chromic acid–sulfuric acid–acetone[17] to afford 14β,21-epoxy-14β-pregnane-3,20-dione (VIIa). The latter compound was brominated at −40°[18] in acetic acid to give presumably the thermodynamically stable 4β-bromo-3,20-dione VIIb which in turn was dehydrohalogenated with lithium chloride in dimethylformamide to 14β,21-epoxy-14β-pregn-4-ene-3,20-dione (VIII). Oxidation of the 14β,-21-epoxy-3β-ol Vb with chromic acid-acetic acid yielded 14β-hydroxy-3,20-diketo-14β-pregnan-21-oic acid 21,14-lactone (IXa). Treatment of IXa with bromine then gave the 4β-bromo lactone IXb which was dehydrohalogenated to 14β-hydroxy-3,20-diketo-14β-pregn-4-en-21-oic acid 21,14-lactone (X). The latter compound was also prepared by chromic acid–acetic acid oxidation of the Δ^4-3-one 14β,21-epoxide VIII. An interesting observation was made with respect to the ultraviolet absorption spectrum of the diketo lactone X. No obvious reason can be seen from a study of models for the hypsochromic effect which occurs when the normal behaving 14β,21-epoxy compound VIII (λ_{max} 240 mμ, ε 15,600) was oxidized to X with an ultraviolet absorption maximum of 232–234 mμ and a molecular extinction coefficient of 13,000–14,000.

Finally, in an investigation designed to study the usefulness of strophanthidin (XIa) as a starting material for a 14β,21-epoxide structure while maintaining a C-19 aldehyde function in the molecule, strophanthidin benzoate (XIb)[19] was treated with methoxyamine hydrochloride and potassium acetate to form the methoxime XIc. This compound was ozonized in the usual fashion to afford 3β-benzoyloxy-5β,14β,21-trihydroxy-19-methoxyimino-14β-pregnan-20-one (XIIa). The latter compound was further treated with methoxyhydrochloride and potassium acetate to give the bismethoxyimino derivative XIIb. Unfortunately, XIIb dib not react suitably with either methanesulfonyl chloride or *p*-toluenesulfonyl chloride in pyridine so that further reactions to form a 14β,21-epoxide as indicated above could not be attempted. Furthermore, the usual acid hydrolysis conditions would not remove the methoxyimino grouping in XIIa, casting additional doubt upon the practicability of this pathway for the desired product.

Experimental[20]

3β-Acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I).—A solution of digitoxigenin acetate (5.0 g.) in pyridine (480 ml.) and ethyl acetate (480 ml.) was cooled to −60°. The solution was treated with a stream of ozone at a rate of 0.3 mmole per minute for 70 min. Excess ozone was removed from the reaction mixture with a stream of oxygen until the blue solution turned colorless. To the stirred solution was added acetic acid (48 ml.) and zinc dust (9.7 g.) and the reaction temperature was allowed to come to room temperature. The mixture was then heated to 60° and filtered through diatomaceous earth. The filtrate was evaporated under reduced pressure, the residue was dissolved in toluene, and the evaporation was repeated. The residual dark brown sirup was dissolved in a mixture of ethyl acetate (250 ml.) and water (100 ml.). The organic layer was separated, dried with magnesium sulfate, and evaporated under reduced pressure leaving a dark brown gum. The crude gum was dissolved in a minimum amount of methylene chloride and placed on a Florisil[21] (200 g.) column. The column was washed with methylene chloride (750 ml.) and then with 2% acetone–methylene chloride (750 ml.). The polarity of the solvent mixture was increased to 10% acetone–methylene chloride and 500-ml. cuts of eluate were taken and evaporated under reduced pressure. Only those cuts which on evaporation produced a solid were combined affording 2.3 g. of solid. Crystallization of this material from acetone–petroleum ether yielded 1.85 g. of I as white crystals, m.p. 159–163°[22]; ν_{max} 3400, 1715, 1720, 1250, 1230, cm.$^{-1}$; $[\alpha]^{25}D$ +52.5° (chloroform).

Anal. Calcd. for $C_{23}H_{36}O_5$ (392.52): C, 70.37; H, 9.24. Found: C, 70.40; H, 9.33.

3β-Acetoxy-20-ethylenedioxypregn-14-en-21-ol (II).—A mixture of 3β-acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I, 200 mg.), benzene (30 ml.), and ethylene glycol (2 ml.) was refluxed with *p*-toluenesulfonic acid monohydrate (30 mg.) (Dean–Stark water separator) for 4.5 hr. The reaction was cooled and water and sodium bicarbonate solution was added. The benzene solution was separated, washed with water, and dried with magnesium sulfate. Evaporation of the benzene produced a white solid which was crystallized from acetone–water to yield 130 mg. of II as white crystals, m.p. 122–127°. Several recrystallizations from the same solvent pair afforded 55 mg. of white needles, m.p. 124–125°, but satisfactory combustion values were not obtained; ν_{max} 3480, 1730, 1715, 1258, 1247 cm.$^{-1}$.

(13) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(14) (a) F. Hunziker and T. Reichstein, *Helv. Chim. Acta*, **28**, 1472 (1945); (d) K. Meyer, *ibid.*, **30**, 1976 (1947).

(15) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **26**, 1230 (1961); Our experiments involved permanganate oxidation of digitoxigenin to the free 3β-ol VIa followed by acetylation to VIb.

(16) We thank Professor T. Reichstein for the authentic sample of VIb.

(17) K. Bowden, J. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(18) J. T. Day, U. S. Patent 2,907,776 (October 6, 1959).

(19) A. Windaus and L. Hermanns, *Ber.*, **48**, 979 (1915).

(20) All melting points are uncorrected. The infrared spectra were determined in a potassium bromide disk. The n.m.r. spectrum of compound II was done on a Varian Associates HR60 spectrometer. All other n.m.r. spectra were done on a Varian Associates A60 spectrometer. The petroleum ether used had a b.p. 60–70°. The thin layer chromatogram was carried out at room temperature on a glass plate coated with approximately 0.25 mm. of Silica Gel G prepared according to E. Stahl, *Chem. Ztg.*, **82**, 323 (1958), and dried for 2 hr. at 70°. The developing system was the upper phase of a benzene:acetone:water partition (2:1:2).

(21) Florisil is the Floridin Co.'s registered trademark for a synthetic magnesium silicate.

(22) Meyer and Reichstein[6] record a melting point of 148–149° and $[\alpha]D$ +5° (chloroform) for this compound. They also give the specific rotation of 3β,21-diacetoxy-14β-hydroxy-14β-pregnan-20-one as $[\alpha]D$ +50.5° (chloroform). The magnitude of such a shift in rotation on acetylation of the 21-hydroxyl function appears to be too large, and the inference must be that their monoacetate was contaminated with levorotatory 17-iso compound.

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.13; H, 9.65.

3β-Acetoxy-21-hydroxypregn-14-en-20-one (III).—A solution of 3β-acetoxy-20-ethylenedioxypregn-14-en-21-ol (II, 460 mg.) in methanol (40 ml.) and 8% sulfuric acid (3 drops) was refluxed for 10 min. The solution was diluted with water, concentrated under reduced pressure, and filtered affording 290 mg. of white solid, m.p. 168–172°. Several crystallizations from acetone–water raised the melting point to 171–172°; ν_{max} 3450, 1725, 1256, 1238 cm.$^{-1}$; $[\alpha]^{25}D$ +39° (chloroform).

Anal. Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 73.94; H, 9.37.

3β-Acetoxy-20-methoxyimino-14β-pregnane-14β,21-diol (IVa).—To a solution of 3β-acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I, 300 mg.) and methoxyamine hydrochloride (300 mg.) in methanol (45 ml.) was added a solution of potassium acetate (600 mg.) in water (6 ml.). The solution was refluxed for 18 hr. and then diluted with water (30 ml.). Most of the methanol was removed from the solution by concentration under reduced pressure. The aqueous residual mixture was extracted several times with ethyl acetate, and the extract was washed with dilute hydrochloric acid and water. The dried extract was evaporated *in vacuo* to yield 290 mg. of IVa as a white glass which could not be crystallized; ν_{max} 3380, 1734, 1710 (sh), 1252, 1230 cm.$^{-1}$.

3β-Acetoxy-21-methanesulfonyloxy-20-methoxyimino-14β-pregnan-14β-ol (IVb).—A solution of crude 3β-acetoxy-20-methoxyimino-14β-pregnane-14β,21-diol (IVa, 290 mg.) in pyridine (5 ml.) was cooled to −32° and methanesulfonyl chloride (0.27 ml.) was added. The reaction mixture was maintained at −5° for 22 hr. The product IVb was precipitated by the dropwise addition of water and collected as 200 mg. of white solid, m.p. 148–149°. Two recrystallizations from acetone–petroleum ether raised the melting point to 149–150° dec.; ν_{max} 3520, 1735, 1720 (sh), 1342, 1270, 1240, 1170 cm.$^{-1}$; $[\alpha]^{25}D$ +14° (chloroform).

Anal. Calcd. for $C_{25}H_{41}O_7NS$ (449.59): C, 60.10; H, 8.27; N, 2.80; S, 6.41. Found: C, 60.45; H, 8.39; N, 2.83; S, 6.60.

20-Methoxyimino-14β,21-epoxy-14β-pregnan-3β-ol (Va).—To a suspension of 3β-acetoxy-21-mesyloxy-20-methoxyimino-14β-pregnan-14β-ol (IVb, 710 mg.) in methanol (71 ml.) was added 3% methanolic potassium hydroxide (10.4 ml.). The solid rapidly dissolved and the resultant solution was refluxed for 3 hr. Water (50 ml.) was added and the solution was concentrated under reduced pressure to remove most of the methanol. The remaining essentially aqueous solution was decanted and the residual gummy solid was triturated several times with water to yield 480 mg. of a tan solid. No satisfactory means of recrystallization of this material could be found. An analytical sample was prepared by dissolving 400 mg. of material in 20 ml. of hot cyclohexane and filtering from a small amount of insoluble material. The filtrate produced a gel which was collected by filtration and dried under reduced pressure affording 200 mg. of Va as an amorphous white powder; ν_{max} 3450, 1052, 1032, 1092, 1082 cm.$^{-1}$; $[\alpha]^{25}D$ −4° (chloroform).

Anal. Calcd. for $C_{22}H_{35}O_3N \cdot 0.5C_6H_{12}$[23] (393.51): C, 74.13; H, 10.49; N, 3.19. Found: C, 74.40; H, 10.24; N, 3.47.

3β-Hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb).—To a solution of 20-methoxyimino-14β,21-epoxy-14β-pregnan-3β-ol (Va, 2.5 g.) in methanol (250 ml.) and acetone (10 ml.) was added 2 *N* hydrochloric acid (250 ml.). The solution was heated at reflux temperatue for 4 hr. and then concentrated under reduced pressure to afford an off-white solid (1.62 g.), m.p. 177–187°. One recrystallization from acetone–water gave Vb (1.2 g.) as white crystals, m.p. 193–197°. Two additional recrystallizations gave constant melting material, m.p. 194–197°, as a hydrate; ν_{max} 3400, 1730, 1090, 1080 (sh) cm.$^{-1}$; $[\alpha]^{25}D$ −23° (chloroform).

Anal. Calcd. for $C_{21}H_{32}O_3 \cdot 1.5H_2O$ (359.49): C, 70.17; H, 9.81; H_2O, 7.50. Found: C, 70.49; H, 9.98; H_2O, 7.40.

3β-Acetoxy-14β,21-epoxy-14β-pregnan-20-one (Vc).—To a solution of 3β-hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb, 800 mg.) in pyridine (75 ml.) was added acetic anhydride (0.61 ml.). The solution was allowed to remain at room temperature for 18 hr. and then diluted with water. The yield of Vb was 750 mg. of white solid, m.p. 120–125°. One recrystallization from acetone–water afforded white crystals (660 mg.), m.p. 130–134°. Further recrystallizations did not alter the melting point; ν_{max} 1732, 1710 (sh), 1257, 1238, 1090, 1083 (sh) cm.$^{-1}$; $[\alpha]^{25}D$ −19° (chloroform).

(23) The presence of 0.5 mole of cyclohexane in the analytical sample was confirmed by a signal at 1.43 p.p.m. for 6 hydrogens in its n.m.r. spectrum.

Anal. Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 73.12; H, 9.63; H_2O, 1.66.

3β,14β-Dihydroxy-20-keto-14β-pregnan-21-oic Acid 21,14-Lactone (VIa).—To a stirred suspension of digitoxigenin (3 g.) in 0.1 *N* sodium hydroxide (270 ml.) was added dropwise 5% potassium permanganate solution (68.5 ml.). The addition required 1 hr., and then 5.5 ml. of 6 *N* hydrochloric acid was added. The precipitated manganese dioxide sludge was extracted with hot ethyl acetate and crude digitoxigenin (0.85 g.) was recovered.

The aqueous filtrate was concentrated to about 10 ml. The addition of 6 *N* hydrochloric acid (2 ml.) and aging at 5° for 18 hr. produced white solid (1.9 g.). A poor crystallization from acetone–water afforded VIa (130 mg.) as white crystals, m.p. 220–224°; ν_{max} 3550, 1742, 1710 (sh), 1285, 1274, 1262 (triplet), 1153, 1130 cm.$^{-1}$.

The material was difficult to purify and was converted directly into the acetate VIb.

3β-Acetoxy-14β-hydroxy-20-keto-14β-pregnan-21-oic Acid 21,14-Lactone (VIb). A.—To a solution of 3β-acetoxy-14β,21-epoxy-14β-pregnan-20-one (Vc, 500 mg.) in acetic acid (12 ml.) was added a solution of chromic acid (500 mg.) in 90% acetic acid (5 ml.). The reaction mixture was allowed to remain at room temperature for 18 hr. and then diluted with methanol (10 ml.). The solution was poured into water and the aqueous solution was extracted several times with ethyl acetate. The extract was washed with sodium bicarbonate solution and with water, dried with magnesium sulfate, and evaporated under reduced pressure with minimal heating. The resultant solid (300 mg.) was crystallized from acetone–water to yield VIb (160 mg.) as white crystals, m.p. 211–214°. Several recrystallizations from the same solvent pair raised the melting point to 230–232°[24]; ν_{max} 1740, 1718 (sh), 1274 (sh), 1260, 1237, 1220, 1153, 1132 cm.$^{-1}$; $[\alpha]^{25}D$ −64° (chloroform).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 70.66; H, 8.18.

B.—A solution of 3β,14β-dihydroxy-20-keto-14β-pregnan-21-oic acid 21,14-lactone (VIa, 130 mg.) in pyridine (2 ml.) was acetylated with acetic anhydride (0.1 ml.) for 50 min. at 100°. The addition of water produced VIb (90 mg.) as white crystals, m.p. 226–229°. The infrared spectrum was identical to that of the sample prepared in A and also an authentic sample.[12a,14] A mixture melting point with sample A and the authentic sample was not depressed.

14β,21-Epoxy-14β-pregnane-3,20-dione (VIIa).—To a solution of 3β-hydroxy-14β,21-epoxy-14β-pregnane-20-one (Vb, 370 mg.) in acetone (43 ml.) at 5° was added a solution of chromic acid (109 mg.) and concentrated sulfuric acid (0.093 ml.) brought to a volume of 0.41 ml. with water. The mixture was stirred at 5° for 5 min. and then diluted with water (190 ml.). The resultant white solid (320 mg.), m.p. 226–231°, was recrystallized five times from acetone–water, m.p. 232–236°; ν_{max} 1738, 1700 (sh), 1086, 1075 cm.$^{-1}$; $[\alpha]^{25}D$ −5° (chloroform).

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 75.76; H, 9.23.

4β-Bromo-14β,21-epoxy-14β-pregnane-3,20-dione (VIIb).—A solution of 14β,21-epoxy-14β-pregnane-3,20-dione (VIIa, 330 mg.) in chloroform (4.5 ml.), methylene chloride (4.5 ml.), and glacial acetic acid (1.13 ml.) was stirred and cooled to −40°. To the stirred solution was added a solution of bromine (0.052 ml.) in 30% hydrogen bromide in acetic acid (0.245 ml.) and glacial acetic acid (0.75 ml.) dropwise over a period of 1 hr. The reaction solution was stirred at −40° for an additional hour and then allowed to come to room temperature.

To the stirred reaction mixture was added a solution of anhydrous sodium acetate (164 mg.) in water (1.4 ml.) and stirring was continued for 30 min.

The organic solvents were evaporated at a bath temperature of 45–50° and water (19 ml.) was added. The resultant precipitate was collected as a white solid (367.5 mg.), m.p. 178–179° dec. Three recrystallizations from acetone–petroleum ether, and one recrystallization from acetone–water afforded VIIb (110 mg.), m.p. 191–192°; ν_{max} 1724, 1080 cm.$^{-1}$; $[\alpha]^{25}D$ +2.5° (chloroform).

Anal. Calcd. for $C_{21}H_{29}O_3Br$ (409.36): C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.22; H, 7.20; Br, 19.68.

14β,21-Epoxy-14β-pregn-4-ene-3,20-dione (VIII).—To a solution of 4β-bromo-14β,21-epoxy-14β-pregnane-3,20-dione (VIIb,

(24) Hunziker and Reichstein[14a] record a melting point of 235–237° and a rotation $[\alpha]^{22}D$ −68.7° ± 2° (chloroform) for this compound.

460 mg.) in dimethylformamide (15 ml.) purified over a molecular sieve was added lithium chloride (920 mg.). The mixture was purged with nitrogen and heated at 100–110° in a slow stream of nitrogen for 5.5 hr. The solution was cooled and methylene chloride (50 ml.) was added. The solution was washed with water and sodium bicarbonate solution. The organic extract was dried with magnesium sulfate and evaporated under reduced pressure at a bath temperature of 45–50°. The resultant white solid gave a positive Beilstein test for halogen and was chromatographed on Florisil.[21] The material was placed on the column with methylene chloride and eluted with 2% acetone–methylene chloride. The first four 100-ml. eluates on evaporation afforded white solids which by Beilstein test contained some halogen. The solids from cuts 5 through 14 were combined and the total 250 mg. was crystallized from acetone–water to yield white plates (212 mg.), m.p. 184–188°. Four recrystallizations from the same solvent pair gave VIII (76.5 mg.), m.p. 193–195°; λ_{max}^{MeOH} 240 mμ (ε 15,600); ν_{max} 1730, 1670, 1650 (sh), 1620, 1085, 1072 cm.$^{-1}$; $[\alpha]^{25}D$ +61° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.68; H, 8.68.

14β-Hydroxy-3,20-diketo-14β-pregnan-21-oic Acid 21,14-Lactone (IXa).—To a solution of 3β-hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb, 250 mg.) in acetic acid (10 ml.) was added a solution of chromic acid (250 mg.) in 90% acetic acid (2.5 ml.). The mixture was allowed to stand at room temperature for 18 hr., then diluted with methanol and water. The aqueous solution was extracted several times with ethyl acetate. The extract was washed with saturated sodium bicarbonate solution and water, dried with magnesium sulfate, and evaporated under reduced pressure. The residual gum, crystallized from acetone–water, afforded a white solid (130 mg.), m.p. 245–250°. Several recrystallizations from the same solvent pair raised the melting point to 255-256°; ν_{max} 1758, 1732, 1720, 1265, 1150 cm.$^{-1}$; $[\alpha]^{25}D$ −58° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 72.99; H, 8.57.

4β-Bromo-14β-hydroxy-3,20-diketo-14β-pregnan-21-oic Acid 21,14-Lactone (IXb).—To a solution of 14β-hydroxy-3,20-diketo-pregnan-21-oic acid 21,14-lactone (IXa, 490 mg.) in acetic acid (32 ml.) was added a solution of bromine (0.073 ml.) in acetic acid (8 ml.) over a period of 20 min. Water (80 ml.) was added dropwise and the resultant solid (446 mg.), m.p. 184–190° dec., was collected.

From the mother liquor, additional IXb (51 mg.), m.p. 195–196° dec., was collected. Two recrystallizations from acetone–water raised the melting point to 197° dec. Thin layer chromatographic analysis revealed homogeneity, only a single spot was revealed with phosphomolybdic acid.

Anal. Calcd. for $C_{21}H_{27}O_4Br$ (423.35): C, 59.57; H, 6.43; Br, 18.88. Found: C, 59.52; H, 6.77; Br, 19.84.

14β-Hydroxy-3,20-diketo-14β-pregn-4-en-21-oic Acid 21,14-Lactone (X). A.—To a solution of crude 4β-bromo-14β-hydroxy-3,20-diketo-14β-pregnan-21-oic acid 21,14-lactone (IXb, 230 mg.) in dimethylformamide (10 ml.) was added lithium chloride (430 mg.). The mixture was heated at 100–110° in a nitrogen atmosphere for 16 hr. The solution was cooled, diluted with methylene chloride, and the organic layer was separated and washed with saturated aqueous sodium bicarbonate solution and water, dried with magnesium sulfate, and evaporated *in vacuo*. The resultant gummy solid was chromatographed on Florisil.[21] The material was placed on the column with methylene chloride and eluted with 3% acetone–methylene chloride. The first eight 50-ml. eluates on evaporation afforded white solids which contained some halogen as shown by the Beilstein test. The solids from cuts 9 through 24 were triturated with 2 ml. of ethanol and yielded a white solid (48.2 mg.), m.p. 249–260°. Two crystallizations from acetone–water raised the melting point to 261–262°; λ_{max}^{MeOH} 234 mμ (ε 13,170); ν_{max} 1752, 1676, 1622, 1270, 1150 cm.$^{-1}$; $[\alpha]^{25}D$ −20° (chloroform).

Anal. Calcd. for $C_{21}H_{26}O_4$ (342.42): C, 73.66; H, 7.66. Found: C, 73.56; H, 7.79.

B.—To a solution of 14β,21-epoxy-14β-pregn-4-ene-3,20-dione (VIII, 84 mg.) in acetic acid (3 ml.) was added a solution of chromic acid (84 mg.) in 90% acetic acid (0.8 ml.). The mixture was allowed to stand at room temperature for 20 hr. and was then diluted with methanol and water. The aqueous solution was extracted several times with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate solution and water, dried with magnesium sulfate, and evaporated *in vacuo*. The residual white solid was crystallized from acetone–water and afforded crystals of X (42.8 mg.), m.p. 248–253°. One recrystallization from acetone–water gave white crystals (23 mg.), m.p. 259–262°; λ_{max}^{MeOH} 232 mμ (ε 14,200). The infrared spectrum was identical to that of the sample prepared in A preceding.

3β-Benzoyloxy-5,14-dihydroxy-19-methoxyimino-5β-card-20-(22)-enolide (XIc).—To a mixture of strophanthidin benzoate (XIb, 500 mg.) methoxyamine hydrochloride (500 mg.) and ethanol (50 ml.) was added a solution of anhydrous potassium acetate (1 g.) in water (10 ml.). The mixture was refluxed for 20 hr., diluted with water, and concentrated under reduced pressure. The resultant precipitate was collected as 440 mg. of white solid, m.p. 255–257°. Two recrystallizations from methanol–water afforded IXc (220 mg.), m.p. 258–260°; ν_{max} 3510, 1780, 1750, 715 cm.$^{-1}$; $[\alpha]^{25}D$ +49° (chloroform).

Anal. Calcd. for $C_{31}H_{39}O_7N$ (537.63): C, 69.25; H, 7.31; N, 2.60; CH_3, 2.61.[25] Found: C, 69.25; H, 7.51; N, 2.66; CH_3, 2.66.

3β-Benzoyloxy-5β,14β,21-trihydroxy-19-methoxyimino-14β-pregnan-20-one (XIIa).—A solution of methoxyimino strophanthidin benzoate (XIc, 2.88 g.) in pyridine (275 ml.) and ethyl acetate (275 ml.) was cooled to −60°. The solution was treated with a stream of ozone at a rate of 0.3 mmole per minute for 75 min. Excess ozone was removed from the reaction with a stream of oxygen until the blue solution turned colorless. To the stirred solution was added acetic acid (27.5 ml.) and zinc dust (5.5 g.) and the reaction temperature was allowed to come to room temperature. The mixture was heated at 60° and filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*, the residue was dissolved in toluene and the evaporation was repeated. The residual dark brown sirup was dissolved in a mixture of ethyl acetate (250 ml.) and water (100 ml.). The organic layer was separated, dried with magnesium sulfate, and evaporated *in vacuo* leaving a dark brown gum (2.7 g.). The crude reaction product was chromatographed on Florisil[21] and the 10% acetone–methylene chloride eluates were evaporated to a clear gum (1.2 g.). Crystallization of the gum from acetone–petroleum ether afforded XIIa (620 mg.), m.p. 187–193°. Four additional crystallizations from the same solvent pair yielded white plates (265 mg.), m.p. 193–196°; ν_{max} 3510, 3320, 1713 (sh), 1698, 1282, 722 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{39}O_7N$ (513.61): C, 67.81; H, 7.65; N, 2.73. Found: C, 67.21; H, 7.85; N, 2.77.

3β-Benzoyloxy-19,20-bismethoxyimino-14β-pregnane-5β,14β,-21-triol (XIIb).—To a mixture of ketol XIIa (440 mg.), methoxyamine hydrochloride (440 mg.), and ethanol (44 ml.) was added a solution of anhydrous potassium acetate (880 mg.) in water (8.8 ml.). The mixture was refluxed for 18 hr., diluted with water, and concentrated *in vacuo*. The resultant precipitate was collected, washed with water, and air-dried to yield 420 mg. of XIIb, m.p. 100–135°; ν_{max} 3575, 3450, 1718, 1692, 1280, 717 cm.$^{-1}$; $[\alpha]^{25}D$ +45° (chloroform); negative blue tetrazolium test.

Anal. Calcd. for $C_{30}H_{41}O_7N_2 \cdot H_2O$ (559.65): C, 64.38; H, 7.74; N, 5.00; CH_3, 5.36[25]; H_2O, 3.22. Found: C, 64.43; H, 7.95; N, 5.06; CH_3, 5.21; H_2O, 3.55.

Acknowledgment.—We wish to thank Louis M. Brancone and associates for the analytical data and William Fulmor and associates for the ultraviolet, infrared, and n.m.r. spectra and the optical rotational data. We also wish to thank Dr. J. Lancaster and M. Neglia of the Stamford Laboratories, American Cyanamid Company, for the n.m.r. spectrum of compound II. We further wish to acknowledge contributions of Dr. Lancaster in discussions concerning the n.m.r. data.

(25) The Zeisel OCH_3 determination was calculated as CH_3.

C-3 Substituted $\Delta^{1(10)}$-Steroids[1,2]

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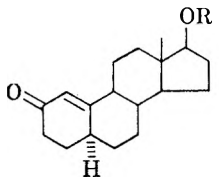
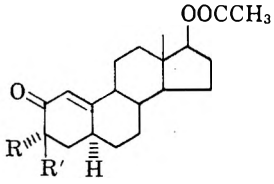
The synthesis of 17β-hydroxy-5α-estr-1(10)-en-3-one is described. The preparation of the corresponding 3α- and 3β-diols also is described. The isomerization of the $\Delta^{1(10)}$-3-ketone to the conjugated Δ^{1}-3-ketone is discussed.

In extension of our previous work[3] on novel 19-norsteroids we wish to report the synthesis of other ring A double bond isomers of 19-nortestosterone, *i.e.*, the $\Delta^{1(10)}$ and Δ^{1} compounds IVc and Va. The starting material employed was 17β hydroxy-5α-estr-1(10)-en-2-one (Ia), the preparation of which has been reported recently from this laboratory.[3] Lead tetraacetate oxidation of 17β acetoxy-5α-estr-1(10)-en-2-one (Ib) yielded a mixture of approximately equal amounts of the epimeric 3-acetoxy compounds IIa and IIb which were separated by chromatography on alumina. The 3α-acetoxy compound IIa, m.p. 147–9° $[\alpha]^{23}D$ −92, was eluted first, followed by the 3β-acetoxy compound IIb, m.p. 198–201° $[\alpha]^{23}D$ +5°. The orientation at C-3 of IIa follows from the epimerization of the axial 3α-acetoxy group with potassium acetate in refluxing glacial acetic acid[4] to give the more stable equatorial 3β-acetoxy compound IIb. The relative order of elution from the chromatogram was also consistent with these structures. With ethanedithiol in the presence of zinc chloride, the two epimeric ketol diacetates IIa and IIb gave the respective thioketal derivatives 2,2-ethylenedithio-5α-estr-1(10)-ene-3α,17β-diol diacetate (IIIa), m.p. 161–164°, and 2,2-ethylenedithio-5α-estr-1(10)-ene-3β,17β-diol diacetate (IIIb), m.p. 166–170°. The thioketal acetates IIIa and IIIb were hydrolyzed with methanolic alkali to give the 2-thioketal-3α,17β-diol IIIc, m.p. 104–110°, and 2-thioketal-3β,17β-diol IIId, m.p. 176–178°. Desulfurization of IIId with sodium in liquid ammonia[5] resulted also in the complete hydrogenolysis of the 3-hydroxyl group to give 5α-estr-1(10)-en-17β-ol (IVd), m.p. 107–110°, in excellent yield. The structure of this product was shown from its identity with the desulfurization product of 2,2-ethylenedithio-5α-estr-1(10)-en-17β-ol (IIIe). When, however, the desulfurization of the thioketal diols IIIc and IIId was effected with W2 Raney nickel in refluxing ethanol, no significant hydrogenolysis occurred and the unsaturated diols, 5α-estr-1(10)-ene-3α,17β-diol (IVa), m.p. 196–198°, and 5α-estr-1(10)-ene-3β,17β-diol (IVb), m.p. 208–211°, were obtained.

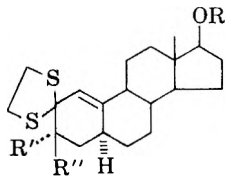
A recently described[6] minor oxidative side reaction during the desulfurization of similar compounds with deactivated Raney nickel suggested that with suitable modifications the side reaction might be enhanced to lead directly to a practical route to the desired β,γ-unsaturated ketone IVc. This indeed proved to be the case when the thioketal diol IIId was refluxed in acetone with Raney nickel which previously has been deactivated by boiling in acetone for twenty-four hours. The products consisted of a 20% yield of the 3β,17β-diol IVb, the normal desulfurization product, and a 50% yield of 17β-hydroxy-5α-estr-1(10)ene-3-one (IVc), m.p. 126–128° $[\alpha]^{24}D$ −36. This latter compound exhibited a single carbonyl in the infrared at 1723 cm.$^{-1}$ in carbon tetrachloride, while the ultraviolet spectrum showed only end absorption. In a similar desulfurization of the epimeric diol IIIc a smaller proportion of the ketone IVc was obtained. This difference in yield could be due to the stereochemistry at C-3, or to the difficulty in duplicating the desulfurization conditions exactly. Reduction of the β,γ-unsaturated ketone IVc with lithium tri-*t*-butoxy aluminum hydride[7] led exclusively and in good yield to the equatorial 3β,17β-diol IVb which serves to confirm the structure of IVc as

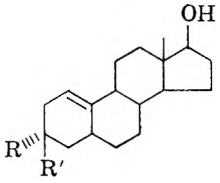


Ia. R = H
b. R = CH_3CO



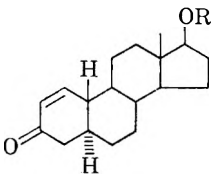
IIa. R = CH_3COO, R′ = H
b. R = H, R′ = CH_3COO





IIIa. R = CH_3CO, R′ = CH_3COO, R″ = H
b. R = CH_3CO, R′ = H, R″ = CH_3COO
c. R = R″ = 4, R′ = OH
d. R = R′ = H, R″ = OH
e. R = R′ = R″ = H

IVa. R = OH, R′ = H
b. R = H, R′ = OH
c. R, R′ = O
d. R = R′ = H



Va. R = H
b. R = CH_3CO

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

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(7) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958); J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

well as the correctness of the assigned configurations at C-3 in the original acetoxy compounds IIa and IIb.

The isomerization of the β,γ-unsaturated ketone IVc to the conjugated ketone Va with mineral acids at room temperature proved to be unusually slow. With 5% hydrochloric acid in methanol the isomerization reached its maximum only after five days at 25°. At reflux temperatures the isomerization was more rapid (two hours) but the yield was only about 50% as determined by absorption at 228 mμ and the product was difficult to isolate pure. This is in marked contrast to the isomerizations of the Δ^5- and $\Delta^{5(10)}$-3-ketones[8,9] under similar conditions since these proceed rapidly and give essentially single products in good yields. Although a new center of asymmetry is created at C-10 during the isomerization only the 10β compound Va, m.p. 147–149°, λ_{max}^{EtOH} 229 mμ (ϵ 10,000), was isolated.[10] On catalytic hydrogenation Va gave the known 17β-hydroxy-5α-estran-3-one.[11] Acetylation of Va gave the 17-acetate derivative Vb identical in all respects with that prepared by another route.[12,13] Hydrolysis of the 17-acetate in Vb by acid gave very poor yields of the ketone Va and the product was difficult to obtain in a pure state. This result together with the difficulty encountered in the isomerization of IVc suggest that the equilibrium between the β,γ-unsaturated ketone IVc and its α,β-unsaturated isomer Va does not favor the latter to the extent usual under such circumstances. Consequently, the 1(10)-double bond probably migrates to other positions in the molecule to yield a variety of isomers which may account for the low yield and difficulty in purification of the conjugated ketone Va.[14]

Among the most useful steroids in current clinical use are the 17α-ethynyl derivatives of 19-nortestosterone and its $\Delta^{5(10)}$ isomer. Both compounds are potent oral progestrogens[15,16] and have found wide acceptance as anovulatory agents. Although the physiological activities of these two double bond isomers are similar, significant differences do exist.[17] Since the new compounds reported in this paper represent further double bond isomers of the 19-nortestosterone structure, they or their derivatives may prove to be of biological significance.

Experimental[18]

17β-Acetoxy-5α-estr-1(10)-en-2-one (Ib).—A solution of 1 g. of 17β-hydroxy-5α-estr-1(10)-en-2-one (Ia) in 10 ml. of pyridine and 10 ml. of acetic anhydride was allowed to stand overnight at room temperature. After the usual work-up, the residue was crystallized from acetone–petroleum ether to give 940 mg. of the product Ib as white needles, m.p. 161–164°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.04; H, 9.15.

Lead Tetraacetate Oxidation of Ib.—To a solution of 7 g. of Ib in 100 ml. of glacial acetic acid was added 16 g. of lead tetraacetate in 275 ml. of glacial acetic acid. After heating on a steam bath for 4 hr., an additional 12 g. of lead tetraacetate was added, and the mixture was heated on a steam bath for another 20 hr. The acetic acid then was removed at reduced pressure and the residue was taken up in water and extracted four times with ether (800 ml.). The ether extract was washed with 5% sodium bicarbonate solution until basic and then with water. After drying, the ether was evaporated and the amber colored residue was taken up in 1:1 benzene–petroleum ether and chromatographed on 450 g. of acid-washed alumina. Elution with benzene gave 2.56 g. of crystals which were recrystallized from ether–petroleum ether to give **2-oxo-5α-estr-1(10)-ener-3α,-17β-diol diacetate (IIa)**, m.p. 140–145°. The analytical sample was obtained from the same solvents and melted at 147–149° $[\alpha]^{23}D$ −92°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.43; H, 8.07.

Further elution with benzene containing 10% ether gave 2.2 g. of crystals, which on recrystallization from ether–petroleum ether gave **2-oxo-5α-estr-1(10)-ene-3β,17β-diol diacetate (IIb)**, m.p. 195–200°. The analytical sample was obtained from the same solvents and melted at 198–201° $[\alpha]^{23}D$ +5°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.38; H, 8.28.

Epimerization of 2-oxo-5α-estr-(1(10)-ene-3α,17β-diol Diacetate (IIa).—A mixture of 10 mg. of IIa and 50 mg. of anhydrous potassium acetate in 3 ml. of glacial acetic acid was refluxed for 17 hr. On cooling, the reaction mixture was poured into water and extracted with ether which then was washed with dilute sodium bicarbonate solution and water. After drying and evaporating the ether, the residue was triturated with ether to give crystals, m.p. 194–200°, identical with the 3β,17β-diacetate IIb, by mixture melting point and infrared spectra comparison.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3α,17β-diol Diacetate (IIIa).—To a solution of 0.48 g. of IIa in 15 ml. of dioxane was added 6.3 g. of freshly fused zinc chloride, 6.3 g. of anhydrous sodium sulfate, and 1.5 ml. of ethanedithiol. After standing at room temperature overnight, the mixture was poured into cold dilute ammonium hydroxide and the white precipitate was filtered off and washed with water. The precipitate was dissolved in acetone, filtered, and the filtrate evaporated to dryness to give 0.60 g. of crude product, m.p. 154–160°. Recrystallization from ether gave the analytical sample of IIIa, m.p. 161–164° $[\alpha]^{21}D$ +30°.

Anal. Calcd. for $C_{24}H_{34}O_4S_2$: C, 63.96; H, 7.61; S, 14.23. Found: C, 64.11; H, 7.77; S, 14.62.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3β,17β-diol Diacetate (IIIb).—A 1-g. sample of IIb was converted to 1.3 g. of crude thioketal IIIb exactly as in the preceding procedure. The analytical sample obtained from ether melted at 166–171° $[\alpha]^{20}D$ −34°.

Anal. Calcd. for $C_{24}H_{34}O_4S_2$: C, 63.96; H, 7.61. Found: C, 63.65; H, 7.68.

2,2-Ethylenedithio-5α-estr-1(10)-en-17β-ol (IIIe).—A 0.1-g. sample of the unsaturated ketone Ia was converted to the thioketal IIIe by the same procedure. The product crystallized from petroleum ether–acetone to give needles (0.11 g.) which melted at 171–175° $[\alpha]^{21}D$ +10°.

Anal. Calcd. for $C_{20}H_{30}OS_2$: C, 68.52; H, 8.63; S, 18.29. Found: C, 68.48; H, 8.59; S, 17.94.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3α,17β-diol (IIIc).—A solution of 0.25 g. of IIIa in 30 ml. of 5% methanolic potassium hydroxide was refluxed for 3 hr. The solution was diluted with water and extracted well with ether which was washed with 5% sulfuric acid solution and then with 5% sodium bicarbonate solution and water. After drying and evaporation of solvent, the residue was crystallized from acetone–petroleum ether to give 0.21 g. of IIIc, m.p. 100–110°. The analytical sample was ob-

(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 50.

(9) A. J. Birch, *Quart. Rev.*, **4**, 49 (1950); A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(10) This compound has been reported in the patent literature, however, without physical constants: U. S. Patent 3,007,947; *Chem. Abstr.*, **56**, 7393 (1962).

(11) A. Bowers, H. J. Ringold, and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958).

(12) R. Villotti, H. J. Ringold, and C. Djerassi, *ibid.*, **82**, 5693 (1960).

(13) U. S. Patent 3,007,947; *Chem. Abstr.*, **56**, 7393 (1962).

(14) In isomerization of a Δ^4-2-ketone to Δ^3-2-ketone, a comparable situation, no crystalline product is obtained and no yield is specified.[6] The authors explain their results as being due to the formation of 5α and 5β isomers. In our case the formation of two isomers at C-10 is not likely since the energetically unfavorable 10α *syn* structure would not be expected to result from the isomerization.

(15) D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958).

(16) F. J. Saunders and V. A. Drill, *Endocrinology*, **58**, 567 (1956).

(17) V. A. Drill, *Fed. Proc.*, **18**, 1040 (1959).

(18) Melting points were determined on a Kofler block and are corrected. Rotations were determined in chloroform unless specified otherwise. Microanalyses were determined by Spang Microanalytical Laboratories.

tained from the same solvents and melted at 104–110° $[\alpha]^{23}D$ +8°.

Anal. Calcd. for $C_{20}H_{30}O_2S_2$: C, 65.24; H, 8.19. Found: C, 65.43; H, 8.49.

2,2-Ethylenedithio-5α-estr-1(10)-ene-3β,17β-diol (IIId).—Hydrolysis of 1.2 g. of IIIb, by the same procedure, gave 0.90 g. of IIId, m.p. 166–170°. The analytical sample obtained from acetone–petroleum ether melted at 176–178° $[\alpha]^{23}D$ +64°.

Anal. Calcd. for $C_{20}H_{30}O_2S_2$: C 65.42; H, 8.19; Found: C, 65.44; H, 8.12.

5α-Estr-1(10)-en-17β-ol (IVd). A. From IIId.—A solution of 0.10 g. of IIId in 20 ml. of tetrahydrofuran was added to 100 ml. of liquid ammonia. To the stirred solution, sodium ribbon was added portionwise until the blue color persisted. After 3 min. of stirring the blue color was discharged with ethanol and the ammonia was allowed to evaporate. The residue was taken up in water and extracted with ether. The ether was dried and evaporated and the residue crystallized from petroleum ether to give 58 mg. of IVd, m.p. 107–110°. The analytical sample showed an unchanged melting point $[\alpha]^{21}D$ −30°.

Anal. Calcd. for $C_{18}H_{20}O$: C, 83.05; H, 10.8. Found: C, 83.20; H, 10.6.

B. From IIIe.—A 50-mg. sample of IIIe was desulfurized as above, to give 30 mg. of IVd, m.p. 106–110°, identical with that prepared before by mixture melting point and infrared spectra comparison.

5α-Estr-1(10)-ene-3α,17β-diol (IVa).—A solution of 80 mg. of the thioketal IIIc in 20 ml. of ethanol was refluxed with 2.5 g. of Raney nickel (W2) for 2 hr. The nickel was filtered off and washed well with ethanol. The filtrate was evaporated to dryness to give 60 mg. of crystals, m.p. 180–190°. Recrystallization from ether gave 47 mg. of the diol IVa, m.p. 194–197°. The analytical sample melted at 196–198° (with sublimation) $[\alpha]^{23}D$ −68.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.2. Found: C, 78.16; H, 9.90.

5α-Estr-1(10)-ene-3β,17β-diol (IVb). A. By Desulfurization.—A 0.1-g. sample of the thioketal IIId was desulfurized with 3 g. of Raney nickel as described. The product was crystallized from dilute methanol to give 70 mg. of crystals, m.p. 194–198°. The analytical sample was obtained from ether, m.p. 208–211° (changes to prisms) $[\alpha]^{23}D$ −4.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.2. Found: C, 78.27; H, 10.4.

B. By Reduction of IVc.—A 25-mg. sample of unsaturated ketone IVc was allowed to stand with lithium tri-*t*-butoxy aluminum hydride in tetrahydrofuran at room temperature for 1 hr. After the usual work-up, 20 mg. of crystals was obtained from ether, m.p. 205–210°. This was identical with the product of method A by mixture melting point and infrared spectra comparison.

17β-Hydroxy-5α-estr-1(10)-en-3-one (IVc).—A suspension of 20 g. of Raney nickel in 400 ml. of acetone was refluxed for 20 hr. To this suspension, a solution of 0.8 g. of the thioketal diol IIId in 50 ml. of acetone was added, and the mixture was refluxed for 4 hr. After filtration the solvent was evaporated and the residue taken up in benzene and chromatographed on 50 g. of acid washed alumina. Elution with benzene gave first 45 mg. of recovered starting material IIId. Further elution with benzene gave 310 mg. of the ketone IVc, which on recrystallization from acetone–petroleum ether melted at 121–125°. The analytical sample obtained from the same solvents melted at 124–126°, $[\alpha]^{23}D$ −36. Carbonyl band absorption in the infrared was at 1723 $cm.^{-1}$ in carbon tetrachloride; only end absorption was observed in the ultraviolet.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.68; H, 9.57.

Subsequent elution of the column with ether and ether–chloroform mixtures gave 113 mg. of the 3β,17β diol IVb.

A similar desulfurization on 0.4 g. of the thioketol diol IIIc gave 45 mg. of the ketone IVc and 0.1 g. of the 3α,17β-diol IVa plus 0.11 g. of recovered starting material.

17β-Hydroxy-5α-estr-1-en-3-one (Va). A. Isomerization of IVc.—A small sample of IVc (10 mg.) was dissolved in 3 ml. of methanol and 1 ml. of 3 *N* hydrochloric acid was added. The solution was allowed to stand at room temperature with aliquots being withdrawn to measure ultraviolet absorption at 229 mμ. Only after 5 days did the absorption at 229 mμ reach a maximum. Longer standing resulted in a decrease in the absorption. A similar study at steam bath temperatures indicated that 2 hr. was the optimum time.

A solution of 80 mg. of the unsaturated ketone IVc in 25 ml. of ethanol and 5 ml. of 3 *N* hydrochloric acid was refluxed on a steam bath for 2 hr. After the usual work-up the residue was subjected to quantitative thin layer chromatography on silica gel containing a zinc phosphor. The main ultraviolet absorbing zone was eluted to give 16 mg. of an oil which crystallized slowly from acetone–petroleum ether to give 10 mg. of the conjugated ketone Va, m.p. 145–147° $[\alpha]^{21}D$ +100 (ethanol), λ_{max}^{EtOH} 229 mμ (ε 10,000).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.56; H, 9.19.

A less polar, nonultraviolet absorbing zone contained 22 mg. of the starting material, IVc. There were also present four other zones which yielded small amounts of intractable oils.

B. Hydrolysis of Vb.—A solution of 80 mg. of Vb in 10 ml. of methanol and 5 ml. of 5% sulfuric acid was refluxed overnight. After the usual work-up the oily residue was chromatographed on a thin layer silica plate. Six different zones were obtained, one of which on elution gave 10 mg. of oil, the infrared spectrum of which was identical with 17β-hydroxy-5α-estr-1-en-3-one (Va).

Acetylation of Va.—A 4-mg. sample of Va was acetylated in the usual manner. On work-up, crystalline material was obtained, which on recrystallization from petroleum ether melted at 132–136°, identical with 17β-acetoxy-5α-estr-1-en-3-one (Vb) by mixture melting point and infrared spectra comparison.

Hydrogenation of Va.—An 8-mg. sample of Va was hydrogenated in ethanol over 10% palladized charcoal. The crystalline product showed no specific ultraviolet absorption and after a Girard T separation the ketonic material, 4 mg., m.p. 124–128°, proved to be identical with 19-nordihydrotestosterone by mixture melting point and infrared spectra comparison.

Acknowledgment.—The author wishes to thank Dr. T. F. Gallagher for his interest and support of this work. He also wishes to thank Mrs. Beatrice Gallagher for the determination of the infrared spectra. The assistance of Mrs. Julia Liang and Mrs. Rosemarie Lehman is also gratefully acknowledged.

A Stereospecific Synthesis of C-21-Methylated Corticosteroids[1a,d]

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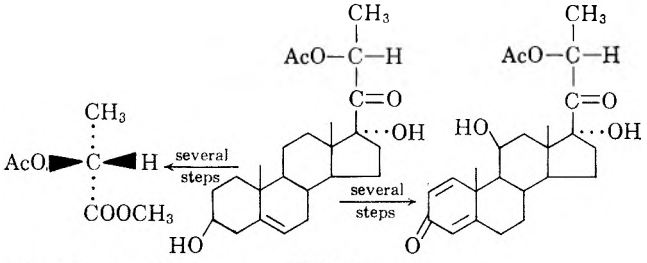
Reduction of 20,21-diketones with fermenting yeast occurs selectively and stereospecifically at C-21 to produce *one* of four possible dihydro derivatives, the 21α_F-hydroxy-21-methyl corticoid. The required 20,21-diketones are best prepared from halohydrins obtainable by hydrogen halide cleavage of 21-methyl-21,21a-epoxides. The latter are prepared by the action of diazomethane on 21-aldehydes.

The rationale for the synthesis of C-21-methylated corticosteroids has been presented in preliminary communications from this laboratory[1] and the glucocorticoid and mineralocorticoid activities of this class of compounds have been reported in recent publications.[2] The present communication provides the details of a synthesis reported earlier in preliminary form.[1a,d] The sequence in its preferred form involves the following transformations: (1) treatment of a C-21 aldehyde with diazomethane to produce a 21-methyl-21,21a-epoxide, (2) opening of the epoxide with hydrogen halide, (3) dehydrohalogenation of the halohydrin with concomitant rearrangement to a 21-methyl-20,21-diketone, and (4) selective reduction of the C-21 carbonyl group to afford the desired C-21-methylated corticoid.

One of the noteworthy advantages of this short synthetic sequence is its applicability to a large variety of complex starting materials, a feature arising from the selective nature of the reagents employed. Another important characteristic of this route is the formation of only *one* (the 21α_F-hydroxy derivative[5]) of each pair of epimeric 21-methyl corticoids by virtue of the stereospecific nature of the reduction of 20,21-diketones by fermenting yeast or sodium borohydride. These tures make available a convenient synthesis of 21-methyl-21α_F-hydroxy corticoids from virtually all of the common steroids containing a dihydroxyacetone side chain, even those bearing several nuclear substituents, without the necessity for employing protective groups.

The usefulness of this synthetic sequence is further enhanced by the availability of a method, recently reported from this laboratory,[1c] for interconverting 21α_F- and 21β_F-hydroxy corticoids *via* their 21-mesylates by displacement with acetate. Thus, the direct conversion of a highly substituted corticoid to either of its two epimeric 21-methyl derivatives can be accomplished readily. Forthcoming publications will describe the details of alternate routes to pairs of epimeric 21-methyl corticoids which involve introduction of the 21-methyl group into simple, readily available starting materials prior to elaboration of the remainder of the molecule.

11β,17 - Dihydroxy - 3,20 - dioxopregna - 1,4 - dien-21-al (prednisolone 21-aldehyde) (I)[6] reacted rapidly[7] with ethereal diazomethane and the major product (40% yield) was 21-methyl-21,21a-epoxy-11β,17-dihydroxypregna-1,4-diene-3,20-dione (II). The epoxide structure was assigned to this product on the basis of its elemental analysis, spectral properties, and reactions with hydrogen halides. Confirmation of the presence of the intact tetracyclic steroid nucleus was obtained by cleavage of the side chain of II with periodic acid (a slow reaction, as expected) and isolation of 11β-hydroxyandrosta-1,4-diene-3,17-dione.[9] Among the five diazomethane reaction by-products detectable by paper chromatography an isomer of II was isolated which



D-(−)-Lactic acid methyl ester acetate

XXIV

11β,17,21β_F-Trihydroxy-21-methylpregna-1,4-diene-3,20-dione 21-acetate (formerly 21A-ol)

(1) For preliminary reports of this work see: (a) E. J. Agnello, S. K. Figdor, G. M. K. Hughes, H. W. Ordway, R. Pinson, Jr., B. M. Bloom, and G. D. Laubach, Abstracts of Papers presented at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, p. 20-N; (b) S. K. Figdor, R. Pinson, Jr., H. W. Ordway, E. J. Agnello, B. M. Bloom, and G. D. Laubach, *ibid.*, p. 21-N; (c) H. J. Hess, S. K. Figdor, G. M. K. Hughes, R. Pinson, Jr., and W. T. Moreland, Abstracts of Papers presented at the 138th National Meeting of the American Chemical Society, New York City, N. Y., September, 1960, p. 39-P; (d) E. J. Agnello, R. Pinson, Jr., S. K. Figdor, G. M. K. Hughes, H. W. Ordway, B. M. Bloom, and G. D. Laubach, *Experientia*, **16**, 357 (1960).

(2) The recently reported results of pharmacological[3] and clinical[4] studies with 21-methyl-9-fluoro-11β,17,21α_F-trihydroxypregna-1,4-diene-3,20-dione (P-1742) (XIV) demonstrate the effectiveness of the 21-methyl function in eliminating the undesirable salt-retaining activity of 9-fluoroprednisolone with only partial reduction of its glucocorticoid activity. Thus, introduction of this substituent transforms 9-fluoroprednisolone into a systemically useful anti-inflammatory agent.[4]

(3) (a) J. G. Llaurado and J. A. Schneider, *Fed. Proc.*, **19**, 159 (1960); (b) J. G. Llaurado, *Acta Endocrinol.*, **38**, 137 (1961).

(4) E. W. Boland, *Am. J. Med.*, **31**, 581 (1961).

(5) (a) Prior to the present publication, the 21-methyl corticoids which were obtained by the reduction of 20,21-diketones with fermenting yeast were arbitrarily designated 21B-ols to differentiate them from the epimeric compounds (designated 21A-ols) prepared by another route. Subsequent stereochemical studies[5b] (the details of which will appear in a forthcoming publication) have established the absolute configuration of the epimeric 21-methyl corticoids, thus allowing the designation of the yeast reduction products as 21α_F-hydroxypregnane derivatives (Fischer convention) or as 17β-[(S)-2-acetoxypropionyl]androstane derivatives (Cahn–Ingold–Prelog convention[27b]). (b) one of the intermediates (XXIV)[1c] belonging to the series originally designated 21A-ols was cleaved at the C-17–C-20 bond and the nonsteroidal fragment was converted in several steps to methyl α-acetoxypropionate. Identification of this product as a derivative of D-(−)-laetic acid establishes its absolute configuration and makes it possible to designate the stereochemistry of XXIV and all other members of the series as 21β_F-ols. Compounds of the opposite configuration (originally designated 21B-ols) are therefore correctly designated 21α_F-ols.

(6) B. G. Christensen, N. G. Steinberg, and R. Hirschmann, *Chem. Ind.* (London), 1259 (1958).

(7) The rapidity of this reaction is noteworthy in view of the recently reported[8] sluggish nature of the reaction of C-20 and C-3 ketones with diazomethane. The difference in rates makes possible the use of the present reaction sequence with complex steroids.

(8) A. L. Nussbaum and F. E. Carlon, *J. Am. Chem. Soc.*, **79**, 3831 (1957).

(9) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro E. P. Oliveto, and E. B. Hershberg, *ibid.*, **77**, 4781 (1955).

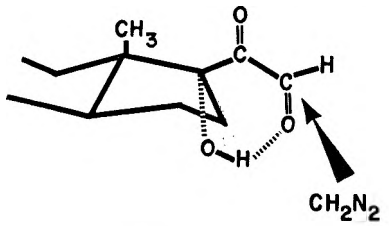
proved to be 21-methyl-11β,17-dihydroxypregna-1,4-diene-3,20,21-trione (III).[10] The α-diketone structure of III was demonstrated by its reaction with *o*-phenylenediamine to form a quinoxaline (VIIIb) possessing ultraviolet absorption spectral characteristics closely resembling those of the quinoxaline (VIIIa) obtained from prednisolone 21-aldehyde (I). The infrared spectrum, elemental analysis, and subsequent transformations of this product also were consistent with the assigned α-diketone structure.

Treatment of the 21,21a-epoxide with hydrogen halides opened the ring predominantly at the terminal carbon atom affording the desired halohydrins [*e.g.*, 21 - chloromethyl - 11β,17,21 - trihydroxypregna - 1,4-diene-3,20-dione (IV)] with hydroxyl at C-21.[11,12] Location of this new hydroxyl function was based on cleavage of IV with periodic acid, which afforded 11β,-17α - dihydroxyandrosta - 1,4 - dien - 3 - one - 17-carboxylic acid,[13] and upon subsequent reactions described.

Preliminary exploration of methods for transforming the C-22 steroids prepared in this way to one or both of the epimeric 21-methylprednisolones led to the choice of diketone III as the most useful intermediate and, therefore, to a search for a more efficient synthesis of 20,21-diketones. It was hoped that the desired diketone would be formed readily from epoxide II by one of the methods commonly employed for epoxide-to-ketone conversion.[14a] However, most of the attempts to convert the epoxide directly to III resulted in disappointingly low yields. For example, treatment of II with anhydrous hydrogen chloride in refluxing ethyl acetate afforded 30% of crystalline diketone.[15]

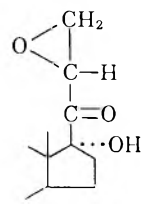
An unexpected and superior method of preparing diketone III was discovered during an attempt to oxidize the 20,21-ketol moiety of IV to the 21-chloromethyl 20,21-diketone VII, from which halogen presumably would be removed more readily by hydrogenolysis. For this purpose a modification of the method of Rigby,[16] which utilizes bismuth trioxide for the oxidation of acyloins to diketones, was employed. However the reaction did not proceed as expected (there was no apparent reduction of the reagent to elemental bis-

(10) With the exception of III the structures of the by-products (each of which assayed less than 5% by paper chromatographic analyses) have not been elucidated. The possibility exists that one of them is the C-21-epimer of epoxide II. However, the absence of significant quantities of the epimer indicates either that it is formed in less than 5% yield due to attack of diazomethane on I from a preferred direction or that the epimer is unstable and decomposes to other products. We favor the former explanation (attack from the less hindered side as shown in XXVI) in view of the likelihood that the aldehyde exists in a *trans* configuration.[10a] This conformation

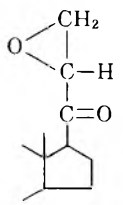


XXVI

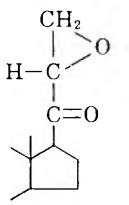
is favored not only by the strong repulsive forces of the dipoles of the carbonyl groups but by the possibility for hydrogen bonding between 17-hydroxyl and 21-carbonyl when the configuration is as shown in XXVI. If the attack of diazomethane on the 21-carbonyl carbon is as postulated above, the absolute stereochemistry of the resulting epoxide can be predicted as belonging to the 21βF-series (XXVII). Supporting data for this configurational assignment will be presented in a subsequent paper from this laboratory. An observation which may be relevant to the degree of



XXVII



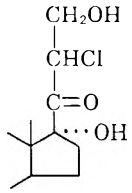
XXVIII



XXIX

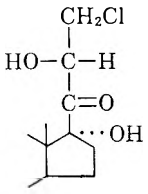
hydrogen bonding in XXVI is the isolation of *two* major products (rather than one) from the reaction of a 17-desoxysteroid 3,20-dioxopregn-4-en-21-al (desoxycorticosterone 21-aldehyde) with diazomethane. The products are isomeric $C_{22}H_{28}O_3$ compounds and are tentatively assigned the epoxide structures XXVIII and XXIX on the basis of their elemental analyses, infrared spectra, and their conversion to halohydrins. (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1956. pp. 233–234.

(11) The reaction of epoxide II with hydrogen chloride invariably produced a minor by-product for which the not unlikely isomeric chlorohydrin structure VI cannot be ruled out by the available data. In contrast to chlorohydrin II, the minor product did *not* produce a color in the tetrazolium test for 20,21-ketols.



VI

(12) If the stereochemistry of epoxide II is as shown in structure XXVII,[10] then the halohydrins will of necessity have the same absolute configuration at



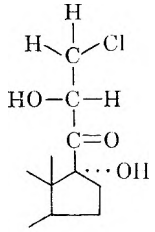
IV

C-21 as the epoxides, *i.e.*, they will belong to the 21βF-hydroxy series (*e.g.*, IV above). Supporting evidence for this assignment was obtained by the use of molecular rotation differences and optical rotatory dispersion and will be presented in a forthcoming publication.

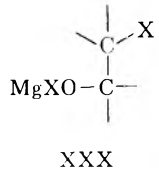
(13) R. Hirschmann, G. Bailey, and J. M. Chemerda, *Chem. Ind.* (London), 682 (1958).

(14) (a) S. Winstein and R. R. Henderson, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 27–58; (b) S. Winstein and R. R. Henderson, *ibid.*, p. 49.

(15) Examination by paper chromatography of aliquots of the reaction mixture during the course of the reaction showed the presence of a compound identical to chlorohydrin IV in mobility and behavior toward blue tetrazolium reagent. Confirmation of the existence of IV as an actual intermediate in the conversion of II to III by isolation of IV might be useful in the elucidation of the mechanism of oxide openings. It has been pointed out by Winstein and Henderson[14b] that it is often not clear whether the oxide rearranges or whether an intermediate is produced (by the acid catalyst) which actually rearranges, *e.g.*, in the magnesium bromide-catalyzed rearrangement of oxide to ketone the halomagnesium salt (XXX) of the halohydrin is formed and this species rearranges. In the case presently under discussion the intermediate which would be analogous to XXX would be chlorohydrin IV. It is known (see text) that IV is converted to III under these conditions.



IV



XXX

(16) W. Rigby, *J. Chem. Soc.*, 793 (1951).

muth), and the major steroidal product proved to be the diketone III.[17a]

Subsequent to the discovery of the effectiveness of bismuth trioxide it was found that other reagents, *e.g.*, anhydrous hydrogen chloride in refluxing ethyl acetate, also were effective in the dehydrohalogenation and rearrangement of chlorohydrin IV to diketone III. Furthermore, the dehydrohalogenation occurred even more readily when bromohydrin V or iodohydrin XI were employed. In contrast to the more stable chlorohydrin, bromhydrin V lost the elements of hydrogen bromide simply upon being heated in refluxing ethyl acetate (without added acid), and solutions of iodohydrin underwent significant decomposition even at room temperature. The most efficient of the above methods utilized bromohydrin V as an intermediate. Thus, when oxide I was treated with methanolic hydrogen bromide and the resultant crude bromohydrin was heated in refluxing ethyl acetate for a period of one to two hours, the elements of hydrogen bromide were lost and 21-methyl-11β,17-dihydroxypregna-1,4-diene-3,20-21-trione (III) was isolated in approximately 50% yield (based on I).

Although the mechanism(s) of the above dehydrohalogenative rearrangement reactions have not been elucidated, it has been established that the analogous 17-unsubstituted halohydrins are stable under reaction conditions which are effective in the 17-hydroxylated series. It would appear, therefore, that the 17-hydroxyl group participates in the reaction, *e.g.*, by assisting in the ionization of halogen *via* hydroxyl–halogen interaction[17b] in C-20–C-21 enol form (Fig. A) which is a

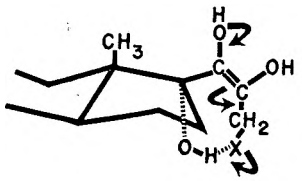


Figure A

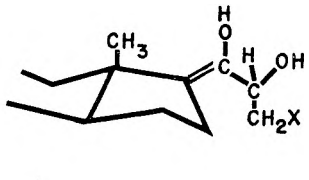
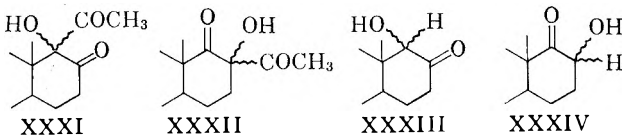


Figure B

likely intermediate. A less reasonable alternative for the lack of reactivity in the 17-desoxy series involves enolization in the opposite direction to afford the C-17–C-20 enol (Fig. B) which would be unfavorable for further reaction. This alternative is not likely, however, since there is evidence that 17-desoxy-20,21-ketols do indeed enolize to the C-20–C-21 enol form.[17c]

(17) (a) An isomeric by-product (XX) also was isolated from this reaction. An attempt to oxidize IV with cupric acetate also gave XX as a major product (part of a mixture) but no diketone III was detected. Although the structure of XX has not been established definitely, the D-homo structures XXXI and XXXII are likely possibilities for the following reasons: (1) treatment with strong alkali gave a new product resulting from the loss of



XXXI XXXII XXXIII XXXIV

C_2H_4O fragment; (2) elemental analyses and infrared spectra were consistent with structures XXXI or XXXII for the original compound XX and with XXXIII or XXXIV for the alkaline degradation product. (b) Another case of hydrogen bonding to halogen (C-17α hydroxyl and C-12α halogen) was reported recently: P. A. Diassi, J. Fried, R. M. Palmere, and E. F. Sabo, *J. Am. Chem. Soc.*, **83**, 4249 (1961). (c) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 573 (1951).

The effectiveness of bismuth trioxide in this transformation probably is related to the complexing ability of bismuth and/or the tendency for the formation of the sparingly soluble bismuthyl chloride (BiOCl)[18] since other oxides (*e.g.*, aluminum oxide, cupric oxide) or acetates (*e.g.*, potassium acetate) are without effect on IV under identical conditions.[19] The role of acid in the observed loss of the elements of HX from the halohydrins in ethyl acetate[20] might consist of promoting their conversion to the proposed enol form (Fig. A) which would be favorable for elimination.

Selective reduction of the 21-carbonyl group of diketone III, required to complete the synthesis of 21-methylprednisolone, could be accomplished by only two of the numerous methods explored. The more satisfactory one was the action of fermenting yeast[21] which gave 21-methyl-11β,17,21α_F-trihydroxypregna-1,4-diene-3,20-dione (XII)[5] in 50–60% yield. No major by-products were detectable.

Reduction of the 20,21-diketone III with sodium borohydride also occurred predominantly at C-21 to form the desired ketol XII, but this was accompanied by a substantial amount of the 20-dihydro derivative 21-methyl-11β,17,20-trihydroxypregna-1,4-diene-3,21-dione (XIII). In view of the well known tendency of sodium borohydride reduction of 20-ketosteroids to produce 20β_F-hydroxyl derivatives[22] the β-configuration would be predicted for the C-20 hydroxyl group of XIII. Additional support for this tentative assignment of configuration was obtained from the observation that microbiological reduction of III with *Streptomyces erythreus*,[23] an organism which is known to reduce other 20-keto steroids to the 20β_F-hydroxy derivatives,[24a,b] afforded the same 20-dihydro product XIII. Assignment of the 20β_F-hydroxy configuration to by-product XIII is also favored by the probable *trans* oriented nature of the diketone[10a] and the expected attack of the borohydride anion from its less hindered side,[22] *i.e.*, the side away from the angular methyl group. Thus, the product which would be predicted from attack on the 21-carbonyl group (XXXV) is the observed 21α_F-hydroxy derivative. Attack from this same side on the 20-carbonyl group

(18) (a) The tendency of bismuth salts to be converted to very insoluble bismuthyl halides (BiOX) is well known and can occur at pHs at least as low as 1.2. *Cf.* J. D. Moyer and H. S. Isbell, *Anal. Chem.*, **30**, 957 (1958). (b) K. B. Yatsimirskii and V. P. Vasilev, "Instability Constants of Complex Compounds," Consultants Bureau, New York, N. Y., 1960. (c) Chelates of the dihydroxyacetone moiety with trivalent metals are known. *Cf.* K. Bernauer and S. Fallab, *Helv. Chim. Acta*, **40**, 1690 (1957), and J. W. Fisher, U. S. Patent 3,010,975 (November 28, 1961).

(19) The ineffectiveness of potassium acetate in *acetic acid* eliminates the possibility that the basic properties of bismuth trioxide might be involved in the elimination of the elements of hydrogen chloride. Interestingly, however, when IV was heated with potassium acetate *in acetone* a good yield of diketone III was isolated.

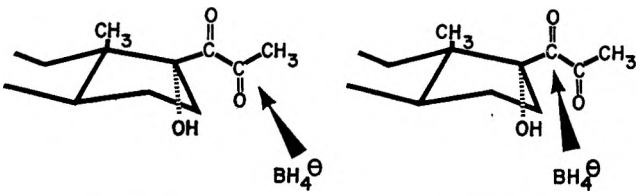
(20) (a) The observed order of stability of the halohydrins is the one which would be predicted on the basis of the ease of heterolysis of the carbon–halogen bond.[20b] Thus chlorohydrin requires an added catalyst while bromohydrin and iodohydrin do not (possibly due to the presence of sufficient amounts of residual HX in these more favorable cases). (b) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 338–339.

(21) C. Neuberg, "Advances in Carbohydrate Chemistry," Vol. 4, Academic Press, Inc., New York, N. Y., p. 86.

(22) L. L. Smith, J. J. Garbarini, J. J. Goodman, M. Marx, and H. Mendelsohn, *J. Am. Chem. Soc.*, **82**, 1437 (1960), and references contained therein.

(23) We are indebted to Dr. J. Sardinas of our Fermentation Research Department for carrying out this microbiological conversion.

(24) (a) G. M. Shull, unpublished results; (b) T. Takahashi and Y. Uchibori, *Agr. Biol. Chem.*, **26**, 89 (1962).

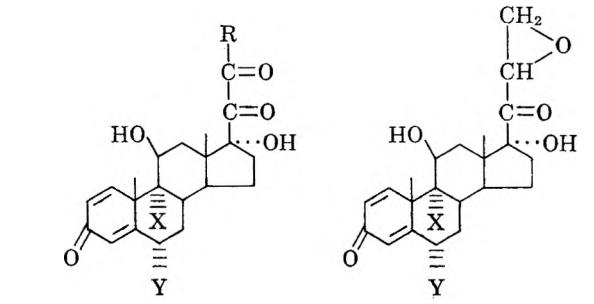


XXXV XXXVI

(XXXVI) instead of on C-21 would, therefore, be expected to produce the 20-dihydro derivative of *opposite* configuration, the 20β_F-hydroxy compound.

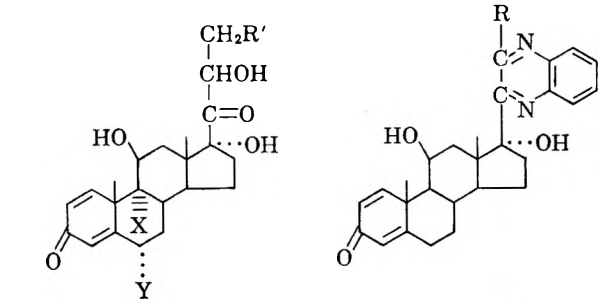
Reduction of the diketone polarographically[25a,b] produced a complex mixture of products from which the 20-dihydro derivative XIII was isolated. None of the 21α_F-ol (XII) could be detected.

Application of XIIa of the familiar sequence for introducing a 9α-fluorine substituent[26] proceeded in the expected fashion *via* the intermediate 9(11)-ene (XXXVII), 9α-bromo-11β-hydroxy (XXXVIII), and 9β,11β-oxido (XXXIX) derivatives to 21-methyl-9-fluoro - 11β,17,21α_F - trihydroxypregna - 1,4 - diene-3,20-dione 21-acetate (XIV).[27] This product was identical to that obtained from 9-fluoro-11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-al (XV) *via* the oxide (IX), bromohydrin (XXI), and α-diketone (XVIII). It is noteworthy that when the diazomethane sequence was applied to the preparation of the 9-fluoro and 6α,9-difluoro derivatives XIV and XVII, the reaction proceeded essentially in the same manner as described for the transformation of prednisolone 21-aldehyde to XII except for the slowness of the final yeast reduction step, which was most probably due to the lower solubility of the 9-fluoro and 6α,9-difluoro 20,21-diketones XVIII and XIX.



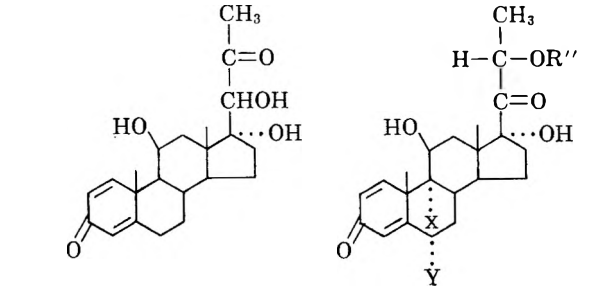
I. R = X = Y = H
III. R = CH_3; X = Y = H
XV. R = Y = H; X = F
XVI. R = H; X = Y = F
XVIII. R = CH_3; X = F; Y = H
XIX. R = CH_3; X = Y = F

II. X = Y = H
IX. X = F; Y = H
X. X = Y = F



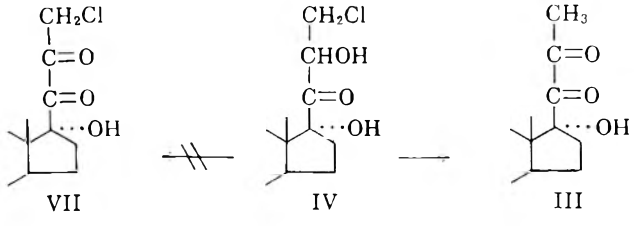
IV. R′ = Cl; X = Y = H
V. R′ = Br; X = Y = H
XI. R′ = I; X = Y = H
XL. R′ = Cl; X = F; Y = H
XXI. R′ = Br; X = F; Y = H
XXII. R′ = Cl; X = Y = F
XXIII. R′ = Br; X = Y = F

VIIIa. R = H
VIIIb. R = CH_3



XIII
XIIIa. Acetate of XIII

XII. R″ = X = Y = H
XIIa. Acetate of XII
XIV. R″ = Y = H; X = F
XIVa. Acetate of XIV
XVII. R″ = H; X = Y = F
XVIIa. Acetate of XVII



VII IV III

Experimental[28]

11β,17-Dihydroxy-3,20-dioxopregna-1,4-dien-21-al (Prednisolone-21 Aldehyde) (I).—Prednisolone was oxidized with cupric acetate according to the method of Christensen, *et al.*[29] An analytical sample, from methanol, exhibited m.p. 186–188° dec., λ_{max} 244 mμ (15,700), infrared λ_{max} 1699 cm.

Anal. Calcd. for $C_{21}H_{26}O_5 \cdot CH_3OH$: C, 67.67; H, 7.74; methoxyl, 7.94. Found: C, 67.28; H, 7.64; methoxyl, 7.23.

21-Methyl-21,21a-epoxy-11β,17-dihydroxypregna-1,4-diene-3,-20-dione (II).—An ice-cold solution of diazomethane prepared from 10 g. of N-methyl-N-nitroso-N′-nitroguanidine in 100 ml. ether was added to an ice-cold solution of 3.88 g. of prednisolone 21-aldehyde in 350 ml. methanol and 170 ml. ether. After 15 min. at 5° and 2 hr. at room temperature the excess diazomethane was destroyed by the addition of dilute acetic acid. The reaction mixture was concentrated to 20 ml. and the residue taken up in 500 ml. of chloroform. The chloroform solution was washed with 5% sodium bicarbonate and water and taken to dryness. The amber residue, upon trituration with 1:2 ethyl acetate–ether, afforded 1.45 g. white microcrystals, m.p. 225–227° dec. After two recrystallizations from ethyl acetate the product (300 mg.) exhibited m.p. 239–241° dec., λ_{max} 243 mμ (15,600), infrared λ_{max} 1709 cm.$^{-1}$, $[\alpha]_D$ + 166°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.71; H, 7.77.

Minor Products of Reaction of Prednisolone 21-Aldehyde with Diazomethane.—After removal of the crude epoxide compound by trituration (see above), the mother liquor residues from several experiments were combined and taken up in methylene chloride and chromatographed on neutral alumina. The components which were isolated (quantitative paper chromatographic assays

(25) (a) S. Wawzonek, *Anal. Chem.*, **28**, 638 (1956); (b) we are grateful to Mr. W. McMullen and Mr. L. Ciaccio of our Analytical Department for performing the polarographic reduction experiments.

(26) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957); R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(27) (a) P-1742, previously named 9α-fluoro-21-methyl-1,4-pregnadiene-11β,17α-21B-triol-3,20-dione 21-acetate[1a,d]; according to Cahn–Ingold-Prelog convention for specifying asymmetric configuration[27b] compound XIV would be named 17β-[(S)-2-acetoxypropionyl]-9-fluoro-11β,17-dihydroxyandrosta-1,4-dien-3-one. (b) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(28) Unless otherwise noted the ultraviolet absorption spectra were determined in methanol solution, the infrared absorption spectra in pressed potassium bromide, and the optical rotations in dioxane solution. All melting points are uncorrected.

(29) This compound has been described as a monohydrate.[6] Our sample (prepared by the same method) was shown by a methoxyl determination to contain an equivalent of methanol.

indicated there was less than 5% of each of the minor products) are described below.

(A) Eluted in methylene chloride containing 15% ether. Recrystallization from acetone–ether afforded an analytical sample, m.p. 233–235°, λ_{max} 243 mμ (14,700).

Anal. Found: C, 72.79; H, 8.18; O, 19.21; methoxyl, 0.68.

(B) Eluted in ether containing 1% acetone. An analytical sample, recrystallized from acetone ether, exhibited m.p. 220–222°, λ_{max} 243 mμ (14,900), infrared λ_{max} 1693 cm.$^{-1}$.

Anal. Found: C, 71.50; H, 7.64; O, 20.91.

(C) Eluted in ether containing 5–25% acetone. The analytical sample, recrystallized from acetone–ether, exhibited m.p. 206–208°, infrared λ_{max} 1715, 1700 cm.$^{-1}$.

Anal. Found: C, 71.18; H, 7.62. Identical with compound III prepared by a different method (below).

(D) Eluted in ether containing 25–50% acetone. Recrystallization from acetone afforded an analytical sample, m.p. 289–295° dec., λ_{max} 256 mμ (20,800), infrared λ_{max} 1680, 1644 cm.$^{-1}$.

Anal. Found: C, 75.03; H, 7.53; O, 17.69; methoxyl, 0.69.

(E) Eluted in 1:1 acetone–methanol. The product consisted of a white glass which gave a positive Tollens test.

Reaction of Epoxide II with Periodic Acid.—A solution of 900 mg. of periodic acid (dihydrate) in 25 ml. of water was added to a solution of 475 mg. of II in 75 ml. of methanol at 40° and allowed to stand 24 hr. The crystalline precipitate which was removed by filtration (60 mg.) was identical to starting material. The filtrate was extracted with 1:1 ethyl acetate–benzene, and the extract was washed with water and concentrated to 3 ml. Another crop of crystalline starting material (62 mg.) was removed by filtration. The filtrate was concentrated to dryness and the residue, upon trituration with 1:1 ethyl acetate–ether, yielded 124 mg. of crystalline product, identical by infrared and paper chromatographic comparison with 11β-hydroxyandrosta-1,4-diene-3,17-dione prepared by the action of sodium bismuthate on prednisolone as described below.

Reaction of Prednisolone with Sodium Bismuthate.—A solution of 10 g. of prednisolone in 500 ml. of 50% acetic acid was stirred with 29 g. of sodium bismuthate at room temperature overnight. The stirring was stopped and after the solid had settled the colorless supernatant was filtered and diluted with 800 ml. of water with cooling. The white precipitate (2.84 g.), recrystallized from ethyl acetate afforded 1.81 g. of 11β-hydroxyandrosta-1,4-diene-3,17-dione,[10] m.p. 185–187°, λ_{max} 242 mμ, (14,850), infrared λ_{max} 1720 cm.$^{-1}$.

21-Methyl-21,21a-epoxy-17-hydroxypregna-1,4-diene-3,11,20-trione.—A suspension of 650 mg. of oxide II (1.75 mequiv.) in 5 ml. of acetic acid was treated with 130 mg. (1.92 equivalents) of chromic acid in 18.4 ml. of acetic acid–water (9:1). The product isolated by extraction, upon trituration with 1:1 ethyl acetate–ether, consisted of 386 mg. of white crystalline solid, m.p. 215–218° dec. Recrystallization once from ethyl acetate and then from methanol afforded the analytical sample (105 mg.) which had m.p. 226–228° dec., λ_{max} 238 mμ (16,900), $[\alpha]_D$ + 226°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.39; H, 7.11.

21-Chloromethyl-11β,17,21ξ$_F$-trihydroxypregna-1,4-diene-3,20-dione (IV). Method A.—A suspension of 500 mg. of II in 50 ml. of chloroform was treated with 50 ml. of a solution of anhydrous hydrogen chloride in glacial acetic acid (4.1 mg./ml.). The resultant solution was allowed to stand for 1.5 hr. at room temperature. After adding 125 ml. of chloroform and 75 ml. of water, the layers were separated and the chloroform layer was washed and dried. The residue (592 mg. of pale yellow solid), upon trituration with 2:1 ether–ethyl acetate, afforded 195 mg. of crude chlorohydrin IV, m.p. 188–189° dec. Two recrystallizations from ethyl acetate yielded 65 mg. of analytically pure IV, m.p. 199–200° dec., λ_{max} 243 mμ (14,500), infrared λ_{max} 1697 cm.$^{-1}$, $[\alpha]_D$ +66°.

Anal. Calcd. for $C_{22}H_{29}O_5Cl$: C, 64.61; H, 7.15; Cl, 8.67; O, 19.57. Found: C, 64.76; H, 7.24; Cl, 8.07; O, 20.27.

Method B.—A suspension of 5 g. of II in a solution of 27 ml. of 2.5 *N* methanolic hydrogen chloride in 50 ml. of chloroform was stirred at room temperature for 2 hr. Addition of 200 ml. of water precipitated the product. Filtration yielded 4.4 g. of product which, by paper chromatographic analysis, contained approximately 70% of IV and 10% of a more polar product (presumably VI). Pure chlorohydrin, identical to the product obtained by method A, was obtained by recrystallization from ethyl acetate.

Treatment of 230 mg. of IV with 2 ml. of pyridine and 1 ml. of acetic anhydride overnight at room temperature afforded 190 mg. of crude acetate. After two recrystallizations from ethyl acetate, there was obtained 97 mg. of the 21-acetate of IV which exhibited m.p. 185–186° dec., λ_{max} 243 mμ (15,000), $[\alpha]_D$ +46°.

Anal. Calcd. for $C_{24}H_{31}O_6Cl$: C, 63.91; H, 6.93; Cl, 7.86. Found: C, 63.85; H, 7.02; Cl, 6.97.

The mother liquors obtained from several preparations of chlorohydrin IV (by either method A or B) were combined and dissolved in 20:1 ether–ethyl acetate and filtered through a column of Florisil. The filtrate contained VI free of other steroids. After three recrystallizations from 1:1 acetone–ether, the by-product VI exhibited m.p. 186–187° dec., λ_{max} 243 mμ (15,050), infrared λ_{max} 1709 cm.$^{-1}$.

Anal. Found: C, 63.44; H, 7.01; O, 19.86; Cl, 8.49.

21-Bromomethyl-11β,17,21ξ$_F$-trihydroxypregna-1,4-diene-3,20-dione (V).—A suspension of 2 g. of II in 150 ml. of 0.37 *N* methanolic hydrogen bromide was stirred at room temperature for 2 hr. Addition of 100 ml. of water to the final solution and removal of 100 ml. of methanol *in vacuo* precipitated the crystalline product. Filtration afforded crude bromohydrin, m.p. 135–136° dec. A sample prepared in chloroform–glacial acetic acid containing anhydrous hydrogen bromide and isolated as described for IV above was recrystallized twice from ethyl acetate for analysis. The best sample of V, which was somewhat unstable (see text), exhibited m.p. 141–142°, λ_{max} 243 mμ ($E^{1\%}_{1\,cm}$ 350), infrared λ_{max} 1696 cm.$^{-1}$, $[\alpha]_D$ +99°.

Anal. Calcd. for $C_{22}H_{29}O_5Br$: C, 58.28; H, 6.45; Br, 17.63. Found: C, 59.65; H, 6.51; Br, 16.96.

21-Iodomethyl-11β,17,21ξ$_F$-trihydroxypregna-1,4-diene-3,20-dione (XI).—A suspension of 3.7 g. of II in 300 ml. of methylene chloride was protected from light by wrapping the flask with aluminum foil. The suspension was stirred vigorously with 29 ml. of 50% aqueous hydrogen iodide for 10 min. The organic layer diluted with 150 ml. of methylene chloride and 30 ml. of ethyl acetate and 300 ml. of water and 100 ml. of 5% sodium thiosulfate solution were added. After stirring for 3 min., the organic layer was separated and the aqueous layer extracted three times with 100-ml. portions of 9:1 methylene chloride–ethyl acetate. The combined organic extracts were washed with water, dried, and concentrated to 200 ml. The first crop of crystalline product (2.48 g.) was isolated by filtration. A second crop (0.87 g.) was isolated by concentration of the filtrate to 20 ml. Recrystallization of 400 mg. of the first crop material from ethyl acetate afforded 103 mg. of crystals in two crops, m.p. 149–150° and m.p. 146–147°. A final recrystallization from ethyl acetate yielded a still impure sample of the very unstable iodohydrin (XI), m.p. 145–146° dec., λ_{max} 243 mμ ($E^{1\%}_{1\,cm}$ 331).

Anal. Calcd. for $C_{22}H_{29}O_5I$: C, 52.81; H, 5, 84; I, 25.36. Found: C, 58.17; H, 6.77; I, 21.32.

21-Methyl-11β,17-dihydroxypregna-1,4-diene-3,20,21-trione (III). From Bromohydrin.—A suspension of 1.0 g. of bromohydrin (V) in 150 ml. of ethyl acetate was heated under reflux for 2 hr. during which time the steroid dissolved. The solution was taken to dryness and the tacky crystalline residue (888 mg.) triturated with 1:1 ether–ethyl acetate. The resultant crystals (524 mg.) were identical by infrared spectral comparison with III prepared from chlorohydrin IV with bismuth trioxide (see below) and with one of the minor products (C) isolated from the reaction of aldehyde I with diazomethane.

III from Chlorohydrin with Bismuth Trioxide in Acetic Acid.—A solution of 7.56 g. of chlorohydrin IV in 380 ml. of glacial acetic acid was immersed in a water bath maintained between 50 and 60°. Bismuth trioxide (29.4 g.) was added and the mixture was stirred for 3 hr. The warm reaction mixture was filtered (Super Cel) and the acetic acid was removed *in vacuo*. The residue was stirred three times with 200-ml. portions of chloroform. The combined chloroform extracts were filtered (Super Cel) and washed with water (twice), 5% sodium bicarbonate (six times), and water (three times), dried, concentrated to a small volume (20 ml.), and filtered to remove 1.71 g. of crystalline material identical to starting material (IV). The filtrate was taken almost to dryness and treated with ethyl acetate. The crystals which were removed by filtration (2.62 g.) were recrystallized once from ethyl acetate and once from acetone–ether to obtain an analytical sample of III, m.p. 206–208°, λ_{max} 243 mμ (15,450), infrared λ_{max} 1715, 1700 cm.$^{-1}$, $[\alpha]_D$ + 91°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.91; H, 7.65.

Chromatography of the mother liquor residue of crude III (p. 1535) on Florisil and elution with 2:1 ether–ethyl acetate yielded 310 mg. of a by-product (XX) (see below) identical to the major product isolated from the reaction of chlorohydrin with bismuth trioxide at slightly higher temperatures (60–70°). Compound XX was also obtained as a major product when chlorohydrin IV was treated with cupric acetate (see below).

III from Chlorohydrin IV with Potassium Acetate in Acetone.—A mixture of 101 mg. of IV and 200 mg. potassium acetate in 10 ml. of acetone was heated at reflux for 2 hr. with stirring. Concentration to 3 ml. and slow addition of the residue to 40 ml. of water produced a white crystalline precipitate which was filtered. The dry solid (46 mg., 50%) was identical by paper chromatographic and infrared spectral comparison to α-diketone III prepared by other methods herein described.

III from Chlorohydrin IV in Refluxing Ethyl Acetate Containing Acid.—A suspension of 100 mg. of IV in 15 ml. of ethyl acetate was heated under reflux while bubbling anhydrous hydrogen chloride through the mixture for 2 hr. Evaporation of the solvent and trituration of the residue gave 23 mg. of crystals which were identical to diketone III by paper chromatographic and infrared spectral comparison. Paper chromatographic assay of the reaction solution prior to isolation of the crystalline product indicated the presence of 40% of the theoretical amount of III.

III from Epoxide II.—A suspension of 1 g. of epoxide II in 150 ml. of ethyl acetate was heated with stirring at reflux temperature, and anhydrous hydrogen chloride was bubbled through the reaction mixture for 2 hr. The final solution was concentrated to an oil which was triturated with ether. Filtration afforded 604 mg. of crystals, m.p. 160–168°, which proved to be crude 20,21-diketone III by paper chromatographic and spectral comparison with III prepared as described above. Recrystallization of the crude material from 4:1 methanol–water gave 300 mg. of crystals, m.p. 203–205° identical with a sample of authentic diketone III.

Reaction of III with *o*-Phenylenediamine.—Compound III (200 mg.) in 10 ml. of ethanol was heated with 200 mg. of *o*-phenylenediamine and 1 ml. of 2 *N* hydrochloric acid for 0.5 hr. at 60°. Dropwise addition of 20 ml. of water to the orange-red solution with cooling resulted in precipitation of 195 mg. of yellow crystals, m.p. 178–181° dec., λ_{max} 238 and 321 mμ and infrared absorption spectrum exhibiting no saturated carbonyl absorption. Recrystallization of the product from 1:2 ethanol–water afforded bright yellow crystals (110 mg.) m.p. above 260°, λ_{max} 238 mμ ($E^{1\%}_{1\,cm}$ 930) and 321 mμ ($E^{1\%}_{1\,cm}$ 198). The infrared and ultraviolet absorption spectra of this product were very similar to those of the derivative obtained from prednisolone 21-aldehyde under identical conditions.

Reaction of III with Periodic Acid.—A solution of 80 mg. of diketone III in 10 ml. of methanol at 40° was treated with 5 ml. of water containing 180 mg. of periodic acid (dihydrate) and stored at room temperature for 15 hr. The solution was evaporated to dryness and the residue washed with water. The crystalline residue was recrystallized from ethyl acetate. The product was identical to 11β-hydroxyandrosta-1,4-diene-3,17-dione[9] by paper chromatographic and infrared spectral comparison.

Reaction of Chlorohydrin IV with Periodic Acid.—A solution of 300 mg. of IV in 25 ml. of methanol was treated with 15 ml. of periodic acid solution (containing 540 mg. of dihydrate) and after 15 hr. the product was isolated as described above. The product (177 mg.) was almost entirely soluble in 5% sodium hydroxide. It was dissolved in 5 ml. of alkali and extracted three times with 10-ml. portions of methylene chloride. The alkaline solution was made acidic by dropwise addition of 2 *N* hydrochloric acid to reprecipitate the acid (113 mg.), which exhibited m.p. 226–227° and infrared absorption spectrum identical to the product obtained from prednisolone with periodic acid under the same conditions (see below).

Reaction of Prednisolone with Periodic Acid.—Treatment of 468 mg. of prednisolone in 25 ml. of methanol with 900 mg. of periodic acid in 25 ml. of water overnight at room temperature afforded (by the isolation procedure above) 240 mg. of 11β,17α-dihydroxyandrosta-1,4-diene-3-one-17-carboxylic acid,[13] m.p. 224–226° dec.

Reaction of Chlorohydrin (IV) with Bismuth Trioxide at 60–70°.—A suspension of 1 g. of IV in 44 ml. of glacial acetic acid was heated to dissolve the steroid and immersed in a water bath kept at 60–70°. The solution was treated with 3.9 g. of bismuth trioxide for 5 hr. with stirring. The reaction mixture was diluted with 50 ml. of chloroform and filtered (Super Cel). The product, isolated as described before for compound III and triturated with 3:1 ethyl acetate–ether, afforded 295 mg. of XX as microcrystals, m.p. 211–213° dec. The analytical sample of XX, prepared by recrystallization from ethyl acetate, exhibited m.p. 215–216°, λ_{max} 242 mμ ($E^{1\%}_{1\,cm}$ 407), infrared λ_{max} 3496, 3389, 1693 (broad), 1650, 1620, 1605 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58; O, 21.48. Found: C, 71.15; H, 7.53; O, 20.87.

The infrared spectrum and paper chromatographic behavior of XX differed from that of diketone III.

Treatment of Chlorohydrin IV with Potassium Acetate in Acetic Acid.—A solution of 100 mg. of chlorohydrin IV in 5 ml. of acetic acid containing 200 mg. of potassium acetate was heated at 50–60° for 5 hr. Paper chromatographic analysis of aliquots taken at hourly intervals showed little or no reaction had occurred in this period. Heating was continued for 2 hr. after which 5 ml. of ethanol was added but no reaction was detected paper chromatographically. The solvents were removed *in vacuo* and the residual white solid was triturated with water and filtered. The resulting white solid (60 mg.) was identical to starting material by infrared spectral comparison.

Treatment of Chlorohydrin IV with Bismuth Trioxide in Acetone.—A mixture of 100 mg. of chlorohydrin IV and 200 mg. of bismuth trioxide in 10 ml. of acetone was heated at reflux under an atmosphere of nitrogen for 2 hr. It was cooled to room temperature and 10 ml. of 1:1 chloroform–methanol was added. The bismuth salts were removed by filtration and the filtrate was concentrated to dryness *in vacuo*. Paper chromatographic analysis indicated that the chlorohydrin was unaffected by this treatment.

Chlorohydrin IV in Refluxing Solvents.—A suspension of 100 mg. of IV in 15 ml. of ethyl acetate was heated at reflux for 72 hr. Only partial dissolution occurred. Evaporation of the solvent left a crystalline residue which was starting material (infrared spectral evidence and paper chromatographic analysis).

A suspension of 100 mg. of IV in 15 ml. of *n*-amyl acetate was heated at reflux for 5 hr. Dissolution occurred in 30 min. After 5 hr. the solvent was evaporated and the residual crystals were examined by paper chromatography and spectrally. The starting material was the preponderant steroid present but there was evidence that some degradation had occurred (intensity of absorption at 240 mμ was approximately two-thirds that of the starting material).

Reaction of Chlorohydrin IV with Cupric Acetate.—A suspension of 1.0 g. of chlorohydrin IV in 64 ml. of methanol was treated with a mixture of 1.5 g. of cupric acetate, 6 ml. of water, and 0.5 ml. of glacial acetic acid at 60° for 30 min. The reaction mixture was cooled to room temperature, treated with 1.0 g. of versene and concentrated to about 5 ml. The residue was diluted with water and the resultant blue-green precipitate was filtered and washed with 30% ammonium hydroxide and water. The resultant pale yellow solid (800 mg.) was a mixture (paper chromatographic analysis) from which compound XX could be isolated by chromatography on Florisil as described before for its isolation from the mother liquor of compound III.

21-Methyl-11β,17,21α$_F$-trihydroxypregna-1,4-diene-3,20-dione (XII).[5] **A. Reduction of III with Yeast.**—A solution of 24 g. of 11β,17-dihydroxy-21-methylpregna-1,4-diene-3,20-21-trione (III) in 4800 ml. of ethanol was added to a stirred solution of 9600 g. of sucrose in 70 l. of tap water. A suspension of 1680 g. of Fleischmann's "active dry yeast" in 9600 ml. of tap water at 40° was stirred for 30 min. and added to the steroid–sucrose solution. The reaction mixture was stirred gently enough to maintain anaerobic conditions and the pH was kept between 3.8 and 4.7 by periodic addition of ammonium hydroxide. After 24 hr. a suspension of 336 g. of yeast and 1920 g. of sucrose in 1620 ml. of water and 96 ml. of ethanol was added. Paper chromatographic assay of the extract of an aliquot at 24 hr. indicated the presence of 78% of the theoretical amount of XII. At 48 hr. the assay of an aliquot was approximately unchanged (81%). At this time Super Cel (4800 g.) was added and the mixture was filtered. The filtrate was extracted four times with 12-l. portions of chloroform and the combined extract was washed with two 6-l. portions of water. The chloroform solution was clarified by filtration through sodium sulfate and concentrated to dryness. The glassy residue was taken up in pyridine (360 ml.), filtered to clarify and another 120 ml. of pyridine was used to wash the filter cake. Acetic anhydride (240 ml.) was added, and the solution was allowed to stand at room temperature overnight. The acetate of XII was precipitated as an oil by addition of water and was extracted with four 1200-ml. portions of ethyl acetate. The ethyl acetate solu-

tion was washed with dilute hydrochloric acid, saturated sodium bicarbonate, and water, dried, and concentrated *in vacuo*. The white crystalline product which separated during the concentration was collected in two crops (10.0 g. and 2.7 g.) of approximately 90% purity (paper chromatographic assay). The yield of acetate in the two crops was 51%. An additional 3.0 g. of 90% purity was isolated by chromatography on Florisil. An analytical sample of 21-methyl-11β,17,21α_F-trihydroxypregna-1,4-diene-3,20-dione 21-acetate (XIIa), obtained from ethyl acetate, exhibited m.p. 221–222°, $[\alpha]_D$ +122°, ultraviolet λ_{max} 244 mμ (14,800).

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.76; H, 7.67.

Crystalline alcohol (XII) (1.69 g.) was obtained by saponification of 2.0 g. of XIIa with methanolic potassium carbonate. The analytical sample obtained from 1:1 isopropyl alcohol–water apparently retained solvent of crystallization. It exhibited m.p. 117–120°, ultraviolet λ_{max}^{MeOH} 243 (15,050), $[\alpha]_D$ +111°.

Anal. Calcd. for $C_{22}H_{30}O_5 + {}^1/_2C_3H_7OH$: C, 69.77; H, 8.47. Found: C, 69.68; H, 8.39.

B. Reduction of III with Sodium Borohydride.—A solution of 186 mg. of III in 15 ml. of methanol cooled to 0° was treated with an ice-cold solution of 13.3 mg. of sodium borohydride in 3.6 ml. of methanol and kept at 0° for 1 hr. Two drops of acetic acid were added to the reaction solution and it was taken to dryness. The white glassy residue was taken up in 40 ml. of chloroform and washed with 4 ml. of water. Assay by paper chromatography at this stage indicated the presence of 60% of the theoretical amount of product XII and four minor products, one of which was identified as the 20-dihydro compound XIII (approx. 13%).

The chloroform was removed *in vacuo* and the residue acetylated in 2 ml. of pyridine with 1 ml. of acetic anhydride overnight at room temperature. The product, precipitated by the addition of water and isolated (70% yield) as described before, was very similar to XIIIa by infrared spectral comparison, but paper chromatographic analysis indicated the presence of four other compounds.

In a similar experiment in which 558 mg. of 20,21-diketone was reduced with sodium borohydride and the crude product was acetylated and isolated as described before, a small first crop of crude acetate (45 mg.) was identical to the acetate of the 20-dihydro compound (XIII) obtained by the polarographic reduction of III (see below).

21-Methyl-11β,17,20ξ-trihydroxypregna-1,4-diene-3,21-dione (XIII). A. By Polarographic Reduction of III.[25]—To a solution of 993 mg. of III in 300 ml. of formamide was added 100 ml. of universal buffer.[30] The solution was adjusted to pH 8 by addition of 6 *N* potassium hydroxide. The resulting solution exhibited two half-wave potentials: −0.87 and −1.54 volts. The reduction was performed using a mercury pool electrode with a shielded anode at −1.00 volts *vs.* a saturated calomel electrode until approximately 94% of 2 electrons per mole had been consumed (disappearance of wave at −0.87 volts).

The solution was diluted with 2000 ml. of water and saturated with sodium chloride before extracting with three 2000-ml. portions of chloroform. The chloroform solution was dried (sodium sulfate) and the solvent removed *in vacuo*. The residual pale yellow oil (1.00 g.) was acetylated in the usual way and the crude acetate isolated by chloroform extraction. The residue after removal of the chloroform was a brown glass (1.05 g.) which, upon trituration with ethyl acetate, afforded 293 mg. of tan crystals, m.p. 234–237° dec. Recrystallization of this material from 1:1 ethyl acetate–ethanol and again from ethanol gave 98 mg. of the acetate of XIII, m.p. above 250°, ultraviolet λ_{max} 244 mμ (14,850).

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.50; H, 8.14.

Saponification of 80 mg. of $XIII_2$ with methanolic potassium carbonate in the usual way afforded 37 mg. of alcohol XIII free of other steroids (analysis by paper chromatography).

Treatment of XIII with Periodic Acid.—A solution of 18.5 mg. of XIII, obtained by saponification of the acetate (see above), in 1.25 ml. of methanol was treated with 45 mg. of periodic acid (dihydrate) in 1.25 ml. of water overnight at room temperature. The reaction mixture was concentrated to about 1 ml. by evaporation with a nitrogen stream, and the resultant white precipitate was filtered. The product (8 mg. of white crystalline solid) was identical by infrared spectral comparison with 11β-hydroxyandrosta-1,4-diene-3,17-dione[10] obtained by the reaction of prednisolone with sodium bismuthate.[31]

B. By the Action of *Streptomyces erythreus*.[23]—A sample of 50 mg. of III was subjected to the action of *Streptomyces erythreus* using essentially the procedure described by F. Carvajal, *et al.*[32]

The broth (2 l.) was extracted with four 200-ml. portions of chloroform and the chloroform extract was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Paper chromatographic comparison of the crude product with the product of polarographic reduction (see A) indicated that the major product was the 20-dihydro derivative XIII. Acetylation of the residue (237 mg.) in the usual way and isolation of the crude acetate by ethyl acetate extraction afforded 58 mg. of yellow oil which was crystallized by trituration with 1:1 ether–ethyl acetate. The filtered product (13 mg.) was identical by paper chromatographic and spectral comparison with the acetate obtained by acetylation of the polarographic reduction product of III.

21-Methyl-17,21α_F-dihydroxypregna-1,4,9(11)-triene 3,20-dione 21-Acetate XXXVII.—To a solution of 70.2 g. of XIIa in 350 ml. of pyridine and 350 ml. of dimethylformamide was added 70.2 g. of anhydrous sodium sulfate and, after stirring at room temperature for 1 hr., 21.1 ml. of methanesulfonyl chloride. Stirring was continued for 20 hr. and the product was precipitated by the addition of 5630 ml. of water to the reaction mixture with cooling. Recrystallization from methanol gave 54.4 g. (80%) of 17,21α_F-dihydroxy-21-methylpregna-1,4,9(11)-triene-3,20-dione 21-acetate, m.p. 193–195°. An analytical sample (two additional recrystallizations) exhibited m.p. 199°, λ_{max} 239.5 mμ (14,700), $[\alpha]_D$ +67°.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.54. Found: C, 72.06; H, 7.47.

21-Methyl-9-bromo-11β,17,21α_F-trihydroxypregna-1,4-diene-3,20-dione 21-Acetate (XXXVIII).—N-Bromoacetamide (17.9 g.) and 10% aqueous perchloric (205 ml.) acid were added to a stirred suspension of 17,21α_F-dihydroxy-21-methylpregna-1,4,9(11)-triene-3,20-dione 21-acetate (49.5 g.) in a mixture of dioxane (1020 ml.) and water (184 ml.) cooled to 25°. The mixture was stirred 18 min., by which time a solution was obtained. Ice (1550 g.) was added followed by sodium sulfite (51.0 g.) and water (3820 ml., 0°). The product was filtered off after stirring the mixture 0.5 hr. at 0° and an additional 0.5 hr. at room temperature. The majority of this crude product was used in the next step. A portion (2.5 g.) was twice recrystallized from aqueous acetone and had m.p. 173° dec., λ_{max} 243 mμ (13,700), $[\alpha]_D$ +141°.

Anal. Calcd. for $C_{24}H_{31}O_6Br$: C, 58.18; H, 6.31. Found: C, 58.25; H, 6.50.

21-Methyl-9β,11β-oxido-17,21α_F-dihydroxypregna-1,4-diene-3,20-dione 21-Acetate (XXXIX).—The preceding moist bromohydrin was heated under reflux in ethanol (1200 ml.) for 5 hr. in the presence of potassium acetate (61.5 g.). The crude oxide (56.6 g., m.p. 200–204°), recrystallized from methanol, afforded two crops of crystals: the first (24.5 g.) had m.p. 210–212°; the second, (8.0 g.) had m.p. 218–219°. An analytical sample prepared from another run had m.p. 221–223°, λ_{max} 251 mμ (14,00), $[\alpha]_D$ +68°.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 69.54; H, 7.30. Found: C, 69.37; H, 7.64.

21-Methyl-9-fluoro-11β,17,21α_F-trihydroxypregna-1,4-diene-3,20-dione 21-Acetate (XIVa).—9β,11β-Oxido-17,21α_F-dihydroxy-21-methylpregna-1,4-diene-3,20-dione 21-acetate (15.2 g.) in chloroform (100 ml.) was added at −70° to a solution of hydrogen fluoride (20 ml.) in tetrahydrofuran (34 ml.) chloroform (16 ml.). The reaction was allowed to proceed at 0° for 4 hr., cooled to −70° again and slowly added to a stirred mixture of 10% sodium carbonate solution and chloroform. After separation of the layers, the aqueous was extracted twice with chloroform, and the combined chloroform extracts were dried by percolation through anhydrous sodium sulfate. Concentration *in vacuo* to 30 ml. yielded the crude product which was recrystallized by dissolution in 300 ml. of acetone, concentration to 200 ml., and slow addition of 50 ml. of hexane. The product, 8.29 g., m.p. 251–253°, contained 1 mole of acetone of crystallization, which it lost on heating *in vacuo* at 100° overnight (volatiles, 11.5%, calcd., 11.8%). This material appeared to be superior to analytically

(30) Composition: 0.1 *M* acetic acid, 0.1 *M* phosphoric acid, 0.1 *M* boric acid, and 0.5 *M* potassium chloride.

(31) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(32) F. Carvajal, O. F. Vitale, M. J. Gentles, H. L. Herzog, and E. B. Hershberg, *J. Org. Chem.*, **24**, 695 (1959).

pure material prepared in an earlier run and recrystallized from ethyl acetate. The sample thus obtained exhibited m.p. 251–253°, λ_{max} 239 mμ (15,350), $[\alpha]_D$ +87°.

Anal. Calcd. for $C_{24}H_{31}O_6F$: C, 66.34; H, 7.19. Found: C, 65.84; H, 7.06.

Saponification of 500 mg. of XIVa in the usual way with methanolic potassium carbonate afforded, after recrystallization from acetone (7 ml.)–hexane (10 ml.), 241 mg. of 9-fluoro-11β,17,-21α_F-trihydroxy-21-methylpregna-1,4-diene-3,20-dione, m.p. 223–224°, λ_{max} 239 mμ (14,900), $[\alpha]_D$ +139°.

Anal. Calcd. for $C_{22}H_{29}O_5F$: C, 67.32; H, 7.40; F, 4.85. Found: C, 67.00; H, 7.46; F, 4.96.

9-Fluoro-11β,17-dihydroxy-3,20-dioxopregna-1,4-diene-21-al (9-Fluoroprednisolone 21-Aldehyde) (XV).[33a]—9-Fluoroprednisolone (500 mg.), treated with cupric acetate as described earlier for the preparation of I, gave 428 mg. of crude aldehyde which was identical to a sample prepared *via* the nitrone.[33b] After two recrystallizations from acetone–water the aldehyde exhibited m.p. 226–228°, λ_{max} 239 mμ, $E^{1\%}_{1\,cm}$ 390.

Anal. Calcd. for $C_{21}H_{25}O_5F \cdot CH_3OH$: C, 64.68; H, 7.16. Found: C, 64.37; H, 7.48.

21-Methyl-9-fluoro-21,21a-epoxy-11β,17-dihydroxypregna-1,4-diene-3,20-dione (IX).—A solution of 394 mg. of 9-fluoroprednisolone 21-aldehyde in 35 ml. of methanol and 17 ml. of ether was treated with 10 ml. of ethereal diazomethane (approximately 5 mmoles). Removal of the solvents *in vacuo* gave 380 mg. of amorphous residue which crystallized upon treatment with 1:1 ether–ethyl acetate. The crystalline product (80 mg.) was recrystallized twice from ethanol to obtain the analytical sample which had m.p. 254–255° dec., λ_{max} 239 mμ (15,600), $[\alpha]_D$ +123°.

Anal. Calcd. for $C_{22}H_{27}O_5F$: C, 67.67; H, 6.97. Found: C, 68.00, H, 6.95.

21-Chloromethyl-9-fluoro-11β,17,21ξ_F-trihydroxypregna-1,4-diene-3,20-dione (XXXV).—A suspension of 178 mg. of oxide IX in 2.3 ml. of 4.5 *N* hydrogen chloride in methanol was diluted with 1.9 ml. of methanol and 7.8 ml. of chloroform and stirred for 2.5 hr. Addition of 35 ml. of water to the resultant solution precipitated the product as an oil which crystallized during removal of the chloroform *in vacuo*. The crude product (814 mg.), isolated by filtration, was recrystallized from ethyl acetate and afforded 418 mg. of white microcrystals, m.p. 178° dec., $[\alpha]_D$ +79°. An analytical sample, obtained by a second recrystallization, had m.p. 174–174.5° dec., λ_{max} 239 mμ (15,250), $[\alpha]^{24}_D$ +72°.

Anal. Calcd. for: $C_{22}H_{27}O_5FCl$: C, 61.89; H, 6.61. Found: C, 61.39; H, 6.63.

Acetylation of XXXV in the usual way and recrystallization of the crude acetate from methanol afforded an analytical sample which had m.p. 117–119°, $[\alpha]_D$ + 73°.

Anal. Calcd. for $C_{24}H_{30}O_6FCl$: C, 61.47; H, 6.45. Found: C, 61.28; H, 6.99.

21-Bromomethyl-9-fluoro-11β,17,21ξ_F-trihydroxypregna-1,4-diene-3,20 dione (XXI).—A suspension of 720 mg. of oxide IX was stirred in 36 ml. of methanolic hydrogen bromide (0.37 *N*) for 2 hr. at room temperature. The product, precipitated by addition of 72 ml. of water, consisted of 531 mg. of ivory microcrystals, m.p. 105–110° dec. Found: Br, 9.34. This material was used without purification for the preparation of the 20,21-diketone XVIII.

21-Methyl-9-fluoro-11β,17-dihydroxypregna-1,4-diene-3,20,21-trione (XVIII).—A solution of 500 mg. of crude bromohydrin XXI (as obtained above) was heated at reflux for 3 hr. and the solvent evaporated *in vacuo*. The residue was triturated with ether to crystallize the crude product, m.p. 110–130°. Recrystallization from ethyl acetate–cyclohexane gave 148 mg. of white microcrystals, m.p. 182–185°. A second recrystallization from ethyl acetate gave an analytical sample which had m.p. 219–220° dec., λ_{max} 239 mμ (15,700), $[\alpha]_D$ +88°.

Anal. Calcd. for $C_{22}H_{27}O_5F$: C, 67.67; H, 6.97; F, 4.87. Found: C, 67.64; H, 6.91; F, 4.75.

Reaction of XVIII with *o*-Phenylenediamine.—Treatment of 20 mg. of XVIII with 20 mg. of *o*-phenylenediamine in 3 ml. of ethanol for 0.5 hr. at steam bath temperature gave 14 mg. of light orange crystals; λ_{max} 238 mμ ($E^{1\%}_{1\,cm}$ 1000) and 321 mμ ($E^{1\%}_{1\,cm}$ 190). The infrared spectrum of the product exhibited no saturated carbonyl absorption bands.

21-Methyl-9-fluoro-11β,17,21α$_F$-trihydroxypregna-1,4-diene-3,20-dione (XIV) from XVIII.—A solution of 500 mg. of 20,21-diketone (XVIII) in 100 ml. of ethanol was added to a solution of sucrose (200 g.) in tap water (1500 ml.). Precipitation of some of the steroid occurred. Active dry yeast (37.5 g.) in 200 ml. of water at 40° was added, and the mixture was stirred for 53 hr. at room temperature with additions of yeast (7.5 g.) and sucrose (4.0 g.) at 24, 48, and 72 hr. After 6 days, paper chromatographic analysis indicated that most of the starting material had been reduced, and the product was isolated as described for XII. Trituration of the crude residue with ethyl acetate afforded 155 mg. of crystalline alcohol.

Acetylation of XIV in the usual way gave 108 mg. of acetate XIVa which was identical in every respect with the sample prepared by the introduction of 9-fluorine into XIIa (described previously).

6α,9-Difluoro-11β,17-dihydroxy-3,20-dioxopregna-1,4-diene-21-al (XVI).—A solution of 217.8 g. of 6α,9-difluoroprednisolone,[34] m.p. 254° dec., was oxidized with cupric acetate in methanol according to the procedure described for the preparation of I. The white crystalline product (172 g.), m.p. 181–184° dec., λ_{max} 238 mμ ($E^{1\%}_{1\,cm}$ 387), was free of starting material (paper chromatographic analysis) and was suitable for use in the next reaction. A portion of the crude aldehyde, recrystallized from methanol–water (2:1), afforded the analytical sample which had m.p. 197–204°, λ_{max} 238 mμ (16,350), $[\alpha]_D$ +90°.

Anal. Calcd. for $C_{21}H_{24}O_5F_2 \cdot CH_3OH$: C, 61.96; H, 6.62. Found: C, 62.26; H, 6.89.

21-Methyl-6α,9-difluoro-21,21a-epoxy-11β,17-dihydroxypregna-1,4-diene-3,20-dione (X).—A solution of 14.8 g. of 6α,9-difluoroprednisolone 21-aldehyde (XVI) in 650 ml. of acetone was treated at 0° with 400 ml. of ethereal diazomethane obtained from 14.7 g. of N-nitroso-N-methyl-N′-nitroguanidine. After standing at 0° for 2 hr., the excess diazomethane was destroyed with acetic acid and the solvent removed *in vacuo*. The semicrystalline residue was triturated with 1:1 acetone–ether, and filtration afforded 3.57 g. of ivory crystals which had m.p. 237–238° dec., 95% pure by paper chromatographic analysis. Another 0.83 g. of product of equal quality was isolated by chromatography of the filtrate residue on Florisil and elution of the product in ethyl acetate containing 1% acetone. The analytical sample, obtained by recrystallization of the crude product from another run from methanol and then from ethyl acetate (acetone), had m.p. 227–228° dec., λ_{max} 238 mμ (16,500), $[\alpha]_D$ +109°.

Anal. Calcd. for $C_{22}H_{26}O_6F$: C, 64.69; H, 6.42; F, 9.30. Found: C, 64.83; H, 6.53; F, 9.21.

21-Chloromethyl-6α,9-difluoro-11β,17,21ξ_F-trihydroxypregna-1,4-diene-3,20-dione (XXII).—A soultion of 816 ml. of oxide X in 4.4 ml. of 4.6 *N* methanolic hydrogen chloride, 3.6 ml. of methanol, and 8 ml. of chloroform was allowed to stand at room temperature for 2 hr. Addition of 33 ml. of water and evaporation of the chloroform and methanol gave the product as a white solid (653 mg.). The analytical sample, obtained from ethyl acetate, exhibited m.p. 181° dec., λ_{max} 237 mμ (17,400), $[\alpha]_D$ +70°.

Anal. Calcd. for $C_{22}H_{27}O_5F_2Cl$: C, 59.40; H, 6.12. Found: C, 59.11; H, 6.28.

21-Bromomethyl-6α,9-difluoro-11β,17,21ξ_F-trihydroxypregna-1,4-diene-3,20-dione (XXIII).—A suspension of 10 g. of crude oxide X in 850 ml. of 0.37 *N* methanolic hydrogen bromide was stirred at room temperature for 3 hr. The product (11.1g.), isolated as described for V, was a mixture containing approximately 60% of the desired bromohydrin, approximately 10% starting material, and 15% of a third compound presumably an isomeric bromohydrin. The crude product was suitable for use in the next reaction.

21-Methyl-6α,9-difluoro-11β,17-dihydroxypregna-1,4-diene-3,20,21-trione (XIX).—The crude bromohydrin XXIII, prepared as described earlier, was dissolved in ethyl acetate (1 l.) and heated at reflux for 2 hr. At the end of this time most of the bromohydrin had been consumed, and a new compound was detected as the major component in the reaction solution by paper chromatography. The ethyl acetate solution was concentrated to 260 ml. and 780 ml. of methylene chloride was added prior to

(33) (a) The preparation of this compound has been reported by L. H. Sarett in U. S. Patent 2,846,456 (August 5, 1958), but its constants were not included. The sample reported in the present paper appears to be a methanolate. (b) W. J. Leanza, J. P. Conbere, E. F. Rogers, and K. Pfister, *J. Am. Chem. Soc.*, **76**, 1691 (1954).

(34) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pedersen, and J. A. Campbell, *Chem. Ind.* (London), 1002 (1958).

subjecting the solution to chromatography on Florisil (350 g.). The first seven fractions contained the most product and were combined and were rechromatographed starting with methylene chloride as the eluting solvent and adding ethyl acetate. Two fractions, obtained in 25 and 50% ethyl acetate in methylene chloride, contained 4.12 g. of approximately 60% purity. Trituration of the two fractions rich in XIX with ethyl acetate gave yellow crystals. Two recrystallizations from ethyl acetate afforded an analytical sample; m.p. 161–167°, λ_{max} 237 mμ (16,400), $[\alpha]D$ +75°.

Anal. Calcd. for $C_{22}H_{26}O_5F_2$: C, 64.69; H, 6.42. Found: C, 65.05; H, 6.54.

A solution of 8 mg. of XIX and 2.37 mg. of *o*-phenylenediamine in 1.5 ml. of ethanol was heated at reflux for 0.5 hr. Addition of water caused the precipitation of a solid, weighing 5 mg., λ_{max}^{alc} 238 mμ ($E_{1\ cm}^{1\%}$ 708) and 320 mμ ($E_{1\ cm}^{1\%}$ 108).

21-Methyl-6α,9-difluoro-11β,17,21α$_F$-trihydroxypregna-1,4-diene-3,20-dione (XVII).—A solution of 10 g. of crude α-diketone XIX in 1200 ml. of ethanol was added to a mixture of 2850 g. of sucrose and 77 g. of active dry yeast in 21.2 l. of tap water. The mixture was stirred slowly for 15 days with daily additions of 60 g. of yeast and 320 g. of sucrose. The reaction mixture was filtered through Super Cel and the product isolated from the filtrate by extraction with ethyl acetate as described above for XIV. Concentration of the washed ethyl acetate extract to 150 ml. gave 6.3 g. of crude crystalline product (66% pure by paper chromatographic assay), which was purified by acetylation with acetic anhydride (12.5 ml.) in pyridine (25 ml.). The crystalline acetate XVIIa was precipitated by the addition of water and recrystallized twice from ethyl acetate. This treatment afforded 3.0 g. of 6α,9-difluoro-11β,17,21α$_F$-trihydroxy-21-methylpregna-1,4-diene-3,20-dione 21-acetate (XVIIa), which had m.p. 256–257° dec., λ_{max} 237.5 mμ (16,200), $[\alpha]D$ +95°.

Anal. Calcd. for $C_{24}H_{30}O_6F_2$: C, 63.70; H, 6.68. Found: C, 63.51; H, 6.91.

Saponification of a 778-mg. sample of XVIIa with methanolic potassium carbonate in the usual way and recrystallization twice from ethyl acetate afforded an analytical sample which had m.p. 211–211.8°, λ_{max} 237 mμ (15,500), $[\alpha]D$ +102°. The infrared spectrum of XVII showed that it retained ethyl acetate of crystallization despite drying at 135° for 16 hr. The following analysis also indicates the presence of solvent of crystallization.

Anal. Calcd. for $C_{22}H_{28}O_5F \cdot {}^1/_2\ CH_3COOC_2H_5$: C, 63.44; H, 7.05. Found: C, 63.47; H, 7.13.

Treatment of 21-Methyl-6α,9-difluoro-11β,17,21α$_F$-trihydroxypregna-1,4-diene-3,20-dione with Periodic Acid.—Treatment of 64 mg. of XVII with periodic acid (55 mg.) in 2 ml. of dioxane and 1.5 ml. of water overnight at room temperature afforded 32 mg. of an acid, m.p. 257–260° dec., identical to the etio acid obtained from 6α,9-difluoroprednisolone[34] under the same conditions.

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Proton Magnetic Resonance and Stereochemistry of 1-Ethynyl-2-tolylcyclohexanols[1]

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The diastereoisomers 1-ethynyl-*cis*-2-tolylcyclohexanol and 1-ethynyl-*trans*-2-tolylcyclohexanol, for the *o*-, *m*-, and *p*-tolyl compounds, were separated by gas chromatography and characterized by n.m.r. The n.m.r. spectra of all six isomers are consistent with structures in which the cyclohexane ring is in a chair conformation with the aromatic ring in an equatorial orientation. The long-range shielding effect of the aromatic ring causes different chemical shifts of the acetylenic hydrogen in *cis* and *trans* isomers. The aromatic *o*-hydrogen of each *o*-tolyl isomer exhibits a downfield chemical shift. Upon reduction of the ethynyl group to an ethyl group this downfield shift persists in the *cis* isomer (OH axial) and disappears in the *trans* isomer (OH equatorial).

The synthesis of 1-ethynyl-2-tolylcyclohexanols was reported in an earlier publication.[2] The separation of the resulting mixtures of *cis* and *trans* diastereoisomers has now been accomplished by gas chromatography for each of the *o*, *m*- and *p*-tolyl compounds. The components have been characterized and their stereochemistry established by nuclear magnetic resonance.

The n.m.r. spectra of the six isomers are consistent with structures in which the cyclohexane ring has the chair conformation with the aromatic ring in an equatorial orientation when measured in carbon tetrachloride. This conformation is indicated for each isomer by the quartet given by the signal of the hydrogen on C-2, which, from first-order approximation, becomes the X component of an ABX system; the two hydrogens on C-3 making up the A and B components. Figure 1 shows this signal at τ = 7.06 for 1-ethynyl-*trans*-2-*o*-tolylcyclohexanol and at τ = 6.92 for 1-ethynyl-*cis*-2-*o*-tolylcyclohexanol. The other four isomers give analogous quartets. First-order treatment of the quartets give axial–axial (*a*,*a*) splitting of 11.5 c.p.s. and axial–equatorial (*a*,*e*) splitting of 3.5 c.p.s. for every isomer with the ethynyl group in equatorial orientation. For the compounds with the ethynyl group in axial orientation the splittings are as follows: *a*,*a* = 10 c.p.s. and *a*,*e* = 4 c.p.s. for the *p*-tolyl isomer; *a*,*a* = 10.5 c.p.s. and *a*,*e* = 3.9 c.p.s. for the *m*-tolyl isomer; *a*,*a* = 10.7 c.p.s. and *a*,*e* = 3.5 c.p.s. for the *o*-tolyl isomer. In every isomer it is necessary that the hydrogen at C-2 be in an axial orientation to account for the observed splitting pattern. This interpretation has been described earlier for related compounds.[3–5] Selectively deuterated compounds are being prepared to determine if the observed splittings are true measures of the coupling constants because of the inherent danger of assigning coupling constants from first-order treatment.[6–8]

Configurations were established from the chemical shifts of the acetylenic hydrogens and the chemical

(1) This investigation was supported in part by PHS research grants no. H-3843 (C2) and no. HE-03843-04, from the National Heart Institute, Public Health Service.

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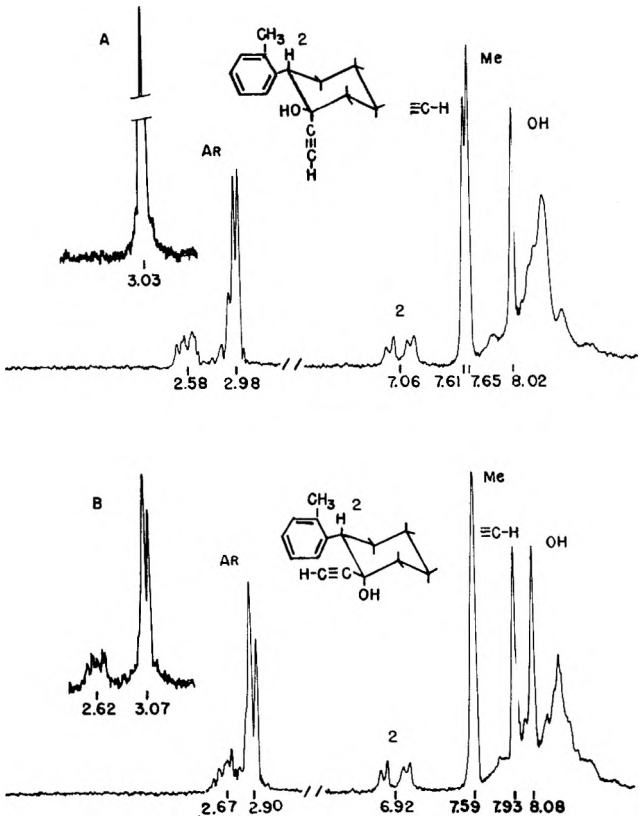

Fig. 1.—N.m.r. spectra of 1-ethynyl-*trans*-2-*o*-tolylcyclohexanol (upper curve) and 1-ethynyl-*cis*-2-*o*-tolylcyclohexanol (60 Mc.; about 1 *M* in carbon tetrachloride at 23°). Curves A and B show the signals of the aromatic hydrogens of the corresponding compounds where the ethynyl group has been reduced to an ethyl group.

shifts of the hydrogens on C-2. The chemical shifts of the hydroxyl hydrogens give additional supporting evidence for the assigned configurations. There is a significant difference in the chemical shift of the acetylenic hydrogen of the *cis* and *trans* components of each pair of diastereoisomers of the 1-ethynyl-2-tolylcyclohexanol series (see Fig. 1 and Table I), but this is not the case for the *cis* and *trans* isomers of 1-ethynyl-4-*t*-butylcyclohexanol. The difference is attributed to the long-range shielding effects of the aromatic ring, the largest effect being a shielding of the acetylenic hydrogen in those isomers having the ethynyl group equatorial. It can be shown with molecular models that in the 1-ethynyl-*cis*-2-tolylcyclohexanols the equatorial ethynyl group hinders rotation of the tolyl group preventing coplanarity of the rings and causing the average time orientation of the aromatic ring to be more closely one in which the plane of the aromatic ring is perpendicular to the cyclohexane ring. With this orientation of the aromatic ring the equatorial acetylenic hydrogen is located in a region of shielding resulting from the magnetic anisotropy of the aromatic ring. The magnetic anisotropy of the benzene ring has been discussed elsewhere,[9-11] and regions and extent of positive and negative shielding have been mapped for the benzene ring by Johnson and Bovey.[11] Calculations from Dreiding models, using the "Nuclear Shielding Values Table" of Johnson and Bovey,[11] give a shielding value of 0.27 τ units for the acetylenic hydrogen of 1-ethynyl-*cis*-2-tolylcyclohexanols (ethynyl group equatorial) when the rings are perpendicular to each other. Counterclockwise rotation[12] of the aromatic ring by about 15° from perpendicular would increase the shielding to a maximum of about 0.4 τ units, and further rotation would result in a gradual decrease of the shielding effect. Rotation in a clockwise direction would cause a decrease of the shielding effect. The observed shielding values of about 0.2 p.p.m. for the *para* and *meta* tolyl isomers and 0.24 p.p.m. for the *ortho* isomers, compared to *cis*- and *trans*-1-ethynyl-4-*t*-butylcyclohexanol (τ = 7.69), are in good agreement with expected values. The greater shielding for the *o*-tolyl isomer is as expected because the additional steric hindrance of the *o*-methyl group will restrict the limits of oscillation of the aromatic ring.

In the 1-ethynyl-*trans*-2-tolylcyclohexanol series the axial ethynyl hydrogen is in a region of deshielding when the rings are perpendicular to each other (calculated deshielding of about 0.2 p.p.m.), but it can be brought into a region of shielding by slight rotation of the aromatic ring in a clockwise direction, while counterclockwise rotation would increase the deshielding effect. The effects appear to cancel out in the *para* and *meta* tolyl isomers, but, as expected, there is a deshielding effect in the *ortho* isomer where clockwise rotation would be hindered to a greater extent by the *o*-methyl group.

The signal of the acetylenic hydrogen was differentiated from that of the hydroxyl hydrogen for each isomer by measuring the n.m.r. spectrum at half the original concentration and also at increased temperature. Under these conditions the signal of the hydroxyl group was shifted to higher field because of decrease in intermolecular hydrogen bonding, while that of the acetylenic hydrogen remained essentially constant. The same was true for the 1-ethynyl-4-*tert*-butylcyclohexanols.

The configurations assigned on the basis of the long-range shielding effects of the aromatic ring on the acetylenic hydrogens are substantiated by the larger chemical shift of the hydrogen at C-2 for the isomer with the hydroxyl group axial in each diastereoisomeric pair. This difference cannot be explained by inductive effect through bonding orbitals. The same phenomenon has been observed in *cis*- and *trans*-2-*o*-tolylcyclohexanol[3] and in the three diastereoisomeric pairs of 2-(chlorophenyl)cyclohexanols,[4] where it was pointed out that this is consistent with the magnetic anisotropy of the C–O bond deshielding the hydrogen at C-2 when the hydroxyl group is axial and shielding it when the hydroxyl group is equatorial. In the 1-ethynyl-*cis*-2-tolylcyclohexanols the steric repulsion between the equatorial ethynyl group and the aromatic ring should cause a greater deshielding of the hydrogen on C-2 by the aromatic ring. In the 1-ethynyl-*trans*-2-tolylcyclohexanols the additional long-range effect resulting from the magnetic anisotropy of the ethynyl group must be considered. The long-range effects of

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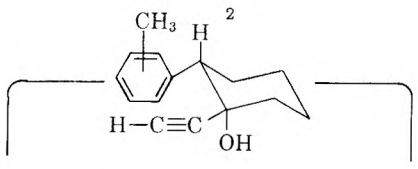
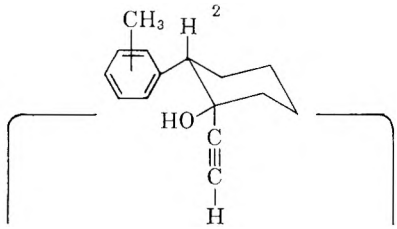
(12) The terms "clockwise" and "counterclockwise" rotation refer to the structures shown in Fig. 1. For the mirror images rotation would be in opposite direction to produce the same effect.

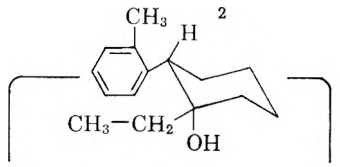
TABLE I

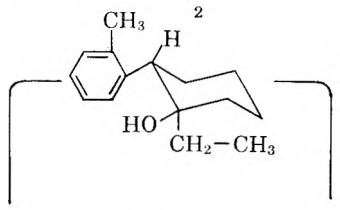
CHEMICAL SHIFTS[a]

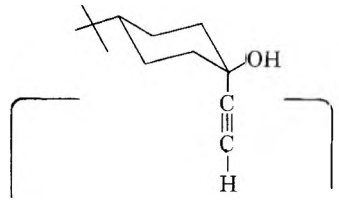


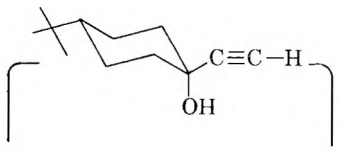


isomer	≡C—H	2	OH	CH_3	AR	≡C—H	2	OH	CH_3	AR
p-Methyl	7.88	7.38	8.15	7.73	2.92	7.72[b]	7.50	8.06	7.72	2.92
m-Methyl	7.88	7.36	8.23	7.69	2.91	7.67	7.49	7.92	7.67	2.86
o-Methyl	7.93	6.92	8.08	7.59	2.90; 2.67	7.61	7.06	8.02	7.65	2.98; 2.58









2	CH_3	AR	2	CH_3	AR	≡C—H	OH	*t*-Bu	≡C—H	OH	*t*-Bu
7.26	7.75	3.07; 2.62	6.98[c]	7.64	3.03	7.70	7.77	9.15	7.68	7.17	9.14

[a] The chemical shifts are expressed as τ values (p.p.m.) referred to tetramethylsilane used as internal reference. [b] The signal of this hydrogen is completely overlapped with the signal of the hydrogens of the methyl group. [c] The signal of the hydrogen at C-2 of this isomer is an unresolved multiplet.

the ethynyl triple bond give conical regions of shielding along the longitudinal axis at both ends of the ethynyl group, and deshielding elsewhere.[13] If the magnetic anisotropy of the ethynyl group exerts any effect on the hydrogen on C-2 through space it must be one of shielding when the group is axial. The shielding effect of the axial ethynyl group is therefore in the same direction as that of the equatorial hydroxyl group. The extent and direction of the shielding effect on the hydrogen at C-2 resulting from the magnetic anisotropy of an equatorial ethynyl group is less certain but the effect is probably small. All factors affecting the chemical shift of the hydrogen on C-2 are consistent with the observed chemical shifts and with the assigned configurations.

The larger downfield shift of the signal of the hydroxyl hydrogen when the hydroxyl group is equatorial, compared to the corresponding isomer where it is axial, is in agreement with similar observations for the *cis*- and *trans*-2-*o*-tolylcyclohexanol[3] and the three diastereoisomeric pairs of 2-(chlorophenyl)cyclohexanols.[4] The same phenomenon is observed for 1-ethynyl-4-*tert*-butylcyclohexanols (Table I). This could result from differences in degree of intermolecular hydrogen bonding.

The n.m.r. spectra of 1-ethynyl-2-*o*-tolylcyclohexanols (Fig. 1) show a significant downfield shift of the signal of one aromatic hydrogen for each isomer, the effect being larger for the isomer with the ethynyl group in axial orientation. This effect does not occur in any of the isomers with the methyl group *meta* or *para*. Furthermore, the phenomenon does not occur in either *cis*- or *trans*-2-*o*-tolylcyclohexanol.[3] The *ortho* methyl group in the isomeric 1-ethynyl-2-*o*-tolylcyclohexanols must cause the *ortho* hydrogen to be located in a region of long-range negative shielding and the ethynyl group must play a role in both isomers. Molecular models show that for both isomers the least hindered position of the aromatic ring is one where the two rings are essentially perpendicular to each other with the methyl group on top. Oscillation from this position is allowed, but clockwise rotation is hindered by repulsion of the methyl group and the equatorial substituents, especially the equatorial ethynyl group, and counterclockwise rotation is hindered by the repulsion of *ortho* hydrogen and the axial ethynyl group in the other isomer. In the favored conformation of the isomer with the ethynyl group axial the *ortho* hydrogen is located in close proximity to the ethynyl group about midway between the two *sp* carbon atoms, a region of negative shielding resulting from the magnetic anisotropy of the ethynyl group.[13] In the isomer with the ethynyl group equatorial the *ortho* hydrogen comes closer to the no. 1 carbon atom of the ethynyl group and in relationship to the ethynyl group it appears to fall more closely in the line of demarcation between regions of shielding and de-

(13) Ref. 9, pp. 17 and 112; ref. 7, p. 179.

shielding of the ethynyl group. The *ortho* hydrogen, however, is in very close proximity of the axial hydroxyl group and it seems likely that the downfield shift of the *ortho* hydrogen in this isomer results from a deshielding effect of the axial hydroxyl group, while the effect in the other isomer results from a deshielding of the *ortho* hydrogen by the axial ethynyl group. The long-range deshielding effect of the hydroxyl group is a recognized phenomenon.[14-16] This interpretation was tested by measuring the n.m.r. spectra of the hydrogenation product of the two ethynyl isomers and found to be correct. If the interpretation is correct the downfield shift of the *ortho* hydrogen should persist in 1-ethyl-*cis*-2-*o*-tolylcyclohexanol (ethyl group equatorial) and disappear in 1-ethyl-*trans*-2-*o*-tolylcyclohexanol (ethyl group *cis* to the tolyl group). Curves A and B of Fig. 1 show that this is exactly what takes place. Actually the paramagnetic shift of the *ortho* hydrogen is greater with the equatorial ethyl group than with the equatorial ethynyl group. The signal of the hydrogen on C-2 of 1-ethyl-*cis*-2-*o*-tolylcyclohexanol gives the typical quartet with *a,a* splitting of 11.2 c.p.s. and *a,e* splitting of 3.5 c.p.s. Indicating the chair conformation with the aromatic group in equatorial orientation as expected, while the signal of the C-2 hydrogen of 1-ethyl-*trans*-2-*o*-tolylcyclohexanol gives a broad unresolved multiplet. This could result from an equilibrium between the two possible chair conformations in this isomer where the tolyl and ethyl groups are *cis* to each other; but it could also possibly result from the difference in long-range shielding effects of the axial ethyl group compared to the axial ethynyl group on the axial hydrogen on C-3. This point will be clarified by the preparation of selectively deuterated compounds.

Experimental

The separation of the liquid mixtures of 1-ethynyl-2-tolylcyclohexanols[2] into their *cis* and *trans* components was accomplished with a Beckman GC-2 gas chromatograph using a 10 ft. × 5/8 in. column packed with 18% Dow Corning Silicone QF-1 on acid-washed Chromosorb W[17] at 160°.

1-Ethyl-*cis*-2-*o*-tolylcyclohexanol and 1-Ethyl-*trans*-2-*o*-tolylcyclohexanol.—These compounds were obtained by catalytic hydrogenation of the corresponding 1-ethynyl-2-*o*-tolylcyclohexanols in ethyl acetate using 10% palladium on carbon under 20 pounds pressure. The calculated amount of hydrogen was picked up rapidly. The products were purified by gas chromatography at 160° using the same column used to separate the ethynyl compounds. The products were also obtained by reduction of the mixture of ethynyl compounds and subsequent separation of the isomers by gas chromatography with a 10-ft. column of 18% Carbowax 20M on acid-washed Chromosorb W at 196°.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found for the *cis* isomer: C, 82.64; H, 10.21. Found for the *trans* isomer: C, 82.53; H, 10.29.

TABLE II

PHYSICAL CONSTANTS AND ANALYSES[a]

Compound	M.p., °C.[b]	—Found, %— C	H
1-Ethynyl-*cis*-2-*p*-tolylcyclohexanol	36–37	83.95	8.16
1-Ethynyl-*trans*-2-*p*-tolylcyclohexanol	65.5–66.5	83.95	8.73
1-Ethynyl-*cis*-2-*m*-tolylcyclohexanol	56–56.5	84.03	8.39
1-Ethynyl-*trans*-2-*m*-tolylcyclohexanol	[c]	84.06	8.23
1-Ethynyl-*trans*-2-*o*-tolylcyclohexanol	56–57	84.29	8.40
1-Ethynyl-*cis*-2-*o*-tolylcyclohexanol	81–82	83.91	8.50

[a] Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. [b] Melting points were determined with a Kofler micro hot stage. [c] This compound was obtained as a viscous, colorless liquid.

1-Ethynyl-*trans*-4-*t*-butylcyclohexanol and 1-Ethynyl-*cis*-4-*t*-butylcyclohexanol.—These two isomers were obtained by the method of Hennion and O'Shea.[18] The configurations assigned by these authors on the basis of kinetics of saponification of the *p*-nitrobenzoate esters are in agreement with the observed chemicals shifts of the hydroxyl protons of these two isomers when compared to the relative chemical shifts of axial and equatorial hydroxyl protons of other cyclohexanols (Table I and ref. 3 and 4). Because of the variability in the chemical shifts of hydroxyl protons this observation does not constitute proof of conformation.

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(15) W. H. Tallent, *J. Org. Chem.*, **27**, 2968 (1962).
(16) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull., Japan*, **10**, 338 (1962).
(17) Wilkens Instrument and Research, Inc., Walnut Creek, Calif.
(18) G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, **80**, 614 (1958).

4-(*p*-Tolyl)-1-pentanol in Douglas Fir Pulping Products[1]

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An optically active alcohol has been isolated from the product of pulping Douglas fir *via* the kraft process. This has been identified by degradation and synthesis as 4S-4-(*p*-tolyl)-1-pentanol. It is suggested that this alcohol is formed during the pulping process from γ-curcumene, a terpene not previously identified in Douglas-fir extractives.

Among the organic products derived from the pulping of wood of the Douglas fir, *Pseudotsuga menziesii*, [Mirb. (Franco)] by the kraft process are some with a considerable biological activity. In particular the toxicity of the by-product toward a number of species of fish has been thoroughly established. Recent work on this campus[2] established that one or more of these toxic substances could be steam distilled. It occurred to us that some of the biologically active materials could be related chemically to the furocoumarin fish

(1) This project was supported by a research grant, no. WP00079-5 from the Division of Water Supply and Pollution Control, Public Health Service.

(2) Robert A. McHugh, "Preliminary report on a study of the factors responsible for the toxicity of waste from a modern kraft pulp mill," Oregon State University, 1954.

poisons such as xanthotoxin, bergapten, imperatorin, and the more complex derivatives like rotenone.[3] The formation of coumarins or benzofurans or both from the substituted γ-phenylpropyl groupings present in lignin[4] would not be surprising in an aqueous polysulfide medium as is present in kraft pulping liquors. Work was initiated, therefore, aimed at the isolation and identification of the biologically active components in the by-products of the kraft pulping process.

A sample of the by-product materials from a kraft cook on Douglas fir was steam distilled and the organic materials in the distillate extracted with ether. There was obtained 63.4 g. of dark colored liquid which was separated into three fractions by distillation *in vacuo*. The fraction boiling from 56–95° (0.3 mm.) was chromatographed on silicic acid and the major component of this fraction, 7.31 g. of colorless oil, exhibited a strong toxicity toward fish. This component, labeled II-2, was shown to be uniform and attention was directed toward ascertaining its structure.

The infrared spectrum of II-2 showed the presence of a hydroxyl group (3400 cm.$^{-1}$) and a benzene ring (1500 cm.$^{-1}$). Although a small peak at 1625 cm.$^{-1}$ and bands at 984 and 895 cm.$^{-1}$ suggested the possible presence of an olefinic double bond, the liquid failed to add hydrogen and did not react with perbenzoic acid. The spectrum suggested a primary alcohol and a 3,5-dinitrobenzoate formed readily. The analysis of both the original oil and the derivative were in good accord with the formula $C_{12}H_{18}O$ for the alcohol. The ultraviolet spectrum was not appreciably altered by the addition of alcoholic sodium hydroxide and the substance was therefore an alcohol and not a phenol.

The pattern of bands between 1700 and 2000 cm.$^{-1}$ and the band at 812 cm.$^{-1}$ suggested that the benzene ring was *para* disubstituted. This was confirmed by the formation of terephthalic acid *via* oxidation with alkaline permanganate. In order to ascertain the partitioning of the carbon atoms between the two chains a differential oxidation with nitric acid[5] was carried out. Paper chromatography showed the presence of *p*-toluic acid, malonic acid, and oxalic acid in the oxidation product. A crude sample of *p*-toluic acid was isolated which showed an infrared spectrum identical with that of an authentic specimen. Amongst the optically active alcohols to be considered at this point 4-(*p*-tolyl)-1-pentanol provided the most reasonable structure for the following reasons.

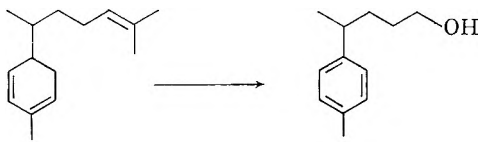
It seems clear that the alcohol could not arise from lignin, and since the optical activity necessitates a natural source a terpene precursor seemed likely. This structure conforms to the isoprene rule. It also provides a ready rationale for the formation of malonic acid during the nitric acid oxidation. Finally a survey of the literature revealed that 4-(*p*-tolyl)-1-pentanol is known[6] and forms a 3,5-dinitrobenzoate which melts at the same temperature. It seemed appropriate, therefore, to prepare a comparison sample.

Racemic 4-(*p*-tolyl)-1-pentanol was prepared from 3-(toluoyl)propionic acid by treatment with methyl Grignard and reduction of the γ-(*p*-tolyl)-γ-valerolactone to 4-(*p*-tolyl)pentanoic acid by the Clemmensen method. This acid was reduced to the required alcohol by lithium aluminum hydride. The alcohol obtained from the hydride reduction showed an infrared spectrum identical with that of the unknown alcohol and the 3,5-dinitrobenzoates had the same melting point. Therefore, II-2 is optically active 4-(*p*-tolyl)-1-pentanol, a substance not previously known to be formed during the kraft process.

Calculations using the conformational asymmetry model[7] predict that the S configuration[8] of 4-phenyl-1-pentanol should have a dextro rotation, $[\phi] = +40°$. The molecular rotation of the 4-(*p*-tolyl)-1-pentanol isolated is +67° which suggests that it has an S configuration and is of high optical purity.

As was noted earlier the lack of structural relationship between this alcohol and the typical γ-phenylpropyl skeleton of lignin breakdown products, and the direct relation to a sesquiterpene skeleton makes a terpene precursor seem reasonable. The sesquiterpene hydrocarbons, bisabolene, zingerberene, and the curcumenes,[9] all have the proper carbon skeleton to be precursors of this alcohol. While none can be eliminated from consideration, only bisabolene[10] and γ-curcumene[11] appear to have been isolated fron conifers. Though bisabolene is biologically the more reasonable parent due to its wide distribution in nature, the great ease of conversion of γ-curcumene to an aromatic compound[11] makes it chemically the more appropriate ancestor.

The conditions of the kraft reaction involve a basic, aqueous sulfide medium which resemble those of the well investigated Willgerodt reaction,[12] except that a lower sulfur content is present under kraft conditions. Both oxidation and reduction of the organic substrate can occur during the Willgerodt reaction, and indeed oxidative cleavage of an olefinic double bond has been observed.[13] Willgerodt media low in sulfur content have been found[12] to lead to partial oxidation so that aldehydes or ketones rather than acid derivatives are the products, and reduction of carbonyl groups by inorganic sulfides[14] has been noted. Thus all of the reactions required to convert γ-curcumene to 4-(*p*-tolyl)-



1-pentanol have been shown to occur at elevated temperatures in basic polysulfide media. No previous evidence for the presence of a sesquiterpene hydrocarbon of this skeleton in Douglas fir extractives has come to the attention of the authors.

(3) For a brief review of these substances see N. Campbell in Rodd, "Chemistry of Carbon Compounds," Vol. IV B, Elsevier, Amsterdam, 1959, pp. 883–887.

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(12) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 127–139.

(13) W. G. Toland, D. L. Hagmann, J. B. Wilkes, and F. J. Brutschy, *J. Am. Chem. Soc.*, **80**, 5423 (1958).

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It is interesting that 4-(*p*-tolyl)-1-pentanol is quite toxic to fish[15] but since the percent of the total toxicity accounted for by this alcohol is lower than its weight percent in the initial sample, more toxic substances are present in the as yet uninvestigated residue. The alcohol also shows inhibitory activity toward the cytochrome–oxidase system *in vitro* which rivals that of cyanide ion. Such high biological activity seems unusual for a molecule of this structure.

Experimental

Sample Preparation.—Raw material for study was obtained from a kraft pulp mill pulping only Douglas fir chips, and producing unbleached pulp. Samples totalling 130 gal. of condensate from the low vacuum stage of the weak black liquor evaporator were collected at random intervals during the summer of 1959. This liquor containing the steam distilled by-products of the kraft cook was distilled under reduced pressure at 85–90° in 5-gal. batches. Each batch was reduced to about 350-ml. residue which was discarded. The distillate was extracted with ether for 24 hr. in a liquid–liquid extractor. The ether extract was dried over anhydrous magnesium sulfate and the ether removed *via* distillation using a Fenske column. The residue consisted of 63.4 g. of viscous dark oil with a characteristic odor. This material was distilled *in vacuo* using a simple Claisen head. Three fractions were obtained: I, b.p. 30–56° (0.3 mm.), 5.4 g. of light yellow mobile oil; II, b.p. 56–95° (0.3 mm.), 11.0 g. of light yellow oil; and III, residue 46.5 g. of dark viscous oil. An attempt to distil a portion of the residue by molecular distillation resulted in decomposition.

Fraction I.—Preparative gas chromatography using an 8.5 ft. × 0.5 in. column of 20% Reoplex 400 on Celite at 170° permitted separation of fraction I into three portions: I-1, 40 mg. of colorless liquid; I-2, 1.14 g. of light tan liquid; and I-3, 4.25 g. of light brown liquid. A chromatogram of I-1 on a 14 ft. × 1/8 in. column of 10% Carbowax 20M on firebrick at 172° using helium as carrier gas showed eighteen peaks. Fraction I-2 was rechromatographed on the original preparative column and two fractions, I-2a, 620 mg. of dark brown oil, and I-2b, 500 mg. of a light yellow oil, were collected.

Fraction I-2a was chromatographed on a 14 ft. × 1/3 in. column packed with 10% Carbowax 20M on firebrick at 133° showing eighteen peaks. This fraction was then chromatographed on a 12 ft. × 1/8 in. column packed with 10% Craig polyester on firebrick at 108°, showing fifteen peaks. The areas under the various peaks were used to provide an arbitrary interrelationship between the peaks on the two columns through only about ten peaks could be reasonably identified in this way. Mixture of fraction I-2a with anisole, β-pinene, *p*-cymene, citronellol, terpinolene, linalool, limonene, terpinene, methone, and menthofuran were run through both columns. When the related peaks on both columns were enlarged by addition of the same component, that component was considered to be satisfactorily identified. Thus limonene, terpinene, *p*-cymene, and anisole were found to be present.

Fraction I-2b was uniform to gas chromatography on the above columns. The liquid had the following properties: mol. wt., 235 (osmometer), ν = 3400, 1725, 1680, λ_{max} 238 (*ca.* 27,000), 280 (*ca.* 5000). A solution containing 43 mg. of I-2b in ethanol was mixed with 1.5 ml. of a solution of 2,4-dinitrophenylhydrazine in diglyme. Two drops of hydrochloric acid were added and the solution allowed to stand 24 hr. The deep red precipitate was recrystallized from benzene and 2 mg. of orange crystals, m.p. > 300° were isolated.

Fraction I-3 was uniform to gas chromatographic tests. It was distilled *in vacuo* giving 4.0 g. of colorless oil, b.p. 95° (0.3 mm.), ν = 3480, 3050, 1610, 1605, 1513, and 750 cm.$^{-1}$. One gram of I-3 was mixed with 0.7 g. of benzoyl chloride and the mixture boiled for 5 min. The mixture was poured onto ice and the residue triturated with 5% sodium carbonate solution. The solid residue was recrystallized from ethanol, m.p. 58°. A mixture with an authentic sample of guaiacol benzoate melted at 58°.

(15) The authors are indebted to Dr. Charles Warren of the Fish and Game Department, Oregon State University, for the biological toxicity determination which will be reported in detail elsewhere.

Fraction II.—Elution chromatography of 6.98 g. of fraction II on 200 g. of predried silicic acid using 2 l. of ligroin, 2 l. of benzene, 1 l. of carbon tetrachloride, 1 l. of chloroform, 1 l. of ether, and 1 l. of methanol in that order as eluants separated five fractions as indicated by a plot of weight of material per tube against tube number. These were combined as the following fractions: II-1, 500 mg. of colorless liquid, II-2, 4.25 g. of light brown oil, II-3, 308 mg. of a dark oil, II-4, 263 mg. of a dark oil and II-5, 850 mg. of a viscous brown liquid.

Fractions II-1, II-3, and II-4 were shown by gas chromatography to contain 16, 17, and 16 components, respectively. These were not investigated further.

Fraction II-2.—was purified by chromatography on activity III (Brockman) alumina and the main fraction eluted in benzene. This was distilled to give 2.6 g. of a clear liquid, b.p. 72–74° (0.1 mm.), $n^{29}D$ 1.5051, d^{23} 0.9635; λ_{max} 237, 259, 265; ν = 3400, 2900, 1860 w, 1760 w, 1622, 1500 s, 1050, 984, 895, 812, and 720 cm.$^{-1}$; $[\alpha]^{25}D$ + 38.1 (95% ethanol, 4.64 mg./ml.). This substance did not add hydrogen or react with perbenzoic acid.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.45, 80.74; H, 10.08, 9.98.

II-2 3,5-Dinitrobenzoate.—A solution containing 100 mg. of II-2 and 200 mg. of 3,5-dinitrobenzoyl chloride in 0.3 ml. of pyridine was warmed on a steam bath for 10 min. The solution was poured into 4 ml. of water, the insoluble residue washed with 2% sodium carbonate, and the solid material recrystalized from ethanol. Thus 50 mg. of bright yellow crystals, m.p. 78°, was obtained.

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.14. Found: C, 61.19, 61.37; H, 5.37, 5.14.

Oxidation of II-2.—A solution containing 37.8 mg. of II-2 and 250 mg. of potassium permanganate in 7.5 ml. of water was heated on a boiling water bath for 6 hr. The manganese dioxide was removed by filtration, the solution acidified with hydrochloric acid, and extracted with ether. The ether extracts were dried over anhydrous mgnesium sulfate. Evaporation of the ether gave 28.2 mg. of white crystals which sublimed without melting at 250°. The infrared spectrum (KBr pellet) was identical with that of an authentic specimen of terephthalic acid.

A solution of 77.5 mg. of II-2 in 1.5 ml. of 3.5 N nitric acid was heated under reflux for 12 hr. Sufficient 1 *N* sodium hyroxide was added to dissolve the precipitate, a small amount of powdered zinc added and the mixture heated for 1 hr. A portion of the solution was distilled to remove reduced nitration products, and the zinc removed from the residue. The aqueous solution was acidified, extracted with ether and the ether extracts dried. Paper chromatography of the extracts on Whatman no. 4 paper using ethanol–ammonia–water (80:4:16) showed four spots, R_f 0.73, 0.44, 0.26, and 0.00. Under the same conditions the following R_f values were observed: *p*-toluic acid 0.72, acetic acid 0.43, malonic acid 0.25, and oxalic acid 0.00. The ether was evaporated from the extracts and 29.9 mg. of white crystals, m.p. 158–166°, were recovered. The infrared spectrum was nearly identical with that of *p*-toluic acid.

Fraction II-5.—gave after standing in the cold a crystalline magna. After recrystallization from benzene–ligroin, 50 mg. of white crystals, m.p. 90–92°, were obtained. These showed infrared absorption at 3400, 2940, 2880, 1625 w, 1470, 1445, 1420, 1380, 1170, 1125, 1010, 987, 947, 900 and 835 cm.$^{-1}$. II-5 decolorized potassium permanganate and bromine water but did not give a color with ferric chloride.

3,5-Dinitrobenzoate of II-5.—was prepared as described above for II-2. Recrystallization from ethanol gave 60 mg. of pale pink crystals, m.p. 170–171°, λ_{max} 230 mμ ($E^{1\%}_{1cm}$ 774). The melting point suggests a di-3,5-dinitrobenzoate and, using λ_{max} 230 mμ (ε 45,000) for the average for such derivatives, the mol. wt. of II-5 is estimated at 190 ± 20. Analytical data were unsatisfactory.

γ-(*p*-Tolyl)-γ-valerolactone.—To a solution containing 0.25 mole of methyl Grignard reagent was added slowly a solution of 23.6 g. (0.123 mole) of 3-(*p*-toluoyl)propionic acid[16] in ether. The reaction mixture was heated at reflux for 2 hr., then decomposed with cold dilute sulfuric acid. The ether layer was separated, washed with dilute sodium hydroxide, and dried. After evaporation of the ether the lactone was distilled, b.p. 98° (0.05

(16) E. de B. Barnett and F. G. Saunders, *J. Chem. Soc.*, 434 (1933).

mm.), 7 g. (40% based on acid used), ν = 1775 cm.$^{-1}$. A melting point of 56° has been reported[17] for this lactone.

4-(*p*-Tolyl)pentanoic Acid.—The previous lactone was reduced according to the procedure of Martin.[18] After 22 hr. the toluene layer was separated and extracted with dilute sodium hydroxide. The basic layer was acidified with hydrochloric acid and extracted with ether. The ether extracts were dried and the product distilled, b.p. 115° (1.5 mm.), 2.7 g. (38%). Boiling points of 173° (9 mm.)[17] and 180° (14 mm.)[6] have been reported.

4-(*p*-Tolyl)-1-pentanol.—The above acid was esterified with ethanol and hydrochloric acid. The ester, b.p. 144 (9 mm.),[6,17] was obtained as a colorless oil in 78% yield. A solution containing 2.3 g. of the ester in ether was added dropwise to a solution containing 0.47 g. of lithium aluminum hydride and the solution stirred at room temperature for 15 min. Excess hydride was destroyed with moist ether. The product was distilled *in vacuo*, b.p. 72–74° (0.1 mm.), 1.28 g. (62%). Simonsen[4] reports a boiling point of 151° (16 mm.) for this alcohol. Its infrared spectrum was identical with that of II-2 and its 3,5-dinitrobenzoate melts at 78° (reported[6] m.p. 80°).

Infrared Spectra.—Infrared spectra were carried out unless otherwise specified on neat liquids using a Perkin-Elmer Model 21 spectrometer.

Gas Chromatography.—A Model 154C Perkin-Elmer vapor fractometer was used with helium as the carrier gas under the conditions indicated in each case.

(17) H. Rupe and A. Steinback, *Ber.*, **44**, 584 (1911).
(18) E. L. Martin, *J. Am. Chem. Soc.* **58**, 1438 (1936).

The *meso* and Racemic Forms of 2,4-Pentanediol and Certain of Their Derivatives

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The *meso* and racemic forms of 2,4-pentanediol have been separated from their mixture *via* fractional distillation of their cyclic sulfite esters, and their structures identified through their proton resonance spectra. The separated diols have been converted to diacetates, bis-3,5-dinitrobenzoates, dichlorides, and dibromides of corresponding structural symmetry and the isomeric pairs characterized. The reduction of acetylacetone by sodium–ethanol, nickel–hydrogen, and sodium borohydride yielded the *meso* and racemic 2,4-pentanediols in the ratios 9:11, 11:9, and 2:1, respectively.

The *meso* and racemic forms of 2,4-pentanediol and their derivatives are of topical interest as model systems for spectroscopic and chemical studies relating to polymers.[1–6] This paper discusses a convenient preparation for the isomeric diols, and their conversion to dihalides and other derivatives.

Previously reported separations of *meso* and racemic forms in 2,4-disubstituted pentane systems are as follows. The sodium hydroxide complexes of the diol cyclic borate esters have been separated in aqueous solution by paper ionophoresis[7] and by chromatography on the borate form of an anion-exchange resin[3]; the diol mono-*p*-bromobenzenesulfonate esters have been separated by solution chromatography on alumina.[8] The dichlorides have been separated in the vapor phase on a dioctyl phthalate column[5] and the diamines were separated long ago *via* crystallization of their acetyl derivatives.[9] Apart from the last system, the above separations are suitable only for small quantities unless very large sized equipment is used. It was, therefore, our aim to develop a simple distillation method for large-scale separation of the diol isomers in a pure state (*via* an ester derivative), using chromatography only as a method of analysis for the isomers. Then, the further goal was to study methods for converting each pure form of the diol to some other useful 2,4-disubstituted pentane derivatives, without loss of isomeric purity.

Results and Discussion

Separation and Characterization of *meso* and Racemic 2,4-Pentanediol.—An experimental review of various methods of reduction of acetylacetone—a readily available starting material—showed that a most straightforward procedure for obtaining a high yield of good-quality diol mixture could be worked out using sodium borohydride, which we recommend in preference to other methods even though it gives an isomer ratio somewhat removed from 1:1 (see Experimental).

A separation of the isomeric diols *via* fractional distillation of their cyclic sulfite esters[10] was found to work quite successfully. Thus, the conversion of the diol mixture to a cyclic sulfite mixture through thionyl chloride was straightforward, requiring only the simplest apparatus; and direct fractionation of the reaction mixture without elaborate work-up was satisfactory. The *meso* and racemic cyclic sulfites, the b.p. of which differ by only 10° at 12 mm., apparently form a sufficiently non ideal boiling mixture for a clean separation to be achieved in a modestly efficient fractionating column (see Experimental). The hydrolysis of the individual cyclic sulfite isomers back to diols with aqueous sodium hydroxide was straightforward, and this type of process is known to occur by sulfur–oxygen bond fission, *i.e.*, without the possibility of change of configuration.[11,12] The over-all yields of pure diol

(1) J. T. Clarke and E. R. Blout, *J. Polymer Sci.*, **1**, 419 (1946). A 2,4-pentanediol mixture having no ultraviolet absorption above 220 mμ had b.p. 201.0 to 201.2° (760 mm.) and n^{20}D 1.4354.
(2) M. Matsumoto and K. Imai, *Kobunshi Kagaku*, **15**, 160 (1958).
(3) E. Nagai, S. Kuribayashi, M. Shiraki, and M. Ukita, *J. Polymer Sci.*, **35**, 295 (1959). The melting points reported for the two isomeric forms of 2,4-pentanediol cyclic borate are 85° and 37°. The microanalyses reported for 2,4-pentanediol isomers separated *via* the cyclic borates are incredibly bad.
(4) M. Shiraki and E. Nagai, *Nippon Kagaku Zasshi*, **81**, 976 (1960); R. Chujo, S. Satoh, T. Ozeki, and E. Nagai, *Reports Prog. Polymer Physics, Japan*, **5**, 248 and 251 (1962).
(5) T. Shimanouchi and M. Tasumi, *Spectrochim. Acta*, **17**, 755 (1961).
(6) T. Takata, *et al.*, *Kobunshi Kagaku*, **16**, 693 (1959); **18**, 235 (1961).
(7) J. L. Frahn and J. A. Mills, *Australian J. Chem.*, **12**, 65 (1959).
(8) H. B. Henbest and B. B. Millward, *J. Chem. Soc.*, 3579 (1960).
(9) C. J. Dippel, *Rec. trav. chim.*, **50**, 525 (1931).
(10) *Cf.* F. M. Robertson and A. C. Neish, *Can. J. Res.*, **25B**, 491 (1947). These authors suggested that the *meso* and *laevo*-2,3-butanediols might be easily separated *via* fractional distillation of their cyclic sulfites.
(11) C. A. Bunton, P. B. D. de la Mare, P. M. Greaseley, D. R. Llewellyn, N. H. Pratt, and J. G. Tillett, *J. Chem. Soc.*, 4751 (1958).
(12) C. A. Bunton, P. B. D. de la Mare, A. Lennard, D. R. Llewellyn, R. B. Pearson, J. G. Pritchard, and J. G. Tillett, *ibid.*, 4761 (1958).

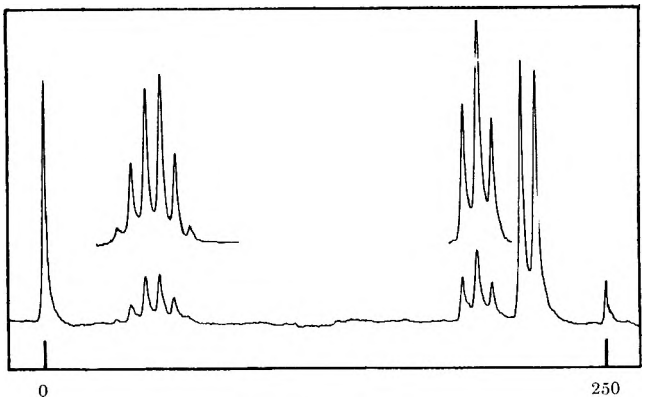


Fig. 1.—Proton resonance spectrum at 60 Mc./sec. of a deuterium oxide solution of the 2,4-pentanediol with m.p. 48–49° and having a bis-3,5-dinitrobenzoate with m.p. 179°. The scale is set arbitrarily at zero for the signal from OH protons and 250 c.p.s. therefrom at a side band.

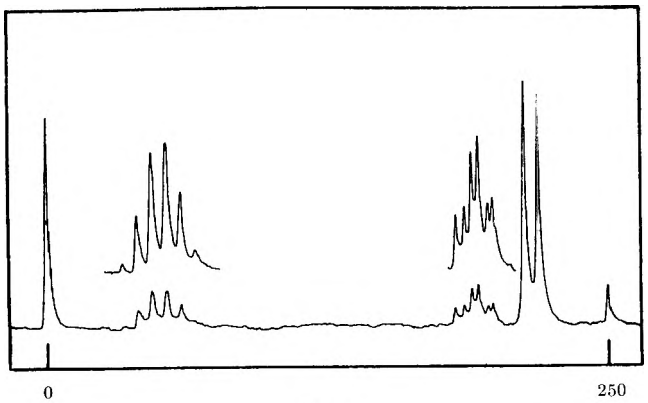


Fig. 2.—Proton resonance spectrum at 60 Mc./sec. of a deuterium oxide solution of the 2,4-pentanediol noncrystallizable at room temperature and having a bis-3,5-dinitrobenzoate with m.p. 190°. (Scale as for Fig. 1.)

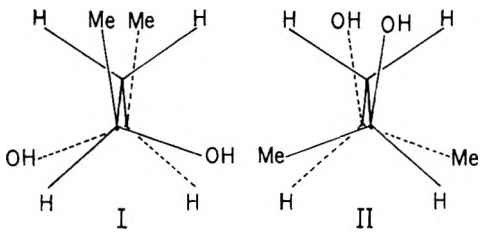
isomers separated from the mixture were 30% of *meso* plus 17% of racemic diol.

The 2,4-pentanediol isomers have not been well characterized in the past. Both microanalytical and infrared studies have left much to be desired,[1-3,13-17] which may be due in part to the very hygroscopic nature of these diols.

Microanalysis of our diol products, separated by way of the diol cyclic sulfites, shows them to be acceptably pure and they are further characterized by bis-3,5-dinitrobenzoates. As a method of identification of the isomers we have avoided the classical, optical resolution of the suspected racemic form in favor of direct comparison of the proton resonance spectra of the diols in aqueous solution (*cf.* Fig. 1 and 2). The signals given by the hydroxyl and methyl groups and by the methenyl protons in 2- and 4-positions are very similar for both isomers (at 0, *ca.* 220, and *ca.* 50 c.p.s., respectively, on the scale of the figures). The hydroxyl proton signals are single resonance peaks, indicating rapid exchange of protons between the diols and the aqueous solvent.[18] For both compounds, the signal from the methyl groups is a doublet due to splitting by the neighboring methenyl protons in the molecule (coupling constant *ca.* 6.3 c.p.s.); and the methenyl proton signal itself is an approximately symmetrical sextet of bands split by the five nearest neighboring protons on carbon (CH-to-CH_2 coupling constants close to 6.3 c.p.s.). However, the signals from the methylene group, at *ca.* 190 c.p.s., are diagnostically different for the two diols. One isomer is observed to give an almost symmetrical triplet with intensities approximately in the ratio 1:2:1 and separation 6.3 c.p.s., which suggests that this isomer has its two methylene protons in almost identical magnetic environments and that they are coupled almost equally with the methenyl protons (allowing that the chemical shift between these two types of proton is sufficiently great compared to the coupling so that first-order spectra are observed).[19] Both optical forms of the racemic diol give identical spectra and each should exist in a set of staggered conformations, the two most stable of which are probably those illustrated by structures I and II. If facile rotations about the C–C bonds are permitted in aqueous solutions of the diols at room temperature, as is almost certainly the case, the racemic form should have methylene protons formally equivalent and there should also be equivalent coupling between the two methylene protons and each methenyl proton. Therefore, the observed simple triplet in Fig. 1 diagnoses the racemic diol. In all conformations of the *meso*-diol the methylene protons can never formally be exactly equivalent, and the effect of rapid rotation from one conformation to another should yield an observable, averaged chemical shift (barring accidental equality). The signal from the methylene protons in Fig. 2 can be construed as essentially two triplets (with apparent separations of 6.2 and 6.9 c.p.s., respectively) the centers of which appear to be separated by 2.8 c.p.s. This suggests the following approximate interpretation. The coupling constant between protons set at the tetrahedral angle on the same carbon atom is about 12 c.p.s.[20] and, if two such protons are chemically shifted, the general form of the spectrum is a quadruplet. Thus, for example, the quadruplet generated by two protons shifted by 9 c.p.s. with coupling constant 12 c.p.s. would have a central doublet separated by 3 c.p.s., and satellites 12 c.p.s. away having only one-ninth of the intensity of the main doublet. Hence, the spectrum of the methylene protons on Fig. 2 may be interpreted as a doublet separated by *ca.* 3 c.p.s., the members of which are split into triplets through slightly different coupling to the two methenyl protons, while the low-intensity, split satellites which are expected cannot be distinguished above the background noise under our experimental conditions. This spectrum is then quite consistent with the structure of *meso*-2,4-pentanediol, the chemical shift between the methylene protons being probably close to 0.15 p.p.m. (9 c.p.s.). We consider this analysis to constitute plausible identification of the isomeric diols.

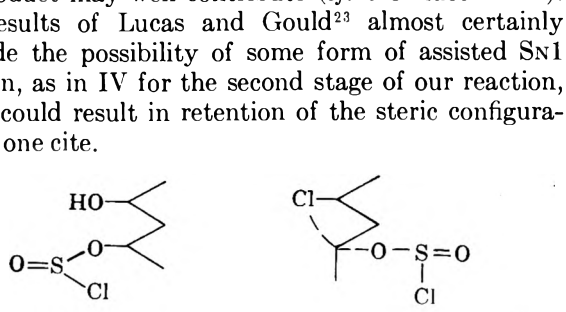
(13) M. Delepine and A. Horeau, *Bull. soc. chim.*, (5) **4**, 31 (1937).
(14) H. Yonemoto, *Yakaguku Zasshi*, **79**, 143 (1959).
(15) J. M. Sprague and H. Adkins, *J. Am. Chem. Soc.*, **56**, 2669 (1934.)
(16) P. S. Stutsman and H. Adkins, *ibid.*, **61**, 3303 (1939).
(17) L. A. Pohoryles, S. Sarel, and R. Ben-Shoshan, *J. Org. Chem.*, **24**, 1878 (1959).

(18) For a simple account of n.m.r. spectra of some aliphatic alcohols see J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 48–51 and 64–66.
(19) A slightly similar situation has been found for *trans*-1,3-cyclohexanediol. *Cf.* H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962).
(20) M. Karplus, D. H. Anderson, T. C. Farrar, and H. S. Gutowsky, *J. Chem. Phys.*, **27**, 597 (1957); H. S. Gutowsky, M. Karplus, and O. M. Grant, *ibid.*, **31**, 1278 (1959).



2,4-Dihalopentanes.—From some of the classical examples of alcohol–halide conversion in the literature, the outlook for converting the separated 2,4-pentanediols to dihalides, without isomeric equilibration, appeared good. Thus, the conversion of a simple secondary alcohol, 2-octanol, to the corresponding chloride by thionyl chloride in the presence of pyridine has been reported to occur with clean inversion of configuration.[21,22] Furthermore, the racemic-*erythro*- and (+)-*threo*-3-chloro-2-butanols have been converted with clean inversion to pure racemic and *meso*-2,3-dichlorobutanes, respectively, by thionyl chloride in pyridine, demonstrating that the presence of the chlorine substituent, neighboring the hydroxyl group being replaced, does not alter the reaction mechanism for this reagent through "participation."[23]

In accord with the previous results, the reaction of thionyl chloride and pyridine at 0° with each 2,4-pentanediol isomer gave a good yield of a 2,4-dichloropentane, in each case pure except for 2–3% of the alternative isomer, as determined by chromatographic analysis. This reaction would be expected to proceed principally with Walden inversion by the S$_N$2 mechanism[24–26] at both reaction cites, so that the resulting dihalide should have molecular symmetry identical with that of the 2,4-pentanediol isomer from which it was derived. It is unclear[24] whether or not the production of the few % of alternative isomer was entirely due to competition of unimolecular internal substitution, by the chlorine in the chlorosulfite intermediate III, with the predominant bimolecular substitution by external chloride, since concomitant rearrangement of the product may well contribute (*cf.* bromides col. 2). The results of Lucas and Gould[23] almost certainly preclude the possibility of some form of assisted S$_N$1 reaction, as in IV for the second stage of our reaction, which could result in retention of the steric configuration at one cite.



A previous study has shown that ethyl (−)-lactate can be converted with little or no racemization to ethyl (+)-α-bromopropionate by phosphorus pentabromide and pyridine.[27] The reagents, thionyl bromide and phosphorus tribromide, with or without pyridine, have produced considerable racemization, on the other hand.[21,28] There appears to be no evidence available concerning the effect of these reagents in the presence of neighboring bromine. However, it would be consistent with the foregoing facts to assume that phosphorus pentabromide in pyridine would consistently invert the configuration in hydroxyl–bromide transformations.

Accordingly, phosphorus pentabromide in pyridine with the racemic 2,4-pentanediol produced a reasonable yield of dibromide containing only 2% of the *meso* isomer. With *meso*-2,4-pentanediol, *meso*-2,4-dibromopentane containing much larger amounts of the racemic form was produced (5–20% depending on experimental procedure) essentially because the lower-boiling, racemic form tended to distil out fractionally in preference to the required *meso* product during isolation. Unfortunately, efficient fractionation was required to remove one tenacious impurity from the dibromides (not required for the dichlorides) and prolonged boiling under reduced pressure was observed to induce rearrangement toward a 50–50 *meso* and racemic mixture. Small amounts of the *meso*-dibromide containing 5–6% of the racemic form could nevertheless be obtained consistently.

P.m.r. spectra of these 2,4-dihalopentane isomers, which need not be detailed here,[29] show characteristics, quite analogous to the diol case, which diagnose molecular symmetry confirming the structures designated above. If the 2,4-dihalopentane isomers are required for purposes in which the presence of small amounts of the alternative isomer can be tolerated, it is our conclusion that the processes described earlier are best suitable for the preparation of quantities in the order of tens of grams and more.

Experimental

Sodium–Alcohol Reduction of Acetylacetone.—Fifty-six grams of sodium was added in small amounts to a stirred solution of 40 g. of acetylacetone in 750 ml. of ethanol held between 0–10°. After *ca.* 14 hr., methanol was added to destroy residual sodium quickly. The solution was neutralized with concentrated hydrochloric acid, and the product freed from salt and alcohol yielding, after distillation, 12 g. (30% yield) of 2,4-pentanediols, b.p. *ca.* 85° (6 mm.). With 100 g. of acetylacetone in the above procedure, the yield of diols was 21 g., representing a lower yield from the acetylacetone but more efficient use of the sodium and alcohol.

Fractional distillation of the diol mixture obtained by the above procedures through a 4-ft. column (described later) gave, apart from a small forerun, only fractions of constant refractive index, n^{20}D 1.4342, and b.p. 74° (3 mm.). Vapor phase chromatography on diverse columns also failed to separate the two isomers present.

Nickel–Hydrogen Reduction of Acetylacetone.—Hydrogen at 1000–2000 p.s.i. was passed into a suspension of *ca.* 20 g. of pyrophoric Raney nickel in a solution consisting of 300 ml. of acetylacetone, 400 ml. of dioxane, and 50 ml. of triethylamine, at 135°. After 5 hr., 80% of the theoretical amount of hydrogen was absorbed and the reaction solution remained colorless. Fractionation yielded 196 g. (75% yield) of diols, b.p. 65° (2 mm.), n^{20}D 1.435. Higher yields were possible by running the reaction longer.

Sodium Borohydride Reduction of Acetylacetone.—A solution of 1 kg. of acetylacetone in 3 kg. of methanol was added slowly to

(21) A. McKenzie and T. M. A. Tudhope, *J. Biol. Chem.*, **62**, 551 (1924).

(22) *Cf.* W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1266 (1937).

(23) H. J. Lucas and C. W. Gould, Jr., *J. Am. Chem. Soc.*, **63**, 2541 (1941).

(24) *Cf.* C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 391–395.

(25) *Cf.* E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, Chap. 5 and 8.

(26) *Cf.* J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 139–141.

(27) W. Gerrard, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 153 (1937).

(28) J. Kenyon, H. Phillips, and G. R. Shutt, *ibid.*, 1663 (1935).

(29) See W. C. Tincher, Abstracts of 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, Polymer Chemistry Section, Appendix, p. 142; and further work to be published.

a stirred solution of 250 g. of sodium borohydride and 5 g. of sodium hydroxide pellets in 2.5 kg. of water, maintained below 20°. The solvents were then removed rapidly at *ca.* 20 mm. pressure. Five kilograms of glycerol was added to the solid residue of sodium hydroxide-coordinated 2,4-pentanediol monoborates and the product was distilled under reduced pressure through a short fractionating column, yielding 885 g. (87% yield) of diols with $n^{20}D$ 1.434.

Separation of 2,4-Pentanediol Mixture.—One equivalent of thionyl chloride (623 ml.) was added slowly to the diol product from the sodium borohydride reduction above (885 g.) dissolved in 400 ml. of ether and contained in a large conical flask equipped with a magnetic stirrer. When the voluminous evolution of hydrogen chloride ceased, the solution was heated to 100° and dry nitrogen bubbled through for 1 hr. Further cleaning up of the reaction mixture by water washing was found to be unnecessary and involved subsequent use of an unwieldy amount of drying agent owing to the high solubility of water in these sulfite esters. Fractional distillation of the product using a 4-ft.-long, vacuum-jacketed column of 0.5-in. i.d., packed loosely with glass helices of 0.25-in. o.d. (which gave a 25-plate separation of benzene–carbon tetrachloride mixtures at atmospheric pressure), gave 70 g. of forerun, b.p. 64–72° (12 mm.), then 545 g. *meso*-2,4-pentanediol cyclic sulfite, b.p. 72° (12 mm.), $n^{20}D$ 1.4403, and 26 g. of cyclic sulfite mixture, b.p. 72–82° (12 mm.), and finally 300 g. of racemic 2,4-pentanediol cyclic sulfite, b.p. 82° (12 mm.), $n^{20}D$ 1.4472. The reflux ratios required were about 100:1 for the forerun, which contained a number of impurities, and about 10:1 for the remainder of the distillation. Chromatography (*cf.* Table I) showed the *meso* isomer to be quite pure. However, the racemic isomer consistently contained a very closely boiling impurity (hence, the poor microanalysis that follows), but this did not seem to affect adversely the purity of the racemic diol finally prepared.

Anal. Calcd. for $C_5H_{10}O_3S$: C, 40.0; H, 6.7; S, 21.35. Found: *meso*-sulfite, C, 40.1; H, 6.6; S, 21.2; and racemic sulfite, C, 40.5; H, 6.9; S, 19.6.

Each cyclic sulfite was saponified, while stirring with five times its volume of water, by gradual addition of two equivalents of sodium hydroxide. The water was evaporated under vacuum and the residue extracted with chloroform. Distillation of the extract gave diol in 75% yield for this step: *meso*-diol, b.p. 73° (3 mm.), $n^{20}D$ 1.4327; racemic diol, b.p. 74° (3 mm.), m.p. 48–49°, $n^{20}D$ 1.4378. Both diols are very hygroscopic.

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.7; H, 11.5. Found: *meso*-diol, C, 57.5; H, 11.5; and racemic diol, C, 57.7; H, 11.0.

One gram of each diol isomer was stirred with 5 g. of 3,5-dinitrobenzoyl chloride in 20 ml. of dry pyridine at 0° for 2 hr. The mixture was diluted with water and the crude, insoluble ester washed with aqueous sodium bicarbonate, then with water, and recrystallized from acetone. The melting points were 190 and 179° for the pure *meso* and racemic diesters, respectively. Yields were almost quantitative.

Anal. Calcd. for $C_{19}H_{16}O_{12}N_4$: C, 46.3; H, 3.3; N, 11.4. Found: *meso*-isomer, C, 46.4; H, 3.5; N, 11.4; racemic form, C, 46.6; H, 3.6; N, 11.3.

The diols were identified through their n.m.r. spectra, so identifying also the other derivatives.

2,4-Pentanediol Isomer Ratios and Diacetates.—Samples of the separated diol isomers were esterified to diacetates using, in turn, all three common reagents: acetic acid and anhydride, and acetyl chloride. Analysis of the products by vapor phase chromatography (see p. 1549 and Table I) showed them to be isomerically pure. Physical data are: for *meso*-2,4-pentanediol diacetate, b.p. 70° (4 mm.), 203° (760 mm.), $n^{20}D$ 1.4172; and for the racemic diacetate, b.p. 62° (4 mm.), 201° (760 mm.), $n^{20}D$ 1.4142.[30]

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.4; H, 8.5. Found: *meso*-diacetate, C, 57.0; H, 8.5; and racemic diacetate, C, 57.2; H, 8.5.

Samples of the diol mixtures from the first three preparations above were converted to diacetate mixtures which were shown by vapor phase chromatography to consist of *meso* and racemic forms in the ratios 9:11 (Na/EtOH), 11:9 (Ni/H_2), and 2:1 ($NaBH_4$). Fractional distillation of the diol diacetates was insufficiently efficient in our apparatus to give a good yield of completely separated products, and is not recommended.

(30) *Cf.* R. L. Frank, R. D. Emmick, and R. S. Johnson, *J. Am. Chem. Soc.*, **69**, 2313 (1947). Data reported for a mixture were b.p. 88–91° (11 mm.), $n^{20}D$ 1.4160.

2,4-Pentanediol Cyclic Borates.—A previous report has claimed that the reduction of acetylacetone by sodium borohydride in aqueous methanol produces almost entirely the *meso*-2,4-pentanediol (isomer ratio *ca.* 45:1).[31] We have repeated the cyclic borate work-up procedure[31] which led to this erroneous conclusion, as follows. Fifty grams of acetylacetone was reduced with sodium borohydride as described.[31] After evaporation of solvent, the residue was neutralized with 2 *N* aqueous sulfuric acid and the slightly acid solution extracted with chloroform. Distillation of the extract yielded 43 g. of viscous oil, b.p. 136° (1 mm.), the tris-2,4-pentanediol di(cyclic borate). The oil was treated with 5 ml. of water and the resulting partly crystalline mixture of diol and diol (mono) cyclic borate was filtered. The solid material was recrystallized twice from benzene–petroleum ether and yielded 4 g. of large, white prisms, m.p. 83–85° (sealed tube). The infrared spectrum of this product as a Nujol mull was identical with that published for the pure, high-melting 2,4-pentanediol cyclic borate isomer.[3]

Anal. Calcd. for $C_5H_{11}O_3B$: C, 46.2; H, 8.5. Found: C, 45.9; H, 8.5.

The above experience is similar to that previously reported[31] and presumably led to the assumption that the entire product consisted of just the one form of 2,4-pentanediol cyclic borate. Modification of procedure, as follows, shows that the two forms are present. (No configurational rearrangements are suspected in these systems.) Thus, in a similar experiment, the viscous oil was treated with water, as before, then the whole mixture was crystallized from benzene–petroleum ether. The noncrystalline residue was treated with 6 g. of boric acid and fractionally crystallized from hexane. Altogether, there was obtained a series of white, crystalline fractions comprised of 7 g., m.p. *ca.* 80°; 28 g., m.p. *ca.* 75–76°; 1 g., m.p. 65–70°; and some residual oil which could not easily be crystallized.

Anal. (*cf.* preceding). Found for the 75–76° material: C, 45.9; H, 8.4.

Some of the 75–76° melting material was distilled with glycerol to recover diol, and this was converted to diacetate. Chromatography showed a mixture of 20% racemic with 80% *meso*-diacetate.

2,4-Dichloropentane Isomers.—One hundred and sixteen grams of thionyl chloride was run slowly into a mixture of 26 g. of *meso*-2,4-pentanediol and 3 ml. of dry pyridine kept at *ca.* 0° by means of an ice–salt bath. After refluxing for 3 hr., the mixture was worked up by addition of iced water, then ether extraction. The ether layer was washed with aqueous sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and fractionated yielding 21 g. of *meso*-2,4-dichloropentane, b.p. 40° (12 mm.), $n^{20}D$ 1.4423. Vapor phase chromatography showed this product to be quite pure apart from *ca.* 2% of its isomer. Pure racemic 2,4-pentanediol treated likewise gave racemic 2,4-dichloropentane of b.p. 36° (12 mm.), $n^{20}D$ 1.4390, which likewise contained a few per cent of its isomer.[32] (If the amount of pyridine is increased this does not alter the final result; it merely complicates the work-up.)

Anal. Calcd. for $C_5H_{10}Cl_2$: C, 42.6; H, 7.1; Cl, 50.3. Found: *meso* isomer, C, 42.4; H, 7.2; Cl, 50.2; racemic form, C, 42.4; H, 6.9; Cl, 50.2.

2,4-Dibromopentane Isomers.—A slurry of phosphorus pentabromide was prepared by allowing 45.6 ml. of bromine to run very slowly on to 97.8 ml. of phosphorus tribromide dissolved in 30 ml. of dry benzene and stirred at 0° under a current of dry nitrogen. Fifty grams of racemic 2,4-pentanediol dissolved in 45 ml. of dry pyridine was run in slowly over a period of 5 hr. attended by vigorous evolution of hydrogen bromide and heat. Passage of dry nitrogen and stirring was then continued overnight while the reaction mixture warmed to room temperature. Iced water was then added and the mixture extracted with benzene. The benzene extract was washed with aqueous sodium carbonate, then by water, dried (Na_2SO_4), and evaporated under vacuum at room temperature. The residue was distilled rapidly at 4 mm. yielding *ca.* 52 g. of at least 96% pure 2,4-dibromopentane. Rapid fractionation of this material yielded racemic 2,4-

(31) J. Dale, *J. Chem. Soc.*, 910 (1961). Note that the reduction of the very similar system 1,3-diphenyl-1,3-propanedione by the same reagent is reported in this reference to have given a diol isomer ratio of *ca.* 3:2, a more authentic result quite similar to that obtained in the present work for acetylacetone (2:1) under parallel reaction conditions.

(32) *Cf.* D. V. Tischenko, *J. Gen. Chem. USSR*, **9**, 1380 (1939). Data reported for a mixture were b.p. 142–147° (761 mm.), $n^{15}D$ 1.4339.

dibromopentane, b.p. 40° (4 mm.), $n^{20}D$ 1.4968, containing only 2% of the *meso* isomer.

The same procedure repeated for the *meso*-diol gave *meso*-dibromide containing substantial quantities of the alternative isomer, 5–20% depending on reaction conditions and the method of isolation. However, fractional distillation of such material through the column described above usually resulted in 25% recovery of a pure dibromide mixture, b.p. 45° (5 mm.), $n^{20}D$ 1.5015, containing not less than *ca.* 95% of the *meso*-dibromide.[33] Isomeric equlibration was noted on prolonged boiling of the product at 4 mm., so setting a limit to the degree of separation of the higher boiling (*meso*) product attainable by fractional distillation.

Anal. Calcd. for $C_5H_{10}Br_2$: C, 26.1; H, 4.35; Br, 69.5. Found: *meso*-isomer, C, 26.1; H, 4.15; Br, 69.6; racemic form, C, 26.1; H, 4.6; Br, 69.4.

Vapor Phase Chromatography.—The retention times given in Table I were obtained with a column 10 ft. long and 0.4-in. i.d., packed with 8% by weight of Carbowax (mol. wt., 9000) on 30/60-mesh firebrick, and with an inlet pressure of 40 p.s.i. of helium gas to an F. and M. Scientific Corporation Model 500 instrument. The retention times quoted in the table were for 1-μl. samples and a flow rate of 570 ml./min. The table also shows the maximum quantities of material in μl. which could be separated under the conditions described, indicating the degree of spreading of the various samples on the column.

N.m.r. Spectroscopy.—Samples of each isomeric form of 2,4-pentanediol with four times their volume of deuterium oxide were degassed and sealed under vacuum in thin-walled tubes, 6 × 0.5 in. in diameter. Spectra were run at room temperature on a Varian machine operating at 60 Mc./sec., equipped with a Varian 12-in. electromagnet, flux stabilizer, and field-homogeneity stabilizer. A side band of 250 c.p.s. was set off at high field from the signal due to the hydroxyl protons. Hence, the arbitrary scale on Fig. 1 and 2 is set at zero for the exchanging hydroxyl protons in an alcohol–water–HDO–deuterium oxide mixture containing *ca.* 4% H and 96% D.

(33) R. G. Kelso, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **77**, 1751 (1955). Data reported for a mixture were b.p. 70° (17 mm.), $n^{20}D$ 1.4960.

TABLE I

RETENTION TIMES IN MINUTES FOR 2,4-DISUBSTITUTED PENTANE DERIVATIVES UNDER CONDITIONS SPECIFIED IN THE TEXT

Derivative	Temp., °C.	Retention time *meso*	Retention time Racemic	Max. quant. (μl.)
Diacetates	130	6.25	5.1	1
Cyclic sulfites	130	4.7	6.45	50
Dichlorides	80	3.8	3.15	1
Dibromides	100	6.7	5.5	10

Acknowledgment.—The authors wish to express their thanks to Mr. W. C. Lawrence for obtaining the n.m.r. spectra shown in Fig. 1 and 2, and to Mr. H. E. Frankfort for his contribution toward the elucidation of the nickel–hydrogen and sodium borohydride reductions of acetylacetone during the initial stages of this work. All microanalyses were by the Alfred Bernhardt Mikroanalytisches Laboratorium, Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), Germany.

The Acetylation of Some Substituted Ferrocenes[1]

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A number of mono- and disubstituted ferrocenes have been acetylated. It has been found that iodine is lost from iodoferrocene under the acetylation conditions employed. Contrary to another report, bromo- and chloroferrocenes are acetylated to give 1′-acetylbromo- and chloroferrocenes in good yield. Acetylation of acetamido- and urethanoferrocenes gives predominantly the heteroannularly substituted isomers, and these substituents are deactivating.

In recent years a number of reports have appeared on the electrophilic substitution reactions of ferrocene derivatives.[3] Rosenblum[4] has reported some studies of this type and has used a molecular orbital calculation to predict the effect of substituent groups. Recently Morrison and Pauson[5] have shown that Friedel–Crafts acetylation of chloro-, methylthio- and methoxyferrocenes leads to the replacement of the substituent by hydrogen. Thus chloroferrocene yields ferrocene and methoxyferrocene yields acetylferrocene. In connection with our work on metallocenyl carbonium ions and for other reasons it was desirable to have in hand substituted ferrocenes. This led to a study of the acetylation reactions of iodo-, bromo-, chloro-, acetamido-, methoxycarbonylamino-, ethoxycarbonylamino-, 1,1′-diethoxycarbonylamino-, and cyanoferrocenes.

Results and Discussion

The results are summarized in Table I.

Structural assignments were made chiefly on the basis of infrared spectral correlations. The pertinent data are summarized in Table II. It can be seen that all disubstituted compounds assigned the 1,2-homoannular structure possess bands near 9 and 10 μ (1111 and 1000 cm.$^{-1}$) in accordance with the 9–10 rule set forth by Rosenblum.[6] In addition the 1,2-disubstituted compounds clearly show hydrogen bonding between the amide hydrogen and the oxygen atom of the acetyl group.[7] 2-Acetyl-1,1′-di(ethoxycarbonylamino)ferrocene also possesses a spectrum indicative of hydrogen bonding whereas 3-acetyl-1,1′-di(ethoxycarbonylamino) ferrocene does not. The compounds assigned the 1,1′-disubstituted structure lack the bands near 9 and 10 μ but do show absorption near 8.95 μ (1117 cm.$^{-1}$) which is known to be indicative of a ferrocene possessing a cyclopentadienyl ring substituted only with an acetyl group.[6]

(1) Supported in part by a grant from the National Science Foundation.

(2)(a) This paper is based on the Ph.D. thesis of D. W. Hall, December, 1962; (b) the Denver Research Center of the Marathon Oil Company.

(3) For a review see K. Plesske, *Angew. Chem.*, **74**, 301, 347 (1962).

(4) M. Rosenblum and W. G. Howells, *J. Am. Chem. Soc.*, **84**, 1167 (1962).

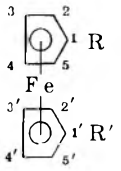
(5) J. G. Morrison and P. L. Pauson, *Proc. Chem. Soc.* (London), 177 (1962).

(6) M. Rosenblum, *Chem. Ind.* (London), 953 (1958).

(7) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947).

TABLE I

ACETYLATION OF MONO- AND DI-SUBSTITUTED FERROCENES



R	R′	Reagents	Starting material recovered, %	Isomer yields, % conversion 1′-	2-	3-
Acetamido-	H	1:1 Aluminum chloride–acetyl chloride	42	37.4	0[a]	0
		Silicon tetraacetate and stannic chloride	39.6	29.7	0[a]	0
		Boron trifluoride and acetic anhydride	17.8	69.2	3.3	0
Ethoxycarbonylamino-	H	Boron trifluoride and acetic anhydride	Not determined	Approx. 50	Under 5	0
Ethoxycarbonylamino-	R = R′	Boron trifluoride and acetic anhydride	21[b]	...	22[b]	46
Methoxycarbonylamino-	H	1:1 Acetyl chloride–aluminum chloride	Not determined	Approx. 50	Under 5	0
Cyano-	H	1:1 Acetyl chloride–aluminum chloride	0	100	0	0
Bromo-	H	1:1 Acetyl chloride–aluminum chloride	0	75	0	0
Chloro-	H	1:1 Acetyl chloride–aluminum chloride	0	81	0	0
Iodo-	H	1:1 Acetyl chloride–aluminum chloride	A mixture of iodoferrocene was recovered	Only acetylferrocene and 1,1′-diacetylferrocene were isolated		

[a] Probably present but not isolated. [b] Estimated; see Experimental.

In accord with the observations of other workers, the 2-substituted compounds were eluted from alumina before the other isomers.[8,9]

Ultraviolet absorption data are summarized in Table III.

Under our conditions, the acetylation of bromo- and chloroferrocenes proceeded smoothly to yield the heteroannularly substituted products. There was no evidence for the presence of homoannularly substituted products in either of these two cases. Nesmeyanov has also found that acetylation of bromoferrocene gives only 1′-acetylbromoferrocene.[10] These results are in contrast with those of Morrison and Pauson[5] and emphasize the influence of conditions on the course of these reactions. In the case of iodoferrocene, repeated attempts at acetylation led only to unchanged starting material and ferrocene, itself. Thus, as would be expected, the iodine is more susceptible to electrophilic displacement by a proton than is chlorine or bromine.

Acetylation of acetamido- and alkoxycarbonylaminoferrocenes yielded predominantly the heteroannularly substituted isomer. In some cases a small yield of 1,2-isomer was isolated though never was any 1,3-product observed. The presence of predominantly heteroannular product indicates that the acetamido and alkoxycarbonylamino groups are deactivating substituents.

Further confirmation for the deactivating effects of these substituents comes from the study of the competitive acetylation of acetamidoferrocene and ferrocene. In this reaction the ferrocene was found to be more reactive than its substituted analogue by a factor of about two.

The acetylation of 1,1′-di(ethoxycarbonylamino)-ferrocene with boron trifluoride and acetic anhydride yielded two or three times more 3-acetyl than 2-acetyl substituted product. These results are similar to those obtained in studies of the acetylation of 1,1′-dimethylferrocene[9] and 1,1′-diethylferrocene.[11,12] Formylation of 1,1′-diethylferrocene produces only the 3-formyl product.[11] Thus in the disubstituted case, the predominance of 3-isomer stands in marked contrast to the absence of the 3-substituted homoannular isomer in the acetylation of monosubstituted acetamido- and urethanoferrocenes.

Pauson[13] has found that another powerfully electron-donating substituent,[14] methylthio-, is also deactivating in the aminomethylation reaction of ferrocene.

The effects of the substituents so far discussed in deactivating the aromatic rings of ferrocene to further electrophilic substitution is quite different from the effects of these groups on the ease of removal of an electron from the iron atom. Thus, it has been found from chronopotentiometric oxidation studies that

(8) M. Rosenblum, W. G. Howells, A. K. Banerjee, and C. Bennett, *J. Am. Chem. Soc.*, **84**, 2726 (1962).

(9) K. L. Rinehart, Jr., K. L. Motz, and S. Moon, *ibid.*, **79**, 2749 (1957).

(10) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk, SSSR*, **137**, 102 (1961).

(11) D. W. Hall, unpublished research, California Institute of Technology.

(12) D. C. Garwood, Ph.D. thesis, California Institute of Technology, 1962.

(13) G. R. Knox, P. L. Pauson, and G. V. D. Tiers, *Chem. Ind.* (London), 1046 (1959).

(14) H. C. Brown and T. Inukai, *J. Am. Chem. Soc.*, **83**, 4825 (1961).

TABLE II

INFRARED ABSORPTION BANDS OF SOME SUBSTITUTED FERROCENES[a]

Compound	Solvent	Absorption maxima, cm.$^{-1}$				
Acetamidoferrocene	CCl_4	3460	1694		1107	1005
	$CHCl_3$	3450	1682		1103	1001
	Nujol	3265	1654	1289	1103	1001
		3220[b]				
2-Acetylacetamidoferrocene	CCl_4	3340	1695, 1653	1292	Poor resolution in other regions	
	CS_2	3360	1700, 1659	1300	1109	1004
	Nujol	3345	1686, 1650	1305	1107	1006
1′-Acetylacetamidoferrocene	CCl_4	3445	1695, 1666	1278	1117	
		(3320)[c]				
	$CHCl_3$	3450	1686, 1666	1279	1112	
		(3320)[c]				
Methoxycarbonylaminoferrocene	CCl_4	3450	1745		1106	1007
2-Acetylmethoxycarbonylamino-ferrocene	CCl_4	3350	1740, 1656	1296	1107	1005
		(3450)[c]				
1′-Acetylmethoxycarbonylamino-ferrocene	CCl_4	3450	1743, 1673	1278	1115	
		(3320)[c]				
Ethoxycarbonylaminoferrocene	Nujol	3245	1715		1106	1001
2-Acetylethoxycarbonylaminoferrocene	CS_2[d]	3315	1722, 1645	1287	1099	994
		(3415)[c]				
	Smear[e]	3350	1730, 1655	1295	1105	1003
1′-Acetylethoxycarbonylaminoferrocene	CCl_4	3445	1738, 1671	1277	1115	
		(3320)[c]				
	Nujol	3270	1717, 1652	1282	1115	
1,1′-Di(ethoxycarbonylamino)ferrocene	CCl_4[f]	3450	1735	1305[h]		
		(3375)[g]				
2-Acetyl-1,1′-di(ethoxycarbonylamino)-ferrocene	CCl4	3447[i]	1735, 1654	1296		
		3345[j]				
	Nujol	3358	1723, 1652	1301	1113[h]	
		3248	(1675)[h]			
3-Acetyl-1,1′-di(ethoxycarbonylamino)-ferrocene	$CHCl_3$	3450	1725, 1664	1305		
	Nujol	3310	1726, 1640	1304		
			1702			
Bromoferrocene	Neat				1107	1005
	CCl_4				1108	1005
1′-Acetylbromoferrocene	CCl_4		1682	1276	1114	
Chloroferrocene	CS_2				1107	1003
1′-Acetylchloroferrocene	CCl_4[d]		1690	1281	1118	
Cyanoferrocene	CCl_4	2232			1109	1012
1′-Acetylcyanoferrocene	CCl_4	2234	1685	1277	1117	

[a] These spectra were determined on a Beckman IR-7 recording spectrophotometer. [b] Shoulder. [c] Very faint peak, presence is uncertain. [d] Spectrum appears to be shifted slightly due to improper tracking. [e] Spectrum of crude material after chromatography but before the material had solidified. [f] Solution was very concentrated. [g] May be due to intermolecular hydrogen bonding in the concentrated solution. [h] Very weak, but definitely present. [i] This peak is due to the urethane group in the 1′-position. [j] This peak is due to the urethane group in the 2-position; the shift is due to hydrogen bonding with the adjacent acetyl group.

acetamido, alkoxycarbonylamino and methoxy groups are strongly electron donating substituents.[15]

If one accepts that the interaction of the electrophile with the iron atom is an important step in the detailed mechanism for the electrophilic substiution of metallocenes[16,17] one would then expect factors which enhance the ease of oxidation also to facilitate electrophilic substitution. This is, however, not true in the present cases and leads to the suggestion that it is not the neutral species alone which are involved in the reactions just discussed but that the substrates exist in the reaction mixtures in large measure as conjugate acids which are markedly less reactive than either their neutral analog or than unsubstituted ferrocenes. In short, the observed effects are the complex result of equilibria between the neutral and protonated species and of the reaction rates for each of these forms.

Precedence for this view can be found in the work of Rosenblum[18] on the anomalous acetylation of ferrocene and in work on the electrophilic substitution of acetanilide. Brown[19] and Stock[20] have reported that the acetamino group is a powerful electron donator in mercuration and bromination reactions of acetanilide. In contrast to this, however, there are several studies which indicate that acetanilide is less reactive than benzene in certain nitration[21] and acetylation[22,23] reactions. In these latter cases the formation of salts or

(15) E. A. Hill, III, D. W. Hall, C. D. Russell, and J. H. Richards, paper in preparation.

(16) J. H. Richards, presented at the 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959; *cf.* Abstracts, p. 86-O.

(17) T. J. Curphey, J. O. Santer, M. Rosenblum, and J. H. Richards, *J. Am. Chem. Soc.*, **82**, 5249 (1960).

(18) Myron Rosenblum and J. O. Santer, *ibid.*, **81**, 5517 (1959).

(19) H. C. Brown and G. Goldman, *ibid.*, **84**, 1650 (1962).

(20) L. M. Stock and F. W. Baker, *ibid.*, **84**, 1661 (1962).

(21) C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 2918 (1927).

(22) F. Kunckell, *Ber.*, **33**, 2641 (1900).

(23) M. J. Sacha and S. R. Patel, *J. Indian Chem. Soc.*, **33**, 129 (1956).

TABLE III

ULTRAVIOLET ABSORPTION DATA FOR SOME SUBSTITUTED FERROCENES[a]

Compound	λ_{max}, mμ[b]	ϵ_{max}[b]
Acetylferrocene	226[c,d]	16,500[c,d]
	269	6,500
Acetamidoferrocene	268	...
1′-Acetylacetamidoferrocene	222	18,300
	262	8,000
2-Acetylacetamidoferrocene	233[c]	21,250[c]
	265–270	10,700
	338–339	3,750
	237–238[e]	19,900[e]
	269–271	9,400
1′-Acetylethoxycarbonylaminoferrocene	222–223	19,000
	222–223[c]	20,200[c]
	220[e]	23,400[e]
	280 (broad shoulder)	3,000
2-Acetyl-1,1′-di(ethoxycarbonylamino)ferrocene	230	22,500
	280 (broad shoulder)	7,550
3-Acetyl-1,1′-di(ethoxycarbonylamino)ferrocene	226–227	22,150
	290 (very broad shoulder)	6,100
1′-Acetylbromoferrocene	223–224	...
	250–260 (inflection)	...
1′-Acetylcholoroferrocene	224–225	...
	270	...
1′-Acetylcyanoferrocene	221	19,900
	253	10,600
	325 (shoulder)	950
	220–222[e]	...
	254	...
	310	...

[a] These spectra were taken on a Cary Model 11M recording spectrophotometer. [b] In methanol unless otherwise indicated. [c] In 95% ethanol. [d] Ref. 9. [e] In cyclohexane.

complexes with the amide group is highly likely making the substituent deactivating.

Experimental

All melting points are uncorrected and were determined on an Eimer and Amend melting point block unless otherwise indicated. Nuclear magnetic resonance spectra were determined on a Varian Associates Model A-60 spectrometer.[24] Elemental analyses were performed by Elek Microanalytical Laboratory, Los Angeles, California, Spang Microanalytical Laboratory, Ann Arbor, Michigan, and Schwartzkopf Microanalytical Laboratory, Woodside, New York.

All reactions were carried out under nitrogen. Chromatography was performed on columns wrapped with aluminum foil to protect the compounds from light.

Preparation of Substrates.—Carbazidoferrocene was prepared in part by a procedure reported in the literature wherein chlorocarbonylferrocene is treated with sodium azide.[25,26] The procedure was modified in that the crude reaction product was purified by extraction with low-boiling petroleum ether in a Soxhlet apparatus. Quite pure carbazidoferrocene (m.p. 84.5–85°; lit.[25,26] m.p. 74–75° and 84–86°) crystallized in the reboiling flask; the yield was about 65% based on the starting amount of ferrocenecarboxylic acid.

Carbazidoferrocene was also prepared in a conversion of 56% by adding an aqueous solution of sodium azide to the mixed anhydride formed by the reaction of ethylchloroformate with a mixture of ferrocenecarboxylic acid and triethylamine. The procedure is identical with that reported by Weinstock for the synthesis of a different carboxylic acid azide.[27] This procedure for the preparation of carbazidoferrocene is very much faster than previously reported methods and it gives good conversion with little decomposition of starting material.

Acetamidoferrocene was prepared by heating carbazidoferrocene in acetic anhydride at about 80° until nitrogen evolution ceased; the resulting diacetylated amine was hydrolyzed to acetamidoferrocene when the crude reaction product was stirred with water for 18 hr. at room temperature. After chromatography on alumina the product was isolated in 73% yield in the form of yellow platelets (m.p. 168–170°; lit.[25] m.p. 170.5–172°). Careful recrystallization gave material melting at 173–173.5°.

Anal. Calcd. for $C_{12}H_{13}NO_2Fe$: C, 59.29; H, 5.39; N, 5.76. Found (Elek): C, 59.32; H, 5.44; N, 5.69.

Methoxycarbonylaminoferrocene and ethoxycarbonylaminoferrocene were prepared from carbazidoferrocene by the procedure of Schlögl.[26] 1,1′-Di(ethoxycarbonylamino)ferrocene was prepared according to the procedure given by Rosenblum.[28] 1,1′-Dibromoferrocene and bromo-, chloro-,[29] cyano-,[30] and iodoferrocenes[31] were prepared by procedures reported by Nesmeyanov.

Acetylation Reactions.—Isomeric products were separated by chromatography on Merck acid-washed alumina. Isomer yields were calculated on the basis of the the weight of materials isolated after removal of solvent from the chromatographic fractions but before any further purification was done. The purity of the materials at this stage of purification was checked by comparing the infrared spectra with spectra determined from analytical samples.

A standard procedure was followed for the acetylation of the ferrocene compounds with acetyl chloride and aluminum chloride. The acetylating reagent was made up according to the Perrier modification of the Friedel–Crafts synthesis by mixing acetyl chloride and excess aluminum chloride in dichloromethane at 0° under nitrogen; the excess aluminum chloride was filtered with glass wool. The acetylating reagent was added by means of a dropping funnel equipped with a pressure-equalizing side tube over a period of about 1 hr. to a solution of the ferrocene compound in dichloromethane at 0°. The reaction mixture was stirred from one to three hours at 0° and then it was poured into ice–water. The organic phase was separated and then dichloromethane washings of the aqueous phase were added to it. The organic solution was washed with saturated sodium bicarbonate solution and with water; it was then dried over anhydrous sodium sulfate. The mixture was filtered and solvent was flash-distilled under reduced pressure. The crude product was then chromatographed.

1′-Acetylacetamidoferrocene.—Acetamidoferrocene (2.2 g., 9 mmoles) and an equimolar amount of the acetylating reagent gave, after a reaction time of 1 hr., 1′-acetylacetamidoferrocene (0.965 g., 37.4% conversion) melting at 115.5–116°.

Anal. Calcd. for $C_{14}H_{15}NO_2Fe$: C, 58.97; H, 5.30; N, 4.91. Found (Elek): C, 59.00; H, 5.41; N, 4.88.

Recovered acetamidoferrocene weighed 0.923 g. (42% recovery). It is very possible that a small amount of 2-acetylacetamidoferrocene was formed but was not detected.

1′-Acetylmethoxycarbonylaminoferrocene and 2-Acetylmethoxycarbonylaminoferrocene.—Methoxycarbonylaminoferrocene gave by this procedure a low yield of the 2-acetyl isomer; the compound was isolated in an impure state as an oil. 1′-Acetylmethoxycarbonylaminoferrocene (m.p. 135–136°) was isolated in a yield of approximately 50%. Only the 1′-isomer was analyzed.

Anal. Calcd. for $C_{14}H_{15}NO_3Fe$: C, 55.84; H, 5.02; N, 4.65. Found (Spang): C, 56.00; H, 5.10; N, 4.54.

1′-Acetylbromoferrocene.—Bromoferrocene and a threefold excess of the acetylating reagent were stirred for 1.5 hr. at 0° and then for an additional 1.0 hr. with the ice bath removed. Chromatography of the crude product which resulted after working up the reaction mixture in the usual manner gave only 1′-acetylbromoferrocene (75% yield, m.p. 56–58°, lit.[10] m.p. 61.5–63°). No bromoferrocene was recovered.

Anal. Calcd. for $C_{12}H_{11}BrOFe$: C, 46.95; H, 3.61; Br, 26.03. Found (Spang): C, 47.02; H, 3.65; Br, 26.10.

(24) We are indebted to Mr. Milton I. Levenberg for the n.m.r. spectral determinations.

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(30) A. N. Nesmeyanov, E. G. Perevalova, and L. P. Jurjeva, *ibid.*, 2729 (1960).

(31) A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Dokl. Akad. Nauk., SSSR*, **100**, 1099 (1955).

1'-Acetylchloroferrocene.—Chloroferrocene was acetylated under the same conditions as bromoferrocene. The acetylating reagent (9 mmoles) and chloroferrocene (0.585 g., 2.7 mmoles) gave, after purification by chromatography, only 1'-acetylchloroferrocene (0.562 g., 81%; m.p., sealed tube, 53–55°). Although the ketone itself was not analyzed, the acetate of the alcohol resulting from its reduction with sodium borohydride was analyzed. The acetate is a red-orange liquid, $n^{25}D$ 1.5806.

Anal. Calcd. for $C_{14}H_{15}ClO_2Fe$: C, 54.85; H, 4.93; Cl, 11.57. Found (Spang): C, 54.79; H, 5.06; Cl, 11.45.

Attempted Preparation of Acetyliodoferrocene.—Two runs on iodoferrocene, one at 0° and one at room temperature, using a slight excess of the acetylating reagent, failed to give any acetyliodoferrocene. In the run at 0° only acetylferrocene and a mixture of ferrocene and iodoferrocene were obtained. The n.m.r. spectrum of the nonketonic fraction indicated that ferrocene and iodoferrocene were present in about equal amounts. The second run gave acetylferrocene in a yield less than 1% and 1,1'-diacetylferrocene in a yield of about 15%. These two compounds were identified by comparing their melting points, infrared spectra, and n.m.r. spectra with those determined from authentic samples. A nonketonic fraction was isolated in a recovery of 45–50% (by weight, based on the weight of starting material). Any coupling products or diiodoferrocene which might have been present could have gone undetected in these two experiments even if they were present in quantities as great as 20% by weight of the total material recovered. It seemed that considerably more ferricinium ion was present at the end of the reactions than was noted in the case of the acetylation of bromo- and chloroferrocenes.

1'-Acetylcyanoferrocene.—Slightly more vigorous conditions were employed in the acetylation of cyanoferrocene than were generally used in the standard procedure. The acetylating reagent (60 mmoles) was added over a period of 20 min. to cyanoferrocene (3.5 g., 17 mmoles) in dichloromethane (100 ml.) at 0°. The ice bath was removed immediately after the addition was completed; the reaction mixture was then stirred for 5 hr. and worked up in the usual manner. Chromatography of the crude product gave only 1'-acetylcyanoferrocene (3.98 g., quantitative conversion; m.p. 99.8–101°).

Anal. Calcd. for $C_{13}H_{11}NOFe$: C, 61.94; H, 4.38; N, 5.54. Found (Elek): C, 61.82; H, 4.48; N, 5.41.

Acetylations Using Acetic Anhydride and Boron Trifluoride. 1'-Acetyl- and 2-Acetylacetamidoferrocenes.—Acetamidoferrocene (2.55 g., 10 mmoles) and acetic anhydride (0.97 g., 10 mmoles) were dissolved in dichloromethane (150 ml.) in a 200-ml. three-necked, round-bottomed flask equipped with a magnetic stirrer and gas inlet and outlet tubes. The solution was flushed with nitrogen and cooled with an ice bath. Boron trifluoride was bubbled into the solution for 3 min.; the color of the solution changed to a deep purple. The reaction mixture was stirred at 0° for 15 min. and then the ice bath was removed. The mixture was stirred for an additional 2.5 hr. and then it was hydrolyzed and worked up in the usual manner. Chromatography of the crude product gave three bands. A leading narrow orange band eluted with ether gave 2-acetylacetamidoferrocene (0.098 g., 4% based on unrecovered starting material) melting at 109–109.5°. A yellow band eluted with ether gave acetamidoferrocene (0.453 g., 17.8% recovery). A broad orange band eluted last with 3% methanol in benzene gave 1'-acetylacetamidoferrocene (2.068 g., 85% of theory based on unrecovered starting material) melting at 115.5–116°. This last compound was chromatographed a second time. Three fractions were collected; each fraction yielded only material having a melting point and infrared spectrum identical with those determined from the sample before chromatography. It should be noted that 1'-acetylacetamidoferrocene sometimes crystallizes in the form of long red-amber needles melting around 50°. These needles will, if heated slowly, undergo transformations at several intermediate temperatures and eventually melt at 115–116°. The infrared and ultraviolet spectra of the low melting crystals are identical with those previously determined for the higher melting crystals. Only 2-acetylacetamidoferrocene was analyzed since the other isomer possessed physical properties identical with those of a previously analyzed sample of 1'-acetylacetamidoferrocene.

Anal. Calcd. for $C_{14}H_{15}NO_2Fe$: C, 58.97; H, 5.30; N, 4.91. Found (Schwarzkopf): C, 59.04; H, 5.31; N, 5.16.

1'-Acetyl- and 2-Acetylethoxycarbonylaminoferrocenes.—Ethoxycarbonylaminoferrocene was acetylated according to the procedure used to acetylate acetamidoferrocene with these same reagents. 2-Acetylethoxycarbonylaminoferrocene was isolated as an oil in low yield. 1'-Acetylethoxycarbonylaminoferrocene. (m.p. 149.5–150°) was isolated in a yield of approximately 50%. Only the heteroannularly substituted isomer was analyzed.

Anal. Calcd. for $C_{15}H_{17}NO_3Fe$: C, 57.16; H, 5.44; N, 4.44. Found (Schwarzkopf): C, 56.93; H, 5.50; N, 4.66.

2-Acetyl- and 3-Acetyl-1,1'-Di(ethoxycarbonylamino)ferrocenes.—A solution of 1,1'-di(ethoxycarbonylamino)ferrocene (0.40 g., 1.1 mmoles) and acetic anhydride (0.15 g., 1.5 mmoles) in dichloromethane (30 ml.) was saturated at 0° with boron trifluoride and then stirred for 5 hr. with the ice bath removed. Chromatography of the crude product resulting after work-up gave four distinct bands. The first two bands, a leading yellow band and an orange band were incompletely separated and were eluted together with 10% ether in benzene as fraction one. A broad orange band was eluted next with 20% ether in benzene as fraction two. A very narrow red-orange band remained at the top of the column; this band did not move down the column even upon elution with pure ether. The material (probably less than 5 mg.) in this last band was not isolated.

Fraction two gave 3-acetyl-1,1'-di(ethoxycarbonylamino)ferrocene (0.206 g., m.p. 140.8–142°).

The material isolated from fraction one was chromatographed a second time; a partial separation of starting material and 2-acetyl-1,1'-di(ethoxycarbonylamino)ferrocene was achieved. Two fractional crystallizations of samples richer in one or the other of the two compounds finally gave pure crystals of each compound. It is estimated that the two compounds were present in nearly equal amounts. Carefully purified crystals of 2-acetyl-1,1'-di(ethoxycarbonylamino)ferrocene melt at 109.5–110°. The yield of the 3-acetyl compound is 46% (58% based on the estimated amount of recovered starting material). The yield of the 2-acetyl- isomer is 22%, based on the estimated amount of starting material recovered. Only the 3-acetyl isomer was analyzed; the many purification steps required gave pure 2-isomer in an amount to small for analysis.

Anal. Calcd. for $C_{18}H_{22}N_2O_5Fe$: C, 53.75; H, 5.51. Found (Schwarzkopf): C, 53.86; H, 5.68.

Acetylation with Silicon Tetraacetate and Stannic Chloride.—Acetamidoferrocene (0.27 g., 1.1 mmoles), silicon tetraacetate (0.16 g., 0.6 mmole), and stannic chloride (0.29 g., 1.1 mmoles) were dissolved in benzene (5 ml.) in a 10-ml. erlenmeyer flask and stirred at room temperature under a nitrogen atmosphere for 28 hr. The reaction mixture was worked up in the customary manner and the crude reaction product was chromatographed on alumina. Three bands were eluted. A leading narrow orange band was eluted with benzene; this material was not isolated but it is likely that it was 2-acetylacetamidoferrocene on the basis of experiments conducted later with other acetylating reagents.

A yellow band eluted second with ether gave acetamidoferrocene (0.107 g.). The melting point and infrared spectrum were identical with those of starting material.

A broad orange band eluted last with 3% methanol in benzene gave 1'-acetylacetamidoferrocene (0.094 g., 50% based on recovered starting material).

Competitive Acetylation of Ferrocene and Acetamidoferrocene.—A 1:1 mixture of acetyl chloride and aluminum chloride (6.07 mmoles) was added over a period of 20 min. to ferrocene (1.13 g., 6.07 mmoles) and acetamidoferrocene (1.48 g., 6.07 mmoles) in 60 ml. of dichloromethane at 0°. The reaction mixture was stirred for 0.5 hr. at 0°; the ice bath was removed and the mixture was hydrolyzed and worked up in the usual manner. Recrystallization of the crude solid resulting gave well-formed platelets of acetamidoferrocene (0.854 g.). Chromatography of the filtrate on alumina gave ferrocene (0.837 g., 74% recovery), acetylferrocene (0.305 g., 22% conversion or 86% based on recovered ferrocene), acetamidoferrocene (0.445 g., total amount recovered is 88%) and 1'-acetylacetamidoferrocene (0.135 g., 7.8% conversion or 65% based on recovered acetamidoferrocene).

In a second run the reaction was carried out at room temperature. Ferrocene (1.052 g., 5.66 mmoles) and acetamidoferrocene (1.377 g., 5.66 mmoles) added initially gave acetylferrocene (0.317 g., 24.5% conversion or 96.5% based on recovered ferrocene) and 1'-acetylacetamidoferrocene (0.174 g., 10.8% conversion or 120% based on recovered acetamidoferrocene). Recrystallization of the 0.174 g. of 1'-acetylacetamidoferrocene isolated after chromatography gave 0.084 g. of well formed

crystals (5.2% conversion of 58% based on recovered acetamidoferrocene). Ferrocene isolated after chromatography of the crude acetylation products weighed 0.784 g. (74.5% recovery); acetamidoferrocene similarly recovered weighed 1.256 g. (91.2% recovery).

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Base Strengths of Alkylpyridines Using Triethylaluminum as the Reference Acid. A Study in F Strain

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The heats of reaction of a series of alkylpyridines with triethylaluminum have been measured. The order of the relative base strengths observed suggests steric factors were operative in qualitatively the manner predicted on the basis of the F strain concept of Brown and coworkers. The magnitude of these effects, however, was considerably smaller than observed previously with trimethylboron as the reference acid. The source of these differences together with some anomalous results obtained are discussed and suggested reaction schemes presented.

Brown and co-workers in a series of investigations have shown that the relative base strengths of alkylpyridines depend on the structure of the reference acid.[3-5] The basicity towards proton increases with alkyl group substitutions on the pyridine ring, as one would predict from simple inductive effects. On the other hand, as the "steric requirements" of the reference acid (Lewis acid) increase, the order of the observed relative base strengths of the alkylpyridines is different than for protonic acids. The basicity of the alkylpyridines depends on the size and position of the alkyl groups. One of the most dramatic examples cited is that of 2,6-lutidine (2,6-dimethylpyridine). Although a strong base for protonic acid ($-\Delta H$ = 19.5 kcal./mole for CH_3SO_3H), a very low heat of reaction was observed with trimethylboron.[3,4]

This result has been interpreted by Brown and coworkers to be due to the steric repulsion of the alkyl groups of the reference acid and the alkyl groups surrounding the nitrogen atom of the pyridine ring. This type of contribution of steric factors to chemical reactivity has been called F strain.[3] Due in large measure to the work of Brown and co-workers, an excellent fund of data is now available on the influence of steric strain in the reactions of hindered nitrogen bases with alkylboron compounds. In contrast, very little is known of the contribution of steric factors to the reactivity of hindered nitrogen bases with other structurally related organometallic compounds, in particular with trialkylaluminum.

In this present study, we have measured the heats of reaction of various alkylpyridines with triethylaluminum. One objective of this work has been to compare the importance of F strain in the chemical reactivity of alkylpyridines as the central atom of the reference acid was changed from boron to aluminum.

Experimental

Materials.—Normal decane was chosen as the solvent for these reactions because of its low vapor pressure at room temperature. A practical grade of normal decane was rapidly stirred with concentrated sulfuric acid (3 l. of decane/1 l. of concentrated sulfuric acid) for several days at room temperature. The ultraviolet spectrum of the decane was scanned to detect residual unsaturation (250–290 mμ). When no ultraviolet absorption was detected, the decane layer was separated, washed twice with dilute potassium hydroxide followed by three washings with distilled water. The *n*-decane was then dried with anhydrous calcium sulfate and finally stored over calcium hydride. The decane was purged with nitrogen and stored in a nitrogen atmosphere.[5b] The middle third (b.p. 115.2°, lit. b.p. 115.3°, $n^{20}D$ 1.5090, lit. b.p. 1.5092) was collected and stored over calcium hydride. The 2,6-dimethylpyridine (99% pure from Matheson, Coleman and Bell) was distilled from potassium hydroxide through a 12-in. Vigreux column under a reduced nitrogen pressure. The middle third ($n^{20}D$ 1.4967) was collected and stored over calcium hydride. The 2-methyl-6-ethylpyridine, 2-methyl-6-*n*-propylpyridine, and 2-methyl-6-isobutylpyridine were obtained as pure research samples from Reilly Tar and Chemical Company. Before use, they were stored over calcium hydride. The triethylaluminum was obtained from the Ethyl Corporation. According to their analysis, this sample was 97.5% by weight triethylaluminum (minimum), the remainder being primarily butylaluminum compounds. All handling of the triethylaluminum was carried out under a protective blanket of dry nitrogen. All of the equipment used in preparing the triethylaluminum solutions in *n*-decane was rigorously dried.

Colorimetric Procedure.—The calorimeter and technique used for measuring the heats of reaction was similar to that described by Brown and Horowitz.[6] Because of a slight difference in the geometry of the mixing chamber, we used 100 g. of mercury to provide the seal between the storage chambers. Thirty milliliters each of the 0.1 *M* solutions of the reagents were used in these experiments. All of these measurements were made at 27.4 ± 0.02°.

Even after completion of the reaction, care was taken to avoid oxidation of the triethylaluminum. After completion of the run, the solution and mercury were drawn out under vacuum. The calorimeter was then rinsed with cyclohexane, disassembled, washed, and dried.

(1) Roy C. Ingersoll Research Center, Borg-Warner Corporation, Wolf and Algonquin Roads, Des Plaines, Ill., to whom requests for reprints should be addressed.

(2) From the thesis of S. Liebman submitted in partial fulfillment of the requirements for the degree of Master of Science, College of Arts and Sciences, American University, 1960.

(3) H. C. Brown, *Rec. Chem. Progr.*, **14**, No. 2 (1953).

(4) H. C. Brown and X. R. Miehm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

(5) (a) H. C. Brown and D. Gintis, *ibid.*, **78**, 5378 (1958). (b) NOTE ADDED IN PROOF.—Pyridine (Fisher reagent grade) was distilled from potassium hydroxide in a nitrogen atmosphere through a 24-in. column packed with glass beads.

(6) H. C. Brown and R. H. Horowitz, *J. Am. Chem. Soc.*, **77**, 1730 (1955).

As Brown and Horowitz described, the heating and cooling curve for the chemical reaction was reproduced electrically as closely as possible. The electrical energy input was determined by measuring the drop in potential across the heating element and across a standard 0.1-ohm resistor (on loan from the National Bureau of Standards) connected in series. The heating element consisted of a 12-in. Manganin wire threaded on a Teflon rod. Strips of 12-gage copper wire strapped to the sides of the heating element reduced current loss. The power supply consisted of a 12-v. storage battery connected to a variable resistor to attenuate the current flow. Voltage changes in the bridge circuit were measured on a standard potentiometer.

The heat capacity of the total system was determined for several temperature changes, corresponding to those observed chemically.

TABLE I

HEAT CAPACITY OF CALORIMETER SYSTEM[a]

ΔT Temp., °C[b]	Voltage drop across heating element	Voltage drop across standard resistor	Watts consumed	Time, sec.	Joules consumed	Cp, cal./°C.
1.60	1.3680	0.2507	3.430	110.6	379.4	56.6
1.18	1.3681	0.2508	3.431	80.4	275.9	55.9
0.94	1.3605	0.2471	3.362	66.5	223.6	56.8
0.74	1.3615	0.2470	3.363	51.1	171.8	55.5
						Av. = 56.2 ± 0.5

[a] Containing 100 g. of Hg, 30 ml. each of 0.1 *N* Et_3Al and pyridine. [b] ΔT on dilution for Et_3Al was found to be 0.04°. This may have been due to trace impurities in the decane.

The observed heats of reaction were calculated from the expression $-\Delta H$ (cal./mole) = 33.33 (ΔT_{cor}) Cp/N, where ΔT is the corrected temperature rise observed, Cp is the heat capacity of the system, N is the molarity of the base solution, and the factor 33.33 arises from the use of 30 ml. of solution.

For the most part, the temperature–time curves for the reaction of pyridine and its derivatives with triethylaluminum were typical of rapid reactions which go to completion. Estimation of the temperature rise was made by standard procedures.[7]

Results

Pitzer and Gutowsky[8] have measured the molal freezing point depression of triethylaluminum in benzene. Their data indicated that triethylaluminum was largely dimeric at low temperatures (*ca.* 90%). In the earlier studies of Laubengayer and Gilliam,[9] triethylaluminum was found to be 12% associated even at 150°. Unfortunately, partial decomposition of the triethylaluminum at these high temperatures precluded the precise determination of the heat of dissociation. Further, no equilibrium data are available for triethylaluminum at lower temperatures.

In this present work, the triethylaluminum was clearly dimeric to a large degree. Lacking a value for the heat of dissociation of the triethylaluminum, the data are presented simply in terms of the observed heats of reaction under a variety or conditions. These results are shown in Table II.

Discussion

A. F Strain in 1:1 Molecular Addition Compounds.—The heats of reaction with excess base were identical to those observed with equimolar concentrations of base and acid (Table II). This was the expected result for the formation of a 1:1 molecular addition compound of the following type.

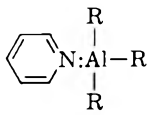
(7) R. Livingston, "Physico Chemical Experiments," Macmillan Co., New York, N. Y., 1948, p. 124.
(8) K. S. Pitzer and H. S. Gutowsky, *J. Am. Chem. Soc.*, **68**, 2204 (1946).
(9) A. W. Laubengayer and W. F. Gilliam, *ibid.*, **63**, 478 (1941).

TABLE II

HEATS OF REACTION OF $(Et_3Al)_2$ WITH ALKYLPYRIDINES

Base[a]	R_3Al, moles/liter:	$-\Delta T_{cor}$, °C. 0.1	0.2	0.3	$-\Delta H$, kcal./mole[b] 0.1	0.2	0.3
Pyridine		1.13	1.63	1.65	21.2	30.5	30.9
2,6-Dimethylpyridine		0.96	1.22	...	18.0	22.9	..
2-Methyl-6-ethylpyridine		0.73	0.98	...	13.7	18.4	..
2-Methyl-6-*n*-propylpyridine		0.73	0.98	...	13.7	18.4	..
2-Methyl-6-isobutylpyridine		0.73	0.98	...	13.7	18.4	..

[a] 0.1 molar in decane; ΔT did not change as base concentration was increased over concentration of R_3Al. [b] Based on concentration of base.

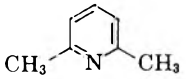


The observed heat of reaction with equimolar amounts of pyridine and triethylaluminum is in fair agreement with that obtained by Bonitz[10] ($-\Delta H$ = 19.4 kcal.).

The observed heats of reaction indicate that *alkyl substituents on the pyridine ring influence the stability of the triethylaluminum–alkylpyridine molecular addition compounds in qualitatively the manner predicted on the basis of the F strain concept of Brown and co-workers.* The contribution of "F strain" to the reactivity of alkylpyridines, however, is substantially less with triethylaluminum than with trimethylboron. Thus, the reader will note in Table III, there was observed a difference of only 3 kcal./mole between the heat of reaction of triethylaluminum with pyridine and 2,6-dimethylpyridine. This is contrasted to the results with trimethylboron; although it formed a stable addition compound with pyridine (15.3 kcal./mole), it showed almost no reaction with 2,6-dimethylpyridine.[3] Since the triethylaluminum molecule is considerably larger than the trimethylboron molecule, this result may seem puzzling. It has been observed, for example, that F strain is considerably greater in the reactions of tri-*t*-butylboron compared to trimethylboron.[11] One might, therefore, have expected the larger triethylaluminum molecule to experience the greater "steric hindrance" to reaction.

TABLE III

RELATIVE STRENGTHS OF PYRIDINE BASES

		
$-\Delta H$,[a] BMe_3[3,4]	15.3	0
$-\Delta H$,[a,b] $AlEt_3$	21.2[b]	18[b]

[a] Kcal./mole. [b] $-\Delta H$ on a comparative basis should be increased by ΔH of dissociation of dimeric $(R_3Al)_2$.

A consideration of the molecular models of addition compounds of triethylaluminum and trimethylboron with 2,6-dimethylpyridine suggests a plausible explanation. Skeletal models of the addition compounds have been drawn using observed and calculated interatomic distances, and are shown in Fig. 1. For the purpose of discussion, the most stable conformation of the 2,6-dimethylpyridine–triethylaluminum addition compound

(10) E. Bonitz, *Ber.*, **88**, 742 (1955).
(11) H. C. Brown, *J. Am. Chem. Soc.*, **67**, 1452 (1945).

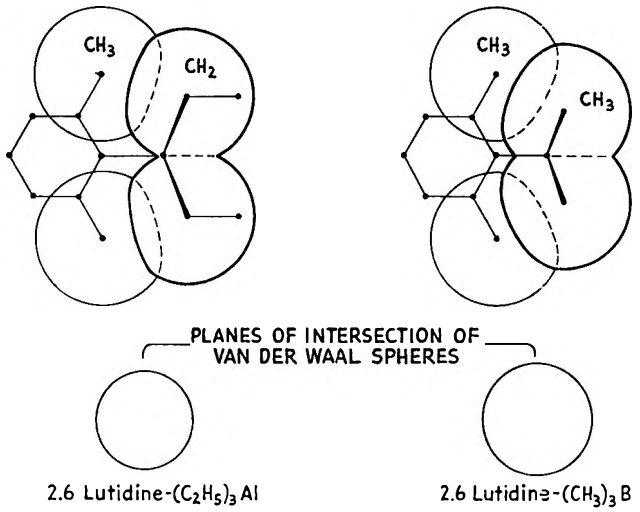


Fig. 1.[12]—F strain in 1:1 molecular addition compounds of 2,6-lutidine with triethylaluminum and trimethylboron.
Scale: 1 cm. = 2.5 Å

has been chosen in which the ethyl groups on the aluminum atom are folded back away from the reaction center, and in which two of the ethyl groups lie equidistant above the plane of the alkylpyridine ring. Nonbonded alkyl group interaction has been indicated by constructing Van der Waal spheres, using the value of 2.0 Å. for the Van der Waal radii of methyl and methylene groups.[12e]

A relative measure of the steric strain in the two structures may be obtained by comparing the depth of penetration of the Van der Waal spheres. The greater steric strain in trimethylboron-2,6-dimethylpyridine model is apparent.[13] *Owing to the larger tetrahedral covalent radius of aluminum compared to boron (43% larger), the aluminum nitrogen bond may be established at a distance which does not require so severe an interpenetration of the alkyl groups surrounding the reaction center.* On this basis, F strain should generally be of less consequence in the reactions of hindered nitrogen bases with alkylaluminum compounds than with the corresponding alkylboron compounds.

Changing one of the substituents on the pyridine ring from methyl to ethyl caused a further drop in the heat of reaction with triethylaluminum (Table II); the heat of reaction, nevertheless, was still substantial (13.7 kcal./mole). It is interesting to note that further changes in the structure of one of the substituents from ethyl, to *n*-propyl, to isobutyl, did not affect materially the stability of the addition compounds formed with triethylaluminum. From the heats of reaction with unsubstituted pyridine, it is also apparent that triethylaluminum is a much stronger acid than trimethylboron.

B. Reactions with Excess Triethylaluminum.—As the concentration of triethylaluminum was increased, the heat of reaction increased. Above 2:1 moles of acid per mole of base, the heat of reaction remained constant (col. 2 and 3, Table II). Apparently, in excess triethylaluminum a structure is involved which contains two molecules of triethylaluminum and one molecule of base. Brown has suggested that in excess triethylaluminum perhaps only half of the bridged dimer structure is opened.[14] From the data obtained with pyridine in excess triethylaluminum, we estimate that the dissociation energy of dimeric triethylaluminum is in excess of 10 kcal./mole. The same order of basicity is observed with excess triethylaluminum, but surprisingly, the effect of ring substitution on the base strength of alkylpyridine appears greater for a 2:1 mole ratio of triethylaluminum to base. The difference in the heat of reaction of pyridine and 2,6-dimethylpyridine with equimolar amounts of triethylaluminum is about 3.2 kcal. While in excess triethylaluminum, the difference is 7.6 kcal. Apparently, whatever structure is involved in excess triethylaluminum, it is more sensitive to alkyl substituents on the pyridine ring.

The possibility of ionic structures of the type $\left[\bigcirc\!\!\!\!\bigcirc\text{NAlR}_2\right]^+\text{AlR}_4^-$ analogous to the $\left[\bigcirc\!\!\!\!\bigcirc\text{NAlCl}_2\right]^+\text{AlCl}_4^-$ suggested by Bax, *et al.*,[15] to explain the partial conduction of benzene solutions of pyridine and aluminum chloride were also considered. But this does not appear likely since conductometric titrations of pyridine in benzene solution with triethylaluminum showed a rise in conduction up to a 1:1 molar ratio of each. Further addition of triethylaluminum did not alter the conduction significantly (the maximum conduction of 0.2 molar solution in benzene was 2×10^{-7} ohm^{-1} cm.$^{-1}$).[16] Bonitz also did not find evidence for a stable 2:1 R_3Al–pyridine reaction product based on his conductivity studies.[10,17] Ultraviolet[15] and infrared[18] spectral studies of the pyridine–triethylaluminum system have also failed to demonstrate the existence of a stable species containing two molecules of triethylaluminum.

The nature of the reaction product formed in excess triethylaluminum and responsible for the high heat of reaction observed remains uncertain. The data at present, however, are most consistent with the suggestion that in excess triethylaluminum only half of the bridged dimer structure of the triethylaluminum is opened up by the base to produce an un-ionized intermediate structure.

Acknowledgment.—The authors acknowledge the cooperation of the Research Division of W. R. Grace

(12) The following premises were used in constructing Fig. 1: (a) Boron and aluminum would use sp^3 hybridized orbitals in bonding in these compounds. (b) The tetrahedral covalent radii for boron and aluminum were taken as 0.88 and 1.26, respectively (L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., p. 179). (c) The bond lengths were calculated on the basis of simple additivity of covalent radii. (d) The radius of the nitrogen atom used in calculating the N-Al and N-B interatomic distance was taken as 0.65 Å. (intermediate between a single and double bond in character); These bonds were further shortened by 0.02 Å. each because of the formal charge placed on the nitrogen (L. Pauling, *ibid.*, p. 169). (e) The Van der Waal radii (nonbonded radii) of methyl and methylene groups used was 2.0 Å. (L. Pauling, *ibid.*, p. 190). (f) For simplicity, the pyridine ring was assumed identical in shape to the benzene ring; hydrogen atoms are not shown in the skeletal models; alkyl groups below the plane of the pyridine ring are not shown.

(13) The penetration of the Van der Waal spheres in the model of the triethylaluminum-2,6-dimethylpyridine compound in Fig. 1 is about the same as that obtained for nonbonded methyl–methyl interaction in a model of durene.

(14) H. C. Brown, personal communication.

(15) C. M. Bax, A. R. Katritzky, and L. E. Sutton, *Proc. Chem. Soc.* (London), 5 (1958).

(16) D. F. Hoeg, unpublished results.

(17) The origin of the partial conduction of R_3Al–pyridine systems has been the subject of some speculation. Bonitz has suggested that heterolysis of the aluminum–carbon bond is the ion-forming reaction. It has also been suggested that alkyl group migration to the ring may occur, but we have found no evidence of this. Only unsubstituted pyridine was isolated from the hydrolyzed reaction product of pyridine and triethylaluminum at 120° for 2 hr.

(18) J. Woodbrey and R. Chadha, private communication.

and Company in providing the facilities for this research. They also acknowledge helpful discussions of this work with Drs. F. X. Werber, A. D. Ketley, and R. H. Horowitz and the valuable assistance of Mr. G. Fulmer in solving several problems in the electrical circuitry. They also express their appreciation to Professors M. L. Bender and H. C. Brown for several valuable suggestions.

Lethargic Reactions. I. The Preparation of Hindered Oximes

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The combination of prolonged reaction times (one to six months at room temperature) and a strongly basic catalyst (potassium *tert*-amylate in *tert*-amyl alcohol) permitted the preparation of hindered oximes in nearly quantitative yields. The high yields are surprising in view of the fact that up to a few years ago the ketoximes were considered to be incapable of direct synthesis from the hindered ketones. Among the hindered ketoximes synthesized was 2,3,4,6-tetramethylacetophenone oxime, the preparation of which was claimed by Claus in 1887 and disputed by Meyer in 1896. Resolution of this dispute is attempted. Any reaction which necessitates prolonged reaction times and which cannot be forced by increasing the temperature is defined as a "lethargic reaction." The term is coined to draw attention to the potentialities of these conditions.

The oximation of hindered ketones, previously believed to be incapable of oximation,[2] was accomplished when it was discovered that a very slow reaction occurred at room temperature.[3] The reaction was so slow that several months' standing was necessary to bring about detectable oximation. At best the yields were low, and it was obvious that a more powerul reagent was needed to increase the yields to a range satisfactory for synthetic use.

The anion of hydroxylamine seemed to be the reagent of choice which possibly could react through the dianion if the medium were alkaline enough.

$$\underset{\text{I}}{NH_2OH} \overset{OH^-}{\rightleftharpoons} \underset{\text{II}}{\overset{\ominus}{N}HOH} \rightleftharpoons \underset{\text{III}}{NH_2\overset{\ominus}{O}} \overset{OH^-}{\rightleftharpoons} \underset{\text{IV}}{\overset{\ominus}{N}H\overset{\ominus}{O}}$$

Combining the long reaction time with a strongly basic medium (potassium *tert*-amylate in *tert*-amyl alcohol), it was found that the oximation of hindered ketones could be brought about in almost quantitative yields as shown in Table I.

TABLE I

Acetophenone (or ketone)	Time, days	Crude yield of oxime, %
2,4,6-Trimethyl-	32	98
	10	53
2,3,4,6-Tetramethyl-	180	90
	10	30
Pentamethyl-	420	81
2,6-Dimethyl-4-*tert*-butyl-	180	95
Benzoylmesitylene	450	16

From the results of Table I, there can be no doubt that the combination of prolonged standing at room temperature and of the use of a strongly basic medium has succeeded in elevating the yields of hindered ketone oximes to satisfactory values. Two other methods of making hindered oximes are available: oximation at very high pressures[4] and oximation of the corresponding imino ketone,[5] but the lethargic method is recommended because of its simplicity and general applicability.

Attempts to oximate the hindered ketones in the strongly basic medium at reflux temperatures of *tert*-amyl alcohol gave appreciable amounts of ketoxime (*ca.* 50%), but the yields could not be raised beyond this figure. The relatively low yields were attributed to the incursion of a competing side reaction at the elevated temperatures, namely the decomposition of hydroxylamine to ammonia, water, and other products.[6]

The attacking species was surmised to be II (and III)[7] rather than IV (see Experimental). IV possibly could be made in a more basic medium, but no attempt was made at this time to prepare IV.

Conditions were now at hand to settle a bitter controversy that began in 1887. Claus[8] claimed that he had made the oxime of 2,3,4,6-tetramethylacetophenone and used this fact and others to criticize the steric hindrance theory of Meyer. In the words of Claus the more precisely and carefully one attempted to abide by Meyer's rule, the more the rule had to be explained and expanded. In a crushing paper Meyer[9] countered with the statement that he had attempted to duplicate Claus' work on the oxime of the above compound, that one of his colleagues had attempted to do so and that neither could repeat a single result. In Meyer's words, the results were "ganz unverstandlich." Meyer's statement seemed to have settled the matter and cast a stigma on Claus' work, for we read later in the obituary of Claus[10] that experimental errors are to be found in the work of Claus but "who among us does not err."

The question remains some sixty years later: Did Claus make the oxime of 2,3,4,6-tetramethylacetophenone or did he not? Obviously, the new conditions permitted an easy synthesis of the oxime, and compari-

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son of the properties of the true oxime with those of Claus' is shown. 2,3,4,6-Tetramethylacetophenone oxime: Claus: m.p. 148°, leaflets; true oxime: m.p. 136–137.5°, fine needles.

Unfortunately Claus gives very little data: no conditions, no analysis, no melting point range. Anyone of these data would have helped in making the final judgment, but we must make it on the basis of the melting point alone. And the melting points do not check well. Furthermore, if the oxime is isolated in small yield from a large amount of unchanged ketone, it has been our experience[3] that the oxime melts low and over a wide range. Claus' melting point is on the high side and yet not high enough to be the Beckmann rearrangement product (m.p. 234°). Therefore, we are forced to conclude that Claus did not have the oxime. We do maintain, however, that the potentiality for making the oxime was in the hands of Claus and that any aspersions cast on his work should not have been based on his oximation experiments.

Liberty has been taken in this paper to coin a phrase which describes this type of reaction. The "lethargic reaction" is defined as one which proceeds slowly but cannot be forced because of the incursion of side-reactions at elevated temperatures. If it were confined to oximation, the coining of the phrase would not be justified. But it is apparent from the work in this laboratory that other lethargic reactions can be found. Thus the name should draw attention to the capabilities of this technique in application to other reaction studies.

Experimental

Potassium *tert*-Amylate.—Oxide free potassium[11] (98 g., 2.5 moles) was dissolved in 1250 ml. of dry *tert*-amyl alcohol; calcd. concentration, 0.19 mole/100 ml.; found by titration with acid, 0.16 mole/100 ml. The solution was amber colored and slightly opaque from a small amount of suspended material. Aliquots were removed by means of a pipet.

2,4,6-Trimethylacetophenone Oxime.—To 125 ml. (0.2 mole) of potassium *tert*-amylate solution were added 5.5 g. (0.08 mole) of hydroxylamine hydrochloride and 10 g. (0.062 mole) of 2,4,6-trimethylacetophenone in a 250-ml. erlenmeyer flask. The flask was stoppered tightly and allowed to stand at room temperature for 32 days. No change other than the precipitation of sodium chloride was noted. The *tert*-amyl alcohol was then removed by means of a rotating evaporator. Ammonium chloride (5.3 g., 0.1 mole) in 100 ml. of water was added to the thick residue and the mixture shaken well. If the oxime came out rather oily, more water was added to dissolve the traces of *tert*-amyl alcohol. The precipitated oxime was filtered and washed thoroughly with water; 10.8 g., m.p. 98–101°, 98% yield. Sublimation at 0.03 mm. gave 9.5 g. (86%) of colorless crystals, m.p. 101.5–102.5°, reported[3] 102.5–104°. All of the hindered oximes in this paper are stable indefinitely on storage, a characteristic not true with regard to most unhindered oximes.

Variations in Oximation Studies.—Similar duplicate runs were made except that the time of oximation was reduced to 10 days. The crude yields were about 53%. Another run for 10 hr. was made at the reflux temperature of *tert*-amyl alcohol. A 57% yield of crude oxime, m.p. 96.5–99.5°, was obtained. Attempts to raise the yield of the oxime using reflux failed.

Is the Dianion ($^{\ominus}NHO^{\ominus}$) the Active Reagent or the Monoanion ($^{\ominus}NHOH$ or $NH_2O^{\ominus}$)?—Two runs were made at the same time. One run had the reagent ratios: ketone 0.02 mole, hydroxylamine hydrochloride 0.03, and potassium *tert*-amylate 0.06. The second run had the ratios: ketone 0.02, hydroxylamine hydrochloride 0.03, and potassium *tert*-amylate 0.124. After 43 days, each run was worked up in the usual manner. The crude yields (88%) of acetomesitylene oxime were identical. It is to be noted that the first run had no excess base since 0.03 mole is needed to neutralize the hydrogen chloride combined with the hydroxylamine; the second run had sufficient base to convert the anion at least partially to the dianion.

2,3,4,6-Tetramethylacetophenone Oxime.—We are indebted to Hutcheson[12] for the preparation and characterization of 2,3,4,6-tetramethylacetophenone (acetoisodurene). The ketone ($n^{22}D$ 1.5251, 0.07 mole) was oximated as described for acetomesitylene except that the reaction mixture was allowed to stand for 6 months. Following the usual isolation procedure, a powder was obtained in 90% yield based on oxime formation, m.p. 132–138°. The powder was recrystallized from aqueous isopropyl alcohol to give small needles, 75% based on starting material, m.p. 136–137.5° (previous sintering).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.71; H, 8.53; N, 7.31.

The oxime was rearranged in quantitative yield to N-acetylisoduridine by refluxing with aqueous hydrochloric acid (von Auwer's method[13] for hindered oximes), m.p. 223–224°, reported[14] m.p. 217.5°.

Anal. Calcd. for $C_{12}H_{17}NO$: N, 7.32. Found: N, 7.26.

An oximation carried out for 10 days instead of 6 months gave a 30% yield of methylisoduryl ketoxime and a 60% yield of recovered ketone.

Oximation for 4 months using sodium ethoxide in ethanol rather than potassium *tert*-amylate in *tert*-amyl alcohol gave a 5% yield (based on original ketone) of an unknown substance, m.p. 108.5–109°.

Anal. (for the suspected oxime of the dypnone of acetoisodurene). Calcd. for $C_{24}H_{29}NO$: C, 82.9; H, 8.4; N, 4.03. Found: C, 81.7; H, 9.13; N, 4.18.

Since the analyses were poor and the characterization scanty, we do not claim to know the structure of the substance, m.p. 109°.

Pentamethylacetophenone Oxime.—The corresponding ketone (m.p. 84–85°, 0.03 mole) was converted to the oxime in 96% crude yield, m.p. 175–179°. The time of oximation was 14 months, probably a much longer time than necessary. The crude oxime was recrystallized from methylcyclohexane and resublimed to give a colorless solid in 81% over-all yield, m.p. 182–183°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.05; H, 9.32.

The oxime was rearranged by von Auwer's method[13] to pentamethylacetanilide, m.p. 216.5–217°, reported[15] m.p. 213°.

2,6-Dimethyl-4-*tert*-butylacetophenone Oxime.—In 6 months the ketone (0.15 mole) was converted to the oxime in 95% crude yield which after recrystallization from methylcylcohexane with Norit gave colorless leaflets in 72% yield, m.p. 158–160°, reported[16] m.p. 157.5–161.5°.

Benzoylmesitylene Oxime.—In 15 months the ketone (0.044 mole) was converted to the oxime in 16% over-all yield, plates from methylcyclohexane, m.p. 147.5–148.5°, reported[5,16] m.p. 142–144°.

Failures.—Anthraquinone in the *tert*-amylate solution containing hydroxylamine gave a dark green precipitate. After 2 months' standing, the mixture was treated in the usual manner and yielded 48% anthraquinone, yellow needles from amyl acetate, m.p. 286.5–287.5°. The poor recovery of starting material together with no oxime formation and the appearance of the intermediate suggested the formation of an anthraquinhydrone system.

2,3,5,6-Tetrachloroacetophenone was cleaved under the oximation conditions to 1,2,4,5-tetrachlorobenzene, m.p. 141–142°, in 70% crude yield. This competing reaction was not unexpected.[17]

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An Arabinoglucoglycan in Chick-Pea Seed

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An arabinoglucoglycan, composed of L-arabinose and D-glucose in a ratio of about 3:7, was isolated in 0.8–1.2% yield from the seed of *Cicer arientinum*. Periodate degradation revealed that all units were attacked. Polarimetry and hydrolysis of the methylated polysaccharide showed the predominance of the α-(1 → 4)-linked glucopyranoside units. The optical rotation in cuprammonium is discussed.

Chick-pea, *Cicer arientinum*, is a leguminous plant which is widely grown in Middle Eastern countries. The seeds are of the size of peas and are borne in separate pods. They have high nutritional value[2] and are used as native food in different forms.

The polysaccharide was obtained in 0.8% or 1.2% yield from the ground seed by extraction with warm water or warm sodium hydroxide solution, respectively, and was purified *via* its copper complex. Hydrolysis of the chick-pea polysaccharide followed by chromatographic separation of the products yielded crystalline L-arabinose and D-glucose. A quantitative estimate of the molecular proportions of the two sugars indicated that they were present in an approximate ratio of 1:2. This ratio remained essentially the same when three different methods for isolating the polysaccharide were applied, indicating the homogeneity of the arabinoglucoglycan.

The polysaccharide then was exhaustively methylated with methyl sulfate and sodium hydroxide. The arabinoglucoglycan exhibited considerable resistance toward complete methylation and seven successive methylation processes were required to yield a methylated product containing 0.88 OCH_3 group per hydroxyl group.

Examination of the fission products of the methylated polysaccharide on paper chromatograms showed the presence of tri-*O*-methylglucose and smaller quantities of di-*O*-methylglucose and mono-*O*-methylarabinose. No tetra-*O*-methylglucose or tri-*O*-methylarabinose was detected. The procedure used for detection of methylated sugars on paper chromatograms is capable of detecting less than one part of tetra-*O*-methylglucose (indicative of end groups) in a hundred parts of tri-*O*-methylglucose[3] and, therefore, the methylated material has a chain length greater than one hundred units.

Separation of the fission products of the methylated polysaccharide by partition chromatography yielded 2,3,6-tri-*O*-methyl-D-glucose (65%), 2,3-di-*O*-methyl-D-glucose (5%), 3,6-di-*O*-glucose (7%), and 3-*O*-methyl-L-arabinose (17%). Comparison of the molecular ratio of methylated arabinose to methylated glucose (1:2.9) with that of arabinose to glucose (1:2) in the original polysacchride showed that some arabinose units were lost during methylation and hydrolysis. The large proportion of 2,3,6-tri-*O*-methyl-D-glucose showed a predominance of (1 → 4)-linkages between the glucose units while the high positive value for the specific rotation of the polysaccharide indicated α-linkages. The isolation of 2,3-3,6-di-*O*-methyl-D-glucose would suggest branching, forming (1 → 6)- and (1 → 2)-linkages. However, in view of the failure to detect any 2,3,4,6-tetra-*O*-methyl-D-glucose in the hydrolyzate of the methylated polysaccharide it is suggested that incomplete methylation of the polysaccharide and demethylation during hydrolysis might be the reason for the presence of all or most of the di-*O*-methyl derivatives. The isolation of 3-*O*-methyl-L-arabinose as the only L-arabinose derivative is suggestive of branching at positions 1, 2, and 4 of the arabinopyranoside. However, similarly the presence of only mono-*O*-methyl-L-arabinose may be due to incomplete methylation or to demethylation. Other authors[4,5] have previously made similar observations.

On oxidation by periodate, the arabinoglucoglycan consumed *ca.* one mole of oxidant per mole of sugar residue. This and the absence of arabinose in the hydrolyzate of the periodate oxidized polysaccharide indicated that the L-arabinose units were nonbranched.

The polysaccharide on reaction with Fehling's solution formed a copper complex which contained one-third atomic equivalent of copper per mole of sugar unit. Comparison of the specific rotation of the arabinoglucoglycan in dilute alkali (+385°) with that in cuprammonium (−12°) showed that a levorotatory complex was formed in cuprammonium. This has been shown[6] to occur in reactions involving the 2- and 3-hydroxyl groups of D-glucopyranoside as well as the 2- and 3- or the 3- and 4-groups of L-arabinopyranoside. Such shifts in the case of starch and glycogen where reaction involves all the sugar units are from +375° to −715° and from +366 to −597, respectively.[7] In the arabinoglucoglycan in chick pea, the copper complex isolated involves only one-third of the sugar units and the levorotatory shift is about one-third of that of starch or glycogen.

Experimental

All specific rotations are equilibrium values and were measured at room temperature. Chromatographic separations were carried out using the following solvent systems: (a) 1-butanol–ethanol–water (40:11:19 v./v.); (b) ethyl acetate–acetic acid–water (9:2:2 v./v.) for unsubstituted sugars; and (c) benzene–ethanol–water (190:50:5 v./v.) for methylated sugars. Separations were made by the descending technique on Whatman no. filter paper. Sugars were located on the paper by *p*-anisidine hydrochloride spray reagent.[8] Solutions were concentrated under reduced pressure.

Isolation of the Polysaccharide.—(a) The finely ground seeds (200 g.) were stirred with water on the water bath (4 × 500 ml.;

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ca. 1 hr. each time). After each extraction the residual seed material was separated on the centrifuge. The combined extracts were treated with diastase for 24 hr., then poured with stirring into alcohol (4 l.). The solid precipitate was washed with alcohol several times and dissolved in warm water (500 ml.). The solution was washed with chloroform (4 × 100 ml.) and it (solution A) was poured into ethanol (1 l.) yielding a white powder (1.6 g.).

Anal. Found: N, 1.95; sulfated ash, 2.7.

(b) The seeds (200 g.) were ground and heated on the water bath with 10% sodium hydroxide solution (2 l.) for 8 hr. with continuous stirring until a jelly-like mass was formed and no more ammonia was evolved. It was then poured with stirring into ethanol (4 l.). The precipitate was washed several times with ethanol, the polysaccharide extracted in warm 0.2% sodium hydroxide solution (4 × 500 ml.), treated with diastase for 24 hr., and reprecipitated from the solution (solution B) by the addition of ethanol (5 l.) yielding a white powder (2.4 g.).

Anal. Found: N, 0.94; sulfated ash, 4.4.

(c) To solution A or solution B (1 l.) was added Fehling's solution (200 ml.) and the mixture was allowed to stand for 7 days. The resulting copper complex (2–3 g.) was separated on the centrifuge, washed with alcohol several times, and dried in a desiccator.

Anal. Calcd. for $[(C_{17}H_{26.2}O_{14}\cdot 0.8\ Cu(NH_3)_2]_n$: Cu, 9.57. Found: Cu, 9.0.

The polysaccharide was recovered from the copper complex by treatment with *N* hydrochloric acid (100 ml.) with stirring and pouring into ethanol (150 ml.). The white precipitate was filtered off, washed successively with ethanol and ether, then dried under reduced pressure. It had $[\alpha]_D$ +385° (*c*, 2.1, 0.9% sodium hydroxide).

Anal. Found: N, 0.5; sulfated ash, 0.5.

Hydrolysis of the Polysaccharide and Identification of the Products.—The polysaccharide (1.65 g.) in *N* sulfuric acid (100 ml.) was heated on the water bath for 15 hr. The reaction mixture was neutralized with barium carbonate and filtered. The filtrate was concentrated to a sirup which on examination on paper chromatograms was observed to contain two components, R_f 0.32 and 0.20. The sirup was fractionated on a cellulose column using 1-butanol–water (10:1 v./v.) as the mobile phase. Two fractions were obtained.

Fraction I gave crystals (1.03 g.) of D-glucose with m.p. 146° $[\alpha]_D$ +51.6° (*c*, 5.6, water). It gave a crystalline phenylosazone with m.p. 205°, undepressed on admixture with an authentic specimen of D-glucophenylosazone.

Fraction II gave crystalline L-arabinose (0.46 g.) with m.p. 160°, $[\alpha]_D$ +104.8° (*c*, 2.2, water). It yielded crystalline L-arabinophenylosazone with m.p. and m.m.p. 166°.

Methylation of the Polysaccharide.—The arabinoglucoglycan (7 g.) was dissolved in sodium hydroxide solution (300 ml., 40%) and methyl sulfate (300 ml.) was added in portions during 5 hr. with vigorous stirring.[9,10] After being stirred overnight, the mixture was nearly neutralized with glacial acetic acid and dialyzed against tap water for 24 hr. The solution was concentrated to *ca.* 100 ml. and the methylation procedure was repeated using 50 g. of sodium hydroxide and 100 ml. of methyl sulfate, then 100 g. of sodium hydroxide and 200 ml. of methyl sulfate. The mixture was neutralized, dialyzed, concentrated, and methylated five times as described. The final reaction mixture was dialyzed for 48 hr. against tap water, concentrated, and extracted with chloroform. After removal of the chloroform under reduced pressure the partially methylated polysaccharide (4.8 g.) was obtained.

Anal. Calcd. for 63% methylation $[C_{17}H_{23}O_9(OCH_3)_5]_n$: OCH_3, 29.50. Found: OCH_3, 30.00.

This material was refluxed in methanol (10 ml.) with methyl iodide (50 ml.) and silver oxide (10 g.; added in portions) for 30 hr. The reaction mixture was then evaporated to dryness and the solid material extracted with chloroform. The chloroform extract was concentrated to a sirup which was treated with methyl iodide (15 ml.) and silver oxide (5 g.) as before, yielding a yellowish solid (4 g.).

Anal. Calcd. for 88% methylation $[C_{17}H_{21}O_7(OCH_3)_7]_n$: OCH_3, 39.2. Found: OCH_3, 39.00.

Identification of the Products.—The methylated polysaccharide (*ca.* 2 g.) was allowed to stand in 40% sulfuric acid (20 ml.), left at room temperature for 3 hr., then diluted again with water (40 ml.), and heated at 60° for 3 more hr. After further dilution with water (80 ml.), the reaction mixture was heated on the water bath for 14 hr. and neutralized with barium carbonate. The barium salts were filtered off and the filtrate concentrated to a sirup (1.42 g.) which on examination on paper chromatograms, using solvent c, was found to contain at least six components with R_f values of 0.0125, 0.075, 0.14, 0.336, 0.45, and 0.75. The sirup was fractionated by paper chromatography, using solvent c, yielding four fractions.

Fraction I yielded crystalline 2,3,6-tri-*O*-methyl-D-glucose (0.83 g.) which, after recrystallization from aqueous ethanol, had m.p. 123° $[\alpha]_D$ +70° (*c*, 1.25, methanol). Irvine and Hirst[11] record m.p. 121–123°, $[\alpha]_D$ +70° (water).

1,4-Di-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-glucose.—A mixture of 2,3,6-tri-*O*-methyl-D-glucose (fraction I) (*ca.* 0.1 g.), dry pyridine (2 ml.), and acetic anhydride (2 ml.) was allowed to stand at room temperature for 24 hr. and then poured into ice–water (*ca.* 20 ml.). The acetylated product was extracted with chloroform (3 × 20 ml.) and the combined extracts were washed successively with 2 *N* hydrochloric acid (2 × 20 ml.), saturated sodium hydrogen carbonate (2 × 20 ml.) and water, and dried (Na_2SO_4). Subsequent concentration gave a colorless sirup which crystallized on standing at 0° (yield, *ca.* 0.1 g.). After recrystallization from ethanol, the acetate had m.p. 67°. Micheel and Hess[12] record m.p. 67–68°.

Fraction II gave 2,3-di-*O*-methyl-D-glucose (0.069 g.) as crystals with m.p. 85°, $[\alpha]_D$ +50° (*c*, 1.0, methanol). Irvine and Scott[13] record m.p. 85–87°, $[\alpha]_D$ +48.3 (acetone).

Fraction III afforded 3-*O*-methyl-L-arabinose (0.215 g.) with $[\alpha]_D$ +96.5° (*c*, 1.15, water). Hirst, *et al.*,[14] record $[\alpha]_D$ +96° (water).

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.32. Found: C, 43.96; H, 7.03.

The compound (30 mg.) yielded the phenylosazone (45 mg.) as crystals with m.p. 163°. Smith[15] records m.p. 163°.

Fraction IV yielded crystalline 3,6-di-*O*-methyl-D-glucose (0.091 g.) with m.p. 113°, $[\alpha]_D$ +63° (*c*, 1.0, methanol). Percival and Duff[16] record m.p. 113–116°, $[\alpha]_D$ +61.5° (water). The compound (35 mg.) gave the phenylosazone as crystals (40 mg.) with m.p. 152°.

Periodate Oxidation.—Aqueous sodium metaperiodate, 0.3 *M*, (10 ml.) was added to the polysaccharide (*ca.* 0.1 g.) in water, the solution adjusted to 100 ml. with distilled water and stored in the dark. A blank was treated concurrently. At intervals the periodate uptake was estimated by transferring samples (5 ml.) from the oxidation mixture and from the blank into mixtures of phosphate buffer (pH 6.98; 25 ml.) and 20% potassium iodide (2 ml.), and the liberated iodine was titrated with 0.01 *N* sodium thiosulfate using starch as indicator.[17] Acid liberated during the oxidation was determined[18] by taking samples (5 ml.) from the oxidation mixture and from the blank, adding ethylene glycol (2 ml.), and, after 10 min., titrating with 0.01 *N* sodium hydroxide using methyl red screened with methylene blue as indicator. Formaldehyde was determined colorimetrically with chromatropic acid[19] using glucose as standard. The results, calculated in moles per mole of sugar unit are presented here in tabular form.

Time (hr.)	0.5	1	2	3	4
Uptake	0.34	0.52	0.70	0.74	0.78
Acid	0.06	0.07	0.09	0.10	0.12
CH_2O					
Time (hr.)		6	9	13	32
Uptake		0.85	0.90	0.91	0.95
Acid		0.14	0.14	0.15	0.15
CH_2O					nil

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In a separate experiment the polysaccharide (100 mg.) was oxidized with periodate[20] for 48 hr. as before. The excess periodate was destroyed by the addition of ethylene glycol and the solution was dialyzed against tap water for 72 hr. The nondialyzable material was recovered by concentration and hydrolyzed with *N* sulfuric acid. The reaction mixture was neutralized with barium carbonate, filtered, and concentrated. On chromatographic examination neither glucose nor arabinose was detected.

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An Investigation of the Hydrolysis of a Reduced 4-*O*-Methylglucuronoxylan[1]

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Uronic acid groups in an elm 4-*O*-methylglucuronoxylan were reduced by diborane without a decrease in degree of polymerization of the polymer. Partial hydrolysis of the reduced polymer gave a neutral hetero-trisaccharide fraction from which a new trisaccharide, *O*-α-4-*O*-methyl-D-glucopyranosyl(1 → 2)-*O*-β-D-xylopyranosyl(1 → 4)-D-xylopryanose, was isolated, and its crystalline phenylosazone was prepared and characterized. An authentic specimen of the new sugar was prepared from the ubiquitous aldotriouronic acid by an adaptation of the diborane procedure. An hypothesis based on conformational resistance was presented to account for the formation of the new trisaccharide and the aldotriouronic acid during partial hydrolysis of the reduced and unreduced 4-*O*-methylglucuronoxylan, respectively.

The 4-*O*-methylglucuronoxylans obtainable from most hardwoods consist of chains of 1 → 4 linked β-D-xylopyranose units with single 4-*O*-methyl-D-glucopyranosiduronic acid units attached as side chains on C-2 of the xylose units[4] as shown in Fig. 1.

Partial hydrolysis of such hemicelluloses in aqueous acid results in the formation of a polymer-homologous series of β-1–4 xylodextrins[5] and a closely related acidic series (Fig. 2). The linkage (α-1–2) between E and B, Fig. 1, is especially resistant, and the amorphous aldobiouronic acid, therefore, is the chief acidic product of the acid hydrolysis of these polymers. The crystalline aldotriouronic acid (EBC)[6,7] is the second most abundant product in the acidic series, but all efforts to find the isomeric acid (ABE) have failed. To account for these facts Hamilton and Thompson[6] suggested that the uronic acid carboxyl "stabilized" the linkages B–E and B–C through an inductive effect. Marchessault and Rånby[8] supported the stabilization hypothesis,[9,10] and further suggested that, simultaneously, the linkage A–B was "activated."

In order to test these hypotheses, the carboxyl groups in a 4-*O*-methylglucuronoxylan, isolated from American elm sapwood (*Ulmus americana*), were reduced to primary hydroxyl groups.[11] Then upon partial hydrolysis of the 4-*O*-methylglucoxylan in dilute aqueous acid, the products of the reduced and the unreduced polymers were compared. As expected, the 4-*O*-methylglucoxylan afforded two series of neutral, reducing oligosaccharides as shown in Fig. 2.

The hetero-trisaccharide component of the hydrolyzate was isolated by a gradient elution technique on a carbon–Celite column[12] followed by preparative paper chromatography. Although the trisaccharide

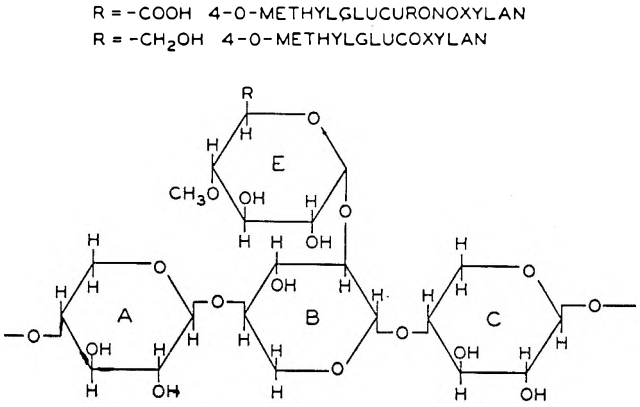

Fig. 1.—Principal linkages in 4-*O*-methylglucuronoxylans.

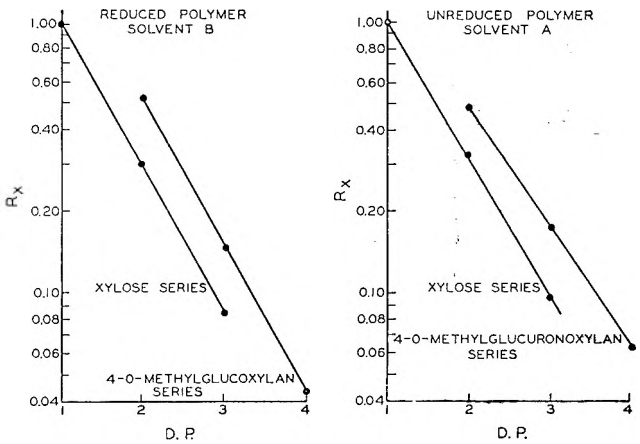

Fig. 2.—log R_x *vs.* D.P. for saccharides from the partial acid hydrolysis of reduced and unreduced 4-*O*-methylglucuronoxylan.

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component was chromatographically uniform, electrophoresis on paper in a sodium borate buffer revealed two distinct components. The major component (about 95% by visual inspection) had the greater mobility which corresponded closely with the mobility of the authentic hetero-trisaccharide (EBC); the minor component was presumed to be the isomer (ABE).[13] Proximate analyses by paper chromatography of partial hydrolyzates of the reduced and unreduced polymers indicated that the yield of the hetero-trisaccharide was 4% and the aldotriouronic acid, 7%. Furthermore, about 20% of the 4-*O*-methylglucose units were recovered as the monosaccharide from the reduced polymer, but no 4-*O*-methylglucuronic acid was detected for the unreduced sample.

These observations illustrate the well known stability toward acid hydrolysis of glycuronides, in contrast to most glycosides, and are compatible with the hypothetical inductive effect of the uronic acid carboxyl. However, the fact that the new trisaccharide predominated about 20:1 over the substance believed to be its isomer suggests that the inductive effect of the carboxyl probably does not extend to the glycosidic linkages of the xylan chain, and that the hypotheses of Hamilton and Thompson[6] and Marchessault and Rånby[8] may require modification. Thus, an alternate hypothesis, based on conformational resistance, suggested itself.

Assuming that glycosidic hydrolysis proceeds *via* the cyclic mechanism[9,10] and that the formation of a carbonium ion necessitates a transformation from the puckered chair form to a planar half-chair form, as suggested by Edward,[14] the large bulky substituent on C-2 of the xylose moiety will diminish its tendency toward the half-chair conformation. This resistance could be sufficient to cause a lower rate of hydrolysis for glycosidic bond B–C relative to A–B in the reduced and unreduced polymers, and in turn would account for the predominance of isomer EBC in hydrolyzates of both polymers.

An authentic specimen of the new trisaccharide, *O*-α-4-*O*-methyl-D-glucopyranosyl-(1 → 2)-*O*-β-D-xylopyranosyl-(1 → 4)-D-xylopyranose, was prepared in a metastable crystalline form from the aldotriouronic acid (EBC), and was identical with the main hetero-trisaccharide obtained from the 4-*O*-methylglucoxylan; the phenylosazone was prepared and characterized.

Experimental

Paper Chromatography.—The following solvents were used in paper chromatography: (A) for uronic acids, ethyl acetate–acetic acid–water (9:2:2); (B) for neutral sugars and oligosaccharides, ethyl acetate–pyridine–water (8:2:1); (C) for galacturonic and glucuronic acids, ethyl acetate–pyridine–water–acetic acid (5:5:3:1); (D) for the separation of xylose and xylitol, butanol–pyridine–water (10:3:3); (E) for quantitative analysis, ethyl acetate–pyridine–water (8:2:1) and 0.15 *N* in silver nitrate.

Sugars were detected in qualitative chromatography with *p*-anisidine hydrochloride[15] for reducing sugars (for electrophoretograms monochloroacetic acid was added), and silver nitrate for nonreducing substances.[16] Aniline–monochloroacetic acid in ether was used for quantitative chromatography.[17]

Isolation of 4-*O*-Methylglucuronoxylan.—Five American elm (*Ulmus americana*) trees, averaging 3.5-in. d.b.h. (diameter at breast height: 4.5 ft.) were cut, peeled, and chipped, and the sapwood portion ground in a no. 1 Wiley mill. The isolation of 4-*O*-methylglucuronoxylan was accomplished in an inverted 5-gal. polyethylene bottle with the bottom removed. About 1 kg. of the undried wood meal (54% oven dry) was extracted twice with 5.5 l. of 70% ethanol for 12 hr. at room temperature, washed with deionized water, and then leached with 8 l. of 0.1 *N* sodium hydroxide for 4 hr. at room temperature; the extract was discarded. The wood meal was washed thoroughly with deionized water, pressed to 25% moisture (oven-dry basis), extracted with 5.5 l. of 10% potassium hydroxide at room temperature for 2 hr., and the extract was poured into two volumes of cold 95% ethanol containing sufficient acetic acid to bring the pH to about 6. The precipitated hemicellulose was washed and solvent-exchanged with 80% ethanol, 95% ethanol, absolute ethanol, and petroleum ether (b.p. 30–60°), and dried *in vacuo* over calcium chloride; yield, 98 g. Analytical data for the large scale preparation and for three small scale experiments using different concentrations of potassium hydroxide are summarized in Table I.

Table I

Effect of Potassium Hydroxide Concentration on Hemicellulose

Sample	1	2	3	4 (Large scale)
70% ethanol extracts, % oven-dry wood		1.5		
0.1 *N* NaOH extract (pptd. by EtOH), oven-dry wood			0.2	
Concentration of KOH soln., % by wt.	5	10	24	10
Yield of hemicellulose, % oven-dry wood	7.4	13.0	13.8	~10
Analysis of hemicellulose				
Moisture, %	8.45	7.94	7.56	9.22
Sulfated ash as K, %	4.17	6.95	7.77	2.85
CO_2,[a] %	3.16	2.77	2.69	3.07
$D.P._n$				162
Yield, of hemicellulose (ash- and moisture-free), % oven-dry wood	6.32	10.1	10.5	~9
CO_2,[a] % on ash- and moisture-free hemicellulose	3.70	3.54	3.51	3.51
Xylose/4-*O*-methylglucuronic acid	~7.5	~8	~8	~8

[a] See ref. 18.

Reduction of 4-*O*-Methylglucuronoxylan.[19]—The 4-*O*-methylglucuronoxylan, 36.0 g., was acetylated according to the method of Carson and Maclay[20]; yield, 90.3%.

Anal. of the acetylated hemicellulose: sulfated ash, 0.03; moisture, 2.38; acetyl,[21] 37.2. The theoretical acetyl content was 37.4% for a polymer of $D.P._n$ = 162 and a xylose/uronic acid ratio of 8.

(13) A. B. Foster, "Advances in Carbohydrate Chemistry," M. L. Wolfrom and R. S. Tipson, Ed., Vol. 12, Academic Press, Inc., New York, N. Y., 1957, p. 95.

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The acetylated hemicellulose, was reduced with diborane (13.3 moles/mole of carboxyl) according to the general procedure of Smith and Stephen.[11] The diborane was generated *in situ* over a period of 4 hr. under mechanical stirring by the dropwise addition of 75.3 ml. of boron trifluoride etherate, diluted with 50 ml. of purified diglyme [bis(2-methoxyethyl) ether],[22] to a solution of 17.0 g. of sodium borohydride dissolved in 440 ml. of diglyme in which 45.5 g. of the hemicellulose acetate was suspended. Stirring was continued for an additional 3 hr., the reaction mixture was allowed to stand overnight, and was decomposed by addition of ice–water. When the evolution of hydrogen ceased, the mixture was neutralized with 0.5 *N* sodium hydroxide to pH 7 and poured into two volumes of 95% ethanol. The precipitate was dissolved in 5% potassium hydroxide, heated for 45 min. at 55°, and the 4-*O*-methylglucoxylan recovered in the usual way (see above isolation procedure); yield, 81.4% of the original hemicellulose, corrected for ash and moisture. Chromatographic examination (in solvents A and B) of the total hydrolyzate from the 4-*O*-methylglucoxylan showed that xylose and 4-*O*-methylglucose were the predominant constituents but that a trace of galactose remained.

Anal. moisture, 2.4; sulfated ash calcd. as potassium acetate, 1.3; uronic acid CO_2,[18] 0.84; D.P.$_n$, 171.

Partial Hydrolysis of 4-*O*-Methylglucoxylan.—4-*O*-Methylglucoxylan, 20.5 g., was dissolved in 420 ml. of 1.0 *N* sulfuric acid, and the solution was heated at 70° (bath temperature) for 8 hr. After cooling and centrifuging, the supernatant hydrolyzate was neutralized with barium hydroxide to pH 5.5, and the barium sulfate was removed by filtration. The hydrolyzate was sorbed on a charcoal–Celite column (5 cm. in diameter by 90 cm. long) which was packed with a mixture of 400 g. of Darco G-60[23] and 400 g. of Celite[24] and treated with stearic acid.[12] The column was washed with 2 l. of distilled water and with aqueous ethanol by the gradient elution technique as described by Alm and coworkers.[12] Fractions were collected automatically and were monitored by paper chromatography. The hetero-oligosaccharides were recovered and further purified on Whatman 3MM paper in solvent B. Upon complete hydrolysis and chromatographic analysis each hetero-oligosaccharide yielded xylose and 4-*O*-methylglucose.

Preparation of *O*-α-4-*O*-Methyl-D-glucopyranosyl-(1→2)-*O*-β-D-xylopyranosyl-(1 → 4)-D-xylopyranose.—Aldotriouronic acid, 0.51 g., was refluxed with 30 ml. of acetic anhydride and 0.35 g. of anhydrous sodium acetate. The reaction mixture was poured into ice–water, extracted with chloroform, and the solvent was evaporated *in vacuo;* yield of aldotriouronic acid acetate, 0.85 g. The acetate was dissolved in purified tetrahydrofuran[25] in a gas washing bottle supplied with a sintered glass gas disperser and diborane (15 moles/mole of carboxyl) was swept from the generator into the solution by a stream of dry nitrogen over a 45-min. period. After a total reaction time of 3.8 hr., the reaction was terminated by the addition of methanol and allowed to stand overnight. The solvents were removed by evaporation *in vacuo* at 35° followed by three successive 30-ml. portions of methanol to remove boric acid as methyl borate; yield, 0.66 g. Deacetylation with barium methylate,[26] followed by neutralization with sulfuric acid and removal of barium sulfate, and concentration *in vacuo* gave a sirup; yield, 0.51 g.

Resolution of the crude sirup on Whatman 3MM paper in solvent B gave a sirup, 0.30 g., which became a slush of hygroscopic, metastable crystals of a new trisaccharide which was assumed to be *O*-α-4-*O*-methyl-D-glucopyranosyl (1 → 2)-*O*-β-D-xylopyranosyl(1 → 4)-D-xylopyranose based on the previously determined structure of the starting material.[5,7] The chromatogram indicated that unreduced acid, xylobiose, xylose, and 4-*O*-methylglucose were also present in the product.

Comparison of the Trisaccharides.—The hetero-trisaccharide ("unknown") from the hydrolysis of reduced 4-*O*-methylglucuronoxylan and the new trisaccharide ("known") prepared from the aldotriouronic acid were indistinguishable by paper chromatography. Paper electrophoresis in 0.1 *M* borate gave the following results: xylotriose (M_G = 0.145); "unknown" mixed trisaccharide, major component (M_G = 0.147), minor component (M_G = 0.058); "known" trisaccharide (M_G = 0.145). Optical rotations of the "known" and "unknown" trisaccharides were measured after first drying the sirups *in vacuo* over calcium chloride; "known" trisaccharide, $[\alpha]^{25}D$ +45.7 (*c* 6.7, water); "unknown" trisaccharide, $[\alpha]^{25}D$ +34.0 (*c* 7.2, water).

Phenylosazones were prepared as follows: a mixture of 0.16 g. of the "known" trisaccharide, 0.45 g. of sodium acetate trihydrate, 0.30 g. of phenylhydrazine, and 3.5 ml. of water were heated in a boiling water bath for 30 min.; osazone formation began at about 14 min.; yield, 0.057 g., after recrystallization from 60% aqueous ethanol, 0.039 g., m.p. 240–241°. The phenylosazone of the "unknown" trisaccharide was prepared in a similar manner from 0.22 g. of the sugar and corresponding quantities of reagents; yield, 0.052 g., after recrystallization, 0.047 g., m.p. 240–241°. The low yields of osazones were due primarily to large mechanical losses. The osazones were dried *in vacuo* over phosphorus pentoxide at 56° for 1.5 hr. prior to analysis.[27]

Anal. Calcd. for $C_{29}H_{40}O_{12}N_4$: C, 54.71; H, 6.33; N, 8.80; OCH_3, 4.88. Found: "known," C, 54.9; H, 6.2; N, 8.9; OCH_3, 4.0. "Unknown," C, 53.9; H, 6.2; N, 8.8; OCH_3, 3.9. Infrared absorption spectra and X-ray diffraction patterns were identical.

Methyl-4-*O*-methyl-α-D-glucopyranoside, xylose, and the "known" and "unknown" trisaccharides were dissolved separately in 0.5 *N* hydrochloric acid, heated on a boiling water bath for 3 hr., neutralized with silver carbonate, and spotted for quantitative chromatography[28] in solvent E. The xylose/4-*O*-methylglucose ratios were as follows: "known," 1.45; and "unknown," 1.67; theoretical ratio, 2.0.

Comparison of the Partial Hydrolyzates of Reduced and Unreduced 4-*O*-Methylglucuronoxylan.—Approximately 0.1-g. samples of reduced and unreduced 4-*O*-methylglucuronoxylan were hydrolyzed with 2.0 ml. of *N* sulfuric acid at 70° for 8 hr. After neutralization with barium acetate, the hydrolyzates were analyzed by quantitative paper chromatography in solvent A for the unreduced sample and solvent B for the reduced sample. Known quantities of aldotriouronic acid (for unreduced sample) and "known" trisaccharide (for reduced sample) were also spotted and served as controls. An aniline–monochloroacetic acid dip was used for spot development, and the quantity of trisaccharide present was estimated by visual comparison with standards using transmitted light; yield of aldotriouronic acid, approximately 7% and of neutral hetero-trisaccharide, about 4%. Considerable 4-*O*-methylglucose was observed in the 4-*O*-methylglucoxylan hydrolyzate but no 4-*O*-methylglucuronic acid was detected in the unreduced polymer hydrolyzate. Movement on paper chromatograms of oligosaccharides from the hydrolyzates relative to xylose are shown in Fig. 2.

Viscosity Measurements.—Viscosity of the polymers was measured in molar cupriethylenediamine utilizing an Ubbelohde-type viscometer manufactured by the Cannon Instrument Co. The degree of polymerization (D.P.$_n$) was calculated from the relationship D.P.$_n$ = $K[\eta]$, where K = 166 (calculated from the data of Gillham and Timell[29]) and $[\eta]$ = intrinsic viscosity. The results are listed in Table I.

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The Synthesis of a Glucosaminyl-Muramic Acid Disaccharide: Methyl 6-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside[1]

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The syntheses of various derivatives of the methyl α-D-glycoside of 2-amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose (muramic acid) and of the disaccharide, methyl 6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside are described.

Muramic acid, a 3-*O*-(D-1-carboxyethyl) derivative of 2-amino-2-deoxy-D-glucose, and its parent hexose, 2-amino-2-deoxy-D-glucose, have been shown to be the main components of the peptidoglycan chain, which constitutes the backbone of the cell wall of numerous Gram-positive and Gram-negative bacteria.[3] The action of egg-white lysozyme on isolated cell walls releases various fragments including a tetrasaccharide and a disaccharide containing muramic acid and 2-amino-2-deoxy-D-glucose.[4] The structure of an *O*-2-acetamido-2-deoxy-D-glucopyranosyl-(1 → 6)-*N*-acetylmuramic acid was proposed for the latter compound.[4-6] It was, therefore, of great interest to synthesize this disaccharide, thereby allowing a comparison with the fragment obtained from the cell walls. The present paper described the synthesis of various derivatives of muramic acid including the *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1 → 6)-*N*-acetylmuramic acid disaccharide. It should also be noted that this represents the first constitutional synthesis of a 2-amino-2-deoxy-(2-amino-2-deoxyglucosyl)glucose disaccharide.

A stereospecific synthesis of 2-amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose, and of several derivatives of it, has been described recently by Matsushima and Park.[7,8] The method used in the present work for the preparation of methyl 2-acetamido-4,6-*O*-benzylidene - (D - 1 - carboxyethyl) - 2 - deoxy - α - D - glucopyranoside (V) from methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III)[9] follows essentially Matsushima and Park's procedure and requires large quantities of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (II).

Glycosidation of 2-acetamido-2-deoxy-D-glucose (I) with methanol in the presence of an acid catalyst for a few hours gives II, contaminated with about 15 to 20% of the β-anomer.[10] Separation of both anomers can be accomplished by fractional crystallization of the 3,4,6-triacetate derivatives[10] or by chromatography on charcoal.[11] The first method, however, lengthens the synthesis by two additional steps, while the second one cannot be carried out conveniently on large amounts of material. It was found that the purification could be accomplished efficiently by crystallization at the step of the benzylidene derivative III, if the amount of α-anomer were increased in the original mixture. When the glycosidation is carried out for a considerable length of time, the amount of α-anomer reaches 87%, but marked de-*N*-acetylation occurs. The crude mixture, consequently, was re-*N*-acetylated and crystallization gave, in 75–80% yield, a compound II containing about 10% of the β-anomer. This compound II was condensed with benzaldehyde, affording a yield of about 60% of III with m.p. 260–262° and $[\alpha]_D$ +40° (in chloroform), in agreement with the values reported by Wiggins.[12] A similar condensation of the mother liquors from II, containing about 65% of the α-anomer, gave an additional amount of III, raising the total yield to 49% calculated from I. Attempts to prepare III by methylation of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucose in dimethyl sulfoxide solution, as described by Roth and Pigman,[13] resulted in the formation of the 3-*O*-methyl ether of III in addition to the required material.

Since the preparation of L-α-chloropropionic acid (IV) starting from L-alanine[8,14] is expensive, it was replaced by the resolution of the commercial DL-α-chloropropionic acid with cinchonine.[15] The condensation of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III) with IV was carried out as described by Matsushima and Park,[8] giving methyl 2 - acetamido - 4,6 - *O* - benzylidene - 3 - *O* - (D - 1 - carboxyethyl)-2-deoxy-α-D-glucopyranoside (V).

The crystalline methyl ester VI was obtained by the reaction of diazomethane with V, and removal of the benzylidene group gave crystalline methyl 2-acetamido-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (VII). Alternatively, removal of the benzylidene group from V gave a glassy derivative VIII,[6] which was converted into crystalline VII by treatment with diazomethane. Condensation of VII with triphenylchloromethane resulted in the triphenylmethyl ether IX,

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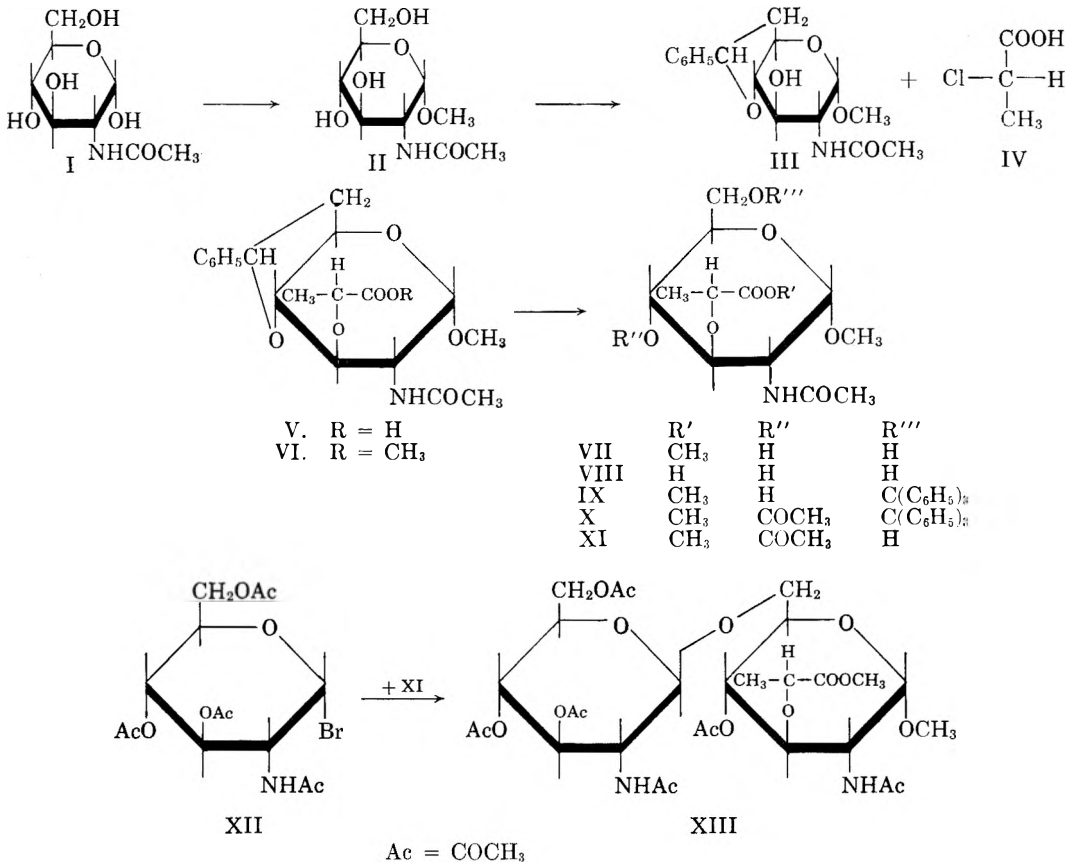

which was further acetylated at position 4 into X. Finally, removal of the triphenylmethyl group gave methyl 2-acetamido-4-*O*-acetyl-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XI). All these derivatives were obtained crystalline and in excellent yields. For the preparation of large amounts of material, steps IX and X were combined and XI was obtained in an over-all yield of 57% from VIII.

Condensation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide (XII)[16] with XI in the presence of mercuric cyanide in a mixture of chloroform and nitromethane gave methyl 6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XIII). Although the yield in this condensation is low (10–15%), a considerable amount of unchanged XI can be recovered from the reaction mixture. Lower yields of a product identical to XIII were obtained when the condensation was carried out in the presence of silver oxide. The β-configuration of the disaccharide linkage formed is established by the low optical rotation ($[\alpha]_D$ +54° in chloroform) of XIII and by its mode of formation.

The synthesis of XIII is a first step in the synthesis of the disaccharide isolated from bacterial cell walls. Removal of the methyl glycoside without scission of the disaccharide bond is being studied at present, and the synthesis of the benzyl glycoside of this disaccharide will be reported later.

Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro or micro (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer Model 237. Chromatograms were made with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950, 60–200 mesh), which was used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluents was hexane, benzene or chloroform, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1:50–100. The proportion of weight of substance in grams to volume of fraction of eluent in milliliters was 1:100. The ratio of diameter to length of column was 1:20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen. The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III) from I.—Preliminary experiments with small amounts of material showed that the glycosidation of 2-acetamido-2-deoxy-α-D-glucose (I) with 2% methanolic hydrochloric acid gave products having a positive ninhydrin test after 2 hr. After isolating the product as described below, the optical rotation in water reached a maximum of 120° after 48 hr. at reflux. Reaction for longer periods of time gave appreciable decomposition.

In a 1-l. flask, 50 g. of commercial I was refluxed with 500 ml. of 2% methanolic hydrochloric acid for 48 hr., with exclusion of moisture. The solution was cooled, then stirred overnight with an excess of finely powdered lead carbonate. After filtration, the lead salts were washed with methanol, and the filtrate was evaporated to a sirup, which was dissolved in water and passed through a column of 300 ml. of Amberlite 45-R in the acetate form. The eluate and washings were evaporated to dryness, and the residue was dissolved in 100 ml. of methanol. In order to remove the last traces of hydrochloric acid, a small amount (0.5 to 1 g.) of silver acetate was added, then 15 ml. of acetic anhydride, and the mixture was left at room temperature

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overnight. It then was refluxed for 30 min., filtered, and the filtrate evaporated to dryness. In order to remove the last traces of acetic anhydride, toluene was added twice and evaporated. The crystalline residue was recrystallized from a mixture of ethanol and ether, giving 41.8 g. of a mixture of II and its β-anomer, m.p. *ca.* 195°, $[\alpha]^{24}D$ +109° in water. The mother liquors (12.7 g.) had $[\alpha]D$ +72°.

To 41.0 g. of the previously described compound was added 32 g. of anhydrous zinc chloride and 125 ml. of benzaldehyde. The mixture was shaken at room temperature for 20 hr., then a mixture of 100 ml. of hexane and 100 ml. of water was added to it, and the shaking was resumed for 30 min. The liquid was decanted, then the addition of water and hexane and decantation were repeated three times. The resulting solid was filtered, washed well on the filter with water and hexane, then dried overnight in a desiccator. It was recrystallized from a mixture of water and methanol, giving 33 g. (55%) of needles (IV), m.p. 260–262°, $[\alpha]^{24}D$ +40° (in chloroform),[17] and 4.5 g. with lower melting point and rotation. The mother liquors with $[\alpha]D$ +72° after similar treatment with benzaldehyde gave an additional crop of 2.5 g., m.p. 258–260°, $[\alpha]D$ +39°, affording a total yield of 35.5 g. (59% from impure II, and 49% from I).

Scission of the benzylidene group of III by heating with 60% acetic acid, or by catalytic hydrogenation, gave methyl 2-acetamido-2-deoxy-α-D-glucopyranoside with melting point and optical rotation identical with those obtained by Kuhn, *et al.*,[10] and by Roth and Pigman.[13]

Acetylation of II with acetic anhydride and pyridine gave the 3-*O*-acetyl derivative, m.p. 209–210°, $[\alpha]^{30}D$ +38° (in chloroform, *c* 0.47).[18]

Methyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (V).—This product was prepared from III and L-α-chloropropionic acid (IV)[15] according to Matsushima and Park,[8] yielding 75–80% of V, m. p. 261–262°, $[\alpha]^{18}D$ +115° (in methanol, *c* 1.28).

Anal. Calcd. for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.64; H, 6.29; N, 3.00.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-[D-1-(methylcarboxylate)ethyl]-α-D-glucopyranoside (VI).—A solution of 1.0 g. of V in 50 ml. of warm methanol was cooled to room temperature and a slight excess of diazomethane in ether was added. After 30 min., the solution was evaporated and the residue was recrystallized from methanol to give 0.90 g. (85%) of needles, m. p. 210–211°, $[\alpha]^{24}D$ +106° (in chloroform, *c* 0.87).

Anal. Calcd. for $C_{20}H_{27}NO_8$: C, 58.67; H, 6.65; OCH_3, 15.16. Found: C, 58.57; H, 6.66; OCH_3, 15.34.

Methyl 2-Acetamido-2-deoxy-3-*O*-[D-1-(methyl carboxylate)-ethyl]-α-D-glucopyranoside (VII).—A solution of 0.90 g. of VI in 8 ml. of 60% acetic acid was heated at 100° for 30 min. The solution was evaporated and the residue co-evaporated successively with water and toluene. The residue was crystallized from a mixture of acetone and ether, giving 0.50 g. (70%), melting after recrystallization from ethyl acetate at 151–152°, $[\alpha]^{27}D$ +129° (in chloroform, *c* 0.65).

Anal. Calcd. for $C_{13}H_{23}NO_8$: C, 48.59; H, 7.22; N, 4.36. Found: C, 48.57; H, 7.21; N, 4.43.

Methyl 2-Acetamido-2-deoxy-3-*O*-[D-1-(methyl carboxylate)-ethyl]-6-*O*-triphenylmethyl-α-D-glucopyranoside (IX).—To a solution of 0.50 g. of VII in 2 ml. of dry pyridine was added 0.48 g. of triphenylchloromethane. The solution was left for 24 hr. at room temperature and then, after being maintained for 1 hr. at 100°, was poured onto cracked ice and extracted with chloroform. The chloroform solution was washed three times with 10% potassium bisulfate solution and three times with water, dried, and evaporated. The residue was recrystallized from benzene, giving 0.85 g. (95%) of prisms, m.p. 213–215°. Recrystallization from methanol raised the m.p. to 217–218°, $[\alpha]^{25}D$ +70° (in chloroform, *c* 1.10).

Anal. Calcd. for $C_{32}H_{37}NO_8$: C, 68.19; H, 6.62; N, 2.49. Found: C, 68.35; H, 6.69; N, 2.53.

Methyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-6-*O*-triphenylmethyl-α-D-glucopyranoside (X).—A solution of 0.40 g. of IX in 2 ml. of acetic anhydride and 2 ml. of pyridine was left overnight at room temperature. The temperature was then raised to 50° for 1 hr. After evaporation of the solution, the residue was recrystallized from methanol to give 0.40 g. (93%) of prisms, m. p. 213–215°. Further purification by chromatography on silicic acid did not raise the melting point, $[\alpha]^{26}D$ +67° (in chloroform, *c* 1.74).

Anal. Calcd. for $C_{34}H_{39}NO_9$: C, 67.42; H, 6.49. Found: C, 67.48; H, 6.50.

Methyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl-α-D-glucopyranoside (XI). From X.—A solution of 130 mg. of XI in 5 ml. of 60% acetic acid was heated at 100° for 15 min. The residue obtained on evaporation was treated with water. After filtration the aqueous extract was evaporated and the residue crystallized from a mixture of benzene and hexane, giving 73 mg. of needles (92%), m.p. 136–138°. Recrystallization from a mixture of ethyl acetate and hexane raised the m.p. to 140–142°, $[\alpha]^{23}D$ +119° (in chloroform, *c* 0.62).

Anal. Calcd. for $C_{15}H_{25}NO_9$: C, 49.58; H, 6.94; N, 3.86. Found: C, 49.50; H, 7.03; N, 3.86.

From VII.—A solution of 4.0 g. of VII in 16 ml. of pyridine and 3.84 g. of triphenylchloromethane was kept overnight at room temperature. After raising the temperature to 100°, 16 ml. of acetic anhydride was added, the solution was allowed to cool and left at room temperature for 24 hr. The cooled solution then was poured into ice water and the precipitate separated, washed thoroughly with water, and dried.

The solid was heated with 5 ml. of 60% acetic acid at 100° for 15 min., the solution evaporated, and the residue treated with water. Evaporation of the aqueous extract and recrystallization from a mixture of acetone and ether gave 2.6 g. (57%) of needles, m.p. 138–140°, $[\alpha]^{27}D$ +119° (in chloroform, *c* 3.12).

Methyl 6-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XIII). A. Using Mercuric Cyanide.—To a stirred solution of 1.06 g. of XI (0.003 mole) in 40 ml. of dry nitromethane was added 0.88 g. (0.0037 mole) of mercuric cyanide and a solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide (XII) in 15 ml. of chloroform, prepared from 1.5 g. of 2-amino-2-deoxy-D-glucose pentaacetate (0.0037 mole) according to Inouye, *et al.*[16] After 20 hr. at room temperature, the preceding quantities of mercuric cyanide and XII were again added and the reaction allowed to proceed a further 24 hr.

The reaction mixture was diluted with chloroform, washed with a little sodium bicarbonate solution and water, and evaporated. The residue was dissolved in ethyl acetate and chromatographed on silicic acid. Ethyl acetate eluted 0.680 g. of unchanged XI melting at 138–140° after recrystallization from a mixture of acetone and ether. A mixture of ethyl acetate and acetone 1:1 eluted a crystalline product which, after one recrystallization from a mixture of alcohol and acetone, gave 0.23 g. (12%) of white needles, m.p. 288–289°, $[\alpha]^{25}D$ +54° (in chloroform, *c* 2.02).

Anal. Calcd. for $C_{29}H_{44}N_2O_{17}$: C, 50.26; H, 6.40; N, 4.04. Found: C, 49.76; H, 6.57; N, 3.92.

The preceding condensation was repeated twice, using XI recovered from the previous condensation, giving a further 0.17 g., m.p. 288–289°, and 0.20 g. of unchanged XI, m.p. 138–140°.

B. Using Silver Oxide.—To a solution of 0.36 g. (0.001 mole) of XI in 25 ml. of dry chloroform was added 2 g. of silver oxide, 2 g. of Drierite (dehydrated calcium sulfate), and XII, prepared from 0.0025 mole of 2-amino-2-deoxyglucose pentaacetate, added in two equal portions, 24 hr. apart. After 48 hr. at room temperature the solution was treated as in A, giving 0.015 g. (2%) of product, m.p. 287–288°, identical with the disaccharide described previously.

Acknowledgment.—The authors are indebted to Charles Pfizer & Co. for a generous gift of 2-acetamido-2-deoxy-D-glucose. They wish to thank Mrs. Doreen Baggett for her assistance in preparing methyl 2-aceta-

(17) Neuberger[9] reported m.p. 255°, $[\alpha]D$ +19° (in chloroform, *c* 0.5); Wiggins[12] reported m.p. 255–256°, $[\alpha]D$ +40.0° (in chloroform, *c* 1.5); Roth and Pigman[13] reported m.p. 261–262°, $[\alpha]^{20}D$ +39.5° (in chloroform, *c* 0.5).

(18) Wiggins[12] reported m.p. 203–205°, $[\alpha]D$ +33 (in chloroform); Meyer zu Reckendorf and Bonner[19] reported m.p. 210–211°, $[\alpha]D$ +37.8° (in chloroform, c 0.06).

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mido - 4,6 - *O* - benzylidene - 2 - deoxy - α - D - glucopyranoside and Dr. J. T. Park for making available before publication the manuscript describing the procedure used in the present study for the preparation of methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside.

Derivatives of 6-Deoxy-6-mercapto-D-fructose[1]

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6-Deoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose and 1,6-dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose are prepared. Acid hydrolysis of the former compound produces 6-deoxy-6-mercapto-D-fructose which seems to exist with sulfur in a pyranose ring. 1,6-Dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose is unstable in acid solution and readily dehydrates to methyl 2-thienyl ketone.

Previous workers[2-6] have prepared a number of aldoses wherein the normal pyranose ring oxygen is replaced with a sulfur atom. Such sugars represent a new class of compounds which are not only of chemical interest but, where they are analogs of metabolic sugars, are also of biological interest. This work reports the preparation of 6-deoxy-6-mercapto-D-fructose, the first ketose which could cyclize with a sulfur atom in a pyranose ring.

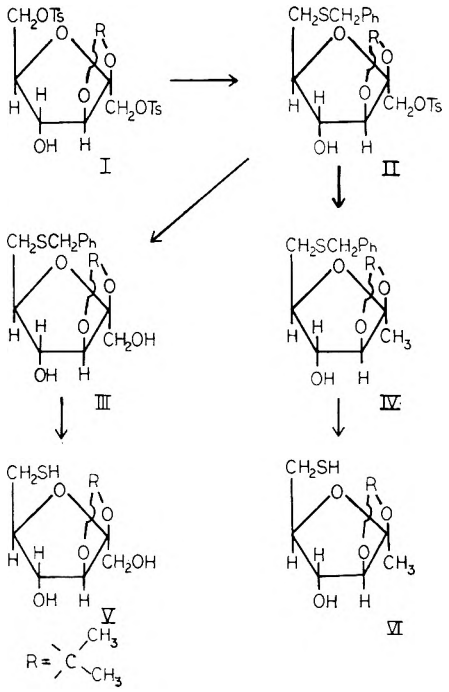
The starting material was 2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-D-fructofuranose (I).[7,8] The 1-*O*-*p*-tolylsulfonoxy group of this compound, as in other analogous sulfonated ketoses,[9,10] does not undergo nucleophilic displacement easily. Thus, reaction of the compound with sodium benzyl mercaptide in boiling methanol leads only to the displacement of the 6-*O*-*p*-tolylsulfonoxy group with the production of 6-deoxy-2,3 - *O* - isopropylidene - 6 - thiobenzyl - 1 - *O* - *p* - tolylsulfonyl-D-fructofuranose (II).

The remaining ester group is hydrolyzed only with difficulty but is removed by lithium aluminum hydride, a reagent successfully employed[11-13] for removal of *p*-tolylsulfonyl substituents. In most instances lithium aluminum hydride removes a primary *p*-tolylsulfonoxy group by alkyl–oxygen fission, but Schmidt and Karrer report that this reagent, on reaction with 2,3:4,5-di-*O*-isopropylidene - 1 - *O* - *p* - tolylsulfonyl - D - fructopyranose, produces the sugar alcohol. They believe this type of cleavage is a consequence of the sterically hindered position of the ester. Reaction of compound II with lithium aluminum hydride, however, involves desulfonoxylation since the major sugar derivative is 1,6 - dideoxy - 2,3 - *O* - isopropylidene - 6 - thiobenzyl-D-fructofuranose (IV). Evidence for this structure is given by desulfurization with Raney nickel to produce the known 1,6-dideoxy derivative.

Examination of models indicates that the *p*-tolylsulfonyl ester is in a more sterically hindered position in the 2,3:4,5-di-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-D-fructopyranose of Schmidt and Karrer than is the ester of compound II, thus supporting the view[14] that the course of desulfonylation with lithium aluminum hydride is dependent on the steric make-up of the attacked molecule.

Desulfonylation of compound II with sodium amalgam produces 6-deoxy-2,3-*O*-isopropylidene-6-thiobenzyl-D-fructofuranose (III) in good yield. Desulfurization of this compound with Raney nickel produces the expected 6-deoxy derivative.

Reaction of compounds III and IV with sodium in liquid ammonia[15] gives 6-deoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (V) and 1,6-dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (VI), respectively.



Both mercapto compounds V and VI are unstable in acid solution. Either methanolysis or hydrolysis of VI

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produces multicomponent sirups. Paper chromatographic analyses indicate that, in some instances, the same compounds are produced by both methanolysis and hydrolysis. Compound VI is easily dehydrated in acid solution. Treatment of it with an acidic aqueous solution of 2,4-dinitrophenylhydrazine produces the crystalline 2,4-dinitrophenylhydrazone of methyl 2-thienyl ketone.

Hydrolysis of V likewise produces a complex mixture but with the reducing sugar as the major component. 6-Deoxy-6-mercapto-D-fructose is obtained from the mixture by Celite column chromatography.

Infrared spectra of this amorphous sugar shows no SH stretching or carbonyl absorption. Thus, it appears that a major portion of the sugar exists in the pyranose ring form. As with D-xylothiapyranose,[3] only 80% of the total sulfur can be titrated iodometrically over a two-hour period.

Experimental

2,3-*O*-Isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-D-fructofuranose (I).—This compound was prepared as described by Morgan and Reichstein,[7] starting with 100-g. portions of D-fructose. On recrystallization from ethyl acetate–hexane, the product had m.p. 131°, $[\alpha]^{25}D$ + 22.1° (*c* 2.4, chloroform).

6-Deoxy-2,3-*O*-isopropylidene-6-thiobenzyl-1-*O*-*p*-tolylsulfonyl-D-fructofuranose (II).—A solution of sodium benzyl mercaptide was prepared by reaction of 15.3 g. of elemental sodium with 78.0 ml. of benzyl mercaptan in 900 ml. of anhydrous methanol. During the reaction, the mixture was maintained under flowing oxygen-free, anhydrous nitrogen and was cooled by an ice bath. Following reaction of the sodium, 90.0 g. of compound I was added and the solution was refluxed for 4 hr. It was then concentrated under reduced pressure to a slurry, and after the addition of 1 l. of chloroform the mixture was extracted twice with water, three times with saturated aqueous sodium hydrogen carbonate solution, and then with water until the washings were neutral. After drying the chloroform solution over sodium sulfate, it was concentrated to a sirup which retained a slight odor of benzyl mercaptan. On standing several hours at 25°, crystallization occurred; yield 60 g. (74%). Several recrystallizations from ethyl acetate–hexane produced a pure compound; m.p. 120–121°, $[\alpha]^{25}D$ −6.7° (*c* 2.0, chloroform).

Anal. Calcd. for $C_{23}H_{28}O_7S_2$: C, 57.47; H, 5.87; S, 13.34. Found: C, 57.55; H, 5.68; S, 13.20.

1,6-Dideoxy-2,3-*O*-isopropylidene-6-thiobenzyl-D-fructofuranose (IV).—A solution of 25 g. of II in 250 ml. of tetrahydrofuran was cooled to 0°, and 3 g. of lithium aluminum hydride was added. After 0.5 hr. the solution was warmed to 25° for 2 hr., and then refluxed for 48 hr. Sufficient water was added to destroy excess reagent and 100 ml. of saturated aqueous sodium sulfate solution was added. The mixture was made slightly acidic with dilute hydrochloric acid, and the tetrahydrofuran phase was drawn off. The aqueous phase was extracted three successive times with 100-ml. portions of chloroform. The chloroform extracts and the removed tetrahydrofuran were combined and extracted once with water. On drying the organic phase with sodium sulfate and evaporation to a sirup, crystals appeared; yield, 12.5 g. (77.5%). Two recrystallizations produced pure compound IV; m.p. 93°, $[\alpha]^{25}D$ −34.8° (*c* 2.0, chloroform). A 1-g. portion of compound IV was dissolved in 30 ml. of ethanol containing 5 g. of freshly prepared Raney nickel. This suspension was stirred at reflux for 40 hr. and filtered. Concentration of the filtrate produced crystals which were sublimed at 60° (0.2 mm.). The resulting 1,6-deoxy-2,3-*O*-isopropylidene-D-fructofuranose[7] was recrystallized from ethyl acetate–hexane; m.p. 59–62°, $[\alpha]^{25}D$ +8.2° (*c* 3.6, methanol).

6-Deoxy-2,3-*O*-isopropylidene-6-thiobenzyl-D-fructofuranose (III).—A 23-g. sample of II was slurried with 300 ml. of methanol and 150 g. of 5% sodium amalgam was added with vigorous stirring. After 2 hr., 50 ml. of water was added and stirring was continued for 24 hr. The decanted methanol solution was cooled to 0°, acidified with 5 *N* hydrochloric acid solution, and extracted with four successive 100-ml. portions of chloroform. The combined chloroform extracts were washed once with saturated sodium hydrogen carbonate solution, then with water, and dried over sodium sulfate. Concentration produced compound III, which crystallized; yield, 14.3 g. (97%). The compound was recrystallized from ethyl acetate–hexane; m.p. 95–96°, $[\alpha]^{25}D$ −13.9° (*c* 2.4, methanol). A 1-g. sample of compound III was desulfurized with Raney nickel as described previously to produce 6-deoxy-2,3-*O*-isopropylidene-D-fructofuranose[7]; m.p. 114°, $[\alpha]^{25}D$ +6.5° (*c* 3.2, methanol), after sublimation at 115–130° and 0.2-mm. pressure.

1,6-Dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (VI).—A 10-g. sample of compound IV was dissolved in 100 ml. of liquid ammonia held in an acetone–Dry Ice bath. The atmosphere above the solution was continuously swept with oxygen-free, anhydrous nitrogen and small pieces of sodium were added while the solution was stirred. The addition of sodium was continued until the characteristic blue color was maintained for 15 min. An excess of ammonium chloride (10 g.) was then added, and the ammonia was allowed to evaporate in a stream of nitrogen. The dry solids were extracted three times with boiling chloroform in 50-ml. portions, and the combined extracts were washed with water and dried over sodium sulfate. Concentration of the chloroform produced a sirup which gave crystals of compound VI. This was recrystallized from ethyl acetate–hexane; yield, 5.8 g. (82%), m.p. 70–72°, $[\alpha]^{25}D$ −2.8° (*c* 2.7, chloroform).

Anal. Calcd. for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.56. Found: C, 49.32; H, 7.54; S, 14.68.

A 250-mg. portion of compound VI was dissolved in 10 ml. of methanol and 10 ml. of 2 *N* hydrochloric acid solution was slowly added. The progress of the hydrolysis, at 25°, was followed by periodically chromatographing aliquots on paper. Chromatograms were irrigated with 1-butanol–ethanol–water (40:11:19 v./v.) and sprayed with silver nitrate solution.[16] After 4 hr. of hydrolysis, there were four chromatographic components of approximately equal intensity having $R_{glucose}$ values of 1.9, 2.8, 4.4, and 4.9. Methanolysis of compound VI for 24 hr. at 25° with 0.5% methanolic hydrogen chloride solution produced components with $R_{glucose}$ values of 2.3, 2.8, 3.3, 4.4, and 4.9.

A 0.5-g. portion of compound VI was dissolved in 5 ml. of 30% perchloric acid solution containing 0.4 g. of 2,4-dinitrophenylhydrazine. After warming the solution at 60° for 5 min. a crystalline precipitate appeared. Recrystallization from dimethylformamide produced material which had m.p. 244–245°.

Methyl 2-thienyl ketone was prepared as described elsewhere.[17] Its 2,4-dinitrophenylhydrazone was prepared as described for compound VI and was recrystallized from dimethylformamide; m.p. 244–245°,[18] m.m.p. with the hydrazone of compound VI, 244–245°. The X-ray diffraction patterns of the two hydrazones were identical.

6-Deoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (V).—This compound was produced by reduction of compound III with sodium in liquid ammonia as described before. Since precipitation occurred as the reaction progressed, it was necessary, for easy stirring, to employ 200 ml. of ammonia for each 10 g. of compound III. After the blue color persisted for 0.5 hr., compound V was isolated in the usual fashion, and recrystallized from hexane; yield, 5.8 g. (81%), m.p. 76–77°, $[\alpha]^{25}D$ +4.9° (*c* 2.1, methanol).

Anal. Calcd. for $C_9H_{16}O_5S$: C, 45.75; H, 6.80; S, 13.57. Found: C, 45.79; H, 6.99; S, 13.75.

Compound V could be easily hydrolyzed to the free 6-deoxy-6-mercapto-D-fructose. A 5-g. portion of V was dissolved in 50 ml. in 1 *N* hydrochloric acid in 50% aqueous methanol. The hydrolysis was allowed to proceed for 24 hr. at 25°. The solution was neutralized with Amberlite IR-4B (OH) and concen-

(16) W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950).

(17) J. R. Johnson and G. E. May, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

(18) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953).

(19) R. V. Lemieux, C. T. Bishop, and G. E. Pelletier, *Can. J. Chem.*, **34**, 1365 (1956).

trated to a sirup. Paper chromatograms, irrigated and sprayed, with the reagents indicated previously, showed one major component having $R_{glucose}$ 1.3.

The sugar was purified by elution from a Celite column[19] using 1-butanol saturated with water as the mobile phase; $[\alpha]^{25}D$ −179° (*c* 0.9, water).

Anal. Calcd. for $C_6H_{12}O_5S$: S, 16.3. Found: S, 16.4.

A 26-mg. sample of this sugar was dissolved in 2% acetic acid solution and titrated with standard iodine solution. After 2 hr. at 25°, 2.0 ml. of 0.0530 *N* iodine solution was consumed.

A portion of the purified sugar was dissolved in water to an initial concentration of 3.8 mg./ml. and used in a series of measurements in a vapor pressure osmometer. Calcd.: mol. wt., 196. Found: mol. wt., 198.

Thioglycosides of 3-Amino-3-deoxy-D-mannose[1]

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The reaction of some D-mannose derivatives with ethanethiol and concentrated hydrochloric acid was investigated. Mercaptolysis of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (II) gives a mixture of the crystalline ethyl 3-amino-3-deoxy-1-thio-α- and β-D-mannopyranoside hydrochlorides (40% I and 60% III) in high yield, readily separable as the crystalline tetraacetates (IV and VII). The structures of I and III were established by periodate oxidation data on the corresponding *N*-acetyl derivatives (V and VIII). The behavior of a number of simple sugars in the mercaptalation reaction was examined.

The objective of this investigation was to study apparent anomalies in the reactions of D-mannose derivatives with ethanethiol in concentrated hydrochloric acid solution and to devise a suitable preparative route to 1-thioglycosides of 3-amino-3-deoxy-D-mannose.

The reaction between aldoses and alkanethiols in concentrated aqueous acid, at about 0°, leads to the formation of the acyclic dithioacetals in high yield when these products are removed from the reaction sphere by crystallization[2] or by rapid neutralization of the acid.[3] If this, apparently initial, product is not so removed or if the dithioacetal is put back into the system,[4] 1-thioglycosides are formed and hydrolysis to the aldose occurs. The 1-thioglycosides found, in the cases investigated, have been pyranosides. The reaction can be influenced by steric factors, such as sugar configuration, and by polar factors, such as those introduced by the presence of an amino group.

Prolonged treatment of D-mannose with ethanethiol and concentrated (12 *N*) hydrochloric acid at room temperature, under conditions wherein any dithioacetal formed would not separate, gave a 31% yield of the ethyl 1-thio-α- and β-D-mannopyranosides, isolated as the tetraacetates.[5] In our hands, a paper chromatographic study of this reaction (Table I) showed that after five minutes all of the D-mannose had reacted, and that the diethyl dithioacetal was the principal product, although small proportions of two thioglycosides were present. Levene and Meyer[6] reported isolation of D-mannose diethyl dithioacetal in 63% yield after five minutes under similar conditions. At longer reaction times, the intensities of the thioglycoside zones increased at the expense of the dithioacetal, and a weaker zone corresponding to D-mannose appeared. The distribution of the four products, by visual comparison, was essentially constant after four hours.

TABLE I

PAPER CHROMATOGRAPHIC DATA[a] ON MERCAPTOLYSIS OF ALDOSE DERIVATIVES AT 25°

Compound (*c* 10, 12 *N* HCl)	Time of reaction, min.	Observed products[b]			
		Aldose	Dithioacetal	Anomeric thiopyranosides[c]	
		R_{man} 1.00	R_{man} 2.66	R_{man} 2.11	R_{man} 2.39
D-Mannose[d]	5	...	++++	+	(+)
	60	+	++++	+++	++
	240	+	++++	+++	+++
	1440	++	+++	+++	+++
		R_g 1.00	R_g 2.75	R_g 2.23	R_g 2.52
D-Glucose[d]	5	(+)	++++	(+)	...
	60	(+)	++++	+	...
	240	++	++	++	+
	1440	+++	...	++	+
		R_{gal} 1.00	R_{gal} 2.85	R_{gal} 2.17	
D-Galactose[d]	5	+	++++	+	
	60	...	+++	+	
	240	...	+++	+	
	1440	++	(+)	++	

[a] Details given in Experimental. [b] Relative intensity, estimated visually. These values do not necessarily represent relative absolute intensities since the components vary in their reactivity with the spray reagent. [c] Probable identities, not compared with known samples. The zone R_{gal} 2.17 was elongated and possibly a mixture of two incompletely resolved zones. [d] The *R* values refer to the respective parent aldose; mannose, glucose, or galactose, denoted as a subscript, with a 4:1:5 1-butanol–ethanol–water system.

Under similar conditions, D-glucose gives ethyl 1-thio-α-D-glucopyranoside in 15% yield, together with unchanged D-glucose and, probably, some β-D anomer; no diethyl dithioacetal was detected.[4] D-Glucose diethyl dithioacetal and ethyl 1-thio-α-D-glucofuranoside are converted into the acid-resistant[7] ethyl 1-thio-α-D-glucopyranoside by 22% hydrochloric acid under the same conditions, whether or not ethanethiol is present, and some D-glucose is formed.[4] Our paper chromatographic studies confirm these results and show that the behavior of D-galactose is closely similar (Table I); in each case the initial reaction of the sugar with ethanethiol and concentrated hydrochloric acid at room temperature is rapid, with almost complete

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(2) E. Fischer, *Ber.*, **27**, 673 (1894).

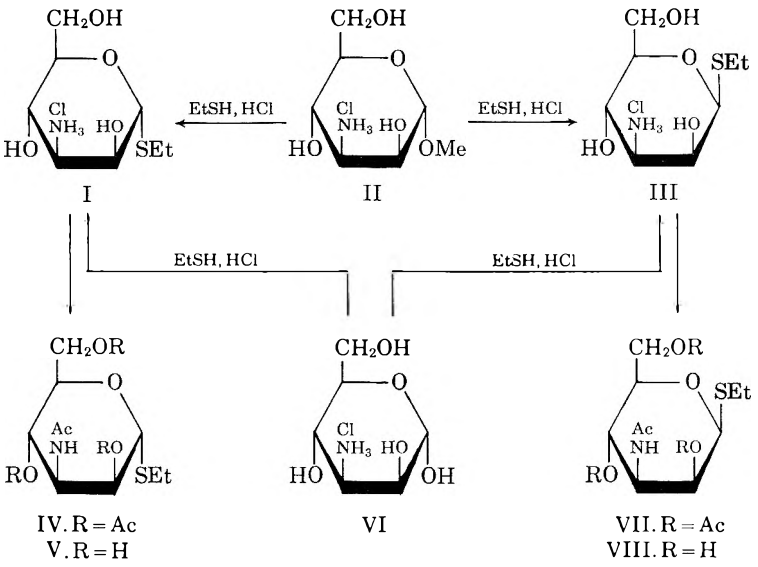
(3) M. L. Wolfrom, M. R. Newlin, and E. E. Stahly, *J. Am. Chem. Soc.*, **53**, 4379 (1931); M. L. Wolfrom and F. B. Moody, *ibid.*, **62**, 3465 (1940).

(4) E. Pacsu and E. J. Wilson, Jr., *ibid.*, **61**, 1930 (1939); P. Brigl, K. Gronemeier, and A. Schulz, *Ber.*, **72**, 1052 (1939).

(5) J. Fried and D. E. Walz, *J. Am. Chem. Soc.*, **71**, 140 (1949).

(6) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **74**, 695 (1927).

(7) E. Pacsu and E. J. Wilson, Jr., *J. Am. Chem. Soc.*, **61**, 1450 (1939).



conversion to the dithioacetal in five minutes. Subsequently the dithioacetal undergoes conversion to other products and is present only in traces after twenty-four hours, while a small amount of the free sugar appears, and zones with the mobilities anticipated for thioglycosides form the principal detected products.

The results would suggest that the dialkyl dithioacetal is formed by a rapid, kinetically controlled reaction, which is followed by a slower acid-catalyzed reaction which gives at equilibrium the distribution of products according to their thermodynamic stabilities in the system.

Glycosidically linked sugars can also react with alkanethiol and hydrochloric acid to give dialkyl dithioacetals,[8] and this reaction is the basis of the mercaptolysis procedure[9] for fragmentation of oligo- and polysaccharides into dialkyl dithioacetals of component sugars or oligosaccharides. It has been noted[10] that D-mannose derivatives exhibit anomalous reactivity. Mercaptolysis of mannosidostreptomycin gave ethyl 1-thio-α- and β-D-mannopyranosides, rather than the expected dithioacetal, from the D-mannose moiety. Mercaptolysis of methyl α-D-mannopyranoside also gave the thioglycoside, ethyl 1-thio-β-D-mannopyranoside,[5] and, although the isolated yield (as the tetraacetate) was low (5%), the reaction offered for the present work the possibility of a one-step conversion of a mannopyranoside derivative into a 1-thiomannopyranoside derivative with avoidance of possible complications in proceeding through the free sugar.

The results of this investigation show that methyl 3-amino-3-deoxy-D-mannopyranoside hydrochloride (II),[11] which can be readily prepared[12] from methyl α-D-glucopyranoside, can be converted by mercaptolysis into the ethyl 3-amino-3-deoxy-1-thio-α- and β-D-mannopyranoside hydrochlorides (40% I and 60% III) in high (71%) yield. The two products are formed in the indicated ratios, based on the rotation of the mixture, and are best separated through their acetylated derivatives (IV and VII). *O*-Deacetylation of IV and VII with methanolic ammonia gave the corresponding ethyl 3-acetamido-3-deoxy-1-thio-α- and β-D-mannopyranosides (V and VIII). The pyranoside ring structure in all six thioglycoside derivatives was established by periodate oxidation (Table II) of V and VIII, since in each case formaldehyde was not released in the oxidation. Both derivatives consumed one mole of oxidant per mole during a three-hour period and no further uptake was observed. The consumption of one mole of oxidant per mole by thioglycosides, in excess of that required for a Malaprade type of oxidation, has been generally observed,[13,14] and appears to involve, at the sulfur function, a reaction whose nature has not been fully established. The lack of further oxidation in the case of V and VIII is fully consistent with the pyranoside structure, deduced from the absence of formaldehyde in the oxidation product and establishes that V and VIII are anomers, assigned the α-D and β-D configurations, respectively, on the basis of Hudson's rules of rotation.[15] The structures assigned to the derivatives I, III, IV, and VII follow from the identification of configuration and ring size in V and VIII.

Table III lists the molecular rotations of the six derivatives of ethyl 3-amino-3-deoxy-1-thio-D-mannopyranoside, together with corresponding data on the ethyl 1-thio-D-mannopyranosides.[5] The A value (rotatory contribution of C-1) shows good correlation between the three pairs of derivatives, and with the reported[5] value for the anomeric ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-D-mannopyranosides.

The two thioglycosides I and III have paper chromatographic mobilities R_m (R_m = mobility of II) of 1.43 and 1.22, respectively. The reaction product

TABLE II

PERIODATE OXIDATION OF ETHYL 3-ACETAMIDO-3-DEOXY-1-THIO-α- AND β-D-MANNOPYRANOSIDES (V AND VIII)[a]

Compound	Time, min.	Oxidant uptake[b]	Formaldehyde release[b]	Formic acid release[b]
V	10	0.67	..	..
	20	.94	..	..
	60	.98	..	..
	120	..	0.00	0.00
	180	.98	..	..
	360	.98	..	..
	1440	1.04	..	0.00
VIII	10	0.61	..	..
	20	.93	..	..
	60	.95	..	..
	120	.95	0.00	0.00
	180	1.03	..	..
	480	1.03	..	..
	1440	1.03	..	0.00

[a] Details given in Experimental. [b] Moles per mole of sample.

(8) F. J. McEvoy, B. R. Baker, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 209 (1960).

(9) M. L. Wolfrom and J. C. Sowden, *ibid.*, **60**, 3009 (1938); C. Araki and S. Hirase, *Bull. Chem. Soc. Japan*, **26**, 463 (1953); A. N. O'Neill and D. K. R. Stewart, *Can. J. Chem.*, **34**, 1700 (1956); M. L. Wolfrom and A. Thompson, "Methods in Carbohydrate Chemistry," R. L. Whistler and M. L. Wolfrom, Ed., Vol. III, Academic Press, New York, N. Y., 1963, p. 150.

(10) J. Fried and H. E. Stavely, *J. Am. Chem. Soc.*, **69**, 1549 (1947); H. E. Stavely and J. Fried, *ibid.*, **71**, 135 (1949).

(11) H. H. Baer and H. O. L. Fischer, *ibid.*, **83**, 1132 (1961).

(12) A. C. Richardson, *J. Chem. Soc.*, 373 (1962).

(13) L. Hough and M. I. Taha, *ibid.*, 2042 (1956).

(14) S. Okui, *Yakugaku Zasshi*, **75**, 1262 (1955); M. L. Wolfrom and Z. Yosizawa, *J. Am. Chem. Soc.*, **81**, 3477 (1959); M. L. Wolfrom, Z. Yosizawa, and B. O. Juliano, *J. Org. Chem.*, **24**, 1529 (1959).

(15) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).

TABLE III

MOLECULAR ROTATORY DATA

Compound	α-D-Anomer [α]D	α-D-Anomer [M]D	β-D-Anomer [α]D	β-D-Anomer [M]D	Solvent	Partial molecular rotation[a] A
	degrees		degrees			
Ethyl 3-amino-3-deoxy-1-thio-D-mannopyranoside hydrochloride (I and III)	+137	35500	−95	−24650	H_2O	30,100
Ethyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-D-mannopyranoside (IV and VII)	+57	22300	−95	−37150	$CHCl_3$	29,700
Ethyl 3-acetamido-3-deoxy-1-thio-D-mannopyranoside (V and VIII)	+93	24650	−146	−38700	MeOH	31,650
Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-D-mannopyranoside[b]	+104	40800	−67	−26300	$CHCl_3$	33,500

[a] See ref. 15. [b] See ref. 5.

contained a third, minor component, R_m 1.85. Its mobility was that expected of the dithioacetal, but it could not be isolated in the crystalline state. In addition a trace of a zone R_m 0.70, with chromatographic behavior identical to that of 3-amino-3-deoxy-D-mannose hydrochloride (VI), was present. Chromatographic analysis of the product at shorter reaction times (Table IV) revealed the presence of starting material (II), but at no intermediate time could a greater amount of the zone R_m 1.85 be detected. When the reaction was conducted for five days at 10° the isolated yield of crystalline I + III was only 34%, although chromatography showed that the remaining sirup still contained these products. The zone R_m 1.85 was still only a minor component, although significantly more of the zone R_m 0.70, apparently 3-amino-3-deoxy-D-mannose hydrochloride (VI), was present in the sirup.

The results indicate that mercaptolysis of II is an excellent preparative route for I and III, but it was considered of interest to study the course of the mercaptalation reaction on free 3-amino-3-deoxy-D-mannose hydrochloride (VI).

Dithioacetal formation from 2-amino-2-deoxy-D-glucose hydrochloride is known to be sluggish,[16] unless forcing conditions, with fuming hydrochloric acid, are used,[17] or the charged amino group is eliminated by use of the acetamido analog.[16] In contrast it was found that 3-amino-3-deoxy-D-mannose hydrochloride (VI) reacts rapidly with 12 *N* hydrochloric acid and ethanethiol at room temperature, and only a trace of VI was present after four hours (Table IV). Considerable conversion to the thioglycosides R_m 1.43 (I) and 1.22 (III) had occurred after five minutes, and a relatively larger proportion of product of R_m 1.85 (probably the dithioacetal) was also present. At longer reaction times, the thioglycosides became the preponderant products, although, even after one day, the proportion of the product of R_m 1.85 present was greater than that formed in the mercaptolysis of II. It is evident that the reactivity of VI is very different from that of 2-amino-2-deoxy-D-glucose and is qualitatively closely similar to the behavior of D-mannose on mercaptalation. The lower over-all reaction rate of VI is presumably due to inhibition, by the positively charged $-NH_3^+$ group in the molecule, of protonation at the glycosidic center, this protonation being the first stage in the mercaptalation reaction.

TABLE IV

PAPER CHROMATOGRAPHIC DATA[a] ON MERCAPTOLYSIS OF 3-AMINO-3-DEOXY-D-MANNOSE DERIVATIVES AT 25°

Compound (*c* 10, 12 *N* HCl)	Time of reaction, min.	Observed products[b,c] VI, R_m 0.70	II, R_m 1.00	III, R_m 1.22	I, R_m 1.43	Dithioacetal, R_m 1.85
VI	5	++		++	+	++
	60	+		++	++	+++
	240	(+)		++	+++	++
	1440	(+)		++	++++	++
II	5	+	+++	(+)	...	...
	60	+	++	+	+	+
	240	+(+)	+	++	++	+
	1440	++	(+)	++	+++	++

[a] See footnote *a* of Table I. [b] See footnote *b* of Table I. [c] R_m values denote mobility relative to II.

(16) M. L. Wolfrom and K. Anno, *J. Am. Chem. Soc.*, **74**, 6150 (1952).

(17) M. W. Whitehouse, P. W. Kent, and C. A. Pasternak, *J. Chem. Soc.*, 2315 (1954).

Experimental[18]

Reaction of Methyl 3-Amino-3-deoxy-α-D-mannopyranoside Hydrochloride (II) with Ethanethiol and Hydrochloric Acid.—Methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (II) was prepared in 23% yield from methyl α-D-glucopyranoside by the sequence of Baer and Fischer[11] with the modifications described by Richardson.[12] A chilled solution of II (5 g.) in concentrated hydrochloric acid (20 ml.) was treated with ethanethiol (10 ml.), and shaken for 24 hr. at room temperature. After dilution with ethanol (100 ml.) the solution was neutralized with lead carbonate, filtered, and the combined filtrate and ethanol washings concentrated to give a crystalline solid; yield 4.0 g. (71%), $[\alpha]^{18}D$ +32 ± 1.5° (*c* 0.4, water). Paper chromatograms of this material showed zones of R_m 1.22 and 1.43. Repeated fractional recrystallization gave fine needles of pure ethyl 3-amino-3-deoxy-1-thio-β-D-mannopyranoside hydrochloride (III); R_m 1.22 as the less soluble component, m.p. 240–245° dec. (browning at 224°), $[\alpha]^{21}D$ −95 ± 0.6° (*c* 1.7, water); $\lambda_{max\ (\mu)}^{KBr}$ 3.0 (OH), 7.90 (SEt), 11.26 (axial H at C-1); X-ray powder diffraction data[19]: 12.72 s (2), 7.79 vs (1), 6.61 vw, 5.37 vw, 4.61 w, 4.37 m, 4.15 s (2,2), 3.99 m, 3.59 w, 3.29 m (3), 3.05 vw, 2.86 vw.

Anal. Calcd. for $C_8H_{18}ClNO_4S$: C, 36.99; H, 6.93; N, 5.39; S, 12.33. Found: C, 37.11; H, 7.48; N, 5.32; S, 12.02.

The second component, ethyl 3-amino-3-deoxy-1-thio-α-D-mannopyranoside hydrochloride (I), R_m 1.43, was isolated as needles from the mother liquors from crystallization of III; m.p. 218–220° dec. (browning at 195°), $[\alpha]^{21}D$ +137 ± 1.8° (*c* 0.55, water); $\lambda_{max\ (\mu)}^{KBr}$ 3.0 (OH), 7.91 (SEt), 11.86 (equatorial H at C-1); X-ray powder diffraction data[19]: 11.63 s (2), 9.36 vw, 7.86 vs (1), 6.71 vw, 6.21 m, 5.42 m, 4.78 vw, 4.52 s (2,2), 3.91 w, 3.57 m (3), 3.43 m, 2.95 vw.

(18) Melting points were taken with a Hershberg apparatus. Specific rotations were determined in a 2-dm. polarimeter tube. Infrared spectra were determined on a Perkin-Elmer Infracord infrared spectrophotometer with pellets pressed from a finely ground mixture of the sample with dried analytical reagent grade potassium bromide. Paper chromatography was carried out by the descending technique with the upper layer of a 4:1:5 1-butanol–ethanol–water system, and R_m refers to mobility relative to that of methyl 3-amino-3-deoxy-α-D-mannose hydrochloride. Zones were detected by the silver nitrate/sodium hydroxide procedure [W. E. Trevelyan, D. P. Proctor, and J. S. Harrison, *Nature*, **166**, 444 (1950)].

(19) Interplanar spacing, Å., CuKα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First few lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

Anal. Calcd. for $C_8H_{18}ClNO_4S$: C, 36.99; H, 6.93; N, 5.39; S, 12.33. Found: C, 37.24; H, 7.40; N, 5.58; S, 12.18.

The reaction was repeated with the same quantities of reactants, but with shaking 5 days at 10° before isolation of products. Crystalline I + III were isolated; combined yield 34%. The residual sirup showed on chromatography zones R_m 1.22 and 1.43 corresponding to III and I, plus additional zones R_m 0.70 and 1.85. The product R_m 0.70 showed chromatographic behavior identical to that of 3-amino-3-deoxy-D-mannose hydrochloride.

At reaction times shorter than 24 hr., at room temperature, the product contained some unchanged starting material, a weak zone R_m 1.85, and a product R_m 0.70, apparently 3-amino-3-deoxy-D-mannose hydrochloride.

Ethyl 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-β-D-mannopyranoside (VII).—The crystalline mixture of I and III from the preceding preparation (1.0 g.) was treated with pyridine (16 ml.) and acetic anhydride (16 ml.) for 24 hr. at room temperature; the mixture was poured into iced water (50 ml.) and after 1 hr. the solution was extracted with two 50-ml. portions of chloroform. The extracts were washed with water, dried (magnesium sulfate), evaporated, and the sirup was crystallized from ether (50 ml.); yield 0.68 g. (45%). The product was recrystallized from ethanol with little loss to give pure VII as needles; m.p. 162–164°, $[\alpha]^{22}D$ −95 ± 1.3° (*c* 0.76, chloroform); $\lambda_{max(\mu)}^{KBr}$ 5.77 (OAc), 5.95, 6.60 (NHAc), 11.14 (axial H at C-1); X-ray powder diffraction data[19]: 10.40 s (1), 7.69 vw, 6.76 s (3), 5.52 vw, 4.63 m, 4.45 vw, 4.13 s (2), 3.81 m, 3.32 w, 2.77 w, 2.70 vw, 2.31 vw.

Anal. Calcd. for $C_{16}H_{25}NO_8S$: C, 49.10; H, 6.39; N, 3.58. Found: C, 48.69; H, 6.47; N, 3.61.

The melting point of the product was undepressed on admixture with a sample of VII prepared from pure ethyl 3-amino-3-deoxy-1-thio-β-D-mannopyranoside hydrochloride (III) by a similar acetylation procedure.

Ethyl 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-α-D-mannopyranoside (IV).—Concentration of the ether mother liquors from the preceding preparation gave a sirup which crystallized on trituration with petroleum ether; yield 0.52 g. (35%). Recrystallization from ether gave pure IV as fine needles; m.p. 122–124°, $[\alpha]^{22}D$ +57 ± 0.9° (*c* 0.52, chloroform); $\lambda_{max(\mu)}^{KBr}$ 5.75 (OAc), 6.05, 6.65 (NHAc), 11.86 (equatorial H at C-1); X-ray powder diffraction data[19]: 15.11 vw, 10.17 w, 9.03 m, 7.94 vs (1), 6.78 m, 5.81 s (2), 5.32 vw, 5.05 vw, 4.62 s (3), 4.43 s (3,3), 4.18 vw, 3.95 s (2,2), 3.70 w, 3.64 w.

Anal. Calcd. for $C_{16}H_{25}NO_8S$: C, 49.10; H, 6.39; N, 3.58. Found: C, 49.36; H, 6.28; N, 3.66.

The melting point of the product was undepressed on admixture with a sample of IV prepared from pure ethyl 3-amino-3-deoxy-1-thio-α-D-mannopyranoside hydrochloride (I) by a similar acetylation procedure.

Ethyl 3-Acetamido-3-deoxy-1-thio-α-D-mannopyranoside (V).—Dry ammonia gas was passed for 30 min. through a solution of ethyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-α-D-mannopyranoside (IV, 0.20 g.) in methanol (10 ml.) at 0°. After 1 hr. at room temperature the solution was evaporated and the crystalline product was recrystallized from ethanol; yield 0.10 g. (74%); m.p. 224–226°, $[\alpha]^{22}D$ +93 ± 1.5° (*c* 0.34, methanol); $\lambda_{max(\mu)}^{KBr}$ 3.0 (OH), 6.05, 6.45 (NHAc), 7.88 (SEt), 11.86 (equatorial H at C-1); X-ray powder diffraction data[19]: 8.42 m, 7.23 w, 6.39 s (2), 5.81 vs (1), 4.90 vw, 4.80 w, 4.20 m (3), 3.88 vw, 3.67 vw, 3.51 vw, 3.20 vw, 2.93 vw.

Anal. Calcd. for $C_{10}H_{19}NO_5S$: C, 45.28; H, 7.17; N, 5.28. Found: C, 45.06; H, 7.13; N, 5.17.

Ethyl 3-Acetamido-3-deoxy-1-thio-β-D-mannopyranoside (VIII).—This compound was prepared from ethyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-β-D-mannopyranoside (VII) by the same procedure as that used for the α-D anomer, and was obtained as needles from ethanol; yield 74%; m.p. 234–235°, $[\alpha]^{22}D$ −146 ± 2° (*c* 0.25, methanol); $\lambda_{max(\mu)}^{KBr}$ 3.0 (OH), 6.05, 6.50 (NHAc), 7.90 (SEt), 11.26 (axial H at C-1); X-ray powder diffraction data[19]: 11.87 m, 10.78 s (3), 4.73 vw, 4.47 s (2), 4.24 s (2,2), 3.74 s (1), 3.01 vw, 2.70 vw, 2.52 vw, 2.41 w, 2.20 vw.

Anal. Calcd. for $C_{10}H_{19}NO_5S$: C, 45.28; H, 7.17; N, 5.28. Found: C, 44.90; H, 7.02; N, 5.15.

Periodate Oxidation of Ethyl 3-Acetamido-3-deoxy-1-thio-α- and β-D-mannopyranosides (V and VIII).—Solutions of the sample (20 mg., 0.75 mmoles) in water were treated with 0.25 *M* sodium metaperiodate solution (10 ml., 2.5 mmoles) and at once made up to 100 ml. and stored at room temperature in the dark. Blanks were prepared similarly, omitting the sample. Periodate uptake was determined on 5-ml. aliquots by the arsenite–iodine method,[20] and formic acid was determined after addition of 2 drops of ethylene glycol by titration with 0.02 *N* sodium hydroxide to the end point with methyl red. Formaldehyde was determined by the chromotropic acid method.[21] The results are summarized in Table II.

Reaction of D-Mannose and 3-Amino-3-deoxy-D-mannose Hydrochloride (VI) with Ethanethiol and Hydrochloric Acid at 25°.—A mixture of the sugar (100 mg.), concentrated hydrochloric acid (1.0 ml.), and ethanethiol (1.0 ml.) was shaken at room temperature (*ca.* 25°). Aliquots of the reaction were withdrawn at selected time intervals, neutralized by stirring with lead carbonate in ethanol, filtered, and evaporated. Paper chromatography of the products revealed, in the case of D-mannose, the presence of a product R_{man} 2.66 corresponding to D-mannose diethyl dithioacetal, and two products, R_{man} 2.11 and 2.39, believed to be thioglycosides. In the case of 3-amino-3-deoxy-D-mannose hydrochloride, products with R_m 1.43 and 1.22, corresponding to I and III, respectively, together with a product R_m 1.85, believed to be the dithioacetal, and a product R_m 0.70, apparently starting material, were obtained. The approximate intensities of the zones on the chromatograms, estimated visually, at various reaction times, are listed in Table IV. Comparable data for the mercaptolysis of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (II) also are listed.

Reaction of D-Glucose and of D-Galactose with Ethanethiol and Hydrochloric Acid at 25°.—The procedure used in the preceding experiment was followed, and the results are recorded in Table I. The zones R_g 1.00 and R_{gal} 1.00 corresponded to the respective parent sugars, and the zones R_g 2.75 and R_{gal} 2.85 corresponded in mobility and behavior to those given by the diethyl dithioacetals of D-glucose and D-galactose, respectively. In both cases rapid conversion of the free sugar to the dithioacetal appeared to take place, followed by a slower reaction wherein the dithioacetal disappeared, the free sugar was formed, and products with mobilities corresponding to thioglycosides appeared.

Acknowledgment.—The technical assistance of W. N. Rond is gratefully acknowledged as is also the counsel of the late Dr. Alva Thompson.

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C-19 Functional Steroids. V.[1] Synthesis of Estrogen Biosynthesis Intermediates[2]

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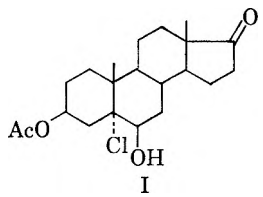
The synthesis of 19-hydroxyandrost-4-ene-3,17-dione, which has already been converted to a variety of C-19 oxygenated biosynthesis intermediates, is described. Treatment of androstenolone acetate with hypochlorous acid gave 5α-chloro-3β-hydroxyandrostan-17-one acetate. The nitrite ester derived from the foregoing chlorohydrin gave, on photolysis, the corresponding 19-oxime, which, on treatment with zinc in acetic acid, gave the corresponding Δ^5 compound, which furnished the 19-nitrile with acetic anhydride. Reduction of the 17-ketone with tri-*t*-butoxy lithium aluminum hydride, followed by partial reduction of the nitrile to the aldehyde with lithium aluminum hydride, gave 19-oxoandrost-5-ene-3β,17β-diol. The corresponding 19-alcohol was obtained with sodium borohydride, and Oppenauer oxidation gave the final product.

The determination of the biosynthetic pathway for the conversion of androgens to estrogens for some years has been an important problem. It has been demonstrated that 19-hydroxyandrost-4-ene-3,17-dione is an intermediate in the conversion of androst-4-ene-3,17-dione to estradiol.[3] More recent research[4] has been concerned with the nature of the intermediates following this 19-hydroxy steroid in the biosynthetic sequence. This work indicates that the Δ^1 derivative of either 19-hydroxyandrost-4-ene-3,17-dione or of the corresponding 19-aldehyde participates in the metabolic pathway.

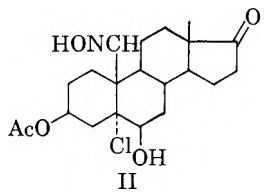
Studies in the entire area have been hampered by poor availability of the C-19 oxygenated intermediates. Ehrenstein and co-workers[5] have developed methods for the preparation from strophanthidin of 19-hydroxyandrost-4-ene-3,17-dione. This substance is a key material in the chemical synthesis of estrogen biosynthesis intermediates, since methods exist for its conversion to the following compounds: 19-hydroxytestosterone[5] and its Δ^1 derivative,[5] 19-oxoandrost-4-ene-3,17-dione,[6] the corresponding C-19-carboxylic[6] acid, 19-norandrostenedione,[6] estrone,[7] and estradiol.[5]

A direct chemical synthesis of 19-hydroxyandrost-4-ene-3,17-dione from conventional steroids would be of value, therefore, since it would obviate the lengthy route from strophanthidin and also make possible the synthesis of C^{14}-labeled biosynthetic intermediates. The synthesis of this 19-hydroxy steroid starting from androstenolone acetate by means of intramolecular lead tetraacetate oxidation recently has been disclosed.[8] The present work deals with an alternate preparation of this substance utilizing partial reduction of steroidal 19-nitriles.

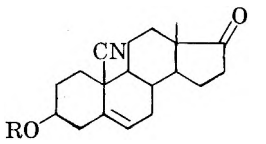
The preparation, in this laboratory, of the requisite 3β,17β-dihydroxyandrost-5-ene-19-nitrile VIII *via* the Barton reaction on steroidal 5,6-chlorohydrins has been described[9,10] and a modification of this method was used in the present study. Treatment of androstenolone acetate with calcium hypochlorite and acetic acid[11] gave the chlorohydrin I, which was allowed to react with nitrosyl chloride in pyridine solution to form the unstable 6-nitrite ester. Photolysis of the nitrite in toluene solution gave the colorless 19-nitroso dimer, which was rearranged in refluxing 2-propanol to afford the oxime II. Removal of the elements of hypochlorous acid from II by the action of zinc in acetic acid[9] gave the Δ^5 derivative III. It was possible to assign the *syn* oxime structure to III on chemical grounds. Acetylation of III gave the diacetate IV, which on melting readily formed VI. This facile



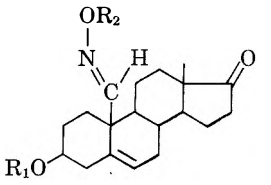
I



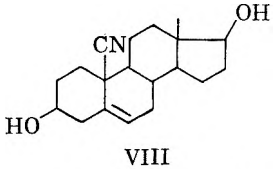
II



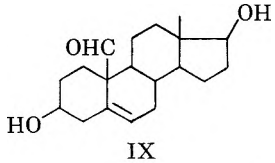
VI. R = Ac
VII. R = H



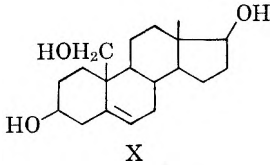
III. R_1 = Ac, R_2 = H
IV. R_1 = Ac, R_2 = Ac
V. R_1 = H, R_2 = H



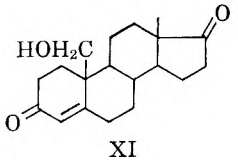
VIII



IX



X



XI

(1) Paper IV, N. Bhacca, M. E. Wolff, and R. Kwok, *J. Am. Chem. Soc.*, **84**, 4976 (1962).

(2) From the Ph.D. thesis of T. Jen, University of California, 1963. This investigation was supported by a PHS research grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. The n.m.r. spectrometer used in this study was provided by a grant (NSF-G 21268) from the National Science Foundation.

(3) J. E. Longchampt, C. Gual, M. Ehrenstein, and R. I. Dorfman, *Endocrinology*, **66**, 416 (1960).

(4) T. Morato, K. Raab, H. J. Brodie, M. Hayano, and R. I. Dorfman, *J. Am. Chem. Soc.*, **84**, 3764 (1962).

(5) M. Ehrenstein and K. Otto, *J. Org. Chem.*, **24**, 2006 (1959), and references cited therein.

(6) H. Hagiwara, *J. Pharm. Soc. Japan*, **80**, 1675 (1960).

(7) H. Hagiwara, *ibid.*, **80**, 1671 (1960).

(8) (a) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962); (b) K. Heusler, J. Kalvoda, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962); (c) also see K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1126 (1962).

(9) R. Kwok, T. Jen, and M. E. Wolff, Abstracts, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 43N; T. Jen and M. E. Wolff, *J. Med. Pharm. Chem.*, **5**, 876 (1962).

(10) R. Gardi and C. Pedrali, *Gazz. chim. ital.*, **91**, 1420 (1961), have described an alternate synthesis of compound VIII *via* the Barton reaction.

(11) *Cf.* S. Mori, *J. Chem. Soc.* (Japan), **64**, 981 (1943).

pyrolysis is known[12] to proceed by *cis* elimination of acetic acid from *syn* oxime acetates. In preparative work, it was more convenient to prepare VI by heating III in acetic anhydride. Hydrolysis of VI gave VII,[9] which on reduction with lithium aluminum tri-*t*-butoxyhydride gave the diol VIII.[9,10]

The next stage in the synthesis called for the reduction of the nitrile function in VIII to an aldehyde. Although a number of methods exist which accomplish this conversion, a simple and convenient procedure was found in lithium aluminum hydride reduction. Whereas this reagent normally reduces nitriles to amines, in the present case the reduction was exceedingly slow, and even after 120 hours the major product was the imine. It is likely that this slow, partial reduction results from either poor solubility of the complexed reduction product in the reaction solvent, or the poor accessibility of the imine–metal complex to the hydride species. The 19-imine was not isolated, but was hydrolyzed in acid solution to the aldehyde IX, which was obtained in 60% yield from VIII. Reduction of IX with sodium borohydride in methanol, or lithium aluminum hydride in boiling tetrahydrofuran, gave the triol X.

Brief (ten-minute) Oppenauer oxidation of triol X gave XI in 26% yield, together with trace amounts of what were probably 19-hydroxytestosterone and 19-norandrostenedione. It is likely that the yield of XI could be raised if the reaction were run on a larger scale. The apparent formation of 19-norandrostenedione is probably due to elimination of formaldehyde from XI.

Experimental[13]

5α-Chloro-3β,6β-dihydroxyandrostan-17-one 3-Acetate (I).—A solution of 24.0 g. (0.0655 mole) of 3β-hydroxyandrost-5-en-17-one acetate in 600 ml. of ether was shaken with a suspension of 60.0 g. of calcium hypochlorite, 1800 ml. of water, and 45 ml. of glacial acetic acid for 20 min., during which the insoluble product precipitated. After separation of the aqueous layer, the ether suspension was washed with water and filtered to provide 12.0 g. of the crude chlorohydrin, m.p. 225–230°. Crystallization from ethanol–acetone–water afforded 10.5 g. (38%) of crystals, m.p. 235–238° (inserted at 230°). Evaporation of the ether filtrate and recrystallization of the residue gave an additional 0.5 g. of product, m.p. 233–237° (11.0 g., 40% total yield). The analytical sample, recrystallized from chloroform–methanol, had m.p. 242–244° (inserted at 235°), $[\alpha]^{25}D$ +11° (*c*, 0.4% in $CHCl_3$), μ_{max}^{KBr} 2.88, 5.77, 8.03.

Anal. Calcd. for $C_{21}H_{31}ClO_4$: C, 65.89; H, 8.16; Cl, 9.26. Found: C, 65.44; H, 8.26; Cl, 9.48.

5α-Chloro-3β,6β-dihydroxy-19-oximinoandrostan-17-one 3-Acetate (II).—A solution of 10.0 g. (0.0243 mole) of I in 100 ml. of pyridine was treated with excess nitrosyl chloride at 15–20° and poured into 1 l. of ice–water. The precipitate was filtered, washed with water, and triturated with a small amount of methanol to remove impurities. The residue was filtered and dried at room temperature under vacuum to afford 10.4 g. (97%) of the unstable nitrite ester, m.p. 212–214°, μ_{max}^{KBr} 5.76, 6.05, 8.05, 12.85, 13.00.

A solution of 5.0 g. (0.0121 mole) of the nitrite ester in 200 ml. of toluene was irradiated with an immersed 200-w. high pressure mercury arc equipped with a borosilicate filter. After the nitrite test[14] was negative, 3.0 g. (60%) of the precipitated 19-nitroso product was removed by filtration. One recrystallization from acetone–hexane at room temperature gave a product with double melting points: 145–146° (nitroso compound inserted at 140°) and 241–243° (oxime).

A solution of 6.0 g. (0.0145 mole) of the crude nitroso compound in 300 ml. of 2-propanol was refluxed for 2 hr. The solvent was evaporated and the residue was washed with ether and filtered. Crystallization from acetonitrile provided 5.5 g. (54% over-all) of the oxime, m.p. 242–244° (inserted a t230°). Further recrystallization gave the analytical sample, m.p. 243–245°, $[\alpha]^{25}D$ +18° (c, 1% in MeOH), μ_{max}^{KBr} 2.92, 2.98, 5.75, 5.85, 7.85.

Anal. Calcd. for $C_{21}H_{30}ClNO_5$: C, 61.23; H, 7.34. Found: C, 60.96; H, 7.26.

3β-Hydroxy-*syn*-19-oximinoandrost-5-en-17-one Acetate (III). A solution of 5.0 g. (0.0124 mole) of II in 60 ml. of glacial acetic acid (preheated to 85°) was stirred with 10.0 g. of zinc dust at 90–95° for 30 min., cooled to 25°, and filtered. The acetic acid filtrate was poured slowly into 600 ml. of water. After standing for 1 hr., the precipitate was filtered, washed with water, and dried to furnish 3.8 g. of crude product. Crystallization from aqueous ethanol yielded 3.3 g. (77%) of III, m.p. 176–182°. Further recrystallization gave the analytical sample, m.p. 182–185°, $[\alpha]^{25}D$ −89° (*c*, 1% in MeOH), μ_{max}^{KBr} 2.96, 5.80, 8.00.

Anal. Calcd. for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13. Found: C, 70.39; H, 8.05.

***syn*-19-Acetoxyimino-3β-hydroxyandrost-5-en-17-one Acetate (IV).**—A solution of 0.15 g. of the oxime (III), 2 ml. of glacial acetic acid, 1 ml. of acetic anhydride, and 0.02 g. of *p*-toluenesulfonic acid was kept at 27° for 5 hr. and poured into water to furnish 0.15 g. of the crude product, m.p. 136–139°. It was recrystallized from aqueous methanol to give the analytical sample, m.p. 140–141°, $[\alpha]^{25}D$ −142° (*c*, 1% in $CHCl_3$), μ_{max}^{KBr} 5.66, 5.78, 8.03, 8.24

Anal. Calcd. for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78. Found: C, 69.03; H, 7.91.

A sample of the diacetate was melted at a temperature of 142°, and allowed to cool. Recrystallization of the resulting solid from aqueous methanol gave VI, m.p. 189–190°.

3β-Hydroxy-*syn*-19-oximinoandrost-5-en-17-one (V).—A solution of 0.6 g. (0.00167 mole) of (III) in 20 ml. of 5% methanolic potassium hydroxide was kept at 27° for 18 hr. Addition of water, followed by acidification of the solution, furnished 0.5 g. (94%) of V, m.p. 243–245°. Recrystallization from aqueous ethanol gave the analytical sample, m.p. 245–246° (inserted at 235°), $[\alpha]^{25}D$ −95° (*c*, 1% in MeOH), μ_{max}^{KBr} 2.91, 3.00, 5.78.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57. Found: C, 71.69; H, 8.58.

3β-Hydroxy-17-oxoandrost-5-ene-19-nitrile Acetate (VI).—A solution of 1.0 g. (0.00278 mole) of III in 20 ml. of acetic anhydride was refluxed for 2 hr. and poured into 200 ml. of ice water. After 1 hr., the precipitate was filtered and washed with water to furnish 0.9 g. (95%), of the crude material, m.p. 183–186°. Several recrystallizations from aqueous methanol gave the analytical sample, m.p. 189–190°, $[\alpha]^{25}D$ −97° (*c*, 1% in MeOH), μ_{max}^{KBr} 4.50, 5.80, 7.96.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97. Found: C, 73.63; H, 7.80.

3β-Hydroxy-17-oxoandrost-5-ene-19-nitrile (VII).—A solution of 0.80 g. (0.00224 mole) of VI in 40 ml. of methanol was combined with a solution of 4.0 g. of potassium hydroxide in 8 ml. of water and kept at 27° for 18 hr. It was diluted with 100 ml. of water, and the resulting crystalline precipitate was filtered to furnish 0.6 g. of the crude material which was recrystallized from acetone–hexane to yield 0.55 g. (78%) of VII, m.p. 192–194°. The sample after further recrystallization had m.p. 193–195°, undepressed upon admixture with the sample obtained from selective oxidation of VIII.[9] Identical infrared spectra were obtained from both samples.

3β,17β-Dihydroxyandrost-5-ene-19-nitrile. (VIII).—A solution of 6.0 g. (0.02 mole) of VII and 9.0 g. of tri-*t*-butoxy lithium aluminum hydride in 60 ml. of tetrahydrofuran was kept at 0° for 1 hr. There was added 20% hydrochloric acid until a clear solution was obtained. The tetrahydrofuran was evaporated under reduced pressure during which the steroid crystallized from the aqueous solution. It was diluted with water and filtered to give 5.4 g. (90%) of II, m.p. 206–209°, lit. m.p. 209–210°,[10] 208–209°.[9]

(12) D. Ambrose and O. L. Brady, *J. Chem. Soc.*, 1243 (1950).

(13) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley. Optical rotations were obtained in a 0.5-dm. tube with a Rudolph photoelectric polarimeter. N.m.r. spectra were obtained at a field strength of 60 Mc. on samples in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. Resonance positions are reported in δ (p.p.m.) values where possible; unresolved humps are described in c.p.s. units (60 Mc.).

(14) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., New York, N. Y., 1960, p. 178.

19-Oxoandrost-5-ene-3β,17β-diol (IX).—A stirred suspension of 5.0 g. (0.0167 mole) of VIII and 2.5 g. of powdered lithium aluminum hydride in 750 ml. of anhydrous tetrahydrofuran was boiled under reflux for 120 hr., chilled in an ice bath, and the excess hydride was decomposed with ethyl acetate. After acidification with 20% hydrochloric acid, the mixture was refluxed for 3 hr. The solution was clarified, if necessary, by addition of acid and was evaporated under reduced pressure until heavy precipitation occurred. Water was added to effect further precipitation. The solid was filtered and washed with water, and, after recrystallization from aqueous ethanol, gave 2.95 g. (60%) of IX, m.p. 184–190°. The analytical sample recrystallized from acetone–hexane had m.p. 185–188°, μ_{max}^{KBr} 3.00 (strong), 3.73 (sh), 5.84 (strong), loss of −CN band at 4.5, $[\alpha]^{25}D$ −247° (c, 1% in MeOH).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.80; H, 9.13.

19-Oxoandrost-5-ene-3β,17β-diol Diacetate.—A solution of IX in pyridine and acetic anhydride was kept at 27° for 18 hr. and poured into ice–water. Filtration of the precipitate gave the crude product, which on recrystallization from aqueous ethanol, had m.p. 150–153°, μ_{max}^{KBr} 3.68 (sh), 5.80, 8.03, $[\alpha]^{25}D$ −252° (c, 1% in $CHCl_3$), n.m.r.: 0.75 (C(18)-H), 2.00, 2.03 (acetate methyls), 258–293 c.p.s. (broad hump) (3α-H, 17α-H), 345–363 c.p.s. (broad hump) (6-H), 9.75 (19-H).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.02; H, 8.27.

Androst-5-ene-3β,17β,19-triol (X).—A solution of 0.4 g. (0.00145 mole) of IX and 0.4 g. of sodium borohydride in 50 ml. of methanol was kept at 27° for 1 hr. and acidified with 10% hydrochloric acid to pH 1. The clear solution was concentrated under reduced pressure, diluted with water, and filtered to give 0.35 g. (87%) of X, m.p. 229–230°. The analytical sample, recrystallized from acetonitrile, had m.p. 232–233°, μ_{max}^{KBr} 3.03, 9.50, 9.70, $[\alpha]^{25}D$ −48° (c, 0.5% in MeOH).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.62; H, 9.81.

The product could also be prepared by reduction of IX with lithium aluminum hydride in boiling tetrahydrofuran solution for 1 hr.

19-Hydroxyandrost-4-ene-3,17-dione (XI).—A mixture of 10 ml. of cyclohexanone and 15 ml. of toluene was heated to boiling and 4 ml. of distillate was collected and discarded. Then 0.35 g. (0.00145 mole) of X was quickly dissolved in the hot anhydrous solution and 1.0 g. of powdered redistilled aluminum isopropoxide was added. The mixture quickly was brought to reflux and maintained there for 10 min. The mixed solvent was removed *in vacuo* at 70–75°, and the residue was taken up in 200 ml. of chloroform which was washed with 1 *N* sulfuric acid (100 ml.) and water and dried over sodium sulfate. Evaporation of the chloroform left a syrupy residue containing some cyclohexanone. The residue was chromatographed on 10.0 g. of neutral alumina; the following eluents were used: (4 × 5 ml.) ether; (4 × 5 ml.) methanol–ether (1%); (4 × 5 ml.) methanol–ether (2%); (4 × 5 ml.) methanol–ether (4%); (4 × 5 ml.) methanol–ether (8%); (4 × 5 ml.) methanol–ether (16%); (4 × 5 ml.) methanol–ether (32%). From the 2% methanol–ether fractions, a trace of what was apparently 19-norandrostenedione was isolated in crystalline form, m.p. 160–167 (reported[15] m.p. 171–172°), λ_{max}^{EtOH} 240 mμ, μ_{max}^{KBr} 5.75, 6.00, 6.18 (absence of —OH band). From the 8% methanol–ether fractions, 0.09 g. (26%) of colorless crystals of XI was isolated, which, after recrystallization from acetone–hexane had m.p. 168–170°, λ_{max}^{EtOH} 243 mμ, log *E* 4.18, $[\alpha]^{25}D$ +195° (c, 0.9% in chloroform), μ_{max}^{KBr} 2.95, 5.75, 6.04, 6.18, (reported[15] m.p. 168–170°, λ_{max}^{MeOH} 242 mμ, log *E* 4.18, $[\alpha]^{30}D$ +178 ± 4° (chloroform), $\mu_{max}^{solid\ film}$ 2.94, 5.80, 6.06, 6.17).[17]

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.05; H, 8.65.

From the 16% MeOH–ether fractions there was obtained 0.01 g. of what is probably 19-hydroxytestosterone, m.p. 199–201°, (reported[6] 201–203°), λ_{max}^{EtOH} 243 mμ, μ_{max}^{KBr} 3.05, 6.10, 6.19.

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Solvent Effects in the Menschutkin Reaction

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The rates of the reaction of pyridine with ethyl bromide and ethyl iodide have been determined in benzene, chlorobenzene, bromobenzene, and iodobenzene. The rate constant increase is proportional to the polarizability of the solvent, and is attributed to the interaction of the solvent with the leaving halide in the transition state.

The effect of the solvent upon the rate of the Menschutkin reaction had been shown to be important by many workers.[3–8] The reaction, in which ions are formed from electrically neutral reagents, proceeds more rapidly in solvents of high dielectric constant.

Attempts to correlate the solvent effect with physical properties of the solvent have been made by several authors. Eagle and Warner[8] correlated the reaction rate constant with the dielectric constant in the mixed solvent alcohol–water. Kosower[9] demonstrated that the rate constant for pure alcohol solvents correlate well with *Z*. A plot of log *k vs. Z* gave a linear relationship. Kerr[10] attempted to correlate the dipole moment with the reaction rate constant, but acknowledged that he had achieved only limited success. Grim, Ruf, and Wolf[11] showed that the rate constant varied with dielectric constant for solvents with a large range of *D* (dielectric constant), but could not demonstrate a quantitative relationship. A frequently used relationship between *D* and the rate constant is given in equation 1.[12]

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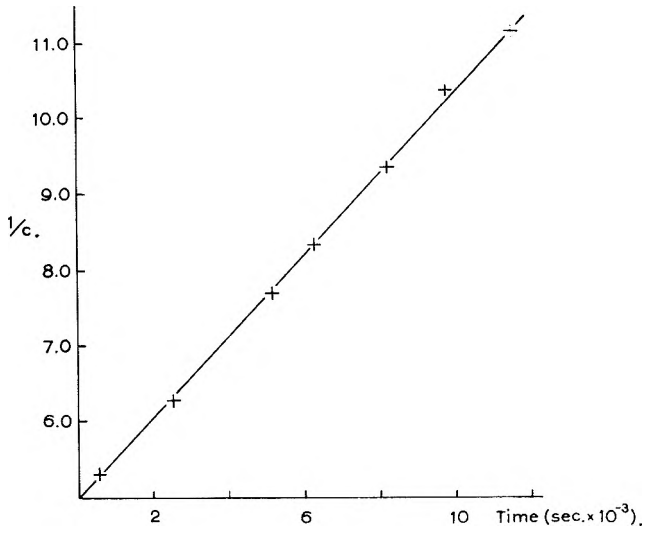

Fig. 1.—Ethyl iodide + pyridine in the solvent bromobenzene at 99.85°.

$$\ln k_2 = \ln k_0 - \frac{1}{kT}\left[\frac{(D-1)}{(2D+1)}\left\{\frac{\omega_A^2}{r_A^3} + \frac{\omega_B^2}{r_B^3} - \frac{\omega_*^2}{r_*^3}\right\}\right] + \sum \frac{\phi}{kT} \quad (1)$$

where k_2 is the rate constant in the solvent 2; k_0 is the rate constant at $D = 1$; ω_A, ω_B and ω_* are the dipole moments of the reagents A and B and the transition state; r_A, r_B, and r_* are the radii of the reagents and the transition state, respectively; ϕ is the contribution of nonelectrostatic forces.

Tommila[13] has showed that this relationship may be used to express the effect of the mixed solvents acetone–water, acetone–benzene, acetone–dioxane, and acetone–tetrahydrofuran on the reaction rate. He assumed that ϕ was negligible with respect to electrostatic forces, and plotted ln k *vs.* $(D-1)/(2D+1)$. The result was a series of straight lines of different slopes.

Two other workers have suggested that this equation does not have universal applicability. Wanatabe and Fuoss[14] have investigated the use of this equation for the reaction of butyl bromide with pyridine and 4-picoline in 5 solvents of relatively high D. The usual assumption that ϕ is negligible was showed to be untenable. These investigators suggested that the transition state probably is a solvated complex. An investigation by Caldin and Peacock[15] also showed that electrostatic forces alone cannot explain solvent effects. They demonstrated that "simple electrostatic theory fails to account for the solvent effects" by calculating the activation energy and the frequency factor from an equation similar to equation 1 and comparing their results with the observed data. Their literature survey of five reactions, one of which was the Menschutkin reaction, led to a classification into three categories, namely aliphatic, aromatic, and hydroxylic solvents. The rate constants for the reactions in aromatic solvents were higher than those in aliphatic solvents. They attributed this to the high polarizabilities of the aromatic solvents.

The present paper reports the results of an investigation to determine if the polarizability of the solvent has a significant influence on the reaction rate constant of the Menschutkin reaction.

Experimental

Ethyl iodide and ethyl bromide, Fisher reagent grade, were dried over Drierite, distilled over copper, and stored over copper metal. All distillations were performed in a 24-in. silvered, vacuum-jacketed column packed with glass helices. Pyridine, Fisher reagent, was dried over potassium hydroxide and distilled. The solvents were refluxed with pyridine, washed with sulfuric acid, then with water. They were dried over Drierite and then distilled through the 24-in. column. The purity of the solvents was confirmed by boiling point range, refractive index, and gas chromatography.

Procedure.—All burets and pipets were calibrated and the thermometers were compared with a thermometer which was calibrated at the National Bureau of Standards. A sealed ampoule technique was used for the kinetic experiments, with seven to nine samples analyzed in each run. The rates were followed by a determination of the ion concentration by means of a potentiometric titration. The rate constants were reckoned from the slope of a plot of $1/(Cl^-)$ *vs.* time, for the concentrations of the reagents were made equal. In all the experiments, the initial concentrations were 0.200 M. The rate constants were corrected for solvent expansion. The products crystallized from the cold reaction mixture and were isolated by filtration. The ethylpyridinium iodide that was isolated had m.p. 85–86°; lit.[16] m.p. 90.5°.

Discussion and Results

Pyridine was treated with ethyl iodide and ethyl bromide in benzene, chlorobenzene, bromobenzene, and iodobenzene. These solvents were chosen, for they give a large variation in polarizability of the substituent group and a small change in D. The rate constants were determined at 80 and 100° with equal molar concentrations for the amine and alkyl halide. The reactions were run with initial concentrations of 0.20 M. Good straight lines were obtained for the plot of $1/C$ *vs.* time, and the duplicate rate constants were reproducible to ±2%. A typical plot is given in Fig. 1 and the rate data and thermodynamic properties are presented in Table II. Comparison of our data with those of Winkler and Hinshelwood[17] showed that the rate constant does not vary greatly with initial concentration. They reported 7.25 and 25.0 × 10^{-4} l./mole sec. for the reaction of ethyl bromide and pyridine at 80 and 100°. Our values were 7.44 and 28.4 × 10^{-4} l./mole sec. for the same reactions at twice the initial concentrations. Norris and Prentiss[4] have reported initial rate constants for the reaction of ethyl iodide and pyridine in acetone, nitrobenzene, methyl alcohol, ethyl alcohol, and other aliphatic alcohols. Their initial concentrations varied from 0.37 to 0.69 for acetone, 0.23 to 1.00 for nitrobenzene, and 0.4 to 0.68 for benzene. The largest variations in initial rate constant with initial concentration occurred with benzene, where k increased from 25 to 28, or about 10%. There was a similar increase with acetone and nitrobenzene, but the per cent increase was smaller. They also observed a slight drift in their rate constants with time. Our plots of $1/C$ *vs.* time showed no evidence of curvature, nor was this mentioned by Winkler and Hinshelwood.

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TABLE I

RATE CONSTANTS FOR THE MENSCHUTKIN REACTION IN VARIOUS SOLVENTS

Ethyl iodide + triethylamine[a] at 100°

Solvent	R,[b] cc./mole	Z[d]	D[c]	k, l./mole sec.
Benzene	1.10	..	2.27	4.0×10^{-4}
Chlorobenzene	6.03	..	5.62	13.8
Bromobenzene	8.80	..	5.40	16.0
Iodobenzene	13.94	..	4.62	26.5
Nitrobenzene	...	..	34.8	138

Ethyl iodide + pyridine[e] at 25°

Benzene	...	..	2.27	7.9×10^{-7}
n-Propyl alcohol	...	78.3	20.1	8.6
Ethanol	...	79.6	24.3	10.8
Methanol	...	83.6	32.6	19.4
Acetone	...	65.7	20.7	100
Nitrobenzene	...	..	34.8	197

[a] Data from ref. 11. [b] Atomic refraction constants for the substituent group on benzene for H_α line. Data from ref. 26. [c] C. P. Smythe, "Dielectric Behavior and Structure," McGraw-Hill Book Co., New York, N. Y., 1955. N. A. Lange, "Lange's Handbook of Chemistry," 9th Ed., Handbook Publishers, Inc., Sandusky, Ohio, p. 1222. [d] Data from ref. 9. [e] Data from ref. 4.

TABLE II

THE RATES AND THERMODYNAMIC PROPERTIES FOR THE REACTION OF EtX AND PYRIDINE IN VARIOUS SOLVENTS

Solvent	$k \times 10^5$, l./mole sec.	ΔS^*, cal./deg./mole	ΔE^*, kcal./mole
Reagent EtBr at 79.3°			
Benzene	0.744	34.5	17.5
Chlorobenzene	2.72, 2.72	35.2	16.45
Bromobenzene	3.22, 3.28	34.9	16.30
Iodobenzene	5.22, 5.32	33.2	16.70
Reagent EtBr at 99.4°			
Benzene	2.84	34.8	
Chlorobenzene	9.50, 9.66	35.2	
Bromobenzene	11.6, 11.2	35.3	
Iodobenzene	19.3, 18.7	33.0	
Reagent EtI at 80.0°			
Benzene	4.26, 4.48	36.0	15.80
Chlorobenzene	11.8, 12.5	30.8	16.91
Bromobenzene	17.0, 16.6	33.2	15.90
Iodobenzene	26.9, 28.0	33.2	15.90
Reagent EtI at 100.0°			
Benzene	14.5, 14.9	36.3	
Chlorobenzene	45.0, 45.1	31.0	
Bromobenzene	56.8, 57.4	33.4	
Iodobenzene	92.4, 93.5	32.2	

The most interesting observation that can be made from our data was that the solvent effect on the rate constant increases in the order iodobenzene > bromobenzene > chlorobenzene > benzene, but several additional observations may also be made.

(1) The rate constant varies with the polarizability of the substituent group on the benzene ring of the solvent. This is showed by the linear plot in Fig. 2.

(2) The relative rates do not seem to depend upon the temperature. The reaction of ethyl iodide and pyridine is 6.25 times as fast in iodobenzene as in benzene at 80° and 6.31 times as fast at 100°. For ethyl bromide, the numbers are 7.08 and 6.69 at the same temperatures.

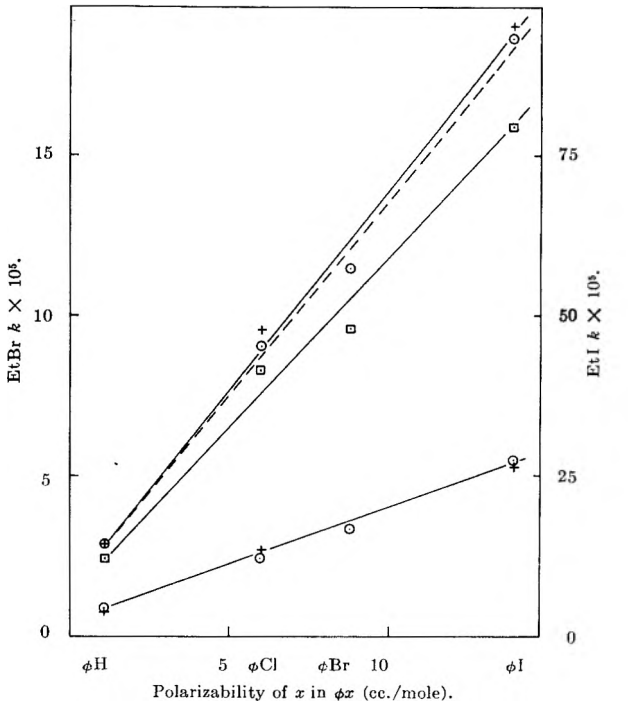

Fig. 2.—Polarizability of the solvent *vs.* rate constant: circles, ethyl iodide + pyridine; crosses, ethyl bromide + pyridine; squares, ethyl iodide + triethyl amine; the scale on the right is exaggerated 5:1 for this reaction. The upper curves are reactions at 100°; the lower curve, 80°.

(3) The nature of the group displaced does not seem to have a great influence on the relative reaction rate constants. This can be seen by comparing the relative rate increases for ethyl iodide and ethyl bromide in the solvents benzene and iodobenzene. With ethyl bromide and pyridine, $k_{\phi I}/k_{\phi H}$ is 7.08, while the same ratio is 6.25 for the reagent ethyl iodide at 80°. At 100°, the ratios are 6.69 and 6.31, respectively.

(4) The nature of the amine does not seem to have a great effect on the relative reaction rate constants. The data of Grim, Ruf, and Wolf[7] for the reaction of triethylamine and ethyl iodide are plotted in Fig. 2. The curve is similar to those for the reaction of pyridine, and the ratio $k_{\phi I}/k_{\phi H}$ is 6.41 at 100°.

What the fundamental causes for the rate increases observed with the change of solvent from benzene to iodobenzene? Some of the possibilities are the effect of electrostatic forces on the activity coefficients of the reagents and the transition state, solvation of the reagents and the transition state by forces other than electrostatic forces, catalysis by salts, and special salt effects in solvents of low dielectric constant.

The salt effects and the effect of electrostatic forces as the major causes for the rate constant increases were rejected for the following reasons.

(1) The only salt present in the reaction mixture is the reaction product, triethylpyridinium halide. If this is to cause the increases by means of surface catalysis or through the effect of its ionic strength, the rate should increase as the concentration of the product increases. The reaction should follow the course of an autocatalytic reaction, and the rate constant would increase during a run. There should be considerable curvature during the run of our plot of $1/C$ *vs.* time. We did not observe such curvature. A second argument is that catalysis depends strongly on the amount

of catalyst present. Changes in initial concentration would cause a different amount of catalyst to be formed when the reaction was proceeding. The data of Norris and Prentiss indicate that the changes in initial concentration do not have a large effect, but one of the order of 10%. These effects are not large enough to account for our factor of 6–7.

(2) Salt effects of considerable magnitude have been observed by Winstein and co-workers.[18] They have suggested that the salt effects can become very large in solvents of low D. Rate increases of factors of more than 10 have been observed for the ionization of alkyl toluenesulfonates. In Winstein's relationship

$$k = k_0 [1 + b(\mathrm{LiClO_4})]$$

the magnitude of b is a measure of the salt effect. In solvents of comparable D, for example acetone and acetic acid, the nonhydroxyllic solvent has the larger b. Generally, the larger b value is associated with lower D for solvents of the same type. For the special salt effect to apply to our data, the b values would have to be in the order iodobenzene > bromobenzene > chlorobenzene > benzene. This is not the order of D, which is given in Table I. Further, the solvent of lowest D should have the highest rate if the special salt effect applies, but we observe the lowest rate for benzene.

(3) The quantitative relationship between electrostatic forces and the rate constant is given by equation 1. This equation represents the effect of electrostatic forces on the activity coefficients of the species present in the reaction mixture. If the assumption is made that ϕ is small compared to the remainder of the equation, a plot of ln k *vs.* $[(D - 1)/(2D + 1)] = X$ should give a straight line. If $\omega_*^2/r_*^3 > (\omega_A^2/r_A^3 + [\omega_B^2/r_B^3])$, then the second term of the equation is positive, and the reaction rate constant increases with increasing D. This seems reasonable, for the dipole moment of the transition state, in which ionic bonds are present, should be much greater than the dipole moments of the uncharged reagents. Tommila[13] has observed this relationship with mixed solvent systems in which acetone was one component of the binary solvent system. Fuoss and Wanatabe[14] found the same relationship for the mixed solvent propylene carbonate–diphenyl ether. Fuoss has summarized the objections to the universal application of this equation however. If equation 1 is followed, then all solvents with $D > 30$ should have the same solvent effect on a given reaction. This follows from the observation that X varies from 0 to 0.476 as D varies from 1 to 30; further increase in D to infinity causes only a slight increase in X to 0.50. Fuoss noted exceptions to these deductions in that the rate constant for the reaction of butyl bromide with pyridine in tetramethylenesulfone (D = 42) is about twice that in propylene carbonate (D = 65). He attributes the unusually high rate in tetramethylenesulfone to "specific short range forces which depend on structure in a way and are superimposed on the longer range electrostatic forces." In the present research, the change in D is small and the observed changes in rate constant do not parallel the changes in the dielectric constant factor X. Electrostatic forces alone cannot explain our rate changes. It is interesting to note in passing that equation 1 seems to hold for mixed solvents. Glasstone, Laidler, and Eyring[19] have suggested that the transition state in the mixed solvent acetone–benzene is solvated by only one of the molecules, acetone. This suggests that the short range nonelectrostatic term which is presumably due to solvation, remains constant, while the D of the bulk of the solution varies. These are the conditions for the linear relationship between ln k and X.

The linear relationship given in Fig. 2 indicates that the polarizability of the solvent is the determining factor in the observed rate increases. Caldin and Peacock have suggested that the high rate constants for the Menschutkin reaction in aromatic solvents is due to the greater polarizability of the benzene ring as compared to aliphatic solvents. We have plotted the polarizability of the substituent group on the ring, rather than that of the entire ring. The solvation of the transition state, as proposed by Fuoss, may be identified as the rate influencing factor and Fuoss "short range forces" are identified as London Forces.

In order to make an estimate of the magnitude of the London force energy of solvation, it is first necessary to know the site of solvation in the reagents and the transition state and the number of molecules of solvation. Gonikberg has provided evidence that the transition state is solvated and that not more than two molecules of solvent are present in the transition state.[20] Since the reagents were pyridine and two different alkyl halides, a reasonable hypothesis was that the common reagent, pyridine, was the site of solvation. As the pyridine molecule approaches the carbon atom of the alkyl halide, it develops a partial positive charge. This charge could attract solvent molecules through an ion-polarizable solvent molecule interaction. A study of the models showed that two solvent molecules could be conveniently placed in the transition state as nitrogen solvating molecules. However, this site does not seem to be tenable for the reaction of triethylamine in the same solvents. In this case, the four ethyl groups completely cover the nitrogen, so that there is no space for the solvent molecules to occupy. Since the relative solvent effect is the same for the two amines, solvation of the nitrogen atom seems to be ruled out. The other likely site is the halogen atom, which also develops charge in the transition state, and which is not sterically hindered. The fact that the solvent effect is the same for both the alkyl iodide and the alkyl bromide seems to be a powerful argument against this site, for the absolute magnitude of the polarizability of the iodine atom and the iodide ion are greater than those for bromine. The surprising observation is that the per cent increase in polarizability in going from the atom to the transition state is the same for iodine and bromine. The figures are $I \rightarrow I^{-1/2} = 13.6 \rightarrow 16.4$, or 18.9%, and $Br \rightarrow Br^{-1/2} = 8.8 \rightarrow 10.7$, or 21.6%. If the change in rate constant is due to the difference in solvation of the halide ion in the transition state and the halogen atom of the reagent, the per cent increase should be the same for both halogens. Some support for the halogen as the site of solvation is given by spec-

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tral studies. Popovici and Popovici[21] have observed that there is a shift in the center of the ethyl iodide absorption band which is proportional to ln k for the reaction of ethyl iodide and triethylamine in nonhydroxylic solvents. The per cent increase in polarizability for the bromine atom is slightly larger than that of the iodine atom. While this is in the expected order, for the solvent effect on ethyl bromide is slightly greater than for ethyl iodide, no quantitative significance is attached to the per cent increase.

Calculations of the London energy of interaction between the polarizable solvent molecule and the leaving halogen atom were made with the aid of equation 2.[22]

$$U = 2.1 + \frac{3}{2}\frac{\alpha_A \alpha_B}{R^6}\left(\frac{I_A I_B}{I_A + I_B}\right) \quad (2)$$

U is the energy of interaction; α_A and α_B are the polarizabilities of the groups involved; I_A and I_B are the ionization potentials; R is the distance between the centers of the groups. The following assumptions were made in the calculations. (a) The dielectric constant was 1. (b) The average values of the radius, ionization potential, and the polarizability could be used for the transition state. The numerical values for the constants were taken from Pauling,[23] Moellar,[24] Rice,[25] and Ingold.[26] (c) One molecule of solvent was in the transition state.

The results of these calculations are given in Table III. The energies given in columns 2 and 3 were obtained with the van der Waal's radii, while those in the 4th column were obtained with an R 0.1 Å. smaller. The ΔH of solvation is obtained by subtracting the values in column 2 from columns 3 or 4. The ΔH for transition state$_1$ has a positive value, while that of the transition state$_2$ with the smaller R has the expected negative value. If the assumption is made that the ΔS^* remains constant, the differences in ΔH give the $\Delta\Delta F^*$. The experimental values for the reaction are given in the last column. The agreement is reasonable, and indicates that the London energies of interaction are of the correct order of magnitude to account for the observed rate changes.

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TABLE III

ENERGY OF SOLVATION OF ETHYL BROMIDE IN VARIOUS SOLVENTS

Solvent	(−)Energy of solvation[a] Reagent EtBr	Trans.[b] state$_1$	Trans.[c] state$_2$	ΔH^d	$\Delta\Delta F^d$ Calcd.	$\Delta\Delta F^e$ Obsd.
Benzene	5.9	5.5	6.7	0.8	0	0
Chlorobenzene	13.4	12.6	14.9	1.5	0.7	0.8
Bromobenzene	15.1	14.4	16.8	1.7	0.9	1.1
Iodobenzene	16.4	15.8	18.2	1.8	1.0	1.3

[a] Energy of solvation for one molecule of solvent. All energies are in kcal./mole. [b] The radius is the sum of the van der Waal's radii. [c] The radius is the sum of the van der Waal's radii minus 0.1 Å. [d] For trans. state$_2$. [e] Temperature, 80°.

The effect of the solvent on the reaction rate constant seems to involve H bonding, electrostatic forces, and London forces. Any one of these may be dominant under a given set of conditions. It does not seem likely that a single analytical expression with one physical property of the solvent as the variable can represent the solvent effects of an entire range of solvents. Vorob'ev and Titova[27] have suggested that the loss of an alcohol of solvation accounts for the different solvent effects in alcoholic solvents. Caldin and Peacock's classification of the reactions into hydroxylic, aliphatic, and aromatic type solvents suggests the importance of H bonding. Kosower's Z correlates the rate constants of alcohols, but he points out that the rate in acetone is too great by a factor of 22. It seems probable that the solvation of the leaving halide has become important rather than the solvation of the amine reagent. Unfortunately, Z values are not available for the aromatic solvents, so that it is not possible to see if acetone is a single exception, or if it represents a general class. Fuoss has pointed out the limits of equation 1 in which ϕ is assumed to be constant. It appears that the effect of nonelectrostatic forces is quite important in nonhydroxylic solvents and these may be the major cause for the lack of correlation of solvent effects in pure solvents. The conclusion that there is no single measure of the solvation capacity is disappointing, but perhaps not unexpected.

Acknowledgment.—The author is grateful to Professor Rolf Huisgen and grateful for the hospitality of the Institut für Organische Chemie der Universität München, where the writing of this paper was completed.

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Addition Reactions Induced by Ionizing Radiation. I. Bromotrichloromethane to Butadiene

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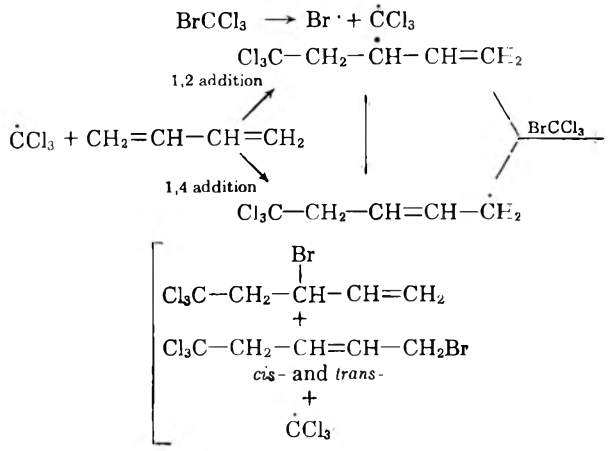
The addition reaction of bromotrichloromethane to butadiene induced by ionizing radiation has been studied. The products were characterized, and their stereoconfigurations were determined by means of infrared and Raman spectroscopy. The kinetics were investigated over the temperature range 25 to 40°; the dose rates ranged from (1.4 to 6.5) × 10^3 rads $min.^{-1}$; and the mole ratio of bromotrichloromethane–butadiene was varied from 1:1 to 46:1. It was observed that the adducts obtained were primarily 1,4-*trans*. The reactions are free radical chain reactions as evidence by the G values (200 to 800 molecules/100 e.v.), by the dose rate dependences (rate $\propto I^{0.5}$; $G \propto I^{-0.5}$), and by a positive activation energy (ΔE_a = 5.5 kcal. $mole^{-1}$). It also has been found that the reaction is zero order in butadiene.

The addition of bromotrichloromethane to butadiene is believed to be a chain reaction consisting of the following steps.



In peroxide- and in light-initiated reactions at 60–80°, Kharasch and co-workers[1,2] obtained ~75% 1,4-addition product and ~25% 1,2-addition product. However, the stereochemistry of the products (*cis–trans*) has not been investigated. In the polymerization of butadiene and other dienes,[3] the relative amounts of 1,2-, *cis*-1,4, and *trans*-1,4 structure in the polymers have received much study. It has been found that the amount of 1,4-*trans* configuration increases with decreasing reaction temperatures.

Several free radical chain reactions induced by ionizing radiation have been reported in the literature.[4–8] The advantage of studying the previously described addition reaction when initiation is induced by radiation lies in the fact that a much wider range of temperatures, especially lower temperatures, can be employed for the reaction. This provides a convenient way of studying at lower temperatures of the isomer distribution in the products. This paper deals with the addition of bromotrichloromethane to butadiene initiated by X-rays at 25–40° and is concerned with the stereochemistry of the products as well as with the reaction kinetics.

Experimental

Materials.—Research grade butadiene (purity, 99.35%) of Phillips Petroleum Co. was employed. Bromotrichloromethane (Eastman Kodak, practical grade) was fractionated (b.p. 104°); its purity was determined by gas chromatography.

Radiation Source.—X-Rays were obtained from a 250-kv. potential X-ray machine (General Electric Maxitron-250) operated at 6–30 ma., and filtered through 1 mm. each of aluminum and copper. The output of the machine was constant within 3–5%.

Dosimetry.—Dosimetry was conducted by using ferrous sulfate solution in the same reaction vessel as that employed in the radiation of experiments. Since filtration of 1 mm. of aluminum plus1 mm. of copper was used, essentially no energy below about 40 kev. was involved, and the average energy transmitted by the filters was determined previously to be about 150 kev.[9] Thus, it was possible to proceed from ferrous sulfate values in the aqueous system to dose rate values in the various nonaqueous systems by using the mass absorption coefficients at 150 kev. for the aqueous and nonaqueous systems ignoring any contribution from photoelectric effect.[10] Different dose rates were achieved by varying the current with the sample being placed at a fixed distance from the target.

Identification of Products.—The products were identified by means of boiling point, elementary analysis, infrared spectroscopy (a Beckman IR-4 was used), refractive index, and gas chromatography (Podbielniak 9580; column packing, 12 ft. of 15% w./w. Hy-Vac silicone grease on 60/80-mesh Chromosorb-W; column temperature, 166°; gas pressure, 15 p.s.i.g. of helium). The configuration of the main product was determined by means of Raman spectroscopy employing a photoelectric spectrometer described previously[11] as well as by infrared.

Method of Following Kinetics.—The initial reaction rates (first 10–15%) were followed by means of optical absorption in the near infrared employing a Cary ultraviolet spectrometer Model 14. A reaction vessel, as shown in Fig. 1, consisting of a flattop cell for irradiation connected to two Pyrex optical cells of different thicknesses (for different concentrations) and provided with a side tube for sealing off was employed. Thus the contents can be transferred into each cell without having to open the system. Known amounts of reactants were charged into the radiation cell. (At atmospheric pressure and 25°, approximately 1 mole of butadiene can be dissolved in 1 mole of liquid bromotrichloromethane.) The vessel was then attached to a vacuum line and the air removed by alternate freezing and melting three times. It was sealed off at the side tube while the mixture was frozen and under a vacuum of 10^{-2}–10^{-3} mm. The vessel was then positioned underneath the X-ray target. The radiation cell containing the reaction mixture was centered directly under

(1) M. S. Kharasch and M. Sage, *J. Org. Chem.*, **14**, 537 (1949).
(2) M. S. Kharasch, E. Simon, and W. Nudenberg, *ibid.*, **18**, 328 (1953).
(3) C. Walling, "Free Radical Reactions in Solutions," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 228–232.
(4) L. C. Anderson, B. G. Bray, and J. J. Martin, International Conference on the Peaceful Uses of Atomic Energy, Vol. 15, United Nations, New York, N. Y., 1956, p. 235.
(5) A. M. Lovelace and D. A. Rausch, Wright Air Development Command Technical Report S-5-461, April, 1956.
(6) T. S. Nikitina and Kh. S. Bagdasaryan, *J. Phys. Chem., USSR*, **31**, 704 (1957).
(7) E. Heiba and L. C. Anderson, *J. Am. Chem. Soc.*, **79**, 4940 (1957).
(8) A. Fontijn and J. W. T. Spinks, *Can. J. Chem.*, **35**, 1384–1413 (1957).
(9) Private communication from Dr. L. A. Siegel of these laboratories.
(10) G. J. Hine and G. L. Brownell, Ed., "Radiation Dosimetry," Academic Press, Inc., New York, N. Y., 1956.
(11) R. F. Stamm and C. F. Salzman, Jr., *J. Opt. Soc. Am.*, **43**, 126 (1953).

the target with the flat side up; the optical cells were shielded from radiation by lead sheets so as to prevent them from discoloring. The distance from the target to the surface of the reaction mixture was 10 cm. A constant temperature bath (precision, ±0.2°) was then raised so that the liquid level of the bath was above that of the reaction mixture.

Butadiene gives several peaks in the near infrared of which the strongest and sharpest is the peak at 1.63 μ (6134 cm.$^{-1}$). Bromotrichloromethane is transparent in the near-infrared region, and the reaction product was also found not to interfere at 1.63 μ. The reactions were followed by the decrease of absorbance ($A_{1.63}$) at 1.63 μ after appropriate intervals of irradiation. The disappearance of butadiene was calculated from an analytical working curve based on standards whose spectra were taken while employing the same cell thickness and the same parameters of the spectrometer.

Formation of 1:1 Adduct and 1:2 Adduct.—Two products have been isolated from reactions covering a wide range of conditions such as different mole ratios of bromotrichloromethane to butadiene (in this paper, unless stated to the contrary, the term mole ratio refers to moles of bromotrichloromethane to moles of butadiene), different dose rates, different total irradiation time (total dose), and different temperatures (25–40°).

The 1:1 adduct was a colorless material with a sharp odor, b.p. 44° (0.05 mm.); $n^{25}D$ 1.5318. A gas chromatogram of the product obtained from a 3:1 starting mole ratio showed a big peak representing 96.3% of the total area with a small peak (2.3% area) immediately before it and another small peak (1.4% area) immediately after it. These are attributed to isomers and will be discussed in the next section.

Anal. Calcd. for $C_5H_6BrCl_3$: C, 23.83; H, 2.40; mol. wt., 253.39. Found: C, 24.05; H, 2.55; mol. wt., 254.6.

The 1:2 adduct was a colorless material with a sharp odor, b.p. 95.5° (0.1 mm.).

Anal. Calcd. for $C_9H_{12}BrCl_3$: C, 35.53; H, 3.95; mol. wt., 306.49. Found: C, 35.12; H, 3.82; mol. wt., 304.5.

It was found that the relative amounts of 1:1 adduct and 1:2 adduct in the products varied with the mole ratio and the total reaction time. An increase in irradiation time increased the total conversion; it also increased the relative amount of the 1:2 adduct in the product mixture. Likewise, a lower mole ratio favored the formation of the 1:2 adduct. When the mole ratio of the reactants was 1:1, it was found that at a conversion below 15% there was no 1:2 adduct formed in the product mixture. For higher mole ratios, *e.g.* 6:1, essentially no 1:2 adduct was formed even at a high conversion (60%). It should be mentioned that the conditions which favored the formation of the 1:2 adduct also favored that of nondistillable polymeric substances. Thus, in experiments where a high total dose and a low mole ratio were employed, a considerable amount (10–20%) of polymeric residue was formed. In all experiments where the products were used for determination of configuration, material balance was maintained so that no fraction was lost, and the true ratio of the isomers was obtained. In kinetic studies, all the reactions were carried out so as not to exceed 15% conversion, and, in all these runs, the 1:1 adduct was the only product.

Results

Determination of Configuration by Infrared and Raman Spectroscopy.—From chemical analysis it was demonstrated that the best fraction of what was thought to be the 1:1 adduct of bromotrichloromethane to 1,3-butadiene probably had the empirical formula $C_5H_6BrCl_3$. If the addition proceeded in a straightforward fashion, the 1-1 adduct is expected to be 1-bromo-5,5,5-trichloro-*trans*-2-pentene, or 4-bromo-5,5,5-trichloropentene-1, or 1-bromo-5,5,5-trichloro-*cis*-2-pentene. At room temperature the *cis* isomer should be the least probable product.

By studying the infrared and Raman spectra of a sample of 1:1 adduct obtained from a reaction mixture having a mole ratio of 1:1, it was possible to show that the major component was the 1,4-*trans* isomer and that the main impurity probably was a monosubstituted ethylene. The details follow.

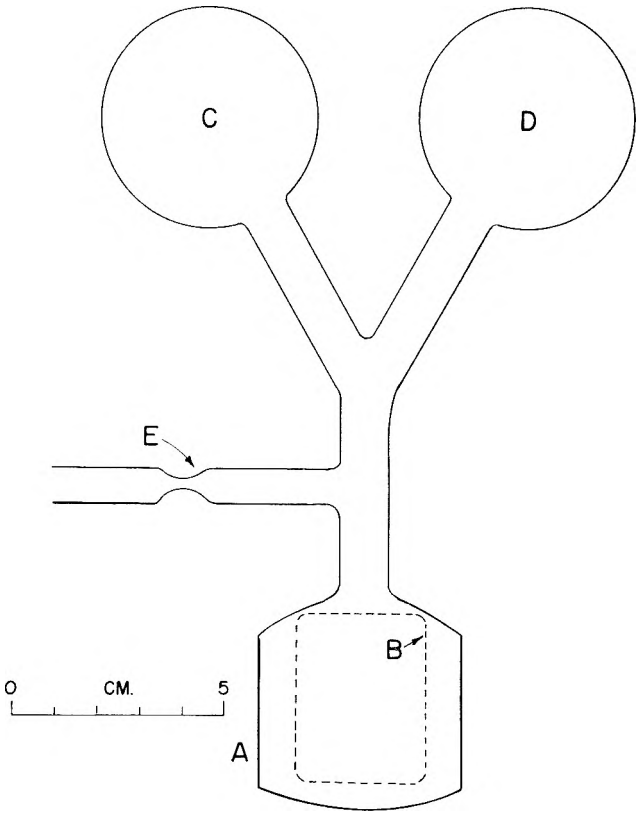


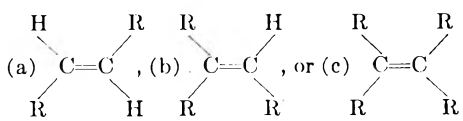
Fig. 1.—Irradiation vessel with attached optical cells. A is irradiation cell with flattened window (B). C and D are Pyrex absorption cells with optically flat windows and path lengths of 10 mm. and 2 mm., respectively. E is constriction for sealing off after degassing.

Infrared.—1. A strong band at 970 cm.$^{-1}$ was assigned to an out-of-plane H-bending mode of a *trans*-disubstituted double bond. (The region from 675–730 cm.$^{-1}$ normally contained in out-of-plane H-bending mode attributable to a *cis*-disubstituted double bond was confused by intense asymmetrical C—Cl stretching frequencies.)

2. Two strong bands normally employed to show the presence of a monosubstituted ethylene should appear at 990 cm.$^{-1}$ (C=C twist) and 925 cm.$^{-1}$ [$\begin{matrix}H\\R\end{matrix}$C=$CH_2$ wag]. These bands were missing. However, the region near 925 cm.$^{-1}$ was partly obscured by the side of a strong band centered at 944 cm.$^{-1}$. From this it was possible to state only that the content of RCH=CH_2 was less than 15%.

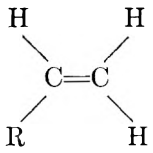
3. The C=C stretch region contained only very weak bands which were of little value in a positive sense.

Raman.—1. There is a very strong C=C stretch at 1670 cm.$^{-1}$ and a much weaker (though well resolved) C=C at 1640 cm.$^{-1}$. From data presented in a review article[12] on the Raman spectra of olefins, it is seen that the line at 1670 cm.$^{-1}$ could arise from the following configurations.



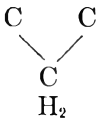
(12) J. Goubeau, *et al.*, *Angew. Chem.*, (A) **59**, 87 (1947), Beiheft Nr. 56 (Table 20).

2. The weak Raman lines at 1640 and 1405 point strongly to a monosubstituted ethylene as the minor component. Admittedly, the frequency of 1405 cm.$^{-1}$ is low for the $=CH_2$ deformation and should be about 1415. However, the band is quite weak and is really not clearly resolved from the low λ side of 1426; thus the measurement of the peak is rendered uncertain. Also there are a few compounds possessing the structure

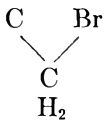


whose Raman spectra have the line in question near 1405 cm.$^{-1}$, *e.g.* allyl alcohol (1407 cm.$^{-1}$). (If this 1405 band showed up in the infrared spectrum, it would be evidence for a *cis* structure. However, there is nothing definite at this position in the infrared spectrum on 25- or 60-min. runs.) As another possibility, if the Raman line at 1405 cm.$^{-1}$ were assigned to the deformation of the $=CH_2$ group of a conjugated system, there would be further complications in the C=C region which are not present. (The C=C stretch of the *cis* isomer would lie at 1647–1650 cm.$^{-1}$ but does not appear in the Raman spectrum.)

Infrared and Raman.—1. The infrared and Raman bands at 1442 and 1292 cm.$^{-1}$ are the CH_2-deformation and CH_2-wagging frequencies of one or more methylene groups.



2. The infrared and Raman bands at 1426 and 1208 cm.$^{-1}$ are the same modes of the following group.



3. The presence of strong infrared bands in the region 710 to 830 cm.$^{-1}$ indicates that a $-CCl_3$ group *could* be present. The presence of a strongly polarized Raman line at 394 cm.$^{-1}$ also indicates that a CCl_3 group (390–430 cm.$^{-1}$) could be present.[13]

4. The weak infrared band and medium intensity Raman line at 1310 cm.$^{-1}$, (probably originating from an in-plane deformation involving two hydrogens) indicate a *trans* structure.

The spectroscopic data, when considered in conjunction with the empirical formula data and the types of structures to be anticipated lead us to conclude that the major component is the 1,4-*trans* isomer, and the minor component is a monosubstituted ethylene presumably attributable to the 1,2-mode of addition. The assignment of a structure to the minor component practically on the basis of the cm.$^{-1}$ value of one line, the C=C stretch, may appear unjustifiable. However, the frequency of this C=C mode belonging to the type of structure postulated is well founded.

Probable Concentrations.—The intensities of the C=C Raman lines (1670 and 1640 cm.$^{-1}$) were used to obtain concentration ratios of major to minor components. For the product (1:1 adduct) derived from the 1:1 starting mole ratio, the average ratio of C=C peak intensities from three photoelectric spectra was 6.57:1 after correcting for overlapping. The Raman spectrum of the fraction obtained from the distillation of the product formed from a reaction mixture having an initial mole ratio of 3:1 gave a lesser amount of the compound having the C=C at 1640 cm.$^{-1}$ (no longer clearly resolved), and an intensity ratio of 15.6:1 (average from two spectra). When the two compounds are present in equal concentrations, the C=C of the monosubstituted ethylene should be about 10% more intense than that of the *trans* isomer.[12] These assumptions lead to concentration levels of 88 and 12% for the fraction obtained from the 1:1 starting ratio, and 94.5 and 5.5% for the fraction derived from the 3:1 starting ratio. The analytical results on the 1:1 adduct achieved by vapor phase chromatography (three components having per cents of 96.3, 2.3, and 1.4%) are not necessarily at variance with those achieved spectroscopically since identical samples were not examined by both techniques. The spectroscopic results show that the major component is a *trans*-substituted C=C and that a minor component is present which probably is a monosubstituted ethylene and not a *cis* C=C. The concentrations found by Raman effect are only semiquantitative since no working standards were available. However, the changes in concentration levels established by Raman effect in the 1:1 adduct derived from 1:1 and 3:1 starting mole ratios are definite. From the fact that three peaks were measured in the sample of 1:1 adduct studied by v.p.c., we assume that they are attributable to *trans*, 1,2-, and *cis*, respectively. If there were 2–3% of the *cis* isomer present, the C=C line would not have been observed in the Raman spectrum since it would be at 1650 cm.$^{-1}$ and would lie even closer to the intense *trans* C=C stretch. From the degree of fractionation that could be achieved and from the data which were obtained, no more precise statements can be made by the authors regarding the concentrations of these isomers. For the 1:1 adduct from the 3:1 starting mole ratio, the agreement between v.p.c. and Raman effect is as good as could be expected.

Since the compound is probably 94–95% pure, the spectroscopic data are given in Table I. The infrared bands occur at essentially the same positions as the Raman lines with the following exceptions. Above 600 cm.$^{-1}$, the weak Raman lines 1185, 1273, 1405, and 3127 cm.$^{-1}$ do not appear in infrared. Conversely, the infrared bands at 1550, 1685, and 1723 cm.$^{-1}$ (plus some higher overtones and combinations) do not appear in the Raman spectrum. The compound is known to be impure, thus there seems to be no point in attempting to assign all the bands. However, this much should be stated: (1) The total number of Raman lines is 49 of which at least 2 belong to an impurity. Accordingly, there are at least 8 lines present in addition to the 39 ($3N - 6$ where N is equal to 15, the number of atoms) which should appear as fundamentals. (2) In the *trans* configuration, there might be a plane of symmetry present in which case there would be 24 vibrational modes of type A′ symmetrical to the plane (perpendicular-type bands in infrared, polarized in

(13) H. Gerding and H. G. Haring, *Rec. trav. chim.*, **47**, 1401 (1955).

TABLE I

RAMAN SPECTRUM OF 1-BROMO-5,5,5-TRICHLORO-*trans*-2-PENTENE[a] (PURITY, 94–95%)

$\Delta\nu$[b]	I[c]	ρ_n[d]	$\Delta\nu$	I	ρ_n	$\Delta\nu$	I	ρ_n
150	0.9	0.51	708	16.9	0.74	1273	5.2	0.78
160	11.0	.31	773	20.2	.65	1292	10.8	.45
178	5.9	.73	797	15.8	.61	1310	14.3	.38
204	10.4	.61	837	4.2	..	1340	1.9	..
235	9.9	.61	865	2.1	..	1405[g]	1.8	..
287	28.0	.67	887	2.3	..	1426	9.5	.70
322	24.9	.40	943	4.2	.82	1442	7.8	.66
347	16.9	.30	975	2.4	..	1640[g]	9.1	P
394	14.4	.15	1027	10.9	.88	1670	119.8	0.33
407	21.5	.27	1065	2.3	..	2787	45.2	.18
428	3.4	.36	1087	7.7	.61	2830	5.5	.26
483	18.5	.21	1149	20.2	.68	2857	2.9	..
516	2.9	..	1185[h]	4.6	..	2872	11.6	.14
573	28.0	.14	1208	72.0	.44	2920	28.4	.13
612	67.4	.29	1226	13.1	.77	2967	38.0	.24
651[h]	..	..	1252	0.7	..	3023	23.6	.43
						3127	6.2	.17

[a] Toronto type spiral arc, Hg λ 4358.35 Å. excitation, $NaNO_2$ filter, 5 cm.$^{-1}$, spectral slit width, spectrum recorded photoelectrically. [b] $\Delta\nu$, cm.$^{-1}$ (vac.). [c] $I = 100[I(\Delta\nu)/I(CHCl_3, \Delta\nu\ 667\ cm.^{-1}) \times n^2(CHCl_3)/n^2(X)]$; direct photoelectric peak intensities. [d] Depolarization values obtained by method of Edsall and Wilson[e] using modification of Rank and Kagarise.[f] [e] J. T. Edsall and E. B. Wilson, Jr., *J. Chem. Phys.*, 6, 124 (1938). [f] D. H. Rank and R. E. Kagarise, *J. Opt. Soc. Am.*, 40, 89 (1950). [g] Believed due to isomer arising from 1,2-addition. [h] Shoulders; poorly defined lines.

Raman effect) and 15 modes of type A″ antisymmetrical to the plane (parallel-type infrared bands, depolarized in Raman effect). Since all the Raman lines (save one weak line) are polarized, there probably is no plane of symmetry.

Kinetics.—The results on the standardizations of butadiene solutions in bromotrichloromethane of low (up to 6%), intermediate (6–10%), and high (10–25%) concentrations with regard to the absorbance [log (I_0/I)] at 1.63 μ are represented in Fig. 2. In all cases Beer's law was obeyed, and it was also verified that appropriate concentrations of bromotrichloromethane and of the 1:1 adduct did not vitiate the calibration plots.

Typical kinetic plots for the X-ray induced reaction between bromotrichloromethane and butadiene are

TABLE II

DATA FOR ADDITION OF BROMOTRICHLOROMETHANE TO BUTADIENE INITIATED BY X-RAYS (250 KV. POTENTIAL)

Mole ratio $BrCCl_3$:C_4H_6	Temperature, °C. ± 0.2	Dose rate[a] rads min.$^{-1}$	Rate × 10^3, moles kg.$^{-1}$ min.$^{-1}$	G value[b]
3.01:1	25	1447	1.22	797
3.08:1	25	3725	2.00	516
3.19:1	25	5977	2.44	394
0.95:1	25	5341	1.11	199
2.67:1	25	5898	2.62	428
4.69:1	25	6081	2.23	354
8.37:1	25	6187	2.54	382
18.4:1	25	6261	2.72	419
46:1	25	6300	2.59	397
2.70:1	32.5	5922	3.08	500
3.14:1	40	5973	3.54	572
2.67:1	40	5898	3.80	621

[a] Dose rate calculated, based on the composition of the starting material, from the dose rate obtained for Fe^{+2}–Fe^{+3} dosimeter under the same conditions. Filtration: 1 mm. of aluminum + 1 mm. of copper. [b] Molecules of butadiene reacted per 100 e.v. absorbed.

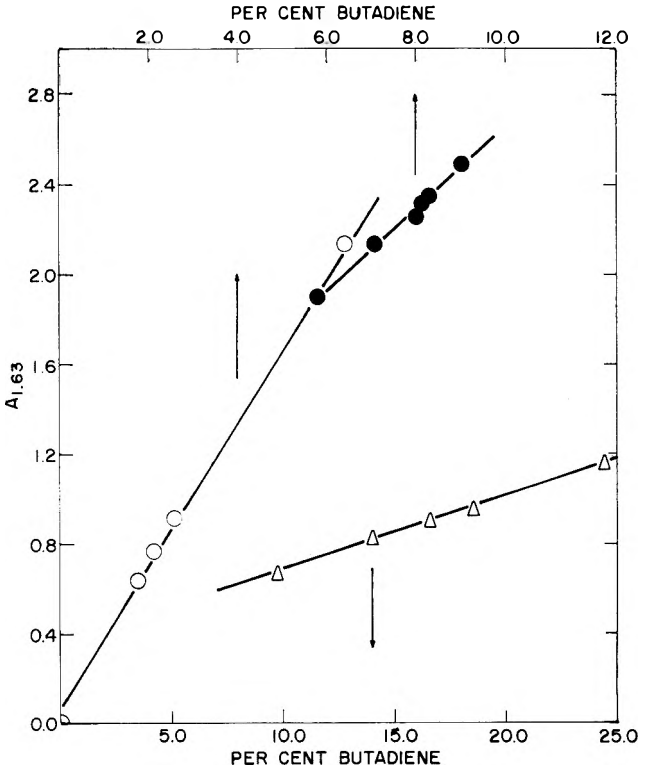


Fig. 2.—Standardization of butadiene solutions in bromotrichloromethane. ○: 10-mm. cell; geometrical slit width = 0.12 mm.; $A_{1.63}$ = 0.3309 (C_4H_6 %) + 0.049. ●: 10-mm. cell; copper screen filter (T = 0.1), slit width = 1.2 mm.; $A_{1.63}$ = 0.224 (C_4H_6 %) + 0.381. △: 2-mm. cell; slit width = 0.12 mm.; $A_{1.63}$ = 0.03362 (C_4H_6 %) + 0.3464.

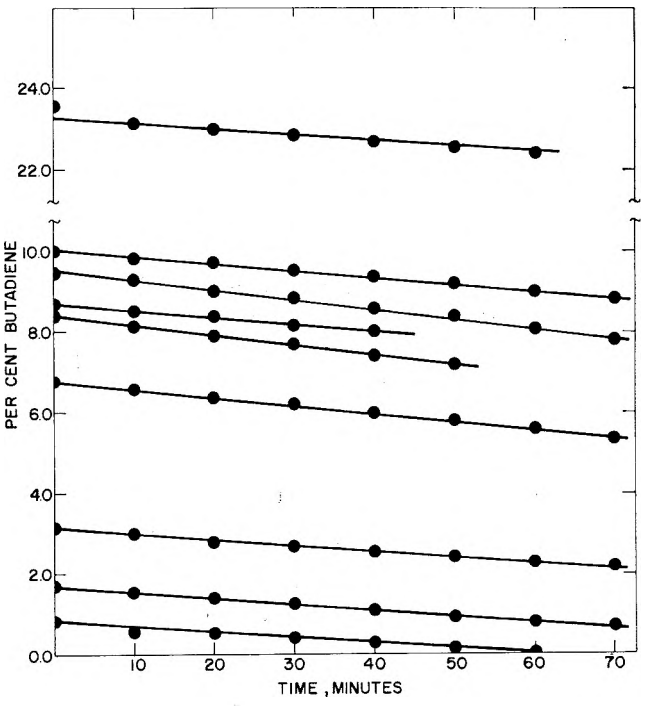


Fig. 3. Some typical plots in reactions between butadiene and bromotrichloromethane as expressed in disappearance of butadiene *vs.* time.

shown in Fig. 3. It is seen that the disappearance of butadiene is linear with time. The kinetic data covering various experimental conditions are recorded in Table II. For the reaction at 25° when employing a mole ratio of 3:1, it was found that the rate was pro-

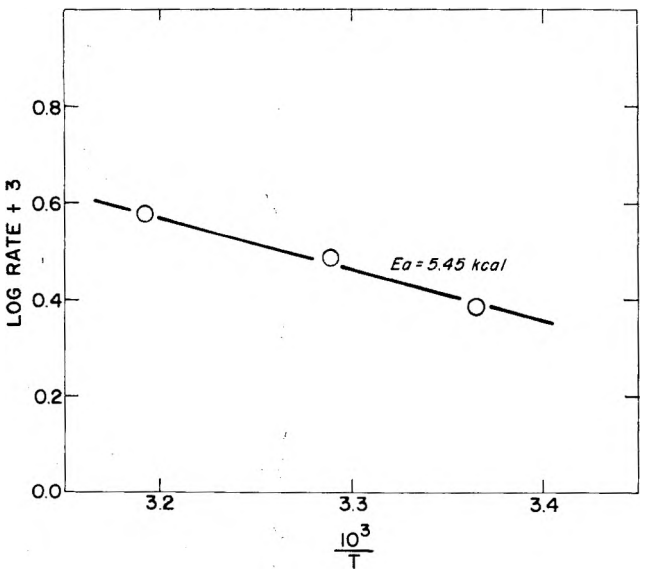


Fig. 4.—Arrhenius plot for addition of bromotrichloromethane to butadiene. Mole ratio, 3:1; dose rate: 6×10^3 rads min.$^{-1}$.

portional to the 0.5 power of the dose rate (rate $\propto I^{0.5}$) and that the G value was inversely proportional to the 0.5 power of the dose rate ($G\ I \propto -0.5$). Table III represents the dependence of rates on the mole

TABLE III

DEPENDENCE OF RATE ON THE CONCENTRATION OF BROMOTRICHLOROMETHANE[a]

Mole ratio $BrCCl_3$:C_4H_6	$[BrCCl_3]$, moles kg.$^{-1}$	Rate $\times 10^3$, moles kg.$^{-1}$ min.$^{-1}$
0.95:1	3.92	1.18
2.69:1	4.58	2.65
3.19:1	4.62	2.46
4.69:1	4.77	2.22
8.37:1	4.88	2.51
18.4:1	4.97	2.67
46:1	5.01	2.53

[a] Dose rate, 6025 rads min.$^{-1}$.

fraction of bromotrichloromethane at 25°. Figure 4 shows the Arrhenius plot involving temperatures of 25, 32.5, and 40°. An activation energy of 5.45 kcal. mole^{-1} was calculated.

Discussion

Based on the results of infrared and Raman spectroscopy described in a previous section it can be stated that the radiation-induced addition of bromotrichloromethane to butadiene in the vicinity of room temperature (25–40°) produces primarily the 1,4-*trans* 1:1 adduct. One might say that the addition is nearly stereospecific; however, the product obtained is also close to the equilibrium mixture of isomers which is high in *trans*-1,4. It is difficult to distinguish between addition products and isomerization product. It has also been found that higher ratios of bromotrichloromethane to butadiene favor the 1,4-*trans* addition as well as the formation of 1:1 adduct as was indicated by the results in the Raman and infrared analyses for the products obtained from reactions involving 3:1 and 1:1 mole ratios of the reactants. The fact that the ratio of 1:2 adduct to 1:1 adduct increases with reaction time suggests that the 1:2 adduct does not result from straight telomerization but rather from reaction of the 1:1 adduct with butadiene.

Because of the pressure, reactions of high mole ratios of butadiene to bromotrichloromethane (>1:1) have not been studied. Also, by the present analytical method the peak at 1.63 μ would be too intense to be measured by Cary 14 spectrometer even with a 1-mm. cell. It can be visualized that under those conditions other types of reactions, telomerization and polymerization, will be favored. Consequently, the rate of disappearance of butadiene probably will increase. It should be emphasized that in all the kinetic studies reported here the conditions were chosen so that the 1:1 adduct was the only product. Therefore, the rates reported are those pertaining to the following reaction.

$$BrCCl_3 + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow Cl_3C{-}CH_2{-}CH{=}CH{-}CH_2Br$$

$$(+\ Cl_3C{-}CH_2{-}\underset{\displaystyle Br}{\underset{|}{C}}H{-}CH{=}CH_2)$$

small amount

This reaction and other addition reactions of polyhalomethane–olefin systems initiated by light or peroxides have been demonstrated to be free radical chain reactions.[1-3] The kinetics have been reported for the systems bromotrichloromethane–cyclohexene and bromotrichloromethane–vinyl acetate for reactions initiated by light by Melville and co-workers[14] and Bengough and co-workers.[15] Our results show that the addition reaction of bromotrichloromethane to butadiene induced by X-rays is a free radical chain reaction as indicated by the high G values (number of molecules reacted per 100 e.v.), by the dose rate dependences, rate $\propto I^{0.5}$ and $G \propto I^{-0.5}$, and by the activation energy (5.45 kcal. mole^{-1}). These kinetic results together with the chemical and spectroscopic results discussed above lend credence to the following homogeneous kinetic scheme.

Initiation: $BrCCl_3 \xrightarrow{I} \dot{B}r + \dot{C}Cl_3$

Propagation: $\dot{C}Cl_3 + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{k_2} Cl_3CCH_2{-}\dot{C}H{-}CH{=}CH_2$

$$Cl_3CCH_2{-}CH{=}CH{-}\dot{C}H_2 + BrCCl_3 \xrightarrow{k_3} Cl_3CCH_2{-}CH{=}CH{-}CH_2Br + \dot{C}Cl_3$$

Termination: $2\dot{C}Cl_3 \xrightarrow{k_4} C_2Cl_6$

$$2Cl_3CCH_2{-}CH{=}CH{-}\dot{C}H_2 \xrightarrow{k_5} (Cl_3CCH_2{-}CH{=}CH{-}CH_2{-})_2$$

$$\dot{C}Cl_3 + Cl_3C{-}CH_2{-}CH{=}CH{-}\dot{C}H_2 \xrightarrow{k_6} Cl_3CCH_2{-}CH{=}CH{-}CH_2{-}CCl_3$$

The linear plots (Fig. 3) obtained for concentrations of butadiene *vs.* time indicate that under the conditions investigated (Table II) the reaction is zero order

(14) H. W. Melville, J. C. Robb, and R. C. Tutton, *Discussions Faraday Soc.*, **10**, 154. 224 (1951); **14**, 150 (1953).

(15) W. I. Bengough and R. A. M. Thomson, *Trans. Faraday Soc.*, **56**, 407, (1960); **57**, 1928 (1961).

in butadiene and that step 2 is not rate determining. Based on the results shown in Table III, from mole ratios of 1:1 to 3:1 the reaction is dependent on the concentration of bromotrichloromethane. However, it is difficult to draw any conclusion about the dependence on bromotrichloromethane at higher mole ratios. For a great change in mole ratio from 3:1 to 46:1 only results in a 30% change in the absolute concentration of bromotrichloromethane.

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Addition Reactions Induced by Ionizing Radiation. II. Bromotrichloromethane to Isoprene and 2,3-Dimethylbutadiene

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For comparison with the previously reported[1] addition of bromotrichloromethane to butadiene induced by ionizing radiation, similar reactions involving isoprene and 2,3-dimethylbutadiene have been investigated. In the isoprene reaction using three moles of bromotrichloromethane to isoprene, the 1:1 adduct was shown to contain products resulting from 72% 1,4-addition, 26% 4,1-addition, and a small amount of 1,2- and 4,3-additions. In the 2,3-dimethylbutadiene reaction, in all mole ratios studied, the product obtained was exclusively the 1:1 adduct resulting from 1,4-addition. The kinetics of the reaction were investigated over the temperature range 25 to 40°; the dose rate ranged from (1.4 to 6.3) $\times 10^3$ rads min.$^{-1}$; and the mole ratio of bromotrichloromethane:diene was varied from 1:2 to 19:1. It was observed that 2,3-dimethylbutadiene was the most reactive among the three dienes. The activation energies were 3.96 kcal. mole^{-1} for isoprene and 3.09 kcal. mole^{-1} for 2,3-dimethylbutadiene. The G values (molecules of diene consumed/100 e.v. absorbed) ranged from 450–1000 for isoprene and 1000–3650 for 2,3-dimethylbutadiene. The dose rate dependences were: for isoprene, rate $\propto$ dose rate$^{0.53}$; G $\propto$ dose rate$^{-0.48}$; for 2,3-dimethylbutadiene, rate $\propto$ dose rate$^{0.58}$; G $\propto$ dose rate$^{-0.42}$. In the cases of both isoprene and 2,3-dimethylbutadiene, the reactions are zero order in the diene over the entire range of mole ratios investigated.

The addition reaction of bromotrichloromethane to butadiene induced by ionizing radiation has been found to yield primarily the 1,4-*trans* adduct.[1] This investigation deals with the same type of reaction involving some substituted butadienes—2-methylbutadiene (isoprene) and 2,3-dimethylbutadiene. One of our purposes was to study the modes of addition of bromotrichloromethane to these dienes induced by ionizing radiation in the vicinity of room temperature. In the case of 2,3-dimethylbutadiene 1,2- and 1,4-additions similar to those described for the butadiene reaction[1] are possible, while in the case of isoprene all 1,2-, 1,4-, 4,1-, and 4,3-additions leading to various products are possible. Another purpose was that of comparing the reactions involving the unsubstituted and substituted butadienes from a kinetic point of view. It was hoped that these findings would help us to understand more clearly the mechanisms of the described reactions.

Experimental

Materials.—Research grade isoprene of Phillips Petroleum Co. was employed. Both 2,3-dimethylbutadiene and bromotrichloromethane were supplied by Eastman Kodak Co. and purified by fractionation shortly before use.

The radiation source, dosimetry, and other experimental procedures were similar to those described for the butadiene reaction.[1]

Gas–liquid chromatographic analyses were carried out using a Podbielniak Co. instrument, Model 9580. A 12-ft. column packed with 15% w./w. Hy-Vac silicone grease on 60/80-mesh Chromosorb-W solid support was used. The column temperature was 166°, and the helium gas pressure was 15 p.s.i.g.

N.m.r. spectra were obtained with a Varian V4300B high-resolution spectrometer at 40 Mc. in carbon tetrachloride solution with tetramethylsilane as an internal standard.

Identification of Products. Bromotrichloromethane–Isoprene Reaction.—Similarly to the bromotrichloromethane–butadiene reactions,[1] the bromotrichloromethane–isoprene reactions produced both the 1:1 adduct [$C_6H_8Cl_3Br$, b.p. 49.0–54.3° (0.025 mm.)] and the 1:2 adduct [$C_{11}H_{16}Cl_3Br$, b.p. 90° (0.075 mm.)].

Anal. (1:1 adduct). Calcd. for $C_6H_8Cl_3Br$: C, 27.05; H, 3.03; Cl, 31.81; Br, 23.89. Found: C, 27.58; H, 3.51. (1:2 adduct). Calcd. for $C_{11}H_{16}Cl_3Br$: C, 39.49; H, 4.82; Cl, 31.81; Br, 23.89. Found: C, 39.33; H, 4.70.

However, the 1:2 adduct was obtained only in cases where the initial concentration of isoprene was high (1:1 mole ratio) or when the mixture was exposed to radiation for a long time; it was also formed in smaller amounts in comparison with the corresponding butadiene reactions.[1]

The 1:1 adduct (I) formed in the addition reaction of bromotrichloromethane to isoprene (3:1 mole ratio) induced by X-rays (dose rate: 6×10^3 rads min.$^{-1}$) was shown by infrared and Raman spectroscopy to contain less than 5% terminal double bond resulting from either 1,2-addition or 4,3-addition. The vibrational spectra showed conclusively the presence of $—CH_2Br$ and $—CCl_3$ groups as major components. In addition, the cleanness of the Raman spectrum indicated that the 1:1 adduct contained either a single compound or else a mixture of compounds whose structures were such as to yield identical spectra for the several components. However, these methods were unable to distinguish between *cis* and *trans* structures with regard to the locations of the H atom and $—CH_3$ group on the residual double bond. Also, the amounts of 1,4- and 4,1-addition products could not be ascertained. A gas–liquid chromatograph of I showed two minor peaks, 0.5 and 1.5%, before two major peaks, 26.1 and 71.9%. The n.m.r. spectrum of I showed a mixture of the 1,4- and 4,1-adduct with the component possessing a doublet at lower field being present in greater concentration. The compound $Br—CH_2—CH=C(CH_3)—CH_2—CCl_3$ would be the more abundant component if the H resonances on the methylene adjacent to the Br atom appear at a lower field than those on the methylene adjacent to the $—CCl_3$ group. A preliminary look at the models $Br—CH_3$ and $Cl_3C—CH_3$ showed that the difference was very slight and possibly in the reverse order. Another approach was

(1) C. S. Hsia Chen and R. F. Stamm, *J. Org. Chem.*, **28**, 1580 (1963).

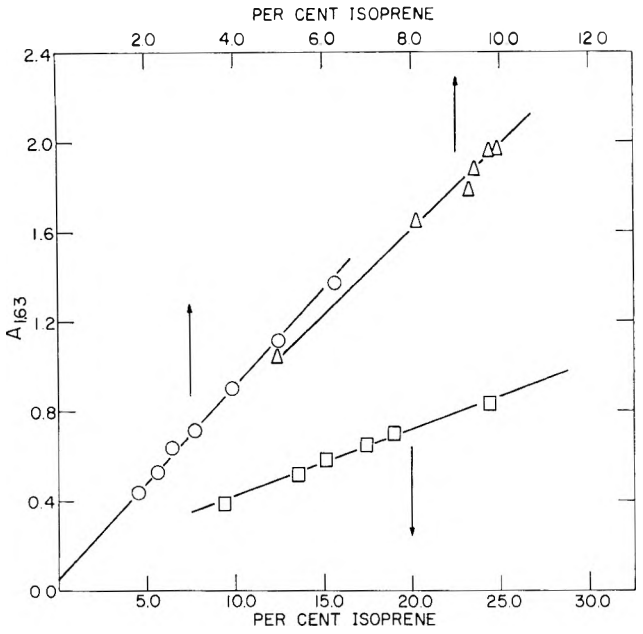

Fig. 1.—Standardization of isoprene solutions in bromotrichloromethane. ○: 10-mm. cell; geometrical slit = 0.12 mm.; $A_{1.63} = 0.2175$ (% C_5H_8) + 0.04100. Δ: 10-mm. cell; copper screen, $T = 0.1$; slit = 1.2 mm.; $A_{1.63} = 0.1886$ (% C_5H_8) + 0.066. □: 2-mm. cell; slit = 0.12 mm.; $A_{1.63} = 0.02927$ (% C_5H_8) + 0.1322.

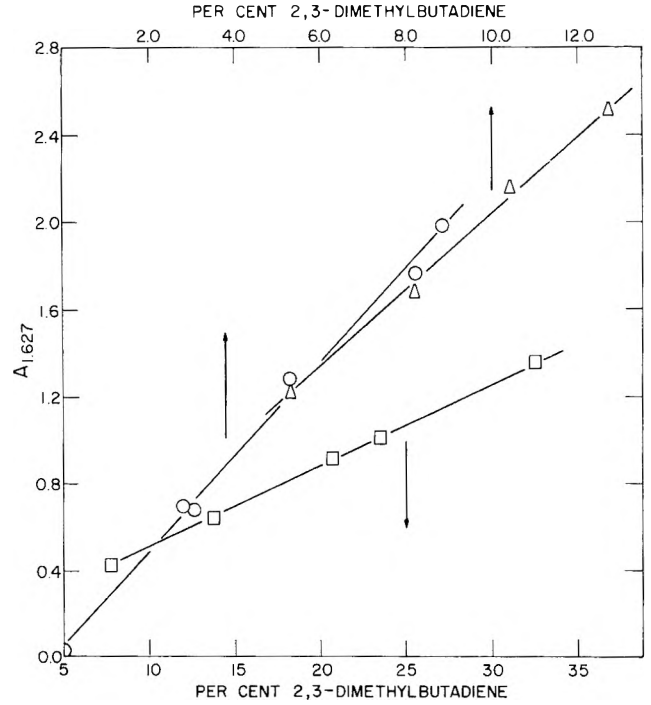

Fig. 2.—Standardization of 2,3-dimethylbutadiene solution in bromotrichloromethane. ○: 10-mm. cell; geometrical slit = 0.12 mm.; $A_{1.627} = 0.2162$ (% C_6H_{10}) + 0.0542. Δ: 10-mm. cell; copper screen, $T = 0.1$; slit = 1.2 mm.; $A_{1.627} = 0.1776$ (% C_6H_{10}) + 0.3013. □: 2-mm. cell; slit = 0.12 mm.; $A_{1.627} = 0.03785$ (% C_6H_{10}) + 0.1400.

then taken. Work by Hatch, *et al.*,[2] has shown that by using lithium aluminum hydride, the bromide in a compound such as $BrCH_2—CH=CH—CH_3$ can be replaced by hydrogen in greater than 95% yield with the double bond remaining intact. Thus, the 1:1 adduct (I) was treated with lithium aluminum hydride under mild conditions favoring replacement of Br in preference to the less reactive Cl. An 86% (or higher) yield of the reduced product (II) was obtained. The results in gas–liquid chromatography showed that II was a mixture of three fractions in the relative amounts of A, 1.0%, B, 22.4%, and C, 76.6%. Fraction C, had a slightly unsymmetrical peak which could not be resolved. Approximately 20 μl. each of fractions B and C were trapped from the gas chromatograph by employing 20 or more passes. N.m.r. spectra of fractions B and C were examined. Fraction C gave a spectrum corresponding roughly to three parts $CH_3—CH=C(CH_3)—CH_2—CCl_3$, derived from $BrCH_2—CH=C(CH_3)—CH_2—CCl_3$, and one part $CH_3—C(CH_3)=CH—CH_2—CCl_3$. The spectrum of fraction B corresponded to $CH_3—CH=C(CH_3)—CH_2—CHCl_2$ derived from $CH_3—CH=C(CH_3)—CH_2—CCl_3$ also, where, aside from the Br atom, one Cl atom was also replaced by H. The gross identity of fraction B was verified by mass spectrometry. Therefore, over-all, II was composed of (76.6 × ¾) + 22.4 = 79.9% of the products derived from the 1,4-addition product and 20.1% from the 4,1-addition product. Since the yield from the lithium aluminum hydride reduction was 86%, and since II contained 80% of products which were derived from the 1,4-addition compound, therefore, in I the largest fraction, 71.9%, must be the 1,4-addition compound, and the lesser fraction, 26.1%, the 4,1-addition product. The remaining minor fractions totaling 2% could be the 1,2- and 4,3-addition compounds or other impurities.

Bromotrichloromethane–2,3-Dimethylbutadiene Reaction.—Unlike the butadiene and isoprene reactions, the addition of bromotrichloromethane to 2,3-dimethylbutadiene yielded only the 1:1 adduct even at 100% conversion. Infrared and Raman spectroscopy established that the 1:1 adduct has the 1,4-configuration, $Cl_3C—CH_2—C(CH_3)=C(CH_3)—CH_2Br$, a clear liquid, b.p. 74° (0.2 mm.).

Anal. Calcd. for $C_7H_{10}Cl_3Br$: C, 29.98; H, 3.59. Found: C, 30.28; H, 3.60

Results

Kinetics.—The results on the standardization of isoprene of different concentration ranges with regard to absorbance [log (I^0/I)] at 1.63 μ are represented in Fig. 1. Similarly, the results on the standardization of 2,3-dimethylbutadiene are represented in Fig. 2. In all these cases Beer's law is followed. In Fig. 3, the results on very concentrated solutions of 2,3-dimethylbutadiene in bromotrichloromethane are shown (30–50%). It is seen that Beer's law is no longer followed and that a curve is obtained. This curve was used graphically for determining the C_6H_{10} concentration in the reaction where the mole ratio was 1:2. (Mole ratio, unless specified otherwise, refers to bromotrichloromethanediene.)

Typical kinetic plots for X-ray induced bromotrichloromethane–isoprene and bromotrichloromethane–2,3-dimethylbutadiene reactions are shown in Fig. 4 and 5, respectively. In both figures all the plots are

TABLE I

DATA FOR ADDITION OF BROMOTRICHLOROMETHANE TO ISOPRENE

Mole ratio $BrCCl_3$:C_5H_8	Temperature, °C. ± 0.2	Dose rate[a] rads min.$^{-1}$	Rate × 10^3, moles kg.$^{-1}$ min.$^{-1}$	G values[b]
2.90:1	25	1454	1.46	969
2.99:1	25	3807	2.30	883
2.98:1	25	5896	3.10	507
3.04:1	32.5	5798	3.60	556
3.18:1	40	5650	4.88	833
1.03:1	25	5235	2.82	520
2.05:1	25	5699	2.70	456
6.19:1	25	6097	3.65	577
8.36:1	25	6154	3.75	564
17.95:1	25	6257	3.46	525

[a] Dose rate calculated from the composition of the system based on Fe^{+2}–Fe^{+3} dosimetry under the same conditions. Filtration, 1 mm. of aluminum + 1 mm. of copper. [b] Molecules of isoprene reacted per 100 e.v. absorbed.

(2) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Am. Chem. Soc.*, **81**, 5943 (1959).

TABLE II

DATA FOR ADDITION OF BROMOTRICHLOROMETHANE TO 2,3-DIMETHYLBUTADIENE

Mole ratio $BrCCl_3:C_6H_{10}$	Temperature, °C. ± 0.2	Dose rate[a] rads min.$^{-1}$	Rate × 10^3, moles kg.$^{-1}$ min.$^{-1}$	G value[b]
2.93:1	25	1423	5.39	3653
3.20:1	25	3611	7.33	1957
2.99:1	25	5749	12.88	2160
2.91:1	32.5	5896	14.32	2381
2.93:1	40	5778	18.63	2737
1:2.06	25	4347	4.80	1065
0.99:1	25	5020	11.17	2146
4.25:1	25	5904	1[illegible].67	2074
6.08:1	25	6043	13.54	2161
10.63:1	25	6160	15.23	2384
11.06:1	25	6106	16.23	2559
11.22:1	25	6158	16.19	2537
18.72:1	25	6223	15.41	2388

[a] Dose rate calculated from the composition of the system based on Fe^{+2}–Fe^{+3} dosimetry under the same conditions. Filtration, 1 mm. of aluminum + 1 mm. of copper. [b] Molecules of 2,3-dimethylbutadiene reacted per 100 e.v. absorbed.

essentially linear. The kinetic data concerning various experimental conditions are recorded in Table I for isoprene and in Table II for 2,3-dimethylbutadiene. When employing a mole ratio of 3:1 for isoprene at 25°, it was found that the rate was proportional to the 0.53 power of the dose rate ($k \propto I^{0.53}$), and the G value was inversely proportional to the 0.48 power of the dose rate ($G \propto I^{-0.48}$). For 2,3-dimethylbutadiene, the rate was proportional to the 0.58 power of the dose rate ($k \propto I^{0.58}$), while the G value was inversely proportional to the 0.42 power of the dose rate ($G \propto I^{-0.42}$). Figure 6 represents the dependence of rates on the mole fractions of bromotrichloromethane at 25° for both isoprene and 2,3-dimethylbutadiene. It shows that maximum rates are in the neighborhood of 0.8–0.9 mole fraction of bromotrichloromethane. Figure 7 shows the Arrhenius plots involving temperatures of 25, 32.5, and 40°. An activation energy of 3.96 kcal. mole^{-1} was calculated for the addition to isoprene, and 3.09 kcal. mole^{-1} for that to 2,3-dimethylbutadiene.

Discussion

From the results obtained for the bromotrichloromethane–isoprene system, it is seen that addition of the trichloromethyl radical ($\dot{C}Cl_3$) is more favorable (3:1) at the end nearest to the methyl group (position 1). Presuming that the initiation is $BrCCl_3 \rightarrow \dot{B}r + \dot{C}Cl_3$, this is expected since $\dot{C}Cl_3$ is an "acceptor-type"[3] radical which preferentially attacks double bonds with electron-donating groups in the propagation step. In the displacement step the polar factor is also more favorable. This is also shown by the relative reaction rates obtained for the addition of bromotrichloromethane to butadiene, isoprene, and 2,3-dimethylbutadiene. For example, at 3:1 mole ratio, 25°, and a dose rate of 6×10^3 rads min.$^{-1}$, the ratios in rates are

$$C_4H_6:C_5H_8:C_6H_{10} = 1:1.27:5.28$$

In the rate *vs.* mole fraction of bromotrichloromethane plots (Fig. 8), in the cases of both isoprene and 2,3-dimethylbutadiene, as well as in that of butadiene,[1]

(3) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Chap. 6.

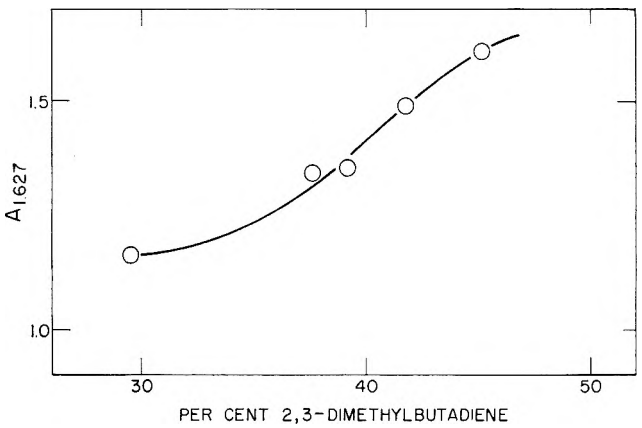

Fig. 3.—Standardization of concentrated 2,3-dimethylbutadiene in bromotrichloromethane; 2-mm. cell; slit = 0.12 mm.

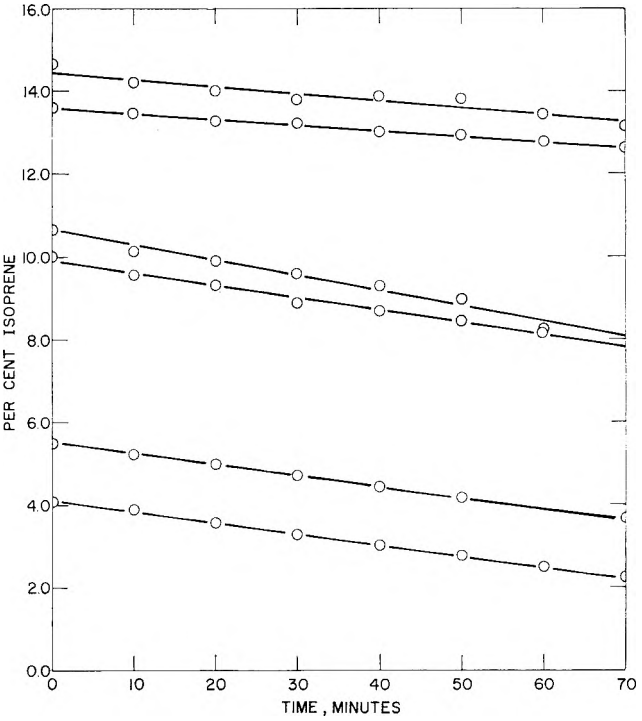

Fig. 4.—Some typical plots in reaction kinetics between isoprene and bromotrichloromethane as expressed in disappearance of isoprene.

the maxima lie in the region of 0.7–0.9 mole fraction of bromotrichloromethane (especially in the case of 2,3-dimethylbutadiene); this is in agreement with the idea of radical reactivities.[3] Since the radicals derived from the dienes are relatively stable due to resonance, these remain as the major radical species in the systems up to a high mole fraction of bromotrichloromethane. Among these three dienes, the steepest rise and highest maximum yield is observed with 2,3-dimethylbutadiene. This may result from the greatest reactivity of this diene in the present "donor–acceptor" type reaction.

In all kinetic runs reported, the conditions were chosen so that the 1:1 adduct was the only product. Therefore, the rates pertain to reactions on p. 1588. The stepwise, free radical reaction schemes for the addition reactions of these dienes are similar to that represented for butadiene.[1] The results from the kinetic studies show that the rates and G values are in the order of butadiene < isoprene < 2,3-dimethylbutadiene

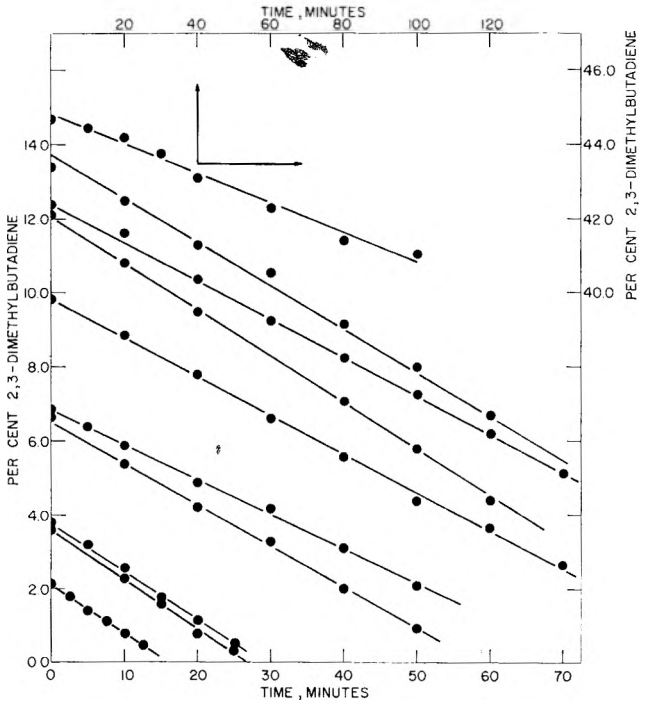

Fig. 5.—Some typical plots in reaction kinetics between 2,3-dimethylbutadiene and bromotrichloromethane as expressed in disappearance of 2,3-dimethylbutadiene *vs.* time. The scales on top and right of the graph belong to the uppermost plot.

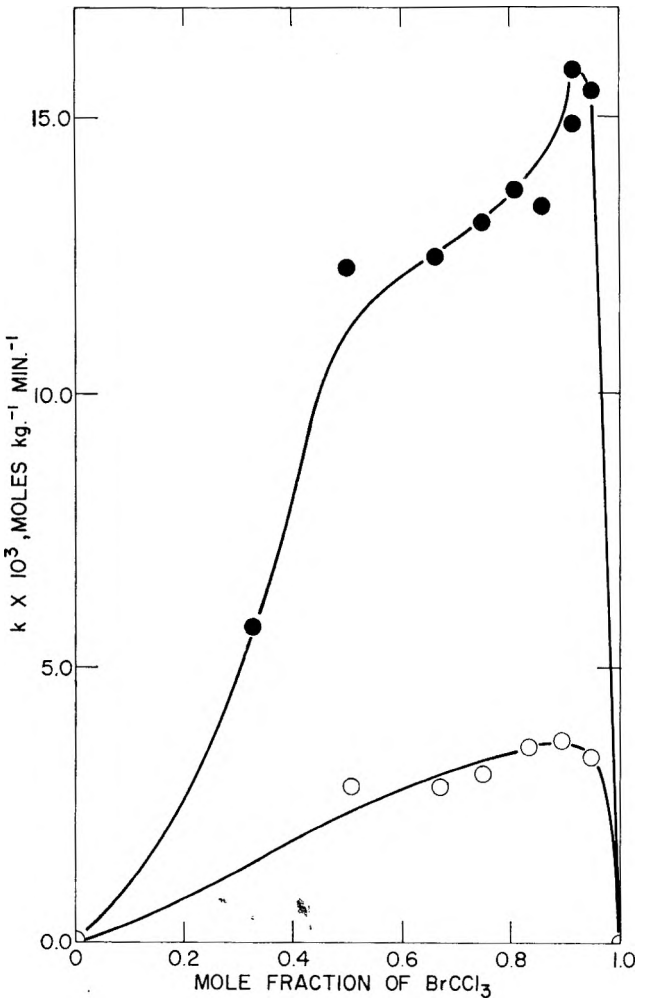

Fig. 6.—Dependence of rate on the mole fraction of bromotrichloromethane at 25°. ○, Isoprene; ●, 2,3-dimethylbutadiene.

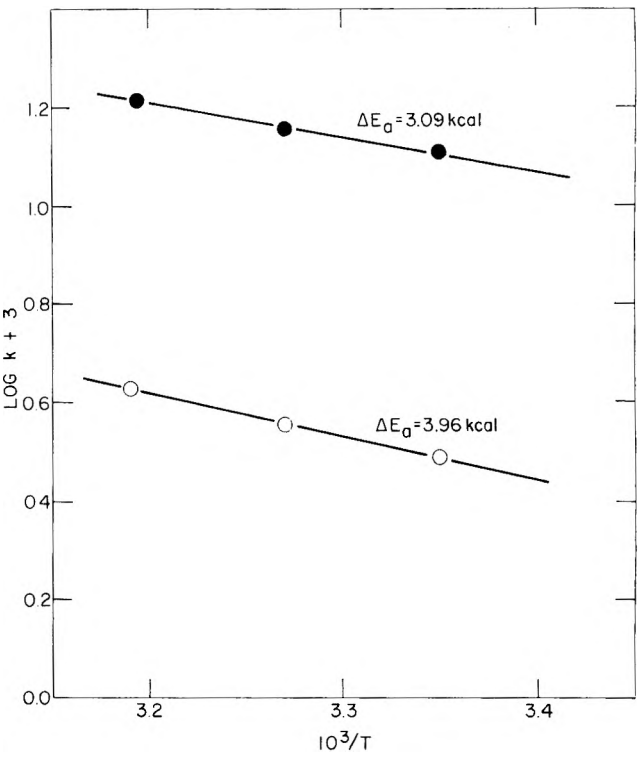

Fig. 7.—Arrhenius plot of addition of bromotrichloromethane to diene. Mole ratio, 3:1, dose rate, 6 × 10^3 rads min.$^{-1}$. ●, 2,3-Dimethylbutadiene; ○, isoprene.

Isoprene: $BrCCl_3 + CH_2{=}C(CH_3){-}CH{=}CH_2 \rightsquigarrow$

$Cl_3C{-}CH_2{-}C(CH_3){=}CH{-}CH_2Br$ ~75% +

$Cl_3C{-}CH_2{-}C(CH_3){=}C(H){-}CH_2Br$ ~25%

2,3-Dimethylbutadiene: $BrCCl_3 + CH_2{=}C(CH_3){-}C(CH_3){=}CH_2 \rightsquigarrow$

$Cl_3C{-}CH_2{-}C(CH_3){=}C(CH_3){-}CH_2Br$

and that the activation energies are in the order of butadiene > isoprene > 2,3-dimethylbutadiene. Also, based on the dose rate dependence, the extent of allylic degradative chain transfer is in the order of 2,3-dimethylbutadiene > isoprene > butadiene. All these observations are in accordance with the structural features of these three dienes. The 2,3-dimethylbutadiene having two electron-donating groups which also carry six allylic hydrogens, is expected to be the most reactive, and the one capable of the highest allylic chain transfer among the three. However, the allylic chain transfer is not extensive in any case as is shown by the nearly square root dependence on the dose rate in all three cases. It is conceivable that considerable attack on allylic hydrogens could have taken place, but the resulting radicals were able to attack the reactive bromotrichloromethane and still propagate the chain.

The linear plots obtained for concentrations of diene *vs.* time (Fig. 4 and 5) indicate that the reactions are zero order in the diene. Table III represents the de-

TABLE III

DEPENDENCE OF RATE ON THE CONCENTRATION OF BROMOTRICHLOROMETHANE[a]

Diene	Mole ratio $BrCCl_3$:diene	$[BrCCl_3]$, moles $kg.^{-1}$	Rate $\times 10^3$, moles $kg.^{-1}$ $min.^{-1}$
Isoprene	1.03:1	2.98	2.84
	2.05:1	4.30	2.74
	2.98:1	4.54	3.09
	6.19:1	4.78	3.58
	8.36:1	4.84	3.66
	17.95:1	4.96	3.34
2,3-Dimethyl-	1:2.06	2.79	5.74
butadiene	0.99:1	3.56	12.29
	2.99:1	4.43	13.10
	4.25:1	4.60	12.70
	6.08:1	4.72	13.38
	10.63:1	4.85	14.88
	11.06:1	4.86	15.95
	11.22:1	4.86	15.83
	18.72:1	4.93	14.97

[a]Dose rate: isoprene, 5860 rads $min.^{-1}$; 2,3-dimethylbutadiene, 5920 rads $min.^{-1}$.

pendence of rate on the concentration of bromotrichloromethane when the rate in each case has been corrected to a common dose rate. It is seen that in the cases of both isoprene and 2,3-dimethylbutadiene, in the mole-ratio range of 1:1 to 18:1, the rates of disappearance of the dienes are essentially constant with variation in the mole ratio (within 25% variation), the maximum rates occurring at a mole ratio of 8:1 for isoprene and 11:1 for 2,3-dimethylbutadiene. However, the rate is much lower when a mole ratio of 1:2 is employed as indicated in the case of 2,3-dimethylbutadiene.

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Potential Radiation-Protective Compounds. Synthesis of the Three Isomeric Three-Carbon Aminohydroxy Bunte Salts and Related Compounds[1]

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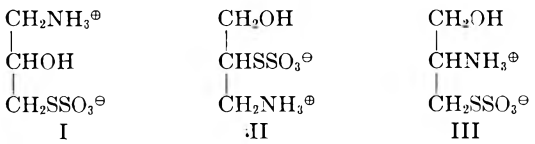
The isomeric internal Bunte salts, *S*-3-amino-2-hydroxypropylthiosulfuric acid (I), *S*-2-amino-1-(hydroxymethyl)ethylthiosulfuric acid (II), and *S*-2-amino-3-hydroxypropylthiosulfuric acid (III), have been prepared as the racemic forms. The last named has also been prepared in a levorotatory form. 3-Amino-2-bromo-1-propanol hydrobromide has been synthesized by the addition of hypobromous acid to the allylammonium ion; the isomeric 1-amino-3-bromo-2-propanol hydrobromide was a minor product of the addition. The acid hydrolysis of *N*,*O*,*S*-triacetyl-L-cysteinol probably proceeds *via* a thiazoline intermediate.

In recent years, Bunte salts,[2] *S*-alkyl thiosulfates, have been the subject of investigation in many laboratories. A Bunte salt related to glutathione, "S-sulfoglutathione", has been isolated from calf lens extracts.[3] Sulfite has been used to obtain soluble protein or peptide fractions from wool,[4] flour,[5] ribonuclease and insulin,[6] and from trypsinogen and α-chymotrypsinogen,[7] the cystine disulfide bonds are cleaved under mild conditions to form "S-sulfocysteinyl residues". The properties and potential uses of the "S-sulfocysteinyl residues" have been discussed by Swan.[8]

Several examples of Bunte salts containing amino or alkylamino groups were prepared by Bretschneider.[9] These, like the amino acids, are internal salts and the simplest compound of this type, *S*-2-aminoethylthiosulfuric acid, was found to have significant radiation-protective activity in mice. It was also 2.4 times less toxic than 2-aminoethanethiol (cysteamine) hydrochloride.[10] Other aminoalkyl thiosulfates have been prepared by Rosenthal and Citarel[11] who found that they were stable compounds which possessed significant anti-radiation activity. The low activity of 3-amino-1-propanethiol compared to the activity of *S*-3-aminopropylthiosulfuric acid[12] suggests that the protective activity of the Bunte salt is not, at least in this case, due to the formation of the thiol.

Aminoalkylthiosulfuric acids are, in general, stable, odorless, crystalline, water-soluble substances and are thus attractive potential anti-radiation drugs. This paper describes the synthesis of the three isomeric internal Bunte salts I, II, and III.



I II III

Bunte salts are prepared conveniently by the reaction of alkyl halides with thallous thiosulfate,[13] the insoluble thallous halide formed being removed easily from the reaction mixture. An aqueous solution of 1-

(1) This work was supported by a grant from the Surgeon General's Office, Medical Research and Development Command, U. S. Army.

(2) H. Bunte, *Ber.*, **7**, 646 (1874).

(3) S. G. Waley, *Biochem. J.*, **71**, 132 (1959).

(4) J. M. Swan, *Nature*, **180**, 643 (1947); *Australian J. Chem.*, **14**, 69 (1961).

(5) E. E. McDermott and J. Pace, *Nature*, **184**, 546 (1959).

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(8) J. M. Swan, "Sulfur in Proteins," R. Benesch, *et al.*, Ed., Academic Press, New York, N. Y., 1959, p. 3.

(9) H. Bretschneider, *Monatsh. Chem.*, **81**, 372 (1950).

(10) B. Holmberg and B. Sörbo, *Nature*, **183**, 832 (1959).

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(13) H. Z. Lecher and E. M. Hardy, *J. Org. Chem.*, **20**, 475 (1955).

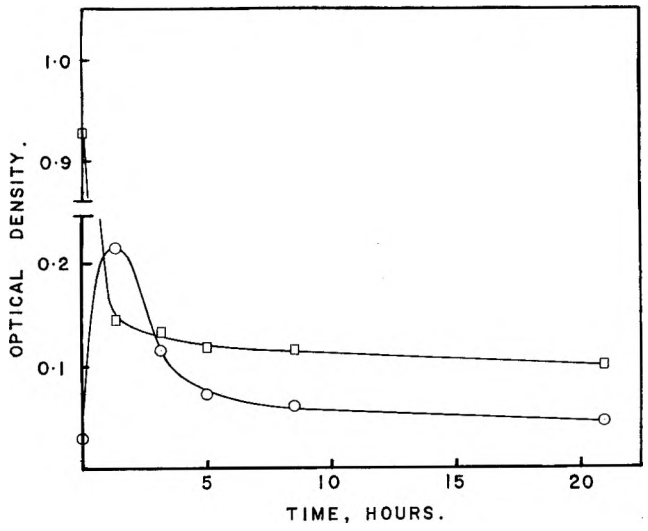
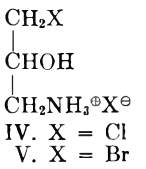
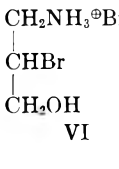


Fig. 1.—Hydrolysis of *N,O,S*-triacetyl-L-cysteinol (2.08×10^{-4} *M*) in hydrochloric acid (1.7 *N*) at 90°: □—optical density at 231.5 mμ; O—optical density at 261 mμ.

amino-3-chloro-2-propanol hydrochloride (IV),[14,15] unlike 2-chloroethylamine hydrochloride,[13] did not react readily with thallous thiosulfate at room temperature. Formation of the internal Bunte salt took place at higher temperatures but extensive decomposition also occurred. The corresponding bromo hydrobromide V



IV. X = Cl
V. X = Br



VI

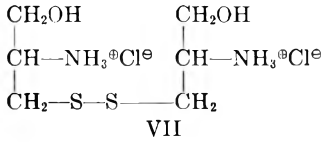
was originally prepared by condensation of potassium phthalimide with boiling epibromohydrin, followed by hydrolysis of the product with hydrobromic acid.[16] When *N,N*-dimethylformamide was added in the condensation step,[17] the reaction proceeded at 35–40° and the yield was improved slightly. Under these conditions, the epoxide ring is slowly opened by the potassium phthalimide. This was demonstrated by the formation of a small amount of a diaminopropanol (presumably 1,3-diamino-2-propanol) after hydrolysis of the condensation product. The bromo hydrobromide reacted more readily than IV with thallous thiosulfate and, after two days at 50°, the Bunte salt I, *S*-3-amino-2-hydroxypropylthiosulfuric acid, was isolated in 67% yield.

No suitable precursor for the Bunte salt II was known and attempts to prepare 3-amino-2-bromo-1-propanol hydrobromide (VI) from 2,3-dibromo-1-propanol and from 2,3-dibromopropylamine and their derivatives, by selective displacements of the primary bromine atoms, were unsuccessful. The hydrobromide VI was eventually obtained from the reaction of the allylammonium ion with hypobromous acid. The latter was conveniently generated *in situ* by the method of Leibman and Fellner[18] whereby a mixture of bromine vapor and air is passed into the reaction solution which contains one equivalent of silver nitrate. Both isomeric amino-bromo alcohols were isolated, the desired 3-amino-2-bromo isomer VI being the major product. The hydrobromide VI did not react with thallous thiosulfate at 40° but, at 75–80°, conversion to the Bunte salt II was essentially complete after twelve hours. Amine impurities, which hindered crystallization, were removed by chromatography on silica gel. Crystallization of the purified material from methanol–ether gave the pure Bunte salt II, *S*-2-amino-1-(hydroxymethyl)-ethylthiosulfuric acid, in 51% yield.

Bunte salts have also been prepared by the action of sulfites on disulfides in the presence of an oxidizing agent. Air or oxygen are often sufficient but cupric ions,[19] iodosobenzoate, and tetrathionate[6] have also been used. The oxidant converts the thiol formed in the reversible reaction (1) to disulfide and eventually this is completely converted to the Bunte salt.

$$RSSR + SO_3^{-2} \rightleftharpoons RSSO_3^{\ominus} + RS^{\ominus} \qquad (1)$$

Cystinol dihydrochloride VII, 3,3′-dithiobis[2-amino-1-propanol]dihydrochloride, is, therefore, a suitable precursor for the internal Bunte salt III. It was



VII

prepared from 2-phenyl-2-thiazoline-4-methanol by Crawhall, *et al.*[20] These authors designated their product as the DL-form but the method of preparation would give a mixture of DL- and *meso*-isomers. We used the L-isomer of the thiazoline in an attempt to obtain the pure L-isomer of VII but hydrolysis of the thiazoline ring required much more vigorous conditions than those reported[20] and racemization occurred at this stage. The resultant DL-thiol ("cysteinol") was oxidized without isolation and a crystalline, optically inactive mixture of, presumably, the DL- and *meso*-forms of VII was obtained. No attempt was made to separate these isomers and the mixture was treated at room temperature with ammonium sulfite solution (pH 7) and oxygen. The reaction was followed by paper electrophoresis and was complete after six to seven hours. The product was freed from inorganic salts by fractionation on a column of a cation exchange resin in the lithium salt form[21] and subsequent recrystallization from methanol–ether gave *S*-2-amino-3-hydroxypropylthiosulfuric acid (III) in 65% yield.

L-Cysteinol, L-2-amino-3-mercapto-1-propanol (VIII), has been prepared recently by Enz and Cecchinato[22] by a method which should not cause appreciable racemization. L-Cysteine ethyl ester was reduced with lithium aluminum hydride and the L-cysteinol formed was isolated as the *N,O,S*-triacetate (IX) in 29% yield. These authors hydrolyzed the triacetate with dilute hydrochloric acid and obtained L-cysteinol as the crystalline hydrochloride, although they did not record the specific rotation. Thin layer chromatog-

(14) S. Gabriel and H. Ohle, *Ber.*, **50**, 819 (1917).

(15) Unless otherwise indicated, all compounds containing an asymmetric carbon atom are racemic mixtures.

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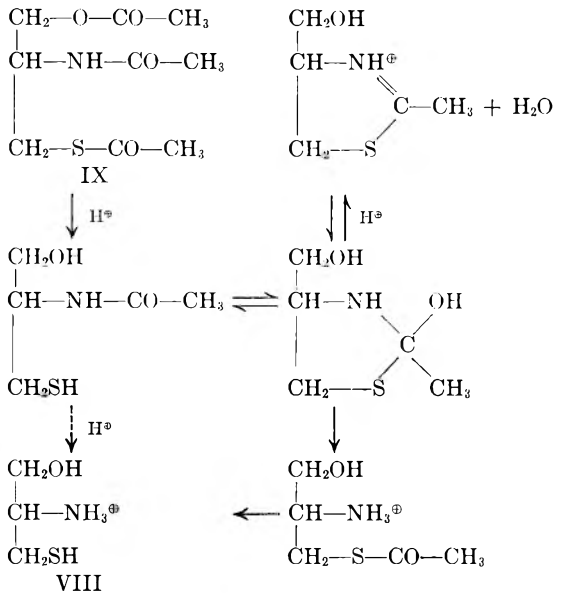
(19) I. M. Kolthoff and W. Stricks, *J. Am. Chem. Soc.*, **73**, 1728 (1951).

(20) J. C. Crawhall, D. F. Elliott, and K. C. Hooper, *J. Chem. Soc.*, 4066 (1956).

(21) J. K. N. Jones, R. A. Wall, and A. O. Pittet, *Can. J. Chem.*, **38**, 2285 (1960).

(22) W. Enz and M. Cecchinato, *Helv. Chim. Acta*, **44**, 706 (1961).

raphy indicated that, during hydrolysis of the triacetate, an intermediate was rapidly formed and that this was slowly converted to cysteinol. In dilute hydrochloric acid at 90°, the absorption at 231.5 mμ (thiolacetate) decreased rapidly. A second absorption at 261 mμ (thiazolinium cation) appeared, increased to a maximum after *ca.* an hour and a half, and then decreased slowly (Fig. 1). It has been shown recently that thiazoline formation occurs in acid solutions of *N*-acetyl cysteine[23] and *N*-2-mercaptoethylacetamide[24] and hydrolysis of cysteinol triacetate (IX) probably proceeds *via* the same mechanism.



L-Cystinol dihydrochloride was prepared from L-cysteinol triacetate by acid hydrolysis followed by oxidation of the resultant thiol which was not isolated. The L-form of VII had a specific rotation of −108° and a much lower melting point than the values obtained for the mixtures of DL- and *meso*-forms.

The internal Bunte salt (III) prepared from this disulfide had a higher melting point than the DL-form and a specific rotation of −31° in water.

The three isomeric internal Bunte salts are stable crystalline solids, very soluble in water and slightly soluble in methanol. They decompose slowly in boiling water. They have been submitted to the Walter Reed Army Institute of Research for testing as radiation-protective agents.

Experimental

Solutions were concentrated under reduced pressure below 40°. Melting points were determined on a Kofler micro hot stage or in a Thomas–Hoover capillary melting point apparatus and are uncorrected, and optical rotations were measured at 5461 Å with an ETL–NPL automatic polarimeter (The Bendix Corporation, Cincinnati, Ohio). Molecular weights were determined in the solvents specified with a vapor pressure osmometer (Mechrolab, Inc., Mountain View, Calif.).

Paper electrophoresis was carried out on strips of Whatman no. 1 filter paper, 5 cm. wide, in 0.2 *M* acetate buffer, pH 5, and at a current of 5 ma. Whatman no. 1 filter paper was also used for paper chromatography by the descending method using the solvent systems (a) 1-butanol–ethanol–water (3:1:1) and (b) 1-butanol–pyridine–water (10:3:3). Ascending thin layer chromatography (t.l.c.) was performed on 0.25-mm. layers of "Silica Gel G acc. to Stahl" (distributed by Brinkmann Instruments, Inc., Great Neck, L. I., N. Y.). Compounds were located by the ninhydrin spray or with an alkaline permanganate spray. Silica gel, grade 950, 60–200 mesh from the Davison Co., Baltimore 3, Md., was used without pretreatment for column chromatography.

The microanalyses were done by Mr. C. DiPietro of this laboratory and by Dr. S. M. Nagy of the Massachusetts Institute of Technology.

1-Amino-3-chloro-2-propanol Hydrochloride (IV).—A suspension of phthalimide (147 g., 1 mole) in epichlorohydrin (300 ml.) was boiled under reflux for 10 hr. The mixture was allowed to cool and residual phthalimide (56 g.) was removed by filtration. The filtrate was concentrated to a yellow sirup which crystallized from benzene. After recrystallization, the product, *N*-(3-chloro-2-hydroxypropyl)phthalimide (77.6 g., 52% based on unrecovered phthalimide), had m.p. 93–97°.[14]

Hydrolysis of this product with 20% hydrochloric acid[14] gave crystalline 1-amino-3-chloro-2-propanol hydrochloride, m.p. 103–106°, in 73% yield. Gabriel and Ohle reported m.p. 103–104°.[14]

1-Amino-3-bromo-2-propanol Hydrobromide (V).—Potassium phthalimide (37.0 g., 0.2 mole) was added to a mixture of epibromohydrin (27.4 g., 0.2 mole) and *N*,*N*-dimethylformamide (100 ml.) and the suspension was stirred magnetically at 35–40° for 5 hr. Chloroform was added and the mixture was poured into stirred ice–water (*ca.* 600 ml.). The two layers were separated and the aqueous layer was extracted twice with chloroform. The combined chloroform extracts were washed with cold 0.1 *N* sodium hydroxide solution (100 ml.) and with water and were dried over sodium sulfate. Concentration afforded a white solid which was recrystallized twice from ethanol. The product, *N*-(2,3-epoxypropyl)phthalimide (32.1 g., 79%), had m.p. 100–102°. Weizmann and Malkowa reported m.p. 93–94°.[16]

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.00; H, 4.68; N, 6.85.

A solution of this product (10 g.) in 48% hydrobromic acid (100 g.) was boiled under reflux for 5 hr. Phthalic acid, which crystallized when the solution was allowed to cool, was removed by filtration and the filtrate was concentrated to a solid (10.1 g.). Paper electrophoresis showed that in addition to the main product, a small amount of a faster moving cation was present. The solid was dissolved in hot ethanol and most of the minor component crystallized when the solution was cooled. It was collected by filtration and, after drying, weighed 0.40 g. and had m.p. 197–200° dec. It analyzed as a diaminopropanol dihydrobromide.

Anal. Calcd. for $C_3H_{10}N_2O{\cdot}2HBr$: C, 14.30; H, 4.80; N, 11.12; Br, 63.43. Found: C, 14.25; H, 4.80; N, 10.80; Br, 62.98.

After removal of this compound, the solution was concentrated to a pale orange solid (9.7 g.) which was dissolved in 1-butanol. The solution was boiled with charcoal, filtered through Celite, and cooled. Crystalline 1-amino-3-bromo-2-propanol hydrobromide (V) was obtained with m.p. 115–117° (lit.[16] m.p. 113–113.5°). Paper electrophoresis indicated the presence of a trace only of the preceding diaminopropanol dihydrobromide.

Anal. Calcd. for $C_3H_8NOBr{\cdot}HBr$: C, 15.34; H, 3.86; N, 5.96; Br, 68.03. Found: C, 15.36; H, 3.94; N, 6.21; Br, 68.17.

Thallous Thiosulfate.—A solution of thallous acetate (52.7 g., 0.2 mole) in water (60 ml.) was clarified by filtration through Celite. To the vigorously stirred solution was added a solution of sodium thiosulfate pentahydrate (24.8 g., 0.1 mole) in water (50 ml.). The heavy white precipitate of thallous thiosulfate was collected by filtration, washed repeatedly with water, and dried. Yield: 50 g., 96%.

***S*-3-Amino-2-hydroxypropylthiosulfuric Acid (I). (A) Attempted Preparation from IV.**—The reaction of thallous thiosulfate with an aqueous solution of IV was followed by paper chromatography, paper electrophoresis, and t.l.c. (methanol). The internal Bunte salt I was formed in trace amounts after 1 day at 40° (compare ref. 13). The rate of reaction was increased by raising the temperature to 70, 85, or 100°, but the occurrence of side reactions at these temperatures led to the formation of by-products. In all experiments, the yield of I appeared to be less than 50%.

(B) Preparation from V.—Preliminary experiments indicated that the reaction of thallous thiosulfate with an aqueous solution of V gave I in good yield after 2 days at 50°. Accordingly, thallous thiosulfate (40 g.) was added to a magnetically stirred solu-

(23) H. A. Smith and G. Gorin, *J. Org. Chem.*, **26**, 820 (1961).

(24) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).

tion of V (11.75 g.) in water (50 ml.). The temperature was maintained at 50° with an oil bath. After 1 day, an additional 20 g. of thallous thiosulfate was added and, after 2 days, the suspension was cooled to 0° and filtered. Concentration of the filtrate gave a sirup which was diluted with methanol, filtered through Celite, and cooled. *S*-3-Amino-2-hydroxypropylthiosulfuric acid (I) crystallized and was collected by filtration, washed with methanol, and dried. Total yield was 6.26 g. (67%), m.p. 164–167° dec., R_f 0.10 in solvent system A.

Anal. Calcd. for $C_3H_9NO_4S_2$: C, 19.24; H, 4.84; N, 7.48; S, 34.25; mol. wt., 187. Found: C, 19.34; H, 4.74; N, 7.50; S, 34.46; mol. wt., 187 (in water).

3-Amino-2-bromo-1-propanol Hydrobromide (VI).—A solution of freshly distilled allylamine (19 g., 0.33 mole) in water (350 ml.) was neutralized (to pH 6) with concentrated nitric acid (*ca.* 22 ml.). Silver nitrate (56.7 g., 0.33 mole) dissolved in water (150 ml.) was added and a mixture of bromine vapor and air was drawn into the well stirred solution which was cooled to 0–10° in an ice bath. Total weight of bromine added was 53.3 g., 0.33 mole. When the addition of bromine was completed (2.5 hr.), the solution was stirred for an additional hour at room temperature, silver bromide was then removed by filtration and the filtrate was neutralized with the weakly basic Amberlite ion-exchange resin IR 45 (OH). Concentration afforded a sirupy residue which was diluted with water. The solution was applied to a column of Dowex ion-exchange resin 50W-X2 (H) (450 g.), nitrate ions were eluted with water, and the amines were then desorbed with 9.7% hydrobromic acid. The acidic effluent was collected in 400–500-ml. fractions, which were separately concentrated with repeated additions of methanol. The following fractions were obtained: (1) 23.2 g., (2) 15.7 g., (3) 2.0 g. Total yield of mixed bromohydrins was 40.9 g. (52%). Fractions 1 and 3 crystallized on standing and fraction 2 crystallized in part. After treatment with charcoal and recrystallization from 1-butanol, fractions 1 and 2 yielded large colorless prisms of 3-amino-2-bromo-1-propanol hydrobromide (VI) (15.6 g., 20%), m.p. 107.5–109.5°, depressed to 75–100° when admixed with 1-amino-3-bromo-2-propanol hydrobromide (V). The infrared spectrum (in potassium bromide) was similar to, but not identical with, that of V.

Anal. Calcd. for $C_3H_8NOBr \cdot HBr$: C, 15.34; H, 3.86; N, 5.96; Br, 68.03. Found: C, 15.28; H, 3.95; N, 6.09; Br, 68.14.

After treatment with charcoal and recrystallization from 1-butanol, fraction 3 yielded pure 1-amino-3-bromo-2-propanol hydrobromide (V) (0.91 g., 1%), m.p. 114–116°, undepressed by admixture with authentic material.

***S*-2-Amino-1-(hydroxymethyl)ethylthiosulfuric Acid (II).**—A solution of VI (7.05 g., 0.03 mole) in water (90 ml.) was stirred magnetically with thallous thiosulfate (15.6 g., 0.03 mole) at 75–80° (oil bath). The reaction was followed by paper electrophoresis and, after 2 hr., an additional portion of thallous thiosulfate (15.6 g., 0.03 mole) was added. After 12 hr., only a trace of starting material remained and the reaction mixture was cooled and filtered. Concentration of the filtrate gave a sirup which was extracted with methanol; the extracts were filtered and concentrated to a sirup (5.83 g.), which slowly deposited crystals when diluted with methanol (10 ml.). The crystals (0.95 g.) were collected by filtration and the residual sirup which contained small amounts of amine impurities (which probably hindered crystallization) was fractionated on a column of silica gel (300 g.) with methanol as solvent. The sirupy product (4.63 g.) still contained one impurity (which appeared on paper chromatograms to be the isomeric Bunte salt I, probably arising from traces of the bromide V in the starting material) but crystallization from methanol–ether gave a further 1.90 g. of crystalline material. Total yield of *S*-2-amino-1-(hydroxymethyl)ethylthiosulfuric acid (II) was 2.85 g. (51%), m.p. 164–172° dec., R_f 0.15 in solvent system A.

Anal. Calcd. for $C_3H_9NO_4S_2$: C, 19.24; H, 4.84; N, 7.48; S, 34.25. Found: C, 19.14; H, 4.95; N, 7.40; S, 34.63.

Preparation of Optically Inactive (DL- + *meso*-) Cystinol Dihydrochloride (VII).—L-2-Phenyl-2-thiazoline-4-methanol was prepared from L-cysteine hydrochloride in an over-all yield of 25% according to Crawhall, *et al.*[20] The thiazoline (m.p. 75.5–76°) was dissolved in concentrated hydrochloric acid (sp. gr. 1.191 at 60°F) and the solution was boiled under reflux in a stream of nitrogen for 6 hr. Fifty per cent of the starting material was recovered as its crystalline hydrochloride (cubes from ethanol), m.p. 135–139°.

Anal. Calcd. for $C_{10}H_{11}NOS \cdot HCl$: C, 52.27; H, 5.26; N, 6.10; S, 13.95; Cl, 15.43. Found: C, 52.06; H, 5.20; N, 6.01; S, 14.07; Cl, 15.48.

Under these conditions, the above workers reportedly obtained a 90% yield of thiol, determined by iodine titration.[20] In trial experiments, we determined the extent of hydrolysis under these conditions by iodine titration and by the weight of benzoic acid liberated. It was found to be 59% and 82% after 7 and 14 hr. respectively. A solution of the thiazoline (9.55 g.) in concentrated hydrochloric acid (190 ml.) was boiled under reflux in a stream of nitrogen for 17 hr. The cooled solution was extracted with ether (two 100-ml. portions); benzoic acid (5.35 g., 88%) was recovered from dried extracts. The aqueous layer was concentrated to a sirup (7.6 g.) which was taken up in water (90 ml.). The pH was adjusted to 8–9 with ammonia and the small amount of unchanged thiazoline which precipitated was removed by filtration. A small crystal of ferrous sulfate was added to the filtrate and air was drawn through the solution until the mauve color was discharged (*ca.* 8 hr.). The solution was then concentrated to half its volume, filtered to remove a little more thiazoline, and evaporated to dryness. The residue was crystallized from a mixture of ethanol and concentrated hydrochloric acid (3:2) giving an optically inactive mixture (DL- and *meso*-) of cystinol dihydrochlorides (VII) (5.71 g., 81%). This preparation had m.p. 199–202°. The so-called "DL-cystinol" previously reported[20] with m.p. 183° was very probably a mixture of DL- and *meso*-forms and the difference in melting points probably reflects a difference in the relative amounts of these isomers in the two preparations.

Anal. Calcd. for $C_6H_{16}N_2O_2S_2 \cdot 2HCl$: C, 25.26; H, 6.36; N, 9.82; S, 22.49; Cl, 24.85. Found: C, 25.08; H, 6.17; N, 9.85; S, 22.36; Cl, 24.68.

***S*-2-Amino-3-hydroxypropylthiosulfuric Acid (III).**—Oxygen was passed through a solution of these cystinol dihydrochlorides, (2.85 g., 0.01 mole) in ammonium sulfite solution, pH 7 (110 ml.) (prepared by adding concentrated ammonia to a 6% aqueous solution of sulfur dioxide). The reaction, which was followed by paper electrophoresis, was complete in 6–7 hr. at room temperature. The solution was left overnight at room temperature and then concentrated to dryness. The residue (11.6 g.) was extracted with absolute methanol (110 ml.) and the filtered solution was concentrated to a solid (7.2 g.), which contained both Bunte salt and inorganic salts. A portion (1.0 g.) of the mixture was fractionated on a column (93 × 2.3 cm.) of Dowex cation-exchange resin, 50W-X2 (200–400 mesh) in the lithium salt form.[21] The column was eluted with water and 15-ml. fractions were collected and tested for sulfite and sulfate (with barium chloride solution) and for amino-Bunte salt (with ninhydrin). Inorganic salts were eluted first (fractions 7–13) and then the Bunte salt (fractions 18–22). Concentration of the latter fractions gave a sirup (0.4 g.) which crystallized slowly from methanol–ether. The remainder of the salt mixture was similarly fractionated (maximum load for the above column was about 1.5 g.) and 3.08 g. (82%) of crystalline *S*-2-amino-3-hydroxypropylthiosulfuric acid (III), m.p. 153–156° dec., was isolated. Recrystallization from methanol–ether gave the pure Bunte salt, m.p. 159–161° dec., R_f 0.16 in solvent system A. This preparation of III had no optical activity.

Anal. Calcd. for $C_3H_9NO_4S_2$: C, 19.24; H, 4.84; N, 7.48; S, 34.25; mol. wt., 187. Found: C, 19.17; H, 4.67; N, 7.31; S, 34.16; mol. wt., 184 (in water).

Preparation of L-Cystinol Dihydrochloride.—*N*,*O*,*S*-Triacetyl-L-cysteinol (IX) was prepared in 29% yield from L-cysteine ethyl ester hydrochloride. The original procedure[22] was modified as follows. Crude cysteinol was separated from inorganic salts remaining after the reduction step by ethanol extraction of the dried residue. After acetylation of this material with acetic anhydride–sodium acetate, the reaction mixture was concentrated to a solid which was extracted with benzene. Concentration of the benzene extracts afforded the crystalline triacetate (IX) which was recrystallized from methanol–ether. The product had m.p. 101–102°, $[\alpha]^{25}D$ −45° (*c* 1.92 in water), $\lambda_{max}^{H_2O}$ 231.5 mμ, ε 4300.

A solution of IX (2.08×10^{-4} *M*) in 1.7 *N* hydrochloric acid was heated at 90–92° under nitrogen and aliquots were removed at intervals for measurements of the absorptions at 231.5 mμ and at 261 mμ. The results are shown in Fig. 1.

In a second experiment, a solution of IX (4.66 g., 0.02 mole) in 1.7 *N* hydrocloric acid (200 ml.) was heated at 90° for 15 hr. The solution was then concentrated to a sirup which was taken up in water (25 ml.). The pH was adjusted to 7–8 with ammonia

and air was drawn through the solution. T.l.c. (1-propanol) indicated a slow conversion to the disulfide which was essentially complete after 2 days. The solution was concentrated to a sirup which was dissolved in methanol containing a little hydrochloric acid. Ether was added and L-cystinol dihydrochloride (VII) (1.91 g., 67%) crystallized. After recrystallization from methanol–ether it had m.p. 145–146°, $[\alpha]^{25}D$ −108° (*c* 1.0 in methanol).

Anal. Calcd. for $C_6H_{16}N_2O_2S_2 \cdot 2HCl$: C, 25.26; H, 6.36; N, 9.82; S, 22.49; Cl, 24.85. Found: C, 25.09; H, 6.15; N, 9.80; S, 22.66; Cl, 24.57.

L-S-2-Amino-3-hydroxypropylthiosulfuric Acid (III).—The Bunte salt III was prepared from L-cystinol dihydrochloride as described previously for the DL-isomer except that sodium sulfite was used instead of ammonium sulfite. The product had m.p. 190–193° dec., $[\alpha]^{25}D$ −31° (*c* 0.62 in water).

Electronic Effects on the Stereochemistry of the Diels–Alder Reaction[1]

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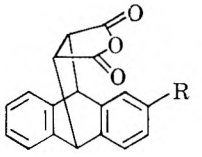
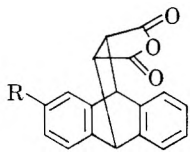
Various 2-substituted anthracenes have been synthesized and their reaction with maleic anhydride investigated. The amounts of the two possible isomers formed, *syn* and *anti*, afforded a medium for the evaluation of the electronic effect on the stereochemistry of the reaction. The results of these studies are discussed.

The Diels–Alder reaction, in which there is the possibility of the formation of more than one product, has been extensively investigated; however, the asymmetrical nature of reacting species has not permitted unequivocal evaluation of the electronic effect in determining the isomer formed.[3] The introduction of a group on the 2-position of the anthracene nucleus permits the formation of two isomeric products in the reaction with maleic anhydride. The amounts of *syn* (I) and *anti* (II) isomers formed would be a function of the



syn Adduct (I)

a. R = NO_2
b. R = NAc
c. R = $N(Me)_2$



anti Adduct (II)

a. R = NO_2
b. R = NAc
c. R = $N(Me)_2$

substituent. The symmetrical nature of the molecule, except for the substituent, would tend to minimize all other effects which determine the isomer ratio and thus reflect the importance of polar attractive forces in the two possible transition states. The substitution of anthracene in the 2-position rather than the 1-position further removes any steric effect the group may have on the reacting centers.

The dimethylamino, acetamido, and nitro groups were selected as substituents. The method of Hodgson and Marsden[4] for the replacement of a diazonium group by a nitro group was used to prepare the reported 2-nitroanthracene.[5] Excellent yields of 2-acetamidoanthracene were obtained by the treatment of 2-aminoanthracene with acetic anhydride[6] and lithium aluminum hydride reduction of 2-N,N-dimethylaminoanthracene methiodide in tetrahydrofuran gave 2-N,N-dimethylaminoanthracene.[7]

All Diels–Alder reactions were carried out in refluxing benzene with a ten- to twentyfold excess of freshly sublimed maleic anhydride present. 2-Dimethylaminoanthracene reacted with the appearance of a transient deep red color and the insoluble 2-acetamidoanthracene dissolved slowly as it reacted. The yellow color of the 2-nitroanthracene solution did not intensify as the reaction occurred and disappeared as the reaction approached completion. The relative rates of reaction of 2-nitroanthracene, anthracene, and 2-dimethylaminoanthracene were determined under pseudo first-order conditions similar to those used by Andrews and Keefer.[8]

Compound	k, l./mole sec.
2-Nitroanthracene	0.086×10^{-5}
Anthracene	$.014 \times 10^{-3}$
2-Dimethylaminoanthracene	$.055 \times 10^{-3}$

The spectra of the products exhibited typical succinic anhydride adsorption in the infrared at 5.34 and 5.60 μ.[9] At least one intense band appearing in the spectrum of starting material was completely absent in all cases. The infrared spectra of chloroform, methylene chloride, benzene, or dioxane solutions of pure *syn*- and *anti*-2-nitro-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydrides (Ia and IIa) differed mainly in the 10.0- to 11.0-μ region. Their ultraviolet spectra were similar and as expected for adducts.[10]

The theoretical dipole moments of the two adducts, which contain rigid ring systems free of rotation, were computed from three main components: 9,10-dihydroanthracene (0.4 Debye),[11] succinic anhydride (4.2 Debyes),[12] and nitrobenzene (3.9 Debyes).[13] A value of 7.11 Debyes was obtained for the *syn* adduct and 2.11 Debyes for the *anti* adduct. The measurement of the dielectric constant and refractive index of a series of

(1) Taken in part from the dissertation of Fred Kaplan presented to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy, September, 1959.

(2) Department of Chemistry, University of Cincinnati, Cincinnati 21, Ohio.

(3) J. Martin and R. Hill, *Chem. Rev.*, **61**, 537 (1961).

(4) H. Hodgson and E. Marsden, *J. Chem. Soc.*, 22 (1944).

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(6) C. Lieberman and A. Bollert, *Ber.*, **16**, 228 (1882).

(7) A. Bollert, *ibid.*, **16**, 1635 (1883).

(8) L. Andrews and R. Keefer, *J. Am. Chem. Soc.*, **77**, 6284 (1955).

(9) L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 28.

(10) I. Gillet, *Bull. soc. chim. France*, 1135 (1950).

(11) I. Campbell, C. LeFévre, R. LeFévre, and E. Turner, *J. Chem. Soc.*, 404 (1938).

(12) M. Raw and N. Anantanaragan, *Proc. Indian Acad. Sci.*, **6A**, 185 (1937).

(13) L. G. Wesson, "Table of Electric Dipole Moments," The Technology Press, Massachusetts Institute of Technology, Cambridge, Mass., 1948, p. 29.

dilute solutions of different concentrations in benzene at a constant temperature[14] established the identities of the adducts.

DIPOLE MOMENT, μ, IN DEBYES

	syn	*Anti*
Calculated	7.11	2.11
Found	6.6 ± 0.9	2.4 ± 1.7

Reduction and acetylation of the *syn*- and *anti*-2-nitro-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydrides (Ia and IIa) to their respective 2-acetamidoanthracene adducts (Ib and IIb) were achieved by the method of Kishi.[15] Major differences occurred in the 10.0-to 11.0-μ region of the infrared spectra of methylene chloride or dioxane solutions of these adducts. The presence of both adducts could not be readily detected in the spectrum of a chloroform solution. The composite spectrum of the *syn* and *anti* adducts was identical with the spectrum of the material obtained from the reaction of 2-acetamidoanthracene with maleic anhydride.

The *syn*-and *anti*-2-dimethylamino-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydrides (Ic and IIc) were obtained by reduction and methylation of the corresponding nitro adducts.[16] The products obtained possessed almost identical infrared spectra in a variety of solvents. The spectra were similar to that of the material obtained from the reaction of 2-dimethylaminoanthracene with maleic anhydride. A difference in chemical shift of the N-methyl peak of the *syn* and *anti* adducts occurred in their nuclear magnetic resonance spectra[17] in deuteriochloroform. The separation of these peaks was enhanced from 2.2 c.p.s. to 8.0 c.p.s. by use of benzene as solvent rather than deuteriochloroform.[18]

Pure *syn* and *anti* adducts of the compounds studied were subjected to reaction conditions for longer periods of time and recovered unchanged. This established that the reaction mixtures obtained were kinetically controlled and that the isomer distribution was a measure of the relative stabilities of the two possible transition states.

The amounts of *syn* and *anti* adducts formed in the reactions of 2-nitroanthracene and 2-acetamidoanthracene with maleic anhydride were determined by quantitative infrared analysis. Comparison of reaction mixture spectra with ones of known concentration confirmed calculated values. Nuclear magnetic resonance spectroscopy was used to analyze the 2-dimethylaminoanthracene–maleic anhydride reaction mixture. Measurement of the relative areas of the two *N*-methyl peaks gave the ratio of the isomers. The following results were obtained:

Group	% *syn*	% *Anti*
NO_2	39 ± 1	61 ± 1
NAc	52 ± 1	48 ± 1
$N(Me)_2$	55 ± 2	45 ± 2

The isomer distribution studies show that the transition state containing the maleic anhydride fragment above the electron-rich aromatic ring is more stable than the other possibility. The ratio of the isomers indicates that the free energies of activation of the two possible transition states differ only by approximately 0.2 kcal. per mole. Many small factors such as the electrostatic interaction[19] of the carbonyl dipole of the maleic anhydride fragment and the greater electron density of one ring can easily account for this small difference.

Although the 2-dimethylaminoanthracene reacts seventy times faster than 2-nitroanthracene the distribution of isomers is not so great. If the dimethylamino group is facilitating a charge transfer of any type, one must assume that the *syn* and *anti* forms resulting from this must be of nearly equivalent energies and do not influence the isomer distribution. It is significant that no major electronic effect be explained in terms of the mechanism of the reaction.

Experimental

Melting points were determined in soft glass capillaries in a Hershberg apparatus and are uncorrected.

Benzin refers to a hydrocarbon solvent boiling at 30–60° and petroleum ether refers to a hydrocarbon solvent boiling at 60–110°. The composition of solvent mixtures is described by the volume of the component before mixing.

Analyses were carried out by Dr. S. M. Nagy and his associates at the Massachusetts Institute of Technology, Cambridge, Mass., and Herr W. Manser at the Eidg. Technische Hochschule, Zürich, Switzerland.

2-Aminoanthracene.—The procedure described by Ruggli and Henzi[20] was altered slightly. To a deep red mixture of 200 g. (0.9 mole) of 2-aminoanthraquinone in 1200 cc. of 10% sodium hydroxide solution stirred at room temperature was added 120 g. of zinc dust. The mixture was then brought to a gentle reflux and 25 cc. of 95% ethanol was added to prevent violent foaming. One hundred grams of zinc dust was added every 0.5 hr. until a total of 320 g. (5 moles) was present. After refluxing for 24 hr., the solid material in the brownish yellow mixture was collected and washed with hot water. Soxhlet extraction with acetone removed the 2-aminoanthracene (deep green fluorescence in acetone). Crystallization from hot acetone gave 110 g. (63%) of 2-aminoanthracene; m.p. 236–237°. Recrystallization from toluene afforded 105 g. (60%) of greenish gold plates; m.p. 238–239°; reported[20] m.p. 238°.

2-Anthracenediazonium Cobaltinitrite.—A mixture of 10 g. (0.052 mole) of 2-aminoanthracene and 20 cc. (0.21 mole) of hydrochloric acid (37.5%) was heated on a steam bath in 100 cc. of water for 1 hr. to form the grayish white hydrochloride salt. To this aqueous mixture, maintained below 5°, was added a solution of 4.14 g. (0.06 mole) of sodium nitrite in 25 cc. of water. Additional water (150 cc.) was added slowly to the resulting red mixture to dissolve the insoluble diazonium hydrochloride. After 20 min., sufficient calcium carbonate was added (4 g.) to neutralize any remaining acid. The mixture was filtered under vacuum (to remove insoluble tars and excess calcium carbonate) into a solution of 20.2 g. (0.05 mole) of sodium cobaltinitrite in 500 cc. of water. The resulting red precipitate was collected and washed with cold water and finally with ether.

2-Nitroanthracene.—The solid 2-anthracenediazonium cobaltinitrite was added slowly to a solution of sodium nitrite (10 g.), cupric sulfate (10 g.), and cuprous oxide (4 g.) in 100 cc. of water stirred at room temperature. Foaming occurred upon addition.

(14) A. Weissberger, "Physical Methods of Organic Chemistry," Vol. 1, Part II, Chap. XXIV, Interscience Publishers, Inc., New York, N. Y., 1949, pp. 1611–1650.

(15) N. Kishi, Japan Patent 4161 (1952); *Chem. Abstr.*, **48**, 5215c (1954).

(16) W. Emerson, U. S. Patent 2,414,031; *Chem. Abstr.*, **41**, 2439b (1949).

(17) Nuclear magnetic resonance spectra were taken with a Varian Associates high resolution spectrometer at 60 megacycles per second. Chemical shifts were measured by the audio-oscillator side-band superposition method with tetramethylsilane as an internal reference in dilute solutions of the compounds examined and are in cycles per second from tetramethylsilane.

(18) J. Pople, W. Schneider, and H. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 422–432.

(19) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 716.

(20) P. Ruggli and E. Henzi, *Helv. Chim. Acta*, **13**, 409 (1930).

After 3 hr. the precipitate was collected and washed with water. Soxhlet extraction of the precipitate with ether yielded a deep red solution. After extraction with 3 *N* hydrochloric acid and 5 *N* sodium hydroxide, the ethereal solution was dried over anhydrous sodium sulfate. Evaporation to dryness yielded 3 g. of red solid. The material was dissolved in a minimum amount of benzene and placed on a chromatography column of aluminum oxide (Woelm, nonalkaline, activity I) prepared in petroleum ether. Elution with 60% petroleum ether–40% benzene removed anthracene. After its complete removal (absence of its characteristic blue fluorescence in solution), a bright yellow band was eluted with benzene. The material obtained upon evaporation of the benzene was crystallized from a hot acetone–petroleum ether mixture twice yielding 1.4 g. (12% from 2-aminoanthracene) of bright yellow needles of 2-nitroanthracene; m.p. 181–182°; reported[5] m.p. 171–172°.

2-Acetamidoanthracene.—Acetic anhydride (35 cc.) and 8.0 g. (0.042 mole) of 2-aminoanthracene were refluxed for 3 hr. The brown solution was cooled to 5° and the resulting white precipitate collected. After the solid material was washed with saturated sodium bicarbonate solution, it was dissolved in hot acetone and placed on a chromatography column of alumina (Fisher, no. A-540) prepared in chloroform. Acetone elution first removed a black impurity. Continued elution with acetone yielded 2-acetamidoanthracene. One crystallization from hot acetone gave 7.7 g. (80%) of light yellow plates of 2-acetamidoanthracene; m.p. 244–245°; reported[21] m.p. 239–240°.

2-N,N-Dimethylaminoanthracene Methiodide.—A mixture of 1.93 g. (0.07 mole) of 2-aminoanthracene and 1.08 g. (0.02 mole) of sodium bicarbonate was heated at 110° in 30 cc. of methyl iodide with a trace of methanol for 8 hr. The precipitate was collected and washed with water and ether. It was then crystallized twice from hot dilute ammonium hydroxide solution yeilding 2.84 g. (73%) of pale yellow plates of 2-dimethylaminoanthracene methiodide; m.p. 227–229°; reported[7] m.p. 215° dec.

2-N,N-Dimethylaminoanthracene.—Three grams (8.56 mmoles) of 2-dimethylaminoanthracene methiodide and 1.50 g. (0.04 mole) of lithium aluminum hydride were refluxed in purified tetrahydrofuran for 4 hr. After decomposition of excess lithium aluminum hydride by the addition of water, the tetrahydrofuran was removed under vacuum. Sodium hydroxide pellets were added to dissolve the aluminum salts and the aqueous layer was extracted with ether. The greenish ethereal layer was dried over anhydrous sodium sulfate and evaporated to dryness, yielding 1.9 g. of a bright yellow solid. The material, dissolved in 60% benzene–40% petroleum ether, was chromatographed over an aluminum oxide (Woelm, almost neutral, activity I) column prepared in petroleum ether. Elution with 40% benzene–60% petroleum ether first yielded anthracene. Continued elution with this solvent mixture gave yellow material. It was crystallized from a benzene–petroleum ether mixture yielding 511 mg. (27%) of yellow needles of 2-dimethylaminoanthracene; m.p. 158–160°; reported[7] m.p. 155°.

Reaction of 2-N,N-Dimethylaminoanthracene with Maleic Anhydride.—A greenish yellow solution of 22 mg. (0.1 mole) of 2-dimethylaminoanthracene in 1 cc. of benzene was added to a refluxing solution of 200 mg. (2.0 mmoles) of freshly sublimed maleic anhydride in 1 cc. of benzene. A deep red color appeared immediately. After 2 hr. the light tan solution was evaporated to dryness and the excess maleic anhydride removed by sublimation at 110° and 10^{-3} mm. The 31.3 mg. (98.5%) obtained was used for quantitative analysis.

Reaction of 2-Acetamidoanthracene with Maleic Anhydride.—A mixture of 34.4 mg. (0.14 mmole) of 2-acetamidoanthracene and 105 mg. (1.1 mmoles) of freshly sublimed maleic anhydride was refluxed in 1.5 cc. of benzene. A deep yellow color resulted as the insoluble 2-acetamidoanthracene slowly went into solution. After 4 hr. the now colorless solution was evaporated to dryness and the excess maleic anhydride sublimed at 110° and 10^{-3} mm. The 49.3 mg. (100%) obtained was used for quantitative analysis.

Reaction of 2-Nitroanthracene with Maleic Anhydride.—1. A yellow solution of 35.1 mg. (0.16 mmole) of 2-nitroanthracene and 100 mg. (1.0 mmole) of freshly sublimed maleic anhydride in 2 cc. of benzene was refluxed for 26 hr. The yellow color still remained. An additional 100 mg. (1.0 mmole) of maleic anhydride was added and the solution refluxed for 30 hr. A faint yellow color still remained. No change in color was observed on continued refluxing or addition of more maleic anhydride. The solvent was evaporated and the excess maleic anhydride removed by sublimation at 110° and 10^{-3} mm. The 49.9 mg. (98.8%) of material obtained was used for quantitative analysis.

2. A solution of 1.079 g. (4.83 mmoles) of 2-nitroanthracene and 5.88 g. (60.0 mmoles) of freshly sublimed maleic anhydride in 50 cc. of benzene was refluxed for 48 hr. The slightly yellow solution was evaporated to dryness. An ethereal solution of the remaining material was extracted with saturated sodium bicarbonate solution to remove excess maleic anhydride. Evaporation of the ethereal layer, after drying over anhydrous sodium sulfate, gave 1.550 g. (100%) of a yellowish white solid. The material, dissolved in 20% acetone–80% benzene, was placed on a chromatography column of silicic acid (Mallinckrodt 100 mesh, no. 2847) prepared in benzene. The column was then washed with petroleum ether to quench any movement caused by the acetone. Elution with benzene first removed traces of impurities. The next fractions contained *anti*-2-nitro-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydride, IIa (identified later), characterized by bands at 10.57 and 10.87 μ in its infrared spectrum in methylene chloride, contaminated with small amounts of the *syn* adduct (Ia), characterized by a band at 10.70 μ. Additional elution with benzene gave fractions consisting of approximately equal amounts of both isomers. Finally, enriched fractions of the *syn* adduct were obtained. The enriched fractions of each adduct were crystallized many times from hot chloroform–petroleum ether until pure adducts were obtained (constant melting point and absence of bands of the other adduct in the infrared spectrum). This procedure gave 437 mg. (28%) of white needles of the *anti* adduct, m.p. 249–250°, and 389 mg. (25%) of white plates of the *syn* adduct, m.p. 279–280°. The adducts were crystallized four times more from hot acetone–petroleum ether and still possessed the same melting points and infrared spectra. These materials were used in the dipole moment determination and quantitative analysis.

Anal. [*anti*-2-Nitro-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydride (IIa)]. Calcd. for $C_{18}H_{11}O_5N$: C, 67.29, H, 3.48; N, 4.36. Found: C, 67.25; H, 3.59; N, 4.47. Ultraviolet spectrum (methanol): λ_{max} 279.5 mμ, ϵ 8000.

Anal. [*syn*-2-Nitro-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydride (Ia)]. Calcd. for $C_{18}H_{11}O_5N$: C, 67.29; H, 3.48. Found: C, 67.19; H, 3.45. Ultraviolet spectrum (methanol): λ_{max} 282 mμ, ϵ 8900.

Dipole Moment Determination.—The *syn*- and *anti*-2-nitroanthracene–maleic anhydride adducts have been described previously. A series of dilute benzene (b.p. 80.0–80.2°, $n^{25}D$ 1.4981) solutions were prepared.

The dielectric constant measuring apparatus[22] was maintained at 25°. The bridge measuring circuit consisted of a 300-kc./sec. oscillator, two equal resistors, two fixed capacitors, a variable capacitor, and a detection system. The cell was of brass and approximately 3.5 in. in diameter and 2 in. in height and contained a variable and a fixed capacitor. The variable capacitor was a micrometer-electrode system type[23] adapted for liquids.

Refractivities were measured on an Abbe refractometer and were referred to the sodium D line at 25°.

DIPOLE MOMENT, $\mu = 0.0128[(P_2 - R_2)T]^{1/2}$

	P_2	R_2	μ
anti Adduct	219 ± 110	100 ± 109	2.40 ± 1.71
syn Adduct	988 ± 141	101 ± 114	6.58 ± 0.88

Reductive Acetylation of *syn*- and *anti*-2-Nitro-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic Anhydrides (Ia and IIa) to *syn*- and *anti*-2-Acetamido-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic Anhydrides (IIa and IIb).—A solution of 26.0 mg. (0.081 mmole) of the *anti*-2-nitroanthracene–maleic anhydride adduct in 5 cc. of acetic anhydride and 0.5 cc. of glacial acetic acid was stirred in an atmosphere of hydrogen in the presence of Raney nickel for 3 hr. at 70°. A white solid was obtained after removal of the catalyst by filtration and evaporation of the filtrate. Extraction of this solid with chloroform gave 28 mg. of material. This material, dissolved in chloroform, was filtered through a

(21) P. Fedorov, *Izv. Akad. Nauk, USSR, Otd. Khim. Nauk*, 582 (1951); *Chem. Abstr.*, **46**, 8077f (1951).

(22) We are indebted to Mr. William B. Westphal of Insulation Research Laboratory, Massachusetts Institute of Technology, Cambridge, Mass., for the use of his apparatus.

(23) A. von Hippel, "Dielectric Materials and Applications," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 50.

small column of silicic acid prepared in chloroform. Ether elution yielded 26 mg. (96%) of material whose infrared spectrum (dioxane) possessed all major bands present in the spectrum of the material obtained from the reaction of 2-acetamidoanthracene with maleic anhydride except one at 10.70 μ. The material was crystallized to a constant melting point from an acetone–benzene mixture by slowly boiling off the acetone. The white plates obtained changed at 146°, became amorphous at 160°, and liquid at 166°. Ultraviolet spectrum (methanol): λ_{max} 253 mμ, ϵ 16,000; λ_{max} 287 mμ, ϵ 1500.

Anal. Calcd. for $C_{20}H_{15}O_4N$: C, 72.06; H, 4.54; N, 4.20. Found: C, 71.85; H, 4.62; N, 4.26.

Reductive acetylation of the *syn* adduct yielded material which possessed in its infrared spectrum all bands present in the spectrum of the material obtained from the reaction of 2-acetamidoanthracene with maleic anhydride except one at 10.80 μ. Crystallizations from acetone–benzene gave white needles, m.p. 149–150°. Ultraviolet spectrum (methanol): λ_{max} 253 mμ, ϵ 16,000; λ_{max} 287 mμ, ϵ 1500.

Anal. Calcd. for $C_{20}H_{15}O_4N$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.53; H, 4.73; N, 4.01.

Reductive Methylation of *syn*- and *anti*-2-Nitro-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic Anhydrides (Ia and IIa) to *syn*- and *anti*-2-Dimethylamino-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic Anhydrides (Ic and IIc).—A solution of 128 mg. (0.4 mmole) of the *anti*-2-nitroanthracene–maleic anhydride adduct in 5 cc. of 95% ethanol, 0.5 cc. of glacial acetic acid, and 0.4 cc. of 36% formaldehyde solution was hydrogenated in the presence of 15 mg. of Adam's catalyst. An uptake of 55 cc. of hydrogen (expected for $-NO_2$ to $-N(CH_3)_2$, 49 cc.) occurred over a period of 24 hr. The solution was evaporated to dryness after removal of the catalyst. The material was extracted with aqueous ether. The ethereal extract, after drying over anhydrous sodium sulfate and evaporation, yielded 107 mg. of material. The white solid was refluxed in 30 cc. of benzene for 20 min. After evaporation of the solvent, 105 mg. (82%) of material was obtained whose infrared spectrum was almost identical with that of the material obtained from the reaction of 2-dimethylaminoanthracene with maleic anhydride. Crystallizations from a methylene chloride–petroleum ether mixture afforded off-white plates, m.p. 208–209°. Ultraviolet spectrum (methanol): λ_{max} 270 mμ, ϵ 12,000; λ_{max} 310 mμ, ϵ 24,000.

Reductive methylation of the *syn* adduct required a longer period of time. The infrared spectrum of the material obtained (79%) was similar but not identical with that of the *anti* adduct. No major difference existed.

Reaction Mixture Analysis.—The ratio of adducts obtained from reaction mixtures of 2-nitroanthracene and 2-acetamidoanthracene with maleic anhydride were determined by quantitative infrared analysis. A variation of the "cell in-cell out" method[24] was used. A constant incident intensity (100% transmission) and zero reading (0% transmission) were obtained in the 10.5- to 11.0-μ region for all samples. Beer's law for a two-component system was used to calculate the composition of the mixture.

The 2-nitroanthracene-maleic anhydride reaction mixture was found to be composed of 39.2% of the *syn* adduct and 60.8% of the *anti* adduct. The 10.57- and 10.87-μ bands of the *anti* adduct and the 10.70 μ band of the *syn* adduct were utilized for the analysis. The 2-acetamidoanthracene–maleic anhydride reaction mixture contained 52.0% of the *syn* adduct absorbing at 10.70 μ and 48.0% of the *anti* adduct absorbing at 10.80 μ. Analyses were performed on solutions of known concentration similar to those of the unknowns using the same technique. The analyses were in good agreement and accurate to 0.3%.

The composition of the reaction mixture of 2-dimethylaminoanthracene and maleic anhydride was determined by analysis of its nuclear magnetic resonance spectrum in benzene solution. The *N*-methyl peaks of the *syn*- and *anti*-dimethylamino adducts appeared at 141 and 149 c.p.s., respectively. The relative areas of the two peaks were determined. The mixture was composed of 45% of the *anti* adduct and 55% of the *syn* adduct. The method of analysis was accurate to 2%.

Attempted Equilibration of *syn*- and *anti*-Adducts.—The infrared spectrum of 5 mg. of pure *syn*- or *anti*- adduct in 0.5 cc. of benzene was recorded. The infrared spectrum of the solution after refluxing for 1 week was identical with that of starting material. To this solution was added 10 mg. of maleic anhydride. After refluxing the solution for 24 hr., no change was observed in the spectrum. No change occurred in the nuclear magnetic resonance spectra of the 2-dimethylaminoanthracene adducts.

Kinetic Data.—Benzene solutions of known concentration (0.00469 *M* anthracene, 0.000158 *M* 2-dimethylaminoanthracene, 0.000184 *M* 2-nitroanthracene—all with 1.2806 *M* maleic anhydride) were placed in a 1-cm. quartz spectrophotometric cell. Five minutes were allowed for complete mixing to occur before initial readings were taken. Measurements of optical density were made with a Beckman DU spectrophotometer at 420 mμ. Only starting material was found to absorb at this wave length. The values of the rate constants, k, were determined from the first-order rate expression $k = 2.303 \log (ODi/ODt)/(MA)t$.

(24) *Perkin-Elmer Instrument News*, **II**, **3**, 6 (1951).

Reactions of Ethylene Diisothiocyanate with Primary and Secondary Amines[1]

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Ethylene diisothiocyanate (I) reacts with an excess of aqueous methylamine and ethylamine to give 1-methyl- and 1-ethylthiocarbamylimidazolidine-2-thione (Va, b). The phenyl analog (Vc) has been obtained upon addition of aniline to I in acetone solution, whereas the reverse mode of addition yielded the substituted ethylenedithiourea (II). Structures Va, b, and c have been prepared by independent syntheses. Reaction of I with excess aqueous dimethylamine and pyrrolidine gave almost exclusively the ethylenedithioureas; with excess of aqueous piperidine, a mixture of bis- and monoadduct was formed. The monoadducts could be conveniently obtained from all the secondary amines studied, by adding them to I in acetone solution. The properties of these monoadducts are consistent with the structures 1-dialkyl- and 1-alkylenethiocarbamylimidazolidine-2-thione, similar to those of Va, b, and c.

Ethylene diisothiocyanate (I) has been reported to react with aqueous ammonia forming ethylenedithiourea (II. R = R′ = H) and a monoadduct for which structure III has been formulated.[2] Alkylene dithioureas had been obtained previously by treating I with aniline,[3] as well as by treating the homolog $(CH_2)_4(NCS)_2$ with ammonia, methylamine, and aniline,[4] and $(CH_2)_6(NCS)_2$ with aziridine.[5]

The structure of the monoadduct formed by the reaction of I with ammonia currently is being elucidated in our laboratories by X-ray diffraction.[6] In this

(1) Part of this work has been treated in a preliminary communication: F. D'Angeli and A. Bandel, *Tetrahedron Letters*, **1**, 5 (1961).

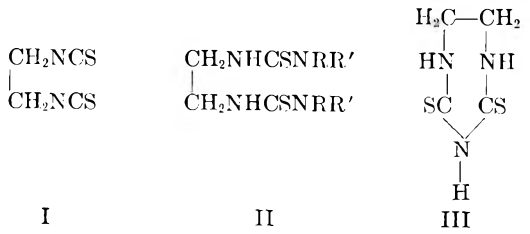
(2) G. D. Thorn and R. A. Ludwig, *Can. J. Chem.*, **32**, 872 (1954).

(3) A. Ya. Yakubovic and V. A. Klimova, *J. Gen. Chem. USSR* (Eng. Transl.), **9**, 1777 (1939); *Chem. Abstr.*, **34**, 3685 (1940).

(4) J. v. Braun and G. Lemke, *Ber.*, **55**, 3552 (1922).

(5) A. G. Bayer, British Patent 753, 247; *Chem. Abstr.*, **51**, 9681 (1957).

(6) Unpublished work.



I II III

paper we report the chemical behavior of I toward primary and secondary amines.

Ethylene diisothiocyanate (I) reacts with these amines at room temperature, giving two different types of compounds whose relative yields depend upon structural factors and experimental conditions. This is shown in Table I.

TABLE I

FORMATION OF MONO- AND BISADDUCTS IN REACTIONS OF ETHYLENE DIISOTHIOCYANATE (I) WITH PRIMARY AND SECONDARY AMINES

Amine	Moles of amine per mole of I	Medium	Order of addition of reagents	% Yield of products Monoadduct	Bisadduct
CH_3NH_2	5	H_2O		52	10
$C_2H_5NH_2$	5	H_2O		63	10
$C_6H_5NH_2$	5	acetone	*a*	Traces	46
	1	acetone	*b*	42	Traces
$(CH_3)_2NH$	5	H_2O		Traces	72
	5	acetone	*a*	–	46
	1	acetone	*b*	42	Traces
$(CH_2)_4NH$	5	H_2O		Traces	66
	5	acetone	*a*	–	60
	1	acetone	*b*	42	Traces
$(CH_2)_5NH$	5	H_2O		30	30
	5	acetone	*a*	–	97
	1	acetone	*b*	75	Traces

[a] I was added to the amine. [b] The amine was added to I.

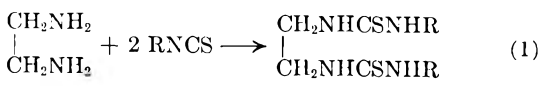
Aqueous Medium.—Excess aqueous methylamine and ethylamine transformed I for the most part into monoadducts. In addition, minor amounts of bisadducts, namely the ethylenedithioureas (II) were formed. The pattern was reversed with secondary amines, which yielded largely (as with piperidine) or almost exclusively (as with dimethylamine and pyrrolidine) the bisadducts II.

Acetone Solution.—In acetone solution, the products which were obtained depended upon the order of addition, and possibly upon molar ratio.

In this paper no distinction is drawn between these two variables, since the purpose of the research was to elucidate the structure of the monoadducts from the reactions of I with primary aliphatic amines and to find suitable conditions favoring monoadduct formation, rather than bisadduct formation with secondary amines. Addition of I to an excess of the secondary amines and aniline resulted in the formation of the dithioureas. On the contrary, the addition of these amines to an equimolecular quantity of I yielded mostly the monoadducts.

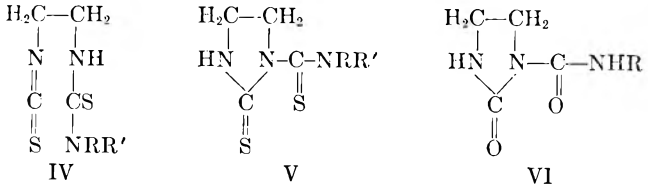
The structures of some of the bisadducts II which had been described incompletely in the literature were

(7) Ethylendiamine reacts with isothiocyanates also in equimolecular ratio; the produced amino-ethylthioureas have been transformed into 2-amino-imidazolines. L. Helgen, O. Stoutland and C. L. Agre, *J. Org. Chem.*, **24**, 818, 884 (1959). German Patent 842, 065; *Chem. Abstr.*, **52**, 10208 (1958).



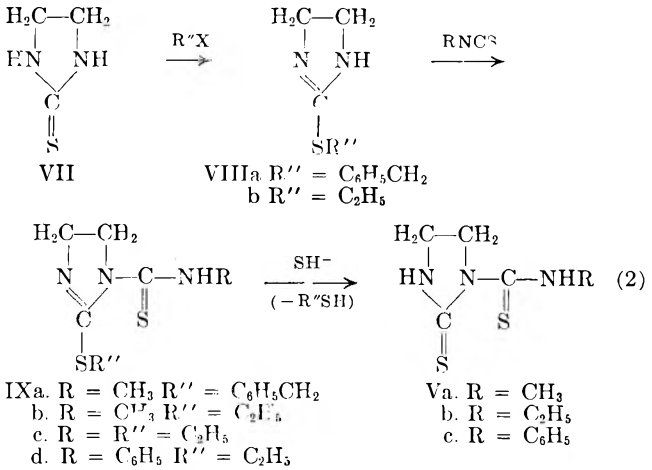
(1)

proven by independent synthesis, using reaction 1.[7] None of the monoadducts of I with the various amines showed the characteristic infrared absorption of the –NCS group in the 2100-cm.$^{-1}$ region. This rules out structure IV for all the monoadducts.



IV V VI

Because of the well known tendency of bifunctional ethylenic systems to form imidazole derivatives,[8] the possibility of the formation of structure V was first investigated. The monoadducts obtained from I with primary amines are identical with the 1-alkyl-, and 1-phenylthiocarbamylimidazolidine-2-thiones obtained by the independent synthesis shown in reaction 2.[9]



VII VIIIa R″ = $C_6H_5CH_2$; b R″ = C_2H_5

IXa. R = CH_3 R″ = $C_6H_5CH_2$; b. R = CH_3 R″ = C_2H_5; c. R = R″ = C_2H_5; d. R = C_6H_5 R″ = C_2H_5

Va. R = CH_3; b. R = C_2H_5; c. R = C_6H_5

(2)

Reaction 2 is an application of synthesis[10] of 1,5-dialkyl-2,4-dithiobiurets, RNHCSNHCSNHR, which are open chain analogs of structure V. It seems unlikely that under the mild conditions in which the last two steps were performed (0° or room temperature), the five-atom ring of 2-alkyl- and 2-benzylmercapto-2-imidazoline (VIIIa, VIIIb) would undergo any transformation besides the expected thiocarbamylation and subsequent thiohydrolysis.[11]

All monoadducts behaved in the same way upon acid and alkaline treatment. Thus they were stable to dilute acid, whereas all yielded imidazolidine-2-thione (VII) on alkaline hydrolysis.

(8) L. K. Hofmann, "Imidazole and its derivatives, Part 1," Interscience Publishers, Inc., New York, N. Y., 1953.

(9) The isosteric structure VI has been attributed, apparently with no experimental evidence, to the compound obtained from $(-CH_2NCO)_2$ and NH_3. W. Nusshag, *Inaug. Diss. zur Erlang. d.W. eines Dr. Med. Vet.*, Berlin, 1913. O. Nitsche, *Centr. Bl.*, **2**, 60 (1914). *Cf.* G. Schroeter and C. Seidler, *J. prakt. Chem.*, **105**, 165 (1922); Th. Curtius and W. Hechtenberg, *ibid.*, **106**, 289 (1923).

(10) (a) F. H. S. Curd, D. G. Davey, D. N. Richardson, and R. de B. Ashworth, *J. Chem. Soc.*, 1739 (1949); (b) A. E. S. Fairfull and D. Peak, *J. Chem. Soc.*, 796, (1955).

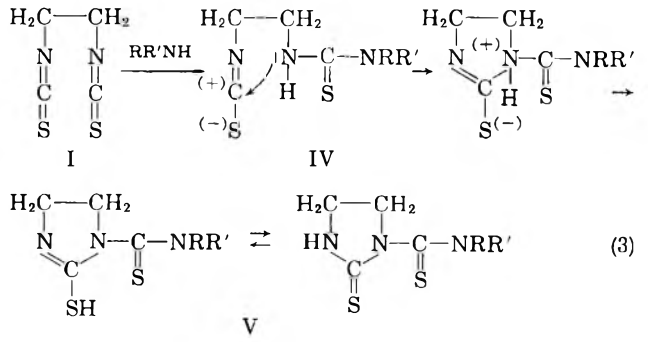
(11) It has been known for many years that N-thiocarbamylaziridines rearrange to thiazoles. More recently, it has been reported that N-thiocarbamylazetidines rearrange to thiazines. N-Thiocarbamylpyrrolidines do not rearrange under comparable conditions. M. Tisler, *Arch. Pharm.*, **291**, 467 (1958); **293**, 621 (1960); *cf.* H. W. Heine, W. G. Kenyon, and E. M. Johnson, *J. Am. Chem. Soc.*, **83**, 2570 (1961).

On the grounds of spectroscopic and chemical data, we also assign structure V to the monoadducts obtained from the reactions of I with secondary amines. Additional evidence from independent synthesis and/or from physical studies will be reported in a subsequent paper.

Discussion

While in suitable conditions monoadducts were obtained both from primary and secondary amines, further research is needed to understand why, in aqueous medium, ring closure occurs preferentially with the former.

Compound IV was never observed to appear and, if it is formed at all in the course of the various reactions, it might act as an intermediate in the formation of the imidazole ring—possibly through scheme 3—because of a particularly favorable steric situation.



(3)

It has been reported, in fact, that acyclic dithiobiurets are not formed from alkyl or aryl isothiocyanates and thioureas.[10a] Research in progress on reactions of homologs of I with ammonia and amines confirms the importance of steric requirements in the formation of the imidazole derivatives V described here.[12]

Experimental[13]

Ethylene diisothiocyanate (I) was obtained by decomposing $(-CH_2NHCSSCOOC_2H_5)_2$ (X) at 110–120° *in vacuo* until a constant weight was reached; each sample was prepared at the time of use and this procedure yielded I in a pure state. X in turn was prepared from sodium ethylene dithiocarbamate (XI) and ethyl chloroformate.[3,14]

Chromatography.—Descending technique, Whatman no. 1 paper sheets, and a *n*-butyl alcohol–acetic acid–water (4:1:5) solvent mixture were used throughout. Grote's reagent[15] gave (i) blue spots with all ethylenedithioureas (as well as with ethylenethiourea VII); (ii) rose spots with monoadducts obtained from primary amines; (iii) yellow spots with monoadducts obtained from secondary amines. Silver nitrate (1% in ethanol) gave, respectively, dark yellow, ochre, and rose to gray-rose spots; furthermore it gave a rose spot with VII, R_f 0.65.[16] R_f values are reported in the following paragraphs for most of the compounds obtained.

Reaction of Ethylene Diisothiocyanate (I) with Methylamine.—To 9.4 g. (0.065 mole) of I was added carefully with stirring 32.5 ml. of aqueous solution of CH_3NH_2 (11.4 g., 0.365 mole). An exothermic reaction took place, and a solid was gradually formed: stirring was continued occasionally for 1 hr., I being completely transformed into a white powder. This was filtered, first washed with water, then with ethanol; the crude compound (5.45 g.) was recrystallized four times from about 700 parts of water, yielding small, colorless prisms, m.p. 202–203°, R_f 0.87. It is slightly soluble in cold, more in warm ethanol, soluble in acetone and pyridine, slightly soluble in chloroform and benzene, almost insoluble in petroleum ether and carbon disulfide. It was identical with the compound obtained through reaction 2 (R = CH_3) with regard to melting point, mixture melting point, infrared spectrum, and chromatographic behavior.

Anal. Calcd. for $C_5H_8N_3S_2$ (Va): C, 34.28; H, 5.18; N, 23.99; S, 36.54. Found: C, 34.10; H, 5.37; N, 23.96; S, 36.30.

By gradual concentration at room temperature of the mother liquor, a green heavy oil separated, followed by several crops of colorless crystals melting at 120–130°; despite the low melting points, paper chromatography of these fractions revealed only the presence of N,N'-dimethylethylenedithiourea (IIa). When the original mother liquor was evaporated to a sirup and this was taken up with ethanol, IIa was obtained in about 10% yield. No depression was observed in mixture melting point with a sample prepared as follows.

N,N'-Dimethylethylenedithiourea (IIa).—To a solution of anhydrous ethylenediamine (0.3 g., 0.005 mole) in 1 ml. of ethanol, methyl isothiocyanate (0.8 g., 0.011 mole) was added. After an exothermic reaction, colorless prisms were obtained (0.93 g., 90%); crystallization from ethanol yielded m.p. 163–164°[17]; R_f 0.76.

Anal. Calcd. for $C_6H_{14}N_4S_2$ (IIa): N, 27.17; S, 31.04: Found: N, 27.01; S, 31.11.

Reaction of Ethylene Diisothiocyanate (I) with Ethylamine.—An aqueous 33% solution of ethylamine (50 ml., 0.36 mole) was cautiously added with stirring to I (9.4 g., 0.065 mole). I gradually turned red and a heterogeneous mass was formed, which was vigorously stirred for 1 hr. The colorless, crystalline powder obtained (7.8 g., 62%) gave, on recrystallization from water, bunches of fine colorless needles, m.p. 166–167°; R_f 0.90.

Anal. Calcd. for $C_6H_{11}N_3S_2$ (Vb): C, 38.09; H, 5.86; N, 22.21; S, 33.83. Found: C, 38.19; H, 6.16; N, 22.42; S, 33.80.

The infrared spectrum, chromatographic behavior, etc., proved the identity of this compound with that obtained through equation 2. Evaporation of the mother liquor gave a semisolid mass (1.9 g.), which was shown by chromatography to be a mixture of Vb and of N,N'-diethylethylenedithiourea (IIb). The latter could be identified conclusively by chromatographic comparison with a specimen obtained through equation 1 (R = C_2H_5); m.p. 130–132°[18]; R_f 0.89.

Reactions of Ethylene Diisothiocyanate (I) with Aniline. A.—The solution of I (1.62 g., 0.0112 mole) in 5 ml. of acetone was added dropwise during 10 min. with stirring, to a solution of aniline (5.35 g., 0.056 mole) in 7 ml. of acetone. There was a mild exothermic reaction; the solution gradually yielded a yellow powder (1.7 g., 46%). Washing with acetone and then with hot ethanol produced a colorless solid melting near 190°, as reported for N,N'-diphenylethylenedithiourea (IIc)[19]; R_f 0.94.

B.—The solution of I (4.75 g., 0.033 mole) in 5 ml. of acetone was carefully added during 10 min. with a solution of aniline (3.1 g., 0.033 mole) in 5 ml. of acetone. A yellow solution was obtained which turned red in 20–30 min. and gave a yellow powder by scratching or seeding (3.28 g., 42%). This was washed with acetone and repeatedly crystallized from ethanol, yielding small colorless prisms, m.p. 175–177°; R_f 0.96.

Anal. Calcd. for $C_{10}H_{11}N_3S_2$ (Vc): C, 50.63; H, 4.67; N, 17.72; S, 26.98. Found: C, 50.45; H, 4.59; N, 17.82; S, 26.72.

This compound was identical with the one obtained according to reaction 2. The mother liquor gave, on evaporation, a solid compound which appeared, by chromatography, to consist of

(12) F. D'Angeli and V. Giormani, *Proc. Israel Chem. soc.*, **11A**, 5 (1962).

(13) Melting points were taken in capillary tubes and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrometer equipped with sodium chloride optics. Solid compounds were examined in potassium bromide disks. We are indebted to Dr. C. Pecile and to the Institute of Physical Chemistry of the University of Padova for the infrared spectra and to Dr. Eloisa Celon for the microanalyses.

(14) Transformation of XI into X is favored by using a slight deficiency of $ClCOOC_2H_5$ at 0 – 5°. Crude X is best washed with cold ethanol till a recrystallization from warm ethanol becomes possible, without formation of $(-CH_2NHCSOC_2H_5)_2$.

(15) I. W. Grote, *J. Biol. Chem.*, **93**, 25 (1931).

(16) R. A. Ludwig and G. D. Thorn, *Rec. trav. chim. Pays Bas*, **79**, 160 (1960).

(17) Structure IIa had been assigned previously to a compound of m.p. 85–86°: T. N. Gosh, *J. Indian Chem. Soc.*, **10**, 583 (1933).

(18) H. Nagele, *Monatsh. Chem.*, **33**, 958 (1912); P. W. Preisler, *J. Am. Chem. Soc.*, **71**, 2849 (1949); O. Stoutland, L. Helgen, and C. L. Agre, *J. Org. Chem.*, **24**, 818 (1959).

(19) E. Lellmann and E. Wurthner, *Liebigs Ann.*, **228**, 234 (1885); K. N. Campbell, B. K. Campbell and S. J. Patelsky, *Proc. Indiana Acad. Sci.*, **53**, 119 (1943); *Chem. Abstr.*, **39**, 881 (1945).

Vc along with several other compounds, one of which was probably IIc (traces).

1-Methylthiocarbamyl-2-benzylthioimidazoline (IXa).—2-Benzylthio-2-imidazoline hydrochloride (VIIIa)[20] (11.4 g., 0.05 mole) was dissolved in 15 ml. of water and treated with methyl isothiocyanate (3.65 g., 0.05 mole), followed by ethanol to produce a clear solution (13 ml.). Twenty milliliters of 2.5 *N* sodium hydroxide was added dropwise in 40 min. with stirring; a solid substance separated and the suspension was stirred for an additional hour, then left overnight at 0°. The solid was filtered, washed with water, then with dilute ethanol (1:3), and dried (12.6 g., 94%). On crystallization from ethanol, colorless shiny prisms were obtained; m.p. 117–122°.

Anal. Calcd. for $C_{12}H_{15}N_3S_2$ (IXa): N, 15.83; S, 24.16. Found: N, 15.9; S, 24.36.

Picrate.—To 0.8 g. (0.003 mole) of IXa dissolved at 40° in 45 ml. of ethanol, 16 ml. of 5% ethanolic picric acid was added. Yellow prisms separated which were washed with ethanol, then with ether, and recrystallized from dimethylformamide and water; m.p. 160–164°; insoluble in the common solvents at room temperature; on warming there was evidence of decomposition (odor of $C_6H_5CH_2SH$).

Anal. Calcd. for $C_{12}H_{15}N_3S_2 \cdot C_6H_3N_3O_7$: N, 17.00; S, 12.94. Found: N, 17.02; S, 12.84.

1-Methylthiocarbamyl-2-ethylthioimidazoline (IXb).—2-Ethylthio-2-imidazoline hydroiodide (VIIIb)[20] (5.16 g., 0.02 mole) was dissolved in water (2.5 ml.) and treated with methyl isothiocyanate (1.46 g., 0.02 mole) then with ethanol (5.5 ml.). The solution was cooled to 0° and 2.5 *M* sodium hydroxide (8 ml., 0.02 equivalent) was added during 30 min. with stirring. After 2 hr. of additional stirring, water was added and colorless crystals were obtained (2.9 g., 71%): the m.p. varied between 40 and 80° and the crystals effloresced when kept *in vacuo*.

Anal. Calcd. for $C_7H_{13}N_3S_2 \cdot 2H_2O$: N, 17.56; S, 26.79. Found: N, 17.40; S, 26.57.

Picrate.—Two tenths of a gram of base, dissolved in ethanol (4 ml.), was treated with 4 ml. of 5% ethanolic picric acid; yellow crystals were recrystallized by dissolving them in acetone and diluting with water; m.p. 147–148°.

Anal. Calcd. for $C_7H_{13}N_3S_2 \cdot C_6H_3N_3O_7$: N, 19.44; S, 14.83. Found: N, 19.57; S, 14.79.

1-Ethylthiocarbamyl-2-ethylthioimidazoline (IXc).—IXc has been obtained as was IXb, from VIIIb, ethyl isothiocyanate, and sodium hydroxide. It separated from the aqueous alcoholic solution as a heavy oil; water was added to complete precipitation and the oil was taken up in ether. The extract, washed (water), dried (sodium sulfate), and evaporated, left a colorless oil (65–70%). For the identification, a sample was converted into the *picrate*; prisms from acetone and water; m.p. 136°.

Anal. Calcd. for $C_8H_{15}N_3S_2 \cdot C_6H_3N_3O_7$; N, 18.82; S, 14.37. Found: N, 18.60; S, 14.24.

1-Phenylthiocarbamyl-2-ethylthioimidazoline (IXd).—This compound was obtained like IXb, using phenyl isothiocyanate; during and after the addition of sodium hydroxide, a solid separated which was filtered after 4 hr., thoroughly washed with water, dried, then washed with ether leaving a colorless powder (66%); m.p. 83–85°. It was analyzed as the *picrate*; m.p. 128–130°, alteration above 110°.

Anal. Calcd. for $C_{12}H_{15}N_3S_2 \cdot C_6H_3N_3O_7$: N, 16.99; S, 12.97. Found: N, 17.10; S, 13.01.

Thiohydrolysis of IXa and IXb; IXc; IXd.—Each thioether has been treated either without a solvent (IXa) or in a saturated alcoholic solution (IXb, IXc, and IXd) with an ethanolic solution of equimolecular sodium hydrosulfide, obtained by passing dry hydrogen sulfide into a 5% solution of sodium in ethanol. In one case (IXd), bubbling of hydrogen sulfide was continued after mixing of the reagents, for an additional hour. In all cases the reaction mixture was kept with occasional stirring at room temperature from 30 min. to a few hours, till no more changes could be noted. The resulting colorless solids were washed first with water and then with ethanol, and recrystallized from an appropriate solvent. No care was taken to secure highest yields; the following have been obtained in the indicated times: Va, 68% in 21 hr., from IXa; 65% in 30 min. from IXb; Vb, 73% in 30 min. from IXc; Vc, 22% in 2 hr. from IXd. They were identical with the compounds described previously with respect to melting point, mixture melting point, infrared spectra, and chromatographic behavior.

Reactions of Ethylene Diisothiocyanate (I) with Dimethylamine. A.—To 0.86 g. (0.006 mole) of I was carefully added under stirring 6 ml. of aqueous 22% dimethylamine (0.03 mole). An exothermic reaction took place and a solid was gradually formed which was thoroughly stirred during 40 min. The colorless microcrystalline powder was filtered, washed with water, and dried (1 g., 72%). It was recrystallized from water, yielding colorless opaque needles, soluble in acetone and chloroform, less so in ethanol, ether, benzene, and petroleum ether; m.p. 179–181°; R_f 0.87.

Anal. Calcd. for $C_8H_{18}N_4S_2$ (IId): N, 23.92; S, 27.32. Found: N, 23.72; S, 27.39.

B.—A solution of I (1.68 g., 0.0116 mole) in 5 ml. of anhydrous acetone was added dropwise with stirring during 10 min. into 13.2 ml. of an acetone solution of dimethylamine (2.8 g., 0.062 mole). The reaction was slightly exothermic at the beginning; after 3 hr. of stirring, small colorless prisms of IId were gradually formed (1.26 g., 46%).

C.—To the solution of I (4.75 g., 0.033 mole) in 14 ml. of acetone, was added dropwise for 10 min., under stirring, 10 ml. of an acetone solution of dimethylamine (1.49 g., 0.033 mole). The dark solution obtained was left overnight with continued stirring; a pink-yellow powder separated. It was filtered, washed with acetone, and then with hot ethanol to remove trace of IId, and crystallized from ethanol in the presence of charcoal. Small colorless prisms were obtained, soluble in acetone and chloroform, less so in ether and cold water or ethanol, more in the warm; m.p. 186–187°; R_f 0.81.

Anal. Calcd. for $C_6H_{11}N_3S_2$ (Vd): C, 38.09; H, 5.86; N, 22.21; S, 33.83. Found: C, 38.13; H, 6.08; N, 22.35; S, 34.32.

Reactions of Ethylene Diisothiocyanate (I) with Pyrrolidine. A.—I (1.67 g., 0.0116 mole) was carefully treated with pyrrolidine (4.1 g., 0.059 mole) diluted with water to give a 30% solution. A pink-yellow mass was obtained which was left overnight, then homogenized in a mortar and filtered. The powder was washed with water and ethanol and dried (2 g., 66%); by several crystallizations from ethanol, in presence of charcoal, colorless platelets assembled in stars were obtained; m.p. 223–224°; R_f 0.91.

Anal. Calcd. for $C_{12}H_{22}N_4S_2$ (IIe): N, 19.56; S, 22.38. Found: N, 19.12; S, 22.37.

B.—A sample of I (3.3 g., 0.023 mole), dissolved in 10 ml. of acetone was added dropwise during 20 min. with stirring, to 8.2 g. (0.115 mole) of pyrrolidine diluted with 10 ml. of acetone. Stirring was continued 2 hr. and 3.9 g. (60%) IIe was obtained.

C.—Another sample of I (4.5 g., 0.031 mole) dissolved in 13 ml. of acetone, was treated dropwise (15 min.) with pyrrolidine (2.23 g., 0.031 mole) diluted with 13 ml. of acetone. Stirring was continued for 3 hr., then the orange powder was filtered, washed (acetone and benzene), and dried (1.43 g.); evaporation of the acetone mother liquor gave an additional 1.4 g. (total 42%). After extraction with boiling ethanol, to remove trace amounts of IIe, it was recrystallized from the same solvent, yielding colorless shiny needles, melting at 196–197°; R_f 0.87.

Anal. Calcd. for $C_8H_{13}N_3S_2$ (Ve): C, 44.62; H, 6.08; N, 19.52; S, 29.78. Found: C, 44.46; H, 6.15; N, 19.73; S, 29.52.

Reactions of Ethylenediisothiocyanate (I) with Piperidine. A.—The suspension of I (1.7 g., 0.0118 mole) in 15.2 ml. of 33% aqueous solution of piperidine (0.055 mole) was stirred 20 min., then left overnight. The solid which formed was filtered, washed with ethanol and water, and dried (2.13 g.). Mono- and bidimensional chromatography (second run in water) indicated that a mixture of IIf and Vf had been obtained. The two compounds were separated using ethanol in which Vf gave supersaturated solutions; their identification is described.

B.—A solution of I (1.4 g., 0.01 mole) in 5 ml. of acetone was added dropwise during 20 min. with stirring, to piperidine (4.15 g., 0.05 mole) diluted with 5 ml. of acetone. A colorless crystalline powder gradually separated, which was washed with acetone and dried (2.95 g., 97%). On crystallization from ethanol, colorless prisms were obtained, very slightly soluble in water, ethanol and benzene, more so in dioxane; m.p. 207–209°; R_f 0.91; in water, R_f 0.56.

Anal. Calcd. for $C_{14}H_{26}N_4S_2$ (IIf): N, 17.82; S, 20.36. Found: N, 17.95; S, 20.44.

(20) J. E. Baer and R. G. Lockwood, *J. Am. Chem. Soc.*, **76**, 1162 (1954); W. Wilson, *J. Chem. Soc.*, 1389 (1955).

C.—A solution of I (3.29 g., 0.022 mole) in acetone (10 ml.) was treated dropwise during 10 min. with piperidine (1.9 g., 0.022 mole) in acetone (10 ml.) and stirring was continued 3.5 hr. The yellow powder (3.55 g., 70%) was extracted with hot ethanol to remove traces of IIf, then crystallized from ethanol; colorless prisms, m.p. 180–181°; R_f 0.88; in water, R_f 0.75.

Anal. Calcd. for $C_9H_{15}N_3S_2$ (Vf): C, 47.15; H, 6.70; N, 18.33; S, 27.92. Found: C, 46.80; H, 6.69; N, 18.28; S, 27.70.

Reactions of Ethylene Diisothiocyanate (I) with Diethylamine.—I was treated with diethylamine in water and in acetone according to runs A to B. The presence of both mono- and bisadducts was ascertained by chromatography (R_f values: 0.90 and 0.87, respectively). The products were not investigated further.

Hydrolysis.—All mono- and bisadducts were stable towards dilute acid. The substituted ethylenedithioureas were also stable towards alkali. The monoadducts, on the contrary, were hydrolyzed by dilute sodium hydroxide with formation of the known imidazolidine-2-thione (VII). This was collected in minute amount after refluxing 30 min. on the water bath Vf (100 mg.) with normal sodium hydroxide (10 ml.); in the other cases, VII was identified by chromatography of the alkaline solutions by comparison with a standard sample. In most cases, additional spots due to unidentified compounds appeared in the chromatograms. Acidification of the alkaline solution caused evolution of hydrogen sulfide.

Acknowledgment.—We gratefully acknowledge the support by Shell Internationale Research, Maatschappij N.V., The Hague, Holland, for the investigation.

Interaction of Phenyl Isocyanate and Related Compounds with Sodium Borohydride[1]

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Catalytic trimerization of phenyl, *p*-tolyl, and *p*-methoxyphenyl isocyanates has been observed with several complex metal hydrides, with and without solvent. Excess sodium borohydride in refluxing diglyme (diethylene glycol dimethyl ether) transforms phenyl isocyanate, its dimer and trimer, and *N*-formyl-*N*,*N*'-diphenylurea into a mixture of aniline, *N*-methylaniline, tris(*N*-methylanilino)borine, and formanilide. The latter compound is itself converted into aniline, *N*-methylaniline, and the aminoborine under the same conditions. Phenyl isothiocyanate yields only *N*-methylaniline and traces of the aminoborine at high temperature, but at lower temperatures thioformanilide is formed. A mechanism for the formation of the observed products is proposed.

The reaction of phenyl isocyanate with lithium aluminum hydride in refluxing ether has been reported by several workers[3,4] to give *N*-methylaniline in high yield. In a careful quantitative study Finholt and coworkers[5] reported the following stoichiometry for the following reaction.

$$4PhNCO + 3LiAlH_4 \rightarrow (PhNCH_3)_4AlLi + 2LiAlO_2$$

Hydrolysis of the intermediate complex then gave *N*-methylaniline.

In addition, other reports[6,7] have appeared on the reduction to substituted methylamines of other isocyanates with lithium aluminum hydride.

Formanilide[3] and phenyl isothiocyanate[4,5] also yield *N*-methylaniline with lithium aluminum hydride while *sym*-diphenylurea[4] was recovered unchanged after thirty hours in contact with lithium aluminum hydride.

This investigation extends complex metal hydride reactions with aryl isocyanates to sodium borohydride.

Results and Discussion

In the presence of catalytic amounts of sodium borohydride phenyl, *p*-tolyl, and *p*-methoxyphenyl isocyanates are converted into the corresponding trimers (isocyanurates) in high yield. Identity of the products was established by mixture melting points and comparison of their infrared curves with those of authentic samples. The formation of trimers was exothermic in either dioxane or diglyme without external heating when as little as 0.01 mole of sodium borohydride per mole of isocyanate was present. When the catalyst concentration was one tenth this value moderate heating was required to initiate reaction. Treatment of phenyl isocyanate with a catalytic amount of lithium aluminum hydride in ether also afforded the trimer.

Bulk polymerization of phenyl isocyanate by a catalytic amount of sodium borohydride also afforded triphenyl isocyanurate, although in this case moderate heating was required. Lithium aluminum hydride, lithium tri-*t*-butoxyaluminohydride, and potassium borohydride are also effective catalysts in the bulk polymerization of phenyl isocyanate. The two lithium hydrides gave exothermic reactions while potassium borohydride, like sodium borohydride, required moderate heating to initiate a reaction.

The catalytic bulk or solution trimerization of phenyl isocyanate by lithium aluminum hydride is noteworthy in view of the several reports of the formation of *N*-methylaniline from the isocyanate and equivalent quantities of this hydride. An explanation may be that, in the presence of excess hydride, reduction is the predominant reaction. Alternatively, an equilibrium may exist between the isocyanate monomer and the initially formed trimer, with gradual catalytic detrimerization to the monomer as reduction of the latter proceeds. Purely thermal displacement of the equilibrium in favor of the monomer is an unsatisfactory explanation for the failure to isolate trimer in refluxing ether since triphenyl isocyanurate represents a structure which is very stable to thermal attack.

(1) Presented before the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(3) F. Wessely and W. Swoboda, *Monatsh. Chem.*, **82**, 621 (1951).

(4) W. Ried and F. Müller, *Chem. Ber.*, **85**, 470 (1952).

(5) A. E. Finholt, C. D. Anderson, and C. L. Agre, *J. Org. Chem.*, **18**, 1338 (1953).

(6) H. H. Zeiss and W. B. Martin, Jr., *J. Am. Chem. Soc.*, **75**, 5335 (1953).

(7) R. L. Dannley, R. G. Taborsky, and M. Lukin, *J. Org. Chem.*, **21**, 1318 (1956).

TABLE I

REACTIONS WITH EXCESS SODIUM BOROHYDRIDE IN REFLUXING DIGLYME

		Product and yield								
		Aniline[a]		N-Methylaniline[a]		Tris(N-methylanilino)-borine[b]		Formanilide[a,c]		
Compound	Moles	Mmoles	%	Mmoles	%	Mmoles	%	Mmoles	%	Total %
PhNCO	0.1	4.8	4.8	25.7	26	13.4	40	3.3	3.3	74
$(PhNCO)_2$	.025	3.4	6.8	11.0	22	5.6	34	...	...	63
$(PhNCO)_3$	.017	2.1	4.1	17.2	34	4.7	28	1.7	3.3	69
PhNHCHO	.1	15.2	15	21.4	21	11.2	34	5.7	5.7	76
PhN(CHO)CONHPh	.024	4.9	10	15.1	31	5.2	32	0.8	1.7	75
PhNCS	.05	..	..	45.3	91	0.3	1.8			93

[a] Yields determined by gas chromatography. [b] Crude product. [c] Minimum yield.

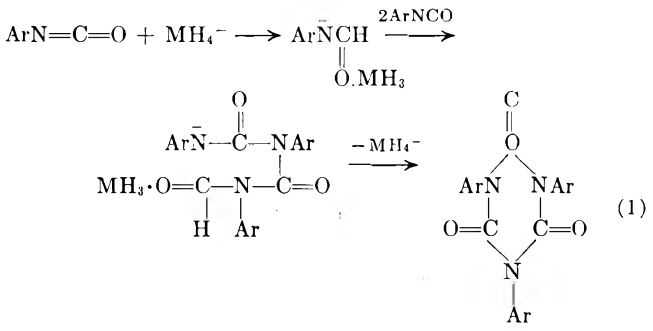
An example of detrimerization of an isocyanurate has been reported by Shapiro and co-workers[8] who found that tris(*m*-chlorophenyl) isocyanurate was converted to ethyl *m*-chlorophenylurethane upon reaction with ethanol for three hours at 120° in the presence of lithium ethoxide. The alkoxide was also a trimerization catalyst for the isocyanate.

When 0.5 mole of sodium borohydride per mole of phenyl isocyanate was employed in diglyme at temperatures up to 60°, triphenyl isocyanurate was isolated, irrespective of the order of addition of reagents. When the hydride was added to the isocyanate, however, a better yield of trimer was realized. In the case of reverse addition, reactions leading to reduction products probably predominated, although this possibility was not investigated fully.

No trimerization occurred with *n*-butyl, *o*-tolyl, and *o*-chlorophenyl isocyanates and catalytic amounts of sodium borohydride, even with heating. The unchanged isocyanates were recovered as the corresponding ureas after reaction with water. Steric factors may account for the lack of reaction in the case of the *o*-substituted phenyl isocyanates, although trimers have been obtained from these compounds using potassium acetate.[9] No reason for the lack of trimerization of *n*-butyl isocyanate is apparent, although the trimerization of alkyl isocyanates has been reported.[10]

Utilization of catalyst in the reduction of the nitro group[11] in *p*-nitrophenyl isocyanate may account for the color change noted when this isocyanate was treated with sodium borohydride. No trimer was obtained and the unchanged isocyanate was converted to urea.

Trimer formation catalyzed by complex metal hydrides may follow the path outlined in equation 1.



(1)

In refluxing diglyme (b.p. 162°) the reaction of phenyl isocyanate and excess sodium borohydride takes an entirely different course. After addition of dilute acetic acid to the cooled reaction mixture, aniline, *N*-methylaniline, and tris(*N*-methylanilino)borine were identified as reaction products, with yields of 4.8, 26, and 40%, respectively. No attempt was made to separate the small quantity of aniline from *N*-methylaniline and diglyme, but it was possible to analyze the mixture by gas chromatography on a silicone column. Reaction of the mixture with tosyl chloride and alkali afforded the *p*-toluenesulfonamides of the two amines. These derivatives were identified by mixture melting points and infrared spectra. In addition, the gas chromatogram of the amine mixture indicated the presence of a peak with the same retention time as formanilide. The yield of formanilide calculated by this analysis was 3.3%. This and the other values for formanilide reported in Table I probably represent only minimum yields of this product since its isolation from the reaction mixtures was not attempted in view of its high water solubility and because of the complex nature of the mixtures.

The identity of the aminoborine was established by mixture melting point with an authentic specimen and by comparison of infrared curves of the two samples.

In addition to phenyl isocyanate, several related compounds were subjected to the same reaction conditions with sodium borohydride, one mole of the hydride being used for each equivalent of compound. The same products were obtained from phenyl isocyanate dimer, trimer, and *N*-formyl-*N*,*N*′-diphenylurea as from phenyl isocyanate, except that no formanilide was detected in the amine fraction obtained from the dimer (although this was no doubt a product of the reaction). These derivatives of phenyl isocyanate probably function as phenyl isocyanate generators under the influence of heat and/or the catalytic activity of sodium borohydride. In addition to the isocyanate, thermal dissociation of the urea derivative yields formanilide. Formanilide gave the two amines and the aminoborine upon treatment with sodium borohydride in refluxing diglyme. Some formanilide was unchanged (Table I).

In contrast to the formation of trimer from phenyl isocyanate and excess sodium borohydride, at 15° phenyl isothiocyanate gave reasonable yields of thioformanilide, the primary reduction product expected from the isothiocyanate. The presence of aniline and *N*-methylaniline in the reaction mixture was not investigated. However, at 90° no thioformanilide was isolated, but the main product was *N*-methylaniline (74%), accompanied by aniline (6%), and a small amount of a solid, m.p. >200°, which was probably tris(*N*-methylanilino)borine. At still higher temperatures

(8) S. L. Shapiro, V. Bandurco, and L. Freedman, **26**, *J. Org. Chem.*, 3710 (1961).
(9) I. C. Kogon, *J. Am. Chem. Soc.*, **78**, 4911 (1956).
(10) J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43**, 203 (1948).
(11) C. E. Weill and G. S. Panson, *J. Org. Chem.*, **21**, 803 (1956).

(162°) the reaction gave predominantly *N*-methylaniline and a trace of the aminoborine, but no aniline (Table I).

No attempt was made to determine the actual hydride balance in the various reactions, but in all cases an excess of hydride was employed, as indicated by the gas evolution upon acidification of the reaction mixtures.

Several likely pathways can be considered for the formation of the observed products in the various reactions in refluxing diglyme. Initial attack by the hydride on phenyl isocyanate probably occurs at the carbon–oxygen bond since the form Ic makes the largest contribution to I. In the case of phenyl iso-

$$\underset{\text{a}}{\text{PhN}^{-}\text{—C}^{+}\text{=Y}} \longleftrightarrow \underset{\text{b}}{\text{PhN=C=Y}} \longleftrightarrow \underset{\text{c}}{\text{PhN=C}^{+}\text{—Y}^{-}}$$

I. Y = O
II. Y = S

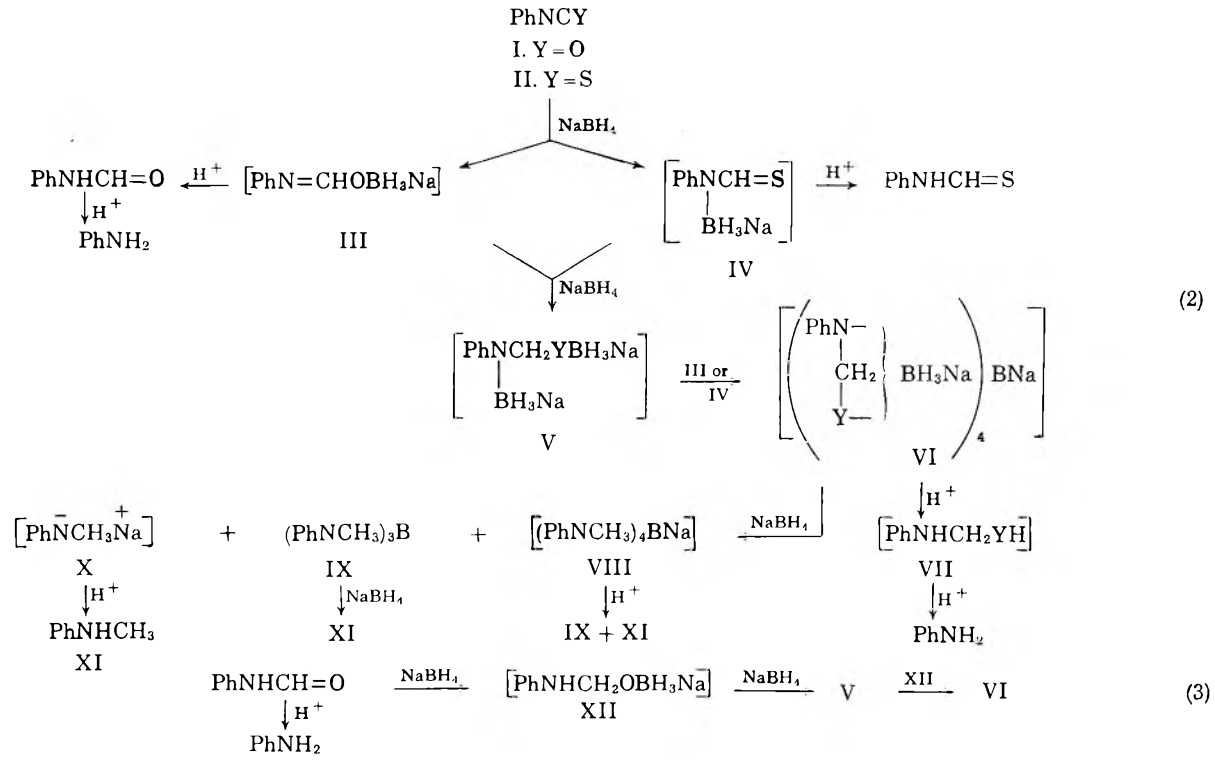
thiocyanate, initial attack is more likely at the carbon–nitrogen bond since IIa would be expected to make the greatest contribution to II, in view of the greater electronegativity of nitrogen relative to sulfur. The sequences of equations 2 and 3 represent the proposed course of the reactions.

The intermediate VI may result from formanilide through reduction and salt formation.

An alternate route to aniline may involve hydrolysis *via* the route VI → VII.

It was determined that tris(*N*-methylanilino)borine was not appreciably hydrolyzed under the weakly acidic conditions used in working up the various reaction mixtures (85–96% recovery). Reaction of IX and sodium borohydride (1:3.5 molar ratio) in refluxing diglyme for one hour gave a 44% yield of XI and recovered IX (12%). The sequence VI → VIII → IX + XI cannot be the sole route by which *N*-methylaniline is formed since, in practice, the amount of the amine formed relative to the amount of the aminoborine isolated is much greater than that predicted by the above sequence. For these reasons it is likely that intermediates such as IX and X are precursors for most of the *N*-methylaniline.

The higher yield of the aminoborine from phenyl isocyanate compared to its sulfur analog would seem to indicate the formation in the former case of an intermediate VI in which many of the boron atoms are bound to three or four nitrogen atoms, while in the latter case most of the boron atoms are probably bound more or less equally to nitrogen and sulfur.



Hydrolysis of the intermediate III leads to formanilide (*via* its tautomeric form), which in turn is partly hydrolyzed to aniline (actually, aniline was found in about 10% yield when formanilide was subjected to the acidic conditions used in working up the various reactions). Further reduction by the hydride of III and IV would eventually lead to the (possibly polymeric) intermediate VI. Random distribution of nitrogen and oxygen (or sulfur) on boron in VI would be expected to furnish, following hydrogenolysis of carbon–oxygen (or carbon–sulfur) bonds by more hydride, intermediates such as VIII and X and tris(*N*-methylanilino)borine (IX). Acid hydrolysis of VIII and X leads to *N*-methylaniline (XI) and IX.

The formation of tris(*N*-methylanilino)borine by reaction of sodium borohydride and phenyl isocyanate, its generators, formanilide, and phenyl isothiocyanate is apparently the first case of the formation of a compound containing a stable boron–nitrogen bond from sodium borohydride and a compound containing a carbon–nitrogen double bond,[12] although the analogous formation of boron–oxygen[13] or boron–carbon[14] bonds

(12) W. Gerrard, "The Organic Chemistry of Boron," Academic Press, Inc., New York, N. Y., 1961.

(13) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 121.

(14) H. C. Brown, "Organometallic Chemistry," H. Zeiss, Ed., Reinhold Publishing Corp., New York, N. Y., 1960, p. 154.

from compounds containing carbon–oxygen or carbon–carbon double bonds, respectively, are known.

Reduction of amides by sodium borohydride apparently has not been reported previously.[15]

Experimental[16]

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer using potassium bromide disks. Gas chromatographic analyses were made on the Aerograph Model A-700 gas chromatograph using acid-washed Chromosorb P coated with silicone high vacuum grease.[17]

Reagents and Solvents.—Liquid isocyanates were redistilled and *p*-nitrophenyl isocyanate was recrystallized before use. Sodium borohydride was purified according to Brown.[18] Diglyme was refluxed over sodium borohydride and redistilled. Dioxane was purified according to Fieser.[19]

Solution Trimerization of Phenyl Isocyanate.—A solution of 6.00 g. (0.05 mole) of phenyl isocyanate in 20 ml. of dioxane, protected with a calcium chloride drying tube, was cooled to 3° in an ice bath and 1 ml. (0.5 mmole) of sodium borohydride solution in diglyme (0.38 g. in 20 ml.) was added as the solution was stirred by a magnetic stirrer. Within 2 min. the temperature rose to 15° as a solid precipitated. After 15 min. in the ice bath, 50 ml. of ether was added to the mixture and the filtered solid was washed with ether. The weight of triphenyl isocyanurate, m.p. 279–280°, was 5.03 g. (84%). Recrystallization from a methylene chloride–petroleum ether (b.p. 30–60°) mixture gave white needles, m.p. 280–281° (lit.[9] m.p. 280–281°), m.m.p. with an authentic sample 278–279°. The infrared spectrum was identical with that of an authentic sample.

In a similar manner tris(*p*-methoxyphenyl) isocyanurate, m.p. 263–264° (lit.[9] m.p. 259–260°), and tris(*p*-tolyl) isocyanurate, m.p. 268–269° (lit.[9] m.p. 264–265°), were obtained in yields of 86 and 91%, respectively, from the corresponding isocyanates with catalytic amounts of sodium borohydride in dioxane. Identification of the isocyanurates was made by mixture melting points and comparison of infrared curves with authentic samples.

A phenyl isocyanate to catalyst molar ratio of 1:0.001 required heating for 45 min. at 70° in dioxane to obtain the trimer (93% yield).

Addition of sodium borohydride (0.05 mole) in diglyme to a solution of phenyl isocyanate (0.1 mole) in diglyme at room temperature caused of phenyl isocyanate (0.1 mole) in diglyme at room temperature caused the solution to heat up to 60°. After pouring the mixture into water and acidifying with 20% acetic acid, the trimer was recrystallized from 95% ethanol, m.p. 277–278° (69%). When the order of addition was reversed a much lower yield of trimer was obtained.

Unsuccessful attempts were made to trimerize *o*-chlorophenyl, (1 hr. at 70°), *o*-tolyl (1.5 hr. at 70°), *p*-nitrophenyl (0.5 hr. at 80°), and *n*-butyl (1 hr. at 70°) isocyanates in dioxane with catalytic amounts of sodium borohydride. In these cases the corresponding ureas were isolated and identified by mixture melting points and infrared data after the unchanged isocyanates were treated with water and acetone.

Trimerization of phenyl isocyanate by lithium aluminum hydride (0.01 mole per mole of isocyanate) in ether at room temperature was achieved in at least 60% yield (the odor of the reaction mixture indicated the presence of some unchanged isocyanate) within 5 min.

Bulk Trimerization of Phenyl Isocyanate.—Triphenyl isocyanurate was obtained by bulk polymerization of the isocyanate using a ratio of 1 mole of isocyanate to 0.01 mole of the following hydrides (% yields): lithium aluminum hydride (78%), lithium tri-*t*-butoxyaluminohydride (89%), potassium borohydride (74%), and sodium borohydride (74%). Trimerization with the first two hydrides was very exothermic while the latter two required heating to 70–80° to initiate reaction.

Bulk polymerization of *o*-tolyl and *o*-chlorophenyl isocyanates was unsuccessful when attempted at 80° for 2 hr.

Reaction of Phenyl Isocyanate with Excess Sodium Borohydride at High Temperature.—To a slurry of 3.78 g. (0.1 mole) of sodium borohydride in 50 ml. of diglyme at reflux was added over 15 min. with stirring a solution of 11.92 g. (0.1 mole) of phenyl isocyanate in 30 ml. of diglyme. The reaction mixture was protected by a calcium chloride tube. During the exothermic reaction most of the sodium borohydride dissolved. Stirring and refluxing was continued for 1 hr. after the addition was completed, and the yellow solution was cooled and poured into 750 ml. of ice and water. After carefully acidifying with 100 ml. of 20% acetic acid to decompose excess hydride, the mixture was left in a refrigerator overnight. Tris(*N*-methylanilino)borine was filtered and washed well with water, 4.42 g. (40%), m.p. 206–211°. The infrared spectrum of an ether-washed sample showed weak bands near 3 and 6 μ, indicating the presence of traces of *sym*-diphenylurea. Upon hydrolysis of the crude aminoborine with refluxing concentrated hydrochloric acid, 3% (based on the weight of crude sample) *sym*-diphenylurea was obtained in addition to 89% of the theoretical amount of *N*-methylaniline and a trace of aniline (probably from hydrolysis of the urea). The aminoborine was stable to hydrolysis by acetic acid of the concentration used in the work-up of the reaction mixture. Sublimation of the crude aminoborine at 185° (*ca.* 0.001 mm.) gave the pure product, m.p. 209–213° (lit.[20] m.p. 210°) and m.m.p. with an authentic sample 212–215°. Its infrared spectrum was identical with the infrared spectrum of an authentic sample.

Anal. Calcd. for $C_{21}H_{24}BN_3$: C, 76.60; H, 7.35; N, 12.76. Found: C, 76.81; H, 7.41; N, 12.73.

The boron-containing, water-soluble sublimation residue gave infrared peaks near 3 and 6 μ.

After filtration of the aminoborine, the acidic filtrate of the original reaction mixture was treated with concentrated hydrochloric acid and ether extracted. The water layer was made alkaline with sodium hydroxide and extracted with ether after saturating wth salt. After washing the extract with salt solution and drying over sodium sulfate, the ether was evaporated and the residue analyzed by gas chromatography. In addition to traces of ether and a large amount of diglyme, the residue contained 0.45 g. (4.8% yield) of aniline and 2.76 g. (26% yield) of *N*-methylaniline. Treatment of the mixture with tosyl chloride and sodium hydroxide allowed the isolation, after the usual work-up, of the *p*-toluenesulfonamides of aniline and *N*-methylaniline, m.p. 103–104° and 94–95°, respectively. In addition to the two amines the gas chromatogram indicated the presence of 0.40 g. (3.3% yield) of formanilide.

Phenyl isocyanate dimer, trimer, formanilide, *N*-formyl-*N*,*N*′-diphenylurea, and phenyl isothiocyanate were treated with sodium borohydride in the same way except that the solid compounds were mixed with the hydride prior to refluxing. One mole of borohydride was used for each mole of phenyl isocyanate equivalent. The yields of the various products are compared with those from phenyl isocyanate in Table I.

Thioformanilide.—To a suspension of 0.95 g. (0.025 mole) of sodium borohydride in 15 ml. of diglyme was added dropwise with stirring over 15 min. 6.75 g. (0.05 mole) of phenyl isothiocyanate while keeping the temperature near 10–15° with an ice bath. The yellow reaction mixture (odor of hydrogen sulfide) was then stirred another 1.5 hr. in the ice bath, poured into 250 ml. of ice–water, and acidified with 8 ml. of 6 *N* hydrochloric acid, heated to 70°, and then cooled in an ice bath. The yield of crude thioformanilide, m.p. 137°, was 4.80 g. (70%). Recrystallization from hot water gave white needles, m.p. and m.m.p. with an authentic sample 139–140° (lit.[21] m.p. 138°), 3.4 g. The product gave an infrared curve identical with that of an authentic sample. The presence of aniline and *N*-methylaniline in the reaction mixture was not investigated.

(15) Ref. 13, p. 592.

(16) Melting points are uncorrected.

(17) Mention of trade names and firms does not imply their endorsement by the Department of Agriculture over similar products or firms not mentioned.

(18) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

(19) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 284.

(20) A. Dornow and H. H. Gehrt, *Angew. Chem.*, **68**, 619 (1956).

(21) A. Reissert, *Ber.*, **37**, 3708 (1904).

A reaction time of 1 hr. at 25° (1:1 molar ratio of reactants) decreased the yield of thioformanilide to 49%; reaction for 1 hr. at 90° (1:1 molar ratio of reactants) gave only aniline (6%), *N*-methylaniline (74%), and a solid melting above 200° which was probably tris(*N*-methylanilino)borine (9%) but was not further investigated.

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S-[ω-(Aminoöxy)alkyl]isothiuronium Salts, ω,ω′-Bis(aminoöxy)alkanes and Related Compounds[1]

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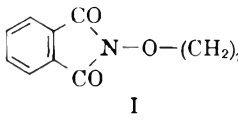
The reaction of N-hydroxyphthalimide with ω,ω′-dibromoalkanes yields ω-(phthalimidoöxy)alkyl bromides, Ia, and ω,ω′-bis(phthalimidoöxy)alkanes, Ib. Reaction of Ia with thiourea, followed by hydrolysis, leads to a facile synthesis of S-[ω-(aminoöxy)alkyl]isothiuronium salts, IIc. Hydrolysis of Ib makes available ω,ω′-bis(aminooxy)alkanes which were characterized by their salts, amide and sulfonamide derivatives.

To continue our studies[2] on the synthesis of potential prophylactic agents capable of protecting animals from otherwise lethal doses of ionizing radiation, we turned our attention to the synthesis of S-[ω-(aminoöxy)alkyl]-isothiuronium salts, IIc. Such molecules are analogs and homologs of the active 2-aminoethanethiol and the corresponding isothiuronium salt, $H_3\overset{+}{N}-(CH_2)_2-S-C(-NH_2)=NH_2^+\ 2X^-$. Structure IIc meets the criteria seemingly essential for protective activity: a basic group, in this instance the aminoöxy moiety, in close vicinity of a thiol or potential thiol group, *viz.*, the isothiuronium group.

In designing these molecules, the aminoöxy function was to be liberated last by the acid hydrolysis of the corresponding phthalimidoöxy derivative.[3] The key intermediates in the synthesis of IIc were the ω-(phthalimidoöxy)alkyl bromides, Ia, which became readily available from the reaction of N-hydroxyphthalimide and ω,ω′-dibromoalkanes.



I

$H_3N^+-O-(CH_2)_n-Z\ \ Br^-$

II

where the substituent Z is, in

(a) Br

(b) 

(c) $S-C(-NH_2)=NH_2^+\ Br^-$

(d) $S-SO_3^-\ Na^+$

(e) $O-NH_3^+\ Br^-$

(f) SH

Displacement of the bromo group in Ia with thiourea furnished the S-[ω-(phthalimidoöxy)alkyl]isothiuronium bromide, Ic, which was hydrolyzed readily by hydrobromic acid to the aminoöxy isothiuronium salt, IIc. This sequence of reactions was used to prepare five homologs of IIc (n = 2 to 6).

The formation of the ω-(phthalimidoöxy)alkyl bromide Ia, was invariably accompanied by some ω,ω′-bis(phthalimidoöxy)alkane, Ib The mixture was separated either by fractional crystallization or column chromatography. Hydrolysis with hydrobromic acid of Ib afforded the corresponding ω,ω′-bis(aminoöxy)-alkane dihydrobromides, IIe. The free bases were characterized by solid amide or sulfonamide derivatives.

These series of reactions are described somewhat in detail for one member of the series, *viz.*, when n = 2. N-Hydroxyphthalimide was treated with 1,2-dibromoethane in the presence of triethylamine at room temperature and gave a mixture of Ia and Ib (n = 2). The reaction of Ia with thiourea afforded the crystalline salt, Ic from which the phthaloyl moiety was readily cleaved off with hydrobromic acid to produce IIc (n = 2). A similar reaction of Ia with N-methylthiourea furnished the crystalline N-methyl analog of Ic (n = 2) but hydrolysis led to an oily salt, $H_3\overset{+}{N}-O-(CH_2)_2-S-C(-NH_2)=NHCH_3^+2Br^-$, which was characterized as a crystalline dipicrate. When Ib (n = 2) was hydrolyzed with hydrobromic acid, 1,2-bis(aminoöxy)-ethane was isolated as the crystalline dihydrobromide. The free base was characterized as its benzamide ($C_6H_5CONHOCH-)_2$, its *p*-toluenesulfonamide, (p-$CH_3-C_6H_4SO_2NHOCH^{2-})_2$, and its *p*-acetamidobenzenesulfonamide. The last one of these was hydrolyzed further to the sulfanilamide analog, (p-$H_2N-C_6H_4SO_2-NHOCH_2-)_2$.

It was also possible to remove the protective phthaloyl group from Ia (n = 2) with hydrobromic acid to give β-(aminoöxy)ethyl bromide hydrobromide (IIa. n = 2).

Benzoylation of this compound produced the crystalline derivative $C_6H_5CONHO(CH_2)_2Br$ which reacted further with thiourea to give the isothiuronium salt, $C_6H_5CONHO(CH_2)_2SC(-NH_2)=NH_2^+Br^-$. An attempt to prepare 2-(aminoöxy)ethanethiol, IIf (n = 2), from Ia (n = 2) by the following approach was un-

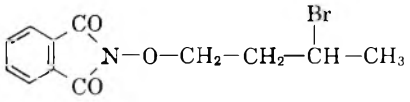
(1) This project was sponsored by the office of the Surgeon General U. S. Army Medical Research and Development Command, whose generous support through a research contract (DA-49-193-MD-2047) is gratefully acknowledged.

(2) Our previous paper, L. Bauer and T. L. Welsh, *J. Org. Chem.*, **27**,4382 (1962), summarizes the background in this field.

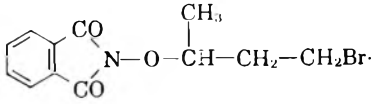
(3) The introduction of the aminoöxy group into a molecule *via* the phthalimidoöxy derivative was first described by A. F. McKay, *et al.*, *Can. J. Chem.*, **38**, 343 (1960), and presents certain advantages. The alkylation of N-hydroxyphthalimide is rapid and usually affords a crystalline derivative which is hydrolyzed with great ease by hydrobromic acid (3–5 min.). Other methods are available for the preparation of aminoöxyalkyl compounds *via* suitable derivatives of hydroxylamine. Recently, E. L. Schulmann, *et al.*, *J. Med. Pharm. Chem.*, **5**, 464 (1962), used acetoxime and benzohydroxamic acid to prepare a series of aminoöxy acids; R. M. Khomutov, *J. Gen. Chem., USSR* (Eng. Transl.), **31**, 1863 (1961), used ethyl N-hydroxyacetimidate, $CH_3-C(=NOH)OC_2H_5$, for the initial alkylation. The three references quoted here summarize this field.

successful. The reaction of Ia (n = 2) with sodium thiosulfate yielded the crystalline Bunte salt Id (n = 2) which on hydrolysis[4] with hydrobromic acid gave phthalic acid and no other identifiable product.

Other members of these series of compounds behaved similarly and important variations are mentioned in the Experimental section. An interesting reaction was encountered when N-hydroxyphthalimide was treated with the unsymmetrical 1,3-dibromobutane. There was isolated a bromo compound to which either structure III or IV could be assigned and a small quantity of 1,3-bis (phthalimidoöxy)butane. Structures III and IV arise if displacement had occurred either at the primary



III



IV

or secondary carbon atom, respectively. To establish the structure of this phthalimidoöxyalkyl bromide, the rates of reaction of 1- and 2-bromobutane with N-hydroxyphthalimide were compared. Under identical conditions, 1-bromobutane reacted with N-hydroxyphthalimide for 48 hours to give N-butoxyphthalimide in 64% yield while the 2-isomer gave N-(1-methylpropoxy)phthalimide in 23% yield. As expected these experiments indicated that the same reagent displaced the primary bromo group faster than the secondary one.

To establish structure of our product, III or IV, it was hydrolyzed to give a salt for which either structure $H_3\overset{+}{N}O-(CH_2)_2CH(Br)CH_3\ Br^-$ or $H_3\overset{+}{N}OCH(CH_3)-(CH_2)_2Br\ Br^-$ is plausible. Reduction of this aminoöxyalkyl bromide hydrobromide with lithium aluminum hydride[5] produced only 1-butanol, thus confirming the structure of the phthalimidoöxyalkyl bromide in question to be III. Thiourea was able to displace the bromo group of III to give the corresponding isothiuronium salt. An attempt to desulfurize this salt with Raney nickel to the corresponding aminoöxybutane was unsuccessful.

Experimental[6]

ω-(Phthalimidoöxy)alkyl Bromides, Ia, and ω,ω'-bis(phthalimidoöxy)alkanes, Ib.—A typical reaction is described, that for the preparation of Ia and Ib when n = 2. A solution of N-hydroxyphthalimide[7] (16.3 g.; 0.1 mole) in N,N-dimethylformamide (120 ml.), ethylene bromide (37 g.; 0.2 mole), and triethylamine (20 g.; 0.2 mole) were allowed to stand at 25° until the red reaction mixture had turned colorless (17 hr.). The precipitate which had formed was filtered off and washed with water to free it from triethylammonium bromide. This product (5.0 g.; 28% based on N-hydroxyphthalimide) consisted mainly of 1,2-bis(phthalimidoöxy)ethane, m.p. 250°. Recrystallization from N,N-dimethylformamide afforded colorless needles, m.p. 254°. Analytical data of it and its homologs are presented in Table II.

The preceding filtrate was diluted with water (800 ml.) and the solid which precipitated was filtered off. It weighed 13.6 g. (50% based on N-hydroxyphthalimide), m.p. 80–89°. This product, as well as those listed in Table I were crystallized from dilute ethanol. Analytical data of it and its homologs are also reported in Table I.

TABLE I

ω-(PHTHALIMIDOÖXY)ALKYL BROMIDES, Ia

n in Ia	Yield, %	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	50	94–96	$C_{10}H_8NO_3Br$	Calcd.	44.46	2.98	5.18
			(270.1)	Found	44.56	3.08	5.15
3	35	60–65	$C_{11}H_{10}NO_3Br$	Calcd.	46.50	3.54	4.92
			(284.1)	Found	46.70	3.65	4.90
4	37	70–72	$C_{12}H_{12}NO_3Br$	Calcd.	48.34	4.05	4.69
			(298.1)	Found	48.28	4.24	4.74
5	49	71–73	$C_{13}H_{14}NO_3Br$	Calcd.	50.02	4.52	4.48
			(312.2)	Found	50.17	4.61	4.54
6	36	66–69	$C_{14}H_{16}NO_3Br$	Calcd.	51.55	4.94	4.29
			(326.2)	Found	51.71	5.06	4.24
R[a]	45	86–89	$C_{12}H_{12}NO_3Br$	Calcd.	48.34	4.05	4.69
				Found	48.43	4.14	4.66

[a] R represents the $-CH_2CH_2CH(CH_3)-$ group, structure III.

When only 1 mole of ethylene bromide was used the yield of β-(phthalimidoöxy)ethyl bromide was 33% and that of 1,2-bis-(phthalimidoöxy)ethane was 39%.

In the reaction of the homologs both products remained in the N,N-dimethylformamide solution and were precipitated by water as a mixture. Other methods of separations were resorted to. The crude reaction product was washed with petroleum ether (b.p. 30–60°) to remove excess dibromoalkane and separation effected in the following way.

The products from the reaction starting with 1,3-dibromopropane and 1,4-dibromobutane were boiled with aqueous methanol and 2-propanol, respectively, in which the bis(phthalimidoöxy)-alkanes were insoluble; the (phthalimidoöxy)alkyl bromides crystallized on cooling the aqueous alcohol solutions.

The reactions which involved 1,3-dibromobutane, 1,5-dibromopentane and 1,6-dibromohexane yielded a mixture of two products which were separated by chromatography on alumina in the following manner. A benzene solution containing 1.5 g. of the mixture was placed on a column of acid-washed alumina (30 g.; Merck Reagent). Elution with benzene (in 20-ml. fractions) gave the phthalimidoöxy alkyl bromide and the bis(phthalimidoöxy) alkanes were eluted by methylene chloride.

S-[ω-(Phthalimidoöxy)alkyl]isothiuronium Bromides, Ic.—This general method is illustrated by preparation of S-[β-(phthalimidoöxy)ethyl]isothiuronium bromide, (Ic. n = 2). A solution of β-phthalimidoöxy)ethyl bromide (2.7 g.; 0.01 mole) and thiourea (1.1 g.; 0.014 mole) in ethanol (30 ml.) was heated under reflux for 4.5 hr. The reaction mixture was cooled and upon addition of ether, the salt crystallized. Purification procedures, yields, constants, and analytical data are given for it and the homologs in Table III. In other cases equimolar quantities of (phthalimidoöxy)alkyl bromide and thiourea were used and the time of reflux was varied from 3.5 to 4.5 hr.

N-Methyl-S-[β-(phthalimidoöxy)ethyl]isothiuronium bromide was obtained when Ia (n = 2) (5.4 g.; 0.02 mole) reacted with N-methylthiourea (1.8 g.; 0.02 mole) in ethanol (50 ml.) for 5 hr. as described before. The reaction mixture was cooled and ether added when a white crystalline product separated. It was dissolved in cold water, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol and precipitated with ether, m.p. 183–185° (4.0 g.; 55%).

Anal. Calcd. for $C_{12}H_{14}N_3O_3SBr$ (360.2): C, 40.01; H, 3.91; N, 11.67. Found: C, 40.16; H, 4.09; N, 11.46.

A reaction between 1-(phthalimidoöxy)-3-bromobutane, III, (2.9 g.; 0.01 mole) and thiourea (0.76 g.; 0.01 mole) in tetrahydrofuran (50 ml.) at reflux for 48 hr. did not afford a crystalline hydrobromide. The solvent was evaporated *in vacuo* to yield a

(4) For references of the hydrolysis of Bunte salts by mineral acid see, E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., Inc., New York, 1958, pp. 32, 328.

(5) Aliphatic halo groups are frequently reduced to alkanes by lithium aluminum hydride. B. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, **45**, 358 (1962), have shown that lithium aluminum hydride in boiling ether reduced 2-(carbethoxyaminoöxy)ethanol, $C_2H_5O_2CNHO(CH_2)_2OH$, to ethylene glycol.

(6) All melting points are uncorrected. The microanalyses reported were performed by Micro-Tech Laboratories, Skokie, Ill., and Dr. Kurt Eder, Geneva, Switzerland.

(7) W. R. Orndorff and D. S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

TABLE II

ω,ω'-BIS(PHTHALIMIDOÖXY)ALKANES, Ib

n in Ib	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	28	$HCON(CH_3)_2$	254	$C_{18}H_{12}N_2O_6$ (352.3)	Calcd.	61.36	3.43	7.96
					Found	61.57	3.46	8.08
3	3	C_2H_5OH	179–181	$C_{19}H_{14}N_2O_6$ (366.3)	Calcd.	62.29	3.85	7.64
					Found	62.33	4.05	7.67
4	18	$HCON(CH_3)_2$	260–265	$C_{20}H_{16}N_2O_6$ (380.3)	Calcd.	63.16	4.22	7.36
					Found	63.34	4.37	7.46
5	11	CH_3OH–$CHCl_3$	172–174	$C_{21}H_{18}N_2O_6$ (394.4)	Calcd.	63.96	4.60	7.10
					Found	63.89	4.66	7.20
6	10	CH_3OH–$CHCl_3$	175–176	$C_{22}H_{20}N_2O_6$ (408.4)	Calcd.	64.69	4.93	6.86
					Found	64.63	5.07	6.92
R[a]	3	CH_3OH–$CHCl_3$	190–192	$C_{20}H_{16}N_2O_6$ (380.3)	Calcd.	63.16	4.22	7.36
					Found	63.19	4.41	7.16

[a] R stands for $—CH_2CH_2CH(CH_3)-$ grouping.

TABLE III

S-[ω-(PHTHALIMIDOÖXY)ALKYL]ISOTHIURONIUM BROMIDES, Ic

n in Ic	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	61	C_6H_6–CH_3OH	188–189	$C_{11}H_{12}N_3O_3SBr$ (346.2)	Calcd.	38.16	3.46	12.14
					Found	38.44	3.77	12.06
3	58	C_6H_6–CH_3OH	182–183	$C_{12}H_{14}N_3O_3SBr$ (360.2)	Calcd.	40.01	3.91	11.66
					Found	40.09	4.09	11.76
4	74	C_6H_6–CH_3OH	161–164	$C_{13}H_{16}N_3O_3SBr$ (374.3)	Calcd.	41.72	4.30	11.23
					Found	41.64	4.54	11.13
5	75	H_2O	194–196	$C_{14}H_{18}N_3O_3SBr$ (388.30)	Calcd.	43.30	4.67	10.82
					Found	43.20	4.60	10.64
6	63	CH_3OH–$(C_2H_5)_2O$	128–130	$C_{15}H_{20}N_3O_3SBr$ (402.3)	Calcd.	44.77	5.01	10.44
					Found	44.82	5.03	10.47

TABLE IV

S-[ω-(AMINOÖXY)ALKYL]ISOTHIOUREA DIHYDROBROMIDES, IIc

n in IIc	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	77	C_2H_5OH–$(C_2H_5)_2O$	135–137 (dec.)	$C_3H_{11}N_3OSBr_2$ (297.0)	Calcd.	12.13	3.73	14.15
					Found	12.22	3.80	14.10
3	85	CH_3OH–$CHCl_3$	159–161 (dec.)	$C_4H_{13}N_3OSBr_2$ (311.0)	Calcd.	15.44	4.21	13.51
					Found	15.73	4.31	13.22
4	67	CH_3OH–$CHCl_3$	158–159 (dec.)	$C_5H_{15}N_3OSBr_2$ (325.0)	Calcd.	18.47	4.65	12.92
					Found	18.71	4.76	12.85
5	72	CH_3OH–$(C_2H_5)_2O$	137–139 (dec.)	$C_6H_{17}N_3OSBr_2$ (339.1)	Calcd.	21.25	5.05	12.39
					Found	21.35	5.10	12.59
6	91	CH_3OH–$(C_2H_5)_2O$	141–144 (dec.)	$C_7H_{19}N_3OSBr_2$ (353.1)	Calcd.	23.81	5.43	11.90
					Found	23.89	5.61	12.08

water-soluble gummy residue which did not crystallize. It formed a picrate (m.p. 230–232°) which crystallized from acetone; m.p. 233–235°.

Anal. Calcd. for $C_{19}H_{18}N_6O_{10}S$ (522.4): C, 43.67; H, 3.47; N, 16.09. Found: C, 43.95; H, 3.57; N, 16.28.

S-[ω-(Aminoöxy)alkyl]isothiourea Dihydrobromide (IIc from Ic).—The hydrolysis of Ic to give IIc is described for one member of the series, *viz.*, $n = 2$: A suspension of S-[β-(phthalimidoöxy)-ethyl]isothiuronium bromide (3.8 g.; 0.012 mole) in glacial acetic acid (10 ml.) and 48% hydrobromic acid (15 ml.) was boiled for 3–5 min. until solution was effected. On cooling, phthalic acid (1.8 g.; 99%; m.p. 206°, m.m.p. 206°) separated and was filtered off. Solvents were removed *in vacuo*, ether added to the residue, and the solid was filtered. Recrystallization solvent, yields, melting points, and analyses are listed for all members of the series in Table IV.

Hydrolysis of N-methyl-S-[β-(phthalimidoöxy)ethyl]isothiuronium bromide did not yield a crystalline product. The residue obtained after evaporating the solvents *in vacuo*, therefore was dissolved in water and treated with aqueous picric acid when N-methyl-S-[β-(aminoöxy)ethyl] isothiourea dipicrate separated. It was crystallized from ethanol; m.p. 204°.

Anal. Calcd. for $C_{16}H_{17}N_9O_{15}S$ (607.4): C, 31.63; H, 2.82; N, 20.75. Found: C, 31.80; H, 2.93; N, 20.65.

ω,ω'-Bis(aminoöxy)alkane Dihydrobromides, IIe.—The hydrolysis of ω,ω'-bis(phthalimidoöxy)alkanes was carried out as has been described for that of S-[ω-(phthalimidoöxy)alkyl]-isothiuronium bromides. Phthalic acid was obtained in 70–90% yield. The residue after evaporating off the solvents were washed with chloroform, filtered, and crystallized from methanol–chloroform unless indicated otherwise in Table V.

ω,ω'-Bis(benzamidoöxy)alkanes.—The dibenzoyl derivatives were prepared from IIe as shown for a typical example ($n = 2$): To an aqueous solution of 1,2-bis(aminoöxy)ethane dihydrobromide (1.0 g. in 15 ml.) was added sodium acetate trihydrate (2.5 g.) and benzoyl chloride (1.0 ml.) and the mixture shaken for 0.5 hr., then poured onto ice. The solid so obtained was purified and its yield, melting point, and analyses for it and similar derivatives are assembled in Table V.

1,3-Bis(benzamidoöxy)propane and 1,5-bis(benzamidoöxy)-pentane could not be obtained in crystalline form and hence their di-*p*-toluenesulfonyl derivatives were prepared.

ω,ω'-Bis(arenesulfonamidoöxy)alkanes.—The general method is given for the preparation of 1,2-bis(*p*-toluenesulfonamidoöxy)-ethane. *p*-Toluenesulfonyl chloride (3.2 g.) was added slowly to an ice-cold solution of IIe ($n = 2$) in pyridine (2.0 g. in 10 ml.). After the addition, the mixture was warmed for 10 min. at 100°, then poured onto ice, and the product purified (see Table V).

TABLE V

DIHYDROBROMIDES AND DERIVATIVES OF ω,ω′-BIS(AMINOÖXY)ALKANES, IIe

n in IIe	Yield, %	M.p., °C.	Mol. formula (mol. wt.)	Analysis, %			Derivatives	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)	Analyses, %		
				C	H	N						C	H	N
2	77	209 (dec.)	$C_2H_{10}N_2O_2Br_2$[b]	Calcd. 9.45	3.96	11.03	Dibenzoyl	68	C_2H_5OH-H_2O	148–150	$C_{16}H_{16}N_2O_4$	Calcd. 63.99	5.37	9.32
			(253.9)	Found 9.61	3.86	10.82					(300.3)	Found 64.11	5.39	9.27
							Di-*p*-toluenesulfonyl	95	C_6H_6 *or* CH_3OH	141–142	$C_{16}H_{20}N_2O_6S_2$ (400.1)	Calcd. 47.99 Found 47.91	5.03 4.88	6.99 7.15
							Di-*p*-(acetamidobenzene)sulfonyl	85	C_6H_6-$CH_3CO_2C_2H_5$	201–202	$C_{18}H_{22}N_4O_8S_2$ (486.5)	Calcd. 44.44 Found 44.63	4.55 4.50	11.52 11.34
							Di-*p*-(aminobenzene)sulfonyl	88	C_2H_5OH	193–195	$C_{14}H_{18}N_4O_6S_2$ (402.5)	Calcd. 41.78 Found 41.96	4.58 4.42	13.92 14.02
3	73	171–173[a] (dec.)	$C_5H_{12}N_2O_2Br_2$ (267.9)	Calcd. 13.45 Found 13.49	4.51 4.55	10.46 10.55	Di-*p*-toluenesulfonyl	94	C_6H_6	120–122	$C_{17}H_{22}N_2O_6S_2$ (414.5)	Calcd. 49.26 Found 49.13	5.35 5.52	6.75 6.72
4	54	206–206.5 (dec.)	$C_4H_{14}N_2O_2Br_2$ (282.0)	Calcd. 17.04 Found 17.16	4.96 5.16	9.93 10.09	Dibenzoyl	68	C_6H_5-CH_3OH	142–143.5	$C_{18}H_{20}N_2O_4$ (328.3)	Calcd. 65.84 Found 65.89	6.13 6.24	8.53 8.63
5	82	158 (dec.)	$C_6H_{16}N_2O_2Br_2$[c] (296.0)	Calcd. 20.29 Found 20.38	5.44 5.47	9.46 9.55	Di-*p*-toluenesulfonyl	66	C_2H_5OH-H_2O	97–99	$C_{19}H_{26}N_2O_6S_2$ (442.5)	Calcd. 51.57 Found 51.78	5.92 6.00	6.33 6.46
6	91	194–195 (dec.)	$C_6H_{18}N_2O_2Br_2$[d] (310.0)	Calcd. 23.24 Found 23.31	5.85 5.95	9.02 9.16	Dibenzoyl	71	C_6H_6	120–120.5	$C_{20}H_{24}N_2O_4$ (356.4)	Calcd. 67.40 Found 67.51	6.78 6.89	7.86 7.98

[a] Recrystallized from methanol–ether. [b] Reported by C. M. Luxmoore, *J. Chem. Soc.*, **67**, 1018 (1895), not to melt up to 250°. [c] The free base has been described by G. Palazzo, E. F. Rogers, and G. B. M. Bettolo, *Gazz. chim. ital.*, **84**, 915 (1954). [d] The dihydrochloride has been reported by A. T. Fuller and H. King, *J. Chem. Soc.*, 963, (1947).

Analytical data for the diverse sulfonamides are tabulated in Table V.

In similar fashion, from the reaction of IIe (n = 2) and *p*-acetamidobenzenesulfonyl chloride there was prepared 1,2-bis(*p*-acetamidobenzenesulfonamidoöxy)ethane (see Table V). Hydrolysis of the latter (8.2 g.) with 10% sodium hydroxide solution (50 ml.) at 100° for 1 hr., followed by acidification with acetic acid to pH 6.5 gave 1,2-bis(*p*-aminobenzenesulfonamidoöxy)ethane also listed in Table V.

1-Aminoöxy-2-bromoethane Hydrobromide.—Hydrolysis of Ia (n = 2) with hydrobromic acid as described above for S-[ω-(phthalimidoöxy)alkyl]isothiuronium salts, Ic, formed the **salt,** (71% yield) m.p. 185–187° (from methanol–chloroform).

Anal. Calcd. for $C_2H_7NOBr_2$ (220.9): C, 10.87; H, 3.19; N, 6.34. Found: C, 11.02; H, 3.33; N, 6.46.

Benzoylation as reported in the procedure for ω,ω′-bis(benzamidoöxy)alkanes gave 2-benzamidooxy-1-bromoethane (97%), m.p. 85–87° (from benzene).

Anal. Calcd. for $C_9H_{10}NO_2Br$ (244.1): C, 44.28; H, 4.12; N, 5.73. Found: C, 44.24; H, 4.01; N, 5.59.

S-[2-(Benzamidoöxy)ethyl]Isothiuronium Bromide.—A solution of 2-(benzamidoöxy)-1-bromoethane (2.44 g., 0.01 mole) and thiourea (0.76 g., 0.01 mole) in tetrahydrofuran was heated under reflux for 3 hr. The solvent was evaporated *in vacuo*, and the gummy residue triturated with anhydrous ether. The solid so obtained was purified by several recrystallizations from methanol–ether; m.p. 127–129°.

Anal. Calcd. for $C_{10}H_{14}N_3O_2SBr$ (320.2): C, 37.51; H, 4.40; N, 13.13. Found: C, 37.61; H, 4.54; N, 13.05.

1-(Aminoöxy)-3-bromobutane Hydrobromide.—This salt was prepared in 40% yield by the hydrolysis of 1-(phthalimidoöxy)-3-bromobutane, III, as described for the conversion of Ic to IIc. The salt was crystallized from methanol and ether; m.p. 121–124°.

Anal. Calcd. for $C_4H_{11}NOBr_2$ (248.9): C, 19.30; H, 4.45; N, 5.63. Found: C, 19.38; H, 4.59; N, 5.74.

Reduction of 1-(aminoöxy)-3-bromobutane Hydrobromide with Lithium Aluminum Hydride.—The salt (5 g.) was added gradually to a stirring suspension of lithium aluminum hydride (1.4 g.) in anhydrous ether (300 ml.) along with a trace of aluminum chloride. The reaction mixture was cooled during addition and then heated under reflux for 3 hr. Methanol (8 ml.) in ether (8 ml.) was added after the reaction, followed by water (40 ml.) and 6 *N* sulfuric acid (40 ml.). The ether layer was separated, dried over anhydrous sodium sulfate, and distilled. The fraction boiling between 70–90° at 50 mm. was collected.

The infrared spectrum was identical with that of 1-butanol.

The identity was further established by heating the liquid (100 mg.) under reflux with 48% hydrobromic acid (5 ml.) and thiourea (0.5 g.) for 1.25 hr. The solvent was evaporated *in vacuo* and the residue treated with aqueous picric acid. The crystals so obtained were purified from ethanol, undepressed on admixture with one authentic specimen; m.p. 178–179°.

The Reaction of 1- and 2-Bromobutane with N-Hydroxyphthalimide.—1-Bromobutane (6.8 g., 0.05 mole) reacted with N-hydroxyphthalimide (8.15 g., 0.05 mole) at 25° for 48 hr. as described for the preparation of Ia to yield N-butoxyphthalimide (7.0 g.; 64%), b.p. 145–151° at 0.3 mm.

Anal. Calcd. for $C_{12}H_{13}NO_3$ (219.2): C, 65.74; H, 5.97; N, 6.38. Found: C, 65.77; H, 5.93; N, 6.65.

Under identical conditions, 2-bromobutane reacted to give a mixture of unchanged N-hydroxyphthalimide (2.1 g.) and N-(1-methylpropoxy)phthalimide (2.5 g., 23%); m.p. 50–53° (from aqueous ethanol).

Anal. Calcd. for $C_{12}H_{13}NO_3$ (219.2): C, 65.74; H, 5.97; N, 6.38. Found: C, 65.95; H, 6.17; N, 6.50.

The yield of the product increased to 40% when the reaction mixture stood for 3 weeks.

1-(Aminoöxy)butane Hydrobromide.—This was obtained in 64% yield by hydrolyzing 1-(phthalimidoöxy)butane as has been described for the transformation of Ic to IIc. The salt crystallized from 48% hydrobromic acid; m.p. 158°.

Anal. Calcd. for $C_4H_{12}NOBr$ (170.0): N, 8.23. Found: N, 8.51.

The hydrochloride (m.p. 152°, lit. m.p. 155–156°[8b], 152–153°[8a]) was prepared in a similar way except that the heating time was 20 min.

(8) (a) L. Neuffer and A. L. Hoffman, *J. Am. Chem. Soc.*, **47**, 1686 (1925); (b) P. Mamalis, J. Green, and D. Mchale, *J. Chem., Soc.*, 229 (1960).

N-(1-Methylpropoxy)phthalimide (4.4 g.) on hydrolysis with hydrobromic acid gave 0.7 g. of a salt (31%), m.p. 128–130° with analysis for hydroxylammonium bromide.

Anal. Calcd. for NH_4OBr: N, 12.15; H, 3.53; Br, 70.13. Found: N, 12.11; H, 3.80; Br, 70.60.

Sodium S-[2-(Phthalimidoöxy)ethyl]thiosulfate.—A mixture of β-(phthalimidoöxy)ethyl bromide Ia (n = 2); (25 g., 0.092 mole) and sodium thiosulfate pentahydrate (24 g., 0.096 mole) was refluxed in 50% ethanol (300 ml.) for 3.5 hr. The reaction mixture was evaporated to dryness and the residue extracted twice with boiling absolute ethanol. On cooling the salt (15 g., 50%) was obtained; m.p. 144°. Recrystallization from methanol raised the m.p. to 153–156°.

Anal. Calcd. for $C_{10}H_8NO_6S_2Na$ (325.3): C, 36.92; H, 2.47; N, 4.30; S, 19.71; Na, 7.06. Found: C, 36.72; H, 3.02; N, 4.26; S, 19.68; Na, 6.94.

Some Chemical Reactions of 3,9-Dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-Dioxide

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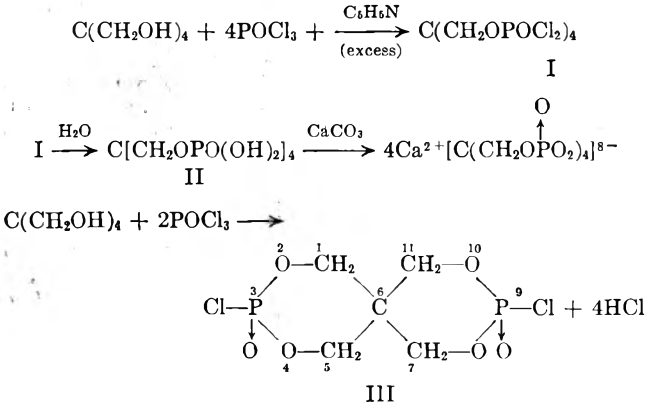
The preparation of pure 3,9-dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-dioxide and its chemical reactivity are described.

Condensation products of pentaerythritol with phosphoryl chloride have been described.[1,2] With an excess of phosphoryl chloride in the presence of pyridine as an acid acceptor, the open-chain structures I and II were obtained,[1] the latter in the form of its neutral calcium salt. Condensation of pentaerythritol with an excess of more than two moles of phosphoryl chloride in the absence of an acid acceptor apparently led to the difunctional cyclic spiro structure III in contaminated crude form. The analytical data reported for III are incomplete, however, and no reference is made to attempted purification.[2]



In the present study, we have found that, for the preparation of pure III, a large excess of phosphoryl chloride has to be employed. The crude reaction product finally obtained must be subjected to treatment with several solvents, followed by recrystallization from glacial acetic acid. The compound so obtained, 3,9-dichloro - 2,4,8,10 - tetraoxa - 3,9 - diphosphaspiro[5.5]-undecane 3,9-dioxide, melted at 233–235°, contrary to a previous report.[2]

Anhydrous dimethylformamide dissolves the phosphospirane in all proportions at room temperature with the formation of clear and colorless solutions. On prolonged standing the solutions remain clear, but become deep yellow after a few hours. Upon careful evaporation at reduced pressure, a yellow-brown glassy material is obtained which possesses the properties of a salt. Structure IV is assigned to this product, which resembles the structure of the so-called Vilsmeier-Haak adducts, since it is soluble in water and contains ionic chlorine.

Such adducts with dimethylformamide are known for highly reactive phosphorus halides, such as phosphoryl chloride[3] and dialkyl phosphorochloridates.[4] The structural formula IV is also supported by the presence of a strong absorption band at approximately 6.0 μ, in its infrared spectrum, indicative of the presence of C=N groups, and the presence of a group of absorptions characteristic of the phosphospirane structure appearing at 10.85–14.60 μ (*cf.* tables of infrared spectra).

A surprising result was obtained when the yellowish solutions of III in dimethylformamide were refluxed in the presence of equimolar amounts of aliphatic compounds containing hydroxyl groups, such as ethylene glycol, 1,4-butanediol, 1,4-hydroxymethylcyclohexane, and 1-octanol. A quantitative amount of the well crystallized acidic dimethylammonium salt (V) separated from the solution after a short heating period. It is apparent that the dimethylammonium cation must have been formed by cleavage of the amide. The relationship of this salt to the hitherto unknown free acid, 3,9-dihydroxy - 2,4,8,10 - tetraoxa - 3,9 - diphosphaspiro-[5.5]undecane 3,9-dioxide (VI), was demonstrated convincingly by titration of an authentic sample, obtained by direct hydrolysis of III in water at 90°, with one mole of dimethylamine. This titration resulted in a crystalline material, m.p. 263°, identical in all respects with V.

The unexpected reaction of solutions of III in dimethylformamide with aliphatic alcohols will be discussed in detail for the case of 1,4-butanediol. In the absence of solvent, III was converted by the diol into VI. Considerable amounts of tetrahydrofuran, 1,4-dichlorobutane, and 4-chlorobutanol were detected in this reaction. Scheme 1 describes in detail the fate of the phosphorus-containing component in the course of this reaction.

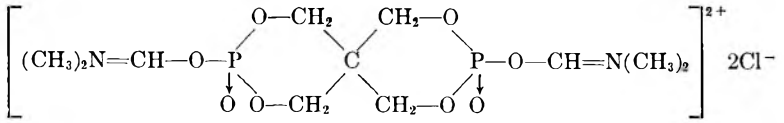
Identification of the diacid VI obtained by the three different routes indicated was made by titration, analysis, and infrared spectrum. The titration curve of VI

(1) V. Bellavita and O. Tiberi, *Ricerca sci.*, **1952**, 69.

(2) R. Charonnat, J. V. Harispe, M. Harispe, O. Efimovsky, and M. L. Chevillard, *Ann. pharm. franc.*, **10**, 666 (1951).

(3) H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Ber.*, **92**, 837 (1959).

(4) F. Cramer and M. Winter, *ibid.*, 989 (1961).

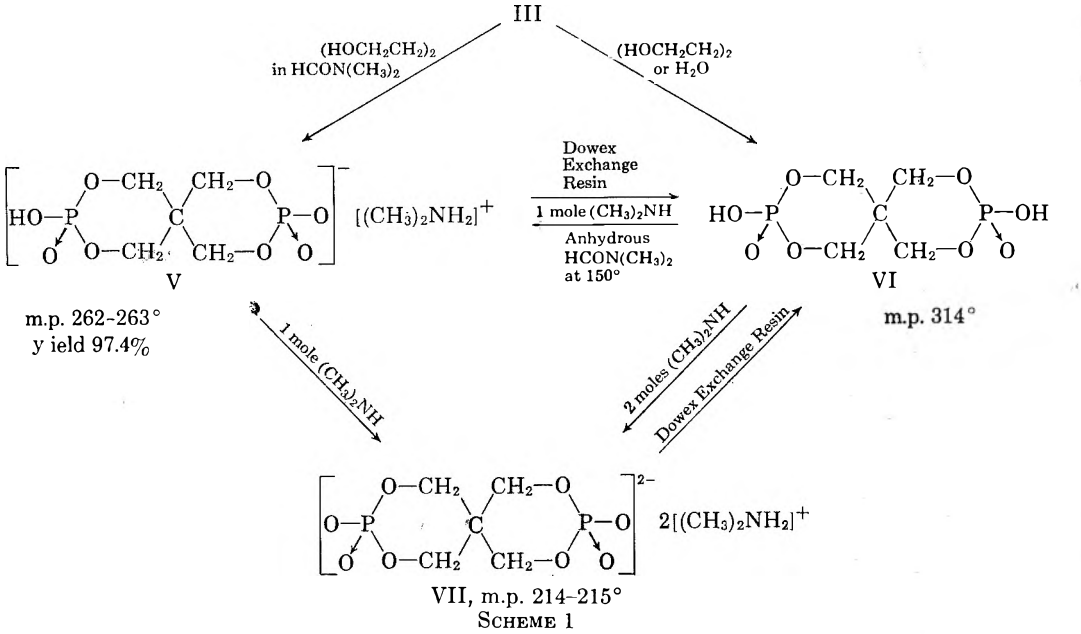


IV

indicates the presence of two strongly acidic hydrogen atoms, both of equal strength. The infrared spectrum shows the broad and shallow P–OH absorption at 2700–2560 cm.$^{-1}$, typical of hydroxyl groups attached to phosphorus[5] (other principal absorptions are listed in Table I). The diacid VI is best prepared from the easily accessible V by ion exchange, since the direct hydrolysis of III produces this compound only in moderate yield. The identity of all samples of VI was proved by mixture melting points and comparison of their infrared spectra.

hydrofuran and water, b.p. 68°. Two other liquid products, isolated from the reaction mixture by distillation at reduced pressure, were identified as 1,4-dichlorobutane and as 4-chlorobutanol, also by vapor phase chromatography.

The formation of tetrahydrofuran and water during the reaction of III with 1,4-butanediol can be easily explained by cyclization of the 1,4-diol under the influence of VI, the latter forming during the same reaction. It could be demonstrated that only small amounts of VI were sufficient for the conversion of large amounts of the diol, and that therefore VI is an excellent catalyst for the intramolecular etherification of 1,4-butanediol. Upon heating a sample of pure VI in a large excess of 1,4-butanediol for only a short period and subsequent cooling to room temperature, white leaflets of



SCHEME 1

TABLE I

INFRARED SPECTRUM OF COMPOUND III

Assignment	Absorption peaks, μ
CH stretching	3.5
CH_2 deformation	6.75
CH_2 vibration	6.85
Not assigned	7.20, 7.30
P → O	7.70
Not assigned	8.05, 8.40, 8.70, 9.35
C—O—P stretching vibration	9.80
Not assigned; present in all compounds containing the 2,4,8,10-tetraoxa-3,9-diphosphaspiro-[5.5]undecane unit	10.85, 11.75, 12.90, 14.60

The equations given show the conversion of III during the reaction with 1,4-butanediol, but not the fate of the latter. By running the reaction with or without dimethylformamide as a solvent, a low-boiling mobile liquid product was separated and identified by vapor phase chromatography as the 20 to 1 azeotrope of tetra-

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 259, 262.

the empirical formula $C_9H_{20}P_2O_{10}$ separated. This empirical formula is in agreement with a 1:1 complex of VI and 1,4-butanediol. The infrared spectrum (Table II) of this compound shows distinct OH-absorption, but the OH-band is shifted to a higher wave length, indicative of hydrogen-bonded hydroxyl groups. Whereas in the free diacid VI, the P → O absorption appears in a region typical of nonhydrogen-bonded phosphoryl compounds (7.9 μ), this absorption is shifted to 8.2 μ in the adduct, a phenomenon usually observed on hydrogen-bonded P → O groups.[6,7]

Scheme 2 (p. 1610) shows the formation, tentative structures, and thermal behavior of the adduct (VIII) of 1,4-butanediol and VI. Alternatively, only one hydroxyl of 1,4-butanediol might be involved in the hydrogen-bonded complex (VIIIa).

Nuclear magnetic resonance P^{31} measurements conducted on VIII in orthophosphoric acid solution indicated the presence of only one type of phosphorus-atom bonding. In addition, the complete chemical inertness toward phenyl isocyanate supports structure VIII over VIIIa. Upon heating of VIII at 125°, dissociation into the free diacid VI, m.p. 314°, and a mixture of tetrahy-

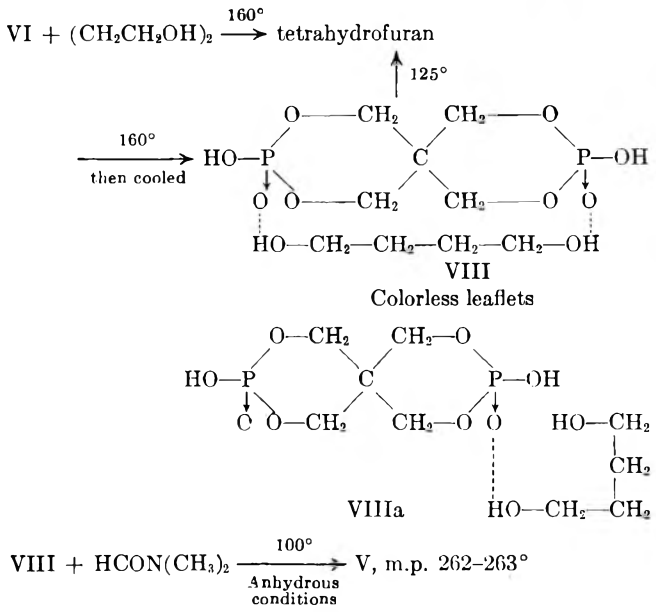
(6) L. F. Audrieth and R. Steinmann, *J. Am. Chem. Soc.*, **63**, 2115 (1941).

(7) K. Niedenzu and J. W. Dawson, *Angew. Chem.*, **72**, 920 (1960).

TABLE II

INFRARED SPECTRA

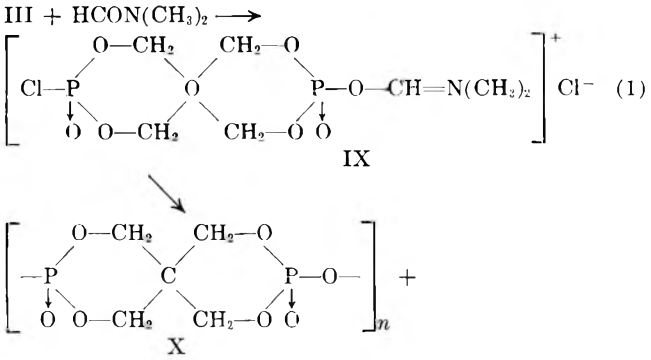
Assignment	Absorption peaks, μ — Compound VI	Compound VIII
OH, hydrogen-bonded	...	3.15
P—OH	3.5–4.0	3.5–4.0
Not assigned	5.60	...
	6.75	6.75
CH_2 deformation	6.80	6.80
Not assigned	7.40	7.30
P → O, not hydrogen-bonded	7.85	...
P → O, hydrogen-bonded	...	8.10
Not assigned	8.35	8.32
	...	8.43
	8.75	8.71
	9.35	9.30
C—O—P stretching	9.70	9.70
C—O—P stretching	9.90	...
OH deformation	...	10.35
Not assigned; present in all compounds containing the 2,4,8,10-tetraoxa-3,9-diphosphaspiro-[5.5]undecane unit	11.00	11.03
	11.77	11.78
	12.75	12.88
	14.50	14.50



SCHEME 2

drofuran and 1,4-butanediol was observed. The latter could be easily detected by reaction with phenyl isocyanate, resulting in the formation of the bis(N-phenylurethane) of 1,4-butanediol, m.p. 183°. It is furthermore of interest that the addition product VIII yielded on heating in anhydrous dimethylformamide at 100° compound V in a very high yield. Since the dimethylammonium cation in V must be derived from the amide, the adduct VIII has a similar ability to cleave anhydrous dimethylformamide, as observed on VI. Compound VIII might rearrange to VIIIa at elevated temperature and the latter might then act as the intermediate necessary to from tetrahydrofuran during heating of VI with excess 1,4-butanediol.

The formation of VI, tetrahydrofuran, 1,4-dichlorobutane, and 4-chlorobutanol by direct interaction of III and 1,4-butanediol can be explained as an attack on phosphorus by the alcohol,[8] with the formation of the bis(4-hydroxybutyl) ester, followed by dealkylation under the influence of hydrogen chloride to yield VI and the 4-hydroxybutyl carbonium ion which can either cyclize to tetrahydrofuran or form the chlorinated products by reaction with hydrogen chloride. From the work reported here and from analogous reactions of other alcohols (among them some which form phosphorus esters with difficulty or not at all),[9] we believe that *in dimethylformamide solution* a Vilsmeier-Haak adduct such as IV or IX forms initially and reacts further as indicated in equations 1–4.



$$XI + HOCH_2CH_2CH_2CH_2OH \longrightarrow (HO)_2CH{-}N(CH_3)_2 + ClCH_2CH_2CH_2CH_2Cl \quad (3)$$

$$(HO)_2CH{-}N(CH_3)_2 \longrightarrow HCON(CH_3)_2 + H_2O$$

$$VI + HCON(CH_3)_2 \longrightarrow V + CO \quad (4)$$

Equation 1 indicates the formation of the Vilsmeier-Haak semi-adduct IX. Its decomposition into a polymeric phosphate with anhydride P–O–P bonds (X) and the amide chloride (XI) is indicated by equation 2. This reaction is analogous to the behavior of the reaction product (XII) of dimethylformamide and phosgene which decomposes easily to the amide chloride XI and carbon dioxide.[10]

$$HCON(CH_3)_2 + COCl_2 \longrightarrow [(CH_3)_2N{=}CHOCOCl]^+Cl^-$$

XII

Amide chlorides of type XI are known to act as powerful chlorinating agents toward aliphatic hydroxyl groups, forming the amide and water (equation 3). The formation of water is essential to the hydrolytic cleavage of the polymer X to the diacid VI. It was demonstrated in an independent experiment that VI is able to cleave dimethylformamide, forming the acidic dimethylammonium salt (V) and carbon monoxide.

The chlorination of the aliphatic hydroxyl groups by the amide chloride XI, as indicated in the over-all equation 3, proceeds *via* an amido ester chloride XIII according to equation 3a.

$$XI + HOCH_2CH_2CH_2CH_2OH \longrightarrow [(CH_3)_2NH{-}CHClOCH_2CH_2CH_2CH_2OH]^+Cl^- \quad (3a)$$

XIII

XIII and the symmetrical analog, $[(CH_3)_2NH{-}CHCl{-}O{-}CH_2CH_2{-}]_2^{2+}\ 2Cl^-$, are extremely unstable compounds which undergo cleavage on warming, yielding the chlorinated hydrocarbon and dimethylformamide. The latter presumably arises through loss of hydrogen chloride by the intermediate formyl dimethylammonium chloride.

(8) W. Gerrard, W. J. Green, and R. A. Nutkins, *J. Chem. Soc.*, 4076 (1952).

(9) Unpublished work done in this laboratory.

(10) H. Elingsfeld, M. Seefelder and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

Experimental

3,9-Dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-Dioxide (III).—Pentaerythritol, 272.3 g. (2.0 moles; Eastman White Label), and 660 g. of freshly distilled phosphoryl chloride (4.3 moles) were placed in a 3-l. round-bottom flask under reflux, protected from atmospheric moisture. The mixture was heated for 2 hr. at 90°, and held for 20 hr. at 100° until evolution of hydrogen chloride had ceased and the mixture was a colorless hard cake. The product was crushed and returned to the flask, dispersed by addition of 500 g. of phosphoryl chloride, and refluxed for 2 hr. The vigorous evolution of gas which initially occurred had ceased entirely after the 2-hr. period. Most of the excess phosphoryl chloride was recovered by decantation; the rest, by heating to 120° at 10 mm. The crude solid was washed four times with 200-ml. portions of carbon tetrachloride. Before the last washing, the product was collected on a Büchner funnel, dried in air, and crushed to a fine powder. In order to remove a small amount of greasy by-product, one washing with 450 ml. of cold absolute ethanol was necessary, followed by rinsing with ether. The product, a colorless powder, m.p. 229–232° (Fisher-Johns block), was obtained in 80% yield, 478 g. The material was recrystallized from glacial acetic acid as fine needles. The melting point of the dichloride depended on the rate of heating. In order to obtain reproducible melting points, a rate of 6° a minute was applied. After the third recrystallization, the melting point was determined as 233–235°, with no further increase.

Anal. Calcd. for $C_5H_8Cl_2O_6P_2$: C, 20.22; H, 2.72; Cl, 23.88; P, 20.86. Found: C, 20.23, 20.35; H, 2.99, 3.28; Cl, 23.92; P, 20.90, 21.00.

Vilsmeier-Haak Type of Adduct from III and Dimethylformamide.—One gram of III was dissolved in 10 ml. of anhydrous dimethylformamide (DMF). The solution developed a yellow color on standing for several hours at room temperature or upon heating at 100° for 5 min., but no separation occurred. The mixture was refluxed for 20 min. and allowed to stand at room temperature. Excess solvent was distilled after 3 days, leaving 1.2 g. of a yellow-orange glass which was subjected to several ether washings. No recrystallization was possible. The material contained nitrogen, chlorine, and the phosphospirane structure. It possessed salt-like properties, such as water solubility, silver chloride precipitation upon addition of silver ion to the aqueous solution, and hydrogen chloride evolution if brought in contact with cold concentrated sulfuric acid. The possibility of a dimethylamine salt is excluded, since both of the possible salts with dimethylamine were prepared, and they are insoluble in dimethylformamide. Strong infrared absorption at 6.0 μ supported structure IV.

3,9-Dihydroxy-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-Dioxide Monodimethylammonium Salt (V).—Nineteen grams of crude III (0.064 mole) was dissolved in 150 ml. of twice-distilled anhydrous dimethylformamide (b.p. 152–154°, 750 mm.) and 5.75 g. 1,4-butanediol (0.064 mole) was added in one portion. The mixture was refluxed for 40 min.; on cooling to room temperature, 17.5 g. of V precipitated and an additional 1.5 g. was recovered from the filtrate after several days' standing, amounting to 19.0 g. (97.4% yield), m.p. 266°, after recrystallization from 1,4-butanediol (the solvent should not be heated above 130° or slow evolution of dimethylamine occurs).

Anal. Calcd. for $C_7H_{19}NO_8P_2$: C, 27.37; H, 6.23; N, 4.56; P, 20.17. Found: C, 27.58, 28.18; H, 5.71, 5.85; N, 4.50, 4.70; P, 20.10.

From the dimethylformamide filtrate, 2.4 g. of mobile liquid was recovered, b.p. 66°, 750 mm.; it was identified by vapor phase chromatography as a tetrahydrofuran–water mixture.

III (5.94 g., 0.02 mole) was dissolved in 150 ml. of twice-distilled anhydrous dimethylformamide and 2.88 g. of 1,4-bis(hydroxymethyl)cyclohexane (0.02 mole) was added to this solution with shaking until a clear and colorless mixture resulted. After 15 min. of refluxing, 6.0 g. of a crystalline white solid separated, was filtered, and washed twice with acetone. It melted at 264–266°, gave no melting point depression with the product first obtained, and was evidently V (98.4% yield). Dimethylformamide in the filtrate was removed by distillation at 5 mm. (oil-bath temperature finally 130°). A yellowish oil, together with a minor amount of solid material, remained. Ether dissolved the oil and left the solid. After removal of the ether, the oil was subjected to vacuum distillation; b.p. 84–85° (0.08 mm.). Chlorine analysis, vapor phase chromatography, and the ability of the oil to decolorize bromine in carbon tetrachloride solution indicated that it consisted of a mixture of 1,4-bis(chloromethyl)cyclohexane and 1-vinyl-4-chloromethylcyclohexane. In addition, the infrared spectrum did not show any OH-absorption but indicated unsaturation.

Interaction of III and 1,4-Butanediol in the Absence of Dimethylformamide.—III (17.82 g., 0.060 mole) was placed in a 100-ml. round-bottom flask and mixed thoroughly with 5.4 g. of 1,4-butanediol (0.06 mole). The joint of the flask was connected *via* an adapter to a 50-ml. receiver. The system was purged with dry nitrogen. The mixture was heated to 110°, whereupon reaction occurred, with hydrogen chloride elimination; in the ice-cooled receiver, 2 g. of a colorless mobile liquid ($n^{25}D$ 1.4140) collected, identified as a mixture of tetrahydrofuran and water by gas phase chromatography. After 1 hr. at 110°, the temperature was raised to 145° for 3 hr. Application of a 14-mm. pressure at 145° caused fast distillation of 1 g. of an almost colorless oil and formation of residual gray powdery material (16.5 g.). By vapor phase chromatography and infrared analysis, the oil was found to be a mixture of 85% 1,4-butanediol and 15% 4-chlorobutanol. The solid residue, extracted with hot ethanol, gave about 9 g. of an insoluble colorless solid mixture. This mixture was separated by treatment with 50 ml. of cold water, resulting in 4.5 g. of water-insoluble unreacted III and 4.4 g. pure VI, the latter being obtained by evaporation of the water at room temperature. An additional crop of 3.8 g. of VI was obtained by evaporation of the ethanol extract to dryness and treatment of the residue with 30 ml. of acetone, which dissolved the hygroscopic brown glass. The combined fractions of VI weighed 8.3 g. (53.2% yield, 71% conversion), pyramidal crystals, after recrystallization from glacial acetic acid, m.p. 306–307°. Mixture melting point with an authentic sample of VI gave no depression.

Reaction of III and 1,4-Bis(hydroxymethyl)cyclohexane.—An apparatus similar to that just described was charged with 5.94 g. of III (0.020 mole) and 2.88 g. of 1,4-bis(hydroxymethyl)cyclohexane. The reaction started smoothly at 150°, thus making it possible to raise the temperature gradually to 195° where it was kept for 5 hr. Additional 3-hr. heating at 175° at 0.1 mm. gave no distillate, only a crystalline solid. Separation was achieved by two extractions with 20-ml. portions of cold acetone, which left 5.5 g. of solid undissolved. The solid residue was composed chiefly of VI but admixed with a minute amount of a polymeric material. Upon treatment with cold water, VI dissolved completely, but the polymer (m.p. 265–275°) did not. Evaporation of the aqueous solution and recrystallization from glacial acetic acid yielded prismatic crystals, m.p. 306°; a mixture melting point taken with authentic VI showed no depression.

After removal of the solvent from the acetone extract, a chlorine-containing yellow oil remained. Fractional distillation gave 1.5 g. of a colorless liquid fraction, b.p. 82–84° (0.08 mm.), $n^{16}D$ 1.4963. The resemblance to the infrared spectrum of the oil obtained from III and 1,4-bis(hydroxymethyl)cyclohexane in dimethylformamide suggested the formation of a similar product in this experiment, though dimethylformamide was absent.

3,9-Dihydroxy-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-dioxide (VI). a. By Hydrolysis of III.—A sample of 3.4 g. of III was suspended in 30 ml. of distilled water and the suspension heated with agitation at 90° for 15 min. During this period, most of the material went into solution with strongly acidic reaction. Evaporation to dryness of the filtered solution at room temperature gave a crystalline residue which was treated first with cold absolute ethanol, followed by one acetone washing. The solvent treatment resulted in 1.7 g. of crystals (57% yield), m.p. 314° after one recrystallization from glacial acetic acid.

Anal. Calcd. for $C_5H_{10}O_8P_2$: P, 23.82%. Found: P, 23.3%.

b. From V and Dowex Exchange Resin.—Crude V (2.2 g.) was dissolved in 25 ml. of distilled water and the solution poured over a Dowex-50-W-X-8 column, having a capacity of 1.7 meq./ml. wet resin.

The solution obtained was evaporated at room temperature, resulting in 1.9 g. of VI, m.p. 287°. A second run through the same column gave the same amount of VI, but of higher m.p. (304°). Bipyramidal crystals, m.p. 314°, were obtained after one recrystallization from glacial acetic acid; yield, 98.8%.

Anal. Calcd. for $C_5H_{10}O_8P_2$: C, 23.09; H, 3.88; P, 23.82. Found: C, 23.24, 23.00; H, 3.74, 3.60; P, 23.32.

c. From V and Hydrochloric Acid.—To 2 g. of V, 10 ml. of 40% hydrochloric acid was added with external cooling. The solution obtained was evaporated to dryness under reduced pressure at room temperature. From the resulting mixture of crys-

tals, dimethylammonium chloride (m.p. 168–170°) was extracted by hot chloroform. The residue, insoluble in chloroform (VI, 1.6 g., 94%), was recrystallized from glacial acetic acid, yielding crystals, m.p. 308°.

Titration of VI.—a. Conductometric titration of 261.96 mg. of VI with 0.106 *N* aqueous dimethylamine required 18.9 ml. to reach the end point; *i.e.*, 2 meq. of acid were present. Equiv. wt.: 261.96/2 = 131. Calcd. for VI: 130.

The titrated aqueous solution was evaporated to dryness, the solid was dissolved in ethanol, filtered, and reprecipitated by acetone, to yield colorless crystals, m.p. 214–216°. As evidenced by mixture melting point and infrared spectrum, this compound VII was identical with crystals obtained from V and excess dimethylamine. VI (0.5 g.) was dissolved in 10 ml. of 25% aqueous dimethylamine, filtered, and excess acetone was added; a colorless oil separated. The aqueous acetone was decanted, the oil was dissolved in 3 ml. of ethanol and excess acetone was added; the resulting oil crystallized within an hour to a solid, m.p. 214–215°.

b. Titration of 261.96 mg. of VI with 9.45 ml. of 0.106 *N* aqueous dimethylamine solution gave after evaporation colorless crystals, m.p. 261–262°, after one washing with absolute ethanol. Infrared spectrum and mixture melting point determination proved the identity of this material with V, previously obtained from III and 1,4-butanediol in dimethylformamide.

c. Titration of 57.61 mg. of V required 4.65 ml. of 0.0947 *N* sodium hydroxide. Equiv. wt. Calcd.: 130.0. Found: 130.8.

A crystalline disodium salt separated upon evaporation of this solution at room temperature.

Hydrogen-Bonded Adduct VIII Obtained from VI and 1,4-Butanediol.—VI (1.0 g.) in a 20-ml. distilling flask was suspended in 4 g. of 1,4-butanediol. When the flask was heated in an oil bath at 160°, a violent reaction occurred, with distillation of 1.8 g. of a tetrahydrofuran–water azeotrope, b.p. 68° (750 mm.). Shiny leaflets separated when the mixture cooled to room temperature. After filtration and drying over phosphoric anhydride, 0.9 g. of a solid was obtained which on heating on a Fisher-Johns plate, partially melted at 125°, resolidified at 185°, and remelted at 314°.

Anal. Calcd. for $C_9H_{20}O_{10}P_2$: C, 30.85; H, 5.73; P, 17.71. Found: C, 30.95, 31.06; H, 5.79, 6.14; P, 16.99.

Equiv. wt.: 39.76 mg. required 2.25 ml. of an aqueous 0.102 *N* dimethylamine solution. Only one inflection was observed. Calcd. for $C_9H_{20}O_{10}P_2$: 175. Found: 175.

Dry distillation of a sample of VIII resulted in elimination of a mixture of tetrahydrofuran and 1,4-butanediol. The latter condensed in the upper cool part of the flask. Reaction with excess phenyl isocyanate resulted in a crystalline material, m.p. 183°, after washing with ether and standing for 2 hr. on a clay plate. Mixture melting point with an authentic sample of the bis-(N-phenyl)urethane of 1,4-butanediol, m.p. 183°, prepared as described in the literature,[11] did not show any depression.

(11) J. Hamonet, *Bull. soc. chim. France*, [3] **33**, 525 (1905).

Acidic Ammonium Salt V from VI and Anhydrous Dimethylformamide.—A sample of 1.0 g. of VI was dissolved in hot anhydrous dimethylformamide and refluxed for a short period. After standing overnight, 1.1 g. of V, m.p. 264–266°, had separated.

Acidic Ammonium Salt V from VIII and Anhydrous Dimethylformamide.—A sample of 0.5 g. of VIII was heated in 5 ml. of anhydrous dimethylformamide for a short period to reflux temperature and allowed to stand 2 days at room temperature; 0.3 g. of crystals, m.p. 263–265°, separated. Mixture melting point determination with an authentic sample of V did not show any depression.

Dimethylacetamide Salt of VI.—In contrast to dimethylformamide, dimethyl acetamide is not cleaved by VI. Thus, from a solution of 1 g. of VI in 10 ml. of anhydrous dimethylacetamide prepared by gentle heating of the mixture, fine needles started to separate after 3 days' standing. The yield was 0.7 g. Partial melting was observed at 175°, resolidification at 220°, and final melting at 303.5° (apparently the melting point of VI). Nitrogen analysis and infrared spectra supported the assumption of an acidic salt of VI with one mole of dimethylacetamide.

Anal. Calcd. for $C_9H_{18}NO_9P_2$: N, 4.05. Found: N, 4.00.

Polymerization of VI by Anhydride Formation.—This experiment was conducted to demonstrate the possibility of the existence of polymeric X as assumed in the reaction mechanism. The presence of P–O–P linkages in X forecasts hydrolytic sensitivity. The anhydrization was conducted according to the work of Grunze, Dostal, and Thilo[12] on inorganic phosphates.

One gram of VI was suspended in 40 ml. of a 1:1 mixture of glacial acetic acid and acetic anhydride. After the mixture had been allowed to stand overnight at room temperature, no visible change was observed. Refluxing of the mixture for 1.5 hr. resulted in a clear and colorless solution from which no crystals separated upon standing for a period of 3 days. The solution was evaporated to dryness at 85° at 10 mm. The deep brown residue, kept for 2 hr. at 125° at 0.1 mm., gave 0.8 g. of shiny brown material which dissolved in water to form a strongly acid solution. The solid softened at 92–105°, and melted at approximately 150°. Very short fibers could be drawn from this melt.

The infrared spectra were measured by use of the Perkin-Elmer Model 21. The samples were embedded in potassium bromide.

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(12) T. Grunze, K. Dostal, and E. Thilo, *Z. anorg. allgem. Chem.*, **302**, 221 (1959).

Reaction of 3,9-Dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-Dioxide with Dimethyl Sulfoxide

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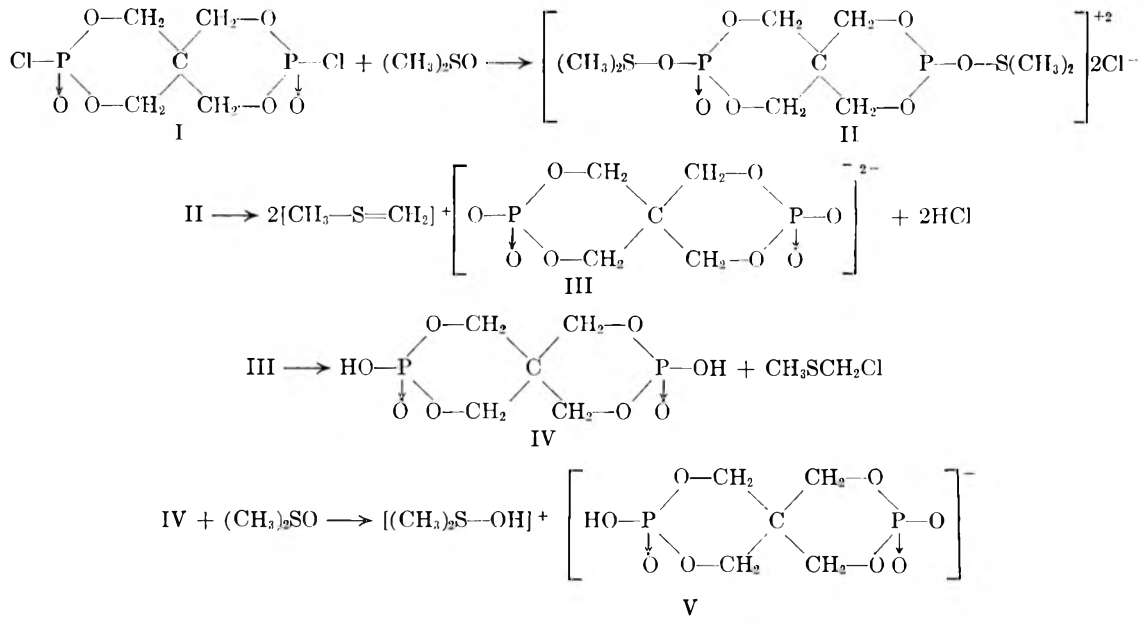
3,9-Dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-dioxide reacts with dimethyl sulfoxide to form a new type of sulfoxonium salt in almost quantitative yield. Methyl chloromethyl sulfide is formed as a by-product during this reaction, and is converted by excess dimethyl sulfoxide into methyl methanethiolsulfonate. The latter reaction exemplifies a new mode of formation for methyl alkanethiolsulfonates.

The preparation of pure 3,9-dichloro-2,4,8,10-tetraoxa - 3,9 - diphosphaspiro[5.5]undecane 3,9 - dioxide-(I) from pentaerythritol and excess phosphoryl chloride has been described in the preceding paper.[1] In the present report, we describe the exothermic reaction of this compound with dimethyl sulfoxide to form a crystalline solid, $C_7H_{16}O_9P_2S$, plus formaldehyde and liquid phosphorus-free materials. The material balance showed that all of the phosphorus was present in the crystalline product, which we believe is the first representative of hitherto unknown sulfoxonium phosphates, for which structure V was elucidated by chemical and

(1) R. Rätz and O. J. Sweeting, *J. Org. Chem.*, **28**, 1608 (1963).



spectroscopic means. We find no previous report of the isolation and identification of defined reaction products deriving from reactions of phosphorus halides with dimethyl sulfoxide.

The probable steps in the formation of V are as indicated above.

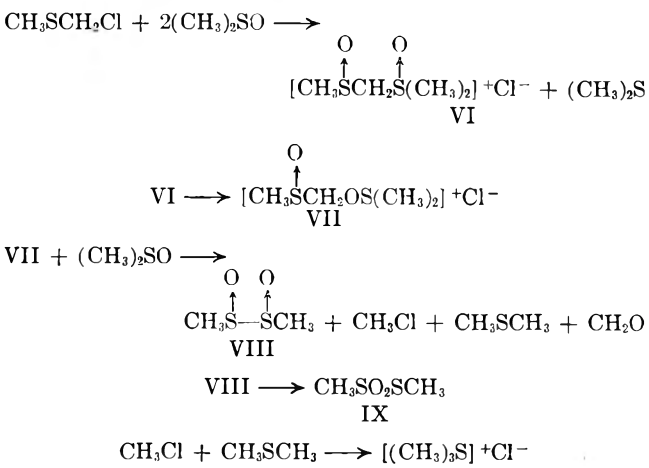
It is postulated that the unstable intermediate II is first formed; by loss of a proton from a methyl group, another unisolated intermediate III forms, with a methylenesulfonium cation associated at either end. Action of the hydrogen chloride present results in formation of the free acid IV and methyl chloromethyl sulfide. IV formed the sulfoxonium salt V in the presence of excess dimethyl sulfoxide, but methyl chloromethyl sulfide could not be separated. Rather, methyl methanethiolsulfonate (IX) was isolated.

The validity of the proposed route from dimethyl sulfoxide to V *via* IV is supported by the fact that a solution of an independently prepared authentic sample of IV in dimethyl sulfoxide, upon cooling, deposited the same acidic sulfoxonium salt V. The existence of methyl chloromethyl sulfide as an intermediate in the formation of the isolated by-product methyl methanethiolsulfonate (IX) was supported by treating authentic methyl chloromethyl sulfide, synthesized according to known procedures,[2-4] with excess dimethyl sulfoxide. The products isolated were IX, paraformaldehyde, and an oily chlorine-containing material, probably trimethylsulfonium chloride,[5] which could not be freed entirely from admixed dimethyl sulfoxide.

Thus the over-all reaction appears to be

$$CH_3SCH_2Cl + 3(CH_3)_2SO \longrightarrow CH_3SO_2SCH_3 + [(CH_3)_3S]^+Cl^- + CH_2O + (CH_3)_2S$$

It was demonstrated that the first step in the reaction of methyl chloromethyl sulfide and dimethyl sulfoxide is probably the formation of an oxidized form of a salt-like addition compound of equimolecular amounts of both reactants with the tentative structure VI, indicated in the following possible scheme of reactions,

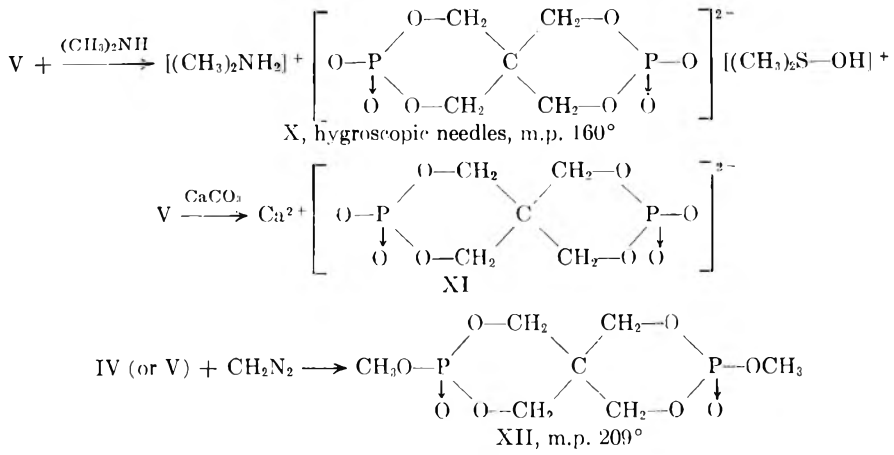


which accounts for all of the isolated products (VII and VIII are hypothetical).

Compound VI showed a powerful absorption peak at 8 μ which is indicative of the presence of S→O groupings in sulfoxonium salts, R_3SO^+.[6] Detection by vapor phase chromatography of considerable amounts of dimethyl sulfide supports the view that dimethyl sulfoxide had acted as an oxidizing agent before or after the combination of dimethyl sulfoxide with methyl chloromethyl sulfide. We assume that, after rearrangement of VI into VII, the latter degrades under the influence of excess dimethyl sulfoxide to form dimethyl disulfoxide (VIII), which rearranges to form the thiolsulfonate (IX).

By infrared and nuclear magnetic resonance spectra, complete elemental analysis, and comparison with physical data in the literature,[7] the formation of IX from methyl chloromethyl sulfide and dimethyl sulfoxide was well established. The strong absorption bands formed at 7.6 μ and 8.8 μ are typical of the sulfonyl grouping; the absence of S→O absorption in the 9.0–10.0-μ region excludes structure VIII. The possible participation of dimethyl disulfide as an intermediate in the conversion of methyl chloromethyl sulfide into IX is unlikely, since it was found that dimethyl sulfoxide cannot oxidize dimethyl disulfide to IX, a result giving further support to the route illustrated.

(2) H. Böhme, *Ber.*, **69**, 1610 (1936); **70**, 379 (1937).
(3) L. A. Walter, L. H. Goodson, and R. J. Fosbinder, *J. Am. Chem. Soc.*, **67**, 655 (1945).
(4) W. E. Truce, G. H. Birum, and E. T. McBee, *ibid.*, **74**, 3594 (1952).
(5) H. Blättler, *Monatsh.*, **40**, 417 (1920).
(6) R. Kuhn and H. Trischmann, *Ann.*, **611**, 117 (1948).
(7) H. J. Backer, *Rev. trav. chim.*, **69**, 1127 (1950).

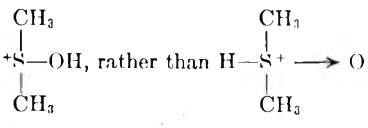


In the past, esters of alkanethiolsulfonic acids have been prepared mainly by oxidation of disulfides with dilute nitric acid[8] or peracetic acid,[9] by alkylation of alkali alkanethiolsulfonates,[10] or by oxidation of methanesulfenyl chloride with concentrated nitric acid.[11] The synthesis of alkyl alkanethiolsulfonates by interaction of alkyl α-haloalkylsulfides with dimethyl sulfoxide is an entirely new route to this class of compounds.

The novel and unexpected reaction between an α-chloromethyl thioether and dimethyl sulfoxide was extended to ethyl chloromethyl sulfide. An almost quantitative yield of methyl ethanethiolsulfonate, $CH_3CH_2SO_2SCH_3$, instead of $CH_3CH_2SO_2SCH_2CH_3$, gave further support to the above route and proved that the $-SCH_3$ group in IX and in its ethyl homolog, $C_2H_5SO_2SCH_3$, must arise from dimethyl sulfoxide.

Chemical reactions performed on V showed that this compound is an acidic sulfoxonium salt of IV. Simple heating of V resulted in dimethyl sulfoxide and small amounts of dimethyl sulfide as volatile materials, and the diacid IV remained as a distillation residue. Compound V can be precisely titrated with dimethylamine solution as a monobasic acid resulting in compound X. Heating of an aqueous solution of V with excess calcium carbonate replaces the sulfoxonium cation, with the formation of the calcium salt XI. Diazomethane reacts with V in the same way as with IV, to form the dimethyl ester XII. These transformations are shown above.

Infrared measurements performed on V in dimethylformamide showed a very distinct OH absorption at 2.95 μ. Since the P—OH group in V cannot cause this absorption and the presence of moisture was discounted by the absence of any band at 6.1 μ, the structure of the sulfoxonium cation of V can be assumed to be



Experimental

Reaction of 3,9-Dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro-[5.5]undecane 3,9-Dioxide (I) and Dimethyl Sulfoxide.—Eight grams of dimethyl sulfoxide, b.p. 74° (10 mm.), was charged into an upright 7.5 × 1 in. tube, 3.0 g. of finely ground I was added, and the tube was connected by a U-tube to a side-arm test-tube receiver immersed in a beaker filled with powdered Dry Ice. After a brief interval, an exothermic reaction occurred which it was necessary to moderate by cooling the reaction tube frequently with ice–water. A clear colorless solution resulted which finally solidified. The receiver contained a few droplets of condensed formaldehyde. The solid residue was washed twice with 15-ml. portions of dry chloroform (previously dried over anhydrous potassium carbonate) and filtered. The chloroform filtrates (A) were combined and studied (see following text).

The dry solid weighed 3.7 g., most of it soluble in water (some insoluble material was identified by conventional methods as paraformaldehyde). Upon recrystallization from absolute ethanol, small colorless needles, m.p. 174–176°, were obtained. The compound was chlorine-free; titration and elementary analysis are in agreement with structure V.

Anal. Calcd. for $C_7H_{16}P_2SO_9$: C, 24.92; H, 4.73; P, 18.32; S, 9.47. Found: C, 24.82; H, 4.91; P, 18.65; S, 9.18.

Equiv. Wt. Calcd.: 169. Found: 168. A 31.74-mg. sample required 2.97 ml. of 0.0636 *N* aqueous dimethylamine to titrate to a phenolphthalein end point. The titrated solution was evaporated at room temperature and kept for a short time over phosphorus pentoxide. A crystalline, extremely hygroscopic salt (X), m.p. 160°, remained.

Infrared Spectrum of V.—The infrared spectrum of the sulfoxium salt V was determined in anhydrous dimethylformamide by use of the Perkin-Elmer Model 21 with carefully purified dimethylformamide in the reference beam. A cell 0.1 mm. thick was used. A strong OH-absorption was found at 2.95 μ. The presence of water was discounted by the absence of a strong absorption at 6.1 μ. Because of hydrogen bonding, the P–OH group cannot be related to this absorption. The nonhydrogen-bonded P O absorption appeared at 7.80 μ and the C–O–P absorption at 9.70 μ. As observed in other compounds of this type, absorptions occurred at 11.3–11.9 μ and at 13.0 μ. In all phosphorus acids examined, broad shallow absorptions appear in the range of 2700–2560 cm.$^{-1}$, instead of in the normal region.[12]

Examination of Filtrates (A).—The solvent was removed by distillation at atmospheric pressure and at a bath temperature not exceeding 70°. A yellow oil (5.2 g.) remained, which was distilled from a 25-ml. Claisen flask at reduced pressure. About 2 g. distilled at 45 to 60° (0.5 mm.), apparently a mixture of dimethyl sulfoxide and a distillable, water-soluble compound, probably trimethylsulfonium chloride (this compound is known to be stable up to 100°[5]). Addition of a drop of this mixture to cold concentrated sulfuric acid liberated copious amounts of hydrogen chloride, indicating the presence of ionic chlorine.

Following this forerun, a 2-g. fraction distilled at 61° at 0.5 mm. (bath temperature 75°), which had a refractive index, $n^{22}D$ 1.5039, and was chlorine-free after redistillation. Analytical results, infrared spectra, and comparison of physical properties with those of an authentic sample of methyl methanethiolsulfonate, prepared as described later, indicated this product to be mainly IX.

Anal. Calcd. for $C_2H_6S_2O_2$: C, 19.05; H, 4.76; S, 50.80. Found: C, 20.36; 20.38; H, 6.23, 6.08; S, 49.06.

The infrared spectrum exhibited strong absorptions at 8.85 and 7.60 μ, characteristic of the sulfone grouping. Absence of an absorption in the 9.1 to 10.0-μ region eliminated from consideration the structure $(CH_3SO)_2$.

Preparation of Methyl Methanethiolsulfonate (IX) from Methyl Chloromethyl Sulfide and Dimethyl Sulfoxide.—Methyl chloromethyl sulfide was prepared from 12.2 g. of paraformaldehyde suspended in 25 g. of methanethiol essentially according to the procedure of Böhme.[7] The flask, equipped with reflux condenser and gas inlet tube, was immersed in ice–salt and a slow stream of hydrogen chloride was introduced. After 4 hr., a clear viscous solution was obtained. After addition of 30 g. of anhydrous cal-

(8) R. Otto, *Ann.*, **145**, 317 (1868); *Ber.*, **13**, 1282 (1880); **15**, 121 (1882).

(9) L. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, **71**, 3565 (1949).

(10) M. A. Belous and I. Ya. Postovskii, *Zh. Obshch. Khim.* (*J. Gen. Chem.*), **20**, 1701 (1950) [*Chem. Abstr.*, **45**, 239 (1951)].

(11) H. Brintzinger and M. Langheck, *Ber.*, **86**, 557 (1953).

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 259, 262.

cium chloride the mixture was allowed to stand overnight. The upper layer was distilled at atmospheric pressure, yielding 11 g., b.p. 112–114° (769 mm.), $n^{20}D$ 1.4923.

(a) **Reaction of Excess Dimethyl Sulfoxide with Methyl Chloromethyl Sulfide.**—Four and three-tenths grams of methyl chloromethyl sulfide was mixed with 15 g. of anhydrous dimethyl sulfoxide and allowed to stand at room temperature. After 4 hr., a gelatinous mass had been formed and no further visible change took place overnight. By consecutive additions of three 15-ml. portions of dry chloroform, solid paraformaldehyde was separated which after filtration was obtained tack-free by one additional acetone washing. The dry product weighed 1.4 g. (calcd., 1.34 g.). The combined chloroform extracts were carefully evaporated at 10 mm. (maximum bath temperature 37°) to yield 4.5 g. of a yellow oil. The chloroform distillate possessed a repugnant odor. Vapor phase chromatographic analysis detected dimethyl sulfide, dimethyl sulfoxide, and trace amounts of dimethyl disulfide. The yellow oil gave in water a strong chloride reaction with silver nitrate; strong evolution of hydrogen chloride was observed when a droplet was mixed with cold concentrated sulfuric acid. The oil was distilled at reduced pressure to give, after a chlorine-containing forerun, a main fraction distilling at 61° (0.5 mm.), $n^{20}D$ 1.5123. The colorless, water-insoluble oil was free from chlorine after redistillation. The infrared spectrum showed strong $-SO_2-$ group absorption at 7.60 μ and 8.85 μ, and was nearly identical with the spectrum of material obtained as a by-product during the formation of V initially. Analysis by vapor phase chromatography indicated a purity of at least 98%.

Anal. Calcd. for $C_2H_6S_2O_2$: C, 19.05; H, 4.76; S, 50.80. Found: C, 19.12, 19.03; H, 4.84, 4.87; S, 50.79.

(b) **Reaction of Dimethyl Sulfoxide and Methyl Chloromethyl Sulfide in 1:1 Mole Ratios.**—Anhydrous dimethyl sulfoxide (0.625 g.) was mixed with 0.7724 g. of methyl chloromethyl sulfide and allowed to stand for 3 days at room temperature. After 2 hr., the mixture had become light yellow, and, after 3 days, the flask contents was a pasty mixture of a solid and a heavy oil. Separation of the solid was effected by adding 5-ml. portions of dry ether, which dissolved the oil and converted the solid gradually into a powder. Two washings with 10-ml. portions of dry acetone gave 0.4 g. of a solid, free from oily contamination. Attempted recrystallization of this sensitive deliquescent material was unsuccessful. It was first believed that purification could be achieved by dissolving the crystals in cold water, followed by careful evaporation at room temperature. Beautiful crystals appeared, but only on the upper part of the porcelain dish, while the main portion remained tacky, even after prolonged standing over phosphorus pentoxide. The crude material melted between 72 and 74° with decomposition. A sample evolved hydrogen chloride when brought into contact with cold concentrated sulfuric acid. The infrared spectrum showed a strong S → O absorption at 8.15 μ. All of these observations are consistent with the assigned structure VI.

Excess dimethyl sulfoxide converted the crystals at room temperature into an oil and paraformaldehyde. Three-tenths gram of the material was dispersed in 10 ml. of anhydrous dimethyl sulfoxide and allowed to stand 24 hr. Dry chloroform was added, which left the paraformaldehyde undissolved. From the filtrate, the chloroform and excess dimethyl sulfoxide were removed by distillation, and the small amount of residual oil was distilled at reduced pressure. The amount of distillate was sufficient only for refractive index ($n^{20}D$ 1.5100) and infrared spectrum. Both indicated that this oil was IX.

Attempted Oxidation of Dimethyl Disulfide by Dimethyl Sulfoxide.—Dimethyl disulfide (4.71 g., 0.050 mole) was dissolved in 15.6 g. (0.20 mole) of anhydrous dimethyl sulfoxide, and the mixture was allowed to stand at room temperature for 3 days. Distillation separated the mixture into two fractions: (1) 3.5 g., b.p. 42° (1.6 mm.), $n^{20}D$ 1.5261 ($n^{20}D$ 1.5282 for purified authentic CH_3SSCH_3); (2) 14.0 g., b.p. 49° (1.6 mm.), $n^{20}D$ 1.4802 [$n^{20}D$ 1.4783 for purified authentic $CH_3S(O)CH_3$]. Neither a higher boiling third fraction, nor a distillation residue was obtained, thus indicating that no IX was formed.

Thermal Decomposition of V.—A sample of 0.2812 g. of V in a 10-ml. distillation flask with bent side arm leading into a receiver cooled with Dry Ice was heated to 190° (oil-bath temperature); distillation of a liquid was observed. Pressure was reduced to 0.01 mm. for a short period. The gray solid residue, weighing 0.2 g. after recrystallization from glacial acetic acid, obtained as bipyramidal crystals, melted at 295–297°. Though the melting point is some 10° low,[1] the material appeared to be 3,9-dihydroxy-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-dioxide.

The distilled liquid was found by vapor phase chromatography to consist mainly of dimethyl sulfoxide admixed with some dimethyl sulfide.

Reaction of V with Calcium Carbonate.—A sample of 0.5 g. of V was dissolved in 6 ml. of distilled water, excess calcium carbonate (Mallinckrodt analytical reagent) was added to this solution until no more carbon dioxide was evolved, unchanged calcium carbonate was removed by filtration, and to the clear filtrate excess ethanol was added. Separation of a microcrystalline, colorless calcium salt (XI) (0.4 g.) occurred, which did not melt below 315°.

3,9-Dimethoxy-1,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]-undecane 3,9-dioxide (XII) was prepared by action of diazomethane on both IV and V.

(a) **From IV and Diazomethane.** A solution of 100 ml. of ether containing 2 g. of diazomethane was placed in a 250-ml. round-bottomed flask, and 2 g. of recrystallized finely divided IV was added in five equal portions at 10-min. intervals. A vigorous evolution of nitrogen occurred after each addition. After 12 hr., gas evolution had ceased and, by filtration, 2.1 g. of the solid ester (XII) was recovered. After recrystallization from absolute ethanol, colorless plates, m.p. 208°, soluble with neutral reaction in water, were obtained.

Anal. Calcd. for $C_7H_{14}O_8P_2$: C, 29.18; H, 4.86; P, 21.55. Found: C, 29.10, 29.30; H, 5.01, 5.15; P, 21.50, 21.20.

(b) **From V and Diazomethane.**—In similar manner 0.5 g. of V was added in three portions to 50 ml. of ether containing 1.0 g. of diazomethane. The yield of ether-insoluble ester was 0.44 g. Recrystallization as before gave small needles, m.p. 208°, which gave no depression by mixture melting point with the product of method a.

As further confirmation of the correctness of the reactions forming methyl methanethiolsulfonate, the ethanethiol analog was prepared by the following method.

Ethyl chloromethyl sulfide was prepared similarly by treating 24.2 g. of paraformaldehyde with 50.0 g. of ethanethiol to yield 38.5 g. of the desired sulfide, b.p. 127–129° (750 mm.), $n^{20}D$ 1.4892.

Methyl ethanethiolsulfonate was prepared from 6.2 g. of double-distilled ethyl chloromethyl sulfide and 16 g. of anhydrous dimethyl sulfoxide. The mixture stood overnight, forming a gel, which was broken by treating with three 20-ml. portions of dry chloroform. A solid, 1.6 g., identified as paraformaldehyde (95.4%) was separated. The combined chloroform extracts gave a yellow oil when evaporated at 39° at 10 mm. Fractional distillation resulted in three fractions: (1) 3.0 g., b.p. 69–76° (0.7 mm.) $n^{20}D$ 1.5100, soluble in water, immediate silver chloride precipitate with silver ion, hydrogen chloride evolution with cold concentrated sulfuric acid; (2) 2.1 g., b.p. 76° (0.7 mm.), $n^{20}D$ 1.4960, sparingly soluble in water, contained only traces of chlorine; (3) 3.0 g., b.p. 78° (0.7 mm.), $n^{20}D$ 1.5021, insoluble in water, free of chlorine. Fraction 3 was subjected to two redistillations; each time a small forerun was discarded. After the second redistillation the liquid has a refractive index, $n^{20}D$ 1.5037.

Anal. Calcd. for $C_3H_8S_2O_2$: C, 25.68; H, 5.71; S, 45.74. Found: C, 26.25, H, 6.14, S, 45.50.

The analytical results are in satisfactory agreement with methyl ethanethiolsulfonate, $C_2H_5SO_2SCH_3$, or its isomer, ethyl methanethiolsulfonate, $CH_3SO_2SC_2H_5$. The infrared spectrum is very similar to that of IX, but shows some S → O absorption in the 1040-cm.$^{-1}$ region, probably as a result of slight contamination by dimethyl sulfoxide.

Nuclear magnetic resonance spectra indicated a methyl group attached to a methylene group, and that the methylene group is attached to an electronegative species. This result strongly favors the methyl ethanethiolsulfonate structure, $CH_3CH_2SO_2SCH_3$, but does not eliminate completely the possibility of the isomeric structure $CH_3SO_2SCH_2CH_3$. One unexplained peak was attributed to some sulfoxide, possibly the following isomer

$$\begin{matrix} O & O \\ \uparrow & \uparrow \\ CH_3CH_2S—SCH_3 \end{matrix}$$

or traces of dimethyl sulfoxide.

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The Dehydrobromination of 3-Methoxy-17α-bromoestra-1,3,5(10)-trien-16-one

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The title reaction is effected with a variety of reagents, leading in part to the formation of 3-methoxyestra-1,3,5(10),14-tetraen-16-one.

Although two different synthetic routes to the C-17α bromides of 16-ketoandrostanes[1] and estratrienes[2] have been described in the literature, few of the reactions of these compounds have been described. To explore the chemical reactivity of this α-halo ketone system as well as the biological activity of resulting products, several transformations of the 17-bromo ketone **1a** were investigated.

One of the initial phases of this problem involved production of 17β-halo steroids by displacement reactions. Accordingly, the bromo ketone **1a** was treated with lithium chloride in dimethylformamide. To effect complete reaction, as measured by the absence of bromine in the product, extended treatment at 100° was necessary. This can be contrasted to the analogous displacement in the 16α-bromo ketone **10** in which case the reaction is complete within a few hours at room temperature.[2] This large difference in reaction rates affords a measure of the relative steric accessibility of the bromine atoms in these two electronically similar systems.

The major product, isolable by direct crystallization, was an unsaturated ketone, $C_{19}H_{22}O_2$, (λ_{max} 5.89 μ and λ_{max} 231 mμ), initially assigned the structure **3**. This product was thought to have been formed by the elimination of the C-17α bromine atom with a simultaneous retropinacolic rearrangement. Due to the *trans* diaxial arrangement of the bromine atom and carbon atoms 13, 17, and 18, this reaction would be expected to occur with fair ease.[3,4] That the assigned structure was incorrect became clear on inspection of its n.m.r. spectrum: the absorption of the methyl group, although shifted, showed that the group was still tertiary and not attached to a carbon–carbon double bond; further, a single vinyl proton showed clearly. The structure 2 was then postulated as best fitting this data. Additional evidence for this structure was obtained by hydrogenation of the unsaturated ketone, a reaction which occurred rapidly. The product, the cyclopentanone **5** (λ_{max} 5.75 μ), showed a molecular rotatory dispersion curve typical of *cis*-hydrindanones; its n.m.r. spectrum was seen to have a tertiary methyl group (72 c.p.s.), but no vinyl proton. A preliminary infrared comparison indicated the unsaturated ketone **2** to correspond to the racemic isomer B of this structure prepared by Wilds and Doban by total synthesis.[5] A more complete infrared comparison of the saturated ketone **5** with their racemic *trans–syn–cis* isomer of that structure confirmed the identity.

A second compound obtained from the lithium chloride reaction was isolated after chromatography. Its analysis and spectrum showed clearly that it was the 17β-chloro ketone **4b**. A comparison with a sample prepared by epimerization[2] of the 17α-chloro ketone **1b** proved the structure of this product.

The unsaturated ketone **2** had also been isolated in earlier epimerization studies of the 17α-bromo ketone **1a**. The acid-catalyzed epimerization of this compound is a very slow reaction, successful conversion requiring prolonged treatment in boiling acetic acid containing toluenesulfonic acid.[2] When ethanolic sulfuric acid was used, an anomalous change in the rotation was seen. Instead of the levorotatory shift expected of the 17α to β isomerization, a marked dextrorotatory change was observed. Analysis of the product by chromatography showed that this phenomenon was due to the competitive formation of ketone **2**, a process precluding measurement of the 17α–β equilibrium ratio here. It is interesting to note that no dehydrohalogenation (to yield ketone **2**) was seen when toluenesulfonic acid–acetic acid was used.

Further work was undertaken to define better the conditions necessary to produce ketone **2** and also to determine the feasibility of producing ketone **3**. To this end a more normal type of elimination reaction was tried, that using collidine. Again the reaction of the 17α-bromo ketone **1a** required much more vigorous conditions than did the 16-bromo-17-ketoandrostane.[6] The product from a sixteen-hour reflux in collidine contained both 17α- and 17β-bromo ketones (**1a**, **4a**) as well as the unsaturated ketone **2**. After the reaction had proceeded for forty hours, no 17α-bromo compound remained. The major product was the unsaturated ketone **2**. Also found were smaller amounts of the 17β-bromo ketone **4a** and the reduction product, 3-methoxyestratrien-16-one (C-14α isomer of **5**). No trace of the isomer **3** was seen despite careful chromatographic inspection.

The reaction of the 17α-bromide with sodium methoxide was expected *a priori* to effect epimerization of the bromide[1,2] and, secondly, to produce the hydroxy ketal

(1) (a) J. Fajkos and J. Joska, *Collection Czech. Chem. Commun.*, **26**, 1118 (1961); (b) J. Fajkos, J. Joska, and F. Sorm, *ibid.*, **27**, 64 (1962); (c) J. Fishman, *J. Org. Chem.*, **27**, 1745 (1962).

(2) G. P. Mueller and W. F. Johns, *ibid.*, **26**, 2405 (1961).

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

(4) See W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961), for references to and the description of similar rearrangements in the steroidal D-ring.

(5) We wish to thank Prof. Alfred Wilds for making possible this comparison; see Robert C. Doban, Ph.D. thesis, University of Wisconsin, 1952; A. L. Wilds and T. L. Johnson, *J. Am. Chem. Soc.*, **70**, 1166 (1948); Donald W. Stoutamire, Ph.D. thesis, University of Wisconsin, 1957.

(6) R. Pappo, B. M. Bloom, and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 6347 (1956).

9.[2] The first of these possibilities was realized by slurrying the α-bromo ketone **1a** in methanolic sodium methoxide, causing a rapid change in crystal form. Filtration of the reaction mixture afforded in good yield the 17β-isomer **4a**. The same procedure on the 17α-chloro compound **1b** similarly effected ready epimerization.[7]

The second product anticipated, the hydroxy ketal **9**. is a normal by-product of the Favorskiĭ reaction.[8] The analogous compound **11** was formed in excellent yields from the 16α-bromo ketone **10**[2] and it was of interest to see if this reaction path would again be favored over the other possibilities available. Using sodium methoxide in a homogeneous reaction effected quick elimination of halogen and afforded a number of products. (The same products were also obtained by prolonged treatment with potassium carbonate in aqueous methanol at room temperature.) The unsaturated ketone **2** was readily isolated and identified by chromatography. Also isolated were two methoxy ketones, easily recognized by their n.m.r. spectra and elemental analyses. One of these was identified by comparison to the known 3,17α-dimethoxyestratrien-16-one (**6**),[9] presumably formed by direct displacement of the C-17β bromide with methoxide ion.

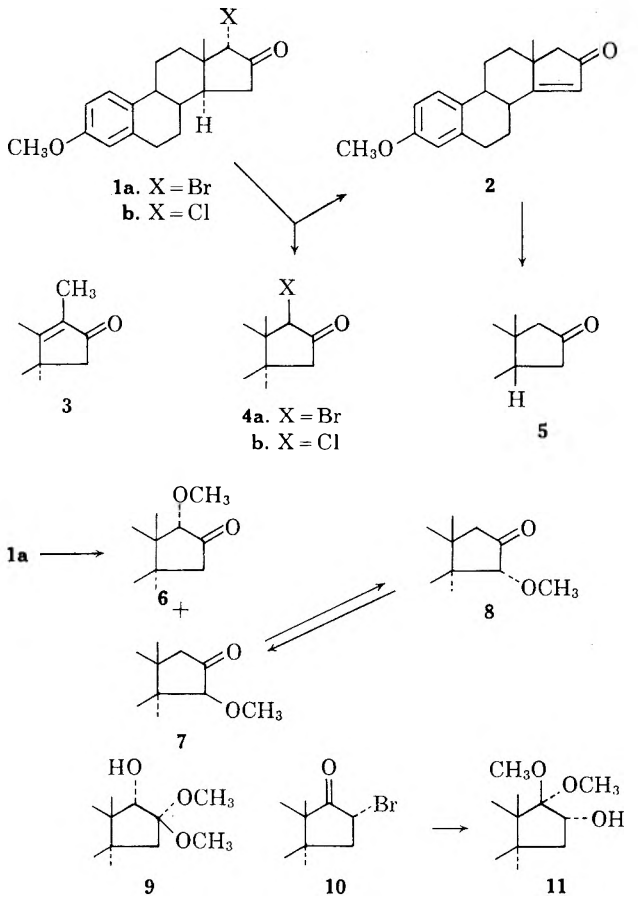
The second methoxy ketone (**7**) was shown to be epimerized by base to another methoxy ketone (**8**), also isolable in small amounts from the original reaction mixture. This interconversion led to an equilibrium consisting approximately of 60% of **8** and 40% of **7**. Assignment of structures to this pair was made possible by observing their clear physical and spectral dissimilarity to any of the known 17-methoxy-16-ketones or 16-methoxy-17-ketones.[9] Deep-seated rearrangements are unlikely because of the normal n.m.r. signal for the angular methyl group. Thus, by elimination there remains only the structures **7** and **8** for this epimeric pair.

Introduction of the 15-methoxyl can be postulated as occurring by an S_N2' reaction,[10] involving the intermediate **i**. Configurational assignments cannot be made from mechanistic considerations, since it is possible that the C-17 bromine may be in either configuration before the displacement occurs. The n.m.r. spectra also presents a confused picture of the methoxyl configurations. Tentative assignments are made on the basis of the preponderance of the epimer **8** at equilibrium and also on the shift observed in the infrared: the pseudo-equatorial isomer (**8**) exhibits a maximum at a slightly lower wave length than the β methoxy ketone **7**.[10b]

i ii

This type of dehydrohalogenation previously has been described in the literature, most typically in the case of 2-bromo-3-keto steroids (although in low yield)[11] and in similarly substituted decalins.[12] The simplest mechanistic path for the reaction would be a vinylogous elimination (through the intermediate **ii**).[13] Other mechanisms involving initial carbonium ion formation at C-17 followed by a hydride ion shift, or alternatively, passage through a Favorskiĭ rearrangement intermediate[14] can be envisioned, but are less likely. Isomerization to the C-17 bromine to C-15 during the acid-catalyzed elimination is also improbable.[15]

In simpler steroids the C-17α hydroxyl or halide is readily eliminated with simultaneous angular methyl migration in contrast to the much more stable C-17β substituted molecules. In the present case, since the 17α halide exists in a definite equilibrium concentration with its epimer, a similar rearrangement would be expected. That this reaction does not occur can be attributed to the presence of the adjacent carbonyl group. Although the carbonyl group is not normally thought of as hindering elimination of an adjacent halogen,[16] in this case, at least, such a hindrance does exist,



(7) Fajkos, see ref. 1a, has since reported the use of dilute potassium hydroxide at room temperature as a quick and efficient method for this epimerization in the androstane series.

(8) See A. S. Kende, *Org. Reactions*, **11**, 261 (1960), for a description of this side reaction and leading references.

(9) Four isomeric α-methoxy ketones have been prepared and identified in these laboratories by Dr. Tyner and will be fully described by him in a forthcoming publication. We wish to thank him for his generous cooperation in this area.

(10)(a) J. S. G. Cox, *J. Chem. Soc.*, 4509 (1960); (b) The n.m.r. data given by Y. Kawazoe, *et al.*, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962), for the C-18 methyl signal of epimeric 15-hydroxylated steroids supports the configurations assigned here.

(11) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947).

(12) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

(13) Another even closer example appeared in the literature after completion of this work: W. G. Dauben, G. A. Boswell, and W. H. Templeton, *J. Am. Chem. Soc.*, **83**, 5006 (1961), have described the dehydrobromination of 1-bromo-A-norcholstan-2-one.

(14) H. O. House and W. F. Gilmore, *ibid.*, **83**, 3972 (1961).

(15) *Cf.* C. W. P. Crowne, *et al.*, *J. Chem. Soc.*, 4351 (1956).

(16) See for example the facile dehydrohalogenation of the steroidal A-ring α-bromo ketones by collidine, as in ref. 11.

leaving the indirect reaction, seen here, as the kinetically favored one.

No significant biological activity was found for any of the new compounds described here.

Experimental[17,18]

The Reaction of the 17α-Bromo Ketone 1a with Lithium Chloride.—A solution of 1.60 g. of the bromo ketone **1a**[2] (m.p. 135–137°) in 50 ml. of dimethylformamide containing 3.2 g. of lithium chloride was heated on the steam bath for 40 hr. The solution was cooled and diluted with water. The pale yellow crystals which formed were collected on a filter, washed with water, and dried in a stream of air, yielding 0.40 g. of crystals, m.p. 135–137°. Recrystallization from ether gave 0.13 g. of the analytically pure 3-methoxyestra-1,3,5(10),14-tetraen-16-one (**2**), m.p. 138–140°; $[\alpha]D$ +319°; λ_{max} 5.82 (sh), 5.89, 5.93 (sh) 6.20, 6.33 μ; 75 (C_{18}-CH_3), 350 (C_{15}H) c.p.s.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.88; H, 8.05.

The infrared spectrum of this material was very similar to a previously recorded spectrum compound prepared by Wilds and Doban[5]; insufficient compound was available for successive recordings on the same spectrograph. The ultraviolet absorption, λ_{max} 231 (25,000) mμ, was also recorded with an equimolar amount of estrone methyl ether in the reference cell to substract the absorption of the aromatic A-ring from the total absorption, thus showing the maximum of the cyclopentenone system: λ_{max} 234 (19,700) mμ.

The aqueous mother liquors from the reaction were extracted with chloroform and the extract was washed three times with water. Concentration of the dried extract gave 0.9 g. of a stiff foam which was combined with the mother liquors of the crystallization and chromatographed on 80 g. of silica. Elution with 1% ethyl acetate in benzene gave 0.22 g. of material recrystallized from acetone–petroleum ether to yield 0.13 g. of 3-methoxy-17β-chloroestra-1,3,5(10)-trien-16-one (**4b**), m.p. 202–208°. Recrystallization from chloroform–methanol gave rods, melting in part at 205°, resolidifying, and melting at 211–213°. This material was identical to an authentic sample[2] by infrared comparison. Eluted at 5% ethyl acetate in benzene was 0.65 g. of crude unsaturated ketone **2**, recrystallized from acetone–petroleum ether to yield an 0.40 g. of pure **2**, m.p. 137–139° (identity confirmed by infrared comparison).

In an earlier run, using the same concentration of reactants, essentially no reaction was seen after 24 hr. at room temperature. When the solution was heated at 100° for 4 hr., a halogen analysis of the product indicated the mixture to consist of 70% bromo ketone, 10% monochloro ketone, and, by difference, 20% dehydrohalogenated compounds.

Anal. Calcd. for $C_{19}H_{23}BrO_2$: Br, 22.00. Found: Br, 16.14; Cl, 1.20.

3-Methoxy-14β-estra-1,3,5(10)-trien-16-one (**5**).—A solution of 0.16 g. of the unsaturated ketone **2** in 30 ml. of ethanol containing 0.10 g. of 5% palladium on carbon was stirred in an atmosphere of hydrogen, absorbing one equivalent of gas in 15 min. The solution was filtered and concentrated.[19] The residue was recrystallized from chloroform–methanol yielding 0.13 g. of the ketone **5**, m.p. 155–157°; $[\alpha]D$ +217°; λ_{max}^{KBr} 5.72 μ; 72 (C_{18}-CH_3) c.p.s. This compound was identical in the infrared to the *dl* compound.[5] The rotatory dispersion curve had a positive Cotton effect: λ_{max} 314.5 ([α] +3610°) and 324 (+3160°) mμ; λ_{min} 318 (+3040°) and 284 (−240°) mμ.[20]

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.31; H, 8.86.

The mother liquors provided another 15 mg. of **5**; no *trans* isomer was isolated.

Acid-Catalyzed Epimerization of the 17α-Bromo Ketone 1a.—A solution of 1.0 g. of the bromo ketone **1a** in 40 ml. of 95% ethanol and 4 ml. of concentrated sulfuric acid was heated at reflux. After 6 days, the solution was cooled, diluted with water, and extracted with benzene. The extract was washed with aqueous potassium bicarbonate solution, then dried, and concentrated. The residue (0.78 g., $[\alpha]D$ +90°) was chromatographed on 110 g. of silica. (An aliquot of the reaction withdrawn after 2 days and worked up in the same way exhibited $[\alpha]D$ +19°.) Eluted with 0–2% ethyl acetate in benzene was 0.56 g. of semicrystalline material, recrystallized from methylene chloride–methanol twice to give 0.35 g. of the starting material **1a**, m.p. 130–133°. (A paper chromatogram of the mother liquors showed the presence of approximately 10% of the 17β-epimer **4a**.) Elution with 5% ethyl acetate in benzene provided 0.21 g. of residue recrystallized from ether to provide 50 mg. of pure **2**, m.p. 135–137° (identity confirmed by spectral comparison with authentic material.)

Reaction of the 17α-Bromo Ketone 1a with Collidine.—2,4,6-Collidine (30 ml.) containing 1.68 g. of the ketone **1a** was heated at reflux under nitrogen for 42 hr. The solution was cooled, diluted with water and excess 5% hydrochloric acid, and the resulting mixture was extracted with benzene. The extract was washed with aqueous potassium bicarbonate, dried, and concentrated under reduced pressure. The product, 1.15 g. of oil, was chromatographed on 60 g. of silica. Elution with benzene provided 0.10 g. of material, recrystallized from methylene chloride–methanol to yield 80 mg. of the 3-methoxy-17β-bromoestra-1,3,5(10)-trien-16-one (**4a**), m.p. 221–224°, identical in the infrared to an authentic sample.[2] Further elution with benzene gave 0.12 g. of residue, recrystallized from petroleum ether (Darco) to yield 40 mg. of 3-methoxyestra-1,3,5(10)-trien-16-one (**5** with 14α-H), m.p. 122–124°, identical in the infrared to an authentic sample. Eluted with 2% ethyl acetate in benzene was 0.60 g. of material, recrystallized from ether to give 0.46 g. of the unsaturated ketone **2**, m.p. 138–140° (spectral comparison satisfactory).

In an earlier run, after 16 hr. at reflux, the product was chromatographed and shown to consist of 30% of a mixture of 17α- and 17β-bromo ketone fractions. Also present was 40% of the unsaturated ketone **2**.

Reaction of the 17α-Bromo Ketone 1a with Sodium Methoxide. A. Reaction in a Heterogeneous System.—A slurry of 1.0 g. of the bromo ketone **1a** in 40 ml. of methanol containing 3.5 g. of sodium methoxide was stirred at room temperature for 25 min. Although the mixture remained heterogeneous, a definite change in crystal form was seen. The mixture was filtered, the precipitate being washed with methanol and then with water, leaving 0.62 g. of crystals, m.p. 175–215°. Recrystallization from methylene chloride–methanol gave 0.36 g. of the pure 17β-bromide **4a**, m.p. 218–222°, identical to the authentic material by the standard comparisons.

The 17α-chloro ketone (**1b**, 0.10 g.) was similarly epimerized by slurrying in 4 ml. of methanol containing 0.50 g. of sodium methoxide for 10 min. The product, isolated by filtration and purified by recrystallization from aqueous methanol, gave 30 mg. of the pure chloro ketone **4b**, m.p. 196–201°, identical by normal criteria to the authentic material.[2]

In a similar experiment, a solution of 0.10 g. of the chloro ketone **1b** in 6 ml. of methanol and 2 ml. of 5% aqueous potassium hydroxide was allowed to stand at room temperature for 20 min. The product, isolated by benzene extraction, was demonstrated by analysis to have lost halogen.

Anal. Calcd. for $C_{19}H_{23}ClO_2$: Cl, 11.12. Found: Cl, 1.14.

B. Reaction in a Homogeneous System.—To a solution of 9 g. of sodium methoxide in 200 ml. of methanol was added a solution of 1.50 g. of **1a** in 10 ml. of benzene at 5°. A precipitate formed very quickly and remained unchanged despite vigorous stirring and removal of the cooling bath. After 1 hr., the solution was filtered, yielding 0.80 g. of the 17β-bromo ketone **4a**, m.p. 200–215° (infrared comparison). This material (0.78 g.) was dissolved in 80 ml. of benzene and added to the sodium methoxide solution within 30 min. of the filtration. After a total of 5 hr. the homogeneous solution was treated with excess acetic acid and water. The product (1.3 g. of oil) was isolated by benzene extraction and chromatographed on 85 g. of silica.

(17) We wish to acknowledge the assistance of Dr. E. G. Daskalakis and staff for the chromatographic work and Dr. R. T. Dillon and staff for the analyses and spectra described here.

(18) Melting points were taken on a Fisher-Johns melting point apparatus and are not corrected. Rotations were determined in chloroform (1%), ultraviolet spectra in methanol, and n.m.r. spectra in deuteriochloroform. The n.m.r. spectroscope was Model A-60, Varian Associates, Inc., operating at 60 Mc; the values reported are $\Delta\nu$ from tetramethylsilane as an internal standard. The petroleum ether used had b.p. 60–80°.

(19) We wish to thank Mr. W. Selby for conducting this hydrogenation.

(20) We wish to thank Dr. N. L. McNiven for this determination. C. Djerassi, J. Fishman, and T. Nambara, *Experientia*, **12**, 565 (1961), describe the dispersion curves of analogous ketones.

Eluted with benzene and 0.5% ethyl acetate in benzene was 0.62 g. of a crystalline mixture. A paper chromatogram of these fractions showed two components to be present in roughly equal amounts. Partial separation of these compounds was effected by crystallization from methanol and from petroleum ether assisted by mechanical separation, giving rectangular plates, m.p. 126–128°, and prisms, m.p. 158–163°. The lower melting material was seen to be identical to the known 3,17α-dimethoxyestra-1,3,5(10)-trien-16-one (6)[9] by comparison of the infrared spectra. The second component was recrystallized from petroleum ether to give the pure 3,15β-dimethoxyestra-1,3,5(10)-trien-16-one (7), m.p. 165–168°; $[\alpha]_D$ −15°; λ_{max} 5.75 mμ; 63 (C_{18}-CH_3), 210 (15-OCH_3) c.p.s.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.12; H, 8.50.

Also eluted with 1% ethyl acetate in benzene was 80 mg. of a crystalline mixture recrystallized from petroleum ether and then from methanol to yield 30 mg. of 3,15α-dimethoxyestra-1,3,5(10)-trien-16-one (8), m.p. 100–102°; λ_{max} 5.72 mμ; 57 (C_{18}-CH_3), 218 (15-OCH_3) c.p.s.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 77.09; H, 8.32.

At 5% ethyl acetate in benzene was eluted 0.19 g. of material, recrystallized from acetone–petroleum ether to yield 0.11 g. of the unsaturated ketone, 2, m.p. 130–135° (spectral comparison satisfactory).

Reaction of the Bromo Ketone 1a with Potassium Carbonate.—To a solution of 0.6 g. of potassium carbonate in 6 ml. of water and 200 ml. of methanol was added 0.30 g. of the bromo ketone 1a. After 72 hr. the solution was poured into water containing excess acetic acid. The resulting mixture was isolated with benzene in the usual way. The crude product (0.25 g.) was analyzed by paper chromatography and was seen to consist of 40–45% of the 15β-methoxy compound 7, 35–40% of the 17α-methoxy compound 6 and 3–5% of the 15α-compound 8. No bromo ketones were seen and less than 5% of the unsaturated ketone 2 was in evidence. Chromatography on silica led to isolation of the two major products as described for the sodium methoxide-catalyzed reaction.

In an earlier experiment, using similar conditions, the reaction was stopped after 18 hr. At that time, analysis of the product by paper chromatography showed 45% of the 17β-bromo ketone 4b, 20% of the 17α-bromo ketone 1a, and 15% each of the methoxy ketones 6 and 7.

Equilibration of the Methoxy Ketones 7 and 8.—A solution of 40 mg. of the methoxy ketone 7 and 0.2 g. of potassium carbonate in 10 ml. of methanol and 2 ml. of water was heated at reflux for 1 hr. The solution was diluted with water and extracted with benzene. Isolation of the product in the usual way afforded 40 mg. of semicrystalline residue. This material was seen by paper chromatography and n.m.r. (methoxyl absorption at 210 and 218 c.p.s.) to consist of about 60% of ketone 8 and 40% of ketone 7. Attempts at separation by fractional crystallization were only partially successful.

Retreatment of the equilibrium mixture with potassium carbonate in methanol for an additional 2 hr. led to no appreciable change in the proportion of isomers 7 and 8 as seen by paper chromatography.

Acyl Transfer during Chromium Trioxide Oxidation in the Pregnane Series. Some Reactions of 5 β-Androstane-16,17-ketols[1,2]

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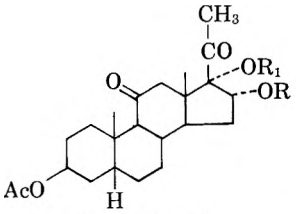
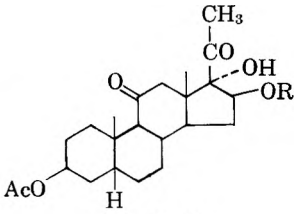
Reaction of 3α,16α-diacetoxy-17α-hydroxypregnane-11,20-dione (Ib) with chromium trioxide in acetic acid proceeded in part anomalously to give the 17α-acetoxy-11,16-20-trione V. The latter compound with base underwent β-ketonic cleavage or rearrangement to give primarily the δ-lactone VIII. Various reactions of the 17β-hydroxy ketol system VIIa are discussed.

In connection with work on the D-homoannulation of the 3α,16-17α-trihydroxy-11, 20-diketopregnanes Ia and IIa,[3] we had occasion to degrade the corresponding 16α- and 16β-acetates, Ib and IIb, to the respective 16-acetoxy 17-ketones by two routes in order to confirm that ring D in the parent compounds was five-membered. In each case, successive treatment with sodium borohydride in aqueous dimethylformamide[4] and sodium metaperiodate[3,5] led to the ketol acetates III and IV, respectively. Both ketol acetates III and IV gave positive blue tetrazolium tests and showed a characteristic shift in the 17-carbonyl infrared band to 5.70 μ from the normal 5.77 μ due to interaction with the 16-acetyl function. This shift was independent of configuration at C-16.[6]



Ia. R = R1 = H
Ib. R = Ac, R1 = H
Ic. R = R1 = Ac



IIa. R = H
IIb. R = Ac

Although the second method of side chain degradation, namely, chromium trioxide in acetic acid, gave analogous results in the 16β-acetoxy series, similar treatment of the 16α-acetate Ib gave a second neutral tetrazolium positive substance (20–25% yield) in addition to the 16α-acetoxy 17-ketone III (30–35%)[7] plus a minor amount of 3α-acetoxy-11-ketoetiobilianic acid (VIb). The infrared spectrum of the new material [λ_{max}^{chf} 5.68, 5.79, 5.84, 8.00 μ] indicated the possible presence of an acetate function adjacent to a carbonyl group as in the ketol acetates III and IV. However, the high negative specific rotation of this substance,

(1) Presented in part before the American Chemical Society, North Jersey Section, Meeting-in-Miniature, February 1, 1960.

(2) In a recent publication entitled, "16-Bromo-D-Homo Steroids," by N. L. Wendler and H. L. Slates [*J. Org. Chem.*, **26**, 4738 (1961)], these authors inadvertently failed to make reference to the reports of C. Djerassi and T. Nakano [*Chem. Ind.* (London), 1385 (1960)] as well as M. Uskoković, M. Gut, and R. I. Dorfman [*J. Am. Chem. Soc.*, **82**, 958 (1960)] bearing on the isomerization and elimination reactions of A and D ring α-halo ketones in related steroid systems. Apologies are herewith expressed for this oversight.—N. L. W.

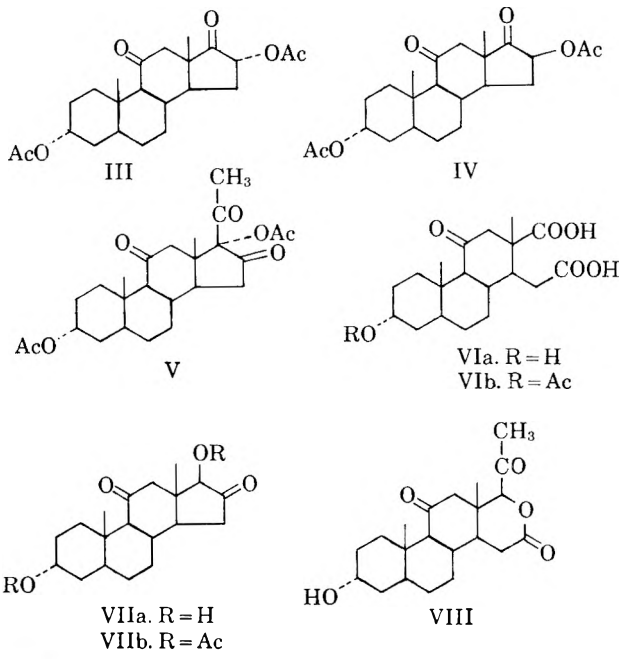
(3) N. L. Wendler, D. Taub, and C. H. Kuo, *ibid.*, **82**, 5701 (1960).

(4) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *ibid.*, **81**, 3291 (1959).

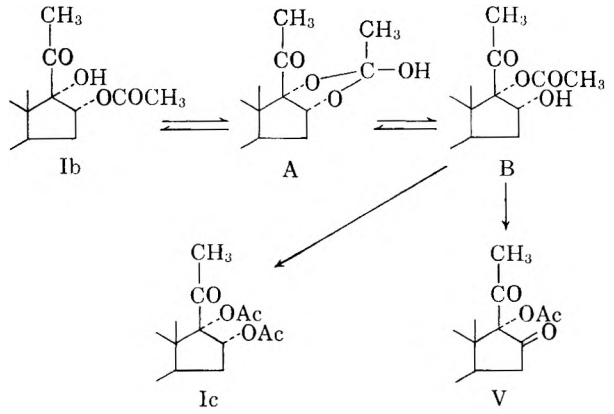
(5) G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4373 (1955), utilized an analogous sodium borohydride-periodate sequence to degrade the side chain in the 3β,16-diacetoxy-5-pregnen-20-one series.

(6) *Cf.* R. N. Jones and G. Roberts, *Chem. Ind.* (London), 1269 (1957).

(7) Cooley, *et al.*, ref. 5, on chromium trioxide oxidation of 3β,16α-diacetoxy-17α-hydroxy-5α-pregnan-20-one observed formation of one neutral product, the expected 16α-acetoxyandrostan-17-one.

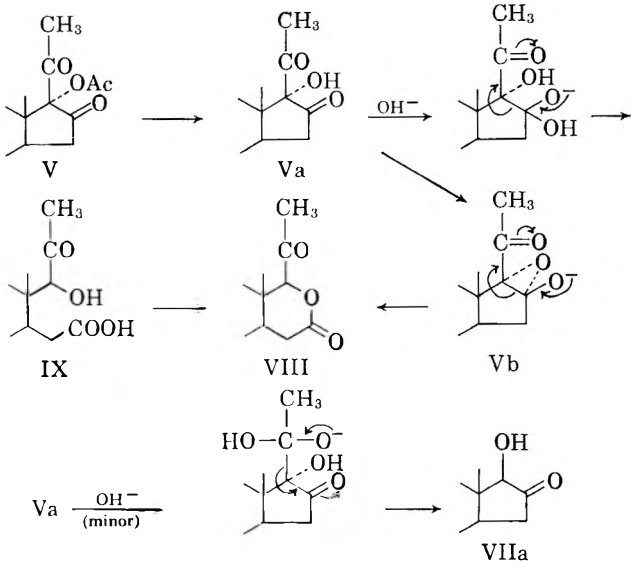


$[\alpha]_D^{Chf}$ −164°, contrasted with the positive rotations of Ia (+98°), III (+133°), and IV (+129°) and was suggestive of a marked structural change. In connection with this problem we had ascertained that the 3α,16α-diacetate Ib was converted in part to the 3α,-16α,17α-triacetate Ic under normal acetylation conditions (acetic anhydride–pyridine at 25°). Acetylation was complete at 90°, and its relative ease in comparison with acetylation of the 17α-hydroxyl group in the absence of the 16α-hydroxyl function suggested the operation of an acyl transfer process[8] in the formation of the triacetate Ic. As formulated below the acetyl group may undergo transfer from the C-16 to the C-17 hydroxyl group through the orthoacetate intermediate A to yield the 17α-acetate B which would be readily acetylated to Ic.



The possibility that acyl transfer might also be involved in the chromium trioxide–acetic acid oxidation of Ib led to consideration of the 17α-acetoxy-16,20-diketo structure V for the new substance. Formula V is in accord with the elemental analysis ($C_{25}H_{34}O_6$), infrared spectrum and the n.m.r. spectrum which indicated the presence of three acyl methyl functions (7.65, 7.72 τ, 17-$COCH_3$, -$OCOCH_3$; 7.86 τ, 3-$OCOCH_3$).

The ability of the tertiary ketol system V to give a positive tetrazolium test characteristic of primary or secondary ketols may appear on first inspection to be inconsistent with its structure. However, under the alkaline conditions of the test, secondary ketol systems are generated. Thus treatment of V with dilute methanolic sodium hydroxide followed by acidification led primarily to a new tetrazolium-positive substance. This substance, $C_{21}H_{30}O_5$, had the base solubility properties of a lactone and absorbed in the infrared at 2.76, 2.94 (OH), 5.74 (δ-lactone), 5.85 (11 C=O) and 9.3 μ (lactone ether oxygen). It was consequently formulated as VIII; the n.m.r. spectrum confirmed the presence of the CH_3CO grouping attached to C-17a (7.60 τ). The above reaction sequence evidently involves cleavage of the β-diketone system of V as formulated below [V → IX → VIII]. Alternatively, an internal rearrangement pathway *via* Vb is also possible.



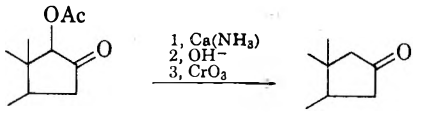
The lactone VIII contains a potential secondary ketol system and would be expected to give a positive tetrazolium test by conversion in alkali to the anion of the corresponding acid IX. The ability of V to give a positive test, therefore, is due to cleavage of its β-diketone system to the secondary ketol system IX. Paper chromatographic evidence indicated the presence of a minor amount of the 17β-hydroxy 16-ketone VIIa which may be formed by the indicated alternate cleavage of the β-diketone system (Va → VIIa).

We previously had prepared the 17β-hydroxy 16-ketone VIIa by equilibration of the ketol acetates III and IV in methanolic sodium hydroxide in the absence of oxygen.[3] Acetylation of VIIa gave the corresponding 3α-17β-diacetate VIIb[3] which clearly differed from III and IV and must, therefore, be a 17-acetoxy 16-ketone. Calcium and liquid ammonia reduction[9] of VIIb gave the corresponding 16-ketone Xa which on hydrolysis and oxidation at C-3 gave 5β-androstane-3,11,16-trione (Xc), identical with an authentic sample.[10] The 17β, quasi equatorial configuration for the

(8) For examples of acyl transfer in the steroid series, see for example: (a) D. K. Fukushima, N. S. Leeds, H. L. Bradlow, T. H. Kritchevsky, M. B. Stokem, and T. F. Gallagher, *J. Biol. Chem.*, **212**, 449 (1955) [C-17 → C-20]; (b) P. Wieland, K. Heusler, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1657 (1958) [C-18 → C-17]; (c) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 3291 (1959) [C-21 → C-20]; (d) R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Letters*, **13**, 448 (1961) [C-17 → C-21].

(9) Method of J. H. Chapman, J. Elks, G. H. Phillips, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(10) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Org. Chem.*, **26**, 2849 (1961).

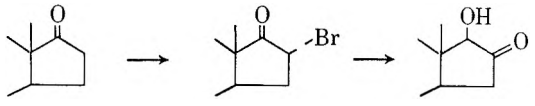


VIIb

Xa, 3α-acetate
Xb, 3α-ol
Xc, 3-one

17-hydroxyl group in VIIa is the predicted one for a thermodynamically equilibrated product and is in accord with results in the estrane and 5α-androstane series.[11]

The ketol VIIa was best prepared from the readily available 17-ketone XI by a new and simple route. Bromination of the latter in chloroform–acetic acid produced the bromo compound XII (probably mainly

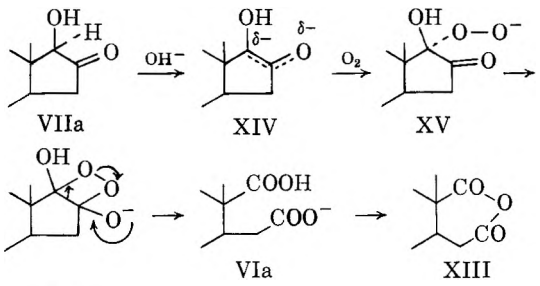


XI
$[\alpha]_D^{chf}$ +150°

XII
$[\alpha]_D^{chf}$ +135°

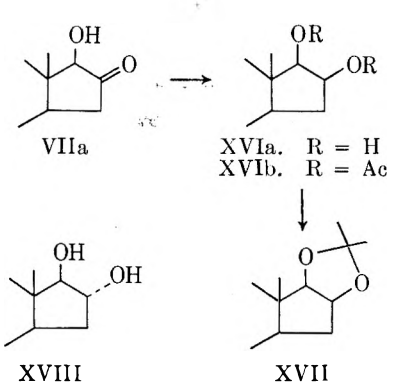
VIIa

16α[12]). Treatment of the latter with dilute potassium hydroxide in *t*-butyl alcohol in the absence of air produced the ketol VIIa in moderate (45–50%) over-all yield from the 17-ketone XI.[13] In the presence of air 3α-hydroxy-11-ketoetiobilianic acid VIa was an important by-product and in some runs the major product. Its structure was secured by conversion to the corresponding 3α-acetoxy anhydride XIII.[14] The reaction may be formulated as involving addition of oxygen to the anion XIV to give an intermediate 17-hydroperoxide XV, which can rearrange as indicated to the diacid VIa. The ketol acetates III and IV similarly were oxidized in part to the diacid VIa on treatment with alcoholic alkali in the presence of air.[15]



Some further reactions of the ketol VIIa are now discussed.

Sodium borohydride reduction of VIIa in aqueous dimethylformamide[4] led to the 16,17-*cis*-β-glycol XVIa the structure of which was confirmed by conversion to the isopropylidene derivative XVII and to the 3α,16β,-17β-triacetate XVIb. Treatment of VIIa with benzaldehyde and alkali did not lead to the expected 15-benzylidene derivative. The crude product which had slight ultraviolet absorption in the 290-mμ region and weak absorption in the 5.70-μ region in the infrared was more polar than VIIa on paper [benzene–chloroform(1:3)–formamide system]. It is believed to consist primarily of the *trans* glycol XVIII formed by crossed Canizzaro reaction,[16,17] together with a small amount of unchanged ketol.



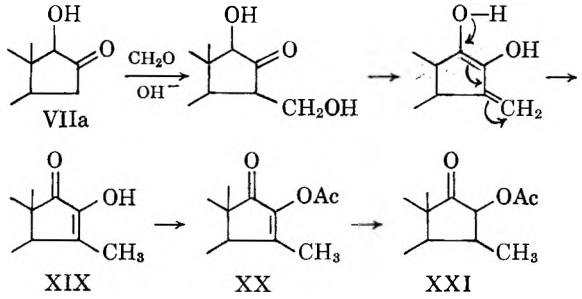
VIIa

XVIa. R = H
XVIb. R = Ac

XVIII

XVII

By contrast with the benzaldehyde case, the ketol VIIa did condense with formaldehyde in the presence of potassium hydroxide in aqueous *t*-butyl alcohol to give in part a base-soluble substance with λ_{max}^{MeOH} 272 mμ, ε 6800, which is formulated as the 15-methyldiosphenol XIX on the basis of its properties and by



analogy with the same reaction in the D-homo series.[18] Acetylation of XIX gave the enol acetate XX, λ_{max}^{MeOH} 244 mμ (9700). Hydrogenation of XX over palladium on charcoal reduced the double bond to form the 15-methylketol acetate XXI which gave a characteristic

(11) M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.*, **71**, 719 (1949), see footnote 9, ref. 11b; N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *ibid.*, **76**, 2943 (1954); (c) W. S. Johnson, B. Gastambide, and R. Pappo, *ibid.*, **79**, 1991 (1957); (d) J. Fishman, *ibid.*, **82**, 6143 (1960).

(12) The 17-carbonyl group of XII absorbed in the infrared at 5.71 μ, but the shift from the normal 5.75 μ cannot be used in structural arguments concerned with the configuration of the 16-bromine substituent. J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 312 (1955), found in a related series that both 16α- and 16β-bromo 17-ketones absorb at 5.70 μ. See also C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958). The 16α-bromo assignment in the present case is based on analogy with the work of Fajkos and Shoppee, *et al.*, and is supported by the optical rotation data.

(13) The procedure of Leeds, Fukushima, and Gallagher (rearrangement of the 16α,17α-epoxy-17β-acetate, ref. 11b) proceeded poorly in the present 11-keto-5β-androstane series. Alternate procedures, acyloin condensation of the dimethyl ester of VI [*cf.* J. C. Sheehan, R. E. Coderre, and P. A. Cruikshank, *J. Am. Chem. Soc.*, **75**, 6231 (1953)] and reduction of the 16-oximino 17-ketone [*cf.* M. N. Huffman, *J. Biol. Chem.*, **169**, 167 (1947); F. H. Stodola, E. C. Kendall, and B. F. McKenzie, *J. Org. Chem.*, **6**, 841 (1941)] were not investigated.

(14) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956).

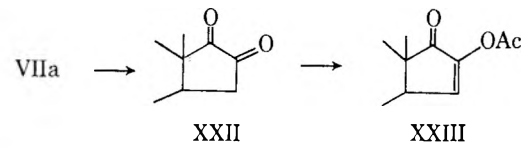
(15) Autoxidation of the above 16,17-ketols io air with aqueous base appears to be considerably more facile than that of simple ketones which in general require *t*-alkoxide and oxygen. *Cf.* W. E. Doering and W. M. Haines, *ibid.*, **76**, 482 (1954); E. Elkik, *Bull. soc. chim. France*, 933 (1959); E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962). It is of interest that autoxidation of 2α- or 2β-hydroxytestosterone in aqueous potassium hydroxide proceeded only to the $\Delta^{1,4}$-2-hydroxy-3-keto stage [R. L. Clarke, *J. Am. Chem. Soc.*, **82**, 4629 (1960)].

(16) For an example of reduction on attempted benzylidene derivative formation in the D-homo series and a discussion of mechanism, see N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

(17) The characterization and additional chemistry of the present product is under study.

(18) N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959).

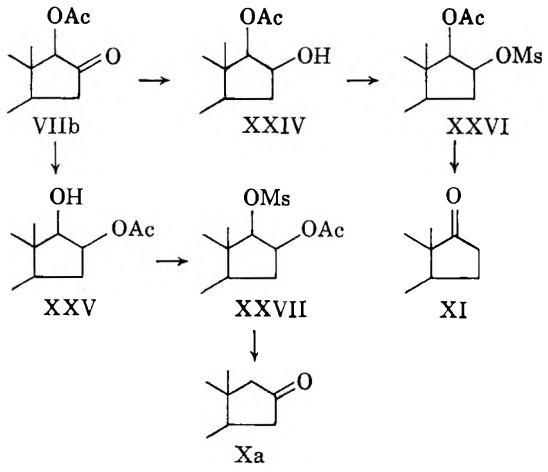
blue tetrazolium test. Under the assumption that hydrogenation occurred from the rear face of ring D the groups at C-15 and C-16 in XXI may be formulated as β.



XXII XXIII

Cupric acetate–methanol oxidation[19] of VIIa provided, in part, the alkali soluble 16,17-dione XXII as an amorphous yellow solid, m.p. ~155–170°, which was not obtained analytically pure. The dione XXII had negligible ultraviolet absorption in methanol and must exist, correspondingly, almost entirely in the α-diketone (or hemiacetal of the diketone) form in this solvent. In methanolic alkali XXII absorbed at 300 mμ (ϵ ~1500) showing the presence of the corresponding enolate anion. By contrast the 15-methyl-16,17-dione XIX exists in methanol in the diosphenol form as shown by strong absorption at 272 mμ. On acetylation XXII was converted into the amorphous enol acetate XXIII, λ_{max}^{MeOH} 236 mμ (5000).

Finally, an additional example of acyl transfer was observed in the following sequence.



Sodium borohydride–aqueous dimethylformamide reduction of the ketol acetate VIIb led to a glycol monoacetate which was mesylated and treated with ethanolic potassium hydroxide. The product, which should have been the 17-ketone XI, was in fact a 40:60 mixture of the 17-ketone and the 16-ketone Xa as indicated by paper chromatography and infrared spectroscopy, from which a small quantity of XI was isolated by crystallization. Evidently acetyl transfer occurred during the reduction step[7b,c] to give a mixture of glycol monoacetates XXIV and XXV which was capable of resolution on paper at the acetate mesylate (XXVI and XXVII) and ketone (XI and Xa) stages.

Experimental[20]

Chromium Trioxide Oxidation of 3α,16α-Diacetoxy-17α-hydroxypregnane-11,20-dione (Ib). 3α,16α-Diacetoxy-5β-androstane-11,17-dione (III), 3α,17α-Diacetoxy-5β-pregnane-11,16,20-trione (V), and 3α-Acetoxy-11-keto etiobilianic Acid (VIb).—To a stirred solution of 2.0 g. of the 16α-acetate Ib in 40 ml. of acetic acid was added 1.0 g. of chromium trioxide in 40 ml. of acetic acid and 0.8 ml. of water. After 20 hr. at 25°, water was added and the mixture was extracted with chloroform The latter extract was washed with water, aqueous potassium bicarbonate, saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated to dryness. The residue (1.8 g.) was chromatographed over 85 g. of Florisil. From the benzene–chloroform eluates was obtained 500 mg. of **3α,17α-diacetoxy-5β-pregnane-11,16,20-trione (V)**, crystallized from acetone–ether, m.p. 201–203°, $[\alpha]_D$ −164°; λ_{max}^{chf} 5.68, 5.79, 5.84, 8.00 μ. N.m.r. spectra: 7.65, 7.72 τ (17-$COCH_3$, $OCOCH_3$), 7.86 τ (3-$OCOCH_3$), 8.70 τ (C_{19}-methyl), 9.14 τ (C_{18}-methyl).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.23; H, 7.62. Found: C, 67.08; H, 7.30.

From the later benzene–chloroform and chloroform eluates was obtained 720 mg. of the known **3α,17α-diacetoxy-5β-androstane-11,17-dione** (III), double m.p. 194–198°, 208–212° (from acetone–ether), identical with an authentic sample[3] by mixture melting point and infrared comparison.

On acidification of the original bicarbonate extract with dilute hydrochloric acid 106 mg. of **3α-acetoxy-11-ketoetiobilianic acid** (VIb)[14], m.p. 247–250°, was obtained.

Chromium Trioxide Oxidation of 3α,16β-Diacetoxy-17α-hydroxypregnane-11,20-dione (IIb). 3α,16β-Diacetoxy-5β-androstane-11,17-dione (IV).—Treatment of 1.0 g. of the 16β-acetate IIb in 20 ml. of acetic acid with 500 mg. of chromium trioxide in 20 ml. of acetic acid and 0.4 ml. of water as previously described, led to **3α,16β-diacetoxy-5β-androstane-11,17-dione (IV)**, m.p. 176–180, undepressed mixture melting point with an authentic sample[3] as the only observed product.

3α,16α,17α-Triacetoxypregnane-11,20-dione (Ic).—Treatment of 200 mg. of 3α,16α-diacetoxy-17α-hydroxypregnane-11,20-dione (Ib) with 1 ml. of acetic anhydride in 2 ml. of pyridine at 90–95° (steam bath) for 18 hr. and crystallization of the residue from ether–benzene led to the **3α,16α,17α-triacetate Ic** (144 mg.), m.p. 244–245°; λ_{max}^{Nujol} 5.70–5.85, 7.9–8.0 μ [no -OH].

Anal. Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.79; H, 7.71.

A similar experiment at 25° led to a mixture of Ib (major) and Ic (minor) as evidenced by paper chromatography [benzene–cyclohexane (1:10)–formamide system]. At 90° for 1 hr. Ic was the major component.

Reaction of V with Methanolic Sodium Hydroxide. 3α-Hydroxy-17a-acetyl-17-oxa-D-homo-5β-androstane-11,16-dione (VIII).—To a solution of 150 mg. of the 11,16,20-trione V in 10 ml. of methanol (under nitrogen) was added 150 mg. of sodium hydroxide in 2 ml. of water. After 1 hr. at 25° the mixture was acidified with dilute hydrochloric acid and the methanol removed by concentration under vacuum. Water was added and the mixture extracted with ether. The ether extract was washed with 5% aqueous potassium bicarbonate, 2% aqueous sodium hydroxide, salt solution, dried over magnesium sulfate, and concentrated to dryness. The basic extracts were acidified with dilute hydrochloric acid, extracted with chloroform, the latter extracts dried over magnesium sulfate, and concentrated to dryness. The bicarbonate extracted material (white solid, 53 mg.) was recrystallized from acetone–ether to give the **lactone VIII** 34 mg., m.p. 252–256°; $[\alpha]_D$ −106°; λ_{max}^{chf} 2.76, 2.94 μ (3α-OH), 5.74 μ (δ-lactone), 5.85 μ (11,20-C=O), 9.3 μ (lactone ether oxygen); in morpholine the 5.74-μ band slowly diminished with concomitant formation of a carboxylate anion band at 6.15–6.20 μ. N.m.r. spectra: 5.36 τ (17aα-H), 7.60 τ (17aβ-$COCH_3$), 8.80 τ (19-CH_3), 8.85 τ (18-CH_3).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.35. Found: C, 69.68; H, 8.31.

The sodium hydroxide extracted material (46 mg.) crystallized with difficulty and probably contained additional lactone VIII as evidenced by paper chromatography (benzene–chloroform (1:5)–formamide system) along with polar components.

The original neutral ether extract (30 mg.) probably contained the ketol VIIa as indicated by paper chromatography.

3α-Acetoxy-5β-androstane-11,16-dione (Xa).—To a stirred solution of 300 mg. of calcium turnings in 30 ml. of liquid ammonia[9] was added (5 min.) 400 mg. of 3α,17β-diacetoxy-5β-androstane-11,16-dione (VIIb) in 5 ml. of dry toluene. After an additional 10 min. 0.5 ml. of bromobenzene was added dropwise followed

(19) *Cf.* M. N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947).

(20) Melting points were taken on a micro hot stage and are corrected. Paper chromatograms were run on strips of Whatman no. 4 filter paper using the formamide based systems of A. Zaffaroni, R. B. Burton, and E. H. Keutmann, *Science*, **111**, 6 (1950). N.m.r. spectra were run in deuteriochloroform at 60 Mc. [see N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961), for procedural details].

by 1.0 ml. of water, and the ammonia was allowed to evaporate. Water (50 ml.) was added and the mixture extracted with chloroform. The latter extract was washed with salt water, dried over magnesium sulfate, and concentrated to dryness under vacuum. The residue (~300 mg.) was chromatographed over 15 g. of neutral alumina. Recrystallization of the crystalline and single spot [benzene–cyclohexane (1:5)–formamide system] petroleum ether–benzene eluates (104 mg.) from ether–petroleum ether gave analytically pure Xa, m.p. 135–137°; λ_{max}^{chf} 5.74, 5.83, 7.99 μ; negative tetrazolium test.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.51; H, 8.43.

Attempted deacetylation of VIIb by refluxing with zinc in acetic acid failed.[21]

5β-Androstane-3,11,16-trione (Xc).—To a solution of 50 mg. of Xa in 2.5 ml. of methanol was added 50 mg. of sodium hydroxide in 1 ml. of water. After 30 min. at 25°, 0.3 ml. of acetic acid was added and the methanol removed under vacuum. Water was added and the mixture was extracted with chloroform. The latter extract was dried over magnesium sulfate and concentrated to dryness. The residue crystallized from ether to give **3α-hydroxy-5β-androstane-11,16-dione (Xb)**, m.p. 130–133°; λ_{max}^{chf} 2.71, 2.8–2.9, 5.74, 5.84 μ. To a solution of 50 mg. of Xb in 1 ml. of acetic acid was added 30 mg. of chromium trioxide in 1 ml. of 90% acetic acid. After 17 hr. at 25° water was added and the mixture extracted with chloroform. The latter extract was washed with 5% aqueous potassium bicarbonate, salt water, dried over magnesium sulfate, and concentrated to dryness. Crystallization of the residue from acetone–ether gave Xc, m.p. 185–190°, undepressed on mixture melting point with an authentic sample, m.p. 189–191°.[10] The respective paper chromatographic mobilities [benzene–cyclohexane (1:1)–formamide system] and infrared spectra were identical.

3α-Acetoxy-16α-bromo-5β-androstane-11,17-dione (XII).—To a stirred solution (*t*, 10°) of 25.3 g. (73 mmoles) of 3α-acetoxy-5β-androstane-11,17-dione (XI) in 400 ml. of chloroform and 1 drop of 15% hydrogen bromide in acetic acid was added dropwise 11.7 g. (73 mmoles) of bromine in chloroform. Addition was complete in 90 min. After an additional 5 min. the pale yellow solution was concentrated to dryness under vacuum and the residue crystallized from ether to give 28.8 g. (93%) of XII, m.p. 191–195°. Recrystallization from ether–acetone raised the m.p. to 198–202°; $[\alpha]_D$ +135°; λ_{max}^{chf} 5.71, 5.80, 5.84, 8.0 μ.

Anal. Calcd. for $C_{21}H_{29}O_4Br$: C, 59.29, H, 6.87, Br, 18.79. Found: C, 58.96; H, 6.49; Br, 18.61.

3α,17β-Dihydroxy-5β-androstane-11,16-dione VIIa.—To a stirred solution of 28 g. of the 16α-bromo 17-ketone XII (m.p. 191–195°) in 1800 ml. of *t*-butyl alcohol maintained under nitrogen was added 1800 ml. of 2% aqueous potassium hydroxide. After 17 hr. at 25° the mixture was neutralized with cold 2 *N* hydrochloric acid and the *t*-butyl alcohol was removed under vacuum. The mixture was extracted with 1:1 benzene–ethyl acetate and the latter extract washed with saturated salt solution, dried over magnesium sulfate, and concentrated to dryness. Two crystallizations of the residue from acetone–ether gave 10.5 g. (50%) pure VIIa, m.p. 199–202°,[3] with additional material in the mother liquors.

Pyridine–acetic anhydride acetylation of VIIa (200 mg.) gave the corresponding 3α,17β-diacetate VIIb,[3] m.p. 184–186°.

3α-Hydroxy-11-ketoetiobilianic acid (VIa). (A) From XII.—A solution of the 16α-bromo 17-ketone XII (1.0 g.) in 6 ml. of tetrahydrofuran and 6 ml. of 2% aqueous potassium hydroxide was kept exposed to air at 25° overnight. The tetrahydrofuran was removed under vacuum and the alkaline solution extracted with ethyl acetate. The latter extract was washed with saturated salt solution, dried over magnesium sulfate and concentrated to dryness. Trituration of the residue with ether gave 200 mg. of the 17β-hydroxy-16-ketone VIIa. Acidification of the basic aqueous layer and extraction with ethyl acetate gave 3α-hydroxy-11-ketoetiobilianic acid VIa (360 mg.), m.p. 227–232; λ_{max}^{Nujol} 3.0–3.6 (broad), 5.82, 5.91 μ.

Anal. Calcd. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.26; H, 7.75.

Reaction of VIa (100 mg.) with 0.5 ml. of acetic anhydride and 1 ml. of pyridine overnight at room temperature gave the known 3α-acetoxy-11-ketoetiobilianic acid anhydride (XIII), m.p. 207–215° (reported m.p. 213–215°[14]), undepressed on mixture melting point with an authentic sample.

(B) **From Ketol VIIa.**—Treatment of 3α,17β-dihydroxy-5β-androstane-11,16-dione (VIIa) (100 mg.) in 4 ml. of methanol with 4 ml. of 2.5% aqueous sodium hydroxide in air for 2 hr. at room temperature led to 70 mg. of acid VIa.

Analogous treatment of the ketol acetates III and IV with aqueous methanolic sodium hydroxide in air also led to the etiobilianic acid VIa.

3α,16β,17β-Trihydroxy-5β-androstane-11-one (XVIa).—To a stirred solution of 400 mg. of ketol VIIa in 10 ml. of dimethylformamide was added 100 mg. of sodium borohydride in 5 ml. of water. After 3 hr. (negative tetrazolium test) 2 ml. of 10% aqueous acetic acid was added dropwise followed by saturated salt water. The mixture was extracted with chloroform, the latter extract washed with saturated salt solution, dried over magnesium sulfate and concentrated to dryness. The residue was crystallized from aqueous methanol, 287 mg., m.p. 262–268°, raised to 270–274° on repeated crystallization; λ_{max}^{Nujol} 2.9–3.0, 5.89 μ.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.53; H, 9.20.

3α-16β,17β-Triacetoxy-5β-androstane-11-one (XVIb).—The triol XVIa (120 mg.) was acetylated in 2 ml. of acetic anhydride and 3 ml. of pyridine overnight at 25°. The mixture was concentrated to dryness under vacuum, flushing twice with benzene. Crystallization of the residue from acetone–ether gave the triacetate XVIb, m.p. 204–207°; λ_{max}^{chf} 5.75, 5.85, 8.0 μ.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.41; H, 8.05.

Isopropylidene Derivative (XVII).—A solution of 100 mg. of triol XVIa in 10 ml. of acetone and 0.1 ml. of concentrated sulfuric acid was kept at 25° overnight. A small quantity of solid was removed by filtration, the filtrate was neutralized with potassium bicarbonate and the acetone removed under vacuum. Water was added and the mixture extracted with chloroform. The latter extract was dried over magnesium sulfate and concentrated to dryness. Crystallization of the residue from acetone–ether gave the isopropylidene derivative XVII (110 mg.), m.p. 182–184°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.84; H, 9.65.

Reaction of Ketol VIIa with Benzaldehyde.—To a solution of 2.0 g. of VIIa in 25 ml. of ethanol was added 1.40 g. of benzaldehyde and 13 ml. of 15% aqueous potassium hydroxide. The solution was stirred at room temperature under nitrogen for 18 hr. and most of the ethanol removed under vacuum. On addition of water a gum precipitated which crystallized on chilling and stirring. It was filtered and dried in air (1.66 g.), m.p. 138–146°; λ_{max}^{chf} 2.7–2.9 (strong), 5.72 (weak), 5.85 μ (strong). Crystallization from methanol–water did not raise the melting point. On paper chromatography (benzene–chloroform (1:3)–formamide) the material showed a major spot ($R_f \sim 0.4$) with nearly the same mobility as the triol XVIa and a minor, more mobile spot (+ tetrazolium test) of identical mobility as VIIa.

3α,16-Dihydroxy-15-methyl-5β-androst-15-ene-11,17-dione (XIX).—To a solution of 250 mg. of ketol VIIa in 10 ml. of *t*-butyl alcohol was added 1.0 g. of potassium hydroxide in 1 ml. of water and 0.5 ml. of 37% aqueous formaldehyde. The mixture was refluxed under nitrogen for 1 hr., the *t*-butyl alcohol removed under vacuum, water added and the mixture extracted with chloroform. The aqueous phase was acidified with dilute hydrochloric acid, extracted with chloroform, and the latter extract washed with dilute sodium bicarbonate, saturated salt solution, dried over magnesium sulfate, and concentrated to dryness. Trituration with ether gave 75 mg. of the diosphenol XIX, m.p. 158–169°, unchanged on crystallization from chloroform–ether; λ_{max}^{MeOH} 272 mμ (6800); λ_{max}^{chf} 2.78, 2.9, 5.85, 6.05 μ.

The original chloroform extract contained 50 mg. of crude starting ketol VIIa, m.p. 178–190°.

3α,16-Diacetoxy-15-methyl-5β-androst-15-ene-11,17-dione (XX).—The diosphenol XIX (80 mg.) was kept overnight at 25° in 2 ml. of pyridine and 1 ml. of acetic anhydride. The mixture was concentrated to dryness under vacuum and the residue crystallized from ether to give the enol acetate XX, 50 mg. with additional material in the mother liquor, m.p. 200–203°; λ_{max}^{MeOH} 244 mμ (9700); λ_{max}^{chf} 5.66, 5.78, 5.84 (shoulder), 6.05 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.11; H, 7.52.

(21) *Cf.* R. S. Rosenfeld and T. F. Gallagher, *J. Am. Chem. Soc.*, **77**, 4367 (1955). Clemmensen reduction of 17-hydroxy-16-keto systems has given 16-keto steroids [M. N. Huffman and M. H. Lott, *ibid.*, **73**, 878 (1951)].

3α,16-Diacetoxy-15-methyl-5β-androstane-11,17-dione (XXI).—A solution of the enol acetate XX (250 mg.) in 12 ml. of ethyl acetate was hydrogenated at 25° and 1 atm. over 150 mg. of 10% palladium on charcoal catalyst. Uptake of one molar equivalent of hydrogen was complete in 2 hr. The mixture was filtered, the filtrate taken to dryness, and the residue crystallized from ether–petroleum ether to give the saturated diacetate XXI, m.p. 176–178°; λ_{max}^{chf} 5.70, 5.78, 5.83 μ; positive tetrazolium test.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.72; H, 8.38.

3α-Hydroxy-5β-androstane-11,16,17-trione (XXII).—A stirred mixture of ketol VIIa (150 mg.), cupric acetate monohydrate (440 mg.) in 20 ml. of methanol was refluxed for 3 hr., cooled, and the methanol removed under vacuum. Dilute hydrochloric acid was added and the mixture extracted with 1:1 benzene–ether. The latter extract was washed with dilute sodium bicarbonate and 1 *N* sodium hydroxide. The sodium hydroxide extract was washed with 1:1 benzene–ether, acidified with dilute hydrochloric acid, and extracted with 1:1 benzene–ether. The latter extract was washed with saturated salt solution, dried over magnesium sulfate and concentrated to dryness to give the base soluble 11,16,17-trione XXII, which on trituration with ether was obtained as an amorphous yellow solid, 60 mg., m.p. 127–130°; ultraviolet in methanol, no maximum; in methanol containing 0.1% sodium hydroxide, λ_{max} 300 mμ (1500); λ_{max}^{chf} 2.75, 2.8–2.9, 5.72, 5.85 μ; negative tetrazolium test.

An analytically pure specimen was not obtained.

Acetylation of XXII (20 mg.) in 0.5 ml. of acetic anhydride and 1 ml. of pyridine overnight at room temperature gave the noncrystalline **3α,16-diacetoxy-5β-androst-15-ene-11,17-dione** (XXIII); λ_{max}^{MeOH} 236 mμ (5000).

Conversion of 3α,17β-Diacetoxy-5β-androstane-11,16-dione (VIIb) to 40:60 Mixture of 3α-Acetoxy-5β-androstane-11,17-dione (XI) and 3α-Acetoxy-5β-androstane-11,16-dione (Xa).—The ketol acetate VIIb (360 mg.) in 10 ml. of dimethylformamide was treated with 70 mg. of sodium borohydride in 3.5 ml. of water as described above for the reduction of VIIa. The amorphous product [XXIV and XXV (350 mg.) negative tetrazolium test; λ_{max}^{chf} 2.75, 5.75, 5.84 μ] in 2 ml. of pyridine at 0°] was treated with 0.3 ml. of methanesulfonyl chloride for 17 hr. Iced water was added and the mixture extracted with chloroform. The latter extract was washed successively with dilute hydrochloric acid, dilute aqueous potassium bicarbonate, saturated salt solution, dried over magnesium sulfate and concentrated to dryness under vacuum to give an amorphous mixture of 16,17-acetate–mesylates XXVI and XXVII (430 mg.) as evidenced by paper chromatography [two spots $R_f \sim 0.3$ and ~0.7; benzene–cyclohexane (1:1)–formamide system]. The acetate–mesylate mixture in 20 ml. of ethanol and 20 ml. of 1 *N* aqueous potassium hydroxide was refluxed for 1 hr. The ethanol was removed under vacuum, water added, and the mixture extracted with chloroform. The chloroform extract was washed with saturated salt solution, dried over magnesium sulfate, and concentrated to dryness. The residue (340 mg.) crystallized slowly from ether to yield 14 mg. of **3α-hydroxy-5β-androstane-11,17-dione,** m.p. 182–187°, identical infrared spectrum and undepressed mixture melting point with authentic sample, m.p. 186–189°. Remainder of product was acetylated (2 ml. of pyridine, 1 ml. of acetic anhydride at 25° overnight). Paper chromatography (ligroin–formamide) along with samples of the individual compounds, showed the acetylation product to consist of a nearly equivalent mixture of 3α-acetoxy-5β-androstane-11,17-dione (XI) and 3α-acetoxy-5β-androstane-11,16-dione (Xa). Infrared spectroscopy *vs.* known mixtures of XI and Xa indicated the mixture to consist of 40% XI and 60% Xa.

In a second run the sodium borohydride reduction product (350 mg.) of VIIb was in part acetylated to give in good yield the triacetate XVIb, m.p. 204–206°, and in part saponified (dilute aqueous methanolic sodium hydroxide, 25° for 40 min.) to give a good yield of the triol XVIa, m.p. 265–270°, indicating the reduction product to be a clean mixture of 16β,17β-glycol monoacetates.

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Synthesis of 2,2-Diarylpropanes by Hydride Transfer[1]

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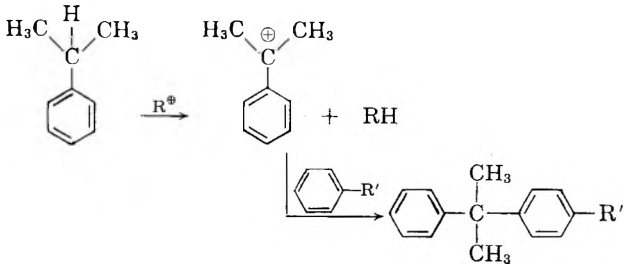
2,2-Diarylpropanes were prepared by hydride transfer reactions of 2-arylpropanes, arenes, and hydride ion acceptors. Hydride ion transfer and alkylation by the cumyl carbonium ion compete with alkylation by the hydride ion acceptors, isomerization, and transalkylation. Conversions of 2-arylpropanes to 2,2-diarylpropanes were surprisingly good in view of all these competing reactions.

Introduction

2,2-Diarylpropanes were needed in this laboratory as intermediates in oxidation studies. This led to a study of their synthesis as they are difficult to prepare by known methods. Most methods depend on alkylation of arenes with a cumyl cation formed from such reagents as α-methylstyrenes,[2] 2-chloro-2-phenylpropanes,[3] or 2-phenylpropanol-2.[4] Unfortunately these reagents readily dimerize to indanes and, except for one reaction,[3] give only a small amount of the alkylation products. Furthermore, ring-substituted α-methylstyrenes, 2-phenyl-2-chloropropanes, or 2-phenyl-2-propanols are not readily available, whereas a large number of ring-substituted cumenes can be easily prepared.

We wished to form the cumyl cations directly from 2-arylpropanes by hydride transfer to another carbonium ion in the following way.



The formation of many types of hydrocarbons by hydride transfer reactions has been reported, such as alkylation of arenes with paraffins,[5] formation of diaryl-

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) R. R. Hiatt, U. S. Patent 2,719,871 (October 4, 1955).

(3) A. T. Coscia, J. T. Penniston, and J. C. Petropoulos, *J. Org. Chem.*, **26**, 1398 (1961).

(4) K. T. Serijan and P. H. Wise, *J. Am. Chem. Soc.*, **73**, 4766 (1951).

(5) J. T. Kelly and R. J. Lee, *Ind. Eng. Chem.*, **47**, 757 (1955).

TABLE I

REACTION OF CUMENE AND BENZENE[a]

Reactants				Products				
				2,2-Diphenylpropane			Other	
Cumene, moles	Benzene, moles	Hydride ion acceptors	Moles	Moles	Mole %[b]	Mole % on recovered cumene		
0.5	2.5	*t*-Butyl chloride	0.5	0.0535	10.7	28.0	*t*-Butylbenzene	0.3 mole
1.0	1.0	*t*-Butyl chloride	.5	.0590	12.0	12.5	*t*-Butylbenzene	.26 mole
0.5	2.5	*t*-Butyl chloride	1.0	.0865	17.0	37.0	*t*-Butylbenzene	.91 mole
.5	2.5	*t*-Butyl chloride	2.0	.117	24.0	34.0	*t*-Butylbenzene	1.02 moles
.5	2.5	*t*-Butyl chloride[c]	0.5	.059	12.0	35.0	*t*-Butylbenzene	0.24 mole
.5	2.5	*t*-Butyl chloride[d]	.5	.020	4.0	11.0		
.5	2.5	*t*-Butyl chloride[e]	.5	.040	8.0	18.5		
.5	2.5	*t*-Butyl chloride[f]	.5	.039	7.8	17.5	*t*-Butylbenzene	0.16 mole
.5	2.5	*n*-Propyl chloride	.5	None			Propylbenzene	.03 mole
.5	2.5	Benzhydryl chloride	.5	0.107	21.4	37.0	Diphenylmethane	.145 mole[g]
							Triphenylmethane	.28 mole
.5	2.5	Benzhydryl chloride[f]	.5	.0873	17.4	29.0	Diphenylmethane	.18 mole
.25	1.3	Trityl chloride	.25	None				
.5	2.5	2-Methylbutene-2[h]	.5	0.030	6.0	22.2		

[a] Conditions: except as noted all reactions at 20–25° using 0.05 mole of aluminum chloride as catalyst. [b] Mole % yield based on cumene. [c] Using 1.0 mole of cyclohexane as a diluent. [d] Using 0.05 mole of anhyd. ferric chloride as catalyst. [e] At 0°. [f] At 55°. [g] 29% of theory for hydride transfer. [h] With a slow stream of dry hydrogen chloride gas.

TABLE II

REACTIONS OF ARENES AND 2-ARYLPROPANES[a]

Reactants				Products					
								Other products	
2-Aryl-propane	Moles	Arene	Moles	2,2-Diarylpropane	Moles	Mole %[b]	Mole % on recovered 2-aryl-propane		
p-Cymene	0.5	Toluene	2.5	2,2-Ditolylpropanes[c]	0.038	7.6	29	*t*-Butyltoluene	0.375 mole
p-Cymene	0.5[d]	Toluene	2.5[d]	2,2-Ditolylpropanes	.065	13.0	27	Diphenylmethane	.20 mole
								Triphenylmethane	.2 mole
Cumene	0.5	Toluene	2.5	2,2-Diphenylpropane	.004	0.8	[e]	*t*-Butyltoluene	.26 mole
				2-Phenyl-2-tolylpropane	.014	2.8	[e]	Cymenes	.25 mole
				2,2-Ditolylpropanes	.047	9.4	[e]		
p-Cymene	0.5	Benzene	2.5	2,2-Diphenylpropane	.036	7.2	17.0	*t*-Butylbenzene	.3 mole
				2-Phenyl-2-tolylpropane	.0095	1.9	4.5		
				2,2-Ditolylpropanes	.0155	3.1	7.4		

[a] Condition: except as noted all runs at 20–25° using 0.05 mole of aluminum chloride as catalyst and 0.5 mole of *t*-butyl chloride. [b] Based on 2-arylpropane. [c] 35% *p,p'*; 28% *p,m'*; 37% *m,m'*. See Experimental. [d] Using 0.5 mole of benzhydryl chloride instead of *t*-butyl chloride. [e] Most of the unchanged cumene was transalkylated to cymene isomers.

methanes,[6-8] formation of indans[9] and 1,1-diarylethanes,[9,10] and alkylation of arenes with cycloalkanes.[11] The preparation of 2,2-diarylpropanes by hydride transfer has been reported in the patent literature[12]; however, only one reaction, the formation of 2,2-diphenylpropane was actually described. The object of the present work, then, was to make a more thorough study of the preparation of 2,2-diarylpropanes by hydride transfer reactions involving 2-arylpropanes and arenes.

Discussion

Tables I and II summarize the reactions for the preparation of 2,2-diarylpropanes by hydride transfer. While we obtained low yields of 2,2-diarylpropanes with ferric chloride, aluminum chloride was a much more effective catalyst, and was used in most reactions. The effect of changing other reaction variables for the preparation of 2,2-diphenylpropane from benzene and cumene are summarized in Table I. Optimum conditions so far determined are equimolar amounts of cumene and hydride ion acceptor in a five-mole excess of benzene at 20–25°. Conversions to 2,2-diphenylpropane were increased by increasing the *t*-butyl chloride; however, a fourfold increase in *t*-butyl chloride gives only a twofold increase in 2,2-diphenylpropane, and the yield based on recovered cumene is approximately the same as reactions using equimolar amounts of *t*-butyl chloride and cumene. The best hydride ion acceptor was benzhydryl chloride. The second hydride transfer product, diphenylmethane, was also isolated in this reaction.

Reaction of toluene and *p*-cymene (Table II) gave the expected 2,2-ditolylpropane isomers. The yield of these ditolylpropanes was slightly lower than the yield of 2,2-diphenylpropane from the benzene–cumene reaction; however, the yield of 2,2-diarylpropanes from either reaction is about the same when based on reacted 2-arylpropane. Use of benzhydryl chloride instead of *t*-butyl chloride as the hydride ion acceptor also increased the conversion to 2,2-ditolylpropanes.

(6) L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Am. Chem. Soc.*, **81**, 2718 (1959).
(7) B. S. Friedman, F. L. Morritz, C. J. Morrissey, and R. Konos, *ibid.*, **80**, 5867 (1958).
(8) S. P. Malchick and R. B. Hannan, *ibid.*, **81**, 2219 (1959).
(9) H. Pines and J. T. Arrigo, *ibid.*, **80**, 4369 (1958).
(10) A. Schneider, U. S. Patent 2,742,516 (April 17, 1956).
(11) L. Schmerling, R. W. Welch, and J. P. Luvisi, *J. Am. Chem. Soc.*, **79**, 2636 (1957).
(12) A. Schneider, U. S. Patent 2,742,512 (April 17, 1956).

Reaction of cumene with toluene and *p*-cymene with benzene are summarized in Table II. Both reactions should yield 2-phenyl-2-tolylpropane. This product was found but was not the major product in either reaction. The *p*-cymene–benzene reaction gave mostly 2,2-diphenylpropane, whereas the cumene–toluene reaction gave more of the 2,2-ditolylpropanes. These unexpected products appear to arise mainly by transalkylation of the expected 2-phenyl-2-tolylpropanes in one case with benzene to yield the 2,2-diphenylpropane, or with the excess toluene in the toluene–cumene reaction to yield ditolylpropanes. Most of the unchanged cumene in the latter reaction also was converted to cymene by transalkylation with toluene.

However, the total yields of 2,2-diarylpropanes from both the toluene–cumene and *p*-cymene–benzene reactions were approximately the same as the yield of 2,2-diarylpropanes from the benzene–cumene and *p*-cymene–toluene reactions. The yields of 2,2-diarylpropanes from all the reactions studied are the same when based on changed cumene or cymene.

Steric hindrance to normal alkylation was the main driving force for many of the hydride transfer reactions previously reported.[4,11] In our study, steric hindrance is not so important, as it is as easy for the hydride ion acceptor to alkylate benzene and toluene as to undergo hydride transfer with cumene or cymene. The main driving force for the reactions described in Tables I and II may be that with the *t*-butyl and benzhydryl cations the main alkylation reaction is the most readily reversible; therefore, equilibria favorable for at least some hydride transfer are established.

Concerning the actual hydride transfer step apparently the tertiary hydrogen of the cumene or cymene is extracted exclusively, for no diarylmethanes or 1,2-diarylpropanes were found. No indanes were found.

Conclusion

In the preparation of 2,2-diarylpropanes by hydride transfer reactions, the number and complexity of possible over-all alkylation reactions is great and the driving force for the desired reactions is small. In addition, 2,2-diarylpropanes containing aryl methyl groups undergo isomerization and transalkylation, so that yields of pure single isomer are quite low. In light of this situation, it is surprising that diarylpropanes are actually obtained, albeit in rather low yields. However, the reaction gives sufficiently high yields to be of preparative value for 2,2-diphenylpropane. This compound as well as certain mixtures of the tolylpropanes can be obtained in 20–25% yields when using benzhydryl chloride as the hydride ion acceptor.

Experimental

Alkylation of Benzene with Cumene.—A typical hydride transfer reaction involving benzene and cumene was run by adding 46 g. (0.5 mole) of *t*-butyl chloride dropwise over 0.5 hr. at 22° to a rapidly stirred mixture of 195 g. (2.5 moles) benzene, 60.0 g. (0.5 mole) cumene, and 6.5 g. (0.05 mole) of anhydrous aluminum chloride. The mixture was stirred another hour after addition and hydrolyzed with water. The hydrocarbon mixture was water-washed, dried over sodium sulfate, then fractionated through a 10-plate Oldershaw column. Fraction 1 was taken from 75–230° at 1.0 atm. (wt. 91.5 g.) and fraction 2 was the remaining undistilled pot residue (wt. 12.5 g.). Both fractions were analyzed directly by gas chromatography.

Fraction 1 contained seven components; only three of the most interest (comprising 94% of the fraction) were identified. These components and their concentration as calculated from the gas chromatogram were: unchanged cumene 37.0 g. (0.31 mole), *t*-butylbenzene 40.0 g. (0.3 mole, 60 mole % of theory for simple *t*-butylation), and *t*-butylcumene 9.0 g. (0.05 mole). The other components, although not separated and identified, may be the various isomerization, de-alkylation, and/or disproportionation products expected by reaction of alkylarenes with aluminum chloride.

Fraction 2 was 86% of the desired 2,2-diphenylpropane. The remaining 14% was composed of four higher boiling unidentified components. The yield of 2,2-diphenylpropane was 10.5 g. (0.0535 mole, 10.7 mole % based on cumene). The yield based on recovered cumene (0.31 mole) was 28 mole %. The identity of this product was established by comparison of physical properties, and infrared and mass spectra with authentic 2,2-diphenylpropane. Authentic 2,2-diphenylpropane was prepared in 30% yield from α-methylstyrene and benzene by a modification of the method reported for the preparation of 2,2-ditolylpropane[3] and had m.p. 28–29°, b.p .74–76° (0.15 mm.) [280° (1 atm.)] and $n^{20}D$ 1.5705. 2,2-Diphenylpropane has been synthesized by two different methods[4,13] with reported physical properties identical to the preceding values.

Alkylation of Toluene with *p*-Cymene.—Reaction of 230 g. (2.5 moles) of toluene, 67.0 g. (0.5 mole) *p*-cymene, 46 g. (0.5 mole) of *t*-butyl chloride, and 0.05 mole of aluminum chloride at 20° gave six simple alkyl–arene components boiling at 107–240° atmospheric pressure. Among these components were 49.5 g. (0.37 mole) of cymene isomers and 55.5 g. (0.375 mole) of *t*-butyltoluene isomers. The next highest boiling product came over at 300° and was the first of the desired hydride transfer products. The following high boiling hydride transfer products were found by gas chromatography (250°, apiezon L columns).

Component	Estimated b.p. at 1 atm., °C.	%	Calcd. wt., g.
m,m'-Ditolylpropane	300	21	2.4
m,p'-Ditolylpropane	310	27	3.1
p,p'-Ditolylpropane	320	26	3.0
Unknown (4 components)	325–350	26	3.0

Fractional distillation through a 100-plate spinning band column gave only gradual enrichment of the components but not complete separation. Pure components were obtained directly from the gas chromatograph by trap-out procedures. The total yield of the three ditolylpropane isomers was 8.5 g. (0.038 mole, 7.6 mole % based on cymene). The yield was 29.3% based on recovered cymene.

The *p,p'*-ditolylpropane was identified by comparison of its physical properties and infrared and mass spectra with authentic *p,p'*-ditolylpropane, which was obtained by low temperature crystallization of mixed ditolylpropane isomers prepared from toluene, 2,2-dichloropropane, and aluminum chloride as previously described.[14] The pure *p,p'*-ditolylpropane had m.p. 76–78°. The reported m.p. is 78–80°.[1,2] Oxidation[15] of this pure *p,p'*-isomer gave a 90 mole % yield of 2,2-di(*p*-carboxyphenyl)propane, neutral equivalent, 142 (calcd., 142), melting at 313–314° (reported[3,14] 313–315°). The *m,m'*- and *m,p'*-ditolylpropane isomers are only tentative assignments of structure; no comparison was made with authentic materials. However, mass spectra show they are 2,2-ditolylpropane isomers and infrared analysis and method of formation strongly indicate the *m,m'*- and *m,p'*-isomers. These two isomers are also identical to the two isomers (in addition to the *p,p'*-ditolylpropane) produced by reaction of toluene and 2,2-dichloropropane described previously.

The highest boiling products (325–350°) from the hydride transfer reaction have not been identified. At least four components were obtained; however, mass spectra show none is a 2,2-ditolylpropane isomer.

Alkylation of Toluene with Cumene. A mixture of 230 g. (2.5 moles) of toluene, 60.0 g. (0.5 mole) of cumene, 46 g. (0.5 mole) of *t*-butyl chloride, and 6.5 g. (0.05 mole) of aluminum

(13) R. Silva, *Bull. soc. chim. France*, (2) **34**, 674 (1880).
(14) C. E. Schweitzer, U. S. Patent 2,794,822 (June 4, 1957).
(15) A. Saffer and R. S. Barker, U. S. Patent 2,833,816 (May 6, 1958).

chloride was treated and the products were worked up in the same way as the *p*-cymene–toluene reaction. The low-boiling simple alkylarenes contained 7 g. (0.058 mole) of cumene, 47 g. (0.35 mole) of cymene isomers, and 38 g. (0.26 mole) of *t*-butyltoluene isomers. The following high boiling hydride transfer products were determined by gas chromatography and mass spectrometry. The total conversion to identified 2,2-

Component	Estimated b.p. at 1 atm., °C.	%	Calcd. wt., g.	Moles
2,2-Diphenylpropane	280	4.7	0.75	0.004
2-Phenyl-2-tolylpropane	290	18.8	2.9	.014
m,m'-Ditolylpropane	300	32.5	5.0	.022
m,p'-Ditolylpropane	310	25.5	3.9	.018
p,p'-Ditolylpropane	320	10.5	1.6	.007
Unknown	325–350	8.0	1.2	

diarylpropanes was 0.065 mole (13.0 mole % on cumene). Authentic 2-phenyl-2-tolylpropane was prepared in 75% yield from α-methylstyrene and toluene using a modification of the method reported for the preparation of 2,2-ditolylpropane.[3] It had b.p. 92–94° (0.15 mm.), $n^{20}D$ 1.5643.

Anal. Calcd. for $C_{16}H_{18}$: C, 91.42; H, 8.58. Found: C, 91.02; H, 8.42.

Oxidation[15] gave fine white needles (from 1:1 ethanol–water) of 2-(*p*-carboxyphenyl)-2-phenylpropane, m.p. 147–148°, and neutral equivalent, 238 (calcd., 240).

Alkylation of Benzene with *p*-Cymene.—Benzene, 195 g. (2.5 moles), *p*-cymene 67 g. (0.5 mole), *t*-butyl chloride, 46 g. (0.5 mole), and aluminum chloride (0.05 mole) were treated and the products worked up as described. The lower boiling alkylarenes contained 34.5 g. (0.29 mole) of unchanged cymene and 40.0 g. (0.3 mole, 60 mole %) of *t*-butylbenzene. The following hydride transfer products were found by gas chromatography.

Components	Estimated b.p. at 1 atm., °C.	%	Calcd. wt., g.	Moles
2,2-Diphenylpropane	280	50.5	7.0	0.0360
2-Phenyl-2-tolylpropane	290	14.5	2.0	.0095
m,m'-Ditolylpropane	300	13.0	1.8	.0080
m,p'-Ditolylpropane	310	12.2	1.7	.0075
Unknown	330–350	9.8	1.2	

The total conversion to 2,2-diarylpropanes was 0.061 mole (12.2 mole % on cymene).

Polynuclear Aromatic Hydrocarbons. XI.[1] The Synthesis of Molecularly Overcrowded Benzo(c)phenanthrenes. I

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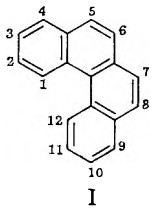
The reaction between β-methallylsuccinic anhydride and *p*-xylene has been examined as a means of obtaining molecularly overcrowded benzo(*c*)phenanthrenes. The synthesis of 1,4,5,5-tetramethyl-5,6-dihydrobenzo(*c*)phenanthrene (XXII) from these starting materials is described.

In an earlier communication,[4] the preparation of benzo(*c*)phenanthrene derivatives (I) from the Friedel–Crafts reaction products of β-methallylsuccinic anhydride (II) and benzene was outlined. In this paper, the feasibility of using *p*-xylene to prepare 1- and/or



I

12-substituted derivatives is discussed. The latter are of interest for resolution studies as well as for testing as carcinogens.

The starting material, β-methallylsuccinic anhydride (II), was prepared conveniently from maleic anhydride and isobutylene according to the method described by Alder and co-workers[5] and revised by Phillips and Johnson.[4] When the anhydride (II) was condensed with *p*-xylene in the presence of aluminum chloride, a mixture of three acids[6] (see Chart 1) and a hydrocarbon[7] was obtained. The tetralone acid (IV) usually crystallized from the acid mixture as the major product, while the other two acids (III and V) remained as an oil. However, these acids were separated easily by fractional distillation of their methyl esters. While the intramolecular acylation product (V) is of no use for the synthesis of benzo(*c*) phenanthrenes, III has all the carbons necessary to prepare 1,12-substituted derivatives of benzo(*c*)phenanthrene and IV provides a means of preparing either the 1-substituted or the 1,12-substituted derivatives.

As illustrated in Chart 1, catalytic reduction of IIIa afforded methyl α-(β-*p*-xylylethyl)-γ-methyl-γ-(*p*-xylyl)valerate (VIa), which in turn was saponified to the corresponding acid (VI). The same acid, VI, was prepared in 15% yield by condensation of *p*-xylene with α-(β-*p*-xylylethyl)-γ-methyl-γ-valerolactone (VIII), which in turn was obtained through catalytic reduction of the corresponding lactone (VII). The lactone (VII) was prepared by condensation of the anhydride (II) with *p*-xylene in the presence of antimony pentachloride. However, VII was obtained in a maximum yield of only 19% and consequently was a less convenient precursor to VI than was III.

Cyclization of VI with anhydrous hydrogen fluoride gave a mixture of tetralones (IX) which was subsequently reduced with lithium aluminum hydride to give a mixture of tetralols. Treatment of the tetralol

(1) Paper X, D. D. Phillips and D. N. Chatterjee, *J. Am. Chem. Soc.*, **80**, 4364 (1958).

(2) To whom inquiries regarding this article should be sent; Shell Development Co., Modesto, Calif.

(3) From the thesis submitted by M. F. Bruno to Cornell University in partial fulfillment of the requirements for the Ph.D. degree, September, 1959.

(4) D. D. Phillips and A. W. Johnson, *J. Am. Chem. Soc.*, **77**, 5977 (1955).

(5) K. Alder, F. Pascher, and A. Schmitz, *Ber.*, **76B**, 47 (1943).

(6) A. W. Johnson, thesis, Doctor of Philosophy, Cornell University, 1957.

(7) Almost invariably, hydrocarbons were obtained in the neutral fraction when catalysts such as aluminum chloride or antimony pentachloride were used in the presence of benzene or *p*-xylene. These hydrocarbons will be the subject of a forthcoming publication.

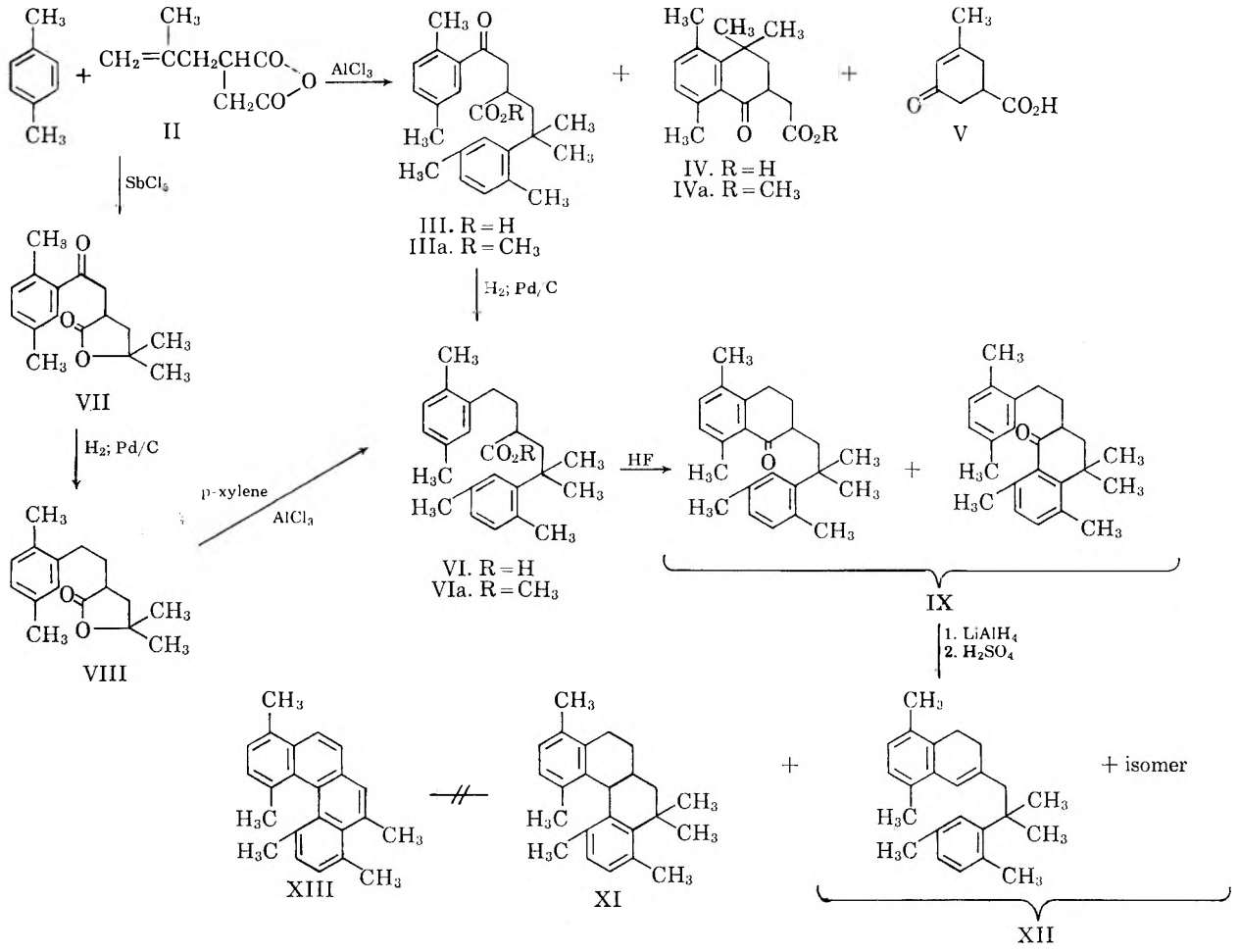
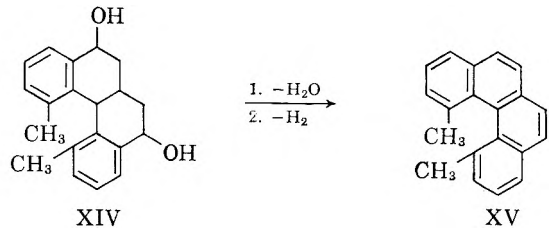


CHART 1

mixture (X) with sulfuric acid gave XI, the cyclodehydration product, and XII, the dehydration product. Attempts then were made to dehydrogenate XI and XII to 1,4,5,9,12-pentamethylbenzo(*c*)phenanthrene (XIII).

Earlier work by Phillips and Johnson[4] suggested that both XI and XII should be capable of aromatization to XIII. However, catalytic dehydrogenation with 30% palladium-on-charcoal catalyst failed to give XIII and dehydrogenation with selenium gave only an unidentified hydrocarbon. The recovery of starting material from the dehydrogenation was poor, carbonization occurring rather than aromatization. However, this was not entirely unexpected since aromatization to XIII would force two methyl groups into overcrowded positions which would result in considerable strain in the molecule. Also, complete aromatization would require the removal of one of the *gem*-dimethyl groups as methane, a reaction which is in itself difficult. Newman and Wolf[8] were able to prepare 1,12-dimethylbenzo(*c*)phenanthrene (XV) from 5,6,6a,7,8,12b-hexahydro - 1,12 - dimethylbenzo(*c*)phenanthrene - 5,8-diol (XIV). In this instance however, preliminary dehydration of the diol afforded unsaturation in each ring, and this undoubtedly facilitated the aromatization to XV.

Another route to reduced benzo(*c*)phenanthrenes, employing the available keto acid (IV), was investigated (Chart 2). In order to prepare the lactone of 1-phenyl-



4,4,5,8-tetramethyl-1-tetralol-2-acetic acid (XVI), IV was treated with phenylmagnesium bromide. However, the majority of IV was recovered along with the Grignard coupling product, biphenyl. In a similar attempt to prepare XVI, the keto ester (IVa) was condensed with phenylmagnesium bromide. In this case, the neutral product contained unidentified hydrocarbons and 4,4,5,8-tetramethyl-2-phenacyl-1-tetralone (XVII), identified by its 2,4-dinitrophenylhydrazone derivative; only a small amount of crude lactone XVI was obtained.

The inability of phenylmagnesium bromide to react with the keto group of IV and IVa was probably due to the steric hindrance provided by the C-8 and/or C-4 methyl groups. Therefore, condensation of IV with phenyllithium, which has smaller steric requirements, was investigated and proved to be more successful for preparing the lactone, XVI.

Reduction of XVI to the acid (XVIII) did not proceed so easily as had been anticipated. Clemmensen reduction afforded only a trace of acid (XVIII), and catalytic reduction failed completely. Therefore, in a

(8) M. S. Newman and M. Wolf, *J. Am. Chem. Soc.*, **74**, 3225 (1952).

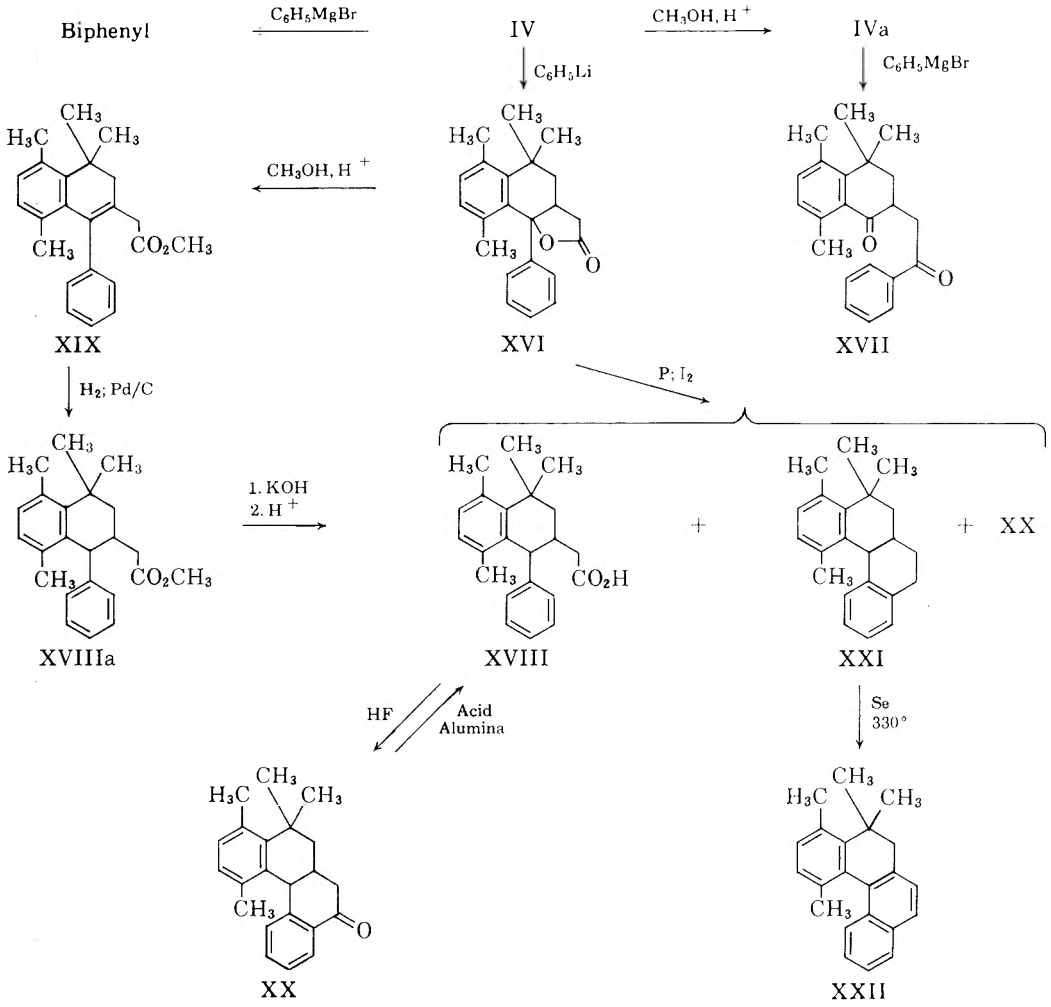


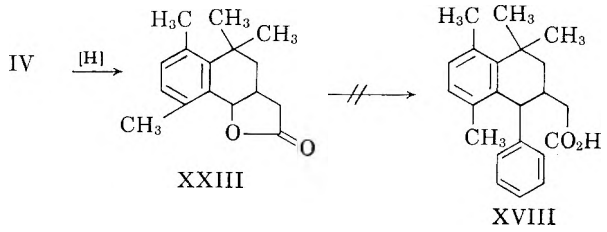
CHART 2

more circuitous route, dry hydrogen chloride was bubbled through a methanolic solution of the lactone (XVI) to give methyl 1-phenyl-4,4,5,8-tetramethyl-3,4-dihydronaphthalene-2-acetate (XIX). The ester (XIX) was catalytically reduced to give methyl 1-phenyl-4,4,5,8-tetramethyltetralin-2-acetate (XVIIIa). Saponification of XVIIIa followed by cyclization of the resultant acid (XVIII) with anhydrous hydrogen fluoride afforded the ketone (XX) as a brown viscous oil which showed infrared absorption at 5.95 μ. The ketone (XX) could not be obtained in a pure condition, nor could a constant melting derivative be obtained.

At a later date it was discovered that the reduction of XVI to XVIII could be accomplished with phosphorus and iodine according to the method described by Marvel and co-workers.[9] However, the acid (XVIII) was not the only product obtained from the reduction. In one instance, the lactone (XVI) was converted almost quantitatively to a mixture containing ketone XX and hydrocarbon XXI. In an effort to separate XX and XXI, the mixture was chromatographed on acid-washed alumina to give the hydrocarbon (XXI) and the acid (XVIII). Although pure ketone XX was not obtained from this reaction, it must have been present since the acid (XVIII) could only have come from the hydrolysis of XX on the alumina column.

Reduction of lactones to acids[10,11] and of conjugated ketones to the corresponding methylenic derivatives[12] has been accomplished with iodine (or hydriodic acid) and phosphorus. This method has also proved successful for the synthesis of α-tetralone from β-benzoylpropionic acid.[13] In the latter case, both reduction and cyclization occurred. However, the reduction of XVI by this method seems to be the first case in which a lactone has been reduced to an acid, the acid cyclized to a ketone, and the ketone reduced to a hydrocarbon, all in one reaction.

When heated with selenium in a sealed tube at 330°, the hydrocarbon (XXI) was converted to 1,4,5,5-tetramethyl-5,6-dihydrobenzo(c)phenanthrene (XXII). Complete aromatization to 1,4,5-trimethylbenzo(c)-phenanthrene could not be accomplished.



A third route to the benzo(c)phenanthrene skeleton envisioned the use of the lactone (XXIII) derived from

(9) C. S. Marvel, F. D. Hager, and E. C. Caudle, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 224.
(10) B. Riegel and J. G. Burr, Jr., *J. Am. Chem. Soc.*, **70**, 1070 (1948).
(11) D. D. Phillips and E. J. McWhorter, *ibid.*, **76**, 4948 (1954).
(12) C. Graebe and F. Trümpy, *Ber.* **31**, 375 (1898).
(13) K. Miescher and J. R. Billeter, *Helv. Chim. Acta*, **22**, 601 (1939).

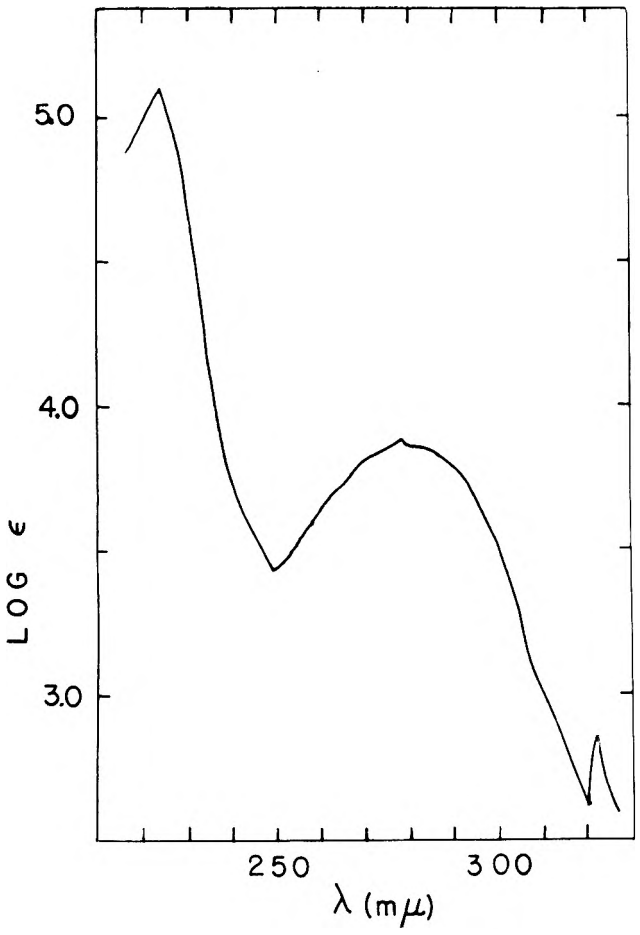


Fig. 1.—Ultraviolet absorption spectrum of XXII in 95% ethanol.

the reduction of keto acid IV. Condensation of XXIII with benzene in order to form XVIII proved abortive, however, and the route consequently was abandoned.

Experimental[14]

Methyl α-(β-p-Xylylethyl)-γ-methyl-γ-(p-xylyl)valerate (VIa). a. **From IIIa.**—The residue (7.3 g.) obtained from the distillation of 35 g. of IVa[6] was dissolved in 150 ml. of 90% methanol containing 1.0 g. of 10% palladium-on-charcoal catalyst and heated with shaking to 60° under 48 p.s.i. of hydrogen. The catalyst was removed after 24 hr. and the solvent distilled *in vacuo* to give 7.1 g. of ester VIa as a viscous oil. Chromatography on acid-washed alumina afforded the ester (VIa) as a colorless viscous oil, $n^{25}D$ 1.5300; λ_{max}^{NaCl} 5.75 and 6.21 μ.

Anal. Calcd. for $C_{25}H_{34}O_2$: C, 81.93; H, 9.35. Found: C, 82.23; H, 9.23.

b. **From the Lactone (VII).**—α-(2,5-Dimethylphenacyl)-γ-methyl-γ-valerolactone (VII) was prepared by adding 62.5 ml. (0.483 mole) of antimony pentachloride over 1.5 hr. at room temperature to a mixture of 25 g. (0.162 mole) of anhydride (II) in 75 ml. of nitrobenzene and 150 ml. of *p*-xylene. The resulting brown complex was stirred under nitrogen for 12 hr. at 25°, 36 hr. at 50°, and 12 hr. at 30°. The complex then was poured into an ice–hydrochloric acid mixture at 5–10° and steam distilled for 3 hr. The residue was extracted with benzene and added to the organic portion of the distillate. This solution was extracted with several 75-ml. portions of 10% potassium hydroxide. The aqueous extract was acidified, extracted with ether, and the ethereal layer dried over magnesium sulfate. Removal of the solvent left 8.9 g. of a black tarry material. The neutral organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to afford 23.8 g. of a brown liquid. Chromatography of the neutral material on acid-washed alumina yielded 15 g. of unidentified hydrocarbons and 8.0 g. (19%) of lactone (VII). Recrystallization from acetone–hexane afforded the lactone as colorless plates, m.p. 86.0–86.5°; λ_{max}^{EtOH} 247 mμ (log ε 3.88) and 292.5 mμ (log ε 3.16); λ_{max}^{KBr} 3.37, 3.42, 5.63, 5.93, 6.17, and 6.38 μ.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.00; H, 7.85.

α-(β-p-Xylylethyl)-γ-methyl-γ-valerolactone (VIII).—A solution of 16.8 g. (0.065 mole) of keto lactone VII dissolved in 160 ml. of 95% ethanol containing 1.7 g. of 10% palladium-on-charcoal catalyst was heated with shaking to 60° under 45 p.s.i. of hydrogen. The catalyst was removed after 20 hr. and the solvent distilled *in vacuo* to yield 14.1 g. (89%) of lactone VIII as a colorless viscous oil which slowly crystallized. Recrystallization from acetone–pentane afforded the lactone as colorless microcrystals, m.p. 56.5–57.0°; λ_{max}^{EtOH} 276.5 mμ (log ε 2.91) and 268 mμ (log ε 2.89); λ_{max}^{KBr} 3.42, 3.52, and 5.69 μ.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.58; H, 8.90.

When this lactone (VIII) was treated with excess *p*-xylene and aluminum chloride at room temperature, it was converted in 15% yield to VI, identified by its infrared spectrum.

4,4,5,8-Tetramethyl-2-(2-p-xylylethyl)-1-tetralone and 5,8-Dimethyl-2-(2-methyl-2-p-xylylpropyl)-1-tetralone (IX).—To 4.8 g. (0.013 mole) of acid VI, obtained by saponification of ester VIa, was added 90 ml. of anhydrous hydrogen fluoride. The dark brown reaction mixture was allowed to remain for 1 hr. at room temperature, with occasional shaking, and then was decomposed by pouring onto cracked ice. The aqueous mixture was extracted with ether and the ethereal solution washed with 10% sodium carbonate solution. The neutral ethereal solution was dried over magnesium sulfate and evaporated to give 3.4 g. (78%) of tetralone mixture IX.

Chromatography of a small portion of the neutral material afforded the tetralone mixture (IX) as a colorless viscous oil which slowly crystallized, m.p. 79–81°; λ_{max}^{NaCl} 5.95 and 6.25 μ; λ_{max}^{EtOH} 259 mμ (log ε 4.16) and 308 mμ (log ε 3.26).

Anal. Calcd. for $C_{21}H_{30}O$: C, 86.17, H, 9.04. Found: C, 86.01; H, 9.26.

4,4,5,8-Tetramethyl-2-(2-p-xylylethyl)-1-tetralol and 5,8-Dimethyl-2-(2-methyl-2-p-xylylpropyl)-1-tetralol (X).—To a stirred slurry of 0.80 g. (0.021 mole) of lithium aluminum hydride in 35 ml. of dry ether, at room temperature under nitrogen, was added, over 1.5 hr., 3.0 g. (9.0 mmoles) of tetralone mixture IX. The resulting mixture was stirred at room temperature for 24 hr. and was decomposed by the addition of a saturated solution of ammonium chloride and worked up in the usual fashion to give 2.5 g. (83%) of tetralol mixture X; λ_{max}^{NaCl} 2.95 μ.

1,4,5,5,9,12-Hexamethyl-5,6,6a,7,8,13-hexahydrobenzo(c)-phenanthrene (XI) and 2-(2-p-Xylylethyl)-4,4,5,8-tetramethyl-3,4-dihydronaphthalene and 2-(2-Methyl-2-p-xylylpropyl)-5,8-dimethyl-3,4-dihydronaphthalene (XII).—Two milliliters of concentrated sulfuric acid was added dropwise over 3 min. to 2.5 g. (7.3 mmoles) of tetralol mixture (X). The dark brown complex was stirred for an additional minute, poured into an ice–water mixture, and extracted with ether. The ethereal solution was dried and evaporated to give 2.1 g. (89%) of a yellow brown oil. Chromatography of the oil on acid-washed alumina afforded the hydrocarbon mixture (XI and XII) as a colorless, viscous oil; λ_{max}^{EtOH} 269 mμ (log ε 3.19) and 277 mμ (log ε 3.16).

Anal. Calcd. for $C_{21}H_{30}$: C, 90.51; H, 9.49. Found: C, 90.40, 90.55; H, 9.55, 9.50.

Attempted Synthesis of 1,4,5,9,12-Pentamethylbenzo(c)phenanthrene (XIII). a. By Catalytic Dehydrogenation of XI and XII.—A mixture of 0.50 g. (1.57 mmoles) of XI and XII and 0.28 g. of 30% palladium-on-charcoal catalyst was heated for 4 hr. at 380° in a Pyrex tube fitted with a reflux condenser. The cooled melt was taken up in hexane an chromatographed on acid-washed alumina to give 0.3 g. of starting material.

b. **By Selenium Dehydrogenation of XI and XII.**—A mixture of 0.62 g. (7.6 mmoles) of selenium powder and 0.3 g. (0.94 mmole) of XI and XII, in a sealed tube, was heated for 19 hr. at 310° and 0.5 hr. at 360°. The mixture was cooled and the melt taken up in hexane–benzene and chromatographed on acid-washed alumina to give 50 mg. of a hydrocarbon which showed

(14) All melting points and boiling points are uncorrected. Infrared absorption spectra of solids were taken in potassium bromide or chloroform on a Perkin-Elmer Model 21 spectrophotometer. Infrared absorption spectra of oils were taken between sodium chloride plates. Ultraviolet absorption spectra were measured in 95% ethanol with a Beckman Model DK automatic recording spectrophotometer, except where noted. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

ultraviolet absorption; λ_{max}^{EtOH} 239 mμ (log ε 4.09), 249 mμ (log ε 4.17), 262 mμ (log ε 3.58), 273 mμ (log ε 3.83), 284 mμ (log ε 4.01), 307 mμ (log ε 3.25), 321 mμ (log ε 3.42), and 335 mμ (log ε 3.60). (Measured with a Cary Mode 14 automatic recording spectrophotometer using 318 as the molecular weight.)

Lactone of 1-Phenyl-4,4,5,8-tetramethyl-1-tetralol-2-acetic Acid (XVI). a. *Via* Phenyllithium.—To a stirred solution of 6.0 g. (0.023 mole) of keto acid IV in 200 ml. of dry ether was added dropwise, over 0.3 hour, 0.046 mole of phenyllithium prepared by heating under reflux a mixture of 7.3 g. (0.046 mole) of bromobenzene, 0.80 g. (0.115 g.-atom) of lithium, and 75 ml. of dry ether. The resulting mixture was heated under nitrogen at 55° for 40 hr., cooled, and the complex destroyed by the addition of 100 ml. of 6 *N* hydrochloric acid. The acidified mixture was stirred at room temperature for 2 hr. to ensure lactonization and worked up in the usual manner to give 3.3 g. of unchanged keto acid IV and 3.8 g. of neutral material as a brown mushy solid. Washing of the neutral material with hexane afforded 2.9 g. (49% based on the amount of acid used) of a tan solid. Recrystallization from hexane–acetone afforded the lactone as colorless, short needles, m.p. 186–187°; $\lambda_{max}^{CHCl_3}$ 5.64 and 6.25 μ; λ_{max}^{EtOH} 274.5 mμ (log ε 2.87) and 282.7 (log ε 2.87).

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.47; H, 7.55; mol. wt., 320. Found: C, 82.65; H, 7.58; mol. wt., 305.

b. *Via* Phenylmagnesium Bromide. 1. From IV.—To a stirred solution of 10.0 g. (0.038 mole) of keto acid (IV) in 200 ml. of dry tetrahydrofuran at room temperature was added slowly 25.6 ml. (0.077 mole) of 3 *M* phenylmagnesium bromide. The amber mixture was stirred under nitrogen at 65° for 24 hr., cooled, and the complex destroyed with 200 ml. of 6 *N* hydrochloric acid. The solvent was distilled and the mixture worked up in the usual fashion to give 9.7 g. of unchanged keto acid and 6.5 g. of neutral material identified as biphenyl.

Subsequent attempts, under various experimental conditions, to prepare the lactone (XVI) from keto acid IV were unsuccessful.

2. From IVa.—To a solution of 8.7 g. (0.033 mole) of keto ester IVa in 250 ml. of dry tetrahydrofuran, stirred under nitrogen at 55°, was added, over 1 hr., 22 ml. of 3 *M* (0.066 mole) phenylmagnesium bromide. The complex was destroyed and worked up in the usual way to give 12.4 g. of a brown neutral oil. The oil was taken up in 60 ml. of methanol and heated under reflux with 10 ml. of water and 6 g. of potassium hydroxide. After 4 hr. the methanolic solution was poured into 200 ml. of water and extracted with several portions of ether. Evaporation of the ethereal solution provided 6.0 g. of a brown neutral oil. The neutral oil was chromatographed on acid-washed alumina and separated into two major fractions. Fraction 1 was a mixture of unidentified hydrocarbons. Fraction 2, λ_{max}^{NaCl} 5.94, 6.24, and 6.37 μ was the diketone, **4,4,5,8-tetramethyl-2-phenacyl-1-tetralone (XVII)**, identified by its 2,4-dinitrophenylhydrazone derivative, m.p. 209–210°.

Anal. Calcd. for $C_{28}H_{28}N_4O_4$: C, 67.19; H, 5.64; N, 11.14. Found: C, 67.25; H, 5.52; N, 11.32.

The aqueous solution was acidified to pH 3 with 6 *N* hydrochloric acid, heated at 60° for 2 hr., cooled, and extracted with ether. The ethereal solution was extracted with several portions of 5% sodium carbonate solution, dried, and evaporated to give 1.04 g. of crude lactone XVI. The carbonate solution was acidified and extracted with ether. Evaporation of the ethereal solution gave 4.7 g. of unchanged keto acid IV; $\lambda_{max}^{CHCl_3}$ 5.84 and 5.95 μ.

Reduction of Lactone XVI. A. Clemmensen Reduction.—Forty grams of mossy zinc, 4 g. of mercuric chloride, 80 ml. of water, and 1 ml. of concentrated hydrochloric acid were shaken for 10 min. The solution was decanted and the zinc washed with several portions of water. To the activated zinc was added 40 ml. of water, 20 ml. of concentrated hydrochloric acid, and 7.5 g. of crude lactone in 25 ml. of toluene. The resulting mixture was heated under reflux for 47 hr., cooled, and extracted with several portions of 5% potassium hydroxide solution. The usual work-up gave 7.2 g. of unchanged starting material and a trace of acid (XVIII).

B. Catalytic Reduction.—A solution of 7.1 g. of lactone XVI in 100 ml. of 95% ethanol and 40 ml. of benzene containing 0.7 g. of 10% palladium-on-charcoal catalyst was heated with shaking to 60° under 47 p.s.i. of hydrogen. The catalyst was removed after 44 hr., and the solvent distilled *in vacuo* to yield 7.0 g. of unchanged lactone.

C. Phosphorus and Iodine Reduction. Run 1.—To a solution of 1.35 g. (4.15 mmoles) of lactone (XVI), m.p. 186–187°, in 50 ml. of glacial acetic acid was added 1.0 g. (3.94 mmoles) of iodine, 3.0 g. (0.097 mole) of red phosphorus, and 1 ml. of water. The mixture was heated under reflux for 24 hr., cooled, and filtered. The filtered solution was added to 300 ml. of water containing 1.0 g. of sodium bisulfite and extracted with ether. The ethereal solution was extracted with 10% potassium hydroxide, dried, and evaporated to give 1.27 g. of neutral material which showed weak absorption in the carbonyl region (5.93 μ) and strong aromatic absorption. Chromatography of the neutral material on acid-washed alumina afforded 0.2 g. of hydrocarbon XXI, eluted with benzene, and 0.8 g. of acid XVIII, eluted with methanol.

Obtention of the acid (XVIII) indicates that the ketone (XX) was formed during the reduction but that it opened to the acid (XVIII) on the alumina column.

Although the hydrocarbon (XXI) was not obtained in a pure condition, it was assumed to be 1,4,5,5-tetramethyl-5,6,6a,7,8,-13-hexahydrobenzo(*c*)phenanthrene because of its ultimate conversion to 1,4,5,5-tetramethyl-5,6-dihydrobenzo(*c*)phenanthrene (XXII), identified by its ultraviolet absorption spectrum.

Run 2.—In a similar experiment, a mixture containing 1.55 g. (4.85 mmoles) of lactone XVI, 65 ml. of glacial acetic acid, 4.0 g. (0.13 mole) of red phosphorus, 1.1 g. (4.32 mmoles) of iodine, and 1 ml. of water was heated under reflux for 36 hr. The mixture was cooled, filtered, and worked up in the usual way to give 0.62 g. of neutral material XX and XXI and 0.45 g. (31%) of acid XVIII, m.p. 210–217°. Recrystallization from hexane–acetone afforded XVIII as colorless crystals, m.p. 227–228°; $\lambda_{max}^{CHCl_3}$ 5.87 μ; λ_{max}^{EtOH} 264 mμ (log ε 2.73), 267 mμ (log ε 2.74), 270 mμ (log ε 2.80), and 280 mμ (log ε 2.67).

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 82.16; H, 8.13.

Methyl 1-Phenyl-4,4,5,8-tetramethyl-3,4-dihydronaphthalene-2-acetate (XIX).—Dry hydrogen chloride was bubbled for 21 hr. through a solution of 175 ml. of 90% methanol containing 3.7 g. (0.014 mole) of crude lactone XVI. Distillation of the solvent *in vacuo* afforded 3.7 g. (97%) of ester XIX as a brown viscous oil; λ_{max}^{NaCl} 5.73 and 6.21 μ.

Methyl 1-Phenyl-4,4,5,8-tetramethyltetralin-2-acetate (XVIIIa).—A solution of 3.6 g. (0.011 mole) of ester XIX in 130 ml. of 90% methanol containing 0.4 g. of 10% palladium-on-charcoal catalyst was heated with shaking to 60° under 42 p.s.i. of hydrogen. The catalyst was removed after 36 hr. and the solvent distilled *in vacuo* to yield 3.5 g. (97%) of ester XVIIIa as a viscous yellow oil; λ_{max}^{NaCl} 5.75 and 6.21 μ.

1,4,5,5-Tetramethyl-8-keto-5,6,6a,7,8,13-hexahydrobenzo(*c*)phenanthrene (XX).—Forty milliliters of anhydrous hydrogen fluoride was added to 1.65 g. (5.2 mmoles) of acid XVIII in a polyethylene bottle. The complex was destroyed after 10 hr. and worked up in the usual fashion to afford 1.2 g. (77%) of ketone XX as a brown viscous oil; λ_{max}^{NaCl} 5.95 and 6.21 μ.

1,4,5,5-Tetramethyl-5,6-dihydrobenzo(*c*)phenanthrene (XXII).—An intimate mixture of 0.20 g. (1.08 mmoles) of XXI and 0.30 g. (3.8 mmoles) of selenium was heated for 12 hr. at 330° in a sealed Pyrex tube. The cooled melt was taken up in benzene–hexane, treated with charcoal, and chromatographed on acid-washed alumina to give 30 mg. of hydrocarbon XXII; λ_{max}^{EtOH} 224 mμ (log ε 5.10), 278 mμ (log ε 3.87), and 322 mμ (log ε 2.86).[15] The ultraviolet absorption spectrum of XXII was identical to that reported by Johnson,[6] except for the small peak at 322 mμ (see Fig. 1).

Lactone of 4,4,5,8-Tetramethyl-1-tetralol-2-acetic Acid (XXIII). a. By Catalytic Reduction of IV.—A solution of 7.8 g. (0.03 mole) of keto acid IV in 125 ml. of ethanol containing 0.3 g. of platinum oxide and 1 ml. of concentrated sulfuric acid was shaken for 24 hr. under 45 p.s.i. of hydrogen pressure. Removal of the solvent and catalyst afforded 7.8 g. of material which showed infrared absorption at 5.67 μ (lactone), 5.77 μ (ester), and 5.96 μ (ketone). This material was saponified by heating under reflux for 5 hr. with 10.0 g. (0.18 mole) of potassium hydroxide in 150 ml. of ethanol. The reaction mixture was poured into 200 ml. of 6 *N* hydrochloric acid and extracted with ether. The ethereal solution was extracted with 10% sodium carbonate, dried, and evaporated giving 2.4 g. (33%) of XVI as a colorless solid. Recrystallization from hexane–acetone afforded colorless

(15) Measured with a Cary Model 14 recording spectrophotometer.

cubic crystals, m.p. 146–147°; $\lambda_{max}^{CHCl_3}$ 5.64, 6.82, 7.73, 8.60, 10.32, and 11.00 μ; λ_{max}^{EtOH} 272.5 mμ (log ϵ 2.95) and 280.8 mμ (log ϵ 2.95).

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.64; H, 8.26. Found: C, 78.50; H, 8.44.

b. By Sodium Borohydride Reduction of IV.—To a stirred, refluxing solution of 26.0 g. (0.10 mole) of keto acid IV, neutralized to the phenolphthalein end point, in 200 ml. of 50% methanol was added 1.25 g. (0.033 mole) of sodium borohydride over 0.5 hr. The reaction mixture was refluxed for 22 hr., decomposed with 6 *N* hydrochloric acid, and worked up in the usual fashion to give 12.15 g. of unchanged acid IV and 12.35 g. (47.5%) of lactone XXIII, m.p. 136–138°. Recrystallization from hexane–acetone afforded colorless microcrystals of XXIII, m.p. 146–147°, identical in all respects to the lactone prepared by catalytic reduction (see method a preceding).

Optical Rotatory Dispersion Studies. LXXXII.[1a] Conformational Analysis. XXXVII.[1b] Determination of the Stereochemistry and Conformation of the Four Isomeric Cyanodihydrocarvones by Optical Rotatory Dispersion and Dipole Moment Measurements[2]

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Of the four possible cyanide addition products of (−)-carvone (I), three have now been isolated in pure form and the presence of the fourth one demonstrated chromatographically. Through a combination of chemical transformations, optical rotatory dispersion measurements, and dipole moment data, it has been possible to assign the correct stereochemistry to the two newly generated asymmetric centers and to assign plausible conformations to the four isomeric 3-cyano-2,3-dihydrocarvones.

Many years ago, Lapworth[4] studied the 1,4-addition of cyanide to (+)-carvone (antipode of I[5]) and isolated two crystalline, isomeric nitriles, both of which exhibited mutarotation. Their chemistry was studied *in extenso*, but no stereochemical assignments were made, and no further work appears to have been done on these substances during the past fifty years. In the cyanide addition to carvone, two new asymmetric centers are generated, thus creating the possibility of four stereoisomers (II–V). Furthermore, since we are dealing here with a flexible ring system, eight conformers (IIA or B–VA or B) must be considered, if we restrict ourselves to chair forms; and many more, if boat and twist forms are also brought into play. It was decided, therefore, to attack this interesting stereochemical problem by attempting the isolation of as many of the dihydrocarvone isomers as possible and to subject them to optical rotatory dispersion scrutiny[6] in the light of the octant rule.[7] The latter has been shown[8] to be of considerable utility in the solution of conformation problems, and it was of interest to examine its applicability to the present cases and to confirm the conformational conclusions by dipole moment measurements.[9]

In the present work, (−)-carvone of known absolute configuration (I)[10] was employed and duplication of Lapworth's conditions[4a] (potassium cyanide in ethanol–water–acetic acid at room temperature) yielded about 70% of the highest melting isomer II (m.p. 95.5°) of 3-cyano-2,3-dihydrocarvone, the physical constants being in reasonable agreement with those reported by Lapworth[4a] for the antipode. Thin-layer chromatography on silica gel was found to be an excellent method for determining the purity of the dihydrocarvones, since a solvent system was used that effected separation of all four isomers. In fact, this method showed that the crude cyanodihydrocarvone prepared by Lapworth's first[4a] procedure consisted principally of isomer II, contaminated with some IV and traces of III.

By conducting the cyanide addition in refluxing aqueous ethanol—in the absence of acetic acid—Lapworth[4b] encountered a second isomer (m.p. 84°, now shown to be III) in high yield. Attempts in our hands to duplicate quantitatively these results failed, since thin-layer chromatography always demonstrated the existence of approximately equal amounts of isomers II and III, as well as traces of IV. By means of gradient elution chromatography, it was possible to isolate the pure second isomer III (m.p. 86.5°), with constants in reasonable agreement with those recorded[4b] for its antipode.

The question then arose whether the two cyanodihydrocarvones (now known to be II and III) of m.p. 95.5 and 86.5° were isomeric at C-2 and/or at C-3, since both these centers are invertible. In order to gain information on this point, each pure isomer was subjected to equilibration in ethyl acetate solution in the presence of *p*-toluenesulfonic acid, the course of the reaction being followed by thin-layer chromatography. Complete equilibration was reached at room tempera-

(1) (a) For preceding paper see C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichý, *Tetrahedron*, in press; (b) for preceding paper see J. M. Conia, J. L. Ripoll, L. A. Tushaus, C. L. Neumann, and N. L. Allinger, *J. Am. Chem. Soc.*, **84**, 4982 (1962).

(2) Financial support was provided by the National Cancer Institute (grant no. CRTY-5061) of the National Institutes of Health to Stanford University, and by the National Science Foundation (grants no. 19981 and G-10346) to Wayne State University.

(3) Recipient of an undergraduate research fellowship at Stanford University from the National Science Foundation.

(4) (a) A. Lapworth, *J. Chem. Soc.*, **89**, 945, 1819 (1906); (b) A. Lapworth and V. Steele, *ibid.* **99**, 1877 (1911).

(5) All structural formulas in this paper represent correct absolute configurations according to the steroid notation.

(6) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1960.

(7) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(8) For pertinent discussion and earlier references see C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962); *Proc. Natl. Acad. Sci., U. S.*, **48**, 1093 (1962); *J. Chem. Soc.*, 2390 (1963).

(9) For discussion and earlier references of the use of dipole moment studies in conformational analysis, see N. L. Allinger, M. A. DaRooge, M. A. Miller, and B. Waegeli, *J. Org. Chem.*, **28**, 780 (1963).

(10) See A. J. Birch, *Ann. Reports Progr. Chem.*, **47**, 192 (1951).

ture in about one week, at which time the equilibration mixture of isomer II (m.p. 95.5°) consisted of two spots, corresponding to II and a new isomer (IV) (15%), but none of isomer III (m.p. 86.5°). When this experiment was conducted on a larger scale and separation was effected by partition chromatography on Celite impregnated with formamide, the new pure isomer was obtained in 13% yield as a low-melting (m.p. 13.5°) solid, which proved to be homogeneous by thin-layer chromatography. Conversely, equilibration of pure III (m.p. 86.5°) did not show any spot attributable to II or IV, but did exhibit a faint spot due to a fourth isomer (V), which, unfortunately, was formed in such small quantity as to preclude preparative isolation.

Previously discussed equilibration experiments suggested strongly that the two readily available cyanodihydrocarvones (II and III) are isomeric at C-3 and are thermodynamically more stable than their epimers at C-2, since equilibration led only to small (II → IV) or negligible (III → V) amounts of new isomers. To substantiate this conclusion, the substituent at C-3 in both II and III was altered in such a manner as to prevent further epimerization at that center. The pure higher melting (m.p. 95.5°) 3-cyano-2,3-dihydrocarvone (II) was reduced with lithium aluminum hydride to a crystalline mixture (VI) of epimeric amino alcohols, which was transformed to the corresponding benzamide mixture VII and oxidized with chromium trioxide in acetone solution.[11,12] The resulting 2-methyl-3-benzamidomethyl-5-isopropenylcyclohexanone (VIII) was a sharp melting (m.p. 180.5°) solid, homogeneous by thin-layer chromatography, in which only C-2 was now equilibratable.

By the same sequence of reactions, the lower melting (m.p. 86.5°) 3-cyano-2,3-dihydrocarvone (III) was transformed *via* the amino alcohol (X) and benzamido alcohol (XI) mixtures into a crystalline, chromatographically homogeneous, 2-methyl-3-benzamidomethyl-5-isopropenylcyclohexanone (XII) of m.p. 145°. Most importantly, while this amide was largely unaffected by methanolic potassium hydroxide, identical base treatment of the m.p. 180.5° benzamide VIII (derived from II) gave preponderantly (65%) a new 2-methyl-3-benzamidomethyl-5-isopropenylcyclohexanone (IX) of m.p. 104°. Since only C-2 is invertible in all of the benzamidocyclohexanones, it follows that the amides VIII (m.p. 180.5°) and XII (m.p. 145°), and, hence their precursor 2-cyano-2,3-dihydrocarvones (II and III), must differ in configuration at C-3.

This crucial point could also be settled by another method in which epimerization at C-2 was made impossible, while equilibration at C-3 could be examined. Thus it was found that sodium borohydride reduction of the highest melting isomer II produced an alcohol, which on reoxidation regenerated essentially pure II, thin-layer chromatography indicating the presence of a trace of its C-2 epimer IV. On the other hand, when the alcohol, produced by sodium borohydride reduction of II, was heated with methanolic potassium hydroxide—conditions which could epimerize only the C-3 center—and the resulting mixture reoxidized, thin-layer chromatography now demonstrated the existence of two strong spots corresponding to the original 2-cyano-2,3-dihydrocarvone (II, m.p. 95.5°) and its C-3 epimer III (m.p. 86.5°). Thus it has been conclusively established that the original 2-cyano-2,3-dihydrocarvone (II, m.p. 95.5°) and its m.p. 86.5° epimer III differ in configuration at C-3 and are of the same orientation at C-2, while II and IV must differ at C-2 but be the same at C-3. With the relative configurations of these compounds established on the basis of chemical evidence, it is now possible to consider the optical rotatory dispersion curves of these ketones and to derive stereochemical assignments from them.

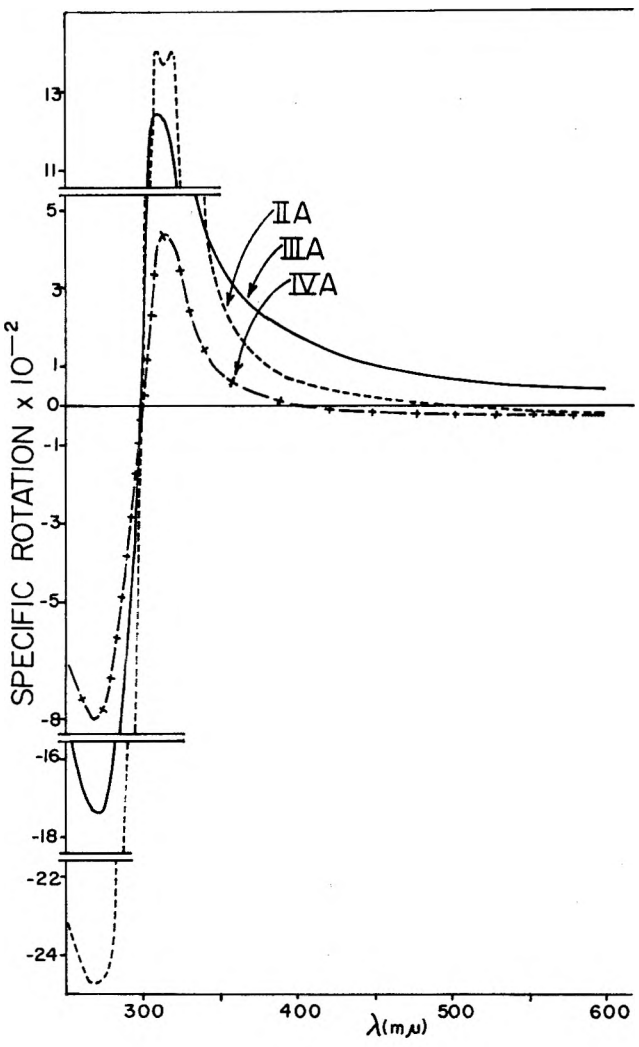


Figure 1

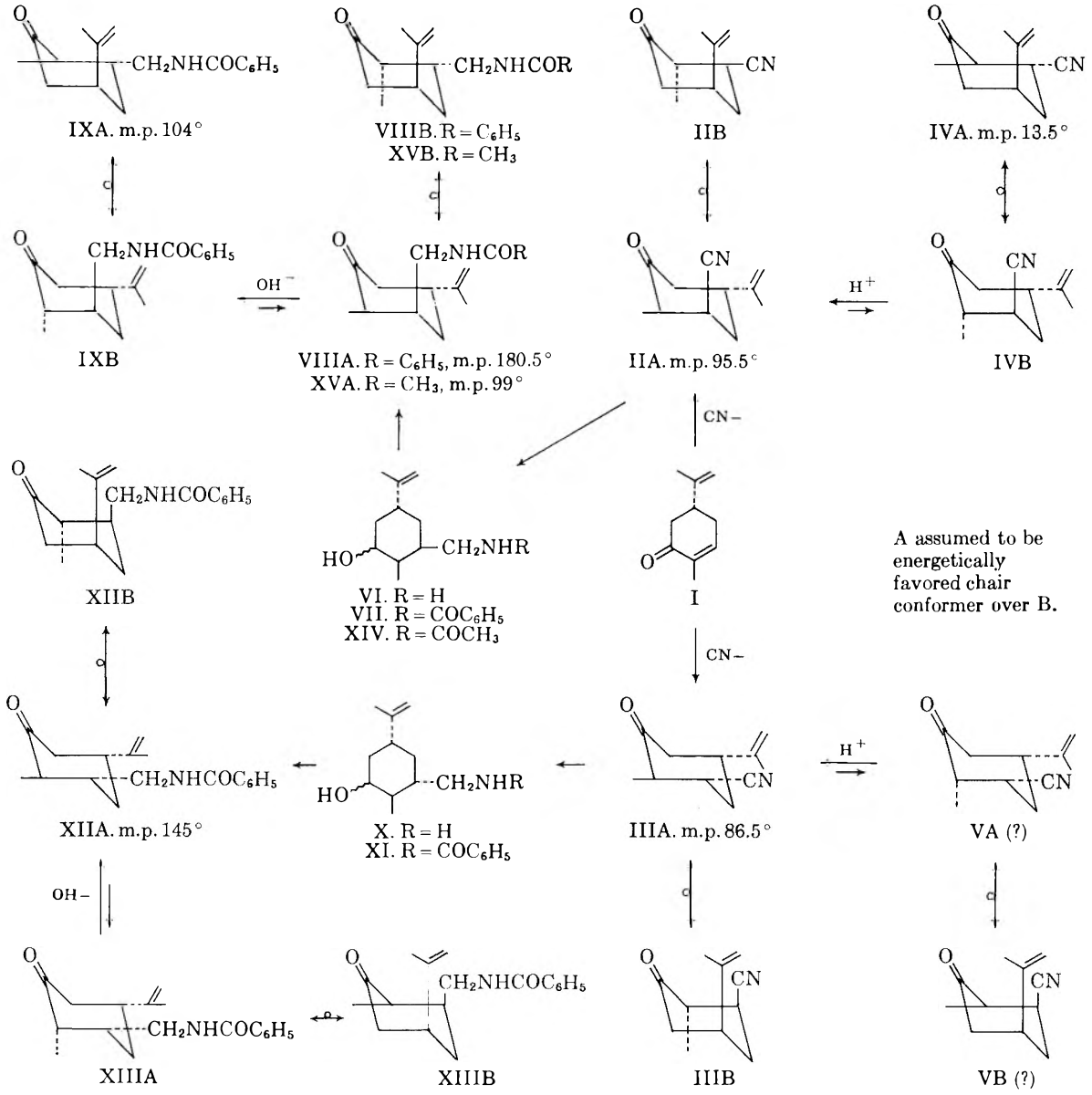
From a qualitative standpoint, consideration of chair forms is probably sufficient and that conformation, labelled A in the formula flow sheet, is considered to be energetically favored over its "flipped" conformer B. A decision between a given conformer pair, A-B, was made by the use of the following energetic parameters. The energy of an axial methyl group adjacent to a carbonyl group in a simple cyclohexanone is of the order of 1.6 kcal./mole[13]; that of an axial cyano group β to a carbonyl group is unknown, but must be quite small as an axial cyano group in a cyclohexane has an energy of only 0.2 kcal./mole.[14] Finally, the energy of an axial iso-

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(12) This procedure does not cause any perceptible epimerization of the adjacent asymmetric center [see ref. 1 as well as G. Ohloff, J. Osiecki, and C. Djerassi, *Ber.*, **95**, 1400 (1962)].

(13) (a) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961); (b) B. Rickborn, *ibid.*, **84**, 2414 (1962).

(14) (a) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962); (b) B. Rickborn and F. Jensen, *ibid.*, **27**, 4606 (1962).



propylidene function is not known with certainty, but is probably somewhat lower than that (2.1 kcal./mole) of an axial isopropyl substituent.[15]

The acid-catalyzed equilibration experiments demonstrated that the two cyanodihydrocarvones of m.p. 95.5 and 86.5° are more stable than their epimers at C-2. Both ketones exhibit positive Cotton effects of appreciable molecular amplitude (*a* as defined in ref. 8), that (Fig. 1) of the higher melting isomer exhibiting $a = +69$ and that (Fig. 1) of the lower melting one, $a = +53$. While these amplitude values cannot be employed to differentiate securely between the two alternative representations IIA and IIIA, there is available also the rotatory dispersion curve (Fig. 1) of the C-2 epimer (IV) of the m.p. 95.5° (II) cyanodihydrocarvone. Its amplitude ($a = +22$) is considerably lower than that of its more stable epimer, thus eliminating immediately the possibility that we are dealing with the pair IIIA → VA, since the axial methyl group in VA would have resulted in a more positive (rather than more negative) Cotton effect, the molecular amplitude increment[1] being nearly +70. We suggest, therefore that the m.p. 86.5° isomer of 2-cyano-2,3-dihydrocarvone should be represented by stereoformula IIIA, since the alternate conformer IIIB possesses three axial substituents. In view of the known[1,13] equilibrium position between an axial and equatorial 2-methylcyclohexanone (over 90% in favor of the latter), it is not surprising that thin-layer chromatography indicated the presence of only trace quantities of VA in the acid-catalyzed equilibration of IIIA.

If expression IIIA is associated with the m.p. 86.5° isomer, then the principal conformer of the higher melting one (m.p. 95.5°) must be represented by stereoformula IIA, the alternate conformer (IIB) again being less stable because of the additional axial substituents. It will be noted from an inspection of Fig. 1 that the molecular amplitude *dropped* [+69 (IIA) → +22 (IVA)] upon epimerization at C-2. If conformation IVB were the correct representation for this C-2 epimer (m.p. 13.5°), then its molecular amplitude should be approximately +136 (due to the +67 contribution[1] of the axial 2-methyl group). Since the amplitude actually decreased, we conclude that the principal conformer of the third isomer (m.p. 13.5°) of 2-cyano-2,3-

(15) (a) N. L. Allinger and S. Hu, *J. Org. Chem.*, **27**, 3417 (1962); (b) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

dihydrocarvone should probably be represented by the stereoformula IVA.[16]

Next, dipole moment studies were undertaken to substantiate the conformational conclusions derived from the optical rotatory dispersion measurements. Such independent confirmation was desired since the rotatory dispersion arguments are based in part on the assumption that conformation VA represents the predominant rotational contributor in the equilibrium VA ⟷ VB, an assumption which may not necessarily be justified. The geometry of cyclohexanone is known fairly accurately, the coordinates of all the atoms being available.[17] The cyanodihydrocarvones contain three functionalities—the olefinic linkage, the ketone and the cyano group—which contribute to the resultant dipole. The directions of the moments of the carbonyl and cyano groups are known and the magnitudes of these group moments may be approximated by those of cyclohexanone (3.06 D.)[18] and of isobutyronitrile (3.6 D.).[19] The magnitude of the moment of the olefin can be taken as 0.4 D.,[20] but as the isopropylidene group rotates, the vector sweeps out a cone which will add in an uncertain way to the resultant of the other groups. If free rotation is assumed, then the olefin contributes a component of 0.4 D. acting along the line from the ring carbon (to which it is bound) to the attached olefinic carbon atom. Since the moment is small, it seems a good approximation to consider the group as freely rotating, even though this is a physically unreasonable assumption.

Having a set of dipole vectors, specified in magnitude and in direction, for conformations IIA, IIIA, IVA, IVB, VA, and VB (the most plausible chair conformations for the four possible isomeric 3-cyano-2,3-dihydrocarvones), it was possible to calculate the dipole moment of each isomer with an IBM 650 computer and the previously described[9] program. The dipole moments of the two principal isomers, II and III, were then determined by dielectric constant measurements, the calculations being carried out by essentially the method of Halverstadt and Kumler,[21] except that an IBM 650 computer and a previously described program[22] were utilized. Comparison of the calculated moments (Table I) with those found experimentally for the two predominant cyanodihydrocarvone isomers of m.p. 95.5° and m.p. 86.5° fully confirm the stereochemical assignments IIA and IIIA.

Previous stereochemical conclusions automatically apply to the derived benzamidomethyl derivatives VIIIA, IXA, and XIIA. The optical rotatory dispersion curve (Fig. 2) of VIIIA differs substantially from that (Fig. 1) of its derived cyanodihydrocarvone (IIA), the negative background, upon which the positive Cotton effect is superimposed, apparently being associated with the amide absorption in the far ultraviolet. This is supported by the observation that the corresponding acetamido analog XVA exhibits a similar dispersion curve (Fig. 2) and that the corresponding benzamido (VII) and acetamido (XIV) precursor alcohols show plain negative dispersion curves. The benzamidomethyl ketone IXA possesses a stronger positive Cotton effect (Fig. 2) than does (Fig. 1) the corresponding cyanodihydrocarvone (IVA); a comparison of the cyanodihydrocarvone (IIIA) optical rotatory dispersion curve (Fig. 1) with that (Fig. 2) of its benzamidomethyl derivative XIIA actually demonstrates an inversion in the sign of the Cotton effect. These apparently contradictory observations are easily accommodated by the assumption that the rotational con-

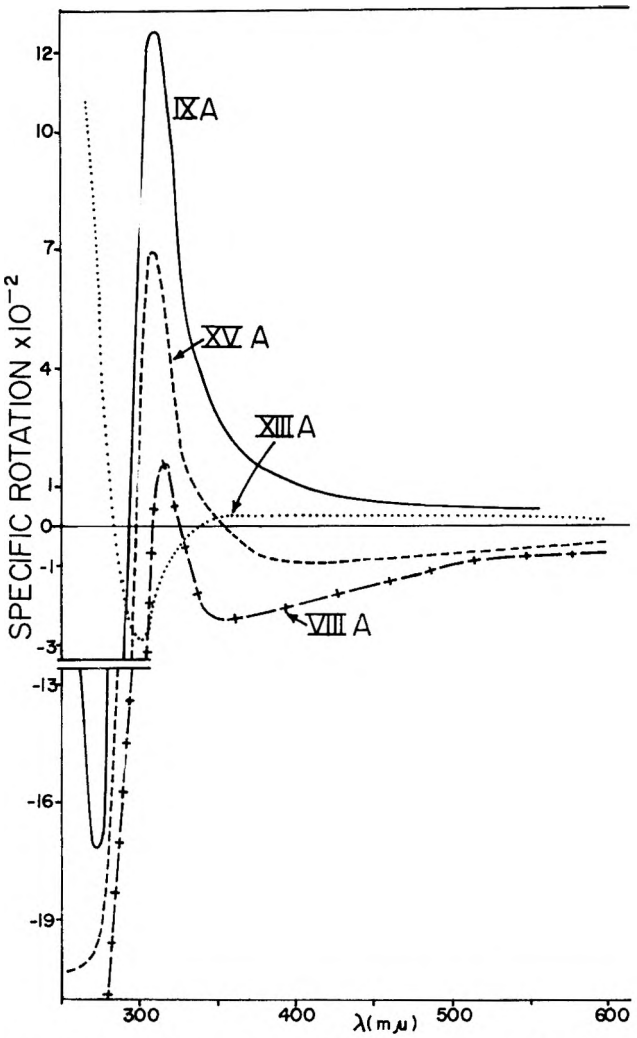


Fig. 2.—Dotted curve marked XIIIA should be marked XIIA.

TABLE I

VALUES FOR RESULTANT DIPOLE MOMENTS (DEBYE UNITS)

Structure	Calculated	Found
IIA	5.30	5.16 (m.p. 95.5° isomer)
IIB	3.13	
IIIA	2.74	2.88 (m.p. 86.5° isomer)
IVA	3.13	
IVB	5.30	
VA	2.74	
VB	5.84	

(16) A twist form of IVB would be expected (ref. 8) to give a strongly positive Cotton effect. In order to explain the stronger positive Cotton effect of IIA over IVA, one must assume that an isopropenyl group (axial or equatorial) β to a carbonyl group makes a stronger rotatory contribution than an equatorial or axial β-cyano substituent. The limited available examples [C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390, (1963); J. Osiecki, Ph.D. thesis, Stanford University, 1960] are in complete accord with this conclusion.

(17) (a) N. L. Allinger and J. Allinger, *Tetrahedron*, **2**, 64 (1958); (b) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955); (c) see also footnote 10 in ref. 7.

(18) N. L. Allinger, J. Allinger, M. A. DaRooge, and S. Greenberg, *J. Org. Chem.*, **28**, in press.

(19) M. T. Rogers, *J. Am. Chem. Soc.*, **69**, 457 (1947).

(20) L. G. Wesson, "Tables of Electric Dipole Moments," The Technology Press, Cambridge, Mass., 1947.

(21) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(22) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

tribution of the hitherto not studied benzamidomethyl grouping is larger than that of a cyano as well as that of an isopropenyl substituent [$-CH_2NHCOC_6H_5 > -C(=CH_2)CH_3 > CN$].

One last point must be emphasized. While the stereochemistry of the isomeric 3-cyano-2,3-dihydrocarvones can be considered as completely settled, the conformational assigments made in this paper to those ketones, where no dipole moment measurements could be performed for lack of material, should be considered to be only of qualitative significance, especially since we do not take into consideration the possible (minor) contributions of nonchair forms. Whether electrostatic repulsion between the C=O and CN dipoles in an axially oriented 3-cyanocyclohexanone plays a significant role is a moot point; it should be noted, however, that the difference in molecular amplitude of the Cotton effect of the axially oriented cyano ketone IIA in methanol *vs.* isooctane solution (see Experimental) is somewhat larger than the difference observed between these two solvents in the equatorial epimer IIIA.

Experimental[23]

2β-Methyl-3β-cyano-5α-isopropenylcyclohexanone (II).[24]—Following the procedure of Lapworth,[4a] 15.0 g. of (−)-carvone (I)[26] in 40 cc. of 95% ethanol was mixed with 9.0 g. of potassium cyanide in 20 cc. of water, followed by the dropwise addition of 6 g. of glacial acetic acid over a 30-min. period, with continuous stirring but without external cooling. After a further 30 min., fine crystals had appeared, whereupon 20 cc. of water was added and after an additional 30 min., precipitation was completed by the addition of 40 cc. of water and cooling in ice. The resulting crystals were collected (12.75 g., m.p. 87–91.5°) and were found by thin-layer chromatography to consist largely of II, contaminated with some IV and traces of III. Recrystallization from aqueous ethanol provided 8.76 g. of chromatographically homogeneous II, m.p. 93.5–95°, while the analytical sample [after sublimation at 70° (0.1 mm.)] exhibited m.p. 95–95.5°, $[\alpha]^{24}D$ −6.2° (*c* 2.75), (lit.[4] m.p. 93.5–94.5°, $[\alpha]^{12}D$ +13.5° for antipode). The relevant infrared bands are listed in Table II, while the rotatory dispersion curve is reproduced in Fig. 1. R.D. in methanol (*c* 0.103): $[\alpha]_{589}$ −12°, $[\alpha]_{318}$ +1400°, $[\alpha]_{314}$ +1360°, $[\alpha]_{310}$ +1400°, $[\alpha]_{270}$ −2490°, $[\alpha]_{250}$ −2300°. The molecular amplitude a = +69 was reduced to +54 in isooctane solution.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.75; H, 8.81.

2β-Methyl-3α-cyano-5α-isopropenylcyclohexanone (III).[24]—To a refluxing mixture of 12.0 g. of (−)-carvone (I) and 7.5 cc. of ethyl acetate was added a hot solution of 6.0 g. of potassium cyanide in 15 cc. of water and 17 cc. of 95% ethanol and heating continued for 20 min., two phases remaining during this period. The cooled solution was extracted with ether, dried, and evaporated to yield 13.2 g. of a yellowish, pasty mass of crystals, which by thin-layer chromatography was shown to contain approximately equal amounts of II and III, as well as traces of IV and less intense spots of very low R_f value (presumably acids and/or amides). Separation was not feasible by gas phase chromatography, three very closely overlapping peaks being observed, and recourse had to be taken to gradient elution chromatography on 850 g. of neutral alumina (activity II), starting with hexane–benzene (3:1) and adding benzene–hexane (3:1). Fractions of 50 cc. each were collected, using an automatic fraction collector, and were divided into three groups on the basis of thin-layer chromatographic analysis. Fractions 1–47 contained only traces (40 mg.) of carvone (I), while fractions 48–70 consisted largely of the desired isomer III (2.28 g., m.p. 30–79°), the remaining fractions representing varying proportions of II, III, and IV. One recrystallization from aqueous ethanol provided 1.58 g. of III, m.p. 78.5–84.5°, raised to 85.5–86.5° (0.96 g.) upon recrystallization from hexane–benzene. The analytical specimen was sublimed at 85° (0.1 mm.), whereupon it showed m.p. 86–86.5°, $[\alpha]_D$ +47° (*c* 1.72) (lit.[4b] m.p. 84°, $[\alpha]_D$ −42.1° for antipode). R.D. (Fig. 1) in methanol (*c* 0.104): $[\alpha]_{589}$ +42° $[\alpha]_{310}$ +1250, $[\alpha]_{270}$ −1740°, $[\alpha]_{250}$ −1580°, the molecular amplitude being practically unchanged in isooctane solution. The characteristic infrared peaks are listed in Table II.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.38; H, 8.52.

2α-Methyl-3β-cyano-5α-isopropenylcyclohexanone (IV).[24]—A solution of 2.37 g. of 2β-methyl-3β-cyano-5α-isopropenylcyclohexanone (II) in 30 cc. of benzene and 15 cc. of ethyl acetate containing 2.4 g. of *p*-toluenesulfonic acid was kept at room temperature for 4 days and then washed with sodium bicarbonate solution and water. Evaporation left a residue, which by thin-layer chromatography was found to consist of a mixture of II and IV with the former predominating. Separation was effected by hexane elution from a column of 170 g. of Celite,[26] impregnated with 75 cc. of formamide. The first fractions (0.34 g.) were combined and recycled to furnish 0.31 g. of a colorless oil, which was virtually pure IV as demonstrated by thin-layer chromatography. Recrystallization from hexane–ethyl acetate between −8° and −22° led to colorless needles, chromatographically homogeneous, which were distilled at 90° (0.1 mm.) to give the analytical sample of IV with m.p. 11.5–13.5°. R.D. (Fig. 1) in methanol (*c* 0.082): $[\alpha]_{589}$ −10°, $[\alpha]_{315}$ +446°, $[\alpha]_{270}$ −806°,

TABLE II

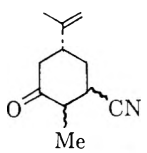
INFRARED MAXIMA (CHLOROFORM) OF 2-METHYL-3-CYANO-5-ISOPROPENYLCYCLOHEXANONES[a]

Wave length	Compound II	Compound II	Compound IV
4.47	s	s	s
5.85	s	...	...
5.86	...	s	s
6.10	m	m	m
7.47	w	...	...
7.56	min	m	m
7.61	w	...	...
7.75	min	min	w
8.00 (broad)	...	m	...
8.33 (broad)	m	...	m
8.71	m	...	...
8.75	...	...	m
8.81	...	m	...
8.95	w	...	w
9.20	...	w	...
9.87	w	min	...
10.06	min	m	m
10.29	m	min	...
10.46	min	m	min
10.68	min	min	w
11.07	...	...	s
11.17	s	s	...

[a] Listed are maxima of important functional groups and maxima which are not the same for all three isomers.

(23) All melting points were taken in capillaries and are corrected. Rotations were measured in 95% ethanol and infrared spectra in chloroform solution. The optical rotatory dispersion curves were determined by Mrs. Ruth Records with a Nippon Bunko (Japan Spectroscopic Co.) automatically recording spectropolarimeter (Model ORD-2); while the microanalyses are due to Messrs. E. Meier and J. Consul. Thin-layer chromatograms were performed on silica gel G (E. Merck, Darmstadt) plates, 10% ethyl acetate in benzene being used as the developing agent. The approximate R_f values were: II (0.37), III (0.52), IV (0.42), and V (0.40).

(24) In order to simplify the nomenclature and, since the absolute configuration of all products is known, we are employing the steroid notation (ref. 5) based on the following representation.



(25) The material [$[\alpha]D$ −60.7° (neat), $n^{25}D$ 1.4968] was purchased from Farmer's Chemical Co., Kalamazoo, Mich., and was homogeneous according to gas-phase chromatography.

(26) Commercial Celite 545 was washed overnight with concentrated hydrochloric acid, then successively with dilute acid, water, sodium bicarbonate solution, and finally water. The material was dried at 110° for 20 hr. before use.

$[\alpha]_{250}$ −649°, the characteristic infrared bands being listed in Table II.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.13; H, 8.56.

Epimerization Experiments at C-2.—A solution of either isomer II or III and an equal weight of *p*-toluenesulfonic acid in ethyl acetate solution produced in each case two spots in a thin-layer chromatogram: II → II + IV; III → III + V. Within 1 week at room temperature, the ratio of intensities for a given pair (II and IV, or III and V) ceased to change and, even after 3 months, no spot corresponding to the other pair appeared. In the equilibration of III, the spot corresponding to its C-2 epimer (V) was so faint that isolation of this isomer was not attempted.

Under more forceful conditions, such as alcoholic potassium hydroxide, the same effects were noted in a matter of seconds, but epimerization also occurred at C-3 as demonstrated by the appearance of all four spots after a very short while.

Epimerization Experiments at C-3.—In a model experiment, 128 mg. of II was dissolved in methanol and left for 1 hr. with a solution of 33 mg. of sodium borohydride in 2 cc. of 50% aqueous methanol. After acidification, the product was isolated with ether and shown to lack completely any infrared carbonyl absorption. The entire alcohol (124 mg.) was oxidized in 10 cc. of acetone at 0° with 8 *N* chromic acid solution,[11,12] small quantities of anhydrous magnesium sulfate being added simultaneously. Thin-layer chromatography of the oxidation product showed that it consisted virtually of only the starting ketone II, contaminated with nonoxidized alcohol and traces of IV.

The sodium borohydride (10 mg.) reduction of 20 mg. of II was repeated but, prior to reoxidation, the alcohol was heated under reflux for 20 min. with 10% aqueous–methanolic potassium hydroxide solution. Thin-layer chromatography of this oxidation mixture demonstrated the presence of strong spots due to II and III, as well as a trace of IV. Conversely, when this sequence was repeated with pure III, thin-layer chromatography clearly showed the production of II, weak spot) in addition to a strong spot corresponding to III, but no indication of spots associated with IV or V.

2β-Methyl-3β-benzamidomethyl-5α-isopropenylcyclohexanone (VIII).[24]—2β-Methyl-3β-cyano-5α-isopropenylcyclohexanone (II) (1.02 g.) was reduced with 0.6 g. of lithium aluminum hydride by heating under reflux for 30 min. in ether (150 cc.) solution and decomposing the reaction mixture by the sodium sulfate technique. The resulting mixture of alcohols (VI) [0.99 g., m.p. 63–84°, $[\alpha]_D$ −10° (*c* 1.19), $\lambda_{max}^{CHCl_3}$ 2.77, 2.95, 6.10, and 11.2 μ, but no bands between 4.0–6.0 μ] was used directly in the next step.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55. Found: C, 72.25; H, 11.55.

The amino alcohol (1.25 g. of VI) was dissolved in a mixture of 100 cc. of chloroform and 15.8 cc. of 2% sodium hydroxide solution and benzoyl chloride (0.87 cc.) in 15 cc. of chloroform was added with vigorous stirring at room temperature over a period of 30 min. After 1.5 hr., the basic aqueous solution was separated and the organic layer washed to neutrality, dried, and evaporated. The crystalline benzamido alcohol mixture VII (1.85 g.), m.p. 105–130°, $[\alpha]_D$ −22° (*c* 1.35). R.D. in methanol (*c* 0.10): plain negative curve, $[\alpha]_{500}$ −76°, $[\alpha]_{400}$ −102°, $[\alpha]_{300}$ −218°, $[\alpha]_{280}$ −384°, showed two spots in a thin-layer chromatogram (2:3 ethyl acetate–benzene) and was oxidized without further separation.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77. Found: C, 74.85; H, 8.80.

A portion (133 mg.) of this mixture (VII) was oxidized at room temperature in acetone solution with 8 *N* chromic acid solution,[11,12] and the quantitatively produced ketone VIII (m.p. 176–179.5°) was recrystallized twice from benzene and sublimed at 150° (10^{-5} mm.), whereupon the analytical specimen exhibited m.p. 179–180.5°, $[\alpha]_D$ −68° (*c* 0.59), $\lambda_{max}^{CHCl_3}$ 5.87, 6.05, and 11.22 μ. R.D. (Fig. 2) in methanol (*c* 0.071): $[\alpha]_{589}$ −62°, $[\alpha]_{317}$ +160°, $[\alpha]_{254}$ −5130°.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.73; H, 8.13.

2α-Methyl-3β-benzamidomethyl-5α-isopropenylcyclohexanone (IX).[24]—The above-described 2β-methyl isomer VIII (174 mg.) was left at room temperature for 1 hr. in 25 cc. of methanol containing 350 mg. of potassium hydroxide. The solution was neutralized, the methanol evaporated, and the product (168 mg.) extracted with methylene chloride. Recrystallization from benzene provide 30 mg. of the starting material (VIII), m.p. 175–179°, and, since chromatography on alumina did not effect any good separation of the mother liquor material, it was subjected to fractional crystallization from acetone–hexane. From the less soluble portion an additional 23 mg. of VIII (m.p. 171–174°) could be isolated, while the more soluble material yielded in three crops a total of 81 mg. of IX. Two additional recrystallizations from acetone–hexane and one from benzene–hexane gave colorless needles of IX which were homogeneous by thin-layer chromatography; m.p. 102–104°, $[\alpha]_D$ +19° (*c* 0.65), $\lambda_{max}^{CHCl_3}$ 5.87, 6.05, and 11.19 μ. R.D. (Fig. 2) in methanol (*c* 0.098): $[\alpha]_{589}$ +24°, $[\alpha]_{310}$ +1260°, $[\alpha]_{273}$ −1730°, $[\alpha]_{265}$ −1020°.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.30; H, 8.17.

On the basis of the weights of the isolated substances in the base-catalyzed epimerization reaction, the equilibrium composition is approximately 39% VIII *vs.* 61% IX. In order to obtain an independent value, 13 mg. each of pure VIII and of pure IX was allowed to stand at room temperature for 30 min. in 1% methanolic potassium hydroxide solution. Each mixture was worked up under identical conditions and in each instance a melting point of 96–145° was encountered for the total crude product (12 mg.). The rotatory dispersion curves were determined in methanol solution (*c* 0.10) and the equilibration mixture of VIII exhibited a peak at $[\alpha]_{303}$ +1000°, while that of IX showed $[\alpha]_{304}$ +930°. Using the rotations observed at 310 mμ (VIII, +210°; IX, +1260°; equilibrium mixtures, +925°), one arrives at a 32% (VIII)–68% (IX) equilibrium composition.

2β-Methyl-3α-benzamidomethyl-5α-isopropenylcyclohexanone (XII).[24]—The lithium aluminum hydride reduction of 2β-methyl-3α-cyano-5α-isopropenylcyclohexanone (III) was performed exactly as described for II and the crude alcohol mixture (X), representing a viscous liquid, was benzoylated in 92% yield to produce the benzamide mixture XI, m.p. 161–173°. R.D. in methanol (*c* 0.107): $[\alpha]_{589}$ +47°, $[\alpha]_{400}$ +94°, $[\alpha]_{300}$ +140°, $[\alpha]_{260}$ +210°.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77. Found: C, 74.88; H, 8.84.

Oxidation of XI in acetone solution provided 97% of colorless crystals, m.p. 124.5–133.5°, which after two recrystallizations from acetone–hexane led to the analytical specimen of XII m.p. 143.5–145°, $[\alpha]_D$ +23° (*c* 1.37), $\lambda_{max}^{CHCl_3}$ 5.87, 6.05, and 11.22 μ. R.D. (Fig. 2) in methanol (*c* 0.10): $[\alpha]_{589}$ +19°, $[\alpha]_{303}$ −280°, $[\alpha]_{255}$ +1070°.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.64; H, 8.21.

Base-catalyzed equilibration of this amide XII in an attempt to prepare the 2α-epimer XIII yielded a product, m.p. 135–140°, [R.D. in methanol (*c* 0.107): $[\alpha]_{589}$ +9°, $[\alpha]_{360-320}$ +35° (broad plateau), $[\alpha]_{293}$ −170°, $[\alpha]_{276}$ 0°] which showed two spots in a thin-layer chromatogram, the new spot (corresponding to XIII) being very faint. Attempts to isolate the new epimer by fractional crystallization proved unsuccessful.

TABLE III

DIPOLE MOMENT DATA, BENZENE SOLUTION, 25° (EXPERIMENTAL ERROR ±0.03 D.)

2β-Methyl-3β-cyano-5α-isopropenylcyclohexanone (IIA)[24]

N_2	d_{12}	ϵ_{12}
0.00000000	0.873322	2.2762
.00079446	.873541	2.3051
.00151767	.873732	2.3319
.00230825	.873982	2.3610
.00299230	.874170	2.3870
α = 37.029	ϵ_1 = 2.2759	d_1 = 0.87332
β = 0.285	$P_{2\infty}$ = 595.3	μ = 5.16 D.

2β-Methyl-3α-cyano-5α-isopropenylcyclohexanone (IIIA)[24]

N_2	d_{12}	ϵ_{12}
0.00000000	0.873345	2.2763
.00043163	.873407	2.2812
.00088528	.873526	2.2868
.00113033	.873513	2.2892
.00162884	.873730	2.2947
α = 11.374	ϵ_1 = 2.2764	d_1 = 0.87331
β = 0.243	$P_{2\infty}$ = 222.0	μ = 2.88 D.

2β-Methyl-3β-acetamidomethyl-5α-isopropenylcyclohexanone (XV).[24]—To a vigorously stirred and ice-cold solution of 626 mg. of the 2β-methyl-3β-aminomethyl-5α-isopropenylcyclohexanol mixture (VI) in 200 cc. of pyridine and 30 cc. of dry benzene, 349 mg. of acetic anhydride in 150 cc. of benzene was added dropwise over a period of 4 hr. After one additional hour at ice-bath temperature, the mixture was poured into water, the product isolated in the usual manner with ether, then chromatographed on 10 g. of neutral alumina (activity III), elution being effected first with 250 cc. of methylene chloride, followed by 150 cc. of ethyl acetate. The desired acetamido alcohol mixture (XIV) was obtained as a colorless oil (135 mg.), which crystallized spontaneously; m.p. 70–96.5°. R.D. in methanol (*c* 0.12): $[\alpha]_{589}$ −21°, $[\alpha]_{500}$ −29°, $[\alpha]_{400}$ −50°, $[\alpha]_{300}$ −134°, $[\alpha]_{260}$ −183°. This material was directly oxidized with chromium trioxide in acetone solution[11,12] and recrystallized from acetone–hexane to give the desired, chromatographically homogeneous ketone XV, m.p. 98–99°, $\lambda_{max}^{CHCl_3}$ 2.90, 5.87, 6.00 and 11.20 μ. R.D. (Fig. 2) in methanol (*c* 0.105): $[\alpha]_{589}$ −48°, $[\alpha]_{308}$ +704°, $[\alpha]_{240}$ −2280°.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48. Found: C, 69.72; H, 9.58.

Dipole Moment Measurements.—The dipole moments were measured in benzene solution at 25°, using the previously described[27] apparatus, the data being summarized in Table III. References to the method of calculation are given in the Discussion. The molar refractivity (50.25 cc.) was calculated from tables[28] and atomic polarization was neglected.

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The Constitution of Otobain

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A new lignan, otobain, for which the structure 5,6-methylenedioxy-2,3-dimethyl-4-(3′,4′-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene (VI) is proposed, has been isolated from the fruit of *Myristica otoba*.

The fat expressed from the fruit of *Myristica otoba* is reputedly used in Colombia as a medicament for skin diseases of domestic animals. It was first examined over one hundred years ago by Uricoechea,[2] who isolated a product which he named "otobite" and to which he attributed the empirical formula $C_{21}H_{26}O_5$. A more extensive examination was performed by Baughman and co-workers,[3] who reported the isolation of isomers, $C_{20}H_{20}O_4$, which they named otobite and isootobite, and suggested that the previously isolated product was a mixture. From a sample of otoba fat collected in 1960 in the Departmento of Tolima, Colombia,[4] we have isolated a lignan for which the name otobain was proposed in a preliminary communication.[5] Gilchrist, Hodges, and Porte[6] since have described work on the isolation and structure elucidation of the same product to which they have fortunately assigned the same name in conformance with lignan nomenclature. The assumption that otobite and otobain are identical[6] we regard as questionable on the basis of reported differences of behavior (*e.g.*, Zeisel determination, action of bromine).[3,5]

Empirical analyses and molecular weight determination established that otobain had a molecular formula, $C_{20}H_{20}O_4$. The absence of absorption bands in the infrared spectrum characteristic of hydroxyl and carbonyl groups indicated that all four oxygen atoms were present as ether functions. The absence of methoxyl groups, established by Zeisel determination, suggested the likelihood that the oxygen functions were two methylenedioxy groups. That at least one such group was present was apparent from the infrared spectrum (potassium bromide disk) which showed a strong band at 928 cm.$^{-1}$, with a weak overtone at 1850 cm.$^{-1}$, considered most characteristic for methylenedioxy groups[7]; the presence of strong bands at 1362, 1242, 1130, and 1045 cm.$^{-1}$, particularly in the demonstrated absence of aromatic methoxyl groups, supports this assignment. Chemical evidence for the presence of two methylenedioxy groups was obtained by treatment of otobain with phosphorus pentachloride followed by sodium carbonate. The isolated product, $C_{20}H_{16}O_6$, had an infrared absorption band at 1830 cm.$^{-1}$ characteristic of five-membered ring strained carbonyl systems[8] of which the derived benzenoid cyclic carbonate is typical.

Kuhn–Roth C-methyl determination indicated the presence of two such groups, leaving unaccounted only two carbon atoms to be incorporated in a ring. This preliminary characterization strongly suggested that otobain is a lignan[9,10] of the phenyltetralin class, of which structure I based on unexceptional biogenetic considerations,[11–13] is the most obvious possibility. Integration of the nuclear magnetic resonance spectrum of otobain established the presence of five aromatic protons, and the ultraviolet absorption spectrum was also consistent with this formulation. Closely related to I are the lignans, isolated from *Himantandra* species by Hughes and Ritchie,[14] named galbulin (II) and galcatin (III), the absolute stereochemical assignments being proposed by two independent groups.[15,16]

(1) Present address, Varian Associates, Palo Alto, Calif.

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(4) We wish to acknowledge our indebtedness to Dr. Alvaro Fernandez-Pérez of the Instituto de Ciencias Naturales, Universidad Nacional de Colombia, through whose kind efforts the material was supplied.

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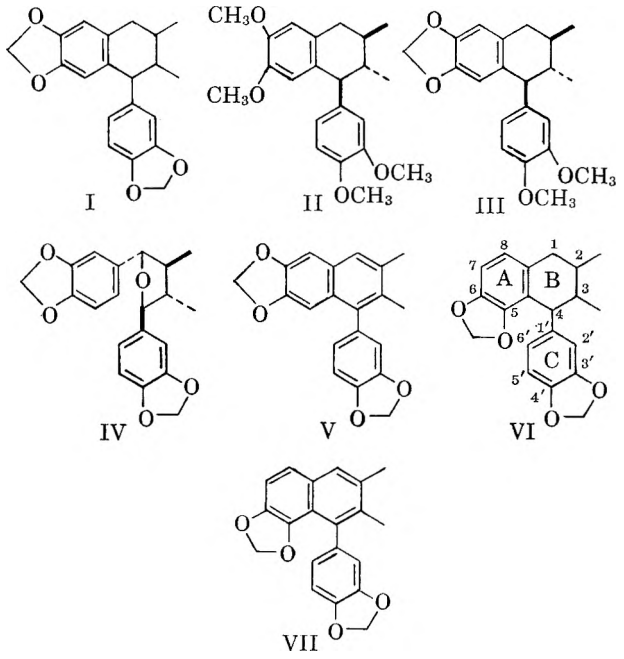
TABLE I[a]

ASSIGNMENTS OF PROTON MAGNETIC RESONANCE DATA (LIGNAN NUMBERING)

Compounds	H_1	H_2	H_3	H_4	H_5	H_7	H_8	$H_{2'}$	$H_{5'}$	$H_{6'}$	$-OCH_2O-$ ring A	$-OCH_2O-$ ring C	Methyl on C-2	Methyl on C-3
Otobain	2.63	*ca.* 1.44	*ca.* 1.44	3.43	..	6.65	6.65	6.58	6.58	6.58	5.58 and 5.64	5.88	0.96 or 1.04	0.96 or 1.04
Dehydrootobain	7.48	...	...	..	..	7.02	7.24	6.68	6.63	6.78	5.78	6.05	2.42	2.08
Dehydroepigalbacin	7.43	...	...	..	6.68	..	7.00	6.68	6.63	6.89	5.89	6.00	2.40	2.08
Dinitrootobain	2.93	*ca.* 1.57	*ca.* 1.57	4.77	..	7.33 or 7.37	..	6.48	7.33 or 7.37	..	5.72 and 5.80	6.03	0.98 or 1.09	0.98 or 1.09
Dibromootobain	2.76	*ca.* 1.45	*ca.* 1.45	4.23	..	6.95 or 7.02	..	6.43	6.95 or 7.02	..	5.62 and 5.68	5.89	0.92 or 1.06	0.92 or 1.06

[a] Tabulation of chemical shifts are indicated in parts per million of the respective protons.

Galbulin and galcatin were unaffected by bromination in carbon tetrachloride solution, and no pure nitro derivatives could be prepared by treatment with nitric acid in glacial acetic acid under a variety of conditions,[14] the latter behavior being regarded as characteristic of the phenyltetralin class of lignans.[9] In contrast, otobain readily gave in our hands crystalline dibromo and dinitro derivatives. At this juncture, we considered that this difference in behavior could be explained by otobain differing in configuration from II and III at one or more of the three asymmetric carbon atoms, particularly since the specific rotation of otobain (−40°) differed from the values for II (−8°) and III (−9°) more than would be expected by replacement of *ortho* dimethoxy groups by methylenedioxy groups. From the sequel, it is now evident that the behavior of phenyltetralin lignans on nitration cannot be regarded as diagnostic unless the ether substitution pattern is known.



Dehydrogenation of otobain with palladium–carbon yielded an optically inactive product, dehydroötobain, $C_{20}H_{16}O_4$, m.p. 185–187°. A compound to which structure (V) had been assigned,[14,16] prepared by acid isomerization of galbacin (IV) followed by dehydrogenation, had been reported with melting point, 168°. Since a comparison specimen was unavailable, we have

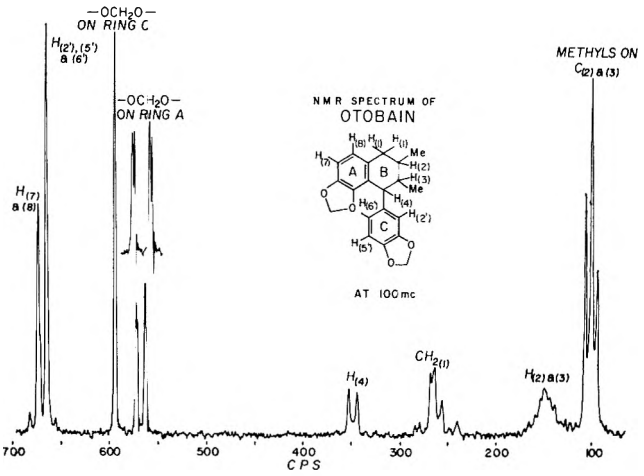


Figure 1

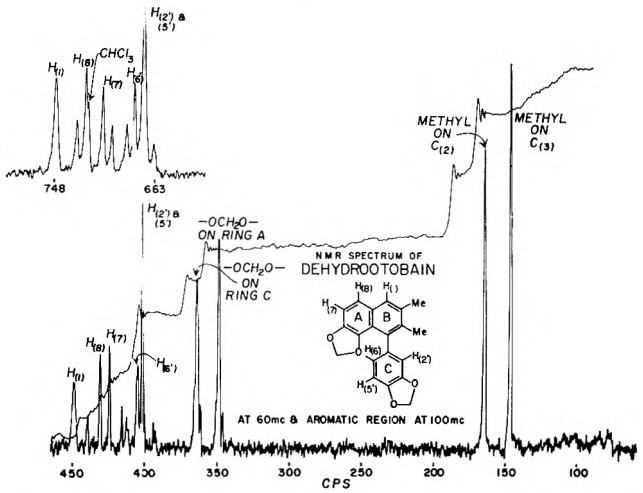


Figure 2

repeated the isomerization and dehydrogenation of galbacin[17] to give a product, m.p. 171–172°, referred to as dehydroepigalbacin, presumably the same as that previously reported. Since we find that dehydrootobain and dehydroepigalbacin differ and the structure (II) of dehydroepigalbacin has recently been confirmed by an independent synthesis,[6] otobain cannot have structure I.

Of alternative formulations in agreement with the above physical and chemical data and consistent with the theory of biogenesis, that represented by VI, in

(17) We wish to thank Professor A. J. Birch, Manchester University, England, for a generous sample of galbacin.

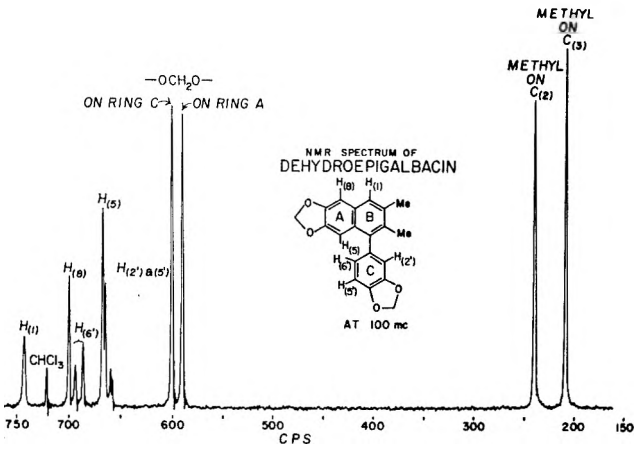


Figure 3

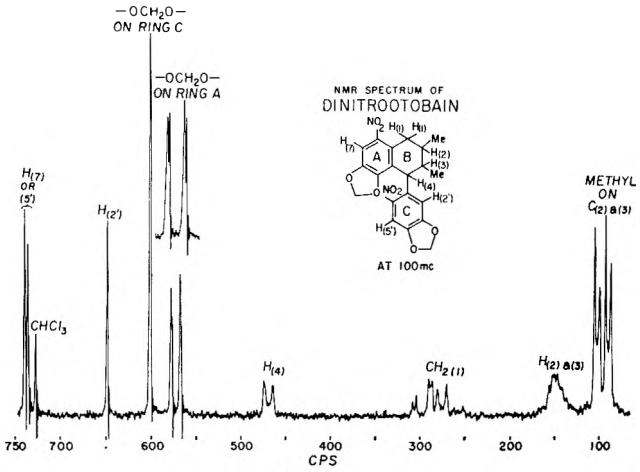


Figure 4

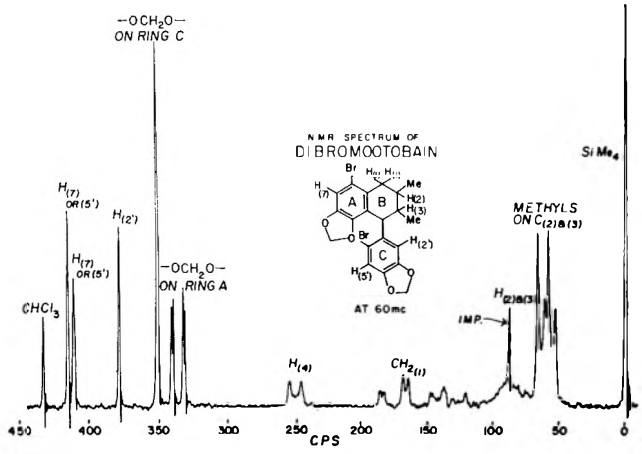


Figure 5

which the ring A methylenedioxy group is located at C-5 and C-6 rather than C-6 and C-7 of I, was considered most probable. A study of the nuclear magnetic resonance spectra of otobain (Fig. 1), dehydrootobain (Fig. 2), dehydroepigalbacin (Fig. 3), dinitrootobain (Fig. 4), and dibromootobain (Fig. 5) confirmed this conclusion. The assignments of the observed peaks to functional groups are summarized in Table I.[18]

In the spectrum of otobain, the pair of overlapping doublets at δ 0.96 and 1.04 with 5 c.p.s. coupling are assigned to the ring B secondary methyl groups. The broad unresolved signal at δ 1.44 can be attributed to the $H_{(2)}$ and $H_{(3)}$ protons which couple with each other, with the 2- and 3-methyl groups and with the $H_{(1)}$ and $H_{(4)}$ protons. As expected, the integral intensity of the signals due to these two sets of protons adds to eight protons. The peaks at δ 2.63, representing two protons, are characteristic of a benzylic methylene group, the corresponding function in α-tocopherol[19] displaying a chemical shift at δ 2.62. The multiplicity of the signals, which show an ABM pattern would strongly indicate the nonequivalence of the methylene protons. The doublet signal at δ 3.43 can be attributed to the dibenzyl methine proton at C-4. The pair of doublets at δ 5.58 and 5.64 indicates the nonequivalence of the two protons of a methylenedioxy group. They exhibit a chemical shift of 0.06 p.p.m. and a spin-coupling of 1.5 c.p.s. A similar case of nonequivalence of methylenedioxy protons was observed in dicentrine and bulbocapnine methyl ether.[20,21] This observation is consistent with the location in ring A of the methylenedioxy group at C-5 and C-6 where the methylene protons are unsymmetrically distributed with regard to ring C and inconsistent with any of the other two possible ring A locations. The second methylenedioxy group on ring C shows a normal singlet at δ 5.88, the same shift value as reported for safrole.[22]

Integration of the aromatic proton region confirmed the presence of five aromatic protons, the two signals showing respectively the intensities of three protons and two protons located at δ 6.58 and 6.65. Comparison with the spectrum of safrole[22] indicates by analogy that the peak at δ 6.58 can be assigned to the ring C aromatic protons, a degenerate ABC resonance pattern being exhibited in both cases. The two remaining ring A aromatic protons must consequently be responsible for the peak at δ 6.65. The absence of observable coupling is unusual for *ortho* protons; this ambiguity is resolved, however, by examination of the spectra of dehydrootobain (VII) and dehydroepigalbacin (V) from which it may be concluded that the $H_{(7)}$ and $H_{(8)}$ protons of otobain must have the same chemical shift and hence do not exhibit any spin–spin coupling. An analogous situation exists in the spectrum of protopine[23] where two similarly situated aromatic protons show a single peak at δ 6.69.

The n.m.r. spectra of dehydrootobain (Fig. 2) and dehydroepigalbacin (Fig. 3) are rather similar, although the few differences can be used to advantage in supporting structure VI of otobain. In accordance with the empirical formulas, integration data of both compounds account for sixteen protons, six from two aromatic methyl groups, four from two methylenedioxy groups, and six aromatic protons. The sharp signals at δ 2.08 and 2.42 (or 2.40) of both are characteristic of aromatic methyl protons. The resonance at δ 2.42 is slightly broader, indicating that these protons are slightly spin coupled to the adjacent $H_{(1)}$ proton, and is consequently assigned to the 2-methyl group; the 3-methyl group, closer to ring C, has the higher field

(18) The numbering system used for otobain (VI), conventional for lignan nomenclature, is also used for comparison purposes with the dehydrogenated phenylnaphthalene derivatives (V and VII).

(19) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," no. 366, Varian Associates, 1962.

(20) S. Goodwin, J. N. Shoolery, and L. F. Johnson, *Proc. Chem. Soc.*, 306 (1958).

(21) Ref. 19, no. 333 and 342.

(22) Ref. 19, no. 253.

(23) Ref. 19, no. 339.

signal. In contrast to otobain, both methylenedioxy groups in the spectrum of dehydroötobain give single resonances at δ 5.78 and 6.05. This is as anticipated, since formation of the naphthalene A/B rings imparts planarity to the system and therefore equivalence of the ring A methylenedioxy protons with regard to the benzenoid C-ring. Again, the higher field aromatic resonance can be attributed to the ring A methylenedioxy protons.

The peaks shown by dehydrootobain at δ 6.68, 6.63, and 6.78 are the resonances of $H_{(2')}$, $H_{(5')}$, and $H_{(6')}$, respectively. They present an ABC pattern with $H_{(5')}$ and $H_{(6')}$ coupled to each other with 8 c.p.s. *ortho*-coupling, while $H_{(6')}$ is further coupled to $H_{(2')}$ with a *meta*-coupling of about 1.5 c.p.s. This ABC pattern is very similar to that exhibited in the spectrum of dehydroepigalbacin. The chemical shifts from $H_{(2')}$ and $H_{(5')}$ in both spectra are virtually identical. The resonance at δ 6.78 from $H_{(6')}$ in VII is at a higher field than the similar resonance of V at δ 6.89. This shift is conceivably due to the proximity of the oxygen atom of the ring A methylenedioxy group and supports formulation VII for dehydrootobain. The resonances at δ 7.02 and 7.24 of dehydrootobain present a typical AB pattern, with a characteristic 8 c.p.s. *ortho*-spin coupling, due to $H_{(7)}$ and $H_{(8)}$. In the spectrum of V, the ring A protons have their resonances at δ 6.68 due to $H_{(5)}$ and δ 7.00 due to $H_{(8)}$, the upfield shift of the $H_{(5)}$ peak being caused by the proximity of the benzenoid ring C. The remaining resonances at δ 7.48 and 7.43 in VII and V, respectively, are attributable to the $H_{(1)}$ proton.

The spectrum of dinitrootobain (Fig. 4) is consistent with the formula proposed for otobain and leads to the tentative conclusion that the nitro groups are located at C-8 and C-6′. Of the three aromatic protons, two resonate at considerably lower field (δ 7.33 and 7.37) suggesting that they are *ortho* to nitro groups. The observed downfield shift of the $H_{(1)}$ and $H_{(4)}$ protons is also consonant with nitro groups being located at C-8 and C-6′. The spectrum of dibromootobain (Fig. 5) is similar, except that the shifts are less pronounced with reference to otobain.

A stereochemical interpretation of the nuclear magnetic resonance spectrum of otobain has been presented.[6]

A cell culture cytotoxicity test[24] carried out on otobain gave an ED_{50} value of 1.0×10^2 μg./ml. The constitution of some minor constituents which we have isolated from *Myristica otoba* will be reported later.

Experimental[25]

Isolation of Otobain (VI).—Otoba fat (100 g.) was steam distilled for 4 hr. to yield a steam-volatile fraction (5.9 g.). The residue was suspended in water (1000 ml.), potassium hydroxide (30 g.) was added, followed by methanol (500 ml.) and the mixture heated under reflux for 5 hr. and allowed to stand overnight at room temperature. Most of the methanol was then removed by distillation, the cooled mixture extracted with ether, the extract well washed with water, dried (sodium sulfate), and the ether removed to give a dark oil (19.5 g.). Otobain crystallized from an ethanol solution of this oil as fibrous needles (6.0 g.), m.p. 125–128°, raised to m.p. 132–134° on one recrystallization. An analytical sample was prepared by filtration of a petroleum ether (b.p. 30–60°) solution through Merck alumina and crystallization of the eluate from ethanol, yielding otobain (VI) as long needles, m.p. 137–138°, $[\alpha]_D$ −40.5° (*c* 3.2), λ 234 (ε 9300) and 287 mμ (ε 6700).

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22; O, 19.73; 2-CMe, 9.27. Found: C, 74.16; H, 6.14; O, 19.77; —OMe, 0.00; —CMe, 7.06. λ 3.41, 3.49, 6.21, 6.65, 6.75, 6.90, 7.36, 7.76, 8–8.4 (broad), 8.87, 9.13, 9.23, 9.48, 9.63, 9.83, 10.65 (broad), 10.78 (broad), 11.59 μ.

Dibromootobain.—A solution of bromine (640 mg.) in ether (4 ml.) was added to a solution of otobain (257 mg.) in ether (10 ml.). The mixture was allowed to stand at room temperature for 2 hr., then shaken with sodium thiosulfate solution, water, dried (sodium sulfate), and evaporated to give a pale yellow gum (410 mg.) which yielded a solid (147 mg.). Crystallization from chloroform–methanol gave dibromootobain as hard prisms, m.p. 197–199°, $[\alpha]_D$ + 64° (*c*, 2.7).

Anal. Calcd. for $C_{20}H_{18}O_4Br_2$: C, 49.82; H, 3.76; O, 13.27; Br, 33.15. Found: C, 49.74; H, 4.02; O, 13.48; Br, 33.49. λ 3.45, 3.51, 6.18, 6.27, 6.73, 6.78, 6.92, 7.15, 7.26, 7.37, 8–8.4 (broad), 8.79, 9.04, 9.19, 9.46, 9.65, 10.18, 10.76, 11.67, 11.89 μ.

Dinitrootobain.—Concentrated nitric acid (0.2 ml.) was added to a solution of otobain (90 mg.) in acetic acid (2.5 ml.), warmed on the steam bath for 1 min., allowed to stand at room temperature for a further 30 min., and diluted with water. Crystallization of the precipitate twice from chloroform–methanol gave dinitrootobain as pale yellow felted needles, m.p. 234–236° dec., $[\alpha]_D$ −170° (*c* 2.45).

Anal. Calcd. for $C_{20}H_{18}O_8N_2$: C, 57.97; H, 4.38; N, 6.76; 2-CMe, 7.26. Found: C, 58.12; H, 4.60; N, 6.62; —CMe, 6.56. λ 3.43, 3.50, 6.19, 6.60, 6.75, 6.89, 7.08, 7.30, 7.53, 7.72, 7.9–8.35 (broad), 8.71, 9.08, 9.44, 9.70, 10.70, 11.50 μ.

Otobain Biscarbonate.—Phosphorus pentachloride (5 g.) was added to a solution of otobain (1.0 g.) in dry toluene (10 ml.). The solution turned orange and hydrogen chloride was immediately liberated. The mixture was heated under reflux for 4 hr., during which the color faded to yellow, concentrated to *ca.* 5-ml. volume, cooled, and aqueous sodium carbonate solution added until effervescence ceased. It was extracted with ether, the extract washed with water, dried (sodium sulfate), and the solvent removed to give a yellow gum which solidified on trituration with methanol. Three recrystallizations of this solid (504 mg., m.p. 169–172°) from chloroform–methanol yielded 5,6-carbonyldioxy-2,3-dimethyl-4-(3′,4′-carbonyldioxyphenyl)-1,2,-3,4-tetrahydronaphthalene[26] as dense prisms, m.p. 178–180°, $[\alpha]_D$ −19° (*c* 2.1).

Anal. Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.17; H, 4.74. λ 3.52, 5.47, 6.12, 6.73, 6.93, 7.44, 7.62, 7.78, 7.9–8.4 (broad), 8.60, 8.78, 9.13, 9.30, 9.71, 10.08, 10.42, 10.55, 10.83, 11.55 μ.

Dehydrogenation of Otobain.—A solution of otobain (932 mg.) in diethylene glycol (25 ml.) was heated under reflux with palladium on carbon (10%, 462 mg.) for 2 hr., filtered, diluted with water, and the resultant precipitate crystallized from methanol to give a solid (470 mg.), m.p. 111–114°, $[\alpha]_D$ −29° (suggesting 75% unchanged otobain). This was dissolved in petroleum ether (b.p. 30–60°, 60 ml.) and chromatographed on alumina (Merck, acid washed). Elution with light petroleum (480 mg.), and light petroleum–benzene (3:1, 130 ml.) gave no residue. The same eluent mixture (390 ml.) gave a semisolid (340 mg.), yielding crude otobain (m.p. 125–127°) on crystallization from chloroform–methanol, and the following 260 ml. eluted a solid (73 mg.) which on two recrystallizations from chloroform–methanol gave dehydrootobain [2,3-dimethyl-3′,4′,7,8-bismethylenedioxy-1-phenylnaphthalene (VII)] as spiky needles, m.p. 185–187°, $[\alpha]_D$ ±0° (*c* 2.0).

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.64; H, 5.17. λ 352 (ε 3800), 311 (7800), 297 (9200), 243 (52,000), 220 mμ (43,500). λ 3.45. 3.58, 6.07, 6.22, 6.35, 6.64 (sh), 6.71, 6.87 (sh), 6.95, 7.32, 7.55, 7.78, 7.9–8.4 (broad), 8.80, 8.98, 9.13, 9.29, 9.65, 10.22, 10.7 (broad), 11.42 μ.

Acid Rearrangement and Dehydrogenation of Galbacin (IV).—Perchloric acid (70–72%, 0.5 ml.) added to a solution of galbacin (600 mg.) in acetic acid (20 ml.) caused an immediate pink → yellow color change. The mixture, after standing at room temperature for 3 days, was poured into 50% aqueous sodium

(24) C. G. Smith, W. L. Lummis, and J. E. Grady, *Cancer Res.*, **19**, 843 (1959).

(25) Melting points were determined on a Gallenkamp melting point apparatus. Specific rotations and infrared spectra were determined in chloroform solution. Ultraviolet absorption spectra were determined in ethanol solution.

(26) In systematic nomenclature, numbering is based on nayhthalene and consequently differs from lignan numbering.

hydroxide solution (40 ml.), and extracted with chloroform. Removal of the chloroform gave a residual gum which was heated under reflux in diethyleneglycol (20 ml.) for 1 hr. The mixture was filtered, the filter washed with methanol, and the combined filtrate diluted with water, extracted with ether, and worked up in the usual way. The product was dissolved in light petroleum–benzene (3:1) and chromatographed on alumina (Merck, acid-washed). Elution with the same solvents (300 ml.) gave an oil (9 mg.) followed by a solid (160 mg.), eluted with the next 600 ml. solvent. Recrystallization of this product from chloroform–methanol gave 2,3-dimethyl-3′,4′,6,7-bismethylenedioxy-1-phenylnaphthalene [dehydroepigalbacin (V)] as prisms, m.p. 171–172°.

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03; O, 19.98. Found: C, 75.40; H, 5.04; O, 19.63. λ 332 (ε 4900), 325 (2800), 318 (3300), 292 (10,200), 284 (9900), 234 mμ (48,500). λ 3.45, 3.58, 6.20, 6.65, 6.71, 6.85, 7.37, 7.50, 8.1–8.4 (broad), 8.59, 8.90, 9.09, 9.68, 10.5–10.8 (broad), 11.34 μ.

Nuclear Magnetic Resonance Spectra.—All samples were run in deuteriochloroform solution with tetramethylsilane added as an internal reference. The peak positions are relative to this standard and were obtained directly from a Varian A-60 spectrometer. The spectra reproduced in Fig. 1–5 were obtained, however, from Varian HR-60 and HR-100 spectrometers. The chemical shifts were measured in the following manner. For sharp lines, the shifts are rounded off to the nearest c.p.s. and converted to p.p.m. In the case of multiplets, the centers of the appropriate multiplets were located within a c.p.s. and also converted to p.p.m. When higher order perturbation was evident in the intensity distribution of a multiplet, the center of gravity was estimated to the nearest c.p.s. and converted to p.p.m.

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Chemistry of Carbon Diselenide. I. Reactions with Primary Amines[1]

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Carbon diselenide has been treated with primary amines to give good yields of seleno-2-benzimidazolinone, seleno-2-benzoxazolinone, seleno-2-benzothiazolinone, seleno-2-imidazolidinone, selenotetrahydro-2(1*H*)-pyrimidinone, and several substituted selenoureas. The diselenocarbamate salts and isoselenocyanates appear to be intermediates in the reaction.

Carbon diselenide has been prepared by the reaction of hydrogen selenide with carbon tetrachloride[2,3] and, more satisfactorily, by the reaction of selenium with methylene chloride.[4] In many respects carbon diselenide behaves like carbon disulfide. It reacts with alcohols to form diselenocarbonates,[2,3] with secondary alkyl amines to form diselenocarbamates,[5] and with chlorine to form perchloromethylselenol.[4] However, carbon diselenide differs from carbon disulfide in that it polymerizes readily,[3,5] especially in the presence of ammonia or amines. This polymerizability, along with the disagreeable odor frequently obtained when working with selenium compounds, apparently has discouraged a more complete study of the chemistry of carbon diselenide. However, with the potential commercialization of carbon diselenide in mind, we have undertaken such a study. In our initial work, we have found that carbon diselenide can react smoothly with primary amines to form the expected products. Most of the products reported are new compounds.

Barnard and Woodbridge[5] studied the reaction of carbon diselenide with secondary amines, and found that it was essential to avoid a localized excess of the diselenide in order to prevent polymer formation. By the slow addition of a 10% solution of carbon diselenide in dioxane to an alkaline solution of the secondary amine at −10°, they obtained high yields of dialkyldiselenocarbamates. The only work previously reported on reactions of carbon diselenide with primary amines is that of Grimm and Metzger[3] who prepared 1,3-diphenylselenourea in low yield by the addition of a dilute solution of carbon diselenide to an excess of aniline.

We have treated carbon diselenide with aniline in refluxing carbon tetrachloride and obtained 1,3-diphenylselenourea in essentially quantitative yield. The reaction of carbon diselenide with the dibasic *o*-phenylenediamine gave the cyclic selenourea, namely, seleno-2-benzimidazolinone.[6] Reactions with *o*-aminophenol and *o*-aminothiophenol gave the cyclic products, seleno-2-benzoxazolinone and seleno-2-benzothiazolinone, respectively. The primary aliphatic amines, benzylamine, ethylamine, *n*-butylamine, ethylenediamine, and 1,3-diaminopropane also gave analogous products in good yield.

Polymer formation was eliminated by maintaining extremely low concentrations of carbon diselenide in most cases. This was done by slowly adding a dilute solution of carbon diselenide to the vigorously stirred amine solution held usually at about 80° to ensure immediate reaction of the added carbon diselenide. Such precautions were not necessary in reactions with *o*-aminophenol and *o*-aminothiophenol, because these amines were not basic enough to promote polymerization of the carbon diselenide.

The reaction of carbon diselenide with a primary amine apparently proceeds in a manner similar to that of carbon disulfide.[7] Thus, the amine salt of the diselenocarbamate forms first, and, upon heating, decomposes with the evolution of hydrogen selenide and the formation of the isoselenocyanate and amine. The isoselenocyanate then reacts with the amine to form a selenourea.

(1) This work was supported by a research contract with The Selenium and Tellurium Development Committee.

(2) B. Rathke, *Ann.*, **152**, 181 (1869).

(3) H. G. Grimm and H. Metzger, *Ber.*, **69B**, 1356 (1936).

(4) D. J. G. Ives, R. W. Pittman, and W. Wardlaw, *J. Chem. Soc.*, 1080 (1947).

(5) D. Barnard and D. T. Woodbridge, *ibid.*, 2022 (1961).

(6) Infrared spectra and n.m.r. spectra were obtained in an attempt to establish the keto–enol equilibria of the products. However, several reference compounds must be studied before a sound interpretation of the spectra can be made. This work, coupled with alkylation studies, is in progress and will be reported later.

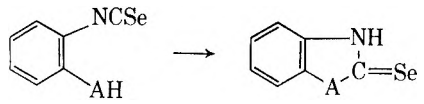
(7) D. C. Schroeder, *Chem. Rev.*, **55**, 189 (1955).

$$2RNH_2 + CSe_2 \rightleftharpoons RNHC(=Se)\overset{\ominus\ \oplus}{S}NH_3R \quad (1)$$

$$RNHC(=Se)\overset{\ominus\ \oplus}{S}NH_3R \longrightarrow RNCSe + RNH_2 + H_2Se \quad (2)$$

$$RNCSe + RNH_2 \longrightarrow RNHC(=Se)NHR \quad (3)$$

When the primary amine is *o*-phenylenediamine, *o*-aminophenol or *o*-aminothiophenol, the isoselenocyanate intermediate cyclizes intramolecularly through the adjacent amino, hydroxyl, or sulfhydryl group.



A = NH, O, or S

Evidence in support of the previous sequence was obtained by the preparation of a mixed selenourea using an amine in step 3 that was different from that used in step 1. The diselenocarbamate salt formed from benzylamine at room temperature was treated with a large excess of diethylamine and refluxed overnight. A nearly quantitative yield of 1,1-diethyl-3-benzylselenourea resulted.

In all cases good yields of product were obtained if the reactions were stopped as soon as hydrogen selenide evolution subsided. The over-all rate-determining step, therefore, appears to be either step 1 or step 2. When an aliphatic amine was used, there was no polymer formation even at room temperature; however, prolonged heating was necessary to complete the evolution of hydrogen selenide. Therefore, with aliphatic amines step 1 is rapid (no carbon diselenide accumulates to undergo polymerization) and step 2 must be the rate-determining step. With aromatic amines, such as aniline or *o*-phenylenediamine step 1 was much slower (heating was necessary to prevent polymer formation), and step 2 was much faster (hydrogen selenide evolution subsided in less than an hour after the last carbon diselenide was added).

The diselenocarbamate salt intermediates were found to be extremely susceptible to air oxidation which resulted in the formation of red or black elemental selenium. All reaction mixtures were protected from air by nitrogen until hydrogen selenide evolution was completed.

The selenoureas and related products obtained are given in Table I. They are colorless, crystalline, and practically odorless solids which melt with decomposition in the presence of air. They have been stored in closed containers at 0° for several months with no apparent decomposition. In the presence of air at room temperature or in solvents containing dissolved oxygen, they gradually darken, presumably from the formation of elemental selenium. The 1,3-diethylselenourea is particularly sensitive to air. Work on the isolation of oxidation products is in progress.

TABLE I

REACTIONS OF CARBON DISELENIDE WITH PRIMARY AMINES

Product	Reactant	Moles of reactant[a]	Reflux time, hr.	Yield, %	M.p., °C.[b]	Formula	C, % Caled.	C, % Found	H, % Caled.	H, % Found	N, % Caled.	N, % Found	Se, % Caled.	Se, % Found[n]
1,3-Diphenylselenourea	Aniline	0.05	1.5[c,d]	98	190–192 dec.[j,k]	$C_{13}H_{12}N_2Se$	...	...	...	...	...	...	...	...
1,3-Dibenzylselenourea	Benzylamine	.05	5[e,f]	93	182–183[k]	$C_{15}H_{16}N_2Se$	59.4	59.4	5.3	5.3	9.2	9.4	26.1	25.6
1,3-Diethylselenourea	Ethylamine	.10	21[e,f,g]	73	94–95[l]	$C_5H_{12}N_2Se$	33.5	33.6	6.7	6.6	15.6	15.7	44.2	44.0
1,3-Di-*n*-butylselenourea	*n*-Butylamine	.05	21[e,f]	67	73–74.5[l]	$C_9H_{20}N_2Se$	45.9	46.0	8.5	8.5	11.9	12.0	33.7	33.6
Selenotetrahydro-2(1*H*)-pyrimidinone	1,3-Diaminopropane	.01	21[f,h]	66	224–226 dec.[k]	$C_4H_8N_2Se$	29.4	29.6	4.9	5.0	17.2	17.1	48.5	48.4
Seleno-2-imidazolidinone	Ethylenediamine	.01	21[f,h]	79	234–236 dec.[k]	$C_3H_6N_2Se$	24.2	24.2	4.0	3.8	18.8	19.0	53.0	53.3
Seleno-2-benzimidazolinone	*o*-Phenylenediamine	.005	2[e,g]	85	234–236 dec.[k]	$C_7H_6N_2Se$	42.7	42.4	3.0	3.2	14.2	14.2	40.1	40.3
Seleno-2-benzoxazolinone	*o*-Aminophenol	.004	16[e,i]	78	201–203 dec.[l]	C_7H_5NOSe	42.4	42.5	2.5	2.6	7.1	7.0	39.9	40.1
Seleno-2-benzothiazolinone	*o*-Aminothiophenol	.004	24[e,i]	62	173–174[l]	C_7H_5NSSe	39.3	39.4	2.3	2.7	6.5	6.7	36.9	37.0
1,1-Diethyl-3-benzylselenourea	Benzylamine + diethylamine	.015 + .50	16[e]	96	93–94[m]	$C_{12}H_{18}N_2Se$	53.5	53.3	6.7	6.8	10.4	10.4	29.4	29.4

[a] The amount of carbon diselenide used was 0.005 mole in each case. [b] All melting points are uncorrected. [c] Includes 1-hr. addition time under reflux. [d] The solvent was CCl_4. [e] The solvent was benzene. [f] Includes 1-hr. addition time at room temperature. [g] Some of the ethylammonium N-ethyldiselenocarbamate intermediate sublimed into the reflux condenser and formed colorless needles; they were water soluble and turned red and black very rapidly when exposed to air. [h] The solvent was ethanol. [i] The carbon diselenide was added all at once. [j] C. Hasan and R. F. Hunter, *J. Chem. Soc.*, 1762 (1935), m.p. 192–194°. [k] Recrystallized from ethanol. [l] Recrystallized from benzene. [m] Recrystallized from a benzene–hexane mixture. [n] Selenium was determined by peroxide decomposition in a Parr bomb followed by reduction with hydroxylamine hydrochloride and 8 *N* HCl saturated with SO_2. Sample quantities sufficient to give 50–100 mg. of elemental selenium were used.

Experimental

The carbon diselenide used initially in this work was prepared in this laboratory by the method of Ives, *et al.*[4] Subsequently, experimental quantities of carbon diselenide were obtained from Noranda Research Centre, Pointe Claire, Quebec.

It has been our experience that redistilled carbon diselenide has an odor very similar to that of carbon disulfide. However, when carbon diselenide vaporizes and becomes mixed with air, extremely repulsive stenches are gradually formed. Many of the reaction residues gave foul odors that were rather persistent. By using an effective hood and working with rather small quantities of materials, as well as using a charcoal trap, Dry Ice trap, or a potassium hydroxide decontamination bath whenever it seemed advisable, pleasant working conditions were maintained.

It should be noted that some of the volatile selenium compounds produced may be extremely toxic as well as foul. For example, hydrogen selenide, a by-product of the reactions described, is about as toxic as hydrogen cyanide. An effective hood, therefore, is essential from a safety standpoint and a trap containing caustic solution is advisable, especially when larger quantities are involved.

1,3-Diphenylselenourea.—A solution of 0.32 ml. (0.005 mole) of carbon diselenide in 100 ml. of carbon tetrachloride was added dropwise over a 1-hr. period with stirring to a refluxing solution of 4.6 ml. (0.05 mole) of aniline in 50 ml. of carbon tetrachloride. The refluxing was continued 30 min. longer, whereupon hydrogen selenide evolution could no longer be detected by moistened lead acetate paper. A stream of nitrogen was passed through the reaction mixture during the entire period. At the end of the reflux period, the mixture was cooled and filtered to give 1.36 g. (98%) of 1,3-diphenylselenourea, m.p. 190–192° dec. The product was colored pale gray from a trace of elemental selenium. Recrystallization from ethanol, using a stream of nitrogen to displace air, gave a colorless product with no increase in melting point.

Modifications of the above procedure for the preparation of other products are given in Table I. Small amounts of black elemental selenium were sometimes removed by filtering the hot reaction mixtures. In some cases the solutions were concentrated on a rotating evaporator and taken up in the recrystallization solvent in order to obtain crystalline products.

Seleno-2-benzoxazolinone.—A mixture of 0.32 ml. (0.005 mole) of carbon diselenide and 0.44 g. (0.004 mole) of *o*-aminophenol in 100 ml. of benzene was refluxed with stirring under nitrogen for 16 hr. The mixture was filtered while hot to remove a small amount of insoluble impurities. The filtrate upon cooling yielded 0.48 g. of nearly colorless needles, m.p. 198–200° dec. Concentration of the mother liquors to 25 ml. yielded an additional 0.14 g., m.p. 194–196° dec. The total yield was 78%. Recrystallization of the product from benzene gave colorless needles, m.p. 201–203° dec.

Seleno-2-benzothiazolinone was prepared similarly.

1,1-Diethyl-3-benzylselenourea.—A solution of 0.32 ml. (0.005 mole) of carbon diselenide in 50 ml. of benzene was added dropwise over a 20-min. period with stirring to 1.6 ml. (0.015 mole) of benzylamine in 100 ml. of benzene at room temperature under nitrogen. A solution of 51.5 ml. (0.50 mole) of diethylamine in 100 ml. of benzene was then added over a 15-min. period with stirring at room temperature. After the addition was complete, the mixture was refluxed for 16 hr. The resulting dark brown mixture was concentrated to a sirup, redissolved in 100 ml. of benzene, and filtered to remove a small amount of black precipitate. The clear yellow filtrate was washed with 60 ml. of 0.2 *N* hydrochloric acid followed by three washings with 50 ml. of distilled water. The benzene layer was dried over anhydrous magnesium sulfate, concentrated to a sirup, and cooled. Filtration followed by washing with a benzene–pentane mixture gave 1.15 g. of 1,1-diethyl-3-benzylselenourea as pale yellow needles, m.p. 62–67°. A second crop of 0.15 g., m.p. 65–68°, was obtained by the addition of pentane to the mother liquor. The total yield was 96%. Recrystallization of the first crop from a benzene–hexane mixture gave 0.91 g., fine colorless needles, m.p. 93–94°, that was used as an analytical sample.

The Claisen Rearrangement of Allyl Ethers of α-Hydroxybenzalacetophenones[1]

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The allyl ethers of several phenylbenzylglyoxals have been prepared and rearranged to the corresponding C-allyl glyoxals. The electron-donating CH_3O– group in the *o*- and *p*-position of the benzyl nucleus promotes the rearrangement, whereas the similarly placed electron-withdrawing NO_2– group retards the rearrangement.

The Claisen rearrangement has been shown to be intramolecular,[3–6] and the kinetics of the reaction have been established as first order.[7] Studies of a series of *p*-X-phenyl ethers[8] and *p*-X-cinnamyl phenyl ethers[9] indicate that both the aryloxy and allyl groups assume partial radical character in the transition state.

While the allyl ethers of the enolic modification of β-diketones have been subjected to the Claisen rearrangement, those of the α-diketones have not. Since the allyl ethers of the α-diketones possess the structural requirements necessary for this rearrangement, one might expect them to rearrange.

In order to test this hypothesis, the chalcones (I–VII) were prepared by condensing the appropriate aldehyde and acetophenone. The chalcones were converted to the corresponding oxides (VIII–XIV). Oxide (VIII) was converted to the glyoxal (XV) by way of the chlorohydrin; oxides (IX–XIV) were isomerized with alkali to the diketones (XVI–XXI). These glyoxals in turn were treated in acetone solution in the presence of potassium carbonate with allyl bromide, yielding the allyl ethers (XXII–XXVIII), which were subjected to the conditions of rearrangement (p. 1645).

The ethers were refluxed in N,N-dimethylaniline in an atmosphere of nitrogen for twenty-four hours. The extent to which rearrangement occurred is

XXII	⟶	XXIX	18%
XXIII	⟶	XXX	20
XXIV	⟶	XXXI	75
XXV	⟶	XXXII	80
XXVI	⟶	XXXIII	0
XXVII	⟶	XXXIV	0
XXVIII	⟶	XXXV	60

(1) This work was supported by a grant from Research Corporation of New York.

(2) In partial fulfillment of the requirements for the Ph.D. degree.

(3) C. Hurd and L. Schmerling, *J. Am. Chem. Soc.*, **59**, 107 (1937).

(4) A. S. Semenow and J. D. Roberts, *J. Chem. Educ.*, **33**, 2 (1956).

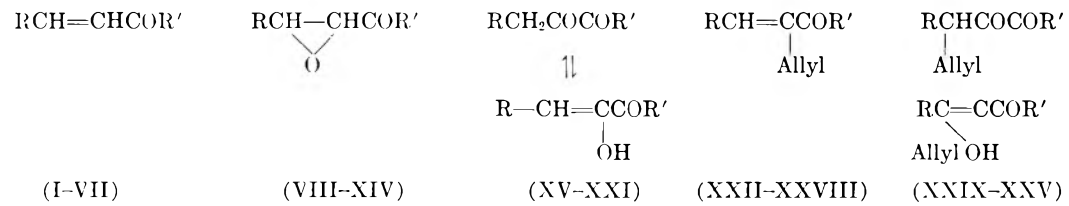
(5) J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.*, **74**, 5366 (1952).

(6) Y. Docker, *Proc. Chem. Soc.*, 141 (1961).

(7) J. Kincaid and D. Tarbell, *J. Am. Chem. Soc.*, **61**, 3085 (1939).

(8) H. Goering and R. Jacobson, *ibid.*, **80**, 3277 (1958).

(9)(a) W. Fife and W. White, 138th National Meeting of American Chemical Society, New York, N. Y., September, 1960, Abstracts of Papers, p. 86; (b) W. White, *et al.*, *J. Org. Chem.*, **26**, 627 (1961).



I, VIII, XV, XXII, XXIX, R = C_6H_5; R' = C_6H_5
II, IX, XVI, XXIII, XXX, R = C_6H_5; R' = Mes
III, X, XVII, XXIV, XXXI, R = o-$CH_3OC_6H_4$; R' = Mes
IV, XI, XVIII, XXV, XXXII, R = p-$CH_3OC_6H_4$; R' = Mes
V, XII, XIX, XXVI, XXXIII, R = o-$NO_2C_6H_4$; R' = Mes
VI, XIII, XX, XXVII, XXXIV, R = p-$NO_2C_6H_4$; R' = Mes
VII, XIV, XXI, XXVIII, XXXV, R = Mes; R' = C_6H_5

When N,N-diethylaniline was substituted for N,N-dimethylaniline, ethers XXVI and XXVII rearranged to XXXIII and XXXIV to the extent of 5% and 6%, respectively.

These results indicate that rearrangement is facilitated by the electron donating methoxyl group and retarded by the electron withdrawing nitro group, and that temperature is a factor.

Experimental

Preparation of the Chalcones. I,[10] II,[11] III,[12] IV,[13] V, VI, and VII.[14]—Chalcones V and VI were prepared in the conventional manner by adding slowly a solution of 2.0 g. of sodium hydroxide in 6 cc. of water to a stirred alcoholic solution of 7.5 g. of the nitrobenzaldehyde and 8.0 g. of acetomesitylene. After standing overnight, the mixture was stirred, chilled, filtered, washed with water until free of alkali, dried, and recrystallized from alcohol.

The yellow *o*-nitrochalcone melted at 93°; the yellow *p*-isomer melted at 116–117°.

Anal. Calcd. for $C_{18}H_{17}O_3N$ (V): C, 73.3; H, 5.8. Found: C, 73.1; H, 5.8.

Anal. Calcd. for $C_{18}H_{17}O_3N$ (VI): C, 73.3; H, 5.8. Found: C, 73.2; H, 5.9

Preparation of the Oxides. VIII,[15] IX,[11] X,[12] XI,[13] XII, XIII, and XIV.[14]—Oxides XII and XIII were prepared according to the method of Barnes and Lucas,[12] and recrystallized from methanol. The *o*-nitro compound melted at 115°; the *p*-isomer melted at 118°.

Anal. Calcd. for $C_{18}H_{17}O_4N$ (XII): C, 69.5; H, 5.5. Found: C, 69.8; H, 5.8.

Anal. Calcd. for $C_{18}H_{17}O_4N$ (XII): C, 69.5; H, 5.5. Found: C, 69.8; H, 5.8.

Preparation of the Glyoxals. XV,[16] XVI,[11] XVII,[12] XVIII,[13] XIX, XX, and XXI.[14]—Glyoxals XIX and XX were prepared according to Barnes.[11] The resulting yellow crystalline solids produced a red color with alcoholic ferric chloride. The *o*-nitro compound melted at 120°; the *p*-isomer melted at 122°. The *o*-nitro isomer was 80% enolic according the modified Kurt H. Meyer method[17]; the *p*-isomer was 99% enolic.

Anal. Calcd. for $C_{18}H_{17}O_4N$ (XIX): C, 69.5; H, 5.5. Found: C, 69.8; H, 5.8.

Anal. Calcd. for $C_{18}H_{17}O_4N$ (XX): C, 69.5; H, 5.5. Found: C, 69.4; H, 5.2.

Preparation of the Allyl Ethers of the Glyoxals. XXII, XXIII,[11] XXIV, XXV, XXVI, XXVII, and XXVIII.—All of the allyl ethers were prepared according to Barnes.[11] After refluxing the glyoxal and allyl bromide in acetone solution with anhydrous potassium carbonate, the inorganic salts were removed by filtration and the acetone by distillation. The residue was dissolved in ether and extracted with Claisen's alkali in order to remove any unchanged glyoxal. The ethereal solution was dried over anhydrous sodium sulfate, filtered, and distilled. The residual oil was crystallized from methanol where possible. (See Table I.)

TABLE I

Allyl ether	M.p., °C.	Reaction with Alc. $FeCl_3$	Analysis
XXII	Yellow oil	Negative	$C_{18}H_{16}O_2$ Calcd.: C, 81.8; H, 6.1
			Found: C, 81.5; H, 6.6
XXIV	103–104	Negative	$C_{22}H_{24}O_3$ Calcd.: C, 78.6; H, 7.1
			Found: C, 78.8; H, 7.3
XXV	73–74	Negative	$C_{22}H_{24}O_3$ Calcd.: C, 78.6; H, 7.1
			Found: C, 78.8; H, 7.2
XXVI	80–81	Negative	$C_{21}H_{21}O_4$ Calcd.: C, 71.8; H, 6.0
			Found: C, 71.9; H, 5.7
XXVI	119	Negative	$C_{21}H_{24}O_4N$ Calcd.: C, 71.8; H, 6.0
			Found: C, 72.0; H, 5.7
XXVIII	Light yellow	Negative	$C_{21}H_{22}O_2$ Calcd.: C, 82.3; H, 7.2
			Found: C, 82.9; H, 7.3

Rearrangement of the Allyl Ethers. XXII–XXVIII to the α-Allylglyoxals XXIX–XXXV.—A solution of 2.0 g. of the allyl ether in 20 cc. of N,N-dimethylaniline was refluxed in an atmosphere of nitrogen for 20 hr. The dimethylaniline was vacuum distilled under a stream of nitrogen, and the residue was dissolved in benzene. The benzene solution was extracted with Claisen's alkali. The alkaline extract was neutralized with dilute hydrochloric acid and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate, filtered, and the ether removed by distillation. The residue was crystallized from methanol where possible.

Recovery of the unchanged ether was effected in good yield from the benzene solution which had been extracted with Claisen's alkali. The benzene was distilled and the residue was crystallized where possible. When the recovered allyl ether could not be crystallized, it was hydrolyzed to the glyoxal by refluxing with dilute hydrochloric acid and alcohol.

In the case of ethers XXVI and XXVII where no rearrangement occurred, recovery was effected to the extent of more than 90%. When N,N-diethylaniline was substituted for N,N-dimethylaniline, ethers XXVI and XXVII rearranged to the extent of 5% and 6%, respectively, and recovery of unchanged ether was effected to about 90%. (See Table II.)

TABLE II

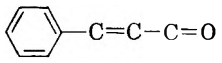
α-Allylglyoxal	M.p., °C.	% Conversion	Reaction with Alc. $FeCl_3$	Analysis
XXIX	Oil	18	Red	$C_{18}H_{16}O_2$ Calcd.: C, 81.8; H, 6.1
				Found: C, 81.5; H, 6.6
XXX	109	20	Red	$C_{21}H_{22}O_2$ Calcd.: C, 82.3; H, 7.2
				Found: C, 82.9; H, 7.4
XXXI	Oil	75	Red	$C_{22}H_{24}O_3$ Calcd.: C, 78.6; H, 7.1
				Found: C, 78.8; H, 7.3
XXXII	113–114	80	Red	$C_{22}H_{24}O_3$ Calcd.: C, 78.6; H, 7.1
				Found: C, 78.8; H, 7.2
XXXIII	Oil	5		$C_{21}H_{24}O_4N$ Calcd.: C, 71.8; H, 6.0
				Found: C, 72.0; H, 5.7
XXXIV	Oil	6		$C_{21}H_{21}O_4N$ Calcd.: C, 71.8; H, 6.0
				Found: C, 72.0; H, 5.7
XXXV	Oil	60	Red	$C_{21}H_{22}O_2$ Calcd.: C, 82.3; H, 7.2
				Found: C, 82.9; H, 7.3

Spectroscopic Analysis.—Infrared absorption measurements were made using a Perkin-Elmer infrared spectrophotometer, Model 21. The solvent used was carbon tetrachloride.

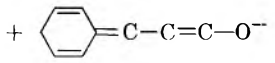
(10) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 78.
(11) R. P. Barnes, *J. Am. Chem. Soc.*, **57**, 937 (1935).
(12) R. P. Barnes and W. M. Lucas, *ibid.*, **64**, 2260 (1942).
(13) R. P. Barnes and H. Delaney, *ibid.*, **65**, 2155 (1943).
(14) R. P. Barnes and R. J. Brown, *ibid.*, **65**, 412 (1943).
(15) E. Weitz and A. Scheffer, *Ber.*, **54**, 2344 (1921).
(16) E. P. Kohler and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 211 (1934).
(17) S. R. Cooper and R. P. Barnes, *Ind. Eng. Chem., Anal. Ed.*, **10**, 379 (1938).

Bands were found at 3.425 and 6.00 μ for the chalcones which are regions of C—H and conjugated carbonyl absorptions, respectively. The enols absorbed at 2.95, 3.425, and 6.00 μ. The diketone (XXI)[11] which is 100% ketonic, adsorbed at 3.425, 5.85, and 5.95 μ. There was no band at 2.95 μ. These observations are in agreement with the findings of Barnes and Pinkney.[18] When the enols were converted to the allyl ethers, the band at 2.95 μ disappeared in each case. Upon equilibration of the enols with deuterium oxide, the band at 2.95 μ disappeared. This observation justified the assignment of this band to O—H stretching frequency.

Ferguson and Barnes[19] studied the ultraviolet spectra of some 1,3-diketones and related intermediates. They observed that the main chromophoric system in the chalcones is



probably due to the resonating form



They concluded that groups such as alkoxyl which readily accept a positive charge, will have a bathochromic effect while negative groups such as NO_2 will have the opposite effect.

Spectra in the ultraviolet region were obtained using the Beckman Model DU spectrophotometer with 95% ethanol as the solvent. The effects observed by Barnes and Ferguson[19] were also observed in the following cases with the exception of the *p*-nitrobenzalacetomesitylene (VI) and the α-hydroxy-*p*-nitrobenzalacetomesitylene (XX). Complete agreement with the observation was obtained in the allyl ethers of the enols. The completely ketonic glyoxal (XXI) absorbs at 255 mμ. (See Table III.)

TABLE III

WAVE LENGTH OF THE MAXIMUM ABSORPTION BANDS

		λ_{max}, (mμ)
I.	$C_6H_5CH{=}CHCOC_6H_5$	305 (313)[a]
II.	$C_6H_5CH{=}CHCO$ Mes	292
III.	*o*-$CH_3OC_6H_4CH{=}CHCO$ Mes	335
V.	*o*-$O_2NC_6H_4CH{=}CHCO$ Mes	250 (252)[b]
VI.	*p*-$O_2NC_6H_4CH{=}CHCO$ Mes	305
XVI.	$C_6H_5CH{=}C(OH)CO$ Mes	318
XVII.	*o*-$CH_3OC_6H_4CH{=}C(OH)CO$ Mes	345
XIX.	*o*-$O_2NC_6H_4CH{=}C(OH)CO$ Mes	295
XX.	*p*-$O_2NC_6H_4CH{=}C(OH)CO$ Mes	345
XXI.	Mes $CH_2COCOC_6H_5$	255
XXIV.	*o*-$CH_3OC_6H_4CH{=}C(O\text{-Allyl})CO$ Mes	335
XXVI.	*o*-$O_2NC_6H_4CH{=}C(O\text{-Allyl})CO$ Mes	265
XXVII.	*p*-$O_2NC_6H_4CH{=}C(O\text{-Allyl})CO$ Mes	275

[a] See ref. 20. [b] See ref. 19.

(18) R. P. Barnes and G. E. Pinkney, *J. Am. Chem. Soc.*, **75**, 479 (1953).
(19) L. N. Ferguson and R. P. Barnes, *ibid.*, **70**, 3907 (1948).
(20) (a) D. Radulescu, *Ber.*, **64**, 2243 (1931); (b) A. Russell, J. Todd, and C. L. Wilson, *J. Chem. Soc.*, 1940 (1934); (c) V. Alexa, *Bull. Chim. Soc. Chim. Romania*, [2] **1**, 77 (1939).

Structures of Substituted Fulvenes. The Reaction Products from Acetone and Dimethylfulvene

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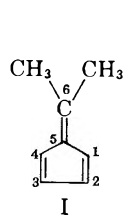
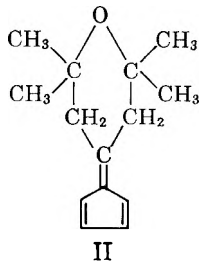
Acetone has been shown to substitute on to the ring carbons of 6,6-dimethylfulvene rather than the side-chain carbons. The structures of the mono-, di-, tri-, and tetrasubstituted 6,6-dimethylfulvenes are discussed. The presence of methanol in the reaction medium leads to the formation of ethers.

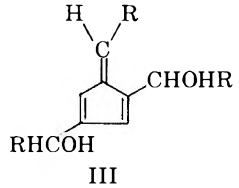
In 1906, Thiele[1] reported that, in addition to the production of 6,6-dimethylfulvene (I), the reaction of acetone and cyclopentadiene in a basic methanolic solution led to the formation of an ether whose analysis corresponded closely to that of $C_{14}H_{20}O$. A compound of very similar properties could be obtained after some purification from acetone and 6,6-dimethylfulvene in a basic alcoholic solution. The analysis, the typical fulvene physical properties of color and oxygen uptake, and the fact that the ether appeared to be composed of one cyclopentadiene and three acetone moieties led Thiele to postulate II for the structure of the ether. Courtot[2] speculated that compounds of structure III were possible when aldehydes (RCHO) reacted with cyclopentadiene under basic conditions. Ziegler[3] therefore considered II, IV, and V as possible structures for Thiele's ether and showed that the reaction product,



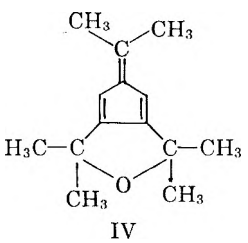
I



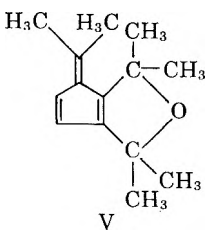
II



III



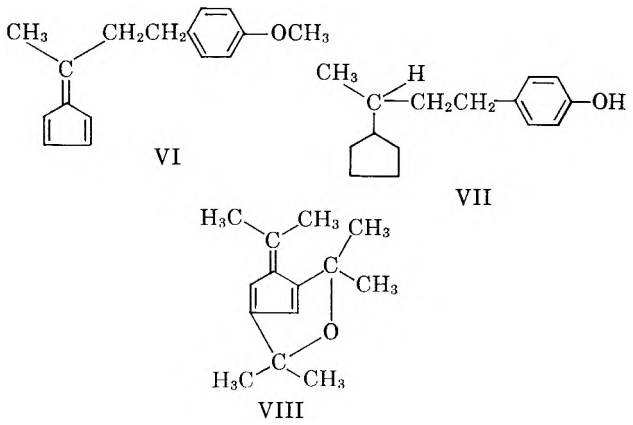
IV



V

(1) J. Thiele and H. Balhorn, *Ann.*, **348**, 1 (1906).
(2) C. Courtot, *Ann. Chim.* (Paris) **4**, 168 (1915).
(3) K. Ziegler and F. Crossman, *Ann.*, **511**, 89 (1934).

VI, of β-*p*-anisylethyl methyl ketone and cyclopentadiene under basic conditions gave, after hydrogenation and cleavage, the phenol, VII, a compound which was quite different from the hydrogenated phenolic derivative of 6,6-dimethylfulvene and *p*-anisaldehyde. Therefore, the anisaldehyde skeleton had to be attached to a ring and not a side-chain carbon.



VI VII VIII

For this reason, structure II was considered unlikely, and emphasis was placed on structures IV and V as the permissible alternatives. More recently, Bergmann[4] has considered VIII as a possible structure for Thiele's ether.

In connection with other work in these laboratories, it was decided to elucidate further the structure of the more highly substituted products of 6,6-dimethylfulvene.

Discussion and Theory

Preliminary experiments showed that two compounds similar to Thiele's ether could be isolated from the reaction products when 6,6-dimethylfulvene and acetone reacted in a basic methanolic solution. One compound had the formula $C_{14}H_{20}O$ and will continue to be called Thiele's ether, while the other had $C_{15}H_{22}O$ and is possibly a methyl ether.[5]

Because the solvent apparently entered into one of the reaction products, experiments were run without solvent in order to maximize the yield of Thiele's ether. However, when alcohols were omitted from the reaction media, only hydrocarbon products were isolated. Most of this report concerns the structure of these hydrocarbon products.

Five products were obtained by fractional distillation from the reaction mixture prepared from cyclopentadiene and acetone, with a less than stoichiometric amount of potassium hydroxide catalyst. All five products were hydrocarbons and their analyses indicated that they correspond to the addition and subsequent dehydration of first one, then two, three, four and, finally, five acetone moieties to one cyclopentadiene. When methanol was used as a solvent, the five products mentioned above were formed, in addition to the two products containing oxygen. The individual compounds are described in the following sections.

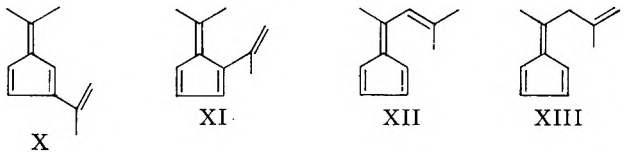
TABLE I

Thiele's product from methanol	Carbon	Hydrogen	Thiele's product from ethanol	Carbon	Hydrogen
Calcd. for $C_{14}H_{20}O$	82.35	9.80	Calcd. for $C_{14}H_{20}O$	82.35	9.80
Calcd. for $C_{15}H_{22}O$	82.51	10.16	Calcd. for $C_{16}H_{24}O$	82.70	10.41
Found	82.87	9.86	Found	82.95	10.18

(4) E. D. Bergmann, J. Cook's "Progress in Organic Chemistry," Vol. 3, Butterworth Scientific Publications, London, 1955, p. 81.

(5) Reexamination of Thiele's limited data showed that his reaction product may also be interpreted as having either the formula $C_{14}H_{20}O$ or $C_{15}H_{22}O$. Similarly, Thiele's product from the basic ethanolic solution may be $C_{16}H_{24}O$, see Table I.

Product $C_{11}H_{14}$(X).—The following four structures were considered for compound $C_{11}H_{14}$, X through XIII, and X was chosen to be the correct structure, based upon the following experiments.



X XI XII XIII

The reaction of cyclopentadiene and diacetone alcohol under basic conditions led to the formation of a mixture of products from which 6,6-dimethylfulvene and compound $C_{11}H_{14}$ could be fractionally distilled. That this compound was really the same product obtained from the acetone reaction was indicated by the similarity of physical constants and the preparation of the same adduct with dimethyl acetylenedicarboxylate. Moreover, since some 6,6-dimethylfulvene was formed, the $C_{11}H_{14}$ compound could not be assigned structures XII or XIII unequivocally because prior dissociation into acetone was probable.

Thiele had shown that the reaction of mesityl oxide and cyclopentadiene under basic conditions produced a typical fulvene color, but no products were isolated. This reaction was repeated and a product was isolated and is designated XII because of its physical constants and method of synthesis. XII is quite different from the $C_{11}H_{14}$ compound from acetone and further suggests that the fulvenes formed from diacetone alcohol under these conditions are the same as those from acetone. On standing, XII formed a new compound with a much higher boiling point, with a molecular weight of 260, but with the same analysis. The molecular weight of XII in refluxing benzene was found to be 230–240. It is probable that a reversible dimerization reaction occurs under these conditions.

When isopropylcyclopentadiene[6] reacted with acetone under basic conditions, a $C_{11}H_{16}$ compound was isolated. This compound must be either dihydro X or dihydro XI. Hydrogenation of the $C_{11}H_{16}$ compound produced a saturated hydrocarbon and a mixture of olefins. This same mixture of olefins was obtained when the $C_{11}H_{14}$ compound obtained from acetone was hydrogenated under similar conditions as determined by physical constants and gas–liquid chromatography (g.l.c.). Therefore, the product obtained from acetone had to be either X or XI.

Nametkin[7] has shown that under similar conditions the hydrogenation of 6,6-dimethylfulvene led to the production of isopropylcyclopentane, isopropylidenecyclopentane, and 1-isopropylcyclopentene. This work was repeated using platinum oxide as catalyst, and quite similar results were obtained. The hydrogenation of X, as stated before, led to the production of a mixture of olefins, of which one made up 75% of the product. However, in one run a diolefin was also pro-

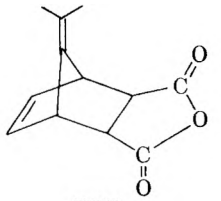
(6) K. Ziegler, H. Gellert, H. Martin, K. Nagel, and J. Schneider, *Ann.*, **589**, 91 (1954).

(7) S. S. Nametkin and M. A. Volodina, *Zh. Obshch. Khim.*, **21**, 331 (1951).

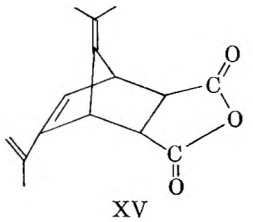
duced. The olefin mixture could not be hydrogenated with Raney nickel at 1000-p.s.i. hydrogen pressure at 100°, but the mixture did readily pick up bromine.

Hydrogenation of XII with a platinum dioxide catalyst gave a mono olefin which was quite different from those obtained from the hydrogenation of X.

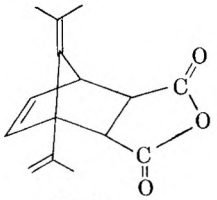
The $C_{11}H_{14}$ compound from acetone reacted with two equivalents of maleic anhydride to give a solid adduct. A consideration of the Diels–Alder reaction of 6,6-dimethylfulvene and maleic anhydride, which leads to the formation of XIV,[8] would indicate that XV and XVI would be the mono adducts from X and XI, respectively. Only XV contains a conjugated system and would be expected to react further to give a double adduct, XVII. Although there may be other structures present, X must be considered as the main constituent of the $C_{11}H_{14}$ fraction.



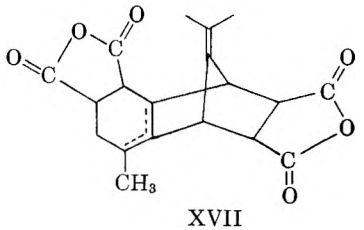
XIV



XV

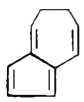


XVI

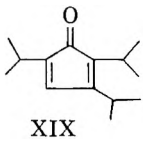


XVII

It was of interest to determine if a compound of type XI could be obtained under these basic conditions of fulvene formation. To this end, an aqueous glutaraldehyde solution was treated with a basic cyclopentadiene mixture. A very small amount of the fulvene XVIII was obtained. This dihydroazulene was readily dehydrogenated with chloranil to give azulene.



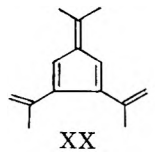
XVIII



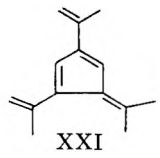
XIX

Product $C_{14}H_{18}$.—The orange liquid, $C_{14}H_{18}$, rapidly picked up oxygen on exposure to air. This crude oxygenated product was hydrogenated on the Paar apparatus to give a bright red liquid, a fulvene ketone, $C_{14}H_{22}O$. Unsubstituted fulvene ketones are not stable because of dimerization reactions,[9] but tri- and tetra-substituted derivatives have been characterized.[10] The fulvene ketone $C_{14}H_{20}O$, in alcohol, would not form a 2,4-dinitrophenylhydrazone, possibly because of steric factors or because of redox reactions.[11] For these reasons, the most likely structure is XIX.

The $C_{14}H_{18}$ compound from acetone was hydrogenated to give a mixture of olefins and dienes. Although the carbon skeleton is indicated by the formation of the hindered fulvene ketone, both XX and XXI are consistent for the structure of the $C_{14}H_{18}$ compound. If Thiele's ether arises from the same sequence of reactions as does the $C_{14}H_{18}$ compound, then structure IV is quite possible for Thiele's ether. Structure VII would be unlikely because of special considerations.

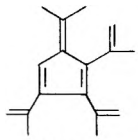


XX

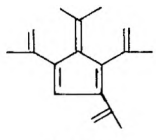


XXI

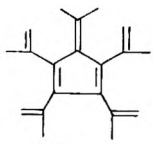
Structure of $C_{17}H_{22}$ and $C_{20}H_{26}$ Compounds.—The orange-red liquid, $C_{17}H_{22}$, was hydrogenated to give a mixture of diolefins. By analogy with the $C_{14}H_{18}$ compound, this compound has either structure XXII or XXIII.



XXII



XXIII



XXIV

The dark red liquid, $C_{20}H_{26}$, was hydrogenated to give a mixture of dienes and trienes. Analogously to the other members in this series, only structure XXIV is possible.

Discussion of Experimental.—In the experiments leading to the formation of the fulvenes without the alcohol solvent, the base, potassium hydroxide, was mainly insoluble in reaction medium. However, after an induction period, during which some color formation was noted, an exothermic reaction ensued leading to the formation of a colored organic layer and an aqueous layer. External heating and the use of large amounts of acetone favored the production of the higher boiling compounds. Although the reaction was sometimes neutralized by the addition of acid to the basic mixture, in the case where ion exchange resins were used this step was certainly not necessary.[12]

If oxygen is allowed to enter into the reaction medium or come in contact with the fulvenes during isolation, a great deal of polymeric material is formed. If large amounts of oxygen are present, a very viscous pot residue, in some cases cross linked, will remain after distillation of the fulvenes. Special care was taken to prevent oxygen from contaminating the analytical samples, although the refractive indices were taken in the normal manner and may, therefore, be subject to some error.

TABLE II

Fraction	B.p., °C.	Color	Yield, g.	$n^{25}D$
1	30–62 (0.6 mm.)	Yellow	25.3	1.5173
2	63–71 (0.6 mm.)	Yellow-orange	14.2	1.5280
3[a]	72–84 (0.6 mm.)	Orange	57.0	1.5458
4	85–105 (1.0 mm.)	Orange-red	5.6	1.5438
5	105–115 (1.2 mm.)	Red	6.4	1.5580
6	115–125 (1.2 mm.)	Red	24.9	1.5694

[a] Fraction 3 was redistilled to give Thiele's ether, b.p. 69–71° (1.0 mm.), 23.5 g., $n^{25}D$ 1.5261. *Anal.* Calcd. for $C_{14}H_{20}O$: C, 82.35; H, 9.80 Found: C, 82.96; H, 9.92. Methyl ether, b.p. 76–79° (0.6 mm.), orange, $n^{25}D$ 1.5281, 26.5 g. *Anal.* Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16; mol. wt., 218. Found: C, 82.40; H, 10.02; mol. wt., 219 ± 2.

(8) K. Alder and K. Ruhmann, *Ann.*, **566**, 1 (1950).

(9) C. Depuy and C. Lyons, *J. Am. Chem. Soc.*, **82**, 631 (1960).

(10) C. Allen and J. Van Allan, *ibid.*, **72**, 5165 (1950); P. Pauson and B. Williams, *J. Chem. Soc.*, 4162 (1961).

(11) W. Josten, *Ber.*, **71**, 2230 (1938).

(12) G. McCain, *J. Org. Chem.*, **23**, 632 (1958).

TABLE III

Compound	B.p., °C.	Color	Yield, g.	$n^{25}D$	Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen	Mol. wt. Calcd.	Mol. wt. Found
I, C_8H_{10}	56–60 (25 mm.)	Yellow	1003	1.5372	90.50	9.50	90.04	9.18		
$C_{11}H_{14}$	75–80 (10 mm.)	Yellow	30	1.5268	90.35	9.68	90.09	9.38		
$C_{14}H_{18}$	80–85 (1 mm.)	Yellow-orange	110	1.5372	90.26	9.74	90.29	9.50	186	193
$C_{17}H_{22}$[a]	105–110 (1 mm.)	Red	15	1.5476	90.20	9.80				
$C_{20}H_{26}$	134–138 (0.8 mm.)	Red	24	1.5635	90.16	9.84	90.50	9.68		
Pot residue		Red	91							

[a] This sample was very difficult to purify by repeated distillation and contained an oxygenated impurity.

The fulvenes could not be isolated by g.l.c. using a Tween 80 stationary phase column with helium as the carrier gas, although their hydrogenated derivatives were easily separated. The molecular weights were taken by ebulliometry using an internal standard.

Experimental

Reaction of 6,6-Dimethylfulvene and Acetone in Methanol.—To 166 g. (1.57 moles) of 6,6-dimethylfulvene were added 11.8 g. of potassium hydroxide, 190 g. (3.28 moles) of acetone and 150 g. of methanol. The mixture was magnetically stirred under nitrogen in a 1-l., three-necked, round-bottom flask equipped with a nitrogen inlet tube, a thermometer and a reflux condenser. The mixture reacted exothermically, the temperature rising to 31° and a red solution was formed. Heat was applied and the solution was refluxed for 4 hrs. After standing overnight, two 300-ml. layers had formed. The layers were not acidified but the water layer was washed with ether and the ether extract was added to the organic fraction. The combined organic fraction was washed with water and dried over magnesium sulfate. The dry organic liquid was fractionally distilled.

Reaction of Cyclopentadiene and Acetone without Added Solvent. A. With Stoichiometric Amounts of Acetone.—To 954.2 g. (14.4) moles of freshly distilled cyclopentadiene in a 5-l., three-necked flask equipped with a nitrogen inlet tube, thermometer, mechanical stirring apparatus and a reflux condenser were added 85 g. of XE-150, a mixed bed ion exchange resin manufactured by Rohm & Haas Co., and 840 g. (14.4 moles) of acetone. The mixture was heated and stirred under nitrogen to a temperature of 42°. Heating was discontinued as an exothermic reaction began. After 1 hr. at reflux, the now dark red mixture was cooled in an ice bath and allowed to stir at room temperature overnight. The resin was filtered and the filtrate separated into two layers. The water layer weighed 174 g. The red organic layer was fractionally distilled. See Table III.

B. With Excess Acetone.—To 20.0 g. of potassium hydroxide in a 1-l., three-necked flask equipped as described previously were added 100 g. (1.51 moles) of freshly distilled cyclopentadiene and 400 g. (6.88 moles) of acetone. The mixture was stirred and heated under nitrogen. Around 30° an exothermic reaction occurred which necessitated the use of an ice bath in order to control the reaction at gentle reflux. The base completely dissolved during this period and a bright red solution was formed. The exothermic reaction lasted for about 2 hr. and then an additional hour of heating at reflux was applied (61°). After standing overnight at room temperature, a solution of 40 ml. of concentrated hydrochloric acid in 250 ml. of water was slowly added to the stirred solution which was cooled in an ice bath. The organic layer was washed with water, dried over magnesium sulfate, and fractionally distilled.

TABLE IV

Fraction	B.p., °C.	$n^{25}D$	Yield, g.
1	62–64 (30 mm.)	1.5368	3.6
2	78–82 (20 mm.)	1.5281	3.1
3	100–106 (20 mm.)	1.5351	17.9
4	105–110 (1.2 mm.)	1.5468	10.2
5	120–125 (0.4 mm.)	1.5692	66.1
6	Pot residue		100

Reaction of Mesityl Oxide and Cyclopentadiene in Basic Methanol.—To 200 g. (2.02 moles) of mesityl oxide in a 2-l., three-necked flask equipped as described previously were added 130 g. (1.97 moles) of freshly distilled cyclopentadiene and 500 ml. of methanol containing 30 g. of sodium hydroxide. The solution was mechanically stirred under nitrogen and reacted exothermically to 60° and maintained this temperature for 2 hr. before cooling. The flask was refrigerated at 5° for 36 hr. and was then acidified with 50 ml. of glacial acetic acid. To the organic layer was added 500 ml. of ether and the ether solution was washed with water, dried over magnesium sulfate, and fractionally distilled. See Table V.

Dimerization of XII.—XII was stored in the refrigerator at 5° but after 7 months partial dimerization had occurred. The yellow liquid formed, b.p. 106–110° (0.5 mm.), $n^{25}D$ 1.5412, did not have the typical fulvene structure in the infrared but did have weak absorption in the conjugated diene region at 1660, 1630, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{28}$: C, 90.35, H, 9.65; mol. wt., 292. Found: C, 90.63; H, 9.72; mol. wt., 260.

The freshly distilled XII gave a molecular weight of 230–240 in refluxing benzene.

Reaction of Cyclopentadiene and Diacetone Alcohol.—In addition to 6,6-dimethylfulvene, there was a fraction isolated from the reaction of 100 g. of cyclopentadiene, 50 g. of potassium hydroxide and 126 g. of diacetone alcohol, which fraction was a yellow-orange liquid, b.p. 68–71° (9 mm.), $n^{25}D$ 1.5241, 12.3 g.

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.30; H, 9.56.

A solution of 10.0 g. of this product, $C_{11}H_{14}$, and 10.0 g. of dimethyl acetylenedicarboxylate containing an inhibitory amount of phenothiazine was heated to 150° for 0.5 hr. under nitrogen. The yellow solution was distilled and the fraction boiling at 150–160° (0.35 mm.), $n^{25}D$ 1.5252, a very viscous orange liquid, was collected, 2 g.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.66; H, 7.23.

The Reaction of the $C_{11}H_{14}$ Compound (from Acetone) and Dimethyl Acetylenedicarboxylate.—From a solution of dimethyl acetylenedicarboxylate and the $C_{11}H_{14}$ compound from acetone was isolated a viscous orange liquid, b.p. 150–154° (0.4 mm.), $n^{25}D$ 1.5248.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.93; H, 7.05.

The infrared spectra of this adduct and that adduct from the fulvene from diacetone alcohol were virtually identical.

The Reaction of Maleic Anhydride and the $C_{11}H_{14}$ Compound From Acetone.—To 6.2 g. (0.042 mole) of compound $C_{11}H_{14}$ from acetone were added 9.0 g. (0.092 mole) of maleic anhydride and 50 ml. of xylene. This yellow solution was refluxed under nitrogen for 2 hr. On cooling, a yellow precipitate formed which was recrystallized from moist chloroform to give a light yellow solid. The infrared spectrum showed the presence of acid groups.

Anal. Calcd. for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 60.59; H, 5.73.

Preparation of Isopropylcyclopentadiene.—Following the procedure given by Ziegler,[6] the reduction of dimethylfulvene by lithium aluminum hydride gave a colorless liquid, b.p. 38–43° (14 mm.), $n^{25}D$ 1.4608 [reported b.p. 28–30° (18 mm.), $n^{25}D$ 1.4639]. After standing 1 month in a closed container the refractive index had changed, $n^{25}D$ 1.4862, indicating possible dimerization. This new material was cracked at a pot temperature around 210° to give the monomer back.

Condensation of Acetone and Isopropylcyclopentadiene.—To 92 g. (0.85 mole) of isopropylcyclopentadiene in a 500-ml. flask equipped with the usual attachments were added 50 g. (0.86 mole) of acetone and 20 g. of potassium hydroxide pellets. The mixture was stirred under nitrogen and heated to reflux for 1 hr.

TABLE V

Compound	Color	B.p., °C.	$n^{25}D$	Yield, g.	Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen
XII	Orange	33–35 (0.5 mm.)	1.5185	176	90.35	9.65	89.00	10.20
Thiele's ether	Orange	59–61 (0.4 mm.)	1.5276	...	82.35	9.80	82.37	9.95
Methyl ether	Orange	70–72 (0.8 mm.)	1.5290	...	82.51	10.16	82.23	10.31

TABLE VI

Compound hydrogenated	Compounds formed	B.p., °C.	$n^{25}D$	Color	Formula	Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen	Mol. wt. Calcd.	Mol. wt. Found
I	Alkane	126–128 (atm.)	1.4292	Colorless							
	Olefin	130–134 (atm.)	1.4334	Very light yellow							
$C_{11}H_{14}$	Olefin	178–180 (atm.) 50–53 (1.2 mm.)	1.4542	Very light yellow	$C_{11}H_{20}$	86.76	13.34	85.63	12.91		
$C_{14}H_{18}$	Diene	190–192 (atm.) 83–86 (25 mm.)	melting point 74–74.5°	Colorless	$C_{11}H_{18}$	87.93	12.07	88.46	11.94		
	Olefin	62–66 (0.5 mm.)	1.4762	Colorless	$C_{14}H_{24}$	86.51	13.49	86.07	13.11		
	Diene	230–234 (atm.) 61–64 (0.8 mm.)	1.4845	Very light yellow	$C_{14}H_{22}$	87.42	12.58	87.42	12.71		
$C_{17}H_{22}$	Diene	86–90 (1 mm.)	1.4913	Light yellow	$C_{17}H_{30}$	87.10	12.90	86.98	12.87	234	215
$C_{20}H_{26}$	Diene	116–120 (1.0 mm.)	1.4814	Light yellow	$C_{20}H_{36}$	86.86	13.12	86.88	13.32		
	Triene	134–138 (1.5 mm.)	1.4829	Light orange	$C_{20}H_{34}$	87.52	12.48	87.34	12.87	274	273
Thiele's ether	Saturated ether	52–55 (0.5 mm.)	1.4574	Colorless	$C_{14}H_{26}O$	79.93	12.46	80.20	13.03	210	211
Compound $C_{11}H_{16}$	Alkane	25–27 (0.7 mm.)	1.4380	Colorless	$C_{11}H_{22}$	85.63	14.37	85.94	14.05		
	Olefin	28–30 (0.7 mm.)	1.4531	Very light yellow							
XII	Olefin	180–182 (atm.) 68–72 (14 mm.)	1.4563	Colorless	$C_{11}H_{20}$	86.76	13.34	86.58	13.00		

After stirring overnight at room temperature, the mixture was cooled in an ice bath. A solution of 40 ml. of concentrated hydrochloric acid in 500 ml. of water was slowly added to the mixture. The organic layer was washed with water, dried over magnesium sulfate, and distilled to give three fractions.

Fraction 1, b.p. 45–48° (0.9 mm.), yellow liquid, $n^{25}D$ 1.5219, 64 g.

Anal. Calcd. for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.80; H, 9.55.

Fraction 2, b.p. 79–81° (0.9 mm.), $n^{25}D$ 1.5029, yellow-orange.

Fraction 3, b.p. 110–115° (0.9 mm.), $n^{25}D$ 1.5308, orange-red.

Preparation of 5,6-Dihydroazulene (XVIII).—To 800 g. (2.0 moles) of a 25% solution of glutaraldehyde in water in a 3-l., three-necked flask equipped as described were added 140 g. (3.9 moles) of freshly distilled cyclopentadiene, sufficient ethanol to give a cloudy dispersion, and 50 g. of potassium hydroxide pellets. The mixture, which was slightly exothermic was stirred overnight under nitrogen. The mixture was acidified with acetic acid. Water and ether were added until two layers easily formed. The ether layer was washed with water and then it was concentrated at aspirator pressures. Hexane was added to the viscous concentrate and the mixture was stirred until no more concentrate was seen to dissolve. The hexane solution was distilled and the red liquid collected, b.p. 38–40° (2 mm.), 3.6 g., which crystallized on cooling into a red solid, m.p. 46–50°.

Anal. Calcd. for $C_{10}H_{10}$: C, 90.91; H, 9.09. Found: C, 90.76; H, 9.09.

Dehydrogenation of XVIII.—To 2.5 g. of the crude XVIII was added 5 g. of chloranil in ethanol. The solution was heated to reflux and turned a dark green-blue. The concentrated solution was chromatographed on alumina with a hexane eluent. Azulene was isolated as dark blue plates, m.p. 98–101°, 1.3 g. (reported m.p. 98.5–99°[13]).

Anal. Calcd. for $C_{10}H_8$: C, 93.71; H, 6.29. Found: C, 93.47; H, 6.43.

Oxidation and Hydrogenation of the $C_{14}H_{18}$ Compound from Acetone.—After standing in contact with air for 35 days, 21 g. of the $C_{14}H_{18}$ compound, now a very viscous red liquid was hydrogenated in an ether solution utilizing platinum dioxide as catalyst on the Paar hydrogenation apparatus. The initial hydrogen pressure was 50 p.s.i. and after 3 hr. at room temperature the pressure had dropped to 38 p.s.i. No more hydrogen was absorbed after this time. The mixture was filtered and the filtrate distilled. After a forerun, a red liquid was collected, b.p. 110–112° (0.3 mm.), $n^{25}D$ 1.5026, 1.7 g. The infrared spectrum showed a strong band at 1715 cm.$^{-1}$ and a weak but very broad band at 1610–1650 cm.$^{-1}$. The reported band range for the carbonyl of fulvene ketones is 1697–1736.[14]

(13) P. Plattner and S. T. Ptau, *Helv. Chim. Acta*, **20**, 224 (1937).

(14) E. D. Bergmann, see ref. 4, p. 118.

Anal. Calcd. for $C_{14}H_{20}O$: C, 81.50; H, 10.75. Found: C, 81.53; H, 10.84.

Several attempts were made to prepare a 2,4-dinitrophenylhydrazone but none was successful.

Hydrogenation Studies.—The data (see Table VI, p. 1650) describes the hydrogenation on the Paar apparatus at a maximum hydrogen press of 50 p.s.i. at room temperature with a platinum dioxide catalyst. The mixtures were mechanically shaken until no more hydrogen was consumed.

Acknowledgment.—The authors wish to thank Mr. Gregory Gallagher for his invaluable laboratory assistance.

The Preparation of Dodecamethylcyclohexasilane

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Directions are given for an improved method of preparation of dodecamethylcyclohexasilane; a proposed mechanism of catalysis by triphenylsilyllithium in this synthesis is considered.

The reaction of dichlorodimethylsilane with sodium at temperatures above 100° in hydrocarbon solvents has been shown to lead to an insoluble polymer as the principal product, with dodecamethylcyclohexasilane (I) being obtained in a low, unspecified yield.[1] It has been reported recently that the yield of I is only 0.05%, when the reaction mixture was worked up by methanol extraction rather than by the vacuum distillation procedure used by Burkhard, and that the use of lithium and tetrahydrofuran at high temperatures increased the yield to 2.5%.[2] Low yields of I also have been obtained from the treatment of dichlorodimethylsilane with sodium[3] and lithium[4] upon extended refluxing in tetrahydrofuran. In the latter case,[4] the yield of dodecamethylcyclohexasilane was 33%, even when dichlorodimethylsilane was added to the lithium at a slow rate.

If the reaction with lithium in the presence of tetrahydrofuran is allowed to proceed in the presence of silyllithium compounds, we have found that the yields of dodecamethylcyclohexasilane are increased significantly to the range of 60–70%.

Initially, dichlorodimethylsilane in tetrahydrofuran is added to lithium in the presence of a small amount of triphenylsilyllithium. Thereafter, the addition of dichlorodimethylsilane is controlled such that silyllithium compounds are present in the reaction mixture throughout the course of the reaction.

The proposed mechanism of catalysis by triphenylsilyllithium is illustrated in the following equations.

$$(C_6H_5)_3SiLi + ClSi(CH_3)_2R \longrightarrow (C_6H_5)_3Si\text{-}Si(CH_3)_2R \xrightarrow{2Li} (C_6H_5)_3SiLi + LiSi(CH_3)_2R \quad (II)$$

(R is Cl, $Si(C_6H_5)_3$, or $[Si(CH_3)_2]_nR$)

Chlorosilanes may then react with either triphenylsilyllithium or with intermediates such as II. Triphenylsilyllithium can also be regenerated by reactions joining dimethylsilylene units, as shown in the following example.[5]

$$R(CH_3)_2Si\text{-}Li + R(CH_3)_2Si\text{-}Si(C_6H_5)_3 \longrightarrow R(CH_3)_2SiSi(CH_3)_2R + (C_6H_5)_3SiLi$$

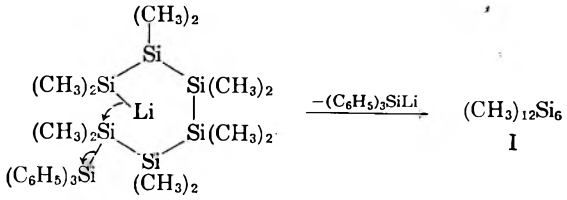
(R is Cl, $Si(C_6H_5)_3$, or $[Si(CH_3)_2]_nR$)

These reactions are supported by the observation that 2,2-dimethyl-1,1,1,3,3,3-hexaphenyltrisilane, upon treatment with lithium in tetrahydrofuran, afforded good yields of dodecamethylcyclohexasilane and triphenylsilyllithium, with the latter forming a derivative with chlorotrimethylsilane. In this case, by means of the cleavage reactions shown in the preceding equations, the formation of the observed products may be illustrated by the following mechanistic pathway. The

$$6(C_6H_5)_3SiSi(CH_3)_2Si(C_6H_5)_3 + 6Li \xrightarrow{-6(C_6H_5)_3SiLi}$$

$$3(C_6H_5)_3Si[Si(CH_3)_2]_2Si(C_6H_5)_3 \xrightarrow{4Li,\ -4(C_6H_5)_3SiLi}$$

$$(C_6H_5)_3Si[Si(CH_3)_2]_6Si(C_6H_5)_3 \xrightarrow[-(C_6H_5)_3SiLi]{2Li}$$



cyclization reaction given here undoubtedly occurs in the reaction involving dichlorodimethylsilane. However, other ring-closure reactions cannot be discounted.

The proposed mechanism of catalysis is further supported by the reaction of five molar equivalents of dichlorodimethylsilane with two equivalents of triphenylsilyllithium in the presence of the calculated amount of lithium. From this reaction, dodecamethylcyclohexasilane was isolated in a 25% yield; there were also obtained crystalline solids which apparently are mixtures of polydimethylsilanes containing terminal triphenylsilyl units. However, only 2,2-dimethyl-1,1,1,3,3,3-hexaphenyltrisilane could be separated in a pure state.

The formation of substituted-dimethylsilylithium intermediates may also occur by the lithium cleavage of tetramethyldisilanyl units. This was demonstrated by allowing the mixture obtained from the triphenyl-

(1) C. A. Burkhard, *J. Am. Chem. Soc.*, **71**, 963 (1949).

(2) (a) E. Hengge and H. Reuter, *Naturwissenschaften*, **49**, 514 (1962); (b) See, also, the report which just appeared by U. Graf zu Stolberg, *Angew. Chem.*, **75**, 206 (1963).

(3) R. P. Anderson, private communication.

(4) H. Gilman and G. L. Schwebke, unpublished studies.

(5) The formation of hexaethyldisilane upon treatment of 1,1,1-triethyl-2,2,2-triphenyldisilane with lithium in tetrahydrofuran has been proposed to occur by a similar mechanism. See, H. Gilman and H. J. S. Winkler, "Organosilylmetallic Chemistry," in H. Zeiss, Ed., "Organometallic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1960, p. 277; and H. Gilman, G. D. Lichtenwalter, and D. Wittenberg, *J. Am. Chem. Soc.*, **81**, 5320 (1959).

silyllithium-catalyzed reaction of dichlorodimethylsilane to stir with excess lithium. The resulting solution was shown to contain a silyllithium content greater than the amount of triphenylsilyllithium used, by means of a recently developed double-titration technique involving allyl bromide.[6] An attempt to form derivatives of the resulting silyllithium compounds with chlorotriphenylsilane gave no isolable products other than dodecamethylcyclohexasilane in low yield and 14.8% of hexaphenyldisilane. The latter compound evidently was formed by a halogen–metal interconversion reaction, followed by a coupling reaction between the thus formed triphenylsilyllithium and chlorotriphenylsilane. Similar results were obtained from the lithium cleavage of dodecamethylcyclohexasilane. In addition, the insoluble dimethylsilylene polymer[4] reacted with lithium in tetrahydrofuran to give a 32% yield of dodecamethylcyclohexasilane, evidently formed by an intramolecular-cyclization reaction along the polymer chain. Furthermore, this reaction provided a considerable amount of distillable products containing silicon–hydrogen groups, apparently formed by the acid hydrolysis of silyllithium compounds.

Attempts to isolate other cyclic polydimethylsilanes from the catalyzed reaction of dichlorodimethylsilane have not been successful. Waxy solids have been obtained by sublimation which show only dimethylsilyl groups in their infrared spectra. By vapor phase chromatographic analysis, this material was shown to consist principally of three major components. The second fraction to come off of the column was collected and identified as dodecamethylcyclohexasilane. It is believed that the first and third fractions are decamethylcyclopentasilane and tetradecamethylcycloheptasilane, respectively. However, the identities of these materials have not yet been established.

Experimental

All reactions were carried out in oven-dried glassware under atmospheres of oxygen-free, dry nitrogen. Tetrahydrofuran (THF) was dried and purified by refluxing for at least 24 hr. over sodium, followed by distillation into lithium aluminum hydride and redistillation from the hydride immediately before use, *except* in the preparation of dodecamethylcyclohexasilane, where drying by storage over sodium wire was found to give satisfactory results. The temperatures reported are uncorrected.

Preparation of Dodecamethylcyclohexasilane.—A solution of 300 ml. (318 g., 2.5 moles)[7] of dichlorodimethylsilane in 700 ml. of sodium-dried tetrahydrofuran was added in a dropwise fashion to 38 g. (5.45 g.-atoms) of lithium wire (cut into *ca.* 5-mm. pieces), and 0.01 mole of triphenylsilyllithium in 15 ml. of tetrahydrofuran. The rate of addition was carefully controlled such that the reaction mixture maintained a definite light brown coloration.[8] Initially, the reaction was sufficiently exothermic that external heating was not required to maintain reflux. After about one-half of the solution was added, it was necessary to heat the mixture to keep it refluxing. The total addition time was between 24 and 36 hr. A small amount of lithium usually remained, after the completion of the addition, which was separated by decantation through a Büchner funnel.[9] The lithium-free reaction mixture is hydrolyzed in dilute acid. The aqueous layer was separated and extracted three times with *ca.* 100-ml. portions of ether. The combined ether extracts and organic layer was washed with water until neutral to litmus. The organic phase was filtered to remove 1–2% of insoluble polymer. The solvents were removed under reduced pressure and the residue treated with cold acetone and filtered to give 96 g. (67%) of impure dodecamethylcyclohexasilane, m.p. 220–240° (m.p. block preheated to 200°). Recrystallization[10] was accomplished by dissolving the product in 10–20 ml. of petroleum ether (b.p. 60–70°) and adding *ca.* 200 ml. of hot acetone. Upon cooling, there was obtained 86 g. (60%) of pure product, m.p. 250–252° (m.p. block preheated to 240°).[11] The crystal form most frequently observed was diamond-shaped plates. However, feathery needles also were encountered.

Anal. Calcd. for $C_{12}H_{36}Si_6$: mol. wt., 348.9. Found: mol. wt., 349 (vapor pressure osmometer).

The solvents were removed from the original mother liquor and the residue heated to 150° (0.5 mm.), affording 25 g. (*ca.* 17.5%) of volatile material, most of which sublimed and was collected in the side arm of the distillation flask. Attempts to recrystallize this material gave only waxy materials melting in the range 120–190°. Sublimation at 40° (0.005 mm.) did not succeed in separating the components. Vapor phase chromatographic analysis, using a silicone–gum rubber packed column heated to 175°, showed three major peaks, with retention times about 5 min. apart. Infrared spectra on each of the samples collected showed only the presence of dimethylsilylene units. The second fraction was identified as dodecamethylcyclohexasilane, m.p.[11] 250–252° (m.m.p.). The first and third major components were not collected in sufficient amounts to establish their structures, but they are believed to be decamethylcyclopentasilane and tetradecamethylcycloheptasilane. They were waxy solids with indefinite melting points between 160–200°.

Dichlorodimethylsilane and Excess Lithium in the Presence of a Trace of Triphenylsilyllithium.—The reaction was carried out as described in the preparation of dodecamethylcyclohexasilane, using 15.9 g. (0.12 mole) of dichlorodimethylsilane, 2.1 g. (0.3 g.-atom) of lithium and 0.001 mole of triphenylsilyllithium in a total of 97 ml. of tetrahydrofuran. Subsequent to completion of the addition, the reaction mixture was stirred at room temperature for 24 hr. Double titration[5] gave the silyllithium content as 0.033 mole. The reaction mixture was decanted from the remaining lithium and added to 10.3 g. (0.03 mole) of chlorotriphenylsilane. Subsequent to acid hydrolysis, filtration afforded 1.3 g. (14.8%) of hexaphenyldisilane, m.p. 360–365° (m.m.p.). The filtrate was worked up in the usual manner and the solvents were removed. Petroleum ether (b.p. 60–70°) was added to the residue to give 1.4 g. (11.5%) of triphenylsilanol, m.p. 148–155°, identified by its infrared spectrum. The solvent was removed from the mother liquor and the residue heated at 100° (0.2 mm.) to give 0.5 g. (7%) of sublimate, identified as dodecamethylcyclohexasilane, m.p. 248–250° (m.m.p.). Attempts to isolate other compounds were unsuccessful.

Reaction of Dichlorodimethylsilane and Triphenylsilyllithium (5:2 Mole Ratio, Respectively) in the Presence of Lithium.—Triphenylsilyllithium was prepared by the cleavage of 10.4 g. (0.02 mole) of hexaphenyldisilane with 1.4 g. (0.2 g.-atom) of lithium. To the resulting mixture, there was added 12.9 g. (0.1 mole) of dichlorodimethylsilane in 50 ml. of tetrahydrofuran solution at a rate which maintained a light brown coloration in the reaction mixture. The addition required 3 hr. The reaction mixture was decanted from the small amount of remaining lithium and hydrolyzed in dilute acid. Subsequent to the usual work-up and solvent removal, petroleum ether was added to the residue. Filtration afforded 9.7 g. of insoluble material melting over the range 129–180°. By fractional recrystallization from benzene, there was isolated 1.1 g. (9.6%) of 2,2-dimethyl-1,1,1,-3,3,3-hexaphenyltrisilane, m.p. 222–225° (m.m.p.). Attempts to purify the remaining solids gave crystalline solids with wide melting point ranges. The infrared spectra of the various

(6) H. Gilman and S. Y. Sim, unpublished studies.

(7) Excellent yields also were obtained from runs using from 0.2–1 mole of dichlorodimethylsilane.

(8) The rate of addition is rather sensitive and a too rapid addition nullifies the catalytic action. If the reaction mixture loses the brown coloration, stop the addition of dichlorodimethylsilane. Reinitiation may be accomplished by one or a combination of the following procedures: stir at reflux for an hour or so; add a few pieces of freshly cut lithium; and/or add another portion of triphenylsilyllithium. Repeat if necessary.

(9) The presence of salts tends to make lithium removal difficult.

(10) For smaller quantities of product, acetone alone may be used as the crystallization solvent.

(11) On slow heating from room temperature, dodecamethylcyclohexasilane undergoes numerous crystal transformations and appears to melt partially and resolidify at temperatures below 200°. Sublimation also occurs. When added to the m.p. block at 240°, the material melts at 250–252°, with considerable sintering from 240°.

fractions indicated the presence of silicon–methyl and silicon–phenyl groups. The solvent was removed from the original mother liquor and the residue heated at 100° under a pressure of 0.5 mm. to give 1.5 g. (25.9%) of sublimate, identified as dodecamethylcyclohexasilane, m.p. 250–253° (m.m.p.). Attempts to obtain products from the sublimation residue were unsuccessful.

2,2-Dimethyl-1,1,1,3,3,3-hexaphenyltrisilane. Preparation.—To 2.6 g. (0.02 mole) of dichlorodimethylsilane, there was added 0.04 mole of triphenylsilyllithium in 50 ml. of tetrahydrofuran. The reaction mixture was hydrolyzed in dilute acid and filtered. The solids were washed with water, methanol, and ether, and dried to give 8.2 g. (71.4%) of product, m.p. 222–226°. Two recrystallizations from a mixture of benzene and cyclohexane gave 5.5 g. (47.7%) of pure 2,2-dimethyl-1,1,1,3,3,3-hexaphenyltrisilane, m.p. 223–227°.

Anal. Calcd. for $C_{38}H_{36}Si_3$: Si, 14.60. Found: Si, 14.48, 14.58.

Reaction with Lithium.—A few milliliters of tetrahydrofuran was added to a stirred mixture of 5.8 g. (0.01 mole) of the trisilane and 0.7 g. (0.1 g.-atom) of lithium. The reaction mixture became yellow after 5 min. A total of 25 ml. of tetrahydrofuran was added over a 30-min. period and the reaction mixture was stirred for an additional 3 hr. To the resulting dark green mixture, 3.4 g. (0.03 mole) of chlorotrimethylsilane was added rapidly. The colorless solution was decanted away from the lithium and hydrolyzed in dilute acid. Subsequent to the usual work-up, the solvents were removed and the residue crystallized from ethanol to give 4.3 g. (65.1%) of 1,1,1-trimethyl-2,2,2-triphenyldisilane, m.p. 106–108° (m.m.p.). The solvents were removed from the mother liquor and the residue heated to 100° (12 mm.) to yield 0.4 g. (66%) of impure dodecamethylcyclohexasilane, m.p. 200–230°. Recrystallization from acetone afforded 0.3 g. (50%) of pure product, m.p. 250–252° (m.m.p.).

Cleavage of Dodecamethylcyclohexasilane with Lithium in Tetrahydrofuran.—Triphenylsilyllithium was prepared by the reaction of 0.13 g. (0.00025 mole) of hexaphenyldisilane and 0.7 g. (0.1 g.-atom) of lithium in a small volume of tetrahydrofuran. To this, 5.25 g. (0.015 mole) of dodecamethylcyclohexasilane was added in 25 ml. of tetrahydrofuran.[12] The resulting mixture was stirred at room temperature for 24 hr. Titration of the brown solution showed the silyllithium content to be 0.009 mole.[6] Chlorotriphenylsilane, 3.5 g. (0.012 mole), was added. The colorless solution was hydrolyzed and filtered to give 0.2 g. of hexaphenyldisilane, m.p. 360–365° (m.m.p.). The filtrate was worked up in the usual manner and the solvents were removed. Petroleum ether (b.p. 60–70°) was added to the residue and filtration afforded 1.6 g. (50%) of triphenylsilanol, m.p. 150–155° (m.m.p.). The solvent was removed from the filtrate and the residue crystallized from acetone to give 1.9 g. (36.4%) of recovered dodecamethylcyclohexasilane, m.p. 250–252° (m.m.p.). Attempts to isolate other pure products were unsuccessful.

Reaction of Lithium with the Insoluble Dimethylsilylene Polymer.—About 0.7 g. (0.1 g.-atom) of lithium, which had been used for the preparation of triphenylsilyllithium, and 5.8 g. of the insoluble dimethylsilylene polymer[13] were stirred for 52 hr. in 20 ml. of tetrahydrofuran. The dark brown reaction mixture was hydrolyzed in excess dilute acid and filtered to give 0.7 g. (12%) of recovered polymer. Subsequent to the usual work-up, the solvents were removed and the residue distilled under reduced pressure and afforded a large number of fractions boiling in the range 65° (0.4 mm.) to 100° (0.003 mm.). The total amount of distillable material was 4.5 g. (77.8%). All of these fractions showed strong absorption bands in their infrared spectra for silicon–hydrogen and silicon–methyl groups. One fraction, b.p. 100–105° (0.4 mm.), partially solidified. Recrystallization from acetone afforded 1.8 g. (32%) of dodecamethylcyclohexasilane, m.p. 250–252° (m.m.p.).

(12) An attempt to cleave dodecamethylcyclohexasilane with untreated lithium in tetrahydrofuan gave no indication of a reaction after 48 hr., and starting material was recovered in a 90% yield.

(13) Obtained from the uncatalyzed reaction of dichlorodimethylsilane with lithium in tetrahydrofuran.[4]

Intramolecular Reactions of Some Cyclic β-Diketones[1]

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The reaction of 3-(4,4-dimethyl-2,6-dioxocyclohexyl)levulinic acid (I) with bromine resulted in an unusual intramolecular reaction. The structure of this product and the reactions of some related model compounds are discussed.

The investigation of the reaction of bromine with ketones has resulted in an understanding of the mechanism of this reaction. It has been shown that the rate of reaction is dependent on the concentration of the ketone and catalyst (acid or base) but is independent of the concentration of the halogen. From this and other data, it is believed that the rate-determining step is the formation of the enol which is then rapidly attacked by halogen.[3] In connection with our structural studies on some cyclic β-diketones,[4] we became interested in the reaction of bromine with certain β-diketones, and this paper describes some novel reactions which we have observed with this system.

When 3-(4,4-dimethyl-2,6-dioxocyclohexyl)levulinic acid (I) was allowed to react with an aqueous solution of bromine, a *neutral product* (II) was obtained which had undergone substitution of a bromine for a hydrogen atom. An examination of the infrared spectrum of the brominated product revealed hydroxyl absorption at 3620 and 3340 cm.$^{-1}$ and carbonyl absorption at 1785 and 1725 cm.$^{-1}$. Furthermore an examination of the ultraviolet spectrum revealed that the β-diketone system was no longer capable of enolization since the characteristic absorption of an enolizable β-diketone was absent; in fact, the only absorption exhibited was at 298 mμ with an ε of 90 which is characteristic of an isolated ketone.[5] In addition, the bromine must be located in this compound in a unique position since when it is allowed to react with sodium hydroxide, a 25% yield of 3-(4,4-dimethyl-2,6-dioxocyclohexyl)levulinic acid (I) is obtained. In order to obtain more

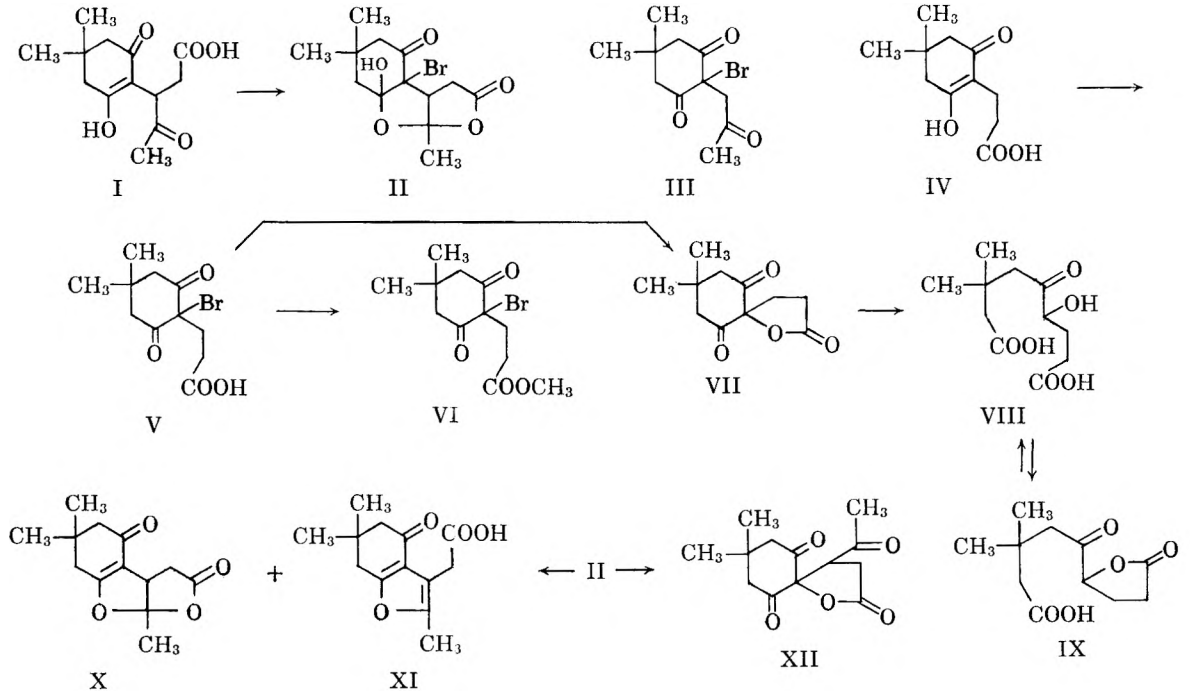
(1) This investigation was supported generously by research grant CY5527 from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) The research described in this paper was used in partial fulfillment of the requirements for the Bachelor of Science degree.

(3) A number of reviews on this subject have been published; see, for example, E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 372.

(4) For the previous paper of this series, see H. J. Schaeffer and R. Vince, *J. Org. Chem.*, **27**, 4502 (1962).

(5) W. R. Brode, "Chemical Spectroscopy," 2nd Ed., John Wiley and Sons Inc., New York, N. Y., 1943, p. 221–226.



information about these reactions, a study of model systems which are related to I was undertaken.

In order to assess the effect of an exocyclic ketone on the bromination of cyclic β-diketone, the model compound, 2-(2-oxopropyl)-5,5-dimethylcyclohexane-1,3-dione, was treated with bromine; the resultant product (III) lost the typical ultraviolet absorption of an enolizable β-diketone.[6] Its infrared spectrum did not exhibit hydroxyl absorption but did exhibit typical carbonyl absorption at 1740 and 1715 cm.$^{-1}$. Thus, the exocyclic ketone did not alter the course of this reaction, as is evidenced by the isolation of the normal bromination product III.

The effect of a β-carboxyethyl chain on the bromination of a β-diketone was investigated by allowing 2-(2-carboxyethyl)-5,5-dimethylcyclohexane-1,3-dione (IV) to react with bromine. The product of this reaction was assigned structure V on the grounds that it lost the typical ultraviolet absorption of an enolizable β-diketone and that it exhibited typical infrared absorption due to acidic hydrogen (2650–2000 cm.$^{-1}$), and C=O of a β-diketone and carboxylic acid at 1745 and 1710 cm.$^{-1}$, but it did not exhibit hydroxyl absorption that was found in II. Thus, a β-carboxyethyl does not affect the formation of the expected product on bromination of a β-diketone. Only in the case where as exocyclic ketone and a β-carboxyethyl group are present in a β-diketone, as in I, do we find participation by these groups in the bromination reaction.

Several interesting reactions were observed on V. For example, when V was recrystallized from absolute methanol, a neutral compound was obtained in a 72% yield which was shown to be the methyl ester (VI). The structure of VI was shown to be correct by an alternate synthesis; *i.e.*, when the methyl ester of IV was allowed to react with bromine, a good yield of VI was obtained. The formation of the methyl ester (VI) from the acid (V) merely by heating of V in methanol most probably occurs by the elimination of a small amount of hydrogen bromide from V, which thereby catalyzes the esterification. If, however, V is heated in water, rather than methanol, a different neutral compound is obtained which has lost the elements of hydrogen bromide. This product exhibited infrared absorption at 1790, 1750, and 1715 cm.$^{-1}$ and has been assigned structure VII.

Compound VII can also be obtained by allowing compound V to react with either sodium bicarbonate or magnesium hydroxide. If VII is allowed to react with excess sodium hydroxide at 0°, the β-diketone system is cleaved and the lactone is opened to generate the dicarboxylic acid VIII whose infrared spectrum exhibited the predicted peaks at 1730 (C=O, ketone) and 1700 (C=O, acid). Distillation or sublimation of VIII gave the corresponding lactone (IX). An attempt to prepare the diester of VIII gave the corresponding monoester of IX. As expected, IX was recovered unchanged upon treatment with sodium bicarbonate but regenerated VIII upon treatment with sodium hydroxide solution. Finally, it was found that when V was allowed to react with sodium hydroxide, a 30% yield of IV was obtained. The reversal of the bromination reaction by sodium hydroxide also occurs with II and III and can be explained by assuming the release of Br^+ to the attacking base, followed by protonation of the corresponding enolate anion.[7]

As a consequence of our studies on model compounds, we felt that in the bromination of I, the bromine must have attacked carbon-2 as the initial reaction, followed by further intramolecular reaction to give the neutral product (II). In an attempt to determine the carbon skeleton of the brominated product, II was treated with zinc dust and acetic acid. The major product of the reaction was 2,6,6-trimethyl-3-carboxymethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (XI) which,

(6) The ultraviolet spectrum of a typical cyclic β-diketone, for example I or IV, exhibits absorption at 264 mμ when determined in ethanol and at 289 mμ when determined in 0.1 *N* sodium hydroxide. The molecular extinction coefficient for the maxima are of the order of 10^3 to 10^4.

(7) The generation of Br^+ or its equivalent from a bromo ketone by the attack of a nucleophile has ample precedence; see, for example, H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955). Other related reactions are the generation of Br^+ when N-bromosuccinimide is allowed to react with sodium hydroxide.

as we have shown earlier,[4] is the product formed when I is treated with acid; however, a second product was isolated in low yield which was found to be X[4]. In order to remove the bromine atom from II under neutral conditions, II was allowed to react with hydrogen using a palladium-on-charcoal catalyst in the presence of magnesium oxide which caused the formation of X in good yields. Finally, treatment of II with a suspension of magnesium oxide in 95% ethanol resulted in the formation of XII, a compound whose infrared spectrum was similar to the infrared spectrum of VII. On these grounds, the assignment of structure II to the bromination product I is the most probably justified. The formation of XII from II establishes that the bromine atom is at carbon-2, and the formation of X from II establishes the gross carbon skeleton. That X is formed from II also establishes the location of the hydroxyl group in II since we visualize the reaction as proceeding in two steps: (a) hydrogenolysis of the bromine atom and (b) dehydration of the resulting β-hydroxy ketone to give X.

Experimental[8]

Bromination of 3-(4,4-Dimethyl-2,6-dioxocyclohexyl)levulinic Acid.—To a solution of 513 mg. (2.01 mmoles) of 3-(4,4-dimethyl-2,6-dioxocyclohexyl)levulinic acid[4,9] (I) in 50 ml. of water was slowly added a saturated solution of bromine in water until a yellow color persisted. The precipitate which formed was collected by filtration, washed with water, and dried *in vacuo* at room temperature; yield, 606 mg. (90.9%), m.p. 120° dec. Recrystallization from a mixture of benzene and hexane gave the analytical sample; yield, 404 mg. (60.7%), m.p. 117–118 dec. $\bar{\nu}$ in cm.$^{-1}$ (chloroform): 3620 and 3340 (OH), 1785 and 1725 (C=O).

Anal.[10] Calcd. for $C_{13}H_{17}O_5Br$: C, 46.88; H, 5.15; Br, 23.98. Found: C, 46.99; H, 5.22; Br, 24.11.

This compound is sensitive to heat since it decomposed on drying *in vacuo* at 65°. The melting point is a poor criterion for purity; we have found that the melting point of the analytical sample may vary from 115 to 124° dec. when determined in an oil bath and may be as high as 150° dec. when determined on the Kofler Heizbank.

2-(2-Oxopropyl)-2-bromo-5,5-dimethylcyclohexane-1,3-dione (III).—To a solution of 500 mg. (2.54 mmole) of 2-(2-oxopropyl)-5,5-dimethylcyclohexane-1,3-dione[4] in 25 ml. of water was added a solution of bromine water until a yellow color persisted, and the reaction mixture was chilled. The white precipitate which formed was collected by filtration and washed with water; yield, 667 mg. (96.8%), m.p. 112°. One recrystallization of the crude product from methanol gave the analytical material, m.p. 111°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1740 and 1715 (C=O).

Anal. Calcd. for $C_{11}H_{15}O_3Br$: C, 48.02; H, 5.49; Br, 29.04. Found: C, 47.82; H, 5.52; Br, 29.33.

2-(2-Carboxyethyl)-2-bromo-5,5-dimethylcyclohexane-1,3-dione (V).—2-(2-Carboxyethyl)-5,5-dimethylcyclohexane-1,3-dione[11] (1.00 g., 4.72 mmoles) was dissolved in 25.0 ml. of water and 10.0 ml. of methanol with heating. After cooling to room temperature the clear solution was treated with bromine water until a slight yellow persisted. The reaction solution was chilled, and the white product which precipitated was collected by filtration and washed with water; yield, 1.06 g. (72%), m.p. 127°. $\bar{\nu}$ cm.$^{-1}$ (potassium bromide): 2650–2000 (acidic hydrogen), 1745 and 1710 (C=O); λ_{max}^{EtOH} 300 (ε 214).

Anal. Calcd. for $C_{11}H_{15}O_4Br$: C, 45.39; H, 5.19; Br, 27.45. Found: C, 45.47; H, 5.06; Br, 27.52.

Reaction of 2-(2-Carboxyethyl)-2-bromo-5,5-dimethylcyclohexane-1,3-dione with Methanol.—A solution of 0.602 g. (2.07 mmoles) 2-(2-carboxyethyl)-2-bromo-5,5-dimethylcyclohexane-1,3-dione (V) in 25.0 ml. of methanol was refluxed for 1 hr., concentrated *in vacuo* to about 10 ml., and chilled. The white solid which precipitated was removed by filtration and washed with water; yield, 0.450 g. (72%), m.p. 70°. $\bar{\nu}$ cm.$^{-1}$ (potassium bromide): 1745 and 1710 (C=O); λ_{max}^{EtOH} 262 (ε 442).

Anal. Calcd. for $C_{12}H_{17}O_4Br$: C, 47.23; H, 5.61; Br, 26.18. Found: C, 47.50; H, 5.69; Br, 26.11.

2-(2-Carbomethoxyethyl)-2-bromo-5,5-dimethylcyclohexane-1,3-dione (VI).—2-(2-Carbomethoxyethyl)-5,5-dimethylcyclohexane-1,3-dione (100 mg., 0.442 mmole) was dissolved in 1 ml. of ethanol and 1 ml. of water at room temperature. Bromine water was added dropwise to the solution until a slight yellow color persisted. Addition of water (5 ml.) to the reaction mixture caused precipitation of a white solid which was collected by filtration; yield, 101 mg. (75%), m.p. 71°. $\bar{\nu}$ cm.$^{-1}$ (potassium bromide): 1745 and 1710 (C=O). The product obtained in this reaction was identical in all respects with the product obtained by esterification of V.

The Lactone of 3-(4,4-Dimethyl-2,6-dioxo-1-hydroxycyclohexyl)propionic Acid (VII).—(a) To 477 mg. (1.64 mmoles) of 2-(2-carboxyethyl)-2-bromo-5,5-dimethylcyclohexane-1,3-dione (V) was added 5 ml. of water and 0.1 ml. of methanol. The mixture was refluxed for 5 min. during which time solution did not occur, but the pH dropped to approximately 1. The reaction mixture was chilled, and the white solid was collected by filtration; yield, 260 mg. (75.5%), m.p. 210°. The crude product was sublimed from an oil bath at 120° (0.10 mm.) and gave 256 mg. of the analytical sample (VII), m.p. 210°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1790 (C=O, γ-lactone), 1750, and 1710 (C=O).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H,6.71. Found: C, 62.90; H,6.68.

(b) To a solution of 200 mg. (0.686 mole) of 2-(2-carboxyethyl)-2-bromo-5,5-dimethylcyclohexane-1,3-dione (V) in 20 ml. of ether was added 20 ml. of 5% sodium bicarbonate solution. After the mixture was stirred for 10 min., a white solid formed at the interface of the ether and water. The mixture was chilled, and the solid (VII) was removed by filtration; yield, 103 mg. (71.5%), m.p. 211°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1790, 1750, and 1710. This product was identical in all respects with the neutral compound obtained by refluxing V with water.

3,3-Dimethyl-5-oxo-hydroxyazelaic Acid (VIII).—A mixture of 1.62 g. (7.71 mmoles) of 3-(4,4-dimethyl-2,6-dioxo-1-hydroxycyclohexyl)propionic acid lactone (VII) and 16 ml. of 10% sodium hydroxide was stirred for 1 hr. in an ice bath. The cold reaction mixture was acidified with hydrochloric acid, and the white solid which precipitated was collected by filtration; yield, 1.29 g. (68.0%), m.p. 121°. Recrystallization from a mixture of *p*-dioxane and hexane gave the pure product, m.p. 122°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 3320 (OH), 1730 (C=O, ketone), 1700 (C=O, acid); λ_{max}^{EtOH} 290 mμ (ε 40.3).

Anal. Calcd. for $C_{11}H_{18}O_6$: C, 53.65; H, 7.35; neut. equiv., 123.0. Found: C, 53.35; H, 7.57; neut. equiv., 124.5, 124.3.

The γ-Lactone of 3,3-Dimethyl-5-oxo-6-hydroxyazelaic Acid (IX).—3,3-Dimethyl-5-oxo-6-hydroxyazelaic acid (VIII) (406 mg., 1.58 mmoles) was sublimed from an oil bath at 130° (0.1 mm.) and 270 mg. (71.6%) of a white solid was collected, m.p. 64–66°. Resublimation gave the pure product (IX), m.p. 64–66°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 2650–2100 (acidic hydrogen), 1780 (C=O, γ-lactone), 1730 (C=O, ketone), 1700 (C=O, acid).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.06. Found: C, 57.71; H, 7.14.

The Lactone of 8-Carbomethoxy-7,7-dimethyl-5-oxo-4-hydroxyoctanoic Acid.—A mixture of 500 mg. (2.03 mmoles) of 3,3-dimethyl-5-oxo-6-hydroxyazelaic acid (VIII), 205 mg. (6.40 mmoles) of methanol, and 10 λ l. of ethanesulfonic acid in 5.5 ml. 1,2-dichloroethane was refluxed for 18 hr. To the cold reaction mixture was added 20 ml. of water and 25 ml. of ether. The two phases were separated, and the aqueous portion was extracted with ether (2 × 25 ml.). The combined ether extracts were washed with 5% sodium hydroxide solution. The organic phase was dried with anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and gave 485 mg. (99%) of crude product. Distillation in a micro distillation apparatus (oil bath temperature,

(8) The infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer, and the ultraviolet were determined on a Perkin-Elmer Model 4000A spectrophotometer. Except where noted, the melting points were determined on a Kofler Heizbank and are corrected.

(9) I. N. Nazarow and S. I. Zavyalov, *J. Gen. Chem. USSR*, **25**, 508 (1955).

(10) The analyses reported in the paper were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(11) H. Stetter, H. Kesseler, and H. Meisel, *Ber.*, **87**, 1617 (1954).

110°, 0.07 mm.) gave 266 mg. of pure product. $\bar{\nu}$ in cm.$^{-1}$ (film): 1790 (lactone), 1740 (C=O, ester).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.47; H, 7.48. Found: C, 58.95; H, 7.40.

Action of Zinc and Acetic Acid on the Bromination Product of 3-(4,4-Dimethyl-2,6-dioxocyclohexyl)levulinic Acid (II).—A mixture of 276 mg. (0.830 mmole) of II and 425 mg. of zinc dust in 10 ml. of glacial acetic acid was stirred for 1.5 hr. at 80°. After filtration, 25 ml. of water was added to the filtrate, and the mixture was extracted with ether (3 × 25 ml.). The combined ether extracts were washed with water (3 × 25 ml.) and then extracted with 5% sodium bicarbonate solution (3 × 25 ml.). The ethereal layer, after drying with magnesium sulfate, was evaporated to dryness and gave 16 mg. (8.2%) of X, m.p. 167°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1805 (enol lactone), 1645 (α,β-unsaturated ketone). This product was identical with X prepared by a different method.[4] The bicarbonate extracts were acidified with concentrated hydrochloric acid and extracted with ether (3 × 25 ml.). The combined ether extracts after the usual processing gave 101 mg. (52.0%) of 2,6,6-trimethyl-3-carboxymethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (XI) (m.p. 125°), which was identical with the product previously prepared by a different procedure.[4]

Hydrogenolysis of the Bromination Product of 3-(4,4-Dimethyl-2,6-dioxocyclohexyl)levulinic Acid (II).—A mixture of 666 mg. (2.00 mmoles) of II, 100 mg. of magnesium oxide, and 150 mg. of 5% palladium-on-charcoal catalyst in 200 ml. of absolute ethanol was hydrogenated at an initial pressure of 60 p.s.i. until the theoretical amount of hydrogen had been absorbed. After filtration, the reaction mixture was concentrated *in vacuo* to 10 ml., and the white solid (X), which precipitated from solution, was collected by filtration; the yield of X was 321 mg. (68.2%), m.p. 167°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1805 (enol lactone), 1645 (α,β-unsaturated ketone). This product was identical in all respects with compound X prepared by a different procedure.[4]

The Lactone of 3-Acetyl-3-(4,4-dimethyl-2,6-dioxo-1-hydroxycyclohexyl)propionic Acid (XII).—A solution of 333 mg. (1.00 mmole) the bromination product of 3-(4,4-dimethyl-2,6-dioxocyclohexyl)levulinic acid (II) and 50 mg. of magnesium oxide in 100 ml. in 95% ethanol was stirred for 2.5 hr. and allowed to stand overnight. The solution was filtered to remove excess magnesium oxide. The filtrate was concentrated to 50 ml. *in vacuo*, chilled, and the white solid product which precipitated was removed by filtration; yield, 167 mg. (66.2%), m.p. 212°. Sublimation from an oil bath at 130° (0.1 mm.) gave the analytical material, m.p. 210°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1790 (lactone), 1745 and 1720 (C=O).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.05; H, 6.58.

Furazan Oxides. III. An Unusual Type of Aromatic Substitution Reaction[1,2]

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Treatment of either 2,4- or 2,3-dinitroaniline in alkaline methanol solution at 50° with aqueous sodium hypochlorite gives rise to an unusual substitution reaction which proceeds by way of the corresponding nitrobenzofurazan oxide as an intermediate. The product in each case is a chloromethoxybenzofurazan oxide in which the nitro group in the nitrobenzofurazan oxide intermediate has been replaced by a chloro group and an adjacent ring hydrogen in this intermediate has been replaced by a methoxy group. An analogous reaction takes place with each of the two nitrobenzofurazans. The structures of the chloromethoxy products were proved by spectral and chemical means. A mechanism for this reaction is suggested.

In 1912 Green and Rowe reported[4] that 2,4-dinitroaniline underwent an unexpectedly complex reaction when it was treated in alkaline methanol solution at 50° with aqueous sodium hypochlorite. Such treatment constitutes a well known method for the preparation of benzofurazan oxides from *o*-nitroanilines; however, the product from 2,4-dinitroaniline was found not to be the corresponding nitrobenzofurazan oxide but rather a chloromethoxybenzofurazan oxide. The chloro and methoxy groups were formulated by Green and Rowe as having the positions relative to the heterocycle which are indicated in structure I,[5] although the structural evidence consisted only in satisfactory analyses for N, Cl, and CH_3O and also the observations

that the compound underwent several reactions typical of furazan oxides.

The use of ethanol in place of methanol in hypochlorite oxidation of 2,4-dinitroaniline was found[4] to give a chloroethoxybenzofurazan oxide whose structure was formulated on similar grounds to be analogous to I.

There appears to be only one other mention in the literature of this unusual type of substitution reaction in which an aromatic nitro group and a ring hydrogen are replaced by chloro and alkoxy groups; in 1958 Dyall and Pausacker reported[6] that treatment of 2,3-dinitroaniline in alkaline ethanol with aqueous sodium hypochlorite gave a product which they formulated solely on the basis of analyses for C, H, and Cl as X-chloro-4-ethoxybenzofurazan oxide.

We have reinvestigated these reactions and have found that in each case the structure which previously was assigned[4,6] to the product is incorrect. Thus, we have established that the product from 2,4-dinitroaniline in methanol has structure II and the product from 2,3-dinitroaniline in methanol has structure III. It is suggested that in substituted benzofurazan oxides of this sort steric compression of the exocyclic oxygen and the adjacent substituent on the six-membered ring may destabilize significantly the configurations such as IIa and IIIa so that the equilibrium mixture would contain predominantly the configurations such as IIb and

(1) Part II: F. B. Mallory and C. S. Wood, *J. Org. Chem.*, **27**, 4109 (1962).

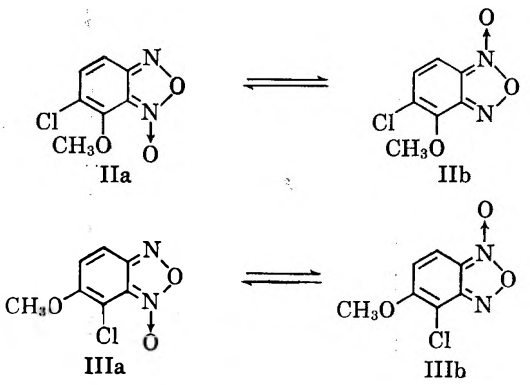
(2) Presented before the Organic Division at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(3) National Science Foundation Cooperative Graduate Fellow, 1960–1961.

(4) A. G. Green and F. M. Rowe, *J. Chem. Soc.*, **101**, 2452 (1912).

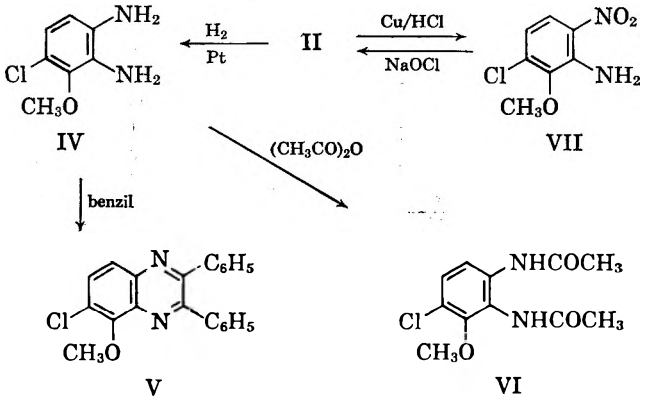
(5) The furazan oxide structure for molecules in this family and the Ia ⇌ Ib type of equilibration by way of *o*-dinitrosobenzenes have been demonstrated by recent work. (See ref. 1 for pertinent references.)

(6) L. K. Dyall and K. H. Pausacker, *Australian J. Chem.*, **11**, 491 (1958).



IIIb in which such steric strain would not be so severe. Thus, to simplify the nomenclature in the present work these two products will be designated as 5-chloro-4-methoxybenzofurazan oxide (IIb) and 4-chloro-5-methoxybenzofurazan oxide (IIIb), respectively.

The proof that the product melting at 80.6–82.0°, which was obtained from the reaction first described by Green and Rowe, has structure II is based on both spectral and chemical evidence. Thus, this product was shown to be a furazan oxide by the characteristic peaks in the 6–7-μ region in its infrared spectrum and also by catalytic hydrogenation to give a compound with properties of an *o*-phenylenediamine; this diamine, which is formulated as 4-chloro-3-methoxy-1,2-phenylenediamine (IV), was characterized by its conversion to a quinoxaline derivative (V) by treatment with benzil and also by its conversion to a diacetyl derivative (VI). Both V and VI gave analyses for C, H, Cl, N, and CH_3O in excellent agreement with the expected values. Further evidence that II is a furazan oxide was obtained by its reduction with copper powder in ethanol containing concentrated hydrochloric acid to give a compound shown by its infrared spectrum and elemental analyses to be a nitroaniline which was formulated as 3-chloro-2-methoxy-6-nitroaniline (VII); this type of reduction is characteristic of benzofurazan oxides.[7] Finally, hypochlorite oxidation of this presumed *o*-nitroaniline VII regenerated II.

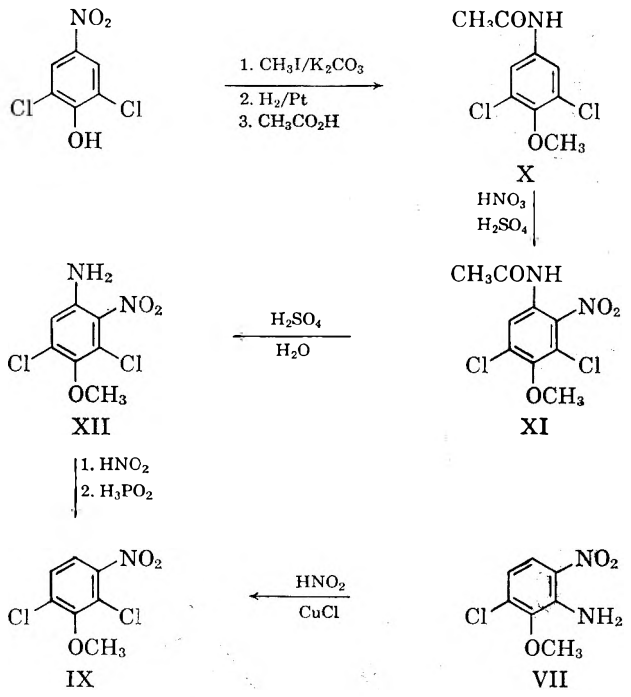


Deamination of VII by diazotization and subsequent treatment with hypophosphorous acid gave 2-chloro-5-nitroanisole (VIII); the identity of VIII was established by comparison with an authentic sample of this known compound which had been synthesized from commercially available 2-amino-5-nitroanisole by a Sandmeyer reaction.

(7) J. H. Boyer, R. F. Reinisch, M. J. Danzig, G. A. Stoner, and F. Sahhar, *J. Am. Chem. Soc.*, **77**, 5688 (1955).

All of the structural evidence given thus far is consistent with the formulation of the furazan oxide as II and the nitroaniline derived from II as VII but it would also be consistent with the formulation of the furazan oxide as I and the nitroaniline as 5-chloro-4-methoxy-2-nitroaniline. These two possibilities were distinguished by the proton n.m.r. spectrum of the furazan oxide which showed the resonance pattern for the ring protons to be that of an AB system with a coupling constant of 9.5 c.p.s. This value is typical[8] for adjacent aromatic protons regardless of other neighboring substituents and is an order of magnitude greater than the value that is characteristic[8] for *para* ring protons; thus, the validity of structure II as opposed to structure I for the furazan oxide is established.

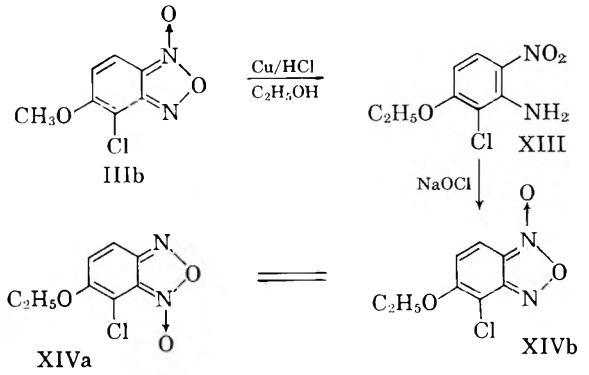
Further proof that structure II is correct was provided by chemical means. The nitroaniline VII was converted to 2,6-dichloro-3-nitroanisole (IX) by a Sandmeyer reaction. Several attempts at reduction of IX followed by diazotization and deamination to give 2,6-dichloroanisole failed to yield any useful product; therefore, the more lengthy process of independent synthesis of IX was carried out as is shown. Commercially available 2,6-dichloro-4-nitrophenol was methylated and the resulting 2,6-dichloro-4-nitroanisole was reduced and subsequently acetylated to give 4-acetamido-2,6-dichloroanisole (X). Mononitration of X gave 4-acetamido-2,6-dichloro-3-nitroanisole (XI) which was hydrolyzed to give 4-amino-2,6-dichloro-3-nitroanisole (XII); both XI and XII were found to have infrared spectra and elemental analyses in agreement with the assigned structures. Deamination of XII gave IX.



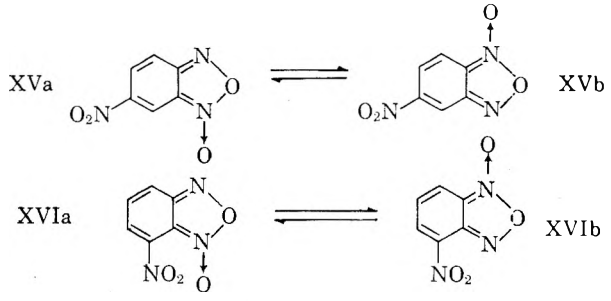
The structure of the furazan oxide, melting at 136.2–137.2° which was obtained from the hypochlorite oxidation of 2,3-dinitroaniline in methanol, was readily established to be III. The method of synthesis, the elemental analyses, and the characteristic peaks in the

(8) (a) H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *ibid.*, **79**, 4596 (1957); (b) R. E. Richards and T. P. Schaefer, *Trans. Faraday Soc.*, **54**, 1280 (1958); (c) J. B. Leane and R. E. Richards, *ibid.*, **55**, 707 (1959).

infrared spectrum of this product indicate that it is a chloromethoxybenzofurazan oxide. The proton n.m.r. spectrum of this compound exhibits an AB resonance pattern for the ring protons with a coupling constant of 9.5 c.p.s. which demonstrates that these two protons are on adjacent ring carbons.[8] Reduction of this furazan oxide with copper powder and hydrochloric acid in ethanol gave a product characterized by its infrared spectrum and elemental analyses as a nitroaniline and formulated as 2-chloro-3-ethoxy-6-nitroaniline (XIII); the exchange of the methoxy group for an ethoxy group under these reaction conditions presumably is due to the influence of the *para* nitro group in XIII. Deamination of XIII gave 2-chloro-4-nitrophenetole as shown by comparison with an authentic sample of this known compound which had been synthesized by ethylation of commercially available 2-chloro-4-nitrophenol. That XIII is an *o*-nitroaniline was shown by its conversion to a furazan oxide by hypochlorite oxidation; this compound is formulated as 4(7)-chloro-5(6)-ethoxybenzofurazan oxide (XIV) and agrees in melting point with the compound obtained[6] from the hypochlorite oxidation of 2,3-dinitroaniline in ethanol. The only structure for the furazan oxide, melting at 136.2–137.2°, which is in accord with all of these observations is III.

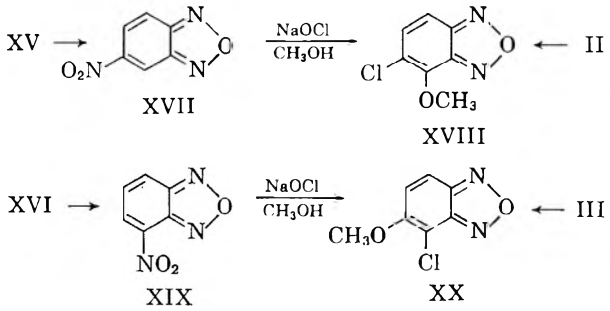


We have shown from two lines of evidence that the substitution reactions leading to II and III are not reactions characteristic of the dinitroanilines themselves, but rather proceed by way of the corresponding nitrobenzofurazan oxides which are presumed to be formed by hypochlorite oxidation of the dinitroanilines under the reaction conditions. Thus, 5(6)-nitrobenzofurazan oxide (XV), synthesized independently by

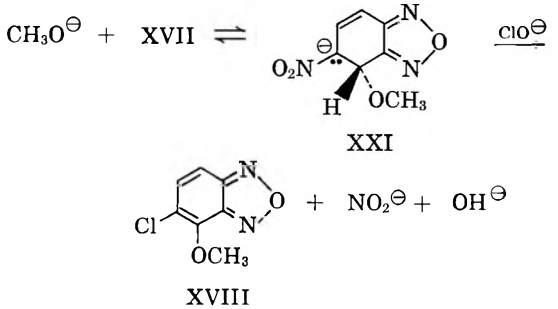


pyrolysis of 2,4-dinitrotriazobenzene, and 4(7)-nitrobenzofurazan oxide (XVI), synthesized independently by nitration of benzofurazan oxide, were found to be converted to the corresponding chloromethoxybenzofurazan oxides II and III, respectively, by treatment in alkaline methanol solution with aqueous sodium hypochlorite.[9] Furthermore, no chloromethoxy products were observed from any of the several compounds related to 2,4-dinitroaniline but having structural modifications that precluded furazan oxide formation which have been subjected to the conditions of this substitution reaction; the compounds investigated were *N*-methyl-2,4-dinitroaniline, 2,4-dinitro-*N*-phenylaniline, 2,2′,4,4′-tetranitrodiphenylamine, 2,4-dinitrophenol, and *m*-dinitrobenzene.

In accord with the presumption that this substitution reaction is not a general one for aromatic nitro compounds but rather depends on the presence of the heterocycle it was found that the nitrobenzofurazans also undergo this reaction: 5-nitrobenzofurazan (XVII), a new compound prepared by deoxygenation of the related furazan oxide XV with triphenylphosphine,[10] gave 5-chloro-4-methoxybenzofurazan (XVIII); and 4-nitrobenzofurazan (XIX) gave 4-chloro-5-methoxybenzofurazan (XX). The structures of XVIII and XX were proved by comparison in each case with a sample which had been obtained by deoxygenation with triphenylphosphine of the corresponding furazan oxide II or III, respectively.



The most satisfactory mechanism that we have been able to devise for this type of substitution reaction is presented for the case of the reaction of 5-nitrobenzofurazan (XVII). The postulate of the reversible



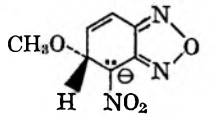
formation of the adduct of XVII and methoxide ion is reasonable by analogy with other systems[11]; the furazan ring would help accommodate the negative charge in this adduct, for which structure XXI is only one of the possible resonance forms. It is suggested that hypochlorite ion could react with XXI to give XVIII, nitrite ion, and hydroxide ion in a concerted process by way of a five-membered cyclic transition state in-

(9) The instability of both XV and XVI in alkaline solution necessitated carrying out these reactions by simultaneous addition of the furazan oxide and the hypochlorite solution to hot alkaline methanol; also, this method was chosen in order to approximate the reaction conditions under which XV and XVI are presumed to be generated *in situ* from the corresponding dinitroanilines. Reactions carried out in this way gave variable yields owing to difficulties in reproducing the technique exactly.

(10) G. Englert and H. Prinzbach, *Z. Naturforsch.*, **17b**, 4 (1962).

(11) J. Meisenheimer, *Ann.*, **323**, 205 (1902).

volving synchronous attack of the chlorine of the hypochlorite ion on C-5 and of the oxygen of the hypochlorite ion on the hydrogen attached to C-4 with concomitant aromatization of the six-membered ring and expulsion of nitrite ion. An analogous mechanism involving attack of hypochlorite ion on the adduct XXII that is shown is proposed as a plausible path from 4-



XXII

nitrobenzofurazan (XIX) to 4-chloro-5-methoxybenzofurazan (XX). Similar mechanisms are suggested for the corresponding reactions of the nitrobenzofurazan oxides XV and XVI to give the chloromethoxybenzofurazan oxides II and III, respectively.

In the absence of specific evidence for the existence of more than one mechanism for this unusual type of substitution reaction it is reasonable on simplicity grounds to reject as a working hypothesis any mechanism which can be demonstrated not to be applicable to all four examples of this reaction (involving the 4- and 5-nitrobenzofurazans and the two corresponding nitrobenzofurazan oxides) which have been found to date. On this basis a mechanism involving cine-substitution of a methoxy group for a nitro group[12] followed by electrophilic chlorination *ortho* to the methoxy group can be excluded since 5(6)-methoxybenzofurazan oxide has been found not to undergo chlorination to give the chloromethoxy compound III under the conditions that III is formed from 4(7)-nitrobenzofurazan oxide. Similarly, mechanisms involving initial replacement of the nitro group by a chloro group can be discarded since 5(6)-chlorobenzofurazan oxide has been found not to give the chloromethoxy compound II under the conditions that II is formed from 5(6)-nitrobenzofurazan oxide.

Experimental[13]

5-Chloro-4-methoxybenzofurazan Oxide (II) from 2,4-Dinitroaniline.—The deep red solution obtained by dissolving 0.92 g. (0.005 mole) of 2,4-dinitroaniline and 1.0 g. (0.015 mole) of potassium hydroxide in 50 ml. of methanol was heated at 48–50° and stirred magnetically during the addition over a period of 5 min. of 80 ml. of an aqueous solution (*ca.* 5%) of sodium hypochlorite.[15] The resulting yellow solution was maintained at 48–50° for an additional 2 min. and then was cooled rapidly using an ice bath to give a precipitate which was collected by suction filtration. This crude solid was sublimed to give 0.64 g. (63%) of bright yellow 5-chloro-4-methoxybenzofurazan oxide (II), m.p. 80.6–82.0° (lit.[4] m.p. 80°). The yields were much lower (*ca.* 30%) from reactions carried out on twenty times this scale.

The 60-Mc. proton n.m.r. spectrum[16] of II in carbon tetrachloride solution with tetramethylsilane as an internal standard showed a singlet for the methoxy group protons with $\tau = 5.47$ and an AB quartet for the ring protons with the resonance of the A proton centered at $\tau = 2.72$ and the resonance of the B proton centered at $\tau = 2.86$ with a coupling constant of 9.5 c.p.s.

Hydrogenation of 5-Chloro-4-methoxybenzofurazan Oxide (II).—A solution of 10.0 g. (0.050 mole) of II in 100 ml. of ethyl acetate was shaken for 21 hr. with 0.1 g. of platinum dioxide in a Parr apparatus under an initial pressure of 30 p.s.i. of hydrogen. The catalyst was removed by gravity filtration under a nitrogen atmosphere and the filtrate was divided into three portions.

A 10-ml. portion of the filtrate was evaporated to dryness under reduced pressure and the residue was sublimed. Recrystallization of the sublimate from water under a nitrogen atmosphere gave gray crystals of **4-chloro-3-methoxy-1,2-phenylenediamine (IV)**, m.p. 49–51°.

A second 10-ml. portion of the original filtrate was added to a solution of 1.0 g. (0.005 mole) of benzil in 100 ml. of glacial acetic acid and the resulting solution was refluxed for 30 min. The ethyl acetate was removed by distillation and the remaining dark colored solution was poured into 500 ml. of ice–water. Treatment of the resulting turbid mixture with dilute hydrochloric acid gave a precipitate which was collected by suction filtration and sublimed. Two recrystallizations of the sublimate from methanol gave 0.10 g. of white, crystalline **6-chloro-5-methoxy-2,3-diphenylquinoxaline (V)**, m.p. 137.2–137.5°.

Anal. Calcd. for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; Cl, 10.22; N, 8.08; CH_3O, 8.95. Found: C, 72.56; H, 4.25; Cl, 10.41; N, 7.92; CH_3O, 8.99.

The solvent from the remaining portion of the original filtrate was removed under reduced pressure to give a dark red oil which was dissolved by the addition of 200 ml. of water and 3 ml. (0.036 mole) of concentrated hydrochloric acid. This solution was stirred magnetically and treated at room temperature with 16 g. (0.16 mole) of acetic anhydride followed by 8 g. (0.10 mole) of sodium acetate; three 8-g. portions of acetic anhydride were added during the subsequent 2 hr. The precipitate was collected by suction filtration and sublimed to give 5.8 g. of ***N,N'*-diacetyl-4-chloro-3-methoxy-1,2-phenylenediamine (VI)**, m.p. 209.4–210.0°. Five recrystallizations from 95% ethanol gave white crystals of VI melting at 209.6–210.0°.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.10; Cl, 13.81; N, 10.91; CH_3O, 12.09. Found: C, 51.62; H, 5.23; Cl, 13.84; N, 10.92; CH_3O, 12.18.

3-Chloro-2-methoxy-6-nitroaniline (VII).—The reduction of II was accomplished by a method previously described.[7] To a solution of 20.0 g. (0.10 mole) of II in 500 ml. of 95% ethanol was added 9.5 g. (0.15 g.-atom) of copper powder and 20 ml. of concentrated hydrochloric acid. The mixture was heated under reflux and stirred magnetically for 24 hr. after which it was concentrated to about 350 ml. and filtered by gravity to remove inorganic material. The filtrate was treated with 150 ml. of 25% aqueous sodium hydroxide solution and the resulting mixture was refluxed for 2 hr. and then the hot mixture was filtered by gravity. The filtrate was refrigerated for 10 hr. and the precipitate was collected by suction filtration and sublimed to give 11.6 g. (57%) of orange crystals of 3-chloro-2-methoxy-6-nitroaniline (VII) with m.p. 86.0–87.4°. Four recrystallizations from 95% ethanol gave a sample of VII with m.p. 87.2–87.6°.

Anal. Calcd. for $C_7H_7ClN_2O_3$: C, 41.50; H, 3.48; N, 13.83. Found: C, 41.54; H, 3.44; N, 13.65.

5-Chloro-4-methoxybenzofurazan Oxide (II) from 3-Chloro-2-methoxy-6-nitroaniline (VII).—The red solution prepared by heating 1.0 g. (0.005 mole) of VII and 0.3 g. (0.005 mole) of potassium hydroxide in 25 ml. of 95% ethanol was cooled to 0° using an ice–salt bath. The reaction temperature was maintained at 0° during the slow addition of 50 ml. of aqueous sodium hypochlorite solution.[15] A red gummy material was removed by suction filtration and sublimed to give 0.10 g. (10%) of yellow crystals melting at 68.5–74.0°. This material was identified as II by comparison of its infrared spectrum with that of the material obtained by hypochlorite oxidation of 2,4-dinitroaniline as described above.

2-Chloro-5-nitroanisole (VIII).—The deamination of VII was carried out by a procedure previously reported.[17] A solution of 1.0 g. (0.005 mole) of VII in 15 ml. of glacial acetic acid was added slowly to a magnetically stirred solution of 0.4 g. (0.006 mole) of sodium nitrite in 3 ml. of concentrated sulfuric acid, maintained at 0–5°, using an ice–salt bath. To this cold solution

(12) An example of such a reaction, the conversion of 2,3-dinitronaphthalene to 1-methoxy-3-nitronaphthalene by treatment with sodium methoxide in methanol at 45°, has been reported by D. C. Morrison, *J. Org. Chem.*, **27**, 296 (1962).

(13) All melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. Sublimations were carried out at a pressure of about 0.05 mm. using an apparatus described elsewhere.[14]

(14) F. B. Mallory, *J. Chem. Educ.*, **39**, 261 (1962).

(15) The aqueous sodium hypochlorite solution used in all of our work was the commercial product "Clorox."

(16) This spectrum was obtained with a Varian HR-60 spectrometer through the courtesy of Mr. E. Anderson of the Bell Telephone Laboratories, Murray Hill, N. J.

(17) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1620 (1933).

was added 7 ml. (0.067 mole) of 50% aqueous hypophosphorous acid. The resulting mixture was stirred for one additional hour at 0–5° and then allowed to stand at room temperature for 24 hr. The mixture was diluted with water to 100 ml. and the yellow solid was collected by suction filtration and washed with 50 ml. of 20% aqueous sodium hydroxide solution followed by several portions of water. Sublimation of the crude product gave 0.70 g. (76%) of 2-chloro-5-nitroanisole (VIII), m.p. 81.0–81.8°. Three recrystallizations from 95% ethanol gave 0.60 g. (65%) of VIII with m.p. 81.8–82.5° (lit.[18] m.p. 83°).

A solution prepared by heating 3.4 g. (0.020 mole) of 2-methoxy-4-nitroaniline, 10 ml. of concentrated hydrochloric acid, and 10 ml. of water was cooled to 0° using an ice–salt bath. To this cold mixture was added slowly a solution of 1.6 g. (0.023 mole) of sodium nitrite in 3 ml. of water. The resulting diazonium chloride solution was then added cautiously to a cold solution of 2.0 g. (0.020 mole) of cuprous chloride in 15 ml. of concentrated hydrochloric acid. When the gas evolution had subsided the mixture was warmed to room temperature and diluted to 400 ml. with water. The precipitate was collected by suction filtration, washed with 10% aqueous sodium hydroxide solution, and sublimed to give 2.4 g. (69%) of 2-chloro-5-nitroanisole (VIII), m.p. 81.0–82.6°. After two recrystallizations from 95% ethanol this sample of VIII melted at 82.4–83.0° (lit.[18] m.p. 83°). Comparison of infrared spectra and a mixture melting point determination showed this material to be identical with that obtained by deamination of 3-chloro-2-methoxy-6-nitroaniline (VII) as described.

2,6-Dichloro-4-nitroanisole.—A previously described method[19] was employed. A suspension prepared from 10.4 g. (0.050 mole) of 2,6-dichloro-4-nitrophenol, 20 ml. (46 g., 0.32 mole) of methyl iodide, 27 g. (0.20 mole) of anhydrous potassium carbonate, and 80 ml. of acetone was heated under reflux for 6 hr. and was then allowed to stand at room temperature for 12 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was treated with 100 ml. of water. The insoluble yellow solid was collected by suction filtration and sublimed to give 9.5 g. (86%) of 2,6-dichloro-4-nitroanisole, m.p. 95.2–97.4° (lit.[20] m.p. 98°).

4-Amino-2,6-dichloroanisole.—Hydrogenation of 4.5 g. (0.02 mole) of 2,6-dichloro-4-nitroanisole in 70 ml. of ethyl acetate was carried out by shaking the solution in a Parr apparatus for 1 hr. with 0.2 g. of platinum dioxide under an initial pressure of 25 p.s.i. of hydrogen. Sublimation of the crude product gave 3.4 g. (87%) of 4-amino-2,6-dichloroanisole, m.p. 76.5–79.0° (lit.[20] m.p. 80.0–80.5°).

4-Acetamido-2,6-dichloroanisole (X).—A solution of 6.3 g. (0.033 mole) of 4-amino-2,6-dichloroanisole in 80 ml. (1.4 mole) of glacial acetic acid was heated under reflux for 8 hr. and then slowly poured into a solution of 52 g. (1.3 mole) of sodium hydroxide in 100 ml. of water. The precipitate was removed by suction filtration and sublimed to give 5.5 g. (72%) of 4-acetamido-2,6-dichloroanisole (X), m.p. 196.2–197.6° (lit.[20] m.p. 196–197°).

4-Acetamido-2,6-dichloro-3-nitroanisole (XI).—A solution of 0.80 g. (0.0034 mole) of X in 1.6 ml. of glacial acetic acid and 4 ml. of concentrated sulfuric acid was cooled to −10° in a Dry Ice–acetone bath. Fuming nitric acid (0.4 ml., min. 90%) was added, the mixture stirred magnetically and maintained at −10 to 0° for 1.75 hr., and then poured into 25 ml. of ice–water. The resulting yellow crystalline solid was collected by suction filtration and amounted to 0.93 g. (98%) of 4-acetamido-2,6-dichloro-3-nitroanisole (XI), m.p. 162.8–163.4°. A small sample of XI which was recrystallized four times from 95% ethanol melted at 163.4–163.8°.

Anal. Calcd. for $C_9H_5Cl_2N_2O_4$: C, 38.73; H, 2.89. Found: C, 38.55; H, 2.70.

4-Amino-2,6-dichloro-3-nitroanisole (XII).—A solution of 6 ml. of concentrated sulfuric acid and 6 ml. of water was added to 0.60 g. (0.002 mole) of XI and the mixture was stirred magnetically and maintained at 100° for 1.5 hr. The resulting orange solution was cooled to room temperature and then poured into a solution of 8 g. of sodium hydroxide in 35 ml. of water. The precipitate was collected by suction filtration and amounted to 0.40 g. (79%) of 4-amino-2,6-dichloro-3-nitroanisole (XII), m.p. 82.5–87.0°. Four recrystallizations from ethanol–water and one sublimation gave orange needles of XII with m.p. 88.2–89.0°.

Anal. Calcd. for $C_7H_6Cl_2N_2O_3$: C, 35.47; H, 2.55. Found: C, 35.68; H, 2.73.

2,6-Dichloro-3-nitroanisole (IX).—The procedure for deamination of XII was the same as that[17] described before for the preparation of 2-chloro-5-nitroanisole (VIII). From 0.50 g. (0.0021 mole) of XII, 0.20 g. (0.0029 mole) of sodium nitrite, and 7 ml. (0.067 mole) of 50% aqueous hypophosphorous acid was obtained after sublimation 0.25 g. (53%) of 2,6-dichloro-3-nitroanisole (IX), m.p. 46.0–46.8°. A mixture melting point determination and infrared spectral comparisons showed this sample of IX to be identical with that obtained from VII as described.

Diazotization of 3-chloro-2-methoxy-6-nitroaniline (VII) was carried out by the method[17] described in connection with the preparation of VIII. A solution of 4.0 g. (0.020 mole) of VII in 30 ml. of glacial acetic acid was added slowly to a magnetically stirred solution of 1.6 g. (0.023 mole) of sodium nitrite in 16 ml. of concentrated sulfuric acid which was maintained at 10–20°. The resulting solution was added dropwise to a solution of 2.0 g. (0.020 mole) of cuprous chloride in 15 ml. of concentrated hydrochloric acid while the reaction temperature was maintained below 30°. The mixture was stirred for an additional 2 hr. and then poured onto crushed ice. The crude solid was collected by suction filtration and sublimed to give 3.8 g. (87%) of 2,6-dichloro-3-nitroanisole (IX), m.p. 45.8–46.4°. Four recrystallizations from 95% ethanol gave yellow crystals of IX melting at 46.4–46.8°.

Anal. Calcd. for $C_7H_5Cl_2NO_3$: C, 37.85; H, 2.27; Cl, 31.93. Found: C, 37.90; H, 2.44; Cl, 31.74.

3-Chloro-2-methoxy-6-nitrobenzonitrile.—This nitrile was synthesized using a previously reported method[21] as the first step in a scheme for proving the structure of VII which was abandoned owing to experimental difficulties later in the scheme. Solutions of 18.0 g. (0.28 mole) of potassium cyanide in 75 ml. of water, 8.3 g. (0.035 mole) of nickel chloride hexahydrate in 25 ml. of water, and 75 g. (0.71 mole) of anhydrous sodium carbonate in 150 ml. of water were combined and cooled to 5° using an ice bath. To this cooled, magnetically stirred solution was added over a period of 5 hr. the diazonium sulfate solution which had been prepared from 10.0 g. (0.049 mole) of 3-chloro-2-methoxy-6-nitroaniline (VII) in 90 ml. of glacial acetic acid and 4.0 g. (0.058 mole) of sodium nitrite in 30 ml. of concentrated sulfuric acid by the method[17] described in connection with the preparation of VIII. During the 5-hr. addition period an additional 75 g. of anhydrous sodium carbonate in 150 ml. of water was added in three equal portions. The reaction mixture was then heated at 80° on a steam bath for 30 min. before it was poured onto crushed ice. The resulting solid was collected by suction filtration and sublimed to give 7.7 g. (73%) of 3-chloro-2-methoxy-6-nitrobenzonitrile, m.p. 108.5–110.0°. A small sample of this nitrile was recrystallized three times from 95% ethanol to give pale yellow needles melting at 110.5–111.2°.

Anal. Calcd. for $C_8H_5ClN_2O_3$: C, 45.20; H, 2.37; N, 13.18. Found: C, 45.32; H, 2.66; N, 13.14.

4-Chloro-5-methoxybenzofurazan Oxide (III) from 2,3-Dinitroaniline.—Acetylation of *m*-nitroaniline with acetic anhydride by a previously reported procedure[22] gave *m*-nitroacetanilide, m.p. 152.2–153.0° (lit.[22] m.p. 152°).

Nitration of *m*-nitroacetanilide followed by recrystallization of the crude mixture of isomers from benzene–acetone (2:1) according to a procedure previously described[23] gave **2,3-dinitroacetanilide**, m.p. 185.8–187.0° (lit.[23] m.p. 187°).

The 2,3-dinitroacetanilide was hydrolyzed by a previously reported method.[24] A mixture of 1.0 g. (0.004 mole) of 2,3-dinitroacetanilide, 5 ml. of concentrated hydrochloric acid, and 15 ml. of absolute ethanol was heated under reflux for 1 hr. The resulting yellow solution was poured into 100 ml. of ice–water and the precipitate was collected by suction filtration. Recrystallization of the crude product from 95% ethanol gave 0.5 g. (61%) of **2,3-dinitroaniline**, m.p. 129.6–130.8° (lit.[25] m.p. 127°).

A solution of 1.0 g. (0.015 mole) of potassium hydroxide in 15 ml. of methanol was added to a solution of 0.92 g. (0.005 mole) of

(18) E. L. Holmes, C. K. Ingold, and E. H. Ingold, *J. Chem. Soc.*, 1689 (1926).

(19) J. P. Brown and E. B. McCall, *ibid.*, 3681 (1955).

(20) C. de Traz, *Helv. Chim. Acta*, **30**, 232 (1947).

(21) F. R. Storrie, *J. Chem. Soc.*, 1746 (1937).

(22) H. I. X. Mager and W. Berends, *Rec. trav. chim.*, **78**, 5 (1959).

(23) B. C. Platt and T. M. Sharp, *J. Chem. Soc.*, 2129 (1948).

(24) K. H. Pausacker and J. G. Scroggie, *Chem. Ind.* (London), 1290 (1954).

(25) P. G. Van de Vliet, *Rec. trav. chim.*, **43**, 606 (1924).

2,3-dinitroaniline in 10 ml. of methanol at 50° to give a pale red solution which was stirred magnetically and heated at 48–52° during the addition over a period of 6 min. of 100 ml. of an aqueous solution of sodium hypochlorite.[15] The resulting pale orange solution was maintained at 48–52° for an additional 1 min. and then cooled using an ice bath to give a precipitate which was collected by suction filtration. The crude product was sublimed and the sublimate recrystallized from 95% ethanol to give 0.20 g. (20%) of yellow 4-chloro-5-methoxybenzofurazan oxide (III), m.p. 134.0–134.8°. This material was identified as III by comparison of its infrared spectrum with that of the sample of III obtained from the hypochlorite oxidation of 4(7)-nitrobenzofurazan oxide (XVI) as described later.

The 60-Mc. proton n.m.r. spectrum[26] of III in deuteriochloroform solution with tetramethylsilane as an internal standard showed a singlet for the methoxy group protons with $\tau = 5.97$ and an AB quartet for the ring protons with the resonance of the A proton centered at $\tau = 2.73$ and the resonance of the B proton centered at $\tau = 2.93$ with a coupling constant of 9.5 c.p.s.

2-Chloro-3-ethoxy-6-nitroaniline (XIII).—The method was similar to that[7] described previously for the preparation of VII. Treatment of 2.5 g. (0.012 mole) of III with 1.1 g. (0.017 mole) of copper powder, 2.5 ml. of concentrated hydrochloric acid, and 87 ml. of 95% ethanol gave on sublimation 1.40 g. (55%) of XIII melting at 86–94°. Six recrystallizations from 95% ethanol gave 2-chloro-3-ethoxy-6-nitroaniline (XIII) with m.p. 100.0–100.8°.

Anal. Calcd. for $C_8H_9ClN_2O_3$: C, 44.35; H, 4.19. Found: C, 44.59; H, 4.22.

2-Chloro-4-nitrophenetole.—The deamination of XIII was carried out by the procedure[17] described above for the preparation of VIII. Treatment of 0.50 g. (0.0023 mole) of XIII with 0.20 g. (0.0029 mole) of sodium nitrite and 3.5 ml. (0.034 mole) of 50% aqueous hypophosphorous acid gave on sublimation 0.30 g. (65%) of material melting at 79.8–80.6°. Three recrystallizations from 95% ethanol gave 2-chloro-4-nitrophenetole with m.p. 81.0–82.6° (lit.[27] m.p. 82°).

A mixture of 0.87 g. (0.005 mole) of 2-chloro-4-nitrophenol, 4.1 ml. (5.9 g., 0.054 mole) of ethyl bromide, 2.5 g. (0.018 mole) of anhydrous potassium carbonate, and 20 ml. of acetone was heated under reflux and stirred magnetically for 16 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was treated with 50 ml. of water. The insoluble material was collected by suction filtration to give 1.0 g. (99%) of 2-chloro-4-nitrophenetole, m.p. 80.8–82.0° (lit.[27] m.p. 82°). This material was shown by a mixture melting point determination and infrared spectral comparisons to be identical with the 2-chloro-4-nitrophenetole obtained from deamination of XIII as described above.

4-Chloro-5-ethoxybenzofurazan Oxide (XIV) from 2-Chloro-3-ethoxy-6-nitroaniline (XIII).—The red solution obtained by adding 0.10 g. (0.0005 mole) of XIII to a solution of 0.20 g. (0.003 mole) of potassium hydroxide in 3 ml. of 95% ethanol was stirred magnetically at room temperature during the addition over a period of 5 min. of 10 ml. of an aqueous solution of sodium hypochlorite.[15] The reaction mixture was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. The ether was removed by evaporation under reduced pressure and the residual solid was sublimed and the sublimate recrystallized from 95% ethanol to give yellow crystals of 4-chloro-5-ethoxybenzofurazan oxide (XIV) melting at 99.8–102.0° (lit.[6] m.p. 101–102°). This material was shown by a mixture melting point determination and comparison of infrared spectra to be identical with the sample of XIV obtained from 4(7)-nitrobenzofurazan oxide (XVI) as described later.

5-Chloro-4-methoxybenzofurazan Oxide (II) from 5(6)-Nitrobenzofurazan Oxide (XV).—The method for the preparation of XV was essentially that described.[28] A solution of 22.0 g. (0.12 mole) of 2,4-dinitroaniline in 175 ml. of glacial acetic acid and 88 ml. of concentrated sulfuric acid was stirred magnetically and maintained at 0–5° during the slow addition of 9.8 g. (0.14 mole) of sodium nitrite dissolved in a minimum volume of water. To the resulting clear solution was added slowly a solution of 17.6 g. (0.27 mole) of sodium azide in 50 ml. of water. The precipitated 2,4-dinitrotriazobenzene was collected by suction filtration and washed with water. A mixture of this crude material in 50 ml. of water was heated on a steam bath for 2 hr. until the evolution of gas had ceased. The reaction mixture was cooled and the solid was removed by suction filtration. Sublimation of the crude solid gave 18.1 g. (83%) of 5(6)-nitrobenzofurazan oxide (XV), m.p. 68.8–70.6° (lit.[28] m.p. 72°).

A solution of 1.0 g. (0.015 mole) of potassium hydroxide in 25 ml. of methanol in a 200-ml. 3-neck flask was stirred magnetically and maintained at 48–50° during the simultaneous addition to this flask of a solution of 0.91 g. (0.005 mole) of XV in 25 ml. of methanol from a dropping funnel and 100 ml. of an aqueous solution of sodium hypochlorite[15] from another dropping funnel. The rates of addition were regulated so that the time required for the addition of each solution was 25 min. The stirred reaction mixture was maintained at 48–50° for an additional 10 min. and then cooled using an ice bath. The precipitate was collected by suction filtration and sublimed to give 0.37 g. (37%) of material melting at 70.6–75.4°. Recrystallization of the sublimate from 95% ethanol gave 0.25 g. (25%) of 5-chloro-4-methoxybenzofurazan oxide (II), m.p. 79.0–79.5°, shown by a mixture melting point determination and infrared spectral comparisons to be identical with the sample of II obtained from 2,4-dinitroaniline as described.

4-Chloro-5-methoxybenzofurazan Oxide (III) from 4(7)-Nitrobenzofurazan Oxide (XVI).—The technique was similar to that described for the preparation of II from XV. Simultaneous addition over a period of 12 min. of 125 ml. of an aqueous solution of sodium hypochlorite[15] and a solution of 0.91 g. (0.005 mole) of XVI in 60 ml. of methanol to a magnetically stirred solution of 1.0 g. (0.015 mole) of potassium hydroxide in 25 ml. of methanol maintained at 48–52° followed by an additional 8 min. of stirring at 48–52° gave 0.40 g. (40%) of yellow 4-chloro-5-methoxybenzofurazan oxide (III), m.p. 137.4–138.2°. A small sample of III from a similar preparation was recrystallized four times from 95% ethanol to give a m.p. of 136.2–137.2°.

Anal. Calcd. for $C_7H_5ClN_2O_3$: C, 41.91; H, 2.51; N, 13.97. Found: C, 42.06; H, 2.68; N, 13.80.

4-Chloro-5-ethoxybenzofurazan Oxide (XIV) from 4(7)-Nitrobenzofurazan Oxide (XVI).—The procedure was identical to that described for the conversion of XVI to III except that ethanol was used in place of methanol and that it was necessary at the completion of the reaction to concentrate the reaction mixture using a rotary evaporator in order to obtain a precipitate. Recrystallization of the crude product from 95% ethanol gave 4-chloro-5-ethoxybenzofurazan oxide (XIV) melting at 102.4–103.2° (lit.[6] m.p. 101–102°).

5-Chloro-4-methoxybenzofurazan (XVIII).—The deoxygenation of 5(6)-nitrobenzofurazan oxide (XV) was carried out using a method previously described.[10] A solution of 0.91 g. (0.0050 mole) of XV and 1.44 g. (0.0055 mole) of triphenylphosphine in 50 ml. of xylene was heated under reflux for 2 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was sublimed to give 0.63 g. (76%) of 5-nitrobenzofurazan (XVII), m.p. 64.6–65.4°. Two recrystallizations from 95% ethanol gave material melting at 65.4–66.2°.

Anal. Calcd. for $C_6H_3N_3O_3$: C, 43.64; H, 1.83. Found: C, 43.54; H, 1.69.

A solution of 0.20 g. (0.0030 mole) of potassium hydroxide in 5 ml. of methanol was stirred magnetically and maintained at 48–52° during the simultaneous addition over a period of 5 min. of 30 ml. of an aqueous solution of sodium hypochlorite[15] and a solution of 0.20 g. (0.0012 mole) of XVII in 5 ml. of methanol. The stirred reaction mixture was maintained at 48–52° for an additional 5 min. and then cooled using an ice bath. The precipitate was collected by suction filtration and sublimed to give 0.10 g. (45%) of material melting at 62.2–64.6°. Recrystallization of the crude product from 95% ethanol gave 5-chloro-4-methoxybenzofurazan (XVIII), m.p. 69.6–70.6°, shown by comparisons of infrared spectra and a mixture melting point determination to be identical with the material obtained by deoxygenation of II as subsequently described.

Reduction of 1.0 g. (0.005 mole) of 5-chloro-4-methoxybenzofurazan oxide (II) with triphenylphosphine in refluxing xylene by the method[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave 0.73 g. (79%) of sublimed XVIII with m.p. 71.0–72.4°. A small sample of the product from a similar preparation was recrystallized three times from 95% ethanol to give pale yellow 5-chloro-4-methoxybenzofurazan, m.p. 71.6–72.6°.

(26) This spectrum was obtained with a Varian A-60 spectrometer through the courtesy of Dr. H. C. Beachell, University of Delaware, Newark, Del.

(27) F. Reverdin and F. Düring, *Ber.*, **32**, 156 (1899).

(28) R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *J. Am. Chem. Soc.*, **76**, 2233 (1954).

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.54; H, 2.73. Found: C, 45.33; H, 2.78.

4-Chloro-5-methoxybenzofurazan (XX).—A solution of 13.6 g. (0.1 mole) of benzofurazan oxide, prepared by a method previously described,[29] in 44.5 ml. of concentrated sulfuric acid was stirred magnetically and maintained at 5–12° during the addition over a period of 45 min. of a mixture of 5 ml. of fuming nitric acid (min. 90%) and 20 ml. of concentrated sulfuric acid. The stirred reaction mixture was cooled in an ice bath for an additional 1.5 hr. and then poured into ice–water. The solid was collected by suction filtration, washed with water, and recrystallized from 100 ml. of glacial acetic acid (Norit) to give 9.8 g. (54%) of **4(7)-nitrobenzofurazan oxide (XVI)**, m.p. 141.6–143.2° (lit.[28] m.p. 143°).

Reduction of 0.91 g. (0.005 mole) of XVI with triphenylphosphine in refluxing xylene according to the procedure[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave on sublimation 0.37 g. (45%) of **4-nitrobenzofurazan (XIX)**, m.p. 96.6–98.2° (lit.[30] m.p. 98°).

The procedure for the conversion of XIX to 4-chloro-5-methoxybenzofurazan (XX) was identical to that described for the conversion of XVII to 5-chloro-4-methoxybenzofurazan (XVIII). From 0.20 g. (0.0012 mole) of XIX was obtained on sublimation 0.15 g. (67%) of 4-chloro-5-methoxybenzofurazan (XX) with m.p. 130.2–130.8°. Three recrystallizations of the sublimate from 95% ethanol sharpened the m.p. to 130.4–130.8°. Mixture melting point determination and comparison of infrared spectra showed this material to be identical with sample of XX obtained by deoxygenation of 4-chloro-5-methoxybenzofurazan oxide (III) as subsequently described.

Treatment of 0.70 g. (0.0035 mole) of III with 1.0 g. (0.0038 mole) of triphenylphosphine in 35 ml. of refluxing xylene according to the method[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave 0.53 g. (82%) of 4-chloro-5-methoxybenzofurazan (XX) which melted at 129.0–130.2° after one recrystallization from 95% ethanol. Two subsequent recrystallizations from 95% ethanol gave pale yellow crystals of XX melting at 130.2–130.6°.

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.54; H, 2.73. Found: C, 45.60; H, 2.80.

Mechanistic Evidence.—A mechanically stirred solution of 3.4 g. (0.02 mole) of 4-methoxy-2-nitroaniline and 3.4 g. (0.05 mole) of potassium hydroxide in 200 ml. of methanol was heated to 50° and 400 ml. of an aqueous solution of sodium hypochlorite[15] was added. The reaction mixture was cooled and filtered by suction to give 2.4 g. (72%) of **5(6)-methoxybenzofurazan oxide**, m.p. 112–115° (lit.[28] m.p. 118°). The infrared spectrum of this material showed the absence of several intense peaks characteristic of 4-chloro-5-methoxybenzofurazan oxide (III).

A mechanically stirred solution of 3.4 g. (0.02 mole) of 4-chloro-2-nitroaniline and 5.3 g. (0.08 mole) of potassium hydroxide in 200 ml. of methanol was heated to 50° and 400 ml. of an aqueous solution of sodium hypochlorite[15] was added. The reaction mixture was cooled and the precipitate was collected and recrystallized from methanol to give 2.1 g. (63%) of **5(6)-chlorobenzofurazan oxide**, m.p. 43–45° (lit.[28] m.p. 48°). The infrared spectrum of this material was essentially identical with that of an authentic sample of 5(6)-chlorobenzofurazan oxide and showed the absence of several intense peaks characteristic of 5-chloro-4-methoxybenzofurazan oxide (II).

(29) F. B. Mallory, *Org. Syn.*, **37**, 1 (1957).
(30) P. Drost, *Ann.*, **307**, 49 (1899).

Electron Density and Orientation of Nucleophilic Substitution in the Purine Ring[1]

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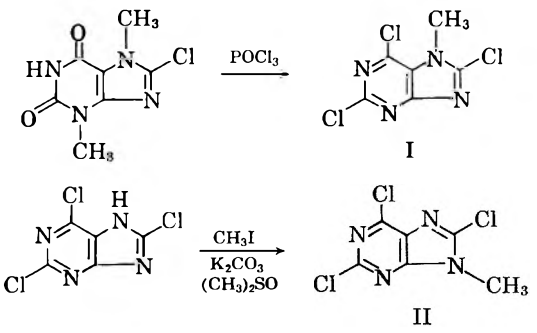
The poor correlation between various electron density calculations and experimental observations relative to the purine ring has resulted in a careful re-examination of nucleophilic substitution in that ring system. It now has been observed that the position of nucleophilic attack can be changed by temporarily blocking the imidazole hydrogen which prevents anion formation in the presence of strong nucleophiles. Acid-catalyzed nucleophilic displacement also may result in a change of orientation. These effects are discussed in terms of a unified theory. It is suggested that similar results might be expected from other related nitrogen heterocyclic systems.

Nucleophilic attack by various reagents on 2,6,8-trichloropurine was first studied by Fischer[2] and extended by later investigators.[3-8] In all cases, with strong bases, nucleophilic displacement occurs first at position 6 followed by position 2 and finally position 8. The reactivities of the various chlorine atoms are such that selective substitution often can be accomplished under the appropriate reaction conditions. When 7-methyl-2,6,8-trichloropurine (I) or 9-methyl-2,6,8-trichloropurine (II) was similarly studied by Fischer,[9] he found that in most instances substitution occurred first at position 8. This would seem at first inspection to be at variance with expectation since modern theory would require that the methyl group at position 7 or 9 should, by the inductive effect, increase the electron density in the imidazole ring and thus favor attack by a nucleophilic reagent in the pyrimidine ring (position 6). Recent electron density calculations for purine[10] would predict nucleophilic substitution at position 6 followed by 2 then 8. Pullman[11] has calculated the localization energy for nucleophilic attack on the purine nucleus and has taken into account induced polarization under these conditions. According to these calculations there is an equal possibility for nucleophilic attack at either position 6 or 8 of the purine ring. Electron density calculations by Mason[12] for nucleophilic attack predict position

(1) This research was supported by grant NSF-G13291 from the National Science Foundation.
(2) E. Fischer, *Ber.*, **30**, 2220, 2226 (1897).
(3) R. K. Robins and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 3624 (1952).
(4) J. Baddiley, J. G. Buchanan, F. J. Hawker, and J. E. Stephenson, *J. Chem. Soc.*, 4659 (1956).
(5) S. R. Breshears, S. S. Wang, S. G. Bechtolt, and B. E. Christensen, *J. Am. Chem. Soc.*, **81**, 3789 (1959).
(6) R. K. Robins, *J. Org. Chem.*, **26**, 447 (1961).
(7) H. Ballweg, *Ann.*, **649**, 114 (1961).
(8) B. G. Boldyrev and R. G. Makitra, *J. Appl. Chem. USSR*, **28**, 399 (1955).
(9) (a) E. Fischer, *Ber.*, **28**, 2490 (1895); (b) **30**, 1846 (1897); (c) **31**, 104 (1898); (d) **32**, 267 (1899).
(10) R. L. Miller and P. G. Lykos, *Tetrahedron Letters*, 493 (1962); R. L. Miller, P. G. Lykos, and H. N. Schmeising, *J. Am. Chem. Soc.*, **84**, 4623 (1962).
(11) B. Pullman, *J. Chem. Soc.*, 1621 (1959).
(12) S. F. Mason, in "The Chemistry and Biology of Purines," a Ciba Foundation Symposium, Wolstenholme and O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p. 72.

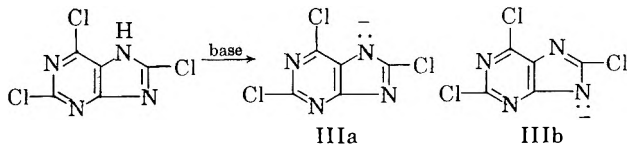
8 most susceptible, followed by position 6 then position 2 of the purine ring.

In an effort to study this problem it was decided to reinvestigate the earlier work of Fischer with 7- and 9-methyl-2,6,8-trichloropurine. Since Fischer prepared these derivatives (I and II) by sealed-tube chlorination procedures,[9] new methods were devised which now make I and II readily available. 7-Methyl-2,6,8-trichloropurine (I) was prepared by the action of phosphoryl chloride on 8-chlorotheobromine. 9-Methyl-2,6,8-trichloropurine (II) was prepared most readily by the methylation of 2,6,8-trichloropurine[6] in dimethyl sulfoxide with methyl iodide patterned after the general method employed by Montgomery and Temple[13] for

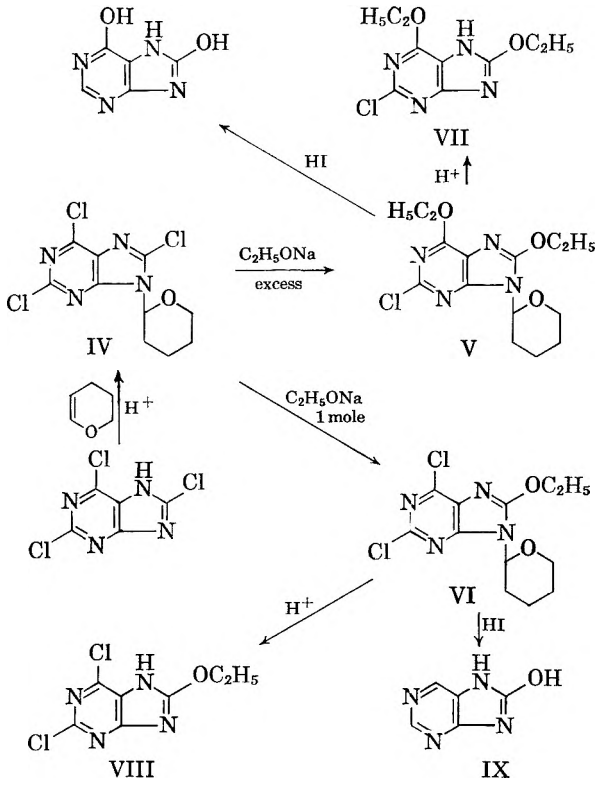


alkylation of 6-chloropurine. In every instance studied, nucleophilic attack on I and II did indeed give the products noted by Fischer,[9] and in all cases structural assignments were verified. It should be noted that 6,8-dichloropurine[14] is similar to 2,6,8-trichloropurine in that strong bases attack position 6 in preference to 8.

An explanation is now proposed which will account for all known facts regarding nucleophilic displacement in the purine ring and which may be extended to other heterocyclic systems. In the case of the reaction of strong bases, such as hydroxide, alkoxide, alkylamines, alkyl mercaptides, etc., with 2,6,8-trichloropurine, the first step involves the removal of the acidic proton from the imidazole ring. Thus, the species which actually reacts with the excess nucleophile is in reality the anion which is stabilized by resonance. Thus, the anions IIIa and IIIb actually increase the electron density at



position 8 and make nucleophilic attack at this position more difficult. Hence, nucleophilic attack under these conditions occurs preferentially at position 6. In the instances where an imidazole anion cannot form, *i.e.*, 7- and 9-methyl-2,6,8-trichloropurine, nucleophilic substitution occurs preferentially (or equally as well) at position 8. In order to examine this hypothesis more closely, it was proposed to block the imidazole anion formation by some group which could readily be removed. Thus, one should be able to control the orientation of nucleophilic displacement by this means. The blocking group chosen for study was the tetrahydropyranyl



SCHEME 1

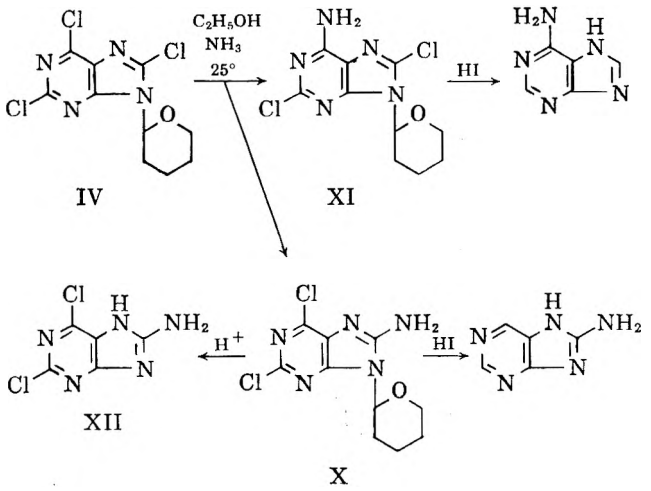
group since 9-(tetrahydro-2′-pyranyl)purines[15] are easily prepared, and the tetrahydropyranyl group is readily removed with acid. 2,6,8-Trichloropurine and 2,3-dihydropyran readily gave 9-(tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV) in good yield. The structure of IV was established by comparison of the ultraviolet absorption spectra with those of the model compounds I and II. When IV was treated with excess sodium ethylate in ethanol at room temperature, 2-chloro-6,8-diethoxy - 9 - (tetrahydro - 2′ - pyranyl)purine (V) was obtained in good yield. The structure of V was established by treatment with hydriodic acid which yielded 6,8-dihydroxypurine.[14] When only one mole of sodium ethoxide was employed, the major product was the 8-ethoxy derivative (VI), although a small amount of 6-ethoxy-2,8-dichloro-9-(tetrahydro-2′-pyranyl)purine was detected. The structure of VI was determined by conversion to 8-hydroxypurine with hydriodic acid. Mild acid hydrolysis of VI and V gave an excellent yield of 2,6-dichloro-8-ethoxypurine (VIII) and 2-chloro-6,8-diethoxypurine (VII), respectively. The syntheses of VII and VIII are recorded here for the first time since these compounds are inaccessible by other routes. Thus, in effect, 2,6-dichloro-8-ethoxypurine (VIII) has been prepared from 2,6,8-trichloropurine which by direct reaction with ethoxide ion yields 2,8-dichloro-6-ethoxypurine.[2] Similarly, an excess of sodium ethoxide and 2,6,8-trichloropurine yields 8-chloro-2,6-diethoxypurine.[2] With IV and excess sodium ethoxide in ethanol, 2-chloro-6,8-diethoxypurine (VII) was obtained *via* V.

An extension of this study with ethanolic ammonia and 9 - (tetrahydro - 2′ - pyranyl) - 2,6,8 - trichloropurine (IV) at room temperature revealed that in this instance both 8-amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X) and 6-amino-2,8-dichloro-9-(tetra-

(13) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961).

(14) R. K. Robins, *ibid.*, **80**, 6671 (1958).

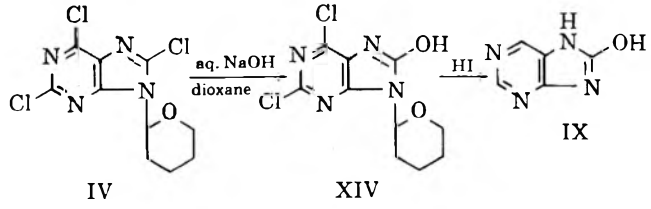
(15) R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis, and A. Jackson, *ibid.*, **83**, 2574 (1961).



SCHEME 2

hydro-2′-pyranyl)purine (XI) were formed. X, however, was obtained in a much greater proportion. The structures of X and XI were established by conversion with hydriodic acid to the known 8-aminopurine[16] and adenine, respectively. Mild acid hydrolysis provided the previously unknown 8-amino-2,6-dichloropurine (XII). The reaction of ammonia and 2,6,8-trichloropurine directly yields 6-amino-2,8-dichloropurine.[2] As expected, IV and excess sodium sulfide at room temperature gave 2-chloro-9-(tetrahydro-2′-pyranyl)-6,8-purinedithiol (XIII). The structure of XIII was established by treatment with Raney nickel in refluxing 2-ethoxyethanol. At this temperature the pyran and mercapto groups were removed simultaneously to yield 2-chloropurine.[17]

When 9-(tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV) was treated with dilute aqueous sodium hydroxide in dioxane at room temperature, only the chlorine at position 8 was removed to yield 2,6-dichloro-8-hydroxy-9-(tetrahydro-2′-pyranyl)purine (XIV). The structure of XIV was determined by its



conversion to 8-hydroxypurine (IX) with hydriodic acid.

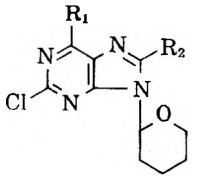
Further indication of the stabilizing effect of anion formation in the imidazole ring is found in the fact that 8-chloropurine[18] is extremely stable to base. Four normal boiling sodium hydroxide and 8-chloropurine gave unchanged starting material after one hour and forty-five minutes.[18] In contrast, 6-chloropurine is reported to yield hypoxanthine in the presence of boiling 0.1 *N* sodium hydroxide.[19]

It is of considerable interest that in the case of 6,8-dichloropurine, thiourea in refluxing ethanol gives 6,8-purinedithiol.[14] Similarly, Ballweg[7] has reported that

(16) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).
(17) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).
(18) A. G. Beaman and R. K. Robins, *J. Appl. Chem.*, **12**, 432 (1962).
(19) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF 9-(TETRAHYDRO-2′-PYRANYL) PURINES

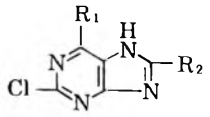


Compound no.	R_1	R_2	pH 1 λ_{max} mμ	pH 1 ε	pH 11 λ_{max} mμ	pH 11 ε
IV	Cl	Cl	279	12,600	282.5	11,400
V	C_2H_5O	C_2H_5O	267	14,100	266	14,900
VI	Cl	C_2H_5O	251	4,590	251	7,350
			281.5	12,000	280.5	12,800
X	Cl	NH_2	243	6,200	226.5	10,200
			289.5	13,800	265	7,480
					299.5	11,800
XI	NH_2	Cl	267.5	15,200	268	16,400
			275[a]	12,900		
XIII	SH	SH	275	6,750	267	15,900
			362.5	17,600	342	18,500
XIV	Cl	OH	249.5	6,550	229.5	13,100
			289	13,700	270	10,100
					302	13,000

[a] Inflection.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF VARIOUS PURINES



Compound no.	R_1	R_2	pH 1 λ_{max} mμ	pH 1 ε	pH 11 λ_{max} mμ	pH 11 ε
VII	C_2H_5O	C_2H_5O	265.5	13,500	274.5	13,800
VIII	Cl	C_2H_5O	282.5	12,300	228.5	14,200
					289	10,700
XII	Cl	NH_2	248.5	4,080	237	16,900
			290	15,900	302	14,300
XV	Cl	*p*-ClC_6H_4NH	299.5	18,900	305.5	28,000

2,6,8-trichloropurine under the same conditions yields 2-chloro-6,8-purinedithiol. In these two instances it is clear that nucleophilic attack occurs without formation of the anion IIIa or IIIb. Thiourea is an example of a good nucleophile but a weak base; therefore, displacement at carbon 8 *does* occur in the absence of a strongly basic nucleophile.

In this regard it is interesting to consider the reaction of 2,6,8-trichloropurine and strong acid. Fischer[2] showed that in the presence of strong acid, reaction occurs at position 8 to give 2,6-dichloro-8-hydroxypurine. Similarly, Robins[14] has shown that under acidic conditions 6,8-dichloropurine yields 6-chloro-8-hydroxypurine. Robins[14] has postulated protonation in the imidazole ring under these conditions, which would greatly lower the electron density at position 8 thus favoring nucleophilic attack at that position.

It is quite probable that in order to obtain good correlation between electron density calculations of nitrogen heterocyclic compounds and laboratory experimental observations, careful examination of the actual species undergoing reaction is a most important factor to be considered. Heterocyclic systems often form ionic species in the reaction media which considerably

change the electron distribution of the isolated molecule. Such a situation has recently been observed[20] for pyrazole and imidazole and is probably quite general for similar heterocycles.

Experimental[21]

2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 1 g.) was stirred for 3 hr. at room temperature with 15 ml. of ethanol containing 0.23 g. of dissolved sodium. The resulting solution was cooled and filtered. The crude product was washed with water and recrystallized from ethanol to yield 0.9 g. (84.8%) of crystals, m.p. 130–131°.

Anal. Calcd. for $C_{14}H_{19}ClN_4O_3$: C, 51.3; H, 5.8; N, 17.1. Found: C, 51.3; H, 6.1; N, 17.2.

9-Methyl-2,6,8-trichloropurine (II).—Anhydrous 2,6,8-trichloropurine[6] (86 g.), 102 g. of methyl iodide, 54.4 g. of anhydrous potassium carbonate, and 3800 ml. of dimethyl sulfoxide were stirred mechanically at room temperature for 24 hr. At the end of this period 1000 g. of ice was added and precipitation occurred. The white solid was filtered, washed with ice–water, and dried to yield 45 g. of crude product, m.p. 168.5–176°. Two recrystallizations from ethanol gave 29 g. of white crystalline needles, m.p. 176–176.5° (lit.[9] m.p. 176.5°). Ultraviolet absorption data: $\lambda_{max}^{pH\ 1}$, 279 mμ, ε 18,100; $\lambda_{max}^{pH\ 11}$, 280.5 mμ, ε 17,800; λ_{max}^{EtOH} 280 mμ, ε 17,500.

Anal. Calcd. for $C_6H_3Cl_3N_4$: C, 30.3; H, 1.3; N, 23.5. Found: C, 30.5; H, 1.5; N, 23.8.

7-Methyl-2,6,8-trichloropurine (I).—8-Chlorotheobromine[22] (44 g.) and 540 ml. of phosphorus oxychloride were refluxed for 24 hr. The excess phosphorus oxychloride was removed under reduced pressure, employing a steam bath as a source of heat, until the rate of distillation slowed down to a few drops per second. The residue was then poured onto 1000 g. of an ice and water mixture and the suspension allowed to stand for 15 min. with occasional stirring. The product was then filtered, washed with water to remove the acid, and finally washed with ethanol to give 17 g. of a yellow-white solid. Recrystallization of the crude product from ethanol gave 9.6 g. (19.7%) of long, slender white needles, m.p. 158.5–160.5° (lit.[9] 159–161°). The acidic filtrate was set aside in the refrigerator for 2 days to yield 20 g. of 8-chlorotheobromine. Ultraviolet absorption data: $\lambda_{max}^{pH\ 1}$, 285 mμ, ε 11,300; $\lambda_{max}^{pH\ 11}$, 285 mμ, ε 10,400; λ_{max}^{EtOH} 284 mμ, ε 10,700.

Anal. Calcd. for $C_6H_3Cl_3N_4$: C, 30.3; H, 1.3; N, 23.5. Found: C, 30.6; H, 1.3; N, 23.8.

2-Chloro-6,8-diethoxypurine (VII).—2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V, 3 g.) was dissolved in 200 ml. of ethanol. The solution was acidified to pH 1 with 1 *N* hydrochloric acid and allowed to evaporate at room temperature. The residue was washed with water and recrystallized from benzene to yield 1.4 g. (62.8%) of 2-chloro-6,8-diethoxypurine (VII), m.p. 202–204.5°.

Anal. Calcd. for $C_9H_{11}ClN_4O_2$: C, 44.5; H, 4.5; N, 23.1. Found: C, 44.6; H, 4.7; N, 23.3.

2,6-Dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl)purine (VI).—To ethanol (75 ml.), containing 0.37 g. of dissolved sodium, was added 5.0 g. of 9-(tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV). The solution was stirred for 3 hr. at room temperature, and then 50 g. of ice was added with vigorous stirring. The resulting precipitate was filtered, washed with water, and dried to yield 4.6 g. of a white solid which was recrystallized from *n*-heptane to yield 3.2 g. of product contaminated with a small amount of 2,8-dichloro-6-ethoxy-9-(tetrahydro-2′-pyranyl)purine. This crude product was twice more recrystallized from *n*-heptane to yield 1.18 g. of 2,6-dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl) purine (VI), m.p. 114–116.5°.

Anal. Calcd. for $C_{12}H_{14}Cl_2N_4O_2$: C, 45.4; H, 4.4; N, 17.7. Found: C, 45.2; H, 4.4; N, 17.6.

The Formation of 6,8-Dihydroxypurine from 2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V).—2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V, 1.1 g.) was treated with 22 ml. of 47% hydriodic acid under reflux for 2 hr. The solution was filtered and evaporated to dryness on the steam bath, and 20 ml. of concentrated aqueous ammonia was added to the residue. The solution was then heated on the steam bath for 10 min. and filtered, and the filtrate was acidified to pH 1 with concentrated hydrochloric acid. The precipitated solid was filtered with suction, washed with water, and recrystallized from boiling water to yield 0.3 g. The acidic filtrate was allowed to evaporate at room temperature, and the remaining residue was washed with and recrystallized from water to give 0.1 g. The over-all yield was 0.4 g. (78.3%) of 6,8-dihydroxypurine. The compound gave a negative test for halogen (sodium fusion). The ultraviolet absorption spectra were identical to those of 6,8-dihydroxypurine.[14]

Anal. Calcd. for $C_5H_4N_4O_2$: C, 39.5; H, 2.6; N, 36.8. Found: C, 39.7; H, 2.7; N, 36.8.

9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV).—2,6,8-Trichloropurine[6] (63 g., anhydrous) was dissolved in 400 ml. of ethyl acetate and slowly heated to 35° with stirring. *p*-Toluenesulfonic acid (100 mg.) was then added, followed by dropwise addition of 43 g. of 2,3-dihydro-4*H*-pyran over a 10-min. period. The temperature rose to 55°; the source of heat was removed, and stirring was continued for another 15 min. The solution was then rapidly cooled to room temperature and extracted with four 25-ml. portions of aqueous (saturated) sodium carbonate, followed by washing with five 25-ml. portions of water until the solution was neutral. The resulting solution was dried over anhydrous sodium sulfate for 5 hr. and filtered, and the excess ethyl acetate was evaporated at 50° under reduced pressure. The resulting solid was recrystallized from *n*-heptane to yield 52.5 g. (60.8%) of a white crystalline solid, m.p. 117–119°.

Anal. Calcd. for $C_{10}H_9Cl_3N_4O$: C, 39.1; H, 2.9; N, 18.2. Found: C, 38.8; H, 3.1; N, 18.0.

2,6-Dichloro-8-ethoxypurine (VIII).—2,6-Dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl)purine (VI, 208 mg.) was dissolved in ethanol to which was added 2 drops of 1 *N* hydrochloric acid. The solution was allowed to evaporate at room temperature, and the residue was washed with water and recrystallized from benzene to yield 2,6-dichloro-8-ethoxypurine (VIII), m.p. 194.5–196°.

Anal. Calcd. for $C_7H_6Cl_2N_4O$: C, 36.1; H, 2.6; N, 24.1. Found: C, 36.2; H, 2.4; N, 24.1.

The Formation of 8-Hydroxypurine (IX) from VI.—2,6-Dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl)purine (VI, 300 mg.) was treated with 10 ml. of 47% hydriodic acid under reflux for 2 hr. The solution was filtered and evaporated to dryness on the steam bath. Water (5 ml.) was added to the residue; the pH was adjusted to 11 with 4 *N* sodium hydroxide, and the solution was filtered. The ultraviolet absorption spectra of the filtrate showed only 8-hydroxypurine. R_f values in solvents A, B, and D were identical to those of an authentic sample of 8-hydroxypurine.[23]

8-Amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X) and 6-Amino-2,8-dichloro-9-(tetrahydro-2′-pyranyl)purine (XI).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 3 g.) in 120 ml. of ethanolic ammonia (saturated at 0°) was stirred for 3 hr. at room temperature in a closed container. The resulting mixture was filtered and the crude product washed with water and recrystallized from water and ethanol to yield 1.95 g. (69.5%) of 8-amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X), m.p. > 300°.

Anal. Calcd. for $C_{10}H_{11}Cl_2N_5O$: C, 41.7; H, 3.8; N, 24.3. Found: C, 41.5; H, 4.0; N, 24.1.

The filtrate from the above reaction mixture was evaporated and the residue washed with water. The crude product was recrystallized from ethanol to yield 0.7 g. (24.9%) of 6-amino-2,8-dichloro-9-(tetrahydro-2′-pyranyl)purine (XI), m.p. > 300°.

Anal. Calcd. for $C_{10}H_{11}Cl_2N_5O$: C, 41.7; H, 3.8; N, 24.3. Found: C, 41.8; H, 4.0; N, 24.0.

Treatment of X and XI with hydriodic acid gave only 8-aminopurine and adenine, respectively. No contamination by the other isomer was detected by paper chromatography.

8-Amino-2,6-dichloropurine (XII).—8-Amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X, 150 mg.) was dissolved in 100 ml. of ethanol. The solution was acidified to pH 1 with 1 *N* hydrochloric acid, allowed to stand overnight at room temperature, and then reduced to dryness under reduced pressure. The residue was washed with water and recrystallized from water and methanol to yield 90 mg. (85.0%) of 8-amino-2,6-dichloropurine (XII), m.p. > 300°.

(20) H. Hamano and H. F. Hameka, *Tetrahedron*, **18**, 985 (1962).

(21) All melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus unless otherwise stated.

(22) H. Biltz and E. Topp, *Ber.*, **44**, 1524 (1911).

(23) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

Anal. Calcd. for $C_5H_3Cl_2N_5$: C, 29.4; H, 1.5; N, 34.3. Found: C, 29.4; H, 1.3; N, 33.7.

Reduction of 2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII) with Raney Nickel to Yield 2-Chloropurine.—2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII, 250 mg.) was dissolved in 40 ml. of 2-ethoxyethanol to which was added 3 g. of Raney nickel, and the solution was refluxed for 2 hr. The ultraviolet absorption spectra and paper chromatographic data in solvents A, B, and C run on the filtrate of the reaction mixture showed 2-chloropurine[16] as the only purine derivative present.

2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 1 g.) was added to 1.03 g. of sodium sulfide (containing 2.7 mole equivalents of water) in 15 ml. of ethanol. The solution was stirred for 3 hr. at room temperature; the mixture was then filtered and the ethanol evaporated at 50° under reduced pressure. The yellow, gummy product was similarly evaporated several times with 50 ml. of benzene until a powdery solid remained. This substance was then dissolved in benzene and methanol, treated with charcoal, filtered, and evaporated to dryness to yield 0.95 g. (96.7%) of a yellow powder, m.p. > 300°.

Anal. Calcd. for $C_{10}H_{11}ClN_4OS_2$: C, 39.6; H, 3.6; N, 18.5. Found: C, 39.7; H, 3.3; N, 18.5.

2,6-Dichloro-8-hydroxy-9-(tetrahydro-2′-pyranyl)purine (XIV).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 5 g.) was dissolved in 500 ml. of anhydrous *p*-dioxane containing 48.8 ml. of 0.9965 *N* sodium hydroxide. The solution was stirred for 22 hr. at room temperature, and the excess *p*-dioxane was removed under vacuum. Water was added to the residue, and a small amount of precipitate which formed was filtered. The filtrate was acidified to pH 1 with 1 *N* hydrochloric acid, and the solid that appeared was filtered, triturated, and washed with water, and dried to yield 2.0 g. (42.6%) of a pure white powder, m.p. > 300°, which could not be recrystallized successfully.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_4O_2$: C, 41.5; H, 3.5; N, 19.4. Found: C, 41.3; H, 3.7; N, 19.5.

Hydrolysis of XV with hydriodic acid as for VI gave 8-hydroxypurine identified by ultraviolet absorption spectra and R_f values in solvents[24] A, B, and D.

Acknowledgment.—The authors are indebted to Brian M. Lynch, Saint Francis Xavier University, Antigonish, Nova Scotia, for helpful suggestions and discussions relative to this work.

(24) Solvent A, *i*-PrOH:H_2O::6:4—descending; B, *n*-BuOH:H_2O:HOAc (glacial)::5:4:1—descending; C, *n*-BuOH saturated with H_2O plus 1% NH_4OH—descending; D, *i*-PrOH:DMF:NH_4OH::65:25:10—descending; E, 5% NH_4HCO_3 in H_2O—descending; F, 5% Na_2HPO_4 in H_2O saturated with isoamyl alcohol—descending; G, *n*-BuOH saturated with H_2O—descending; H, EtOH:H_2O::7:3—ascending; I, *n*-BuOH:H_2O:HOAc (glacial)::5:4:1—ascending; J, $(NH_4)_2SO_4$:1 *N* NaOAc:*i*-PrOH::40:9:1—ascending.

Aromatic Fluorine Compounds. XI. Replacement of Chlorine by Fluorine in Halopyridines

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The α-halogenated pyridines react with potassium fluoride in various solvents to give replacement of the α-halogen by fluorine. A 50% yield of 2-fluoropyridine was obtained from 2-chloropyridine by heating with potassium fluoride in dimethyl sulfone or tetramethylene sulfone for twenty-one days; 2-bromopyridine gave a similar yield with a heating period of only seven days. The α-halogens of the polyhalopyridines undergo the exchange reaction more readily than do the halogens of the α-monohalopyridines. The proposed structures of the fluoropyridines are supported by alternate syntheses and by n.m.r. studies.

It previously has been found by Finger and coworkers that chlorine in certain positions in polychlorobenzenes[5] can be replaced by fluorine using the potassium fluoride exchange reaction. For example, hexachlorobenzene will react with potassium fluoride to give 1,3,5-trichloro-2,4,6-trifluorobenzene as a major product,[5] and small amounts of dichlorotetrafluorobenzene and chloropentafluorobenzene.[6] This shows that chlorine is not only a strong activating group from the *meta* position as expected in nucleophilic reactions,[7] but is also a significant activator even from the *ortho* and *para* positions.

In this study halogen activation has been demonstrated also in the polychloropyridines. A second halogen atom (chlorine or bromine) either adjacent to or opposite an α-chlorine on the pyridine ring gives increased lability to atoms in the α-position for reaction with potassium fluoride. These findings make it possible to synthesize many fluoropyridines more simply than can be done by the multi-step Schiemann operations.

Several years ago in the early stages of this study progress was slow with the reaction media then in use,[8] until it was discovered that dimethyl sulfone[9] was a better solvent medium for many exchange reactions. Unfortunately early work with 2-chloropyridine[9-11] and potassium fluoride led to the belief that activation by a ring nitrogen alone was insufficient for an exchange reaction; however, it has now been established that on prolonged heating 2-fluoropyridine (I) can be obtained in a significant yield. For instance, heating a mixture of 2-chloropyridine and potassium fluoride in dimethyl sulfone for twenty-one days gave a 50% yield of 2-fluoropyridine.[12] 2-Bromopyridine in dimethyl sulfone

(1) Address reprint requests to G. C. Finger, Illinois State Geological Survey, Urbana, Ill.

(2) Rayonier, Inc., Olympic Research Div., Shelton, Wash.

(3) N.m.r. discussion and data by H. S. G., Noyes Laboratory, University of Illinois. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for partial support of this research.

(4) Exchange studies on 2-chloropyridine by J. H., Tulane University, New Orleans, La.

(5) G. C. Finger, C. W. Kruse, R. H. Shiley, R. H. White, and H. A. Whaley, Abstracts, Organic Chemistry Division, XVIth International Congress of Pure and Applied Chemistry, Paris, July, 1957, p. 303. Also unpublished results.

(6) J. T. Maynard, *J. Org. Chem.*, **28**, 112 (1963).

(7) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(8) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956).

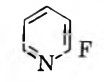
(9) L. D. Starr and G. C. Finger, *Chem. Ind.* (London), 1328 (1962).

(10) G. C. Finger and L. D. Starr, *J. Am. Chem. Soc.*, **81**, 2674 (1959).

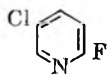
(11) J. Hamer, W. J. Link, A. Jurjevich, and T. L. Vigo, *Rec. trav. chim.*, **81**, 1058 (1962).

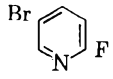
(12) A similar result was obtained with tetramethylene sulfone ("Sulfolane") as a reaction solvent.

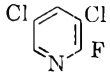
gave a similar yield in seven days. Somewhat greater activation exists in 2,6-dichloropyridine as a 52% of the difluoro analog was reported,[13] for a heating period of one hundred hours in dimethyl sulfone.

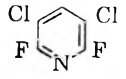

I


II


IIIa


IIIb


IV


V

The other halopyridines which were studied also showed α-chlorine or bromine replacement by fluorine, giving compounds II–V. The 4-halopyridines were not studied because of their reported thermal instability.[14]

It was found that heating 2,5-dichloropyridine with potassium fluoride in dimethyl sulfoxide gave both 5-chloro-2-fluoropyridine (IIIa) and 5-chloro-2-methylthiopyridine; the latter compound was obtained in the larger amount. In the absence of potassium fluoride neither 2,5-dichloropyridine nor 5-chloro-2-fluoropyridine reacted with dimethyl sulfoxide to give the thioether which apparently resulted from the reaction of some intermediate with the solvent. The use of dimethyl sulfone,[9] however, avoided this difficulty, as the sulfone structure prevented the sulfur from acting as an effective nucleophile. Furthermore, this solvent gave a much higher yield of the desired 5-chloro-2-fluoropyridine. From this example it is seen, that in certain cases, dimethyl sulfone is a superior solvent in that it affords higher yields and minimizes side reactions involving the solvent.

Dimethyl sulfone was found to be a satisfactory reaction medium in the remainder of the exchange reactions which were studied. That the 2-chlorine in 2,5-dichloropyridine was replaced was confirmed by the Schiemann conversion of 2-amino-5-chloropyridine to 5-chloro-2-fluoropyridine which was identical with that obtained from 2,5-dichloropyridine. The same 2-chlorine replacement was observed with 5-bromo-2-chloropyridine. The replacement of the 2-chlorine by fluorine in 2,3-dichloropyridine and 2,3,5-trichloropyridine was possible with potassium fluoride in dimethyl sulfone and gave 3-chloro-2-fluoropyridine (II) and 3,5-dichloro-2-fluoropyridine (IV), respectively. These examples illustrate that a chlorine adjacent to the chlorine which is being replaced provides increased activation and does not interfere sterically with the replacement. 2-Amino-3,5-dichloropyridine subjected to the Schiemann synthesis gave 3,5-dichloro-2-fluoropyridine which served as an authentic reference sample. The infrared spectrum of this material and that from the exchange reaction were identical.

The reaction of 2,3,5,6-tetrachloropyridine with potassium fluoride in dimethyl sulfone, which gave a 33% yield of 3,5-dichloro-2,6-difluoropyridine (V) in only twenty-four hours of heating is of special interest as it provided further convincing evidence not only of the exchangeability of the α-chlorine atoms but also of the activating influence of adjacent chlorine atoms. By contrast, 2,6-dichloropyridine gave a 50% yield of 2,6-difluoropyridine in one hundred hours.[11] As two chlorines were replaced, presumably stepwise, it appeared that the introduction of the first fluorine did not cause the deactivation[7] which might have been expected in the replacement of the second chlorine atom.

The structures proposed for II and V are supported by their n.m.r. spectra, in comparison with the spectrum of the related compound of known structure, 3,5-dichloro-2-fluoropyridine (IV).[15]

The proton spectrum of IV corresponds to the ab part of an abx system.[16,17a] Analysis of this spectrum is straightforward; there is one splitting common to the resonance lines from both protons. This is J_{46}^{HH}; the observed coupling of 2.45 c.p.s. agrees well with the value of 1.9 c.p.s. found in pyridine.[17b] The two values found for the H–F coupling are 7.60 and 1.45 c.p.s. Of these, the 7.60-c.p.s. value is assigned as J_{24}^{FH} and 1.45 c.p.s., as J_{26}^{FH}. This is based upon the similarity in the H–H coupling constants for benzene[16] and pyridine[17b] in combination with the 6.3- to 8.3-c.p.s. range found for the *meta* H–F coupling in fluorobenzenes.[16]

The proton spectrum of V is a simple 1:2:1 triplet which shows that the two fluorine atoms in the molecule are equivalent. The 7.75 c.p.s. H–F coupling constant agrees well with the corresponding value of 7.60 c.p.s. for J_{24}^{FH} in IV. However, this alone is not proof that V has the structure shown. In fact, in the fluorobenzenes it was found that the *ortho* H–F coupling ranges from 7.8 to 10.1 c.p.s., which overlaps the range for *meta* H–F coupling. Therefore, in principle the same proton spectrum might result if V were 2,6-dichloro-3,5-difluoropyridine. However, on the basis of the general chemical data, the latter possibility is excluded.

The correctness of this approach is borne out by the detailed analysis[18] made of the much more complicated proton spectrum of II, for which the coupling constants obtained agree with those found in IV and V, and for which the proton chemical shifts are similar to those in pyridine.[17b] The proton spectrum of II indicates the presence of three nonequivalent protons, and the values found for the H–H and H–F coupling constants eliminate all structures other than II.

Experimental[19]

Procedure A. Fluoropyridines by Halogen Exchange.—The fluoropyridines were prepared in dimethyl sulfoxide[10,20] or dimethyl sulfone[9,20] by the action of anhydrous potassium fluoride, usually 2 moles of potassium fluoride for each atom of halogen to

(13) A private communication by G. C. F. to Dr. W. J. Link suggested the use of dimethyl sulfone as a solvent. This materially assisted the Tulane group in obtaining 2-fluoropyridine and 2,6-difluoropyridine[11] by the exchange reaction.

(14) J. P. Wibaut and F. W. Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

(15) The n.m.r. spectra of compounds II, IV, and V were observed with a Varian Associates Model A-60 high resolution spectrometer. Compounds IV and V were run in saturated solutions of carbon tetrachloride and II as the pure liquid, all at room temperature.

(16) H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *J. Am. Chem. Soc.*, **79**, 4596 (1957).

(17) J. A. Pople, W. G. Schneider, and H. G. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959; (a) p. 132; (b) p. 266.

(18) H. S. Gutowsky and R. A. Meinzer, paper to be submitted to *J. Mol. Spectry.* See also the recent article, W. Brugel, *Z. Elektrochem.*, **66**, 159 (1962), which summarizes the proton spectra of a large number of substituted pyridines, including that of 2-fluoropyridine.

(19) Unless otherwise specified, all melting and boiling points are uncorrected.

(20) These solvents are commercially designated as DMSO and DMSO$_2$, respectively.

be replaced, on the appropriate halopyridine; good stirring is essential throughout the reaction. With dimethyl sulfone (m.p. 109°) the halopyridine and solvent were heated together until the latter melted and solution was complete. When the temperature reached about 110°, the potassium fluoride was added and the mixture heated to the desired reaction temperature. This temperature was maintained until the reaction was sensibly complete as verified by the usual probe test, then the mixture was cooled, diluted with warm water, and steam distilled. The product was separated from the distillate by extraction with ether or chloroform or by filtration, whichever was appropriate, and purified by distillation or recrystallization.

Procedure B. Fluoropyridines by the Schiemann Reaction.—The aminopyridine was added in small portions to 50% fluoboric acid. Powdered Dry Ice was added as needed to prevent excessive heating. If the amine did not dissolve readily, the amine–fluoboric acid mixture was heated (*ca.* 40–65°) until the amine dissolved completely and then cooled to 0°. The fluoborate salt of the amine separated during cooling. Powdered sodium nitrite was slowly added to this slurry and ether was added as needed to control foaming. The mixture was stirred for approximately 30 min. at 0°, then heated to 50°, cooled to 0°, poured onto ice, neutralized with sodium carbonate, and steam distilled. The product was collected and purified as described in procedure A.

2-Fluoropyridine (I).—(1) **From 2-Chloropyridine.**—A mixture of 2-chloropyridine (34.1 g., 0.3 mole), anhydrous potassium fluoride (35 g., 0.6 mole), and dimethyl sulfone (138 g.) heated for 510 hr. (*ca.* 21 days) at 200–210° by procedure A gave a yield of 14.4 g. or 49.5% of 2-fluoropyridine, b.p. 126–7°, $n^{23.6}$D 1.4663 (lit.[21] b.p. 125°, n^{20}D 1.4678). With tetramethylene sulfone ("Sulfolane") as a solvent, a yield of 58% was obtained.

(2) **From 2-Bromopyridine.**—A mixture of 2-bromopyridine (158 g., 1 mole), potassium fluoride (116 g., 2 moles), and dimethyl sulfone (450 g.) was heated at 200° by procedure A. After 2 days of heating, additional potassium fluoride (58 g., 1 mole) was added, and heating was continued for a total reaction time of 7 days. Yield of pure 2-fluoropyridine, 41 g. (42%), b.p. 124–125°.

3-Chloro-2-fluoropyridine (II).—A mixture of 2,3-dichloropyridine (14.8 g., 0.1 mole), anhydrous potassium fluoride (11.6 g., 0.2 mole), and dimethyl sulfone (30 g.) was heated at 192–201° for 48 hr. by procedure A to give 3-chloro-2-fluoropyridine; yield, 8.64 g. (65%), b.p. 92–96° (100 mm.). A second distillation gave a purified product; yield, 7.49 g. (56%), b.p. 94–95° (100 mm.), n^{25}D 1.5020.

Anal. Calcd. for C_5H_3ClFN: C, 45.65; H, 2.30; N, 10.65; Cl, 26.95. Found: C, 45.58; H, 2.35; N, 10.48; Cl, 26.91.

5-Chloro-2-fluoropyridine (IIIa).—(1) A mixture of 2,5-dichloropyridine (45.0 g., 0.304 mole), anhydrous potassium fluoride (35.3 g., 0.608 mole), and dimethyl sulfoxide (180 ml.) upon heating at 170–175° for 52 hr. by procedure A gave a product which was distilled into two crude fractions: (1) 13.07 g., b.p. 84–95° (100 mm.); (2) 26.37 g., b.p. 118–130° (40–45 mm.). Fraction 1 was redistilled to give 5-chloro-2-fluoropyridine; yield, 11.59 g. (29%), b.p. 81–83.5° (100 mm.), n^{25}D 1.4973.

Fraction 2 was distilled two more times to give 5-chloro-2-methylthiopyridine; yield, 19.37 g. (39%), b.p. 129–130° (40 mm.), n^{25}D 1.6000.

(21) A. E. Chichibabin and N. D. Rjazancev, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915).

Anal. Calcd. for C_6H_6ClNS: C, 45.15; H, 3.79; Cl, 22.21; S, 20.08. Found: C, 45.37; H, 3.76; Cl, 22.00; S, 20.35.

(2) A mixture of 2,5-dichloropyridine (45.0 g., 0.034 mole), anhydrous potassium fluoride (35.3 g., 0.608 mole), and dimethyl sulfone (180 g.) upon heating at 194–205° for 24 hr. by procedure. A gave 5-chloro-2-fluoropyridine; yield, 27.9 g. (70%), b.p. 88° (100 mm.), n^{25}D 1.4970.

(3) 2-Amino-5-chloropyridine (40.0 g., 0.311 mole), 50% fluoboric acid (800 ml.), and powdered sodium nitrite (32.2 g., 0.464 mole) by procedure B gave 5-chloro-2-fluoropyridine; yield, 37.6 g. (61%), b.p. 86–89° (100 mm.), n^{25}D 1.4948. A center cut [b.p. 89° (100 mm.), n^{25}D 1.4943] from a distillation was used for analysis.

Anal. Calcd. for C_5H_3ClFN: C, 45.65; H, 2.30; Cl, 26.95. Found: C, 45.45; H, 2.18; Cl, 26.84.

5-Bromo-2-fluoropyridine (IIIb).—(1) A mixture of 5-bromo-2-chloropyridine (17.0 g., 0.088 mole), anhydrous potassium fluoride (10.3 g., 0.18 mole), and dimethyl sulfone (70 g.) upon heating at 204° for 24 hr. by procedure A gave 5-bromo-2-fluoropyridine; yield, 10.68 g. (68%), b.p. 62–63° (15 mm.), n^{25}D 1.5300.

(2) 2-Amino-5-bromopyridine (17.3 g., 0.1 mole), 50% fluoboric acid (400 ml.), and powdered sodium nitrite by procedure B gave 5-bromo-2-fluoropyridine; yield, 10.76 g. (61%), b.p. 63° (15 mm.), n^{25}D 1.5293–1.5296. A center cut, n^{25}D 1.5294, from this distillation was used for analysis.

Anal. Calcd. for C_5H_3BrFN: C, 34.12; H, 1.72; Br, 45.41; N, 7.96. Found: C, 34.27; H, 1.75; Br, 45.24; N, 7.85.

3,5-Dichloro-2-fluoropyridine (IV).—(1) A mixture of 2,3,5-trichloropyridine (20.0 g., 0.11 mole), anhydrous potassium fluoride (12.8 g., 0.22 mole), and dimethyl sulfone (65 g.) upon heating at 200–205° for 24 hr. by procedure A gave a colorless solid (8.6 g., m.p. 29–37.5°) which was filtered from the steam distillate. This was sublimed to give 5.31 g. of pure 3,5-dichloro-2-fluoropyridine, m.p. 41–42°. The filtrate from the steam distillation upon extraction with ether and working up in the usual manner gave 1.6 g. of residue which was sublimed and recrystallized from ethanol and water to give an additional 0.66 g. of 3,5-dichloro-2-fluoropyridine, m.p. 42–43°. The total yield was 5.97 g. (33%).

(2) 2-Amino-3,5-dichloropyridine (10.0 g., 0.06 mole), 50% fluoboric acid (200 ml.), and powdered sodium nitrite (6.35 g., 0.09 mole) by procedure B gave 3,5-dichloro-2-fluoropyridine as a white solid; yield, 5.0 g. (49%) m.p. 42–43°. Recrystallization from petroleum ether did not alter the melting point.

Anal. Calcd. for $C_5H_2Cl_2FN$: C, 36.18; H, 1.21; N, 8.44; Cl, 42.72. Found: C, 36.19; H, 1.17; N, 8.44; Cl, 42.57.

3,5-Dichloro-2,6-difluoropyridine (V).—A mixture of 2,3,5,6-tetrachloropyridine[22] (10.0 g., 0.046 mole), anhydrous potassium fluoride (10.7 g., 0.184 mole), and dimethyl sulfone (30 g.) by procedure A with heating at 205° for 24 hr. gave a small amount of a semisolid which was extracted from the steam distillate with ether. After the ether was dried and evaporated, the residue (3.84 g.) was sublimed to give 3,5-dichloro-2,6-difluoropyridine as a white solid; yield, 2.8 g. (33%), m.p. 45–46.3°. Recrystallization from petroleum ether and sublimation did not significantly alter the melting point.

Anal. Calcd. for $C_5HCl_2F_2N$: C, 32.64; H, 0.55; Cl, 38.54; N, 7.61. Found: C, 32.57; H, 0.50; Cl, 38.43; N, 7.63.

(22) The authors thank the Dow Chemical Co., Midland, Mich., for this compound.

Aromatic Cyclodehydration. LIII.[1] 6a-Azonianaphthacenequinones

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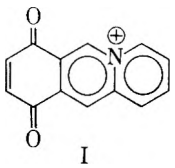
Received December 18, 1963

The reaction of 1,4-dimethoxy-2-(bromomethyl)naphthalene with picolinaldoxime or 2-benzoylpyridine, followed by cyclization with concomitant ether-cleavage and oxidation, has afforded 6a-azonianaphthacenequinones. These are the first compounds known to contain both a quinone and a quinolizinium nucleus.

The synthesis of a number of quinolizinium benzologs or azonia[3] polycyclic aromatic hydrocarbons has been reported,[4] but to date none of the related quinones has been described.

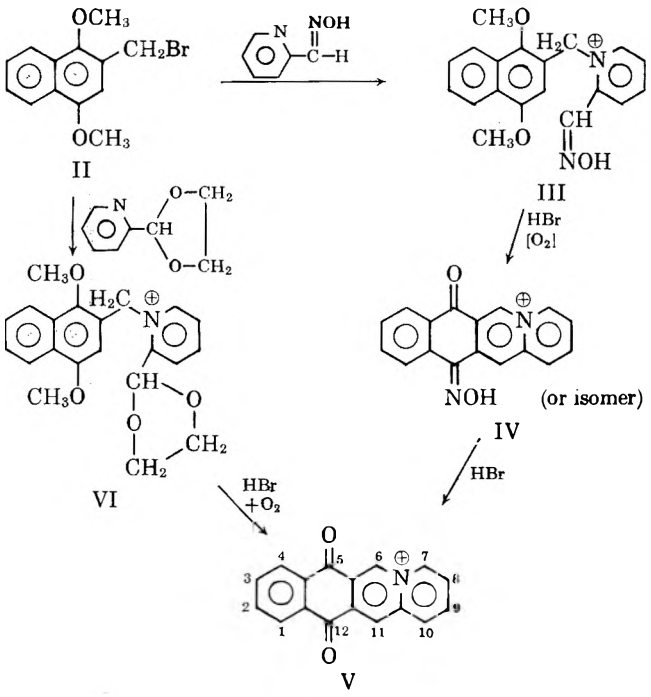
It seems unlikely that the quinolizinium ion could yield a stable *para* quinone since such a compound would be an acylammonium salt capable of reacting with a hydroxylic solvent. The simplest possible *para* quinone of the series would be 8a-azonia-1,4-anthraquinone (I) or its angular isomers.



I

We wish to report the synthesis of a benzolog of I. The reaction of 2-bromomethyl-1,4-dimethoxynaphthalene (II), with picolinaldoxime, afforded a 99% yield of the quaternary salt III. Cyclization, ether-cleavage, and oxidation of III were carried out by heating it for twenty-four hours in 48% hydrobromic acid, affording a small quantity (15%) of an insoluble product. This product had the composition expected for a monooxime (IV) of 6a-azonianaphthacenequinone. When the monooxime (IV) was boiled for forty-eight hours with a mixture of glacial acetic and 48% hydrobromic acid, a small quantity of 6a-azonianaphthacenequinone (V) was obtained. The quinone V could be obtained more directly by the use of 2-(1,3-dioxolan-2-yl)pyridine,[5] *via* the quaternary salt VI in an over-all yield of 63%. If air was bubbled through the cyclization mixture, a 70% yield of the quinone was obtained at the end of seven hours. A comparable experiment without bubbling in air afforded only an intractable gum.

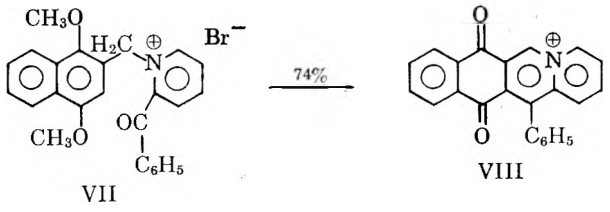
The infrared absorption spectrum of the quinone monooxime (IV) and the quinone (V) afforded some evidence as to the correctness of the formulation of V. Anthraquinone monooxime has a strong absorption band at 5.98 μ while anthraquinone has one at 5.93 μ[6]



II III IV V VI

(a 0.05-μ difference). The 6a-azonianaphthacenequinone monooxime (IV) has an absorption at 5.94 μ (0.04 μ lower than anthraquinone monooxime), but the quinone obtained upon hydrolysis, has an absorption at 5.89 μ (again a 0.05-μ difference). The oximido group appears more likely to be at position 12 (IV) rather than at position 5 for mechanistic reasons.[7] The formation of the oxime is most likely a true rearrangement, for when the quinone (V) was heated in hydrobromic acid with one mole of hydroxylamine hydrochloride, under the conditions of the cyclization, no oxime was obtained, and the quinone was recovered.

By use of 2-benzoylpyridine with 2-bromomethyl-1,4-dimethoxynaphthalene (II) 11-phenyl-6a-azonianaphthacenequinone VIII was synthesized in an over-all yield of 44% *via* the quaternary salt (VII).



VII VIII

The 6a-azonianaphthacenequinones (V and VIII) were yellow salts which gave a blue (in the case of V) or green (in the case of VIII) solution is distilled water

(1) For the preceding communication of this series, see C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).

(2) This research was supported by a research grant NSF-G6215 of the National Science Foundation.

(3) The 1957 report of the IUPAC Nomenclature Committee, *J. Am. Chem. Soc.*, **82**, 5545, 5572 (1960), suggests the designation *azonia* as the quaternary nitrogen counterpart of the trivalent nitrogen *aza*. In this system of nomenclature, the quinolizinium ion would become 4a-azonianaphthalene.

(4) *E.g.*, (a) C. K. Bradsher and L. E. Beavers, *ibid.*, **78**, 2459 (1956); (b) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958); (c) C. K. Bradsher and T. W. G. Solomons, *J. Am. Chem. Soc.*, **82**, 1808 (1960).

(5) A recent paper (ref. 1) has described the use of 2-(1,3-dioxolan-2-yl)-pyridine in the synthesis of the acridizinium ion.

(6) The accepted value for the carbonyl absorption of anthraquinone is 5.95 μ (M. S. Flett, *J. Chem. Soc.*, 1441 (1948). We have used the value 5.93 μ, observed on our instrument, for purposes of comparison with other observed values.

(7) If as the evidence indicates, the transfer of hydroxylamine from carbon 11 is intramolecular, it appears more likely that it will be made to neighboring carbon 12 of the quinone, rather than the more distant carbon 5.

and in common polar organic solvents such as methanol, ethanol, acetonitrile, and acetone.

The formation of the blue and green colors was reversed by the addition of acid, and acidified solutions were found to be most effective in recrystallizing samples. When an acidified solution of V in distilled water was back titrated with standard base, the color change occurred at a pH of about 3.1. These observations suggest that even in distilled water the quinone salts are partially hydrolyzed to a highly colored pseudobase. It would be predicted that the adjacent quinone nucleus would make the carbon at position 6 more positive than the comparable (6) position of the acridizinium nucleus, and that the quinone salts would be in equilibrium with significant concentrations of the pseudobase at a pH lower than that required for pseudobase formation in the acridizinium system.

It may be seen from the ultraviolet absorption spectra in Table I that there is only a small difference between the spectra of the acidified (yellow), and the neutral (blue) solution of 6a-azonianaphthacenequinone (V) and only an insignificant difference in the case of the phenyl analog (VIII). The neutral (blue) solution of V, when exposed to diffuse daylight for only five days, changes to yellow-brown and the absorption spectrum is greatly altered. The change does not occur in the dark, and can be prevented by acidification of the solution.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA (AND LOG EXTINCTION COEFFICIENTS) OF 6a-AZONIANAPHTHACENEQUINONE SALTS

		Neutral	
Compound	Acidified (*ca.* 10^{-3} *M* H^+)	Freshly prepared	After exposure
V	237 (4.45)	247 (4.47)	228 (4.67)
(Bromide)	248*[a] (4.37)	322* (3.86)	243* (4.67)
	312* (3.81)	357* (4.11)	
	358* (4.12)	372* (4.13)	
	372 (4.15)		
VIII	253 (4.55)	253 (4.54)	
(Perchlorate)	363* (4.14)	363* (4.13)	
	377 (4.16)	377 (4.15)	

[a] An asterisk indicates a shoulder.

Experimental

All analyses were by Dr. Ing. A. Schoeller, Mikroanalytisches Laboratorium, Kronach, West Germany. Melting points were determined using a Laboratory Devices Mel-Temp block and are uncorrected. Infrared spectra were measured in potassium bromide pellets using the Perkin-Elmer Model 21 spectrophotometer. The ultraviolet absorption spectra were recorded using a Cary Model 14 recording spectrophotometer with methanol as the solvent. Wave lengths are recorded in millimicrons and shoulders are indicated by an asterisk (*).

2-Bromomethyl-1,4-dimethoxynaphthalene (II).—A suspension of 1,4-dimethoxynaphthalene (13 g.) and paraformaldehyde (2.5 g.) in a mixture of glacial acetic acid (30 ml.) and carbon tetrachloride (200 ml.) was saturated with hydrogen bromide at room temperature. The reaction was considered complete when complete solution occurred. The carbon tetrachloride was removed under reduced pressure (aspirator) and water was added to the residue. The mixture was extracted thoroughly with benzene. The benzene extracts were washed with water and then with sodium bicarbonate solution. The dried (magnesium sulfate) benzene solution was concentrated (steam bath) and the residue crystallized from hexane yielding 16.6 g. (86%) of a yellow solid, m.p. 96.5–98.5°. The analytical sample crystallized from hexane as yellow needles, m.p. 98–99.5°.

Anal. Calcd. for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.43. Found: C, 55.70; H, 4.50; Br, 28.87.

1-(1,4-Dimethoxy-2-naphthylmethyl)-2-oximidomethylpyridinium (III) Bromide.—A solution containing 7.6 g. of 2-bromomethyl-1,4-dimethoxynaphthalene and 3.7 g. of picolinaldoxime in 20 ml. of dimethylformamide was allowed to stand for 24 hr. at room temperature. The yellow product was collected and washed with ethyl acetate, yield 10.7 g. (99%), m.p. 179–180°. Recrystallization of the salt from water afforded short pale yellow needles, m.p. 176–176.5°.

Anal. Calcd. for $C_{19}H_{19}BrN_2O_3$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.78; H, 4.93; N, 7.38.

The **perchlorate** was prepared from an aqueous solution of the bromide as yellow needles, m.p. 165.5–166°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_7$: C, 53.97; H, 4.53; N, 6.63. Found: C, 54.09; H, 4.75; N, 6.80.

The chloride was prepared by a quaternization reaction using 2-chloromethyl-1,4-dimethoxynaphthalene[8] in the quaternization reaction (19 days, 58% crude yield). The analytical sample formed yellow needles from ethanol, m.p. 188–189°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_3$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.72; H, 5.45; N, 7.91.

6a-Azonianaphthacenequinone Monooxime (IV) Bromide.—A suspension of 1.8 g. of the quaternary bromide (III) in 48% hydrobromic acid was heated for 24 hr. on the steam bath. The mixture was cooled and the brown precipitate collected, 0.25 g. (15%), m.p. >350°. No pure product could be isolated from the filtrate. Recrystallization of the brown precipitate from methanol yielded short red needles, m.p. >350°.

Anal. Calcd. for $C_{17}H_{11}BrN_2O_2$: C, 57.48; H, 3.12; N, 7.89. Found: C, 57.66; H, 3.22; N, 7.75.

The infrared spectrum of this compound contained a band in the carbonyl region at 5.94 μ, and a strong band in the C=N region (6.08–6.19 μ).

The **perchlorate** crystallized from methanol as red needles, m.p. >350°.

Anal. Calcd. for $C_{17}H_{11}ClN_2O_6$: C, 54.48; H, 2.96; N, 7.47. Found: C, 54.52; H, 2.99; N, 7.37.

1-(1,4-Dimethoxy-2-naphthylmethyl)-2-(1,3-dioxolan-2-yl)-pyridinium (VI) Bromide.—A solution of 10 g. of 2-bromomethyl-1,4-dimethoxynaphthalene and 6 g. of 2-(1,3-dioxolan-2-yl)-pyridine[5] in 25 ml. of dimethylformamide was allowed to stand at room temperature for 24 hr. The gummy precipitate, formed when ethyl acetate was added, solidified on vigorous stirring, yield 14 g. (90%), m.p. 143.5–145°. This material crystallized from methanol–ethyl acetate as colorless needles, m.p. 146.5–147°.

Anal. Calcd. for $C_{21}H_{22}BrNO_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.34; H, 5.09; N, 3.45.

The **perchlorate** was recrystallized from methanol–ethyl acetate, m.p. 149–149.5°.

Anal. Calcd. for $C_{21}H_{22}ClNO_8$: C, 55.81; H, 4.91; N, 3.10. Found: C, 56.10; H, 4.75; N, 3.15.

6a-Azonianaphthacenequinone (V) Bromide. (A) By Cyclization of Quaternary Salt (VI).—A mixture of 4 g. of crude 1-(1,4-dimethoxy-2-naphthylmethyl)-2-(1,3-dioxolan-2-yl)pyridine (VI) with 40 ml. of 48% hydrobromic acid was heated on the steam bath for 7 hr., while air was passed through. The solution was diluted with 100 ml. of water and cooled, affording 2.2 g. (70%) of a yellow solid, m.p. above 350°. Recrystallized from water containing a trace of hydrobromic acid, the product was obtained as yellow needles, m.p. above 350°, infrared absorption at 5.89 μ (carbonyl region).

(B) By Hydrolysis of the Monooxime (IV) Bromide.—A small sample of the monooxime (IV) bromide was refluxed for 48 hr. in a mixture of acetic and 48% hydrobromic acids. A part of the material appeared to dissolve. The unchanged monooxime was removed by filtration, and the filtrate was concentrated affording a yellow compound, m.p. >350°, which was identical in infrared spectrum with the material obtained by method A.

Anal. Calcd. for $C_{17}H_{10}BrNO_2$: C, 60.02; H, 2.96; N, 4.12. Found: C, 59.75; H, 3.26; N, 4.40.

Neutral solutions of 6a-azonianaphthacenequinone salts in distilled water or common organic solvents such as methanol, ethanol, acetonitrile, and acetone were blue. The color of the solution turned to yellow upon acidification with mineral acid.

(8) B. R. Baker and G. H. Carlson, *J. Am. Chem. Soc.*, **64**, 2657 (1942).

By dissolving a sample of the quinone in hydrochloric acid and titrating with sodium hydroxide it was determined that the pH of the color change was about 3.07.

A sample of 6a-azonianaphthacenequinone bromide was heated for 24 hr. on the steam bath with an equimolar amount of hydroxylamine hydrochloride in 48% hydrobromic acid (cyclizing conditions). No insoluble material was formed, and only starting material could be recovered from the solution.

The **perchlorate** of 6a-azonianaphthacenequinone (V) crystallized from water as yellow needles, m.p. 331.5–332°.

Anal. Calcd. for $C_{17}H_{10}ClNO_6$: C, 56.76; H, 2.80; N, 3.91. Found: C, 56.87; H, 2.91; N, 4.07.

1-(1,4-Dimethoxy-2-naphthylmethyl)-2-benzoylpyridinium Bromide (VII).—A solution of 4 g. of 2-(bromomethyl)-1,4-dimethoxynaphthalene and 3.1 g. of 2-benzoylpyridine in 10 ml. of dimethylformamide was allowed to stand at room temperature for 4 days. The addition of ether precipitated 3.9 g. (60%) of a yellow solid, m.p. 132–133°. The analytical sample crystallized from methanol–ethyl acetate as yellow needles, m.p. 132–133°.

Anal. Calcd. for $C_{25}H_{22}BrNO_3$: C, 64.66; H, 4.78; N, 3.02. Found: C, 64.44; H, 4.69; N, 3.39.

11-Phenyl-6a-azonianaphthacenequinone (VIII) Bromide.—A mixture containing 1.5 g. of the 2-benzoylpyridinium salt (VII) and 15 ml. of 48% hydrobromic acid was heated for 16 hr. on the steam bath. The acid was removed under reduced pressure, and the yellow residue recrystallized from methanol–ethyl acetate, yield 0.99 g. (74%), m.p. above 350°. The analytical sample formed yellow plates, m.p. >350°, and a strong absorption at 5.87 μ (carbonyl region).

Anal. Calcd. for $C_{23}H_{14}BrNO_2 \cdot 1/2\ H_2O$: C, 64.95; H, 3.56; N, 3.29. Found: C, 64.84; H, 3.48; N, 3.54.

This compound formed green solutions in distilled water and in the common polar organic solvents. The green color was turned to yellow by the addition of mineral acid.

The **perchlorate** crystallized from methanol as yellow plates, m.p. 332–334°.

Anal. Calcd. for $C_{23}H_{14}ClNO_6$: C, 63.38; H, 3.23; N, 3.21. Found: C, 63.11; H, 3.24; N, 3.38.

The Reaction of 3-Acyl-4-hydroxycoumarins with Ammonium Salts[1]

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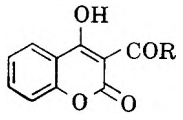
Ammonium acetate or amines in acetic acid react readily with 3-acetyl- or 3-benzoyl-4-hydroxycoumarin to form amino or imino substitution products. By using H_2O^{18} it was shown that the substitution took place in the 3α-position of the 3-acylcoumarin.

The reaction of 3-acyl-4-hydroxycoumarins with ammonium salts represents an interesting extension of the well established[3] reaction of β-diketone systems with amines.



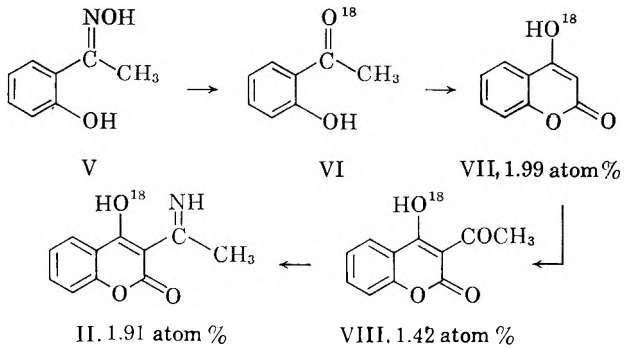
Ia. R = CH_3
Ib. R = C_6H_5

In our initial experiments ammonium acetate, the acylcoumarin, and ethyl cyanoacetate were refluxed in benzene in an attempted Knoevenagel condensation. 3-Acetyl- (Ia) and 3-benzoyl-4-hydroxycoumarin (Ib) yielded the corresponding amino or imino compounds II and III. It is of interest to note that Iguchi and Hisatune[4] assigned structure II to a product obtained by treatment of Ia with ammonia. No supporting evidence was given.

When 3-carbethoxy-4-hydroxycoumarin, 4-hydroxycoumarin, and dibenzoylmethane were treated with ammonium acetate in benzene, no imino compounds were formed. When ethylamine, isopropylamine, aniline, or ethanolamine reacted with equimolar quantities of acetic acid and Ib, good yields of the corresponding amino or imino compounds were obtained. Diethylamine and piperidine under the same conditions gave only the salts of Ib.

The nitrogen function could enter Ia and Ib either at the 2-, 4-, or 3α-position. Substitution at the 2-position was considered least likely since aniline[5] and morpholine[6] substitute in position 4 of 4-hydroxycoumarin (IV) . If ammonium acetate reacted with Ia labeled with O^{18} in position 4, the position of the nitrogen substitution could be shown by the retention or loss of the O^{18}. Scheme A shows the approach used. Hydrolysis of *o*-hydroxyacetophenone oxime (V) in acidified H_2O^{18} formed *o*-hydroxyacetophenone-C=O^{18} (VI). This was condensed with diethyl carbonate to form 4-hydroxy-O^{18}-coumarin (VII). 3-Acetyl-4-hydroxy-O^{18}-coumarin (VIII) was obtained by the reaction of VII with acetyl chloride in pyridine. It was found that VIII (1.42 atom % excess) and ammonium acetate yielded II (1.91 atom % excess). The calculated value was 1.89 atom % excess for II if the nitrogen entered the 3α-position.

Both Davis and Hurd[7] and Dudek and Holm[8] have assigned specific structures to the β-diketone derivatives they investigated; we feel that the analogy between the



SCHEME A

(1) Published with the approval of the director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation. This work is from the Ph.D. theses of Robert A. Kloss, 1956, and C. Wiener, 1960, done under the supervision of Professor Karl Paul Link.

(2) Department of Chemistry, Northern Illinois University, DeKalb, Ill.

(3) N. H. Cromwell, *Chem. Rev.*, **38**, 83 (1946).

(4) S. Iguchi and K. Hisatune, *J. Pharm. Soc. Japan*, **77**, 98 (1957).

(5) R. Anschutz, *Ann.*, **367**, 204 (1909).

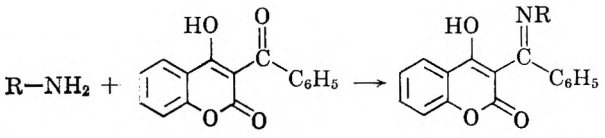
(6) O. P. Spaulding, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, **72**, 5338 (1950).

(7) R. B. Davis and P. Hurd, *ibid.*, **77**, 3284 (1955).

(8) G. O. Dudek and R. M. Holm, *ibid.*, **84**, 2691 (1962).

TABLE I

REACTION OF 3-BENZOYL-4-HYDROXYCOUMARIN WITH PRIMARY AMINES

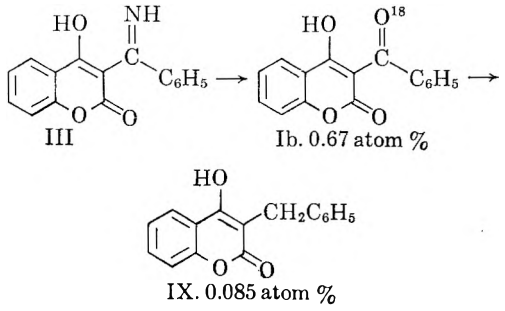


R—	M.p., °C.	Yield, %	Formula	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3CH_2—	129–130	78.5	$C_{18}H_{16}NO_3$	73.77	73.37	5.16	5.56
CH_2OH—CH_2—	119–121	91 0	$C_{18}H_{15}NO_4$	69.89	69.28	4.89	5.07
C_6H_5—	155–157	95.0	$C_{22}H_{15}NO_3$	77.40	77.77	4.43	4.43
$(CH_3)_2CH$—	136–138	97.2	$C_{19}H_{17}NO_3$	74.25	74.72	5.58	5.91

reported compounds and ours is not sufficiently close to permit assignment of a specific tautomer.

The reaction sequence shown in Scheme A could not be used to locate the nitrogen in the product from Ib, since Ib cannot be synthesized directly from VII.[9]

Compound III, when hydrolyzed in acetic acid–sulfuric acid–H_2O^{18}, gave Ib containing 0.66 atom % excess O^{18}. The Ib was in turn hydrogenolyzed[10] to 3-benzyl-4-hydroxycoumarin (IX), which was found to contain 0.085 atom % excess O^{18}. This approach is shown in Scheme B.



SCHEME B

A control experiment showed that Ib became labeled by exchange when subjected to the conditions used for the hydrolysis of III. Hydrogenolysis of this labeled Ib (0.57 atom % excess) gave IX with a residual O^{18} content of 0.089 atom % excess.

The control experiment shows that the 3α-position in Ib exchanges extensively, but if the nitrogen were not at the 3α-position of III, two positions would become labeled during hydrolysis. The structure 3-(α-iminobenzyl)-4-hydroxycoumarin (III) is, therefore, assigned.

The residual O^{18} in the samples of IX obtained by hydrogenolysis of Ib shows that there is some exchange of oxygen in the 4-hydroxycoumarin moiety. This would be expected from O^{18} studies which showed that the carbonyl oxygen of dimedone is replaced in the acid-catalyzed formation of dimedone enol ether.[11]

The definitive proof of structure of the products resulting from the reaction of the two 3-acyl-4-hydroxycoumarins with various amines has not been attempted.

(9) H. R. Eisenhauer, and K. P. Link, *J. Am. Chem. Soc.*, **75**, 2046 (1953).
(10) I. M. Hellbron and D. W. Hill, *J. Chem. Soc.*, **1927**, 1795,
(11) K. B. Wiberg and K. A. Saegebarth, *J. Org. Chem.*, **25**, 832 (1960).

Experimental

Preparation of Iminocoumarins.—The synthesis of II and III illustrates the method. The same methods were used with other ammonium salts and with the various amines and acetic acid. See Table I for compounds obtained from amines.

3-(α-Iminoethyl)-4-hydroxycoumarin (II)—3-Acetyl-4-hydroxycoumarin(Ia)[12,13] (10.2 g.) and 4.0 g. of ammonium acetate refluxed in 50 ml. of ethanol for 12 hr. gave 10.5 g. (quantitative yield) of II, m.p. 221–225°. Recrystallization from dioxane gave II, m.p. 230–231°; λ_{max}^{KBr} 3.05 (w), 3.43, 5.85 (w), 6.20 μ.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46. Found: C, 64.83; H, 4.50.

3-(α-Iminobenzyl)-4-hydroxycoumarin (**III**).—3-Benzoyl-4-hydroxycoumarin (Ib)[9] (6.65 g.) in 50 ml. of absolute ethanol gave, when treated with 2 g. of ammonium acetate, 6.3 g. (94%) of colorless crystals, m.p. 223–226°; λ_{max}^{KBr} 3.00, 3.15, 3.44, 5.96, 6.15, 6.21 μ.

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.43; H, 4.18. Found: C, 72.30; H, 4.53.

Materials and Methods Used in the Oxygen-18 Analyses.—The methods used for O^{18} analyses were similar to those reported by Rittenberg and Ponticorvo.[14]

Each of the samples (8–10 mg.) was mixed with 100 mg. of mercuric chloride and heated in a Pyrex tube at 510–550° for 1.5 hr.

When the ratio of masses 46:44 of tank carbon dioxide deviated from the normal (0.00409), the measured ratios for the enriched samples were corrected accordingly.[15] The O^{18} contents were determined in duplicate or triplicate. The deviations from the mean were less than 1.5% of the average value.

***o*-Hydroxyacetophenone-C=O^{18}** (**VI**).—To O^{18} enriched water (1.8 ml., 6.48 atom % excess) saturated with hydrogen chloride was added 15.1 g. of *o*-hydroxyacetophenone oxime. The solution was refluxed for 1.5 hr., cooled, and extracted twice with 50-ml. portions of ether. The ether was dried (magnesium sulfate) and evaporated. The remaining oil was distilled at 95–98° (0.05 mm.).

4-Hydroxy-O^{18}-coumarin (**VII**).—A method similar to that reported by Dickenson[16] was used. Diethyl carbonate (50 g.), 3.4 g. of sodium ethoxide, and 10 g. of the labeled *o*-hydroxyacetophenone (VI) were heated on a steam bath 4 hr. Water (150 ml.) was added and the aqueous layer was separated and acidified with hydrochloric acid. Crystallization from ethanol–water yielded 5.2 g., m.p. 209–212°, O^{18} content, 1.99 atom % excess.

3-Acetyl-4-hydroxy-O^{18}-coumarin (**VIII**).—A procedure similar to that reported by Eisenhauer and Link[13] was used for this preparation. The product from 3.0 g. of 4-hydroxy-O^{18}-coumarin was crystallized from ethanol–water to yield 2.1 g., m.p. 130–131°, O^{18} content, 1.42 atom % excess.

(12) T. Ukita, N. Shosichi, and H. Matsumoto, *J. Am. Chem. Soc.*, **72**, 5143 (1950).
(13) H. R. Eisenhauer and K. P. Link, *ibid.*, **75**, 2044 (1953).
(14) D. Rittenberg and L. Ponticorvo, *J. Appl. Radiation Isotopes*, **1**, 208 (1956).
(15) W. G. Miller and L. Anderson, *Anal. Chem.*, **31**, 1668 (1959).
(16) H. G. Dickenson, U. S. Patent 2,449,162 (1949).

3-(α-Iminoethyl)-4-hydroxy-O^{18}-coumarin (Labeled II). 3-Acetyl-4-hydroxy-O^{18}-coumarin (1.0 g.) and 0.3 g. of ammonium acetate were refluxed in 10 ml. of absolute ethanol for 9 hr. The solid which separated on cooling was recrystallized from absolute ethanol; yield 0.9 g., m.p. 233–235°, O^{18} content, 1.91 atom % excess.

3-Benzoyl-4-hydroxy-O^{18}-coumarin (Labeled IB). A. By the Hydrolysis of III in an O^{18} Enriched Medium.—Acetic acid (3.10 ml.), 1.68 ml. of O^{18} enriched water (6.48 atom % excess), 0.21 ml. of concentrated sulfuric acid, and 0.3 g. of III were refluxed 1.5 hr. The product which separated was crystallized twice from absolute ethanol; yield 0.2 g., m.p. 145°, O^{18} content, 0.667 atom % excess.

This seemingly low O^{18} value results from isotopic exchange with the acetic and sulfuric acids.[17] The theoretical O^{18} content is 0.70 atom % excess.

B. By Equilibration of 3-Benzoyl-4-hydroxycoumarin with an O^{18} Enriched Solution (Control Experiment).—When 0.3 g. of Ib was treated in the same manner as reported for the hydrolysis of III, the product had an O^{18} content of 0.561 atom % excess.

3-Benzyl-4-hydroxycoumarin (IX). A. By Hydrogenolysis of O^{18} Labeled Ib Obtained from III.—Labeled Ib obtained from the hydrolysis of III (80 mg.) was shaken for 3 hr. in 10 ml. of anhydrous methanol with 80 mg. of 10% palladium on charcoal and hydrogen at 38–40 p.s.i. The catalyst was removed and the solvent was evaporated to 1 ml. by a stream of nitrogen. Cooling to −10° yielded 40 mg. of product, m.p. 205°, O^{18} content, 0.085 atom % excess.

B. By Hydrogenolysis of O^{18} Labeled Ib Obtained from Equilibration with O^{18} Water (Control Experiment).—3-Benzoyl-4-hydroxy-O^{18}-coumarin obtained in the exchange experiment with 3-benzoyl-4-hydroxycoumarin and O^{18} water was reduced as in part A. The starting material had an O^{18} content of 0.561 atom % excess; the product was found to have an O^{18} content of 0.089 atom % excess.

(17) T. C. Hoering and J. W. Kennedy, *J. Am. Chem. Soc.*, **79**, 56 (1957).

Acknowledgment.—The writers are indebted to Professor Karl Paul Link and his associates, Dr. Bruce D. West and Dr. C. H. Schroeder, for valuable suggestions in the development of this work. Professor Laurens Anderson kindly loaned us his apparatus for isotope analysis and also helped with the interpretation of the analytical data and the preparation of the manuscript.

1,2-Dicarbonyl Derivatives Resulting from the Action of Nitrosyl Chloride on Alcohols

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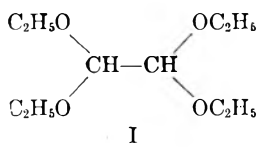
From the synthesis of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone in ethanol solution, considerable yields of an unknown by-product were isolated. This proved to be 1,1,2,2-tetraethoxyethane and resulted from the action of nitrosyl chloride upon ethanol, presumably by way of oxidation of the intermediate ethyl nitrite. Treatment of a large excess of ethanol with nitrosyl chloride afforded about 50% yields of 1,1,2,2-tetraethoxyethane, assuming four moles of nitrosyl chloride are required for the oxidation, at 30–50° and with a reaction time of three to four hours. The reaction was not accelerated upon illumination with an intense source of visible light. Application of the reaction to 1-propanol led to an inseparable mixture which, however, yielded derivatives of pyruvaldehyde upon treatment with carbonyl reagents. Isopropyl alcohol with nitrosyl chloride afforded a low yield of pyruvohydroxamyl chloride as the only isolable product. Both ethylene glycol and propylene glycol yielded complex mixtures upon treatment with nitrosyl chloride. Although none of the reaction products were positively identified in either case, it was possible to demonstrate the presence of glyoxal-yielding compounds in the ethylene glycol product and pyruvaldehyde-yielding compounds in the propylene glycol product by treatment of the distilled products with 2,4-dinitrophenylhydrazine and identification of the corresponding 2,4-dinitrophenylosazone derivatives.

During a recent study[1] of the preparation of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone in ethanol solution, a by-product [b.p. 80–84° 10 (mm.)] was observed in yields amounting to as much as one-third of the weight of the desired phenylglyoxal acetal. Elemental and infrared analyses and molecular weight determination suggested the identity of the by-product to be 1,1,2,2-tetraethoxyethane (I). Confirmation of the structure then was obtained



I

by acid hydrolysis of the by-product to ethanol and glyoxal followed by conversion of the latter to glyoxime by reaction with hydroxylamine. The possibility that the glyoxal acetal (I) arose solely from reaction of nitrosyl chloride with the solvent then was considered. Nitrosyl chloride was fed to a large excess of ethanol while maintaining the solution at slightly above room temperature. Upon warming to 38° a vigorous reflux of ethyl nitrite occurred and an exothermic reaction began, accompanied by rapid evolution of a mixture of nitric oxide, nitrous oxide, and nitrogen. The reaction mixture was allowed to stand for several hours and, after treatment with hot aqueous sodium hydroxide to remove any acidic or ester by-products, was distilled to give 1,1,2,2-tetraethoxyethane in an amount equivalent to 38.5% of the weight of nitrosyl chloride employed. In subsequent trials the time required for completion of the nitrosyl chloride reaction was found to be as short as three to four hours. Despite the uncertainty surrounding the mechanism, it is likely that at least three and possibly four moles of nitrosyl chloride are required for oxidation of the methyl and methylol groups of ethanol, the latter situation being represented by the following over-all equation.

$$4NOCl + 5C_2H_5OH \longrightarrow (C_2H_5O)_2CHCH(OC_2H_5)_2 + 2H_2O + 2NO + N_2O + 4HCl \quad (1)$$

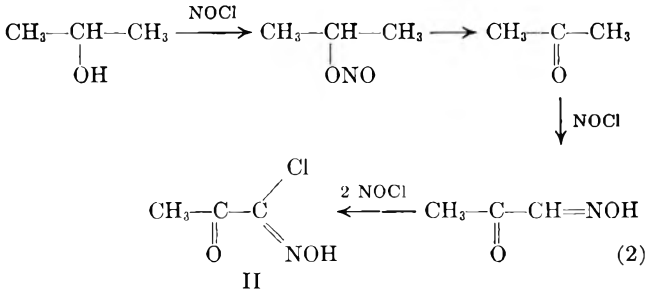
A requirement of three moles of nitrosyl chloride corresponds to a yield of 37% while a four-mole requirement would indicate a 49% yield.

Study of this surprising oxidation occurring under the mild condition of a ketone nitrosation was then

(1) David T. Manning and Harry A. Stansbury, Jr., *J. Org. Chem.*, **26**, 3755 (1961).

extended to other alcohols. The reaction of nitrosyl chloride with a large excess of 1-propanol for five hours at 30–52° yielded a complex liquid mixture, b.p. 45–120° (3 mm.), amounting to approximately 38% by weight of the nitrosyl chloride employed. Infrared analysis of the distillate revealed the presence of carbonyl, ether, and acetal-type functions. The presence of pyruvaldehyde derivatives in the distillate was confirmed by acid hydrolysis of the combined fractions followed by reaction with hydroxylamine, yielding methylglyoxime. In another similar experiment, material distilling at 63–73° (5 mm.) yielded the 2,4-dinitrophenylosazone of pyruvaldehyde upon treatment with 2,4-dinitrophenylhydrazine.

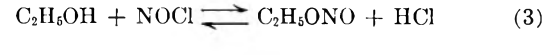
The reaction of nitrosyl chloride with isopropyl alcohol proceeded in a different manner. Distillation of the reaction mixture afforded no high-boiling liquid fraction. The bulk of the reaction product occurred in a rather sizeable residue from which was isolated a low yield of pyruvohydroxamyl chloride (II), probably arising from the following sequence.



(2)

Reaction of both ethylene glycol and propylene glycol with nitrosyl chloride produced complex mixtures which could not be resolved by fractional distillation. The presence of glyoxal-yielding compounds in the product from ethylene glycol and of pyruvaldehyde-yielding compounds in the propylene glycol product was demonstrated, however, by treatment of the distilled reaction mixtures with 2,4-dinitrophenylhydrazine and isolation of the appropriate 2,4-dinitrophenylosazones.

The reaction of nitric acid with ethanol to give glyoxal has been reported.[2] Nitrosyl chloride, however, is known to react rapidly with ethanol[3] yielding ethyl nitrite and hydrogen chloride according to the following equilibrium.

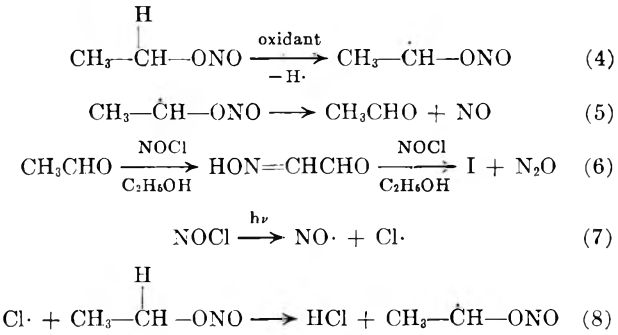


(3)

No further decomposition of this system, under mild conditions, apparently has been observed. Previous preparations of 1,1,2,2-tetraethoxyethane have involved the acid-catalyzed reactions of glyoxal[4] or of a derivative[5] thereof with ethanol and have resulted in low (23–26%) yields even after prolonged reaction periods.

The mechanism of the present reaction, though unclear, may involve the general steps 4–6.

It was felt that hydrogen abstraction (step 4) might be accomplished by a chlorine atom as in the photonitrosation of hydrocarbons by nitrosyl chloride.[6]



(4)

(5)

(6)

(7)

(8)

Exposure of our reaction system to intense visible light failed, however, either to increase the yield or rate of acetal formation, or to accelerate the decomposition of nitrosyl chloride as judged by disappearance of brown color from the reaction mixture. Other possible means of accomplishing step 4 include oxidation (a) by molecular chlorine generated from the thermal decomposition of nitrosyl chloride and (b) by dinitrogen tetroxide, present as an impurity in the nitrosyl chloride.

Experimental[7]

Identification of the Low-Boiling By-product from the Synthesis of Phenylglyoxal Diethyl Acetal.—In a series of preparations of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone and ethanol, various samples of the reaction product were found to contain, in addition to phenylglyoxal diethyl acetal, low-boiling fractions (approximately 76–130° (10 mm.), amounting to 19–27% of the total weight of organic product. Several of the low-boiling fractions were combined (weight 295.6 g.) and redistilled to yield a main fraction weighing 197.4 g., b.p. 80–84° (10 mm.), $n^{20}D$ 1.4074. The material showed no aromatic absorption upon infrared analysis which revealed only two strong bands at 8.9 and 9.2 μ in addition to aliphatic C–H absorption. Elemental and molecular weight analysis gave the following results in accord with the empirical formula $C_{10}H_{22}O_4$.

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.22; H, 10.75; mol. wt., 206.3. Found: C, 58.26; H, 10.70; mol. wt., 210.

The reported boiling point of 1,1,2,2-tetraethoxyethane ($C_{10}H_{22}O_4$) is 88–89° (14 mm.) or close to that odserved. A comparison of the previously mentioned infrared scan with a scan of 1,1,2,2-tetrabutoxyethane showed them to be almost identical.

A 41.3-g. (0.2 mole) sample of the material was hydrolyzed by refluxing under a still with 200 ml. of water containing 15 drops of concentrated sulfuric acid for a 2-hr. period. Ethanol was then recovered by distilling the mixture, which gave an aqueous solution containing 59% ethanol, by weight. The yield of ethanol (28.3 g.) was 76.8% and the composition of the aqueous ethanol solution was confirmed by mass spectrometric analysis.

The distillation residue was then filtered and to it was added 28 g. (0.403 mole) of hydroxylamine hydrochloride and 40 g. of anhydrous sodium acetate. The resulting mixture was heated on the steam bath for 1 hr. and worked up to give, upon drying, 9.5 g. of white crystalline glyoxime, m.p. 177–177.5° (reported[8] m.p. 178°). An additional crop of 2.3 g. was obtained from the filtrate. The total yield of glyoxime was 67.1%.

Reaction of Nitrosyl Chloride with Ethanol.—To 1 l. of ethanol was added, with stirring, 114 g. (1.74 moles) of nitrosyl chloride[9] through a gas diffuser over a period of approximately 1 hr. while maintaining a temperature of 23–31°. Upon completing the feed, the temperature of the mixture was raised to 38° whereupon a vigorous reflux of ethyl nitrite occurred and a colorless gas was evolved which had the composition: nitric oxide, 86.6%; nitrogen, 10.3%; nitrous oxide, 3.2%.

The reaction mixture was held at 38–43° for 21 min. and then stored overnight. The solution was then stirred and heated to 58°, 667 g. of 20% sodium hydroxide solution was added, and

(2) A. Hantzsch, *Ann.*, **222**, 65 (1884).

(3) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 366 (1951).

(4) C. Harries and P. Temme, *Ber.*, **40**, 165 (1907).

(5) H. Fiesselmann and F. Hörndler, *Chem. Ber.*, **87**, 906 (1954).

(6) M. A. Naylor and A. W. Anderson, *J. Org. Chem.*, **18**, 115 (1953).

(7) All temperatures are uncorrected.

(8) Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.

(9) Purchased from the Matheson Co. and used without further purification.

the mixture then refluxed for 1.5 hr. After removing ethanol at reduced pressure, the residue was extracted with ether and the extract evaporated to give the crude liquid product. Distillation of the latter afforded 43.9 g. of 1,1,2,2-tetraethoxyethane, b.p. 65–79° (10 mm.), which had an infrared spectrum identical to that of the material previously established as 1,1,2,2-tetraethoxyethane. The main portion distilled at 78.5–79° (10 mm.) and gave the following analysis.

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.22; H, 10.75. Found: C, 58.47; H, 10.65.

The following yields would correspond to the requirement of either 3 or 4 moles of nitrosyl chloride per mole of acetal: for 3 moles, 36.8% yield; for 4 moles, 49.0% yield.

The possible influence of light upon the nitrosyl chloride–ethanol reaction then was studied as follows: nitrosyl chloride (114 g., 1.74 moles) was fed, with stirring, to 1 l. of ethanol over a 1-hr. period while illuminating the system with three 275-watt sun lamps placed close to and surrounding the reaction flask. The temperature of the exothermic reaction was maintained at 25–28° during the feed period by external cooling. Following the feed period, the reaction mixture was allowed to warm to 31° and then gradually to 51°, with stirring over a 3.68-hr. interval at which time the brown color of nitrosyl chloride had disappeared. The reaction mixture was then worked up in the previously described manner. A total yield of 49.5 g. (0.24 mole) of crude 1,1,2,2-tetraethoxyethane, boiling over the range of 62–78° (10 mm.), was obtained.

The previous procedure was repeated in identical fashion. but without the illumination. Following the 1-hr. feed period the disappearance of nitrosyl chloride color was actually somewhat faster than in the presence of light, requiring only 2.87 hr. at 29–50°. Working up the reaction mixture at this point yielded 55.2 g. (0.269 mole) of crude acetal, b.p. 57–78° (10 mm.).

Reaction of 1-Propanol with Nitrosyl Chloride.—To 1 l. of 1-propanol was added, with stirring, 2 moles of nitrosyl chloride (92 ml. at −30°) over a period of 69 min. while maintaining a temperature of 24–28° with cooling. The reaction mixture was allowed to warm to 32° over a 19-min. period and then, in sequence, held at 30–36° for a period of 2.58 hr. and at 51–52° for 1 hr. Volatile materials (788 g.) were then flashed from the mixture leaving 91 g. of residue. The latter was extracted with ligroin (most of it dissolved) and the extract distilled to give 49.9 g. of liquid, b.p. 45–120° (3 mm.). This was redistilled to give a total of fourteen fractions boiling over the range of 63–141° (5 mm.) and fairly uniform in size. The fractions possessed remarkably similar infrared spectra including strong carbonyl absorption at 5.6–5.7 μ and bands at 8.9 and 9.3 μ similar to those of 1,1,2,2-tetraethoxyethane.

In order to demonstrate the presence of pyruvaldehyde-yielding compounds in the distillation fractions, eleven of the cuts, totaling 33.1 g., were combined and refluxed with a solution of 10 drops of concentrated sulfuric acid in 200 ml. of water for a 14-hr. period to hydrolyze the acetal and/or ketal linkages. At the end of this time, a solution of 28.0 g. (0.403 mole) of hydroxylamine hydrochloride and 40 g. (0.488 mole) of anhydrous sodium acetate in 100 ml. of water was added to the mixture and the new mixture refluxed, with stirring, for a period of 7 hr. Working up the mixture gave a small amount of pyruvaldehyde dioxime which was purified by vacuum sublimation to give fine white crystals, m.p. 146–147° (reported[8] m.p. 153°, 157°).

Anal. Calcd. for $C_3H_6O_2N_2$: C, 35.29; H, 5.92; N, 27.44. Found: C, 35.87; H, 6.57; N, 26.57.

The infrared spectrum confirmed the structure as that of pyruvaldehyde dioxime.

The previous run was repeated on a larger scale giving, upon work-up, 95 g. of a flashed distillate, b.p. 35–109° (1 mm.). Fractional distillation of this gave thirteen cuts of fairly uniform size, several of which were tested for the presence of pyruvaldehyde derivatives by reacting samples of them with 2,4-dinitrophenylhydrazine reagent. Only the first two cuts, boiling over the combined range of 63–75° (5 mm.), gave pyruvaldehyde 2,4-dinitrophenylosazone. The derivative of cut 1, b.p. 63–68° (5 mm.), melted at 298° (reported[8] for pyruvaldehyde 2,4-dinitrophenylosazone, m.p. 299–300°), and gave the following analysis.

Anal. Calcd. for $C_{15}H_{12}N_8O_8$: N, 25.92. Found: N, 25.33.

Reaction of Isopropyl Alcohol with Nitrosyl Chloride.—One liter of isopropyl alcohol was stirred while 2 moles (92 ml. at −30°) of nitrosyl chloride were fed over a period of 1.27 hr., maintaining a temperature of 26–29°. Evolution of nitric oxide became apparent at the end of the feed period and the stirred mixture was allowed to warm to 30–33° where it was held, with gentle reflux, for a 1.67-hr. period. At this time, the reaction mixture was heated to 50–51° and stirred at this temperature for a 1-hr. period.

Volatile material (777 g.) then was removed from the reaction mixture under reduced pressure leaving a residue, weight 65 g. Attempted distillation of the latter led to partial decomposition and some crystalline material sublimed into the lower part of the column. A portion (0.6 g.) of this material was recrystallized from benzene and further purified by vacuum sublimation to give crystals of pyruvohydroxamyl chloride, m.p. 106–107° (reported[10] m.p. 105–106°).

Anal. Calcd. for $C_3H_4NO_2Cl$: C, 29.65; H, 3.32; N, 11.53; Cl, 29.17. Found: C, 29.70; H, 3.51; N, 11.46; Cl, 29.73.

The infrared spectrum was identical to that of an authentic sample of pyruvohydroxamyl chloride.

Reaction of Ethylene Glycol with Nitrosyl Chloride.—To 1 l. of ethylene glycol was added, with stirring and cooling, 131 g. (2.0 moles) of nitrosyl chloride over a period of 1.78 hr. The mixture then was warmed to 35° and held at this temperature, where a mildly exothermic reaction occurred, for a 2-hr. period. The reaction mixture was then heated to 61° and stirred at this temperature for a period of 1.25 hr.

The reaction mixture was then distilled to give a series of fractions (total wt., 1101 g.) boiling over the approximate range of 40–93° (0.5 mm.). All the fractions reacted with 2,4-dinitrophenylhydrazine to give the crude 2,4-dinitrophenylosazone of glyoxal, m.p. 311–317° dec. (reported[11] m.p. 318° dec).

Reaction of Propylene Glycol with Nitrosyl Chloride.—To 1 l. of propylene glycol was added, with stirring, 131 g. (2.0 moles) of nitrosyl chloride over a 1.67-hr. period with cooling to maintain the temperature at 25–26°. The reaction mixture was allowed to warm, exothermically, to 35–38°, where it was stirred for 1 hr. at which time the brown reaction solution had become colorless. The mixture was then heated to 60° and stirred at this temperature for 1 hr.

The reaction mixture was next distilled at reduced pressure to give a series of fractions [final b.p. 110° (0.5 mm.)] all of which reacted with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylosazone of pyruvaldehyde. The identity of the material from two recrystallized (nitrobenzene) preparations (both melting at 297°) was verified by determining the melting point upon mixture with authentic material.

Acknowledgment.—The authors are indebted to Mr. C. M. Lovell and Dr. H. F. White for the infrared studies performed.

(10) H. Reinboldt and O. Schmitz-Dumont, *Ann.*, **444**, 113 (1925).
(11) C. Neuberg and E. Simon, *Biochem. Z.*, **256**, 485 (1932).

Effect of Remotely Positioned Groups on the Reactivities of Olefins toward Radical Addition[1]

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Competition reactions show that the reactivities of terminal olefins toward free radical addition by mercaptans are influenced by the extent of substitution on the 4-carbon of the olefin. An order of reactivity of 2-methyl-1-pentene > 2,4-dimethyl-1-pentene > 2,4,4-trimethyl-1-pentene toward addition by *n*-amyl mercaptan at 80° has been demonstrated. This order of reactivity is parallel to that predicted by Newman's empirical "rule of six." Addition of methyl mercaptan is not so markedly influenced by substitution on the 4-carbon of the olefin as are additions of *n*-amyl and *n*-dodecyl mercaptans. There are no appreciable differences in the reactivities of these olefins toward addition of bromotrichloromethane. An explanation is proposed for the anomalous behavior of these olefins toward addition of these reagents and an explanation of the nature of the effect of these remotely positioned groups on the reactivities of these olefins toward addition of mercaptans is suggested.

The generally accepted mechanism for the free radical addition of a reagent XY across the double bond of an olefin involves the following two free radical chain propagating reactions.[2]

$$Y\cdot + CH_2{=}CHR \longrightarrow YCH_2\dot{C}HR \quad (1)$$

$$YCH_2\dot{C}HR + XY \longrightarrow YCH_2CXHR + Y\cdot \quad (2)$$

Relative reactivities of olefins toward addition by free radicals can be determined by competition reactions of two or more olefins with an adding reagent. Removal of olefin by reaction of the adduct radical with olefin rather than with the adding reagent (reaction 2) can be eliminated as a complicating factor by using very reactive adding reagents such as bromotrichloromethane or mercaptans. Such studies have been reported by Kharasch and co-workers who used bromotrichloromethane[3] to determine the relative reactivities of various olefins toward addition by trichloromethyl radicals ($Y\cdot = Cl_3C\cdot$) and by Walling and Helmreich who used mercaptans[4] to obtain the relative reactivities of olefins toward addition by thiyl radicals ($Y\cdot = RS\cdot$). Reversibility of the addition of thiyl radicals to olefins, a possible complicating factor as far as reactivities toward addition by thiyl radicals are concerned, has been demonstrated by the rapid isomerization of unchanged olefin in the addition of methyl mercaptan to *cis*- and to *trans*-2-butene.[4] Walling and Helmreich have, however, demonstrated that reliable ratios of reactivities of various olefins toward mercaptan addition can be obtained by maintaining a constant mercaptan:olefin concentration ratio. Their values for the relative reactivities of several olefins toward addition by thiyl radicals are in general agreement with those found by Kharasch and co-workers for the trichloromethyl radicals.

We have employed the method of competition reactions to determine the effect of groups remotely positioned from the reaction center on the reactivities of terminal olefins toward free radical addition of various mercaptans and bromotrichloromethane. The olefins used in our investigation were 2-methyl-1-pentene (I), 2,4-dimethyl-1-pentene (II), 2,4,4-trimethyl-1-pentene (III), and 2,3,3-trimethyl-1-butene (IV).

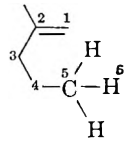
$$\underset{\text{I}}{CH_3CH_2CH_2C(CH_3){=}CH_2} + XY \xrightarrow{k_I} CH_3CH_2CH_2CX(CH_3)CH_2Y \quad (3)$$

$$\underset{\text{II}}{(CH_3)_2CHCH_2C(CH_3){=}CH_2} + XY \xrightarrow{k_{II}} (CH_3)_2CHCH_2CX(CH_3)CH_2Y \quad (4)$$

$$\underset{\text{III}}{(CH_3)_3CCH_2C(CH_3){=}CH_2} + XY \xrightarrow{k_{III}} (CH_3)_3CCH_2CX(CH_3)CH_2Y \quad (5)$$

$$\underset{\text{IV}}{(CH_3)_3CC(CH_3){=}CH_2} + XY \xrightarrow{k_{IV}} (CH_3)_3CCX(CH_3)CH_2Y \quad (6)$$

These particular olefins were chosen because they could involve the type of steric effect suggested by Newman's "rule of six," namely that reaction at an unsaturated linkage is sterically hindered by the atoms or groups positioned six atoms from the site at which the reaction is taking place.[5] In olefin I, there are three hydrogens in the 6-position. Substitution of a second



methyl on the 4-carbon of the olefin would result in a compound with six such hydrogens and substitution of a third methyl on the 4-carbon would result in nine such hydrogens. Since the primary steric factors (all are terminal olefins), resonance factors, and any polar contributions are essentially the same in I, II, and III, any observed differences in the reactivities of these olefins toward addition must very likely result from the extent of substitution on the 4-carbon. Olefin IV has no hydrogens in the 6-position that might exert a steric influence on the addition reaction. However, IV does have two less allylic hydrogens available to stabilize the adduct radical and might be expected to be lower in reactivity with respect to I, II, and III toward radical addition.

Relative reactivity ratios of these olefins toward free radical addition by various mercaptans and bromotri-

(1) This work was supported by a grant from the Petroleum Research Fund, administered by the American Chemical Society.

(2) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 240.

(3) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.*, **14**, 239 (1949); M. S. Kharasch and M. Sage, *ibid.*, **14**, 537 (1949); M. S. Kharasch, E. Simon, and W. Nudenberg, *ibid.*, **18**, 328 (1953).

(4) C. Walling and W. Helmreich, *J. Am. Chem. Soc.*, **81**, 1144 (1959).

(5) M. S. Newman, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 206.

chloromethane were determined by allowing mixtures of known quantities of two of the olefins to react with the adding reagent. The adding reagent was always present in a large excess to eliminate any polymerization of the olefin. Further, the mole ratio of the adding reagent to the total olefin content was kept constant in all cases. The chain reactions were initiated either chemically with azobisisobutyronitrile (AIBN) or photochemically with a sun lamp and were allowed to proceed until an appreciable amount of each olefin had reacted to allow for the calculation of the reactivity ratio. The amounts of the olefins that had reacted were determined by gas chromatographic analyses of the reaction mixtures. The relative reactivity ratio of two olefins A and B (k_A/k_B) could be found by substituting the values for the amounts of the olefins before and after reaction in the equation

$$k_A/k_B = \frac{\log (A_0/A)}{\log (B_0/B)}$$

where A_0 and B_0 are the amounts of the olefins before reaction and A and B are the amounts after reaction. In our hands, this method gave reactivity ratios of these olefins toward addition that were fairly consistent for two or more runs (see Table I). In the duplicate runs for each reactivity ratio, the initial amount of each olefin was significantly altered. The reliability of the values for the reactivity ratios is further supported by the cross-check experiments.

The relative reactivities of these olefins, using the reactivities of 2-methyl-1-pentene (I) as a standard, to addition by the various reagents serve better to illustrate the following discussion (see Table II).

TABLE I

COMPETITION REACTION STUDIES OF OLEFINS TOWARD FREE RADICAL ADDITION

Adding reagent	Temp., °C.	Init.	Reactivity ratio	Value	No. of runs	Average deviation
n-$C_5H_{11}SH$	80	AIBN	k_I/k_{II}	3.8	4	0.6
n-$C_5H_{11}SH$	80	AIBN	k_I/k_{III}	13.0	4	2.7
n-$C_5H_{11}SH$	80	AIBN	k_I/k_{IV}	2.6	4	0.2
n-$C_5H_{11}SH$	80	AIBN	k_{II}/k_{III}	2.9	2	.3
n-$C_5H_{11}SH$	80	AIBN	k_{IV}/k_{III}	4.2	2	.05
n-$C_{12}H_{25}SH$	80	AIBN	k_I/k_{III}	13.3	4	3.0
CH_3SH	0	$h\nu$	k_I/k_{III}	6.3	2	0.9
$BrCCl_3$	40	$h\nu$	k_I/k_{II}	1.05	8	.11
$BrCCl_3$	40	$h\nu$	k_I/k_{III}	0.99	6	.05
$BrCCl_3$	0	$h\nu$	k_I/k_{III}	1.01	2	.05
$BrCCl_3$	40	$h\nu$	k_{II}/k_{III}	0.96	2	.08
$BrCCl_3$	40	$h\nu$	k_I/k_{IV}	2.4	3	.10

TABLE II

RELATIVE REACTIVITIES OF OLEFINS TO ADDITION BY VARIOUS ADDING REAGENTS

Olefin	n-$C_5H_{11}SH$[a]	CH_3SH[b]	n-$C_{12}H_{25}SH$[a]	$BrCCl_3$[c]
$CH_3CH_2CH_2C(CH_3)=CH_2$	1.00	1.00	1.00	1.00
$(CH_3)_2CHCH_2C(CH_3)=CH_2$	0.26	..	..	1.05
$(CH_3)_3CCH_2C(CH_3)=CH_2$	.08	0.16	0.08	0.99
$(CH_3)_3CC(CH_3)=CH_2$	.39	..	..	.42

[a] Temp., 80°. [b] Temp., 0°. [c] Temp., 40°.

Examination of the relative reactivities shown in Table II shows that: (1) increasing the number of methyl groups on the 4-carbon of the olefin (and hence increasing the number of hydrogens in the 6-position relative to the terminal carbon of the double bond) does markedly lower the reactivity of an olefin toward addition by mercaptans; (2) this effect is not observed in the addition of bromotrichloromethane; and (3) the reactivity of an olefin with no hydrogens in the 6-position but with two less allylic hydrogens (olefin IV) is the same to addition by mercaptans and bromotrichloromethane. If these reactivity ratios are to be taken as the relative reactivities of the olefins to addition by thiyl radicals and trichloromethyl radicals, one might conclude that thiyl radical additions are sterically hindered by remotely positioned groups whereas trichloromethyl radical additions are not. Such a conclusion would be surprising in light of the similar effects of other factors (primary steric, resonance, and polar) on the reactivities of various other unsaturates to addition by these radicals. We find in our own work that a structure change that decreases the resonance factor has the same effect on the reactivity of the olefin to addition by both mercaptans and bromotrichloromethane.

One explanation for these anomalous results is that reversibility of the thiyl radical addition to olefins may be an important factor in our work in spite of our efforts to minimize this factor by maintaining a constant mercaptan:olefin ratio. Examination of the kinetic aspects of the chain sequences for the additions of mercaptans (reactions 7 and 8) and for the additions of bromotrichloromethane (reactions 9 and 10) show

$$RS\cdot + CH_2{=}CR'CH_3 \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} RSCH_2\dot{C}R'CH_3 \qquad (7)$$

$$RSCH_2\dot{C}R'CH_3 + RSH \xrightarrow{k_{tr}} RSCH_2CHR'CH_3 + RS\cdot \qquad (8)$$

$$Cl_3C\cdot + CH_2{=}CRCH_3 \xrightarrow{k_a} Cl_3CCH_2\dot{C}RCH_3 \qquad (9)$$

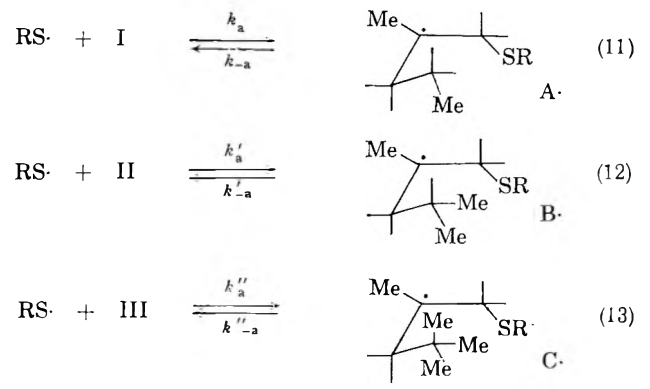
$$Cl_3CCH_2\dot{C}RCH_3 + BrCCl_3 \xrightarrow{k_{tr}} Cl_3CCH_2CBrRCH_3 + Cl_3C\cdot \qquad (10)$$

that the reversibility of the thiyl radical addition is the only kinetic factor that is significantly different.[6] In the bromotrichloromethane reactions, it follows that the relative rates of removal of the olefins from the reaction mixture (what we are actually measuring in our competition reactions) is dependent only on the relative rates of addition of the trichloromethyl radical to the olefins. In the mercaptan additions, the relative rates of removal of the olefins are equal to the relative rates of addition of the thiyl radicals only if the rates of elimination (k_{-a}) are the same for all of the adduct radicals and the rates of chain transfer are the same (reaction 8). This latter requirement is met by maintaining a mercaptan:olefin ratio that is significantly greater than one and essentially constant for various runs. Since there is no difference in the reactivities of olefins I, II, and III to addition by trichloromethyl radicals, we might conclude that the rates of addition of thiyl radicals to these olefins is also the same. This leaves only the elimination of the thiyl radicals from the

(6) Skell and Woodworth found that there was no isomerization of the unchanged olefins in the addition of bromotrichloromethane to *cis*-2-butene and to *trans*-2-butene. P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **77**, 4638 (1955).

adduct radicals to explain the reactivities of olefins I, II, and III to addition by mercaptans.

The order of reactivity I > II > III toward mercaptan addition is consistent with this conclusion that the elimination of the thiyl radical is the determining factor for their different reactivities. The adduct radicals A·, B·, and C· resulting from addition of a thiyl radical to I, II, and III, respectively, can assume (among many others) the cyclic conformations shown.



The reaction rate constants for formation of these adduct radicals may well be the same, that is $k_a = k_a' = k_a''$. Relief of strain caused by steric crowding that results when the adduct radical is in a cyclic conformation may well accelerate the elimination of the thiyl radical. Since the extent of crowding would depend on the number of methyl groups on the 4-carbon (and presumably on the number of hydrogens in the 6-position), the predicted order of the rate constants for the elimination reactions would be $k_{-a}'' > k_{-a}' > k_{-a}$. The elimination reaction of the adduct radical must be faster than its chain transfer reaction with the mercaptan as evidenced by the isomerization of the 2-butenes.[4] Thus, the concentration of a crowded adduct radical would be lower than that of a less crowded one in a competition reaction and its rate of removal, and consequently that of the olefin from which it was formed, would be slower.

The lower reactivity of IV with respect to I toward addition by *n*-amyl mercaptan very likely results from its lower reactivity to addition by the thiyl radicals themselves. This conclusion appears valid in light of the very similar relative reactivity ratio of these two olefins to addition by trichloromethyl radicals. Further, the alkyl chain in the adduct radical obtained from IV is not long enough to permit the type of crowding that is encountered in the adduct radicals obtained from the pentenes. The lower reactivities of II and III compared to that of IV indicate that the elimination reaction is accelerated to a much greater extent when there are two or three methyls on the 4-carbon than when there is only one.

The smaller difference in the reactivities of I and III toward addition of methyl mercaptan compared to the larger differences noted with *n*-amyl and dodecyl mercaptans is also consistent with the above explanation. Cyclic conformations of the *n*-amyl and *n*-dodecyl groups may be responsible for some of the crowding in the adduct radicals making elimination of *n*-amyl and *n*-dodecyl thiyl radicals more favorable than the elimination of methyl thiyl radicals.

In summary, it appears that β-elimination of thiyl radicals is markedly accelerated if the radical, which is undergoing fragmentation, can assume conformations which involve crowding near the reaction site. The addition of the radical is not, however, sterically hindered by remotely positioned groups.

Experimental

Materials.—*n*-Amyl mercaptan, *n*-dodecyl mercaptan (both from Aldrich Chemical Co., Inc.), and methyl mercaptan (Matheson) were used without further purification. Bromotrichloromethane (Dow Chemical Co.) was redistilled under vacuum until it gave a single peak on gas chromatographic analysis. 2-Methyl-1-pentene and 2,4,4-trimethyl-1-pentene (both from Phillips, Pure Grade) were redistilled and each gave a single peak on gas chromatographic analysis. 2,4-Dimethyl-1-pentene (b.p. 80°) was prepared by the acetate pyrolysis of 2,4-dimethyl-1-acetoxypentane which was obtained from an authentic sample of 2,4-dimethyl-1-pentanol (K and K Laboratories). 2,3,3-Trimethyl-1-butene (b.p. 77°) was prepared by the dehydration of 2,3,3-trimethyl-2-butanol over alumina at 550°. This alcohol was prepared by a standard Grignard reaction of methyl magnesium iodide with pinacolone.

The azobisisobutyronitrile (Matheson Coleman and Bell) was used without further purification. The photochemical reactions were induced with a 275-watt Sylvania Sunlamp.

Experimental Procedure.—The reactivity ratios reported in Table I were all determined in the following manner. A mixture consisting of 0.1 to 0.3 g. each of the two olefins, the amount of each accurately determined on an analytical balance, was diluted with an excess of the adding reagent. In the case of the mercaptans, the initial mole ratio of the adding reagent to the total amount of the olefins was 4:1 in all runs. A sample of the mixture (0.01 ml.) was removed by means of a pipet and injected on the gas chromatographic column through a Fisher sample injection valve. The areas of the two olefin peaks (and in some cases the adding reagent peak) were determined. In the AIBN induced reactions, about 5 mg. of this initiator was added to the reaction mixture. The reaction mixtures were sealed in Pyrex tubes and the tubes immersed in a constant temperature oil bath set at 80° for the chemically initiated reactions. The photochemically induced reactions were performed by immersing the tube in constant temperature water baths set at either 40° or 0°. The reaction mixture was then illuminated by a sun lamp which was placed about 6 in. from the side of the bath. The reactions were stopped in all cases before either of the two olefins was completely consumed. The tube was removed from the constant temperature bath and allowed to come to room temperature before another 0.01-ml. sample was removed by means of a pipet and subjected to gas chromatographic analysis under the same conditions used for the first sample. Determination of the amounts of each of the olefins remaining in the reaction mixture was made by comparison of the olefin peak areas with those obtained before reaction. The data were treated in the manner described previously.

Isomerization and Disproportionation of *d*-Limonene on Silica Gel

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d-Limonene, from rectified orange essential oil, in the presence of silica gel at elevated temperatures exhibited disproportionation *via* a two-phase process. A study was made showing the disappearance of *d*-limonene with time at 100° and 150° to give initially α-terpinene, γ-terpinene, terpinolene, and isoterpinolene which, subsequently, disproportionated into 1-*p*-menthene, *trans*-2-*p*-menthene, 3-*p*-menthene, *t*-8(9)-*p*-menthene, and *p*-cymene. The isomerization products of *d*-limonene also were studied. The reactions were monitored by gas chromatography and constituent identity confirmed by infrared spectroscopy.

As part of the study of flavor changes in orange products it became necessary to elucidate the chemical composition of the whole oil. The procedure for the separation of the terpenes from the terpenoids on a silicic acid column, published by Kirchner and Miller,[2] was employed using silica gel. It had been observed that terpene hydrocarbons isomerized when passed through a silica gel column at room temperature;[3] Rudakov and Shestaeva[4] have shown that silica gel free of aluminum oxide did not promote isomerization of α-pinene at 100°; further, they showed that deposition of 0.1% aluminum oxide on silica gel raised the activation 1500-fold equivalent to the level of clays.

The disproportionation of *d*-limonene in the presence of palladium–barium sulfate catalyst[5] and palladized asbestos[6] has been reported to occur under rather vigorous conditions to give mostly *p*-cymene and *p*-menthane with some *p*-menthenes in the former. It has been shown also that *p*-menthenes undergo isomerization in the presence of sodium organo-sodium catalyst under reflux.[7] The present paper shows that these reactions can be accomplished using silica gel under mild conditions.

Limonene (I) was isomerized at 100° into terpinolene (II), α-terpinene (III), γ-terpinene (IV), and isoterpinolene. Isomerization began immediately exhibiting very little disproportionation as shown in Fig. 1. These reactions can be explained by assuming adsorbed carbonium ions on the surface of the catalyst. It is proposed that hydrogen transfer takes place in the presence of silica gel as observed by Turkevitch and Smith[8] in the interconversion of 1-butene to 2-butene. *d*-Limonene (I) must extract a proton from the surface of the catalyst to give the 8-menthenyl carbonium ion which can give up the remaining tertiary proton to form terpinolene (II). The 8-menthenyl ion experiences a proton shift to give the 4-menthenyl carbonium ion which, upon loss of a proton, gave both α-terpinene and γ-terpinene. This reversible hydrogen shift is further evidenced by the presence of trace quantities of dipentene during the silica gel isomerization of II, III, IV, and V.

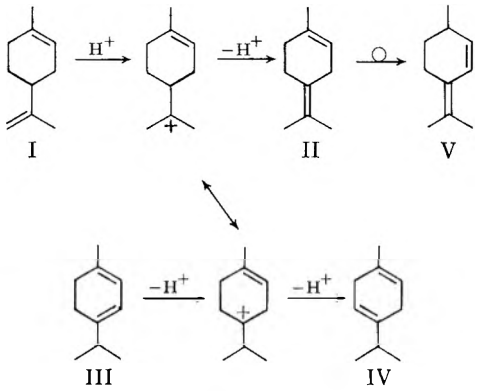


Figure 2 shows the initiation and short duration of the isomerization phase at 150° as evidenced by the rapid conversion of *d*-limonene into *p*-menthadienes requiring only two minutes. Isoterpinolene (V) appears only after terpinolene (II) had achieved very close to its maximum concentration which is attributed to isomerization of II to the more stable conjugated con-

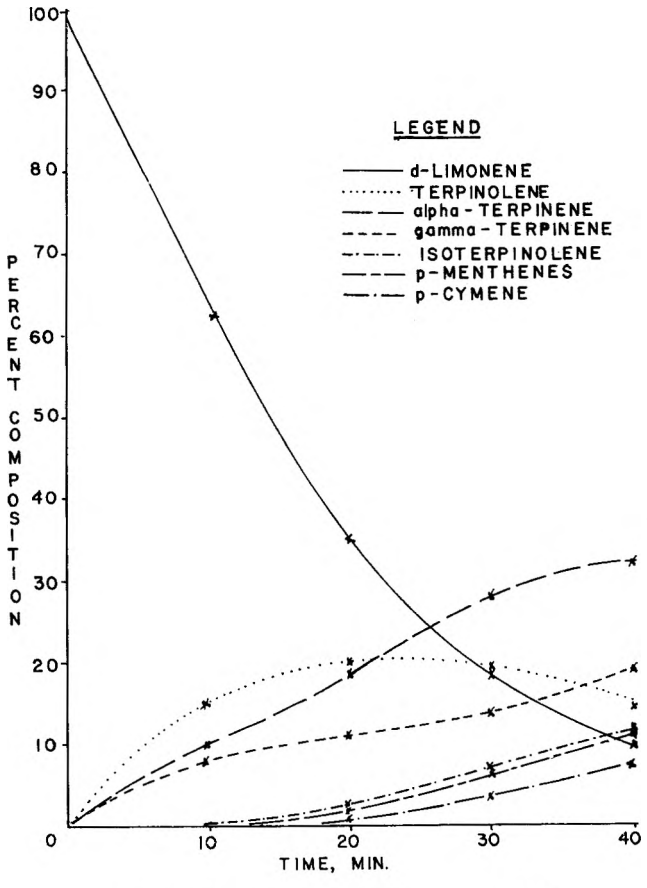


Fig. 1.—Isomerization of *d*-limonene at 100°.

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. References to specific products of commercial manufacture are for illustration only and do not constitute endorsement by the U. S. Department of Agriculture.

(2) J. G. Kirchner and J. M. Miller, *Ind. Eng. Chem.*, **44**, 318 (1952).

(3) B. A. Arbuzov and Z. G. Isaeva, *Izv. Akad. Nauk, SSSR, Otdel. Khim. Nauk*, 843 (1953); *Chem. Abstr.*, **49**, 1654i (1955).

(4) G. A. Rudakov and M. M. Shestaeva, *Zh. Obshch. Khim.*, **29**, 2062 (1959); *Chem. Abstr.*, **54**, 8880h (1960).

(5) H. E. Eschinazi and H. Pines, *J. Am. Chem. Soc.*, **78**, 1176 (1956).

(6) H. E. Eschinazi and E. D. Bergmann, *ibid.*, **72**, 5651 (1950).

(7) H. Pines and H. E. Eschinazi, *ibid.*, **78**, 1178 (1956).

(8) J. Turkevitch and Smith, *J. Chem. Phys.*, **16**, 466 (1948).

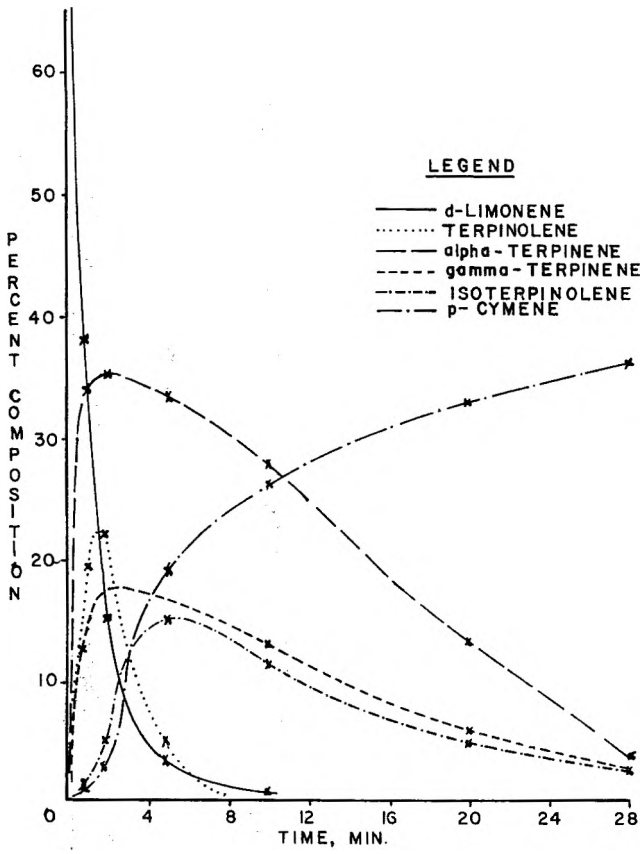
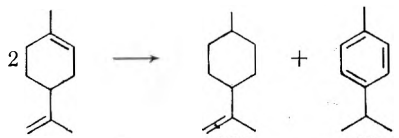
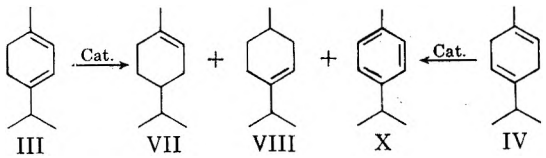


Fig. 2.—Isomerization and disproportionation of *d*-limonene at 150°.

figuration as is also the case with the predominant formation of III over IV. Figure 3 shows the disproportionation of these substances as the latter phase progressed to give 1-*p*-menthene (VII), *t*-2-*p*-menthene (VI), 3-*p*-menthene (VIII), *t*-8-(9)-*p*-menthene (IX), and *p*-cymene (X). None of the other isomeric *p*-menthenes have been found to be present in the mixtures. Further treatment of these products with silica gel failed to yield *p*-menthane, the completely disproportionated product. Treatment of VI and VIII separately with silica gel at 150° for one hour yielded only the starting materials; however, IX under these conditions, isomerized to VIII. It was observed that the concentration of IX increased in proportion to the decrease in the concentration of *d*-limonene with subsequent formation of *p*-cymene (X). Since the concentration of IX remained proportional to that of *d*-limonene during the transformations it is postulated that IX is a direct disproportionate of I. Its concentration remained small due to isomerization to 3-*p*-menthene (VIII). Eschinazi and Bergmann[6] had observed this disproportionation and, in addition, reported the presence of *p*-menthane. They propose a scheme based on the hydrogen transfer studies of Ipatieff, *et. al.*[9] This same mechanism could account for the presence of VII and VIII from III and IV, respectively. The absence of 4(8)-*p*-menthene is attributable to steric factors inhibiting the proposed concerted mechanism. Hydrogen transfer appeared to occur by 1,4-addition as a consequence of polarization of the conjugated diene. This postulation is based on the absence of 4(8)-*p*-menthene which would be expected from a 1,2-addition

(9) V. N. Ipatieff, H. Pines, and R. C. Olberg, *J. Am. Chem. Soc.*, **70**, 2123 (1948).



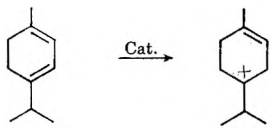


of II. α-Terpinene gave VI which is believed to be its principal source, and II gave VIII contributing to its abnormally high yield.

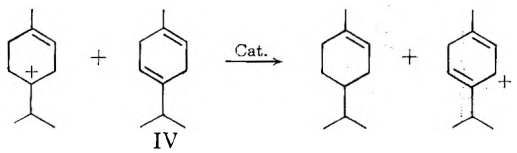
It is proposed that a catalytic hydrogenation occurred concurrently with the disproportionation reactions described above. *p*-Cymene (X) dimerized[9] to give 1,3,3,6-tetramethyl-1-*p*-tolylinden (XII) and two moles of hydrogen. Compound XII has been found to be a constituent of the polymeric residue.

It was of interest to study the behavior of the isomeric products of *d*-limonene. γ-Terpinene (IV), α-terpinene (III), terpinolene (II), and isoterpinolene (V) were individually treated with silica gel at 150° according to the method used for *d*-limonene. In each case isomerization occurred rapidly to give the product obtained from *d*-limonene including dipentene followed by the typical disproportionation compounds exhibited by *d*-limonene on silica gel. Dimers and polymers were formed at 150° as has been reported in heterogeneous catalytic systems with terpenes.[10-12] These were observed to occur primarily during disproportionation.

The major source of the endocyclic *p*-menthenes is probably through disproportionation of the isomeric *p*-menthadienes. As an example α-terpinene reacts with the catalyst to form a carbonium ion.



An exchange reaction probably occurs.

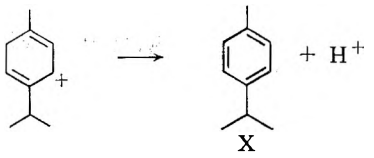


(10) G. Dupont, R. Dulou, and G. Thuet, *Bull. Soc. Chim.*, **8**, 891 (1941); *Chem. Abstr.*, **37**, 4716 (1943).

(11) V. E. Tishchenko and G. A. Rudakov, *Zh. Prikl. Khim.*, **6**, 691 (1933); *Chem. Abstr.*, **28**, 4052 (1934).

(12) M. Ya. Levshuk, *et al.*, *Z. Prikl. Khim.*, **13**, 1178 (1940).

A proton is lost to give *p*-cymene.



The presence of an abundance of hydrogen acceptors probably was responsible for the absence of *p*-menthane.

Experimental

Analytical Procedure.—Reactions were monitored from initiation to completion by gas chromatography using an F and M flame ionization detector in conjunction with a 250 ft. × 0.020 in. i.d. capillary column. The column was coated with Carbowax 20 M and maintained at a temperature of 85°. A preparatory column measuring 0.5 in. × 36 ft. containing 30% Carbowax 20 M on Chromosorb P at a temperature of 130° was used to obtain sufficient material for infrared analysis. The material represented by each peak was trapped and identified by comparison of their infrared spectra with those of authentic compounds or spectra. This system was incapable of separating *t*-8(9)-*p*-menthene from *t*-2-*p*-menthene; therefore, the former was estimated by its characteristic peaks at 1620 cm.$^{-1}$ and 883 cm.$^{-1}$ in the infrared.[5] Since the analytical procedure must accommodate very small quantities, the analysis was accomplished entirely by gas chromatography. The instrument was calibrated for 1-μl. injection of *d*-limonene. The quantities of each constituent, as shown in Fig. 1–3, were estimated as a part of the total chromatographic peak area. The nonvolatile constituents were calculated to be the difference between the area represented by one microliter of *d*-limonene and that obtained from the total peak area of the volatile constituents.

***d*-Limonene (I).**—Chromatographically pure *d*-limonene was obtained by rectification of cold pressed Valencia orange oil.[13]

Silica Gel.[14]—The silica gel used for these experiments was Fisher cat. no. S157, 28–200 mesh suitable for chromatography. This material was more active than Mallencrodt's analytical reagent grade precipitated silicic acid suitable for chromatography which gave the same products, but required more time. Least active was Baker's silica gel suitable for chromatography which required a 20-fold reaction period to give the same products. Research Specialties' silica gel-G for thin-layer chromatography was also shown to contain a very high activity. These materials vary from lot to lot and their activity should be determined before use on systems which are prone to isomerization or disproportionation.

***d*-Limonene (100°).**—A slurry of *d*-limonene and silica gel was divided into four test tubes. The composition of the slurry was not found to be critical; however, it was such that a thin layer of liquid formed at the top. The test tubes were placed in a water bath at 100°. The first tube was analyzed after remaining in the bath for 10 min. Each successive tube was removed in 10-min. intervals and analyzed so that the last tube remained in the bath a total of 40 min. The reaction was quenched by cooling in tap water upon removal from the bath. A microliter of material was withdrawn directly out of the slurry for analysis. The remainder was filtered and upon standing in the refrigerator showed no change in composition. The yield of volatile constituents was 95% or better, being within experimental error.

***d*-Limonene (150°).**—The procedure described above was repeated using a Silicone 710 bath at 150°. Samples were analyzed at intervals of 1, 2, 5, 10, 20, and 30 min. for analysis of the volatile constituents shown in Fig. 2. The ratio of volatile constituents to polymer formation were carried out for longer periods to show a leveling out of polymer formation after 1 hr. (See Table I.)

γ-Terpinene (IV).—Fifty milliliters of *d*-limonene was slurried with silica gel and heated at 100° for 30 min. and cooled. The silica gel was removed by filtration and 20 ml. of the filtrate was placed on the preparative scale gas chromatograph.[15] The various constituents were trapped in liquid nitrogen cooled traps and thus made available the products of bond migration for further study. γ-Terpinene was slurried with silica gel and heated at 150° for 10 to 40 min. The composition of the products was essentially that shown in Fig. 3 for *d*-limonene under similar conditions including dipentene.

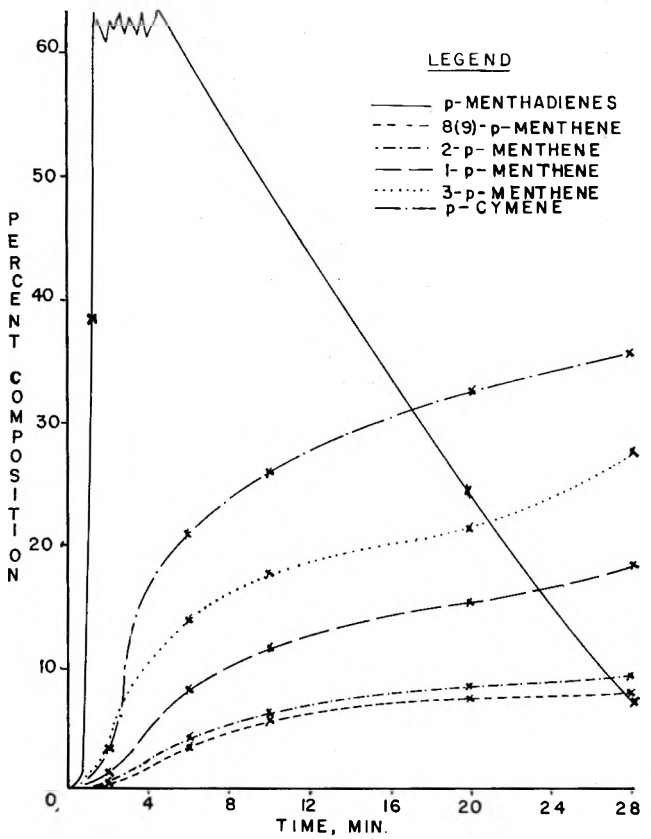


Fig. 3.—Disproportionation of the *p*-methadienes from limonene at 150°.

TABLE I

Time, min.	Yield of volatiles, %
0	100
10	62
30	46
60	33
120	30

α-Terpinene (III).—α-Terpinene was obtained as a trapped product from the preparative scale gas chromatographic separation as described previously. It was slurried in silica gel and heated at 150° for 20 min. to give essentially the composition of products obtained for γ-terpinene.

Isoterpinolene (V).—Isoterpinolene appeared as the last peak on the chromatograph and was collected as described previously. It was slurried with silica gel for 20 min. at 150° to give essentially the same composition of products obtained from γ-terpinene with the exception of a noticeable increase in α-terpinene and γ-terpinene.

Terpinolene (II).—Terpinolene was obtained from a preparative scale gas chromatographic separation of commercial terpinolene. It was slurried with silica gel and heated for 20 min. at 150° to give essentially the same composition of products obtained from γ-terpinene.

1,3,3,6-Tetramethyl-1-*p*-tolylinden (XII).—The mixture obtained in the disproportionation of *d*-limonene was vacuum distilled and a fraction boiling at 155–160° (5.5 mm.) was subjected to infrared analysis. The spectra and boiling point were the same as that reported by Ipatieff, *et al.*[9]

(13) Obtained from Birds Eye Division of General Foods, Florence Villa, Fla.

(14) K. G. Miesserov, *Dokl. Akad. Nauk, USSR*, **87**, 627 (1952); *Chem. Abstr.*, **47**, 3675 (1953).

15 Column—1.5 in. × 80 ft., containing 30% Carbowax 20 M on Chromosorb P at a temperature of 150°.

8(9)-*p*-Menthene (IX) Isomerization.—A sample of IX obtained from The Glidden Co.[15] was treated with silica gel at 150° as described, for 20 min. The gas chromatographic and infrared analysis showed complete isomerization to 3-*p*-menthene (VII).

3-*p*-Menthene (VII) Isomerization.—3-*p*-Menthene, obtained by a preparative scale gas chromatographic separation of *d*-limonene disproportionation products, was treated for 1 hr. at 150° on silica gel. Analysis by gas chromatography and infrared spectroscopy showed no isomerization.

2-*p*-Menthene (VI) Isomerization.—2-*p*-Menthene, obtained by chromatography as described, when treated for 1 hr. at 150° on silica gel, showed no isomerization.

(16) Contributed by The Glidden Co., Jacksonville, Fla.

Acknowledgment.—The authors wish to thank Dr. Herman Pines, Department of Chemistry, Northwestern University, Evanston, Illinois, for infrared curves of 8(9)-*p*-menthene and *t*-2-*p*-menthene; Gordon S. Fisher, USDA, Olustee, Florida, for infrared curves of 1-*p*-menthene, 3-*p*-menthene, α-terpinene, and γ-terpinene; and Dr. John M. Derfer, The Glidden Company, Jacksonville, Florida, for samples of 8(9)-*p*-menthene.

Pyrazines. III. The Action of Phosphoroyl Chloride on Pyrazine N-Oxides[1,2]

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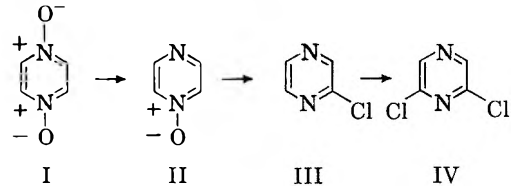
The action of phosphoroyl chloride on pyrazine N-oxides is described. Thus, pyrazine 1-oxide is converted to 2-chloropyrazine, while pyrazine 1,4-dioxide yields 2,6-dichloropyrazine. By contrast, 2-methylpyrazine 1,4-dioxide gives a mixture of dichloromethylpyrazine and a monochloromethylpyrazine N-oxide which is isomeric with the N-oxide produced by direct oxidation of 2-chloro-3-methylpyrazine or 2-chloro-6-methylpyrazine. The mechanisms of halogenation of these pyrazine N-oxides are discussed and the role of possible intermediates is examined.

Since its demonstration by Meisenheimer[3] and later by Bobranski and associates,[4a] the conversion of heterocyclic N-oxides by chlorinating agents to nuclear substituted chlorine derivatives has served as a useful syntheses.[4b,c] Among pyrazines, this procedure was used by Newbold and Spring[5] and Klein and Spoerri[6] to prepare 2-chloro-3,6-dimethylpyrazine from 2,5-dimethylpyrazine 1-oxide. When the di-N-oxide was used, the 2,5-dichloro-3,6-dimethylpyrazine was obtained. In this report, additional experiments are presented, describing the action of phosphoryl chloride on pyrazine mono- and di-N-oxide and by contrast, on 2-methylpyrazine 1,4-dioxide.

After the work presented here was completed and this manuscript was in preparation, the present authors learned of a paper by Bernardi and associates[7] also describing the action of phosphoroyl chloride on pyrazine 1,4-dioxide, 3-chloropyrazine 1-oxide, and 3-carboxamidopyrazine 1-oxide. Their observations were in essential agreement with portions of the work reported in this paper.

Pyrazine 1-oxide on treatment with phosphoryl chloride gave 2-chloropyrazine, which on further treatment with hydrogen peroxide in acetic acid formed 3-chloropyrazine 1-oxide. This agreed with an earlier observation that N-oxidation of a pyrazine bearing a halogen or an electron-donating substituent in the nucleus will take place on the nitrogen furthest from that substituent.[8] Oxidation of either 2-chloro- or 2-ethoxy-3,6-dimethylpyrazine produced the 4-oxide only. These compounds resisted further oxidation. The present investigators have prepared 2-ethoxypyrazine 1,4-dioxide by direct oxidation of 2-ethoxypyrazine.[9]

When pyrazine 1,4-dioxide was heated with excess phosphoryl chloride, 2,6-dichloropyrazine was obtained. Initially, the course of the reaction was thought to be: pyrazine 1,4-dioxide → pyrazine 1-oxide → 2-chloropyrazine → 2,6-dichloropyrazine:



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Support for this reaction sequence was derived from: (a) phosphorus halides are recognized deoxygenating agents[10]; (b) the formation of 2,6-dichloropyrazine from 2-chloropyrazine and chlorine[11]; (c) treatment of 2-hydroxypyrazine with phosphoryl bromide produced a mixture of 2-bromopyrazine and 2,6-dibromopyrazine.[12,13]

This assumption was quickly shown to be incorrect, since treatment of 2-chloropyrazine with excess phosphoryl chloride failed to produce 2,6-dichloropyrazine. Further, the smaller yield of 2-chloropyrazine from pyrazine 1-oxide obtained under similar conditions (without the formation of the 2,6-dichloro compound) would indicate that they could not arise in sequence from the same precursor. A simultaneous or sequential ionic chlorination of both N-oxide functions would

(1) Portions of this work were reported at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(2) The work reported here was supported in part by a grant (CY-5343) from the National Institutes of Health.

(3) J. Meisenheimer, *Ber.*, **69**, 1848 (1926).

(4) (a) B. Bobranski, L. Kochanska, and A. Kowaleska, *ibid.*, **71B**, 2385 (1938); (b) G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, **9**, 302 (1944); (c) R. W. Goulay, G. W. Moersch, and H. S. Mosher, *J. Am. Chem. Soc.*, **69**, 303 (1947).

(5) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).

(6) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 2951 (1951).

(7) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. chim. ital.*, **91**, 1431 (1961); *Chem. Abstr.*, **57**, 2223e (1962).

(8) R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1859 (1948).

(9) Unpublished observations.

(10) E. Ochiai, *J. Org. Chem.*, **17**, 534 (1953).

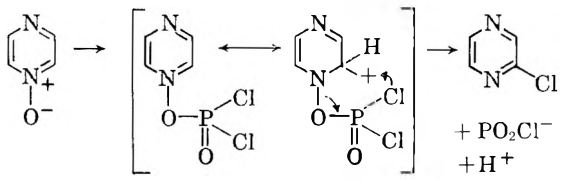
(11) W. E. Taft, U. S. Patent 2,797,219 (June 25, 1957).

(12) A. E. Erickson and P. E. Spoerri, *J. Am. Chem. Soc.*, **68**, 400 (1946).

(13) K. Schaaf and P. E. Spoerri, *ibid.*, **71**, 2043 (1949).

favor formation of 2,5-dichloropyrazine or to a lesser extent the 2,3-isomer. This was demonstrated by treating 3-chloropyrazine 1-oxide, an intermediate in such a sequence, with phosphoroyl chloride. The dichloropyrazine thus obtained closely resembled the physical characteristics of 2,5-dichloropyrazine.[14]

A mechanism of chlorination of heterocyclic N-oxides was suggested by Eisch and Gilman.[15] As applied to pyrazine N-oxides and phosphoryl chloride, this would involve initial formation of the N-O-dichlorophosphite salt, followed by attack by chloride on the electron-deficient α-carbon and removal of the oxygen.



This mechanism would provide a plausible explanation for the formation of 2-chloropyrazine and other simple ring-substituted chloropyrazines. It would appear that the formation of 2,6-dichloropyrazine is more complex.

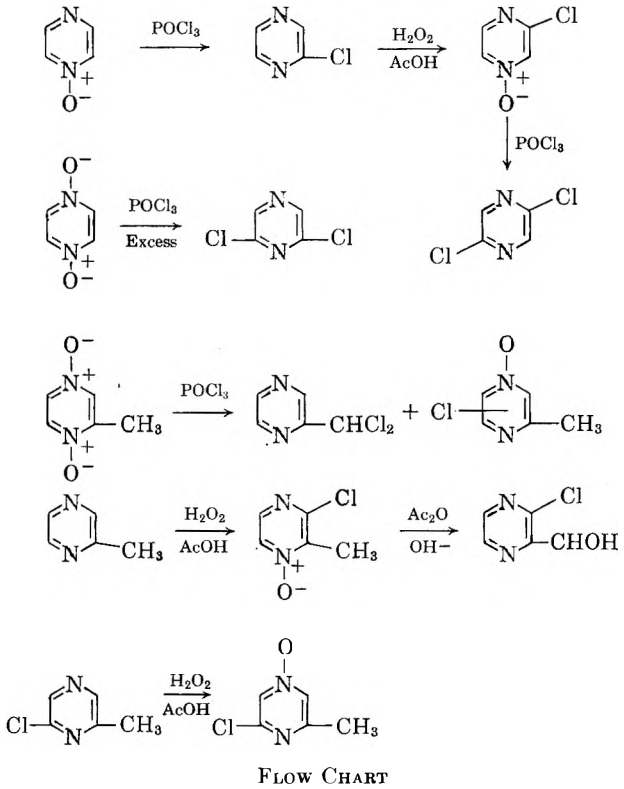
Two other possible reaction pathways, well documented in pyridine chemistry,[16-19] are being considered. Both involve halogenation of an intermediate quaternary pyrazinium salt. This is now under study.

In the reaction of 2-methylpyrazine 1,4-dioxide with phosphoryl chloride,[20a] an even more complex mechanism is suggested. A mixture of halogenated products was obtained containing mostly an intense lachrymator and vesicant and a smaller amount of a chloromethylpyrazine N-oxide. The former compound appeared similar to the dichloromethylpyrazine reported by Behun and Levine[20b] who prepared it by hypohalite oxidation of pyrazyl methyl ketone. Attempts to convert the compound to the dimethyl acetal reported by Behun and Levine[20b] were unsuccessful. In every attempt, a product still containing halogen was obtained, whose elemental analysis and infrared spectrum indicated a mixture of the desired dimethoxy derivative and a chloropyrazyl ether. Difficulty in the preparation of substituted pyrazyl diethers by conventional methods has also been reported by Karmas and Spoerri.[21]

Baxter and associates[22] describes an example of side-chain halogenation of 2-ethoxy-3,6-dimethylpyrazine 1,4-dioxide with phosphoryl chloride in which a mixture of the expected 2-chloro-5-ethoxy-3,6-dimethylpyrazine and 2-ethoxy-6-methyl-3-chloromethylpyrazine were formed.

Of further interest in this regard are the recent observations of Hirschberg and Spoerri[23] and Gainer and associates[24] that gaseous chlorine, at atmospheric pressure and with only moderate warming produced only ring halogenation of methylpyrazine and 2,5-dimethylpyrazine. Yet the same reaction conditions caused side-chain halogenation of 2,6-dimethylpyrazine.

The minor product of the reaction between 2-methylpyrazine di-N-oxide and phosphoryl chloride was isomeric with the 2-chloro-3-methylpyrazine 4-oxide obtained by direct oxidation of 2-chloro-3-methylpyrazine and the N-oxide produced by direct oxidation of 2-chloro-6-methylpyrazine. The position of the N-oxide in 2-chloro-3-methylpyrazine 4-oxide was established by rearrangement with acetic anhydride and hydrolysis to 2-chloro-3-pyrazylmethanol. As demonstrated earlier,[25] this rearrangement among pyrazine N-oxides occurs only when the N-oxide is adjacent to a methyl-bearing carbon. Attempts similarly to rearrange the N-oxide of the compound under examination with



FLOW CHART

acetic anhydride were unsuccessful, indicating that the N-oxide was not adjacent to the C-methyl. Possible structures for this compound include 2-chloro-5-methylpyrazine 1-oxide or even the 2-chloromethyl derivative. Some evidence is available that N-oxida-

(14) A. A. Miller, U. S. Patent 2,573,268 (October 30, 1951).

(15) J. Eisch and H. Gilman, *Chem. Rev.*, **57**, 561 (1957). See also, R. C. Elderfield, "Chemistry of Quinoline," in "Heterocyclic Compounds," R. C. Elderfield, Ed., Vol. 4, John Wiley and Sons, Inc., New York, ref. 11, p. 241.

(16) E. Shaw, "Pyridine N-Oxides," in "Heterocyclic Compounds, Pyridine and Derivatives," Erwin Klingsberg, Ed., Interscience Publishers, New York, N. Y., part II, pp. 34, 124.

(17) F. Ramirez and P. von Ostwalden, *Chem. Ind.* (London), 46 (1957); *J. Am. Chem. Soc.*, **81**, 156 (1959).

(18) B. M. Bain and J. E. Saxton, *J. Chem. Soc.*, 5216 (1961).

(19) E. E. Garcia, C. V. Greco, and I. M. Hunsberger, *J. Am. Chem. Soc.*, **82**, 4430 (1960).

(20)(a) NOTE ADDED IN PROOF.—Since this manuscript was submitted, the n.m.r. spectrum of the product resulting from the phosphoryl chlorination of 2-methylpyrazine 1,4-dioxide was determined. Three resonances were noted, the first, unsplit at 7.4 τ, the second, barely split at 5.1 τ, and a third group at 1.6 τ (all relative to tetramethylsilane), in area ratios 5:1:3. This would indicate that the product is a mixture of a dichloromethylpyrazine and a monochloromethylpyrazine. The authors are grateful to Dr. David I. Schuster, Department of Chemistry, New York University, for this determination. (b) J. D. Behun and R. Levine, *J. Org. Chem.*, **23**, 406 (1958).

(21) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **79**, 680 (1957).

(22) R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1859 (1948).

(23) A. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 2356 (1961).

(24) H. Gainer, M. Kokorudz, and W. K. Langdon, *ibid.*, **26**, 2360 (1961).

(25) B. Klein, J. Berkowitz, and N. E. Hetman, *ibid.*, **26**, 126 (1961).

tion of chloromethylpyrazines stabilizes the compound.[26] The identification of this compound is under further study.

The reactions described in this paper are summarized in the accompanying flow chart.

Experimental[27,28]

2-Chloropyrazine.—In an oven-dried two-neck flask containing a Teflon magnetic stirring bar, fitted with an efficient condenser whose upper end was closed with an oven-dried cotton plug, was placed 15.7 ml. (0.173 mole) of phosphoryl chloride. This was warmed with stirring to about 55° and 8.3 g. (0.086 mole) of pyrazine 1-oxide[29] was added in small portions over a 30-min. period,[30] at a rate to maintain gentle boiling. When the addition was complete, the mixture was heated under reflux for an additional 15 min. A dark solid formed during this time. The dark mixture was chilled and poured cautiously onto 200 g. of chopped ice with good stirring.

The filtered mixture was neutralized with 50% sodium hydroxide and brought to pH 9 with 10% sodium hydroxide. The solution was extracted with seven 125-ml. portions of ether with careful mixing to avoid emulsification. The combined extracts were washed with water and dried over calcium chloride.

The solvent was removed at atmospheric pressure and the residue distilled, collecting 2.44 g. (25%) product, b.p. 60.5° (26 mm.), n^{25}°D 1.5343 [lit.[6] b.p. 62.5° (29 mm.), n^{28}°D 1.5340].

The dark solid was insoluble in most organic solvents and was not further characterized.

3-Chloropyrazine 1-Oxide.—To a solution of 13.8 g. (0.12 mole) of 2-chloropyrazine[31] in 36 ml. of glacial acetic acid 23.3 ml. of 30% hydrogen peroxide was added and the solution was heated for 17 hr. at 65–75°. The solution was concentrated to one-third volume, diluted with an equal quantity of water, and reconcentrated. The residue was extracted with chloroform and the combined organic extracts were cross washed with water and dried over calcium chloride. The solvent was stripped leaving a residue of 6.8 g., m.p. 85–91°.

The aqueous portion was brought to pH 8.5–9 and re-extracted with chloroform. From this extract, on removal of solvent, an additional 0.9 g. was obtained. Total yield: 7.7 g. (49%). Recrystallization from 95% ethanol brought the m.p. to 95–96°.[32]

Anal. Calcd. for $C_4H_3N_2OCl$: C, 36.80; H, 2.31; N, 21.47%. Found: C, 36.94; H, 2.51; N, 20.98.

2,6-Dichloropyrazine.—To 73 ml. (0.8 mole) of phosphoryl chloride about 1 g. of pyrazine 1,4-dioxide[29] was added and the suspension was gradually heated with stirring until the exothermic reaction, which occurs at about 80°, subsided. The remainder of a total of 22.4 g. (0.2 mole) was added gradually in small portions. After the addition was complete (50 min.), a probe sample showed an absorption at 218 and 296 mμ with a shoulder at 275 mμ. Heating under reflux was continued for an additional 45 min.[33]

The dark mixture was cooled and poured cautiously on chopped ice with good stirring. After the decomposition was complete, the precipitated solid was collected and washed with ice–water. This weighed 11.0 g., m.p. 49–52°.

From the filtrate, on extraction with chloroform, another 1.0 g. of product, m.p. 50–54°, was obtained. Total yield: 12.0 g. (40.4%). A portion was sublimed for analysis, m.p. 51–53°. Mixture melting point with authentic material[34] produced no depression. Comparison of ultraviolet and infrared absorption spectra also established their identity.

Anal. Calcd. for $C_4H_2N_2Cl_2$: C, 32.24; H, 1.36; N, 18.81. Found: C, 32.49; H, 1.40; N, 18.33.

2,5-Dichloropyrazine.—To 12.4 ml. (0.13 mole) of warm phosphoryl chloride (60°) 6.0 g. (0.046 mole) of 3-chloropyrazine 1-oxide was added in small amounts with good stirring, keeping the reaction under good control until all was added. The solution darkened while being heated under reflux for an hour. The solution was chilled and poured cautiously onto 150 g. of chopped ice with good stirring. The product was isolated by extraction into a total of 150 ml. of chloroform. The extract was washed with water, 25 ml. of 5% sodium bicarbonate, again with water, and dried over calcium chloride.

After removal of the solvent at atmospheric pressure the residue was distilled collecting 4.4 g. (64.2%) of product, b.p. 90–91° (44 mm.), n^{27}°D 1.5592, which solidified completely on storage in a freezer (lit.[14] m.p. 0°).[35]

Anal. Calcd. for $C_4H_2N_2Cl_2$: C, 32.24; H, 1.36; N, 18.81. Found: C, 32.60; H, 1.46; N, 18.90.

2-Methylpyrazine 1,4-Dioxide.—The preparation of this compound has been simplified and improved.

One mole (94.0 g.) of 2-methylpyrazine in 570 ml. of glacial acetic acid was treated with 400 ml. of 35% hydrogen peroxide and the solution was heated 16 hr. on a steam bath under a reflux condenser.

Two-thirds of the liquid was removed under reduced pressure, the volume was restored with water, and the solution was reconcentrated. This was repeated twice more to remove most of the acetic acid and the solution was finally taken to dryness under reduced pressure (water aspirator and rotary flash evaporator). The crude product was recrystallized from 90% methanol. Yield: 99.0 g. (76.3%), m.p. 230–231°.[36]

Dichloromethylpyrazine.—To 91 ml. (1.0 mole) of warm (70°) phosphoryl chloride, 31.5 g. (0.25 mole) of 2-methylpyrazine 1,4-dioxide was added in small portions over 50 min. An exothermic reaction ensued following each addition and heat was applied only when required to maintain reflux. After the addition was complete, the dark solution was heated under reflux for an additional 30 min. A probe sample showed an absorption at 221 and 298 mμ, with a shoulder at 278 mμ.

The dark mixture was chilled and poured carefully over 300 g. of chopped ice. After all the excess reagent was decomposed, the oily layer was taken up in ether and the aqueous layer was extracted with more ether, the combined extracts were dried over anhydrous magnesium sulfate, and the solvent was stripped at atmospheric pressure. The residue was intensely lachrymatory and contained a small amount of colorless crystals.

The residue was re-dissolved in ether and extracted with 50 ml. of 20% sodium hydroxide. The ether layer was washed with water and dried ($MgSO_4$). Removal of the solvent left a residue which was distilled collecting a total of 17.9 g. (44%) of product in four fractions, b.p. 109–115° (27–31 mm.), n^{23}°D 1.5542–1.5554; and another liquid fraction, 0.4 g., b.p. 121–123° (28 mm.), n^{23}°D 1.5603–1.5610, in which a colorless solid deposited, m.p. 120–134°.

For analysis the first liquid was redistilled collecting the fraction, b.p. 105–108° (18 mm.), n^{26}°D 1.5495.

On standing this liquid underwent a series of color changes, first to pale blue, then green, and finally darkened to a dull brown with specks of polymeric material that adhered to the walls of the container.

Behun and Levine[20] give the b.p. of their compound as 87–90° (10 mm.)

Anal. Calcd. for $C_5H_4N_2Cl_2$: C, 36.84; H, 2.47; N, 17.19. Found: C, 37.03; H, 2.73; N, 17.34.

(26) B. Klein and N. E. Hetman, unpublished observations.

(27) Melting points were taken on a heated metal block and are uncorrected.

(28) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(29) B. Klein and J. Berkowitz, *J. Am. Chem. Soc.*, **81**, 5160 (1959).

(30) Pyrazine mono- and di-N-oxides react with almost explosive violence, when mixed with phosphoryl chloride and heated above 60°.

(31) The authors are grateful to Mr. Fred Dorf, American Cyanamid Co., Calco Division, Bound Brook, N. J., for a generous supply of 2-chloropyrazine and 2,6-dichloropyrazine.

(32) The melting points of this compound was reported, without experimental details, as 96° by H. Shindo, *Chem. Pharm. Bull.* (Japan), **8**, 33 (1960). Bernardi, *et al.*,[7] give the m.p. as 97–98°.

(33) Among many attempts to moderate the vigor of the reaction, one experiment was conducted in the presence of dimethylaniline. A purple colored solid soon formed. This is doubtless similar to the observation by N. A. Coats and A. R. Katritzky, *J. Org. Chem.*, **24**, 1836 (1959).

(34) The authors acknowledge with thanks the gift of an authentic specimen of 2,6-dichloropyrazine by Dr. W. E. Taft, Lederle Laboratories, Pearl River, N. Y.

(35) Bernardi and associates[7] reported that both 2,3-dichloro- and 2,6-dichloropyrazine in about equal amounts were obtained following a reaction similar to the one described. It is difficult to account for the appearance of the 2,6-dichloro isomer under these circumstances. The present authors looked diligently for the 2,3-isomer, by slowly cooling the product to complete solidification and slowly allowing the temperature to rise. All the product reliquefied between 0–4°. The melting point of the 2,3-dichloropyrazine is given as 23–24°.[14]

(36) This is in closer agreement with the melting point reported by Koelsch and Gumprecht than by the present authors.[8j] C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.*, **23**, 1603 (1958).

The solid obtained in the last fraction was shown to be the hydrochloride of a chloromethylpyrazine N-oxide, since it gave an immediate precipitate with aqueous silver nitrate. A solution of the material in methanol was passed through a small column containing 4.0 g. Amberlite IRA-400 (OH^-) and eluted with methanol to give needles which on recrystallization from 95% ethanol melted 114–115°.

Anal. Calcd. for $C_5H_5N_2OCl$: C, 41.53; H, 3.49; N, 19.38. Found: C, 41.46; H, 3.81; N, 19.48.

2-Chloro-3-methylpyrazine 4-Oxide.—2-Chloro-3-methylpyrazine, b.p. 74–75° (23.5 mm.), $n^{25}D$ 1.5290–1.5299, was prepared in 81% yield from 2-hydroxy-3-methylpyrazine by the method of Karmas and Spoerri.[37]

To a solution of 12.9 g. (0.1 mole) of 2-chloro-3-methylpyrazine in 30 ml. of glacial acetic acid, 9.7 ml. of 35% hydrogen peroxide was added and the solution was heated on a water bath at 70° for 3.5 hr. A similar quantity of hydrogen peroxide was added and the heating was continued for another 3.5 hr., diluted with 30 ml. of water, and refrigerated overnight.

The solution was concentrated under reduced pressure in a rotary flash evaporator to about one-quarter the original volume, diluted with water, and reconcentrated. This was repeated twice more to remove most of the acetic acid. The residue was brought to pH 8.5 with 20% sodium hydroxide and the product extracted with chloroform. The extract was washed with water, dried over calcium chloride, and concentrated at atmospheric pressure. The residue weighed 6.2 g. (43%) and melted 69–71.5°.[38]

For analysis a portion was sublimed *in vacuo* (120°, 14 mm.) and melted 71–72.5°.

Anal. Calcd. for $C_5H_5N_2OCl$: C, 41.53; H, 3.49; N, 19.38. Found: C, 41.42; H, 3.43; N, 19.45.

2-Chloro-6-methylpyrazine 4-Oxide.—2-Chloro-6-methylpyrazine, m.p. 47–49°, was prepared in 63% yield from 2-hydroxy-6-methylpyrazine (Karmas and Spoerri[36]).

One gram (0.008 mole) in 2.4 ml. of glacial acetic acid was treated with a total of 1.6 ml. of 35% hydrogen peroxide in two portions, the second added midway in the 8-hr. heating period (65–70°). The solution was worked up as described previously to give 0.3 g. (26%) of yellowish needles, m.p. 97–110°. This was recrystallized from absolute ethanol, m.p. 108–110°.

For analysis a sample was sublimed *in vacuo*, m.p. 109–110°.

Anal. Calcd. for $C_5H_5N_2OCl$: C, 41.53; H, 3.49; N, 19.38. Found: C, 41.38; H, 3.39; N, 19.48.

2-Chloro-3-pyrazylmethanol.—To a solution of 3.8 g. (0.026 mole) of 2-chloro-3-methylpyrazine 4-oxide in 7.4 ml. of glacial acetic acid, 5.3 g. (0.052 mole) of acetic anhydride was added and the solution heated under reflux for 45 min. A probe sample at this time showed a single peak at 273 mμ, indicating that the N-oxide peak had disappeared.[29] The solution was poured into ice water, neutralized with 50% sodium hydroxide, and brought to pH 9 with 10% sodium hydroxide.

The product was extracted with ether, the extract was washed with water and dried ($MgSO_4$) and the solvent removed at atmospheric pressure. The residue which was a strong lachrymator was distilled collecting 1.4 g. (37.3%) product, b.p. 120–123° (10 mm.), $n^{31}D$ 1.5600.

Anal. Calcd. for $C_5H_5N_2OCl$[39]: C, 41.53; H, 3.49; N, 19.38. Found: C, 41.16; H, 3.53; N, 19.32.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

Compound	Solvent	mμ, max.	log ε
Pyrazine			
2-Chloro-[a]	Ethanol	268	3.80
		274	3.80
	pH 1	273	
2-Chloro-3-methyl-	Methanol	275.5	4.13
		295 (sh)	
2-Chloro-6-methyl-	Methanol	276	3.70
		295 (sh)	
2-Hydroxy-3-methyl-[b]	Water	222	3.92
		311	3.83
2-Hydroxy-6-methyl-	Water	233	3.62
		324	3.97
2,5-Dichloro-[c]	Methanol	215	4.03
		278	3.84
2,6-Dichloro-[c]	Methanol	214.5	4.03
		278	3.84
2-Dichloromethyl-	Methanol	215	3.95
		278	3.81
		292 (sh)	
3-Chloro-, 1-oxide	Water	223	4.14
		268	4.15
2-Chloro-3-methyl-, 4-oxide	Water	219	4.14
		266	4.01
		305 (sh)	3.60
(x)Chloro-2-methyl-, N-oxide	Water	218	4.24
		259	3.91
		290 (sh)	
2-Chloro-6-methyl 4-oxide	Water	222.5	4.03
		268	4.02
		300	3.53
		309	3.46
2-Chloro-3-pyrazyl-methanol	Methanol	274	3.98
2-Chloro 3,5-dimethyl-	Methanol	279	4.24

[a] F. Halverson and R. C. Hirt [*J. Chem. Phys.*, 19, 711 (1951)] give $\lambda_{max}^{cyclohexane}$ 270 mμ (log ε 3.8); 303 mμ (sh). [b] J. Dutcher [*J. Biol. Chem.*, 171, 321 (1947)] gives λ_{max}^{EtOH} 225 mμ (log ε 3.8), 320 mμ (log ε 3.7). [c] Halverson and Hirt (see *a*) give $\lambda_{max}^{cyclohexane}$ 2,5-dichloropyrazine: 217 mμ (log ε 3.8), 273 mμ (log ε 3.6), 303 mμ (sh); 2,6-dichloropyrazine: 217 mμ (log ε 3.9), 273 mμ (log ε 3.9), 303 mμ (sh).

2-Chloro-3,5-dimethylpyrazine. To 31.5 ml. (0.35 mole) of warm phosphoroyl chloride (60–70°), 10.9 g. (0.087 mole) of 3,5-dimethylpyrazine 1-oxide was added portionwise over 40 min. and, after the addition was complete, heated under reflux for an additional 20 min. A probe sample at this time indicated a single absorption peak at 295 mμ.

Excess reagent was removed by distillation under reduced pressure and the dark residue was poured onto chopped ice with good stirring. The solution was brought to pH 8 with 20% sodium hydroxide and the product extracted with ether. The combined extracts were washed with water and dried ($MgSO_4$). The residue, after removal of solvent, was distilled collecting a

(37) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1583 (1952). The authors are grateful to Dr. George Karmas, Ortho Research Foundation, Raritan, N. J., for a generous quantity of 2-hydroxy-3-methylpyrazine and 2-hydroxy-6-methylpyrazine.

(38) Attempts to prepare this compound using redistilled commercial 2-chloro-3-methylpyrazine, b.p. 81–84° (42 mm.), $n^{25}D$ 1.5278, obtained from Wyandotte Chemicals Corp., Wyandotte, Mich., resulted in a mixed product, containing mostly the compound just described and a second monochloromethylpyrazine N-oxide, m.p. 51–52°, colorless needles from petroleum ether (b.p. 30–60°) after repeated chromatography on neutral alumina with much loss.

Anal. Calcd. for $C_5H_5N_2OCl$: C, 41.53; H, 3.49; N, 19.38. Found: C, 41.78; H, 3.30; N, 19.30.

$\lambda_{max}^{H_2O}$ 223 mμ (log ε 4.23), 266 mμ (log ε 4.12), 299 mμ (log ε 3.71), 308 mμ (sh) (3.63). This may be the N-oxide of 2-chloro-5-methylpyrazine which was reported formed as a by-product of the action of chlorine on 2-methylpyrazine (see Hirschberg and Spoerri[24]) or an isomer of 2-chloro-6-methylpyrazine 4-oxide (private communication from Wyandotte Chemicals Corp.). However, see preceding.

(39) It had been assumed that the reaction product was the expected 2-chloro-3-pyrazylmethanol acetate. After the results of the elemental analysis were received, indicating a compound of lower carbon content, an examination of the infrared absorption spectrum indicated the presence of hydroxyl (2.9 μ) and also the absence of any absorption in the carbonyl region.

Examples of similar ease of hydrolysis of pyrazylmethanol acetates have been reported (ref. 26). This has been shown to be a common occurrence among N-heterocyclic methanolacetates (B. Klein and N. E. Hetman, unpublished observations). See Abstracts of New York–New Jersey Section Regional Meeting, New York, N. Y., January, 1962.

total of 9.7 g. (78.3%) in three fractions, b.p. 87–91° (22 mm.), n^{27}°D 1.5241–1.5259. This product was a colorless oil, with small amounts of suspended colorless solid. On refrigeration the entire product crystallized in large needles, which reliquefied on warming to room temperature. This was redistilled collecting a total of 7.3 g., b.p. 92–94° (42 mm.), n^{27}°D 1.5246–1.5248. Karmas and Spoerri[37] give the boiling point of this compound as 111–112° (70 mm.), n^{24}°D 1.5230.[40]

Absorption Spectra.—The ultraviolet absorption spectra were taken either on a Beckman DU spectrophotometer or a Bausch and Lomb Model 505 recording spectrophotometer. These are given in Table I. Infrared absorption spectra were taken on a Perkin-Elmer Model 21 recording specctrophotometer calibrated with a polystyrene film.

(40) After this manuscript was completed, the present authors were informed by Dr. Robert I. Meltzer, Warner Lambert Research Institute, Morris Plains. N. J., that the second product resulting from the direct chlorination of 2-methylpyrazine (ref. 23 and 24) had been identified as 2-chloro-6-methylpyrazine. On the basis of this and other work contained in a paper submitted for publication by Dr. Meltzer and his associates, it is now believed that the 51–52° monochloromethylpyrazine N-oxide (ref. 38) is probably 2-chloro-3-methylpyrazine 1-oxide. The present authors are grateful to Drs. Meltzer and Wilson B. Lutz and their co-workers for the opportunity to read their paper prior to publication.

Carbonium Ion Intermediates in the Deamination of 3-Methyl-2-butylamine and Isopentylamine[1]

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The products from the solvolysis of 3-methyl-2-butyl tosylate and the deamination of 3-methyl-2-butylamine and isopentylamine in aqueous acetic acid have been determined. Comparison of the tosylate solvolysis with the deamination of 3-methyl-2-butylamine leads to the conclusion that an open 3-methyl-2-butyl carbonium ion is an important intermediate in the latter reaction. The *t*-pentyl carbonium ion from deamination of 3-methyl-2-butylamine and the *t*-pentyl and 3-methyl-2-butyl carbonium ions from deamination of isopentylamine do not behave as normal solvolytic carbonium ions. Formation of 1,2-dimethylcyclopropane in the deamination reactions is considered in relation to the general question of cyclopropane formation, 1,3-hydride shifts, and 1,2-alkyl migrations in simple carbonium ion systems.

Our general interest in exploring the relationship between the mode of formation and the behavior of carbonium ions has led to an investigation of carbonium ions generated in halide solvolyses and amine deaminations. Figure 1 diagrams the system chosen for our initial research; an earlier report has considered[2] reactions of *t*-pentyl and neopentyl starting materials in terms of the intermediates in the upper part of Fig. 1. The present paper analyzes carbonium ion reactions of 3-methyl-2-butyl and isopentyl compounds using an approach whose merits and limitations were evaluated previously[2] (*cf.* Fig. 1).

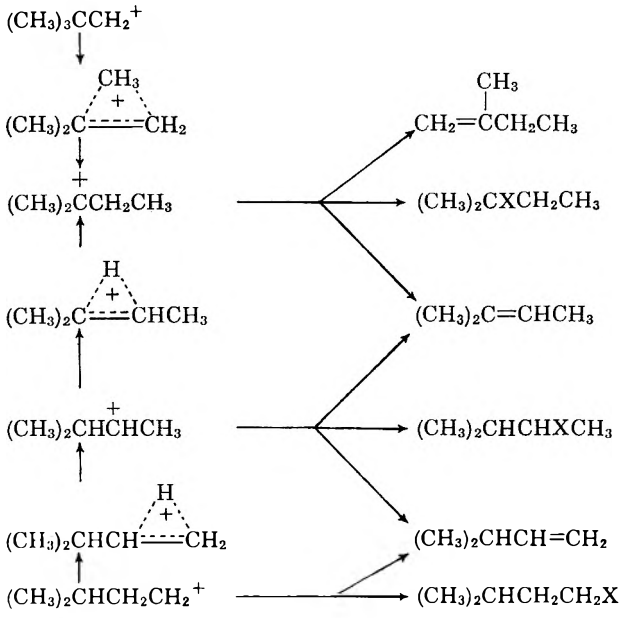


Figure 1

(1) 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.

(2) M. S. Silver, *J. Am. Chem. Soc.*, **83**, 3482 (1961).

Results

Table I records the observed composition of the products from the deamination of 3-methyl-2-butylamine and isopentylamine, as determined by gas–liquid partition chromatography (g.l.p.c.) and infrared analysis. Reproducibility in duplicate runs is seen to be good. Control runs established the stability of the acetates and *t*-pentyl alcohol, the instability of 3-methyl-2-butanol and isopentyl alcohol and the selective destruction of 2-methyl-2-butene under the deamination conditions. The Experimental discusses determination of corrections for product instability and Table II summarizes product compositions after such corrections. Comparison of lines 7 and 11 to lines 13 and 14 (Table I) and of Table I to Table II demonstrates that corrections for the instability of the two alcohols alter the composition of the substitution product detectably but not significantly. The same comparisons reveal that corrections for olefin fractionation are more important. Since the fact that relatively little 2-methyl-2-butene is formed in the deaminations will play a prominent part in our discussion, we have applied maximum corrections for 2-methyl-2-butene destruction. The observation that the uncorrected olefin compositions for runs 9 and 12 agree with the corrected values for runs 7 and 11 (Table I), respectively, confirms the validity of these corrections. The first two reactions produced large quantities of olefin, and in such instances olefin fractionation becomes insignificant. The degree of olefin fractionation also diminishes as the water content of the solvent increases, as may be seen by comparing the data in Tables I and II for different solvent compositions.

Discussion

The 3-Methyl-2-butyl System.—Winstein and Takahashi[3] established neighboring group rate enhancement

(3) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).

TABLE I

COMPOSITION OF THE PRODUCT MIXTURE ISOLATED FROM THE DEAMINATION OF 3-METHYL-2-BUTYLAMINE AND ISOPENTYLAMINE IN AQUEOUS ACETIC ACID[a-c] AT 55°

Run	Compd.	HOAc, %	Amine, g.	$NaNO_2$, g.	RX, g. (%)[d]	Olefin, g. (%)[d]	t-X,[e] %	s-X,[e] %	p-X,[e] %	2-Me-1-butene,[f] %	2-Me-2-butene,[f] %	3-Me-1-butene,[f] %	1,2-Me$_2$-cyclopropane,[f,g] %
1	p-NH_2	25	20	30	11 (51)	2.3 (14)	41	20	39	4	11	85	—
2		25	20	30	14 (61)	—	42	19	39	—	—	—	—
3		50	20	30	14 (59)	2.9 (18)	33	20	47	8	16	77	—
4		75	20	30	15 (59)	—	22	19	59	—	—	—	—
5		100	25	30	19 (58)	3.7 (19)	19	16	65	15	17	68	—
6		100	25	29	21 (66)	—	19	15	66	—	—	—	—
7		100	27	50	21 (54)	3.6 (17)	20	16	64	15	19	64	1.5
8		100	20	30	—	—	—	—	—	18	17	66	—
9		100[h]	66	100	—	12	—	—	—	17	22	60	1.9
10	s-NH_2	50	20	30	12 (52)	4 (25)	39	61		19	34	34	13
11		100	20	30	8 (38)	3.7 (28)	27	73		20	24	38	18
12		100[h]	24	45	10 (33)	8 (41)	27	73		18	32	35	15
13	p-NH_2	100[i]					18	20	63	14	25	59	1.5
14	s-NH_2	100[j]					24	76		18	33	31	18

[a] Abbreviations are as follows: p = isopentyl; s = 3-methyl-2-butyl; t = t-pentyl; R = $p + s + t$; X = alcohol + acetate. [b] Mole % used throughout. [c] A dash (—) indicates quantity not measured. [d] % Yield based on unrecovered amine. [e] Total RX = 100%. [f] Total C_5H_{10} fraction = 100%. [g] *Trans–cis* was about 2:1; no attempt was made to determine relative stability of these compounds under reaction conditions. [h] No correction was applied to olefin from this run because of the high yield of olefin. [i] Corrected composition of run 7. [j] Corrected composition of run 11.

TABLE II

PRODUCTS FROM THE SOLVOLYSIS OF SOME RELATED C_5 COMPOUNDS AT 55° IN AQUEOUS ACETIC ACID[a,b]

Compd.	HOAc, %	t-X, %	s-X, %	p-X, %	2-Me-1-butene	2-Me-2-butene	3-Me-1-butene	1,2-Me$_2$-cyclopropane
p-NH_2	25	35	24	41	4	11	85	
	50	28	24	48	7	18	76	
	75	19	23	58	—	—	—	
	100	17	20	64	15	23	60	2
s-NH_2	50	36	64		19	38	31	13
	100	24	76		18	33	33	17
s-OTs	94	96	4		13	86	1	
	100	92	8		13	86	1	
	100[c]	90	10		21	77	2	
t-NH_2[d]	0				61	39		
	50				58	42		
	75				64	36		
	100				63	37		
t-Cl[d]	50[e]				20	80		
	75				21	79		
t-Br[d]	94				23	77		
	100				26	74		

[a] The footnotes of Table I pertain where applicable. [b] This work unless otherwise noted. [c] Ref. 3, 75°. [d] Ref. 2. [e] 78°.

by the tertiary hydrogen in the acetolysis of 3-methyl-2-butyl tosylate. This hydrogen participation reinforces the natural tendency[4] of a tosylate or halide to undergo E 1 elimination in the Saytzeff sense, and nearly all the acetolysis product from 3-methyl-2-butyl tosylate is derived from loss or rearrangement of the tertiary hydrogen (Table II).[3] Only a trace of 3-methyl-1-butene and a few per cent of 3-methyl-2-butyl acetate are formed. The immediate precursors of the products cannot be assigned, but the difference between the products from acetolysis of t-pentyl halides and 3-methyl-2-butyl tosylate establishes that the t-pentyl carbonium ion is not the sole precursor in reactions of the latter.[3]

The neighboring tertiary hydrogen plays a considerably smaller role in the acetic acid deamination of 3-methyl-2-butylamine than in the acetolysis of 3-methyl-2-butyl tosylate. The amine yields about 75% unrearranged substitution product, where the tosylate gives less than 10% (Table II). A direct displacement mechanism does not explain the large amount of 3-methyl-2-butyl substitution product in the deamination, since 2-butylamine gives only 28% inversion in acetic acid and 22% inversion in water.[5] Involvement of the tertiary hydrogen in the tosylate reaction also magnifies the usual[2] difference in olefin composition from halide solvolyses and deaminations, and 3-methyl-2-butylamine affords far more 3-methyl-1-butene than does the tosylate. Postulation of an open 3-methyl-2-butyl carbonium ion as an intermediate in the deamination provides the most economical rationalization for the above results (we ignore methyl-bridged intermediates for now). The open carbonium ion presumably undergoes rearrangement and directly forms 3-methyl-1-butene, 2-methyl-2-butene, and 3-methyl-2-butyl product (Fig. 1).

An estimate of the lower limit to the amount of 2-methyl-2-butene arising from this open 3-methyl-2-butyl carbonium ion is useful for subsequent discussion. The estimate can be made by comparing the deamination of 3-methyl-2-butylamine and 2-butylamine,[6,7] and by employing the following facts: (1) statistically, internal elimination[8] is favored in the 2-butyl system by a factor of two; (2) thermodynamically, internal elimination is favored in the 3-methyl-2-butyl system, where a trisubstituted ethylene is formed; (3) the effect of relative conformational considerations[5] for the two amines on the amounts of internal and external elimination is difficult to predict; (4) 2-butylamine in water gives[6,7] about 3 for the ratio 2-butene/1-butene. On the basis of these considerations, a prediction that the open 3-

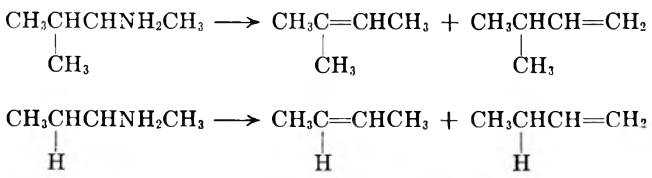
(4) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

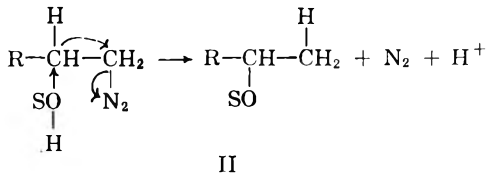
(5) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957), and citations therein.

(6) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957).

(7) W. B. Smith and W. H. Watson, Jr., *ibid.*, **84**, 3174 (1962).

(8) Internal elimination equals formation of the more highly substituted olefin; external elimination, the opposite.





II

methyl-2-butyl carbonium ion from deamination of 3-methyl-2-butylamine yields approximately equal amounts of 2-methyl-2-butene and 3-methyl-1-butene appears reasonable. Because the reaction produces the two olefins in nearly a 1:1 ratio (Table II) *most* of the 2-methyl-2-butene certainly must come from the open 3-methyl-2-butyl carbonium ion.

The *t*-pentyl carbonium ion generated in the deamination of 3-methyl-2-butylamine, therefore, gives rise to very little 2-methyl-2-butene, but considerable quantities of 2-methyl-1-butene and *t*-pentyl substitution product (Table II). Since the *t*-pentyl carbonium ion from *t*-pentylamine shows the same behavior (Table II), we conclude that *t*-pentyl carbonium ions from the two deaminations are similar. The observation that the ratio of *t*-pentyl substitution product to 2-methyl-1-butene is about 2.0 for the acetic acid deamination of 3-methyl-2-butylamine (Table I) and *t*-pentylamine,[2] but 5.9 for the solvolysis of 3-methyl-2-butyl tosylate (Table II) and 3.2 for the solvolysis of *t*-pentyl bromide[2] in 94% acetic acid[9] supports this conclusion.

The possible role of a hydrogen-bridged intermediate in the deamination of 3-methyl-2-butylamine is unclear.[10] Such a species should favor formation of *t*-pentyl substitution product and 2-methyl-2-butene. Since the intermediates already invoked adequately account for the former and more than account for the latter, no benefit derives from introducing further complications.

Isopentylamine.—Acetic acid deaminations of isopentylamine (Table II), 3-phenyl-1-butylamine,[11] and 1-butylamine[6] yield 60, 62, and 65% nonrearranged substitution product, respectively. The degree of rearrangement is remarkably constant for these deaminations where an initial primary carbonium ion, or precursor thereof, can rearrange to a secondary carbonium ion by hydride shift.[12] The products of this rearrangement are relevant to our argument.

Since isopentylamine furnishes about equal amounts of secondary and tertiary substitution products (Table II), relatively more secondary product is formed than in the acetolysis of 3-methyl-2-butyl tosylate but less than in the deamination of 3-methyl-2-butylamine. One possible explanation is that a hydrogen-bridged intermediate, which produces considerable amounts of secondary substitution product and 3-methyl-1-butene, intervenes between the primary and secondary carbonium ions (Fig. 1). Any carbonium ions formed thereafter are then "normal." Concerted displacement–rearrangement reactions, akin to SN2′ reactions, can also be visualized as leading to 3-methyl-2-butyl product (II).

Although arguments such as these, with suitable modifications, will explain all data, we prefer simply postulating open carbonium ions as the prime intermediates. The ratio of secondary to tertiary product suggests that the 3-methyl-2-butyl carbonium ion from isopentylamine is identical to the 3-methyl-2-butyl carbonium ion from neither 3-methyl-2-butyl tosylate nor 3-methyl-2-butylamine, but partakes of some of the properties of each.[13] Such a hybrid 3-methyl-2-butyl species can also rationalize the trace of 1,2-dimethylcyclopropane from the deamination of isopentylamine.

Examination of olefin compositions (Table II) further illuminates the nature of the intermediates in the deamination of isopentylamine. A solvolytic *t*-pentyl carbonium ion produces about three times as much 2-methyl-2-butene as 2-methyl-1-butene (Table II). If a solvolytic *t*-pentyl carbonium ion were formed in the acetic acid deamination of isopentylamine, about 45% 2-methyl-2-butene should be produced from this intermediate (Table II), together with 2-methyl-2-butene from the 3-methyl-2-butyl carbonium ion. Because the 23% 2-methyl-2-butene actually found is not enough to satisfy these conditions, the *t*-pentyl carbonium ion from isopentylamine cannot be a normal solvolytic one.[15] This nonsolvolytic *t*-pentyl carbonium ion can be formulated as arising from isopentylamine by successive 1,2-shifts[16] or a single 1,3-shift.[17–19] The absence[11] of 2-phenyl-2-butanol from the deamination of 3-phenyl-1-butylamine implies that the 1,3-shift is unlikely, although it transforms a primary carbonium ion into a tertiary one.

In conclusion, deamination of 1-butyl-,[7] neopentyl-,[2] 3-methyl-2-butyl-, or isopentylamine gives rearranged carbonium ions which differ in behavior from the corresponding solvolytic species. As the water content of the solvent increases in reaction of the last two compounds (Table II), the per cent of rearrangement (at least in substitution product), the ratio of *t*-pentyl to 3-methyl-2-butyl product, and the ratio of 2-methyl-2-butene to 2-methyl-1-butene all increase. Although the first trend presumably arises in part from the diminishing importance of ion-pair reactions,[20] together the three trends may reflect the increasing importance of

(9) Because of the corrections made in determining the products of the deaminations, we hesitate to put too much reliance on ratios of substitution to elimination.

(10) For an extended discussion of ethylene protonium ions see D. J. Cram and J. Tadanier, *J. Am. Chem. Soc.*, **81**, 2737 (1959).

(11) A. W. Fort and R. E. Leary, *ibid.*, **82**, 2494 (1960).

(12) L. G. Cannell and R. W. Taft, Jr., *ibid.*, **78**, 5812 (1956), report that *i*-butylamine in water gives only about 10% nonrearranged substitution product. The greater amount of rearrangement must at least in part stem from the fact that here a tertiary carbonium ion arises from hydride shift.

(13) A referee has objected to terming this a "warm" 3-methyl-2-butyl carbonium ion.[14]

(14) J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4094 (1959), considered but discarded "warm" carbonium ions as intermediates in the deamination of *endo*-norbornylamine.

(15) The fact that the ratio of *t*-pentyl substitution product to 2-methyl-1-butene is about 3.1:3.2 in acetic acid somewhat mars the appeal of this argument (see first section of Discussion).

(16) By two migrations concerted with loss of nitrogen from the alkyldiazonium ion [W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **78**, 6127 (1956)], rearrangement from bridged ion to bridged ion,[11] etc.

(17) O. A. Reutov and T. N. Shatkina, *Tetrahedron*, **18**, 237 (1962).

(18) G. J. Karabatsos and C. E. Orzech, Jr., *J. Am. Chem. Soc.*, **84**, 2838 (1962).

(19) P. S. Skell and R. J. Maxwell, *ibid.*, **84**, 3963 (1962).

(20) Two recent reviews of the amine–nitrous acid reaction are (a) J. H. Ridd, *Quart. Rev.*, **15**, 418 (1961) and (b) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961.

solvolytic carbonium ions in more highly aqueous solvents.

Cyclopropane Formation.[21]—Investigations of cyclopropane formation,[22] 1,3-hydrogen shifts and 1,2-methyl migrations in carbonium ion reactions have undergone a recent renaissance. In the deamination of *n*-propylamine, cyclopropane is formed, 1,3-hydrogen migration occurs and methyl migration is absent.[17,18,23] In the deoxidation of 2-methyl-1-butanol, all three processes take place.[19] A brief study of the deamination of 2-methyl-1-butylamine, which is related to our system of amines, gave results in general agreement with those for the corresponding deoxidation.

Deamination of 3-methyl-2-butylamine affords 15% 1,2-dimethylcyclopropane and less than 1% 2-methyl-1-butyl substitution product, the result of 1,3-hydrogen shift. The hydrogen shift should be insignificant, as it converts a secondary to a primary carbonium ion.[24] 1,2-Methyl migration is undetected, but not unexpected, since the acetolysis of 3-methyl-2-butyl tosylate gives[25] 1–2% methyl migration. Deamination of isopentylamine yields 2% 1,2-dimethylcyclopropane, and no detectable 1,1-dimethylcyclopropane. 1,3-Hydrogen and 1,2-isopropyl shifts have not yet been studied. Table III summarizes the experimental data.

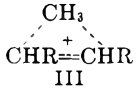
TABLE III

TABULATION OF CYCLOPROPANE FORMATION, 1,3-HYDRIDE SHIFTS AND 1,2-ALKYL MIGRATIONS IN SOME SIMPLE "HOT" CARBONIUM ION REACTIONS[a]

System	Cyclopropanes,[b] %	Shift, % 1,3-H	Shift, % 1,2-R
n-Propyl	10	8–12	0
2-Methyl-1-butyl	4	>1	Much
3-Methyl-2-butyl	15	<1	Probable
Isopentyl	0[c]	?	?
Neopentyl	0	0	100

[a] For references, see text. [b] % of hydrocarbon fraction. [c] No 1,1-dimethylcyclopropane.

Skell[19,22] combines cyclopropane formation and 1,3-hydride shift in, and excludes 1,2-alkyl shifts from, the category of "1,3-interactions." An interplay between 1,2-alkyl shifts and "1,3-interactions" is hinted at in the realization that the greatest cyclopropane formation (Table III) occurs where intermediate III is symmetrical and is expected to have the highest stability relative to its nonbridged isomers.[26] For this and other reasons, we believe that it may be more useful to examine the reasons for the presence or absence of *all three* effects in



R = H, Me

III

any particular reaction. For example, an explanation of why there is no 1,3-hydride shift or cyclopropane formation by the "hot" neopentyl carbonium ion[2,27] should be part of any satisfactory theory. We are unable to offer such a theory at the present.

Comparison to a Similar System.—The 3-methyl-2-butyl, isopentyl series is analogous to the 3-phenyl-2-butyl,[28] 3-phenyl-1-butyl[11] series in many ways. Acetolysis of 3-phenyl-2-butyl tosylate gives almost exclusive phenyl and hydrogen participation, whereas deamination of 3-phenyl-2-butylamine involves phenyl, hydrogen, and methyl participation plus open carbonium ions.[28] These results closely parallel the observation that acetolysis of 3-methyl-2-butyl tosylate proceeds with almost exclusive hydrogen participation,[3,25] while deamination of 3-methyl-2-butylamine gives much more methyl participation (as witnessed by cyclopropane formation) and open carbonium ion reaction. Comparison of Fort and Leary's data[11] for 3-phenyl-1-butylamine with our results with isopentylamine is not so satisfying. Fort and Leary report[11] no 2-phenyl-2-butene, 2-phenyl-2-butanol, or phenylisopropylcarbinol from the deamination of 3-phenyl-1-butylamine. They analyze their data in terms of a 3-phenyl-2-butyl carbonium ion which, surprisingly, shows an even smaller variety of reactions than does the normal solvolytic 3-phenyl-2-butyl carbonium ion. These observations are at variance with those on the isopentyl, 3-methyl-2-butyl, neopentyl[2] and 1-butyl[7] systems, which lack a phenyl group and which yield "hot" rearranged carbonium ions.

Experimental[29]

Materials.—3-Methyl-2-butyl tosylate had m.p. 19–21° (lit.[30] m.p. 20.1–20.8°). Isopentylamine was purchased from Matheson Coleman and Bell. 3-Methyl-2-butylamine, prepared according to Buck and Hjort,[31] had b.p. 85–87° (lit.[32] b.p. 84–87°); the phenyl isocyanate derivative had m.p. 141–143° (lit.[33] m.p. 144°). We attempted to check the purity of the amines with g.l.p.c. The quality of the chromatograms was poor, but each amine appeared to be free of isomeric amines. A mixture of *cis*- and *trans*-1,2-dimethylcyclopropane was prepared[34] and the isomers separated by g.l.p.c. over col. A. The *trans* isomer, b.p.[35] 28.2°, had the lower retention time (*cis*, b.p.[35] 37.0°). The infrared spectrum of the *cis* isomer agreed with the A.P.I. spectrum of the same material. 1,1-Dimethylcyclopropane was prepared according to Shortridge, *et al.*[36]

G.l.p.c.—All chromatograms were run on a Perkin-Elmer 154-C vapor fractometer, utilizing columns A (diisodecyl phthalate), K (Carbowax 1500), and Ag (homemade column containing a saturated solution of silver nitrate in ethylene glycol). Calibration solutions were used throughout to determine retention times and the relative response of the detector to different components.

Acetolysis of 3-Methyl-2-butyl Tosylate.—The procedure was that previously described[2] for the acetolysis of *t*-pentyl bromide. The ester (33.5 g.) was heated at 55° for 4.5 days with 150 ml. of acetic acid and 17.4 g. of potassium acetate. There was obtained 5.7 g. of acetates (30%) and 4.7 g. of olefin (46%). The composition of the acetate was determined on col. A at 100° and the

(21) A preliminary report of this work has appeared: M. S. Silver, *J. Am. Chem. Soc.*, **82**, 2971 (1960).

(22) The work of P. S. Skell and I. Starer, *ibid.*, **84**, 3962 (1962), demonstrates that cyclopropane formation is not the result of a carbene intermediate.

(23) P. S. Skell and I. Starer, *ibid.*, **82**, 2971 (1960).

(24) Because the deamination of 2-methyl-1-butylamine gives primarily rearranged products, a small amount of 1,3-hydride shift cannot be excluded.

(25) A. J. Finlayson and C. C. Lee, *Can. J. Chem.*, **37**, 940 (1959).

(26) III is also helpful in interpreting the ratio of *trans* to *cis* 1,2-dimethylcyclopropane.

(27) P. S. Skell, I. Starer, and A. P. Krapcho, *J. Am. Chem. Soc.*, **82**, 5257 (1960). 1,2-Methyl migration to give the *t*-pentyl carbonium ion may be so favorable that hydride shift cannot compete; III will be highly asymmetric if it is present.

(28) D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957).

(29) Typical procedures are given.

(30) S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1120 (1952).

(31) J. S. Buck and A. M. Hjort, *ibid.*, **59**, 2567 (1937).

(32) D. Trasciatti, *Gazz. chim. ital.*, **29**, **II**, 92 (1899) [*Chem. Zentr.*, **70**, **II**, 801 (1899)].

(33) A. Mailhe, *Bull. soc. chim. France*, **29**, 219 (1921).

(34) Procedure of J. D. Bartleson, R. E. Burk, and H. P. Lankelma, *J. Am. Chem. Soc.*, **68**, 2513 (1946).

(35) R. G. Kelso, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *ibid.*, **77**, 1751 (1955).

(36) R. W. Shortridge, *et al.*, *ibid.*, **70**, 946 (1948).

composition of the olefin on col. A at room temperature. Comparison of the infrared spectra of the reaction products and standard solutions confirmed the g.l.p.c. analysis.

Deamination Reactions.—The procedure was that previously described[2] for the deamination of *t*-pentylamine. Realization that some of the reaction products were unstable led us to settle on a standard reaction of 20 g. of C_5-amine and 30 g. of sodium nitrite. This standardization simplified the application of corrections for product instability. Some early runs were not run under standard conditions. Product analysis was primarily by g.l.p.c. Col. A at 100° readily resolved tertiary and secondary products and isopentyl acetate. However, isopentyl alcohol had the same retention time as *t*-pentyl acetate on col. A and was determined with col. K at 70°. For ease in tabulation, we report only the sum alcohol plus ester in Tables I and II. Col. A at room temperature clearly resolved 3-methyl-1-butene, 2-methyl-2-butene, and 2-methyl-1-butene.

Substitution Products from the Deamination Reaction.—A mixture (7 g.), 53% *t*-butyl alcohol and 47% *t*-butyl acetate, was treated with 17 g. of 2-butylamine and 30 g. of sodium nitrite in 200 ml. of 75% acetic acid. The recovered ester–alcohol layer contained these materials in the relative amounts 52.5% and 47.5%, respectively. From this and earlier work[2] we deduce that *t*-pentyl alcohol and acetate are entirely stable under the reaction conditions. However, many control studies indicated that the primary and secondary alcohols are partially destroyed during the course of the deamination (oxidation?) while the corresponding acetates are stable. The destruction amounted to about 0.8–0.9 g. of alcohol, and appeared to be fairly independent of solvent, the nature of the alcohol, or the amount of alcohol initially present. We assumed that 0.9 g. of 3-methyl-2-butanol and isopentyl alcohol were destroyed in each deamination in determining the corrected composition of the alcohol–ester fraction (Table II). Here is an example of controls on the destruction of isopentyl alcohol: 10 g. and 6 g. of a solution which was 26% isopentyl alcohol (E) and 74% isopentyl acetate (F) were treated with 19.5 ml. of isopropylamine and 30 g. of sodium nitrite in 200 ml. of acetic acid. The recovered ester–alcohol layer from the former showed 20% E, 80% F, and from the latter, 17% E, 83% F, corresponding to losses of 0.8 g. and 0.7 g., respectively. In the same way 4.6 g. and 3.3 g. of a solution which was 81% 3-methyl-2-butanol (G) and 19% 3-methyl-2-butyl acetate (H) was treated with 19.5 ml. of isopropylamine and 30 g. of sodium nitrite in 300 ml. of 50% acetic acid. The recovered ester–alcohol layer from the former showed 76% G, 24% H and from the latter, 75% G, 25% H, corresponding to losses of 0.9 g. and 0.8 g., respectively, of 3-methyl-2-butanol. G.l.p.c. analyses of a few of the alcohol–ester fractions were confirmed by infrared analyses.

An effort was made to determine if 2-methyl-1-butyl acetate was formed in the deamination of 3-methyl-2-butylamine in acetic acid. On col. A at 100°, a small peak appeared in the chromatogram of the reaction mixture at the same retention time as this ester. On col. K at 75°, there was a very slight bump in the chromatographic curve of the reaction mixture at the point where this ester should appear. By observing the chromatogram of the reaction mixture to which a known amount of 2-methyl-1-butyl acetate had been added, it was determined that less than 1% of this ester could have been originally present.

Olefins from the Deamination Reaction.—We previously reported[2] that, in the deamination of *t*-pentylamine, some fractionation occurs between 2-methyl-2-butene and 2-methyl-1-butene. Similar effects were encountered in the present work. In 200 ml. of acetic acid were placed 18 g. of 2-butylamine and 3.9 g. of a mixture which was 22% 2-methyl-1-butene (B), 42% 2-methyl-2-butene (C), and 37% 3-methyl-1-butene (D). After the addition of 30 g. of sodium nitrite, the per cents were 24, 32, and 45, respectively. A duplicate run gave values of 24, 34, and 42. These particular controls were used to correct the olefin composition from the deamination of 3-methyl-2-butylamine in acetic acid. In another control run, 18 g. of *n*-butylamine and 3.2 g. of a mixture which was 13% B, 13% C, and 74% D were treated with 30 g. of sodium nitrite. The recovered olefin had per cents 14, 3, and 83, respectively, and a duplicate run gave values of 15, 6, and 79. These controls were applied to the deamination of isopentylamine in acetic acid. In agreement with previous experiments,[2] fractionation of olefin decreased with decreasing acetic acid content of the solvent. For example, a mixture (3.2 g.) which was initially 15% B, 14% C, and 72% D was 16% B, 12% C, and 72% D after treatment with 18 g. of *n*-butylamine and 30 g. of sodium nitrite in 300 ml. of 50% acetic acid. No controls were run for olefin destruction in 25% acetic acid or for runs 9 and 12 of Table I (see Results). Infrared analysis of some reaction mixtures confirmed the correctness of the g.l.p.c. analysis.

1,2-Dimethylcyclopropane from the Deamination of 3-Methyl-2-butylamine.—With col. K and Ag in series, g.l.p.c. cleanly separated *cis*- and *trans*-1,2-dimethylcyclopropane from the other C_5H_{10} hydrocarbons present and from each other. The C_5H_{10} fraction from the deamination showed peaks with retention times corresponding to those of the cyclopropanes. In operations with other g.l.p.c. columns, these peaks behaved entirely in accord with this assignment. When the C_5H_{10} fraction was stirred with aqueous permanganate for 23 hr. at 25°, the band assigned to the *trans* isomer increased to 61% from 10%. At the time of this experiment, we had not yet found a way to separate the *cis* isomer from 2-methyl-2-butene. After permanganate treatment, this composite band had also increased in size, in agreement with the supposition that *cis*-1,2-dimethylcyclopropane was present. The infrared spectrum of the hydrocarbon recovered from the permanganate treatment was nearly identical to that of a mixture of 66% *trans*- and 34% *cis*-1,2-dimethylcyclopropane. The slight differences in the two spectra were readily accounted for by the small amounts of C_5H_{10} olefin that had survived the permanganate treatment.

1,2-Dimethylcyclopropanes from the Deamination of Isopentylamine.—Consideration of the C_5H_{10} fraction from this reaction, in the manner outlined, indicated the possibility of the presence of traces of 1,2-dimethylcyclopropanes. Many passes of small samples of the hydrocarbon fraction from one deamination through col. Ag enabled us to collect a dilute solution of the cyclopropanes in carbon tetrachloride. The infrared spectrum of this solution confirmed the formation of 1,2-dimethylcyclopropanes. We were unable to detect with g.l.p.c. any 1,1-dimethylcyclopropane in the C_5H_{10} fraction.

The Isolation of a Second Octulose and of a Heptose from the Avocado: D-*glycero*-L-*galacto*-Octulose and D-*glycero*-D-*galacto*-Heptose[1]

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In addition to the well known D-*manno*-heptulose and the recently discovered D-*talo*-heptulose and D-*glycero*-D-*manno*-octulose, the avocado contains very small amounts of a second octulose. The new sugar was isolated as an amorphous solid, with $[\alpha]^{20}D$ about $-60°$. Its structure was proved to be D-*glycero*-L-*galacto*-octulose by degradation with lead tetraacetate and with oxygen in alkaline solution, and was confirmed by synthesis, both enzymatic and chemical. Although aldoheptoses have been reported previously as constituents of bacterial polysaccharides, the isolation of D-*glycero*-D-*galacto*-heptose from the avocado marks the first known appearance of an aldoheptose in the plant world.

LaForge[3] discovered D-*manno*-heptulose in the avocado in 1917 and in the same year LaForge and Hudson[4] discovered sedoheptulose (D-*altro*-heptulose) in *Sedum spectabile* Bor. More than forty years elapsed before any additional higher-carbon ketoses were found in nature. In 1959–1960 Charlson and Richtmyer[5] reported the isolation of D-*glycero*-D-*manno*-octulose (I) from both the avocado and from *Sedum* species, and obtained strong evidence for the presence of D-*talo*-heptulose, also, in the avocado.

We have now extracted 95 kg. of the ripe pulp from 400 California avocados (Calavo, Hass variety) with 20% ethanol and, after precipitating the gums with methanol, deionizing, and removing most of the perseitol, D-*manno*-heptulose, D-*erythro*-D-*galacto*-octitol,[5] and *myo*-inositol by crystallization, obtained 304 g. of a residual sirup. This material was chromatographed and the octulose–nonulose fraction rechromatographed several times on columns of cellulose powder by elution with aqueous 1-butanol; some improved techniques that we believe have not been published before are described in the Experimental section. After the faster-moving, dextrorotatory D-*glycero*-D-*manno*-octulose (I) had been separated, a very small amount of a second octulose was obtained that appeared to be homogeneous and was a colorless, hygroscopic, amorphous solid showing $[\alpha]^{20}D$ $-57°$ in water. It was characterized further through its crystalline 2,5-dichlorophenylhydrazone melting at 178–180°. This second octulose from the avocado was proved to be D-*glycero*-L-*galacto*-octulose (II) by the following reactions. First, upon degradation with two molecular equivalents of lead tetraacetate in glacial acetic acid, according to the procedure of Perlin and Brice,[6] it yielded an aldose with the mobility of D-gulose (III) on paper chromatograms, together with a pentose indistinguishable from D-xylose on paper chromatograms and formed probably by further degradation of the D-gulose. Second, upon degradation with oxygen in alkaline solution, according to the procedure of Spengler and Pfannenstiel,[7] it yielded an acid and a lactone with the same mobilities on paper chromatograms as D-*glycero*-L-*galacto*-heptonic acid and its lactone (IV). Third, while the mobilities of the degradation products do not distinguish between enantiomorphs, a comparison of rotations gave a good clue. Hudson[8] called attention to the similarity of physical and chemical properties of the higher-carbon sugars to those of a corresponding hexose that possessed like configuration for the asymmetric carbon atoms 2, 3, 4, and 5. Montgomery and Hudson[9] compared D-*manno*-heptulose and D-mannose similarly. Wolfrom found that comparisons of rotations were valid also when extended to include octuloses[10] and nonuloses.[11] Since the second octulose (II) isolated from the avocado had a molecular rotation ($[M]^{20}D$ $-13,680$) similar to that of L-galactose ($-14,450$), L-*galacto*-heptulose ($-18,000$), and L-*glycero*-L-*galacto*-octulose ($-14,880$[12]), it was assumed to have configuration II rather than that of the enantiomorph of II.

Finally, the D-*glycero*-L-*galacto*-octulose (II) was obtained through synthesis, both enzymatic and chemical. Jones and Sephton[12] earlier had condensed 1,3-dihydroxy-2-propanone phosphate (V) with D-xylose (VI) in the presence of rabbit muscle aldolase and obtained an octulose phosphate from which they prepared 6 mg. of a product that was believed to be, but not positively identified as, D-*glycero*-L-*galacto*-octulose (II). We repeated their enzymatic synthesis, with slight modifications, and obtained a product whose mobilities on paper chromatograms in four different solvent systems were identical to those of the second avocado octulose. These results, together with those described in the next paragraph, give confirmatory proof of the structure of the octulose of Jones and Sephton.

Chemical synthesis of the octulose (II) was achieved by application of Sowden's 2-nitroethanol synthesis, previously used only for the preparation of heptuloses from pentoses.[13] For this, D-gulose (III) was condensed with 2-nitroethanol (VII) in the presence of sodium methoxide. The solid product, isolated as a mixture of

(1) A preliminary account of a part of the work on the octulose was presented before the Division of Carbohydrate Chemistry, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961. Unfortunately, the octulose was reported incorrectly at that time as D-*glycero*-D-*talo*-octulose; Abstracts of papers, p. 1D.

(2) Visiting Scientist of the Public Health Service, September, 1959, to October, 1962.

(3) F. B. LaForge, *J. Biol. Chem.*, **28**, 511 (1917).

(4) F. B. LaForge and C. S. Hudson, *ibid.*, **30**, 61 (1917).

(5) (a) A. J. Charlson and N. K. Richtmyer, *J. Am. Chem. Soc.*, **81**, 1512 (1959); (b) **82**, 3428 (1960).

(6) A. S. Perlin and C. Brice, *Can. J. Chem.*, **34**, 541 (1956).

(7) O. Spengler and A. Pfannenstiel, *Z. Wirtschaftsgruppe Zuckerind.*, **85**, Tech. Tl. 547 (1935).

(8) C. S. Hudson, *Advan. Carbohydrate Chem.*, **1**, 26 (1945); R. M. Hann, A. T. Merrill, and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 1912 (1944), and earlier papers from their laboratory.

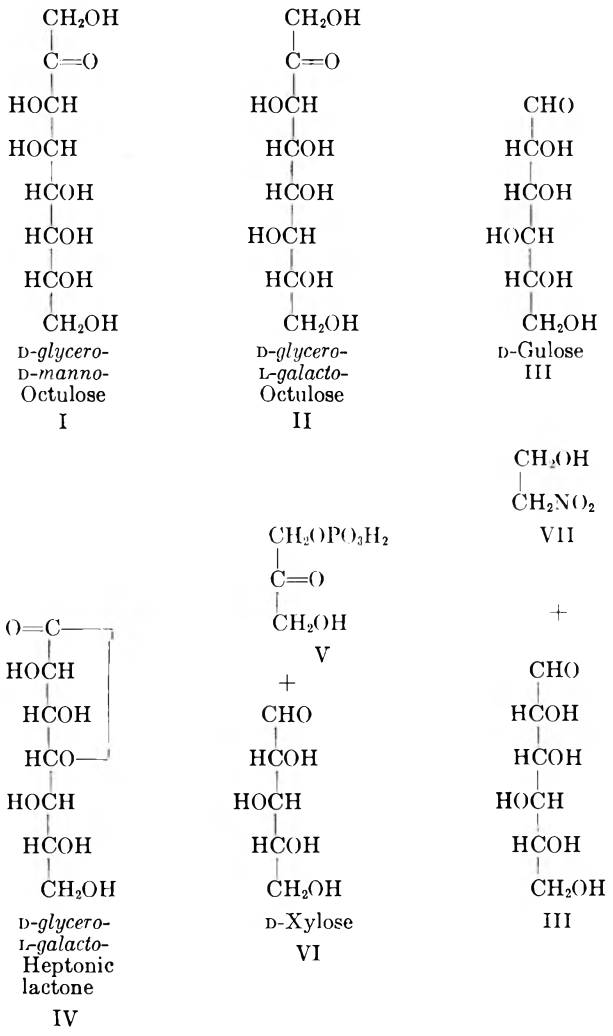
(9) E. M. Montgomery and C. S. Hudson, *ibid.*, **61**, 1654 (1939).

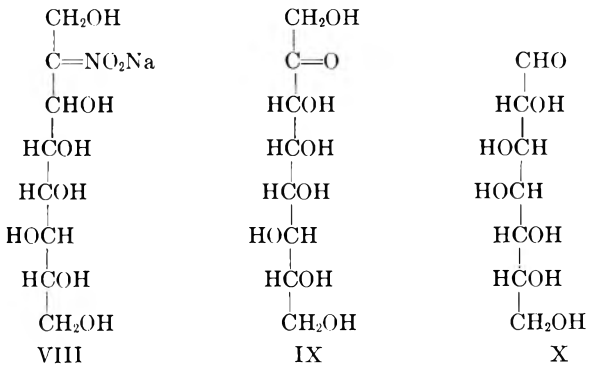
(10) M. L. Wolfrom and P. W. Cooper, *ibid.*, **72**, 1345 (1950).

(11) M. L. Wolfrom and H. B. Wood, Jr., *ibid.*, **77**, 3096 (1955).

(12) J. K. N. Jones and H. H. Sephton, *Can. J. Chem.*, **38**, 753 (1960).

(13) J. C. Sowden, *J. Am. Chem. Soc.*, **72**, 3325 (1950); *Advan. Carbohydrate Chem.*, **6**, 291 (1951); J. C. Sowden and D. R. Strobach, *J. Am. Chem. Soc.*, **80**, 2532 (1958).





sodium salts (VIII), was decomposed with sulfuric acid to give the desired octulose (II) and, presumably, its epimer, D-*glycero*-L-*talo*-octulose (IX).[14] Separation on a cellulose column afforded amorphous D-*glycero*-L-*galacto*-octulose (II), which showed $[\alpha]^{20}D$ $-61°$ in water, a value similar to that ($-57°$) observed for the second avocado octulose. Paper chromatography and infrared spectroscopy failed to reveal any difference between the synthetic and the natural octuloses and both octuloses afforded the same 2,5-dichlorophenylhydrazone.

Although several aldoheptoses have been reported as constituents of the polysaccharides of Gram-negative bacteria,[15] including D-*glycero*-D-*galacto*-heptose (X) from *Chromobacterium violaceum* (Birch), they have not been found previously as the free sugar, or in either plant or animal sources.[16] We have found, unexpectedly, that D-*glycero*-D-*galacto*-heptose (X) was a heavy contaminant in several of the fractions containing the avocado octuloses and nonuloses.[17] Its presence was first suspected after a portion of one of the octulose fractions was oxidized with two molecular equivalents of lead tetraacetate and D-arabinose was detected; this could not be derived from either avocado octulose, I or II. Later, the D-*glycero*-D-*galacto*-heptose was found to be separable from the second octulose by electrophoresis or by paper chromatography in borate buffers, and finally it was obtained directly from an octulose fraction as its 2,5-dichlorophenylhydrazone and from an octulose–nonulose fraction by direct crystallization. Although D-*glycero*-D-*galacto*-heptose is closely related to D-*manno*-heptulose, we do not believe that our solutions were ever sufficiently alkaline to bring about a Lobry de Bruyn–Alberda van Ekenstein transformation of ketose to aldose. It is conceivable, however, that the heptose may have been a component of an oligosaccharide and was liberated by acid hydrolysis (see Experimental section), but the precise origin of X has not been established.

(14) To be described in a later paper.

(15) See the review by D. A. L. Davies, *Advan. Carbohydrate Chem.*, **15**, 271 (1960).

(16) For a recent review of the higher-carbon sugars, both aldoses and ketoses, natural and synthetic, see J. M. Webber, *ibid.*, **17**, 15 (1962).

(17) In fact, it was the presence of this heptose that was chiefly responsible for our earlier incorrect identification of the second avocado octulose; see ref. 1.

Experimental

Paper chromatography was carried out on Whatman no. 1 filter paper by the descending method at room temperature. The following solvent systems were used: A, ethyl acetate–acetic acid–formic acid–water (18:3:1:4); B, 1-butanol–ethanol–water (40:11:19); C, 1-butanol–pyridine–water (6:4:3); and D, ethyl acetate–pyridine–water saturated with boric acid (12:5:4). Spray reagents used were aniline hydrogen phthalate for aldoses, orcinol-hydrochloric acid for ketoses, alkaline hydroxylamine–ferric chloride for lactones and esters (acids were detected by first converting them into esters by hanging the chromatograms for 10 min. in a tall cylinder containing diazomethane vapors), and silver nitrate (ammoniacal, or in conjunction with sodium hydroxide in ethanol) or sodium metaperiodate–potassium permanganate for alditols, sugars, and other polyhydroxy substances in general. All concentrations were carried out *in vacuo* at temperatures not over 50°; the final drying of sirups was completed in evacuated desiccators over granular calcium chloride. Melting points were determined on a Kofler micro hot stage.

Isolation of Sugars from Avocado Pulp and Chromatographic Separation into Fractions.—Four hundred ripe avocados (Californian Calavo, Hass variety[18]) were freed from skin and seeds, and the pulp (95 kg.) was extracted with 20% ethanol; the extract was freed from gums and deionized as described earlier[5b] and then concentrated until perseitol began to crystallize when the solution was cooled to room temperature. The perseitol weighed 162 g., and on further concentration and cooling the mother liquor deposited two additional crops (the last being slightly contaminated with *myo*-inositol); the total was 332 g. of perseitol. The mother liquor was concentrated to 700 ml., diluted with an equal volume of methanol, and the solution inoculated with seed crystals of perseitol, D-*erythro*-D-*galacto*-octitol,[6] and *myo*-inositol, and cooled slowly to 0°. After removal of the first crop (28 g.), the filtrate was concentrated to a sirup; this was dissolved in 700 ml. of methanol at 45°, and the solution inoculated and cooled to 0°. The second batch (5 g.) was removed, and the filtrate concentrated to a sirup; this was dissolved in 300 ml. of methanol and the solution diluted at 40° with ethanol to incipient cloudiness, inoculated, and cooled slowly to 0°. The total yield of mixed polyhydric alcohols was 42 g. The final filtrate was concentrated to 420 g. of a thick sirup that was dissolved in 300 ml. of methanol at 45° and inoculated with D-*manno*-

(18) Charlson and Richtmyer (ref. 5) used the Fuerte variety of Calavo; the choice of avocado has been dictated only by the variety available in the market at the time the researches were begun.

heptulose. After standing for a week at 0° the D-*manno*-heptulose (109 g.) was filtered and the filtrate concentrated to a dry sirup weighing 304 g.

The residual sirup was dissolved in 200 ml. of methanol and to the solution was added 150 g. of Whatman standard grade cellulose powder that had previously been washed well with hot water and then acetone and dried. The slurry was stirred and 200 ml. of 1-butanol, half saturated with water, added to precipitate the sirupy material onto the cellulose. The methanol was removed on a rotary vacuum evaporator and the free-flowing slurry in 1-butanol transferred to the top of a large cellulose column (100 cm. × 12 cm.); the column had been prepared by packing it under air pressure with an acetone slurry of 2.5 kg. of washed Whatman cellulose powder and the acetone displaced later with half-saturated aqueous 1-butanol. Elution of the column was effected with half-saturated aqueous 1-butanol gradually increasing to fully saturated aqueous 1-butanol. With an automatic collector, 52 fractions, each containing 2.2 l., were obtained and combined later according to their contents as assayed by paper chromatography. Fractions 1–24 contained lower monosaccharides and D-*manno*-heptulose totaling 228 g. Fractions 25–27 consisted principally of D-*glycero*-D-*manno*-octulose[5] (I, 11.2 g.). Fractions 28–37 (total 18.3 g.) appeared to contain the same octulose (I), a second octulose, and also two nonuloses; a partial examination of these fractions will be described later. Fractions 38–52 (36 g.) contained mostly oligosaccharides composed of both aldoses and ketoses, and these fractions, together with fractions 1–27, were saved for further examination at a later date.

Fractions 28–30 and 31–37, being already partially resolved into octulose and nonulose components, respectively, were dissolved separately in small amounts of methanol and additional amounts of polyhydric alcohols (0.5 and 2.6 g., respectively) isolated by slow concentration and crystallization of the solutions at 0°. The filtrates were concentrated to sirups whose paper chromatographic examination showed the presence of oligosaccharides. Accordingly, these components were hydrolyzed by dissolving the sirups each in 5 ml of 0.2 *N* aqueous hydrochloric acid and heating 12 hr. at 95°. The hydrolyzates were deacidified with Duolite A-4 ion-exchange resin. Examination of these hydrolyzates by paper chromatography indicated that the liberated sugars were principally *manno*-heptulose and xylose, with lesser amounts of fructose, glucose, and arabinose.

To maintain the partial separation of octuloses and nonuloses already achieved and to effect their further separation and purification, a cellulose column (85 cm. × 5 cm.) was prepared; on top of this were placed the combined, hydrolyzed fractions 28–30 that had been precipitated onto cellulose and slurried in half-saturated aqueous 1-butanol as described above; the cellulose in the slurry was allowed to settle in a horizontal layer and the solvent was drained to the level of that layer; and finally fractions 31–37 were deposited similarly in a layer on top of fractions 28–30. Elution of this column with half-saturated aqueous 1-butanol removed the lower monosaccharides (2.7 g.), D-*manno*-heptulose (3.3 g.), D-*glycero*-D-*manno*-octulose (2.3 g.), then five fractions (total 4.4 g.) of partially separated octuloses and nonuloses, and finally 2.1 g. of unhydrolyzed oligosaccharides plus some of the second nonulose.

The five fractions that contained most of the remaining octuloses and nonuloses were concentrated to dryness and an additional 0.3 g. of polyhydric alcohols was removed by dissolving the residues in small amounts of methanol and filtering. The five filtrates were precipitated separately onto cellulose powder and the slurries deposited on the top of a cellulose column (100 cm. × 3 cm.) in layers in the same order in which they had been eluted from the previous column. Elution with quarter-saturated aqueous 1-butanol increasing to half-saturated aqueous 1-butanol yielded seven fractions. Fraction A (0.49 g.) was chromatographically pure D-*glycero*-D-*manno*-octulose (I) with $[\alpha]^{20}D$ +26.5° in methanol (*c* 5; previously reported[5] +20°). Fraction B (0.50 g.) was a mixture of the two octuloses (I and II) and a heptose. Fraction C (0.32 g.) contained the second octulose (II) and a heptose (X) separable from it by electrophoresis and by chromatography in solvent D but not in solvents A, B, or C. Fraction D (0.49 g.) contained the second octulose (II), the first nonulose, and some heptose (X). Fraction E (1.08 g.) contained principally the first nonulose, fraction G (0.42 g.) principally the second nonulose, and fraction F (0.50 g.) a mixture of the two nonuloses.

Isolation of D-*glycero*-L-*galacto*-Octulose (II) from Fraction B.—The 0.5 g. of fraction B was dissolved in 100 ml. of water and the heptose contained therein destroyed by adding 0.5 g. of barium carbonate and 0.5 ml. of bromine and stirring vigorously for 10 min. at room temperature. The excess of bromine was removed by aeration, the solids were removed by filtration, and the filtrate was deionized by passage through Dowex 50 and Duolite A-4 ion-exchange resins. Concentration left 0.27 g. of a dry sirup. This residue was dissolved in 10 ml. of methanol, precipitated onto cellulose powder, and the slurry put on top of a cellulose column (100 cm. × 2.5 cm.) in the manner described earlier in this publication. Elution with quarter- to half-saturated aqueous 1-butanol afforded one fraction that appeared to be homogeneous and to contain only the second octulose (D-*glycero*-L-*galacto*-octulose, II) when examined by paper chromatography in all four solvent systems. After filtration through activated carbon (Darco X) the solution was concentrated to a colorless, amorphous, hygroscopic solid that weighed 57 mg. and showed $[\alpha]^{20}D$ −57° in water (*c* 2).

A 19-mg. portion of the second octulose (II) was heated with twice its weight of 2,5-dichlorophenylhydrazine in 1 ml. of methanol on the steam-bath until near dryness. Additional methanol was added and the heating repeated until a total of 5 ml. of methanol had been used and the total heating time had been 45 min. Upon cooling to room temperature the residue crystallized in part; it was washed with ethyl ether seven times by decantation to remove the excess of reagent and the residue was recrystallized from methanol. The D-*glycero*-L-*galacto*-**octulose 2,5-dichlorophenylhydrazone** separated into aggregates of nearly colorless, small needles that melted at 178–180°. The recrystallized first crop weighed only 1.6 mg.; two additional crops (6.5 mg.) were obtained by reheating the original mother liquor with the ethyl ether extract containing the excess of reagent from the first crop of crystals.

Anal. Calcd. for $C_{14}H_{20}Cl_2N_2O_7$: Cl, 17.8. Found: Cl, 18.1.

Degradation of D-*glycero*-L-*galacto*-Octulose (II) to D-Gulose (III) and D-Xylose (VI) with Lead Tetraacetate.—To a solution of 10 mg. of the second octulose (II) in 10 ml. of glacial acetic acid was added 2 ml. of 0.04 *M* lead tetraacetate in glacial acetic acid (2 molecular equivalents). After 15 min. at room temperature the lead was precipitated as the oxalate by the addition of a slight excess of a 10% solution of oxalic acid in acetic acid. The precipitate was removed by centrifugation and the acetic acid evaporated by a current of air. The residue was heated in 10 ml. of 5% aqueous acetic acid for 8 hr. on the steam bath to hydrolyze formyl and glycolyl groups, and the solution was then deacidified with Duolite A-4 ion-exchange resin and concentrated. The product, on paper chromatographic examination in solvents A, B, and C, showed aldose spots corresponding to gulose and xylose only.

Degradation of D-*glycero*-L-*galacto*-Octulose (II) to D-*glycero*-L-*galacto*-Heptonic Acid with Oxygen in Alkaline Solution.—A 2-mg. portion of the second octulose was deposited on the inside surface of a 25-ml. flask by concentrating its solution in 1 ml. of methanol on a rotary evaporator. By means of a three-way stopcock, the flask was evacuated and filled with oxygen from a balloon attached to one branch of the stopcock; through another branch, 0.5 ml. of *N* aqueous potassium hydroxide was introduced; and the flask, with oxygen balloon attached, was rotated overnight. The solution was diluted with water, decationized with Dowex 50 resin, and concentrated. Paper chromatographic examination in solvents A, B, and C showed that the product contained an acid and a lactone with the same mobilities as D-*glycero*-L-*galacto*-heptonic acid and lactone (IV). The lactone was readily distinguishable from D-*glycero*-L-*talo*-heptonic lactone on paper chromatograms.

Enzymatic Synthesis of D-*glycero*-L-*galacto*-Octulose (II) from D-Xylose (VI).—The Jones and Sephton[12] procedure was modified as follows. A mixture of 0.1 g. of D-fructose 1,6-diphosphate tri(cyclohexylammonium) salt, 0.05 g. of D-xylose, and 20 mg. of a commercial muscle aldolase in 9 ml. of water at pH 6.7 was kept at room temperature for 3 days. The proteins were coagulated by heat and filtered; the filtrate was cooled and adjusted to pH 5; and 30 mg. of acid phosphatase was added to hydrolyze the sugar phosphates. The solution was then deproteinized, deionized, and concentrated. Paper chromatographic examination of the product showed, besides fructose and xylose, an octulose with the same mobility in all four solvent systems as the second octulose (II) from the avocado.

The 2-Nitroethanol Synthesis of D-*glycero*-L-*galacto*-Octulose (II) from D-Gulose (III).—A solution of D-gulose was prepared by deionizing 20 g. of α-D-gulose·$CaCl_2$·H_2O with Dowex 50 and

Duolite A-4 resins, and concentrated to a dry sirup. To a solution of this sirup in 20 ml. of methanol was added 10.5 g. of 2-nitroethanol (VII, freshly distilled from a commercial product) in 15 ml. of methanol followed by a solution of sodium methoxide made by dissolving 2.6 g. of sodium in 60 ml. of methanol. The mixture was stirred vigorously at room temperature for 6 hr., then cooled to 0°, and the precipitated sodium salts were filtered and washed in succession with cold methanol, ethyl ether, and petroleum ether (b.p. 90–100°). While still moist, the filter cake was dissolved in ice-cold water and decationized without delay by passage through a column of Dowex 50 resin. Concentration of the effluent yielded 11.6 g. of a dry sirup containing the 2-deoxy-2-nitrooctitols but attempts to crystalline them from methanol and ethanol were unsuccessful. The sirup, therefore, was dissolved in a cold solution containing 1.7 g. of sodium hydroxide in 35 ml. of water and the solution added dropwise, with stirring, to 30 ml. of cold aqueous 50% sulfuric acid. The solution was warmed to 30°, deionized with Dowex 50 and Duolite A-4 resins, and concentrated to a sirup. Paper chromatography indicated that the sirup contained the two expected octuloses and two other orcinol-positive compounds (possibly anhydrooctuloses) in addition to a small amount of D-gulose. These components were separated on a cellulose column (100 cm. × 4 cm.) by elution with quarter- to half-saturated aqueous 1-butanol. The sirupy D-*glycero*-L-*galacto*-octulose fraction (1.36 g., 8.8% over all from the D-gulose calcium chloride compound) showed $[\alpha]^{20}D$ −61° in water (*c* 12) as compared with the value $[\alpha]^{20}D$ −57° observed for the second avocado octulose (II).[19] The infrared spectrum (dried film from methanol) of the chemically synthesized octulose was almost identical with that of the second octulose (II) from the avocado, and paper chromatography in all four solvent systems indicated the identity of the chemically synthesized octulose, the enzymatically synthesized octulose, and the second octulose from the avocado.

The **2,5-dichlorophenylhydrazone** of this synthetic D-*glycero*-L-*galacto*-octulose was prepared as described for the second avocado octulose, but in better yield (59 mg. from 50 mg. of octulose sirup). The twice-recrystallized product melted at 179–181° alone and when mixed with the previously described compound. The infrared spectra of the two products in Nujol mulls were almost identical.

Anal. Calcd. for $C_{14}H_{20}Cl_2N_2O_7$: C, 42.12; H, 5.05; Cl, 17.76; N, 7.02. Found: C, 42.11; H, 5.43; Cl, 17.57; N, 6.93.

Lead Tetraacetate Oxidation of Fraction C to D-Arabinose. Isolation of D-*glycero*-D-*galacto*-Heptose (X) from Fraction C.—A 13-mg. portion of fraction C was oxidized with two molecular equivalents of lead tetraacetate in the manner described earlier in this paper for D-*glycero*-L-*galacto*-octulose (II). The 9 mg. of resulting sirup showed $[\alpha]^{20}D$ −72° in water (c 3). On paper chromatograms developed with solvents A, B, and C the main component of the sirup was found to be a pentose with the same mobility as arabinose but readily separable from lyxose, ribose, and xylose. A 3.2-mg. portion of this sirup and 3.5 mg. of 1,1-diphenylhydrazine in 1 ml. of ethanol, kept in the dark at room temperature for 3 days, deposited crystals that were identified as D-arabinose 1,1-diphenylhydrazone by its m.p. of 197–199° and m.m.p. of 198–201° with authentic material prepared similarly.

Another portion (25 mg.) of fraction C in 0.05 ml. of water was applied in a 28-cm. streak to a sheet of S & S no. 589 electrophoresis paper moistened with sodium borate buffer at pH 10. Separation of the heptose and octulose was obtained by applying a 900-v. potential (38–55 ma.) for 3.5 hr. at −5°. The positions of the sugars were determined by spraying test strips with 0.06% sodium metaperiodate in 10% aqueous acetic acid (10 min.) followed by 2% *p*-anisidine in 2% aqueous acetic acid. The slower-moving component was recovered by extraction with methanol, removal of ions and boric acid in the usual manner, and concentration to 10 mg. of dry sirup. The product, crystallized readily from methanol, weighed 4 mg. and was identified as D-*glycero*-β-D-*galacto*-heptose by m.p. 139–141° and m.m.p. 140–141° with an authentic sample of that sugar recrystallized from methanol.

Another portion (27 mg.) of fraction C was refluxed for 2 hr. with 40 mg. of 2,5-dichlorophenylhydrazine in 10 ml. of methanol and then evaporated carefully to dryness on a steam bath. The residue solidified on cooling and was freed from excess of reagent by washing by decantation several times with ether. The **D-*glycero*-D-*galacto*-heptose 2,5-dichlorophenylhydrazone**, on recrystallization from methanol, separated in clusters of small needles (18.4 mg.), m.p. 203–204°. The 2,5-dichlorophenylhydrazone prepared in the same way from an authentic specimen of the heptose also melted at 203–204°, and a mixture melting point was not depressed. The infrared spectra (Nujol mulls) of the two derivatives were identical.

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_6$: C, 42.29; H, 4.91; Cl, 19.2; N, 7.6. Found (derivative of compound from avocado): C, 42.19; H, 5.23; Cl, 19.2; N, 7.6.

Direct Crystallization of D-*glycero*-β-D-*galacto*-Heptose from Fraction D.—The 0.49 g. of fraction D, containing D-*glycero*-D-*galacto*-heptose and also some of the second octulose (II) and first nonulose, was dissolved in 1 ml. of methanol and nucleated with a tiny crystal of authentic D-*glycero*-β-D-*galacto*-heptose. During the course of several weeks at room temperature a mass of prismatic crystals formed. The product, filtered and washed with methanol and air dried, weighed 58 mg., melted at 139–140° alone and at 140–141° when mixed with authentic heptose. It mutarotated from $[\alpha]^{20}D$ +47° (5 min.) to +64° (7 hr., constant) in water (*c* 0.5). Montgomery and Hudson[20] reported m.p. 145° and $[\alpha]^{20}D$ +43.9° (4.8 min.) to +69.1° (equilibrium) for anhydrous D-*glycero*-β-D-*galacto*-heptose.

Anal. Calcd. for $C_7H_{14}O_7$: C, 40.00; H, 6.71. Found: C, 40.19, 40.16; H, 7.07, 6.94.

Acknowledgment.—The authors wish to thank Mr. Harold G. McCann and his associates in the Analytical Services Unit of this laboratory for obtaining the infrared spectra and elemental analyses, and Dr. John C. Keresztesy and his associates in the Section on Fractionation and Isolation, also of this Institute, for their help in obtaining and concentrating the avocado pulp extracts.

(19) The values $[\alpha]^{28}D$ −43.4 → −13.4° reported by Jones and Sephton (ref. 12) refer to a very small and obviously rather impure sample of enzymatically synthesized D-*glycero*-L-*galacto*-octulose.

(20) E. M. Montgomery and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 247 (1942).

Hydride Ion Abstraction with Antimony Pentachloride

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The hexachloroantimonate salts of several stable carbonium ions have been prepared by the reaction of antimony pentachloride with certain hydrocarbons.

In connection with another problem it was observed that cycloheptatriene reacted with antimony pentachloride to produce tropylium hexachloroantimonate. This observation was not unexpected since there are several reported instances of analogous reactions of cycloheptatriene and strong Lewis acids. For example, phosphorus pentachloride,[1] stannic chloride,[2] and boron halides[3] each react with cycloheptatriene under various conditions to produce salts of the tropylium cation.

However, the present reaction with antimony pentachloride was intriguing in that the yields of tropylium salt appeared to be high and also because of the fact that the reaction could be carried out smoothly at ambient temperatures and in such inert solvents as dry carbon disulfide or benzene. These factors suggested that the method might be useful for the isolation of salts of other carbonium ions which have been observed to be stable for prolonged periods, but only in solutions which did not allow for their isolation, *e.g.*, the carbonium ions formed upon protonation of aromatic hydrocarbons in strong acids.[4] The results of several such attempts are discussed.

Results and Discussion

The reaction of antimony pentachloride with cycloheptatriene in 2:1 molar ratio proceeds readily at 0° in solvents such as carbon disulfide and benzene to give a gray, crystalline precipitate of tropylium hexachloroantimonate and simultaneous formation of antimony trichloride and hydrogen chloride. In large scale preparations the salt formed is much darker and contains small amounts of polymeric material which possibly results from the impurity in the cycloheptatriene (~5%) or from other possible side reactions.

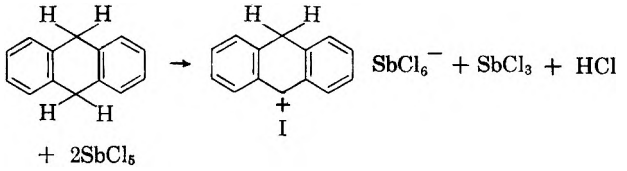
The reaction between triphenylmethane and antimony pentachloride in carbon disulfide followed a similar course[5] to produce yellow, crystalline triphenylmethyl hexachloroantimonate together with antimony trichloride, both in practically quantitative yields. The stoichiometry of the reaction is found to be as shown in the following equation.

$$Ph_3CH + 2SbCl_5 \longrightarrow Ph_3C^+SbCl_6^- + SbCl_3 + HCl$$

The triphenylmethyl salt obtained in this reaction is identical with that obtained from the reaction of triphenylmethyl chloride and antimony pentachloride. It reacted immediately with water to produce triphenylmethanol and with cycloheptatriene to give tropylium hexachloroantimonate and triphenylmethane, a reaction typical of the triphenylmethyl cation.[6]

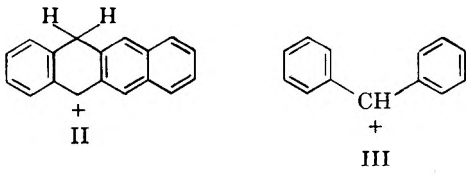
The antimony trichloride produced in these reactions was identified by conversion to the cesium chloride complex[7] and comparison of this with authentic material.

Utilizing the same reaction we have isolated the hexachloroantimonate salt of the 9-anthracenium σ complex (I). 9,10-Dihydroanthracene when treated with two moles of antimony pentachloride in cold anhydrous benzene produced a yellow, microcrystalline precipitate of the $SbCl_6^-$ salt of I in yields of better than 95%. Quantitative amounts of antimony trichloride were formed and hydrogen chloride was again liberated. There can be little doubt that the reaction has taken the same course as indicated below. The isolation of quantitative amounts of antimony trichloride indicates that the salt is not an antimony pentachloride–hydrocarbon complex of the σ type or charge transfer type.[8]



The salt, I, rapidly decomposes on exposure to moist air. It reacts immediately with water to form anthracene. Solutions of the salt in nitromethane, when treated with cycloheptatriene, give rise to tropylium hexachloroantimonate.

In a similar manner, reaction of antimony pentachloride with dihydrotetracene gave a yellow precipitate to which addition of water produced tetracene. Although in this instance the yield of salt was less than the previous cases (25% based on recovered tetracene) it seems certain that the material involves the protonated tetracene σ complex II. The salt also rapidly decomposes on exposure to air.



(1) (a) D. N. Kursanov and M. E. Volpin, *Dokl. Akad. Nauk, SSSR*, **113**, 339 (1957); (b) D. Bryce-Smith and N. A. Perkins, *J. Chem. Soc.*, 1339 (1962).

(2) Unpublished work of H. J. Dauben and K. M. Harmon (personal communication). Cycloheptatriene also forms tropylium salts when treated with stannic chloride and *t*-butyl chloride [D. Bryce-Smith and N. A. Perkins, *J. Chem. Soc.*, 2320 (1961)]; whether this reaction involves hydride abstraction by stannic chloride is not clear.

(3) K. M. Harmon, A. B. Harmon, and F. E. Cummings, *J. Am. Chem. Soc.*, **83**, 3912 (1961).

(4) V. Gold and F. L. Tye, *J. Chem. Soc.*, 2172 (1952).

(5) The isolation of a complex from this reaction was first reported by S. Hilpert and L. Wolf [*Ber.*, **46**, 2218 (1913)] but the nature of the material was not then discussed.

(6) H. J. Dauben, Jr., F. A. Gadecki, K. M. Harmon, and D. L. Pearson, *J. Am. Chem. Soc.*, **79**, 4557 (1957).

(7) G. W. Watt, *Inorg. Syn.*, **4**, 6 (1953).

(8) W. I. Aalbersberg, G. J. Hoijtink, E. L. Mackor, and W. P. Weijland, *J. Chem. Soc.*, 3055 (1959).

In view of the stability of the protonated anthracene cation attempts were made to prepare the chloroantimonate salt of the diphenylmethyl cation (III) in a similar manner from diphenylmethylane and antimony pentachloride. Although copious amounts of hydrogen chloride were liberated, the reaction did not lead to the separation of a solid salt. However, it seems most likely that a salt of the cation III is formed to some extent at least. The ultraviolet spectrum of a solution of diphenylmethane in methylene chloride containing antimony pentachloride shows a strong absorption at 451 mμ; this same peak appears in the spectrum of the hexachloroantimonate salt of III prepared as described later. Gold and Tye[4] report that the cation displays a strong broad absorption peak at 446 mμ when dissolved in concentrated sulfuric acid.

The hexachloronatimonate salt of III is easily prepared by treatment of antimony pentachloride with diphenylchloromethane in an inert solvent such as carbon disulfide.[9] The yellow salt is fairly stable when kept in an inert atmosphere; when treated with water it forms bisdiphenylmethyl ether and it reacts with cycloheptatriene to give tropylium hexachloroantimonate and diphenylmethane.

As yet we have no evidence for any mechanism which might apply in the reactions just described. A direct hydride ion abstraction seems to be the simplest explanation.

$$RH_2 + SbCl_5 \longrightarrow RH^+ + HSbCl_5^-$$

$$HSbCl_5^- + SbCl_5 \longrightarrow SbCl_6^- + SbCl_3 + HCl$$

However, in view of the charge transfer reactions known to occur between aromatic hydrocarbons and strong Lewis acids,[8] a possible alternative for the first step in this sequence is indicated.

$$RH_2 + SbCl_5 \longrightarrow RH_2^+ + SbCl_5^- \longrightarrow RH^+ + HSbCl_5^-$$

It should be noted that Harmon and co-workers[3] have shown, in the case of cycloheptatriene at least, that such a direct hydride abstraction is not the mechanism common to all Lewis acids.

Experimental

Tropylium Hexachloroantimonate.—A solution of antimony pentachloride (30.0 g.) in carbon disulfide (30 ml.) was added dropwise with stirring to a solution of cycloheptatriene (5.2 g.) in carbon disulfide (100 ml.) contained in an ice–water bath. After the addition, the mixture was stirred for 10 min. and the brown precipitate of tropylium hexachloroantimonate (22.0 g.) was filtered. The pure salt was obtained as pale yellow prisms, m.p. 190°, from nitromethane.[10]

Anal. Calcd. for $C_7H_7SbCl_6$: C, 19.72; Cl, 50.00; H, 1.64. Found: C, 20.01; Cl, 49.99; H, 1.44.

In a separate experiment on 0.2 the preceding scale the mother liquors from the initial reaction gave, upon evaporation, 2.3 g. of antimony trichloride. This was converted to the $(CsCl)_3$–$(SbCl_3)_2$ complex in the manner described. The X-ray powder pattern of this material was identical to that of an authentic sample.[11]

Triphenylmethyl Hexachloroantimonate.—Antimony pentachloride (18.0 g.) in carbon disulfide (20 ml.) was added slowly to a solution of triphenylmethane (7.3 g.) in carbon disulfide (100 ml.) and the mixture was stirred at room temperature for 1 hr. The yellow crystals of triphenylmethyl hexachloroantimonate were collected (17.0 g.); evaporation of the mother liquors afforded white prisms of antimony trichloride (6.1 g.). The salt crystallized from nitromethane in yellow prisms, m.p. 218°.[10]

Anal. Calcd. for $C_{19}H_{15}SbCl_6$: C, 39.45; H, 2.60; Cl, 36.85. Found: C, 39.58; H, 2.57; Cl, 36.73.

The same salt was obtained in quantitative yield upon vigorous shaking of equimolar amounts of triphenylmethyl chloride and antimony pentachloride in carbon tetrachloride.

Reaction of the salt (5.0 g.) in dry nitromethane (20 ml.) with cycloheptatriene (1.0 g.), followed by addition of dry ether, gave tropylium hexachloroantimonate (3.5 g.) and, upon evaporation of the solvent, triphenylmethane (2.0 g.).

9-Anthracenium Hexachloroantimonate.—Antimony pentachloride (6.0 g.) in carbon disulfide (20 ml.) was added to a stirred solution of 9,10-dihydroanthracene (1.8 g.) in dry carbon disulfide (100 ml.) at 0°. The yellow precipitate was collected upon a pad of Celite under nitrogen, then washed several times with dry carbon disulfide and benzene. Evaporation of the mother liquors gave antimony trichloride (2.3 g.). The salt, together with the Celite, was immediately shaken with a mixture of benzene and dilute hydrochloric acid. The benzene layer, after drying and treatment with decolorizing charcoal, gave, upon evaporation of the solvent, anthracene (1.7 g.).

The salt had a λ_{max} at 448 mμ (log ε, 4.0).[12] When treated with cycloheptatriene in nitromethane in the usual manner the material gave tropylium hexachloroantimonate.

9-Tetracenium Hexachloroantimonate.—Dihydrotetracene (0.40 g.) in dry benzene (75 ml.) was treated with antimony pentachloride (1.5 g.) in the usual way. The yellow material which separated was collected on Celite, washed several times with benzene, then shaken with a mixture of benzene and dilute hydrochloric acid. The residue obtained after evaporation of the benzene and trituration with hot ethanol was tetracene (0.10 g.), identified by means of its characteristic ultraviolet absorption spectrum and comparison with that of an authentic specimen.

Diphenylmethyl Hexachloroantimonate.—Antimony pentachloride (8.0 g.) in carbon disulfide (50 ml.) was added with stirring to diphenylchloromethane (5.0 g.) in carbon disulfide (150 ml.). The yellow precipitate was collected under nitrogen, washed several times with dry carbon disulfide, then transferred to a flask, and the excess solvent removed under reduced pressure. The yield of salt is quantitative; m.p. 98–99°; λ_{max}, 451 mμ (log ε 4.6).

Anal. Calcd. for $C_{13}H_{11}SbCl_6$: C, 31.11; H, 2.19. Found: C, 31.02; H, 2.62.

The salt derived from 5.0 g. of diphenylchloromethane was added at −10° to nitromethane (30 ml.) containing cycloheptatriene (2.5 g.). The mixture was allowed to warm to 10° and dry ether (300 ml.) then added. Tropylium hexachloroantimonate (4.4 g.) separated and was collected. The mother liquors were washed several times with water and dilute hydrochloric acid; removal of the solvent followed by chromatography of the residue on alumina and elution with pentane gave diphenylmethane (1.1 g.) identified by a comparison of its infrared spectrum and v.p.c. retention time with that of an authentic sample.

In a separate experiment, the salt derived from 5.0 g. of diphenylmethyl chloride was shaken vigorously with a mixture of benzene and water. Evaporation of the organic layer and recrystallization of the residue from ethanol afforded bisdiphenylmethyl ether (1.6 g.), m.p. 109–110°.

Acknowledgment.—We thank the Robert A. Welch Foundation and the Alfred P. Sloan Foundation for financial assistance.

(9) This same salt of III has also been prepared by an identical method by H. J. Dauben and co-workers (personal communication from H. J. Dauben). These workers also found that III abstracts hydride ion from cycloheptatriene.

(10) The melting point appears to vary as much as 10° depending on the rate of heating.

(11) We thank Mr. David Butler for providing the X-ray data.

(12) The spectra were determined in methylene chloride. The salt decomposes slowly in this solvent and the log ε values quoted were obtained by extrapolation to zero time. Solutions in methylene chloride containing 1% antimony pentachloride are much more stable.

Notes

Enamine Chemistry. III. The Reaction of Ketene Acetals, O,N-Acetals, and N,N-Acetals with Acetylenic Esters

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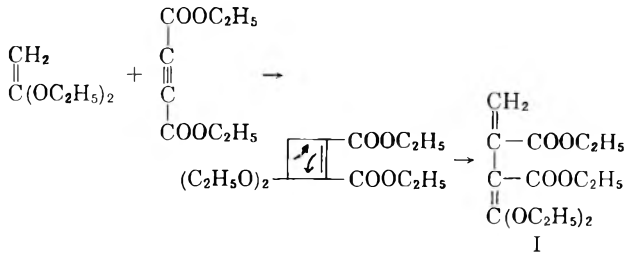
The reaction of enamines with acetylenic esters has been reported.[1] It appeared of interest to determine whether the closely related ketene acetals, O,N-acetals, and N,N-acetals would undergo similar reactions with acetylenic esters, and this indeed proved to be the case.

The products derived from the reaction of ketene acetals with acetylenic esters are those arising from the cyclobutene rearrangement of the initially formed cycloaddition products. This is illustrated for the reaction of ketene diethyl acetal with diethyl acetylenedicarboxylate.



I

McElvain[2] previously had reported the reaction of excess ketene diethyl acetal with diethyl acetylenedicarboxylate under rather drastic conditions (*i.e.*, 195° for 24 hr.) to lead in poor yield to a product ultimately converted to 3,5-diethoxyphthalic acid. It appears reasonable that McElvain's product could have arisen from a Diels–Alder addition of I and another mole of the ketene acetal.

Experimental[3]

Materials.—1-Ethoxy-N,N-dimethylvinylamine was prepared by the method of Meerwein[4] except that one equivalent of alcohol-free sodium ethoxide suspended in ether was used in place of excess ethanolic sodium ethoxide. Yields of 73% and 70% were obtained in runs of 1 and 3 moles, respectively.

1,1-Dipiperidinoethylene was prepared by the method of Baganz and Domaschke.[5] Ketene diethyl acetal[6] and dimethylketene dimethyl acetal[7] were prepared as described by McElvain.

Ketene Diethyl Acetal with Diethyl Acetylenedicarboxylate.—Diethyl acetylenedicarboxylate (29.2 g., 0.17 mole) was added to a mixture of ketene diethyl acetal (20 g., 0.17 mole) and acetonitrile (50 ml.). The addition was made rapidly over a 4-min. period and the temperature of the reaction mixture rose to a maximum of 66° after 8 min. After standing for 1.5 hr., the mixture was distilled through a 4-in. Vigreux column to give, after removal of a 12-g. forerun, 26 g. (53%) of diethyl 2-(diethoxymethylene)-3-methylenesuccinate, b.p. 116–120° (*ca.* 0.5 mm.), $n^{20}D$ 1.4741.

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.8; H, 7.7. Found: C, 58.8; H, 7.8.

To diethyl 2-(diethoxymethylene)-3-methylenesuccinate (5 g., 0.017 mole) was added water (5 ml.), ethyl alcohol (5 ml.), and concentrated hydrochloric acid (1 drop). The temperature of the resulting mixture rose immediately to 38°. After 5 min., the mixture was heated to 55° on the steam bath. A solution of potassium hydroxide (5 g., 0.09 mole) in water (10 ml.) was added and the mixture was heated for 1 hr. on the steam bath at 80–85°. It was then made acidic with concentrated hydrochloric acid (10 ml.) and heated an additional hour. The mixture was then cooled and extracted twice with an equal volume of ether. Evaporation of the ether on the steam bath left 1.7 g. (75%) of crude itaconic acid, which was recrystallized once from an ethyl acetate–hexane mixture to give 1.3 g. (57%), m.p. 165–166°. The infrared spectrum of the material was identical with that of an authentic sample.

Dimethylketene Dimethyl Acetal with Dimethyl Acetylenedicarboxylate.—Dimethylketene dimethyl acetal (38.6 g., 0.33 mole) and dimethyl acetylenedicarboxylate (47.3 g., 0.33 mole) were combined and refluxed for 2 hr. and 10 min. Distillation of the reaction mixture through a 6-in. Vigreux column gave 51 g. (59%) of dimethyl 2-(dimethoxymethylene)-3-isopropylidenesuccinate, b.p. 95–110° (*ca.* 0.5 mm.), $n^{20}D$ 1.4978.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.8; H, 7.0. Found: C, 56.1; H, 7.1.

Dimethyl 2-(dimethoxymethylene)-3-isopropylidenesuccinate (25.8 g., 0.1 mole) was combined with water (25 ml.) and methanol (25 ml.) containing 2 drops of concentrated hydrochloric acid. The mixture was refluxed for 30 min. and then distilled through a 6-in. Vigreux column to give, after removal of the methanol and water, 21.5 g. (88%) of dimethyl 2-isopropylidene-3-methoxycarbonylsuccinate, b.p. 96–103° (0.5–0.7 mm.), $n^{20}D$ 1.4701.

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.2; H, 6.6. Found: C, 54.4; H, 6.8.

Dimethyl 2-isopropylidene-3-methoxycarbonylsuccinate (20 g., 0.082 mole) was combined with a solution of potassium hydroxide (25 g., 0.45 mole) in water (50 ml.). An insoluble salt was formed and the mixture was diluted to 250 ml. to give a homogeneous solution which was heated under reflux for 2 hr. The solution was then acidified with concentrated hydrochloric acid (50 ml.) and heated on the steam bath for 1 hr. The solution was chilled and the solid which separated was collected and dried in the vacuum oven to give 9.1 g. (70%) of crude teraconic acid, m.p. 171–172.5°. A sample of this was recrystallized from water, m.p. 174–175°. The infrared spectrum of the material was identical with that of authentic teraconic acid.

Dimethylketene Dimethyl Acetal with Methyl Propiolate.—Dimethylketene dimethyl acetal (28 g., 0.24 mole) and methyl propiolate (20 g., 0.24 mole) were combined and heated under reflux for 20 hr., during which time the temperature of the reaction mixture rose from 101° to 169°. Distillation of the reaction mixture through a 6-in. Vigreux column gave 23 g. (42%) of methyl 2-(dimethoxymethylene)-4-methyl-3-pentenoate, b.p. 72–75° (*ca.* 1 mm.), $n^{20}D$ 1.4903.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.9; H, 8.1. Found: C, 59.7; H, 8.0.

1-Ethoxy-N,N-dimethylvinylamine with Dimethyl Acetylenedicarboxylate.—Dimethyl acetylenedicarboxylate (28.4 g., 0.2 mole) was added to a solution of 1-ethoxy-N,N-dimethylvinylamine (23 g., 0.2 mole) in 50 ml. of ether at a rate such as to

(1) Paper II of this series: K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(2) S. M. McElvain and H. Cohen, *J. Am. Chem. Soc.*, **64**, 260 (1942).

(3) Boiling points and melting points are uncorrected. Melting points were determined using a Fisher-Johns apparatus.

(4) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann. Chem.*, **641**, 1 (1961).

(5) H. Baganz and L. Domaschke, *Chem. Ber.*, **95**, 2095 (1962).

(6) S. M. McElvain and D. Kundiger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 506.

(7) S. M. McElvain and J. T. Venerable, *J. Am. Chem. Soc.*, **72**, 1661 (1950).

maintain the mixture at reflux. The solution was then heated under reflux for 1 hr. and distilled to give 30 g. (58%) of dimethyl 2-[(dimethylamino)(ethoxy)methylene]-3-methylenesuccinate, b.p. 121–124° (0.5 mm.), $n^{20}D$ 1.5270.

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.0; H, 7.5; N, 5.5. Found: C, 56.1; H, 7.5; N, 5.5.

1,1-Dipiperidinoethylene with Dimethyl Acetylenedicarboxylate.—Dimethyl acetylenedicarboxylate (7.8 g., 0.055 mole) was added in portions to 1,1-dipiperidinoethylene (10.6 g., 0.055 mole) in 25 ml. of ether with cooling to keep the temperature at 25–30°. Chilling and filtration of the reaction mixture gave 15 g. (82%) of dimethyl 2-(dipiperidinomethylene)-3-methylenesuccinate, m.p. 101–102°.

Anal. Calcd. for $C_{18}H_{28}N_2O_4$: C, 64.3; H, 8.4. Found: C, 64.6; H, 8.6.

Determination of the Configuration of C-9 in Levopimaric Acid[1]

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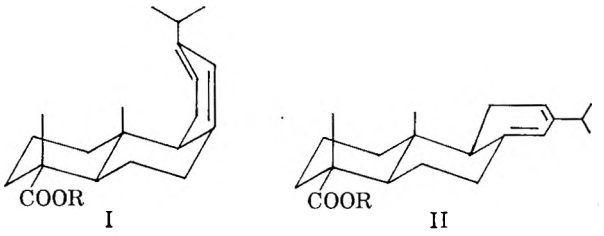
Although the gross structure of levopimaric acid has been well known for many years,[3] the stereochemistry of the material is known with less certainty. The absolute steric arrangement of C-4, C-5, and C-10 (steroid numbering) was established by conversion of levopimaric acid to abietic acid which, in turn, has been related to lanosterol.[4,5] In agreement with these results is the more recent work relating pimaric acid, which has been related to abietic acid,[6,7] to cholesterol.[8]

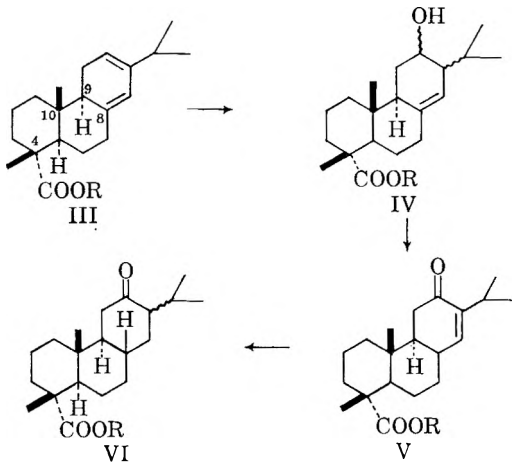
The configuration of C-9 in levopimaric acid has been more difficult to determine with certainty because the position is allylic to the reactive diene system and most interconversion studies have involved acid-catalyzed reactions. If the stereochemistry of this center were the less stable arrangement, these chemical studies might well have led to inversion of the center. Nevertheless, much chemical evidence has been presented in favor of an *anti*-backbone for levopimaric acid. For the most part the α-configuration at C-9 has been assigned by correlation with abietic and neoabietic acids,[9–11] the configuration in the latter materials having been assigned on the basis of conformational concepts and rotatory dispersion studies.[3,12,13] Recent investigations of the maleic anhydride adduct of levopimaric acid[14] also were best interpreted by assuming a C-9 α-configuration.

Purely physical methods also have been employed by various workers interested in this stereochemistry question. By comparison of the molecular rotations of levopimaric acid and $\Delta^{2,4}$-cholestadiene, it was concluded that the C-9 hydrogen has a β-orientation.[12] More recently it has been established that the direction of the skew of the diene rather than the configuration of the allylic center determines the sign of the Cotton curve of an optically active cyclohexadiene.[15] Using this concept, it was concluded that, if levopimaric acid did possess a 9α-configuration, the diene containing ring must assume a folded conformation (I) rather than the expected extended form II.[15] Surface film measurements were well in accord with this hypothesis.[16]

With such an accumulation of data, the α-assignment at C-9 appears preferable. However, since a rather unusual conformation is required to explain the dispersion curve, an unequivocal determination would



be desirable. In the course of another study, we have obtained the unsaturated keto ester V which has permitted settlement of this stereochemistry problem.



Selective hydroboration of methyl levopimarate (III) with disiamylborane[17] gave mainly one unsaturated alcohol (IV) in 40% yield. Oxidation of IV to the ketone followed by base-catalyzed isomerization of the double bond into the α,β position afforded the conjugated isomer V. Hydrogenation of V yielded the saturated ketone VI which showed a positive Cotton curve.[18] Application of the Octant Rule showed that only with a *trans* 8β,9α B/C ring fusion would

(1) This work was supported in part by grant no. A-709, U. S. Public Health Service.

(2) National Science Foundation Cooperative Predoctoral Fellow, 1960–1962.

(3) D. H. R. Barton, *Quart. Rev.*, **3**, 36 (1949).

(4) E. Kyburz, B. Riniker, H. R. Schenk, H. Heusser, and O. Jeger, *Helv. Chim. Acta*, **36**, 1891 (1953).

(5) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelley, *J. Chem. Soc.*, 1131 (1957).

(6) L. Ruzicka, G. B. R. deGraaff, M. W. Goldberg, and B. Frank, *Helv. Chim. Acta*, **15**, 915 (1932).

(7) E. Wenkert and J. W. Chamberlain, *J. Am. Chem. Soc.*, **81**, 688 (1959).

(8) G. W. A. Milne and H. Smith, *Chem. Ind.* (London), 1307 (1961).

(9) W. H. Schuller and R. V. Lawrence, *J. Am. Chem. Soc.*, **83**, 2563 (1961).

(10) P. F. Ritchie and L. F. McBurney, *ibid.*, **71**, 3736 (1949).

(11) J. C. W. Chien, *ibid.*, **82**, 4762 (1960).

(12) W. Klyne, *J. Chem. Soc.*, 3072 (1953).

(13) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(14) W. L. Meyer and R. W. Huffman, *Tetrahedron Letters*, 691 (1962).

(15) A. W. Burgstahler, H. Ziffer, and U. Weiss, *J. Am. Chem. Soc.*, **83**, 4660 (1961); A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *ibid.*, **83**, 4661 (1961); U. Weiss, H. Ziffer, and E. Charney, *Chem. Ind.* (London), 1286 (1962).

(16) U. Weiss and N. L. Gershfeld, *Experienta*, **18**, 355 (1962).

(17) G. Zweifel, K. Nagase, and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 190 (1962).

(18) We are indebted to Professor C. Djerassi for determination of the optical rotatory dispersion curve.

such a Cotton result be expected.[19,20] Accordingly the hydrogen on C-9 must have an axial (α) orientation in the ketone VI. Since none of the reactions and conversions from levopimaric acid should affect the geometry at C-9, this center must be α in the resin acid itself.

Experimental[21]

Hydroboration of Methyl Levopimarate.—A 300-ml., three-necked, round-bottomed flask was equipped with an addition funnel and a mechanical stirrer. The third neck was covered with a serum cap to permit removal of aliquots by means of a syringe. The system was flushed with dry nitrogen and cooled in an ice bath. Sodium borohydride (2.04 g., 0.054 mole) and a solution of 9.52 g. (0.132 mole) of 2-methyl-2-butene in 25 ml. of dry diglyme were placed in the cooled flask and a solution of 9.36 g. (0.066 mole) of boron trifluoride etherate in 25 ml. of dry diglyme was added, with stirring, over a period of 30 min. The mixture was allowed to stir for an additional 15 min. and then allowed to stand at ice temperature for 12 hr.

A solution of methyl levopimarate (prepared from 9.04 g. of levopimaric acid,[22] $[\alpha]^{16}D$ −252°, λ_{max} 272 mμ (ϵ 6500), by reaction with excess diazomethane) in 25 ml. of dry diglyme was added, at 0°, to the above reagent over a period of 45 min. The course of the reaction was followed by observing the disappearance of the maximum in the ultraviolet. After 5 days, about 50% of the diene had been consumed. At this time, an additional 33 mmoles of disiamylborane was added to the reaction mixture. At the end of 4 additional days the optical density in the ultraviolet had dropped to 10% of the original absorption.

To the reaction mixture there was added, slowly (frothing), 30 ml. of 3 *N* sodium hydroxide solution followed by the addition of 40 ml. of 30% hydrogen peroxide. The mixture was stirred at 0° for 1 hr. and then at room temperature for 2 hr. The reaction was diluted with water and the product extracted with benzene. The benzene solution was washed with water, acidic 5% ferrous sulfate solution, water, and then dried. The solvent was removed under reduced pressure and the white waxy product dried overnight at 70° (5 mm.), yield 10.0 g.

The crude product was chromatographed on 300 g. of activity III alumina. Elution with pentane separated diglyme and nonhydroxylated material. Elution with pentane–benzene (3:1 and 5:2) gave a total of 795 mg. of a minor alcohol. Pentane–benzene (2:1) yielded mixtures of two alcohols and elution with pentane–benzene (1:1), benzene, and benzene–ether (20:1) gave 4.79 g. of a major alcohol. Elution with ether yielded 200 mg. of a diol which was not examined further.

The major alcohol was recrystallized from methylcyclohexane, yield 4.01 g. (40%), m.p. 120–125°. This material was shown to be homogeneous by thin layer chromatography on silica gel (pentane–ether 1:1). An analytical sample was obtained by repeated crystallization from both methylcyclohexane and from methanol, m.p. 126.0–127.5°, $[\alpha]^{25}D$ +56° (*c* 1.49), ϵ_{205}^{EtOH} 10,000. Major peaks in the n.m.r. were found at τ 4.62, 6.08, and 6.34.

Anal. Calcd. for $C_{21}H_{34}O_3$ (334.48): C, 75.40; H, 10.25. Found: C, 75.45; H, 10.48.

The major alcohol was acetylated with acetic anhydride in pyridine and the crude product chromatographed on alumina. The acetate was recrystallized from aqueous methanol, m.p. 85.5–86.5°, $[\alpha]^{25}D$ +60° (*c* 2.00), ϵ_{205}^{EtOH} 9300. The n.m.r. spectrum showed peaks at τ 4.72, 5.08, 6.38, and 8.05.

Anal. Calcd. for $C_{23}H_{36}O_4$ (376.52): C, 73.36; H, 9.64. Found: C, 73.08; H, 9.52.

The minor alcohol was recrystallized from hexane and from aqueous methanol, m.p. 133.5–134.0 and 139.5–141.0°, $[\alpha]^{27}D$ −43° (*c* 1.88), ϵ_{205}^{EtOH} 9000. The major peaks in the n.m.r. were at τ 4.88, 6.30, and 6.71.

Anal. Calcd. for $C_{21}H_{34}O_3$ (334.48): C, 75.40; H, 10.25. Found: C, 75.66; H, 9.98.

Methyl 12-Keto-$\Delta^{8,14}$-dihydrolevopimarate.—To a solution of the major alcohol (402 mg., 1.2 mmoles, m.p. 120–125°) in 8 ml. of C.P. acetone cooled in an ice bath there was added 0.45 ml. (1.80 mmoles) of standard chromic acid–sulfuric acid solution (prepared from 26.7 g. of chromium trioxide and 23 ml. of concentrated sulfuric acid diluted to 100 ml. with water) over a period of 5 min. The mixture was allowed to stir for an additional 3 min. and then the reaction quenched with methanol. The mixture was diluted with water and extracted with ether The ether layer was washed, dried, and then evaporated to dryness to yield 348 mg. of solid yellow material. The compound crystallized well from either hexane or methanol but little if any purification was obtained as shown by the m.p. range of 123–135° and the presence of two spots on thin layer chromatography (silica gel, pentane–ether 1:1).

The crude material was chromatographed on 10 g. of Woelm activity III alumina. Elution with pentane–benzene mixtures and with pure benzene yielded 164 mg. (41%) of the β,γ-unsaturated ketone. There also was obtained about 50 mg. of more polar material but it was not examined. The unsaturated ketone is sensitive to air and should be isomerized immediately.

The β,γ-unsaturated ketone (164 mg.) was dissolved in 15 ml. of methanol, the solution flushed with nitrogen, sodium methoxide (75 mg.) added, and the solution allowed to stir for 5 hr. under a nitrogen atmosphere. The isomerization was followed by observing the development of a maximum at 238 mμ. The reaction was stopped by addition of 10% sulfuric acid, most of the methanol was removed under reduced pressure, and the product isolated by chloroform extraction. After evaporation of the chloroform the product was chromatographed on 5 g. of activity II alumina and the eluted material recrystallized from aqueous methanol, yield 48 mg. (12% from starting alcohol), m.p. 102.0–102.5°, $[\alpha]^{25}D$ +54° (*c* 1.15), λ_{max}^{EtOH} 238 mμ (ϵ 8800). The major n.m.r. bands were found at τ 3.78, 6.39, and 7.25.

Anal. Calcd. for $C_{21}H_{32}O_3$ (332.47): C, 75.86; H, 9.70. Found: C, 75.96; H, 9.78.

Methyl 12-Ketotetrahydrolevopimarate.—The α,β-unsaturated ketone (220 mg., 0.66 mmole) was hydrogenated in ethanol over prereduced platinum oxide (25 mg.) at atmospheric pressure. Theoretical hydrogen uptake was obtained in 90 min. The product was isolated in the usual manner and recrystallized from aqueous methanol, yield 114 mg. (51%), m.p. 98.5–99.5°, $[\alpha]^{27}D$ 11 ± 1° (*c* 1.27). The rotatory dispersion curve (*c* 0.106 in methanol) showed a peak at 311 mμ (amplitude +604°) and a trough at 269 mμ (amplitude −755°).

Anal. Calcd. for $C_{21}H_{34}O_3$ (334.48): C, 75.40; H, 10.25. Found: C, 75.06; H, 10.06.

(19) R. H. Bible, Jr., and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).

(20) Although the isopropyl group is probably equatorial, its configuration does not affect the predictions based on the Octant Rule.

(21) All melting points were taken in evacuated sealed capillaries and are uncorrected. Optical rotations were measured in chloroform. The n.m.r. spectral data are relative to tetramethylsilane as an internal standard. Chromatographies were performed of Woelm neutral alumina which had been deactivated to the desired activity by the addition of distilled water. All analyses were conducted by the Microanalytical Laboratory, College of Chemistry, University of California.

(22) The acid was obtained from *Pinus palustris* oleoresin (Sheldon Naval Stores Co., Valdosta, Ga.) by the procedure of Loeblich, Baldwin, O'Connor, and Lawrence (*J. Am. Chem. Soc.*, **77**, 6311 (1955)).

β-Bromocrotonolactone from the Bromination of Furoic Acid

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We wish to report the isolation, albeit in low yield, of β-bromocrotonolactone ($C_4H_3BrO_2$, m.p. 78°) from the bromination of furoic acid. The controversy[2a] regarding the early reports[3] (unconfirmed by later workers[4])

(1) This work was carried out in the Department of Chemistry, Rice University, Houston, Tex.

(2) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953; (a) pp. 173–175; (b) pp. 118–121.

(3) (a) H. Limpricht, *Ann.*, **165**, 253 (1873); (b) H. H. Hodgson and R. R. Davies, *J. Chem. Soc.*, 806 (1939).

(4) P. S. Bailey and J. V. Waggoner, *J. Org. Chem.*, **15**, 159 (1950).

that the bromination of furoic acid produced an 84–85° melting $C_4H_3BrO_2$ compound has not been resolved. However, our first experiment provided a few crystals of a substance (m.p. 84°) whose infrared and ultraviolet spectra were identical to those observed for β-bromocrotonolactone which was isolated in all other experiments. This suggests that the higher melting product may be a polymorphic crystalline form of β-bromocrotonolactone.

Hodgson and Davies[3b] described their compound (m.p. 85°) as 2-bromo-3-hydroxyfuran and reported its reduction to an unauthenticated product, 3-hydroxyfuran. If 3-hydroxyfuran were actually the product, it would probably exist in its tautomeric keto form in accordance with results observed by Eugster and coworkers[5] regarding the keto–enol equilibrium of related compounds. Limpricht[3a] also reduced his bromo compound but did not obtain sufficient quantities to investigate the product. Only unidentified dark oils were produced when the reduction procedures of Hodgson and Davies[3b] were applied to β-bromocrotonolactone.

The identity of our 78° melting bromo compound was established by comparing its properties with those observed for an authentic sample of β-bromocrotonolactone prepared by hydrobromination of hydroxytetrolic acid.[6] The small coupling constant (J = 1.8 c.p.s.) between the α and γ-hydrogens observed in the n.m.r. spectrum[7] of β-bromocrotonolactone supports the previous assignment[2b,8] of the bromine to the β-position in this isomer. The α-hydrogen appeared as a triplet centered at 3.67 τ while the two γ-hydrogen gave rise to a doublet at 5.14 τ.

4-Bromo-2-furoic acid[4a,9] may be an intermediate in the conversion of furoic acid to β-bromocrotonolactone. Hill and Cornelison[10] demonstrated that the action of bromine water on 4-bromo-2-furoic acid produced β-bromocrotonolactone, while the isomeric α-bromocrotonolactone was formed from the treatment of 4,5-dibromo-2-furoic acid,[8a,9] with hydrobromic acid. The bromination of furoic acid may initially produce a small amount of 4-bromo-2-furoic acid which might be converted to β-bromocrotonolactone during the steam distillation.

In some experiments the crude products obtained from the bromination of furoic acid were not submitted to steam distillation but were worked up directly. In these instances bromofuroic acids corresponding to those reported by Bailey and Waggoner[4] were found.

Experimental

Bromination of 2-Furoic Acid.—Ten grams of furoic acid (m.p. 133°) was mixed with 10 ml. of water. Following Hodgson and Davies' procedure,[3b] the paste was stirred vigorously at 28–30° for 40 min. during the addition of 30 g. of bromine. After stirring the mixture for an additional 20 min., it was dissolved in 100 ml. of water and steam distilled. Extraction of the first 500 ml. of distillate with three 100-ml. portions of ether afforded, on evaporation, 340 mg. (3% yield) of β-bromocrotonolactone, m.p. 78°; $\lambda_{max}^{H_2O}$ 224.5 mμ (ε 13,500); $\nu_{max}^{CS_2}$ 1782, 1609, 1470, 1250, 1140, 1020, 860, and 758 cm.$^{-1}$.

The same product (m.p. 78°) was also obtained in low yield when the reaction was carried out by Hodgson and Davies' alternate procedure[3b] using chloroform as the reaction medium.

Our β-bromocrotonolactone showed no depression in melting point when mixed with a sample of β-bromocrotonolactone prepared by the method of Lespieau and Viguier[6] (see following); the β-anilino derivative[10] of our compound, m.p. 217–219°, agrees in melting point with that of the β-anilino derivative from the Lespieau and Viguier preparation (217–218°[10]; 220°[11]).

In the first experiment using the chloroform reaction medium a few crystals of an 84° melting substance were obtained from the ether extract of the steam distillate. This compound was characterized only by infrared (carbon disulfide) and ultraviolet (water) spectra which were identical in all respects to those observed later for β-bromocrotonolactone. Lack of material prevented further investigation of this compound.

When the product obtained from the bromination of furoic acid in water was not steam distilled but rather allowed to stand overnight in 100 ml. of water, crystals were obtained, m.p. 186–187°, corresponding to the 5-bromo-2-furoic acid (m.p. 186–187°) isolated by Bailey and Waggoner.[4] Similarly, the crude product from the bromination in the chloroform medium was dissolved in an ether–petroleum ether solution. On cooling this solution, a crystalline product (m.p. 158–160°) was obtained which corresponds to the 2,3,4,5-tetrabromotetrahydro-2-furoic acid (m.p. 159–160°) isolated by Bailey and Waggoner[4] from a similar reaction.

Attempts to Reduce β-Bromocrotonolactone.—β-Bromocrotonolactone was submitted to Hodgson and Davies' reduction procedure[3b] using 30% aqueous sodium hydroxide and 2.5% sodium amalgam and alternatively, sodium and ethyl alcohol. In both instances only a small amount of a dark brown oil, not characterized, was obtained.

β-Bromocrotonolactone from Hydroxytetrolic Acid.—Propargyl alcohol (16.8 g., b.p. 112–114°) was converted to hydroxytetrolic acid (13.3 g., m.p. 115–116°) by the procedure developed by Haynes and Jones[12] and modified by Henbest, Jones, and Walls.[13] Hydrobromination of hydroxytetrolic acid (10 g.) by Lespieau and Viguier's method[6] produced β-bromocrotonolactone (12.1 g.), m.p. 78°.

Acknowledgment.—The author expresses his thanks to Dr. M. G. Ettlinger for his helpful guidance during the course of this work.

(5) C. H. Eugster, R. E. Rosenkranz, K. Allner, and A. Hofmann, *Angew. Chem.*, **73**, 737 (1961).

(6) R. Lespieau and P. L. Viguier, *Compt. rend.*, **146**, 295 (1908); **148**, 419 (1909).

(7) For this n.m.r. spectrum the author is indebted to Dr. J. C. Davis, Jr., of the Department of Chemistry, University of Texas. The spectrum was taken in dueteriochloroform on the Varian HR-60 spectrometer using tetramethylsilane as an internal reference.

(8) The controversy regarding the position of the bromine in the two isomeric bromocrotonolactones (m.p. 58° and m.p. 78°) was clarified by (a) R. J. Vander Wal, *Iowa State Coll. J. of Sc.*, **11**, 128 (1936–37) [*Chem. Abstr.*, **31**, 2207 (1937)]; (b) M. C. Whiting, *J. Am. Chem. Soc.*, **71**, 2946 (1949); (c) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3105 (1949); (d) K. Sukigara, Y. Hata, Y. Kurita, and M. Kubo, *Tetrahedron*, **4**, 337 (1958); (e) Y. Hata, S. Senoh, and M. Murakami, *Nippon Kagahu Zasshi*, **79**, 1531 (1958) [*Chem. Abstr.*, **54**, 24620 (1960)]; (f) M. Murakami, S. Senoh, and Y. Hata, *Mem. Inst. Sci., Ind. Res. Osaka Univ.*, **16**, 219 (1959) [*Chem. Abstr.*, **54**, 22555 (1960)].

(9) The question relating to the position of the bromine in these substituted furoic acids was resolved by: (a) H. Gilman and G. F. Wright, *Chem. Rev.*, **11**, 323 (1932); (b) H. Gilman, R. J. Vander Wal, R. A. Franz, and E. V. Brown, *J. Am. Chem. Soc.*, **57**, 1146 (1935).

(10) H. B. Hill and R. W. Cornelison, *Am. Chem. J.*, **16**, 188, 277 (1894).

(11) L. Wolff and W. Schimpff, *Ann.*, **316**, 151 (1901).

(12) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 503 (1946).

(13) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *ibid.*, 3646 (1950).

Triethylsilyltriethylgermane[1]

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We wish to report the synthesis and some properties of triethylsilyltriethylgermane which appears to be the

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(2) E. I. du Pont de Nemours and Co., Inc., Wilmington, Del.

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first fully alkylated mixed-metal compound of group IV-A metals reported to date. The compound was prepared by a mixed Wurtz coupling reaction of triethylbromosilane, triethylbromogermane, and sodium, in the absence of solvent, and was separated and purified by gas phase chromatography.

In the reaction of equimolecular quantities of triethylbromosilane and triethylbromogermane in the presence of a slight excess of sodium, it was found that the first product produced was hexaethyldigermane, followed by triethylsilyltriethylgermane, and then hexaethyldisilane. The possibility that the triethylsilyltriethylgermane arises by cleavage of hexaethyldigermane was ruled out by examining the reaction of triethylbromosilane, hexaethyldigermane, and sodium at 230–260°. The only product produced was hexaethyldisilane with no evidence for the cleavage of the digermane. It appears, therefore, that in the reaction of triethylbromosilane, triethylbromogermane, and sodium, three coupling reactions compete to produce the digermane, mixed-metal compound, and the disilane in decreasing rates, respectively.

Hexaethyldigermane was prepared by coupling triethylbromogermane in the presence of lithium in tetrahydrofuran (THF). In an effort to prepare hexaethyldisilane by the same method, it was found that the major product consisted of tetrahydrofuran cleavage products containing silicon. Infrared, partial elemental analysis (C, H only), and molecular weight data on the two major components indicate they are butoxytriethylsilane derivatives.[4] This result contrasts with that reported for the reaction of triphenylsilyllithium with tetrahydrofuran where the major product is 4-triphenylsilylbutanol-1.[5] This difference can be accounted for in terms of the greater stability of the triphenylsilyl anion compared to the triethylsilyl anion. In particular, triethylsilyl bromide may undergo preferential nucleophilic attack by tetrahydrofuran rather than significant metalation. The apparent absence of tetrahydrofuran cleavage products in the reaction of triethylbromogermane with lithium in tetrahydrofuran may be due to the greater ease of forming triethylgermyllithium which, in turn, more rapidly attacks triethylbromogermane than tetrahydrofuran.

The properties of the three ethylated intermetallics are summarized in Table I. An interesting fact is that the molar refraction [R_D] of the mixed-metal compound is very close to the average for disilane and digermane values. Similarly, the infrared spectrum of the mixed-metal compound appears, in general, to be a composite between those of the disilane and digermane. Distinguishing differences can however be noted at 15.2–15.4 μ (broad band), 10.65 μ (shoulder), 8.55 μ (weak band), and at about 8.25 μ (shoulder) for triethylsilyltriethylgermane in the liquid state.

TABLE I

PROPERTIES OF HEXAETHYLATED DISILANE,[a] SILYLGERMANE, AND DIGERMANE[a]

	B.p., °C. (760 mm.)	$n^{25}D$	d^{25}_4	[R_D]
$Et_3SiSiEt_3$	252.0	1.4771	0.8407	77.49
$Et_3SiGeEt_3$	254.5	1.4860	0.9791	80.65
$Et_3GeGeEt_3$	266.3	1.4952	1.1168	83.48

[a] Literature values: $Et_3SiSiEt_3$, b.p. 251.7° (760 mm.), $n^{20}D$ 1.4790; $Et_3GeGeEt_3$, b.p. 265° (760 mm.). H. C. Kaufman, "Handbook of Organometallic Compounds," D. Van Nostrand Company, Inc., 1961, pp. 617, 742.

(4) The indicated analytical evidence suggests that they are *n*-butoxytriethylsilane and its next higher homolog, 4-triethylsiloxybutyl *n*-butyl ether. One of the referees has suggested that the latter might instead be 4-triethylsiloxybutyltriethylsilane. Calcd. for $C_{16}H_{38}OSi_2$: C, 63.55; H, 12.63; mol. wt., 303.

(5) (a) H. Gilman, *et al.*, *WADC Technical Report*, 53-426, (June 1959); (b) H. Gilman and D. Wittenberg, *J. Am. Chem. Soc.*, **80**, 2677 (1958).

Experimental[6]

Hexaethyldigermane.—Two methods were used. The first method consisted of refluxing triethylbromogermane and sodium for 6 days followed by distillation of the product.[7] Triethylbromogermane was prepared in near quantitative yield by brominating tetraethylgermane in ethyl bromide with an equimolecular quantity of bromine. The second method, which was similar to that employed for the preparation of hexaphenyldisilane,[8] consisted of reacting triethylbromogermane with lithium in tetrahydrofuran. To a solution of 12.0 g. (0.05 mole) of triethylbromogermane in 50 ml. of tetrahydrofuran was added 0.35 g. (0.05 g.-atom) of lithium under argon. After dissolution of the lithium, the mixture was refluxed about 6 hr. The tetrahydrofuran was removed at this point and the mixture heated until the pot temperature rose to 212° (2 hr.). The product was distilled *in vacuo* to yield 5 g. (63% yield) of hexaethyldigermane, b.p. 69–72° (0.1 mm.). Hexaethyldigermane was then purified to 99.9% purity or better by gas phase chromatography employing a 244 cm. long × 1.65 cm. i.d. preparative scale column packed with regular grade Chromosorb W (60–80 mesh) containing 20% by weight of a silicone rubber gum stock coating (Union Carbide, W95). The column was programmed to rise from 50–200° at a rate of 7.9°/min. (75 ml./min. helium flow). The retention time at 200° was 33.0 min.

Anal. Calcd. for $C_{12}H_{30}Ge_2$: C, 45.10; H, 9.46; mol. wt., 320. Found: C, 44.8; H, 9.50; mol. wt., 321 (osmometric).

Hexaethyldisilane.—A mixture of 19.5 g. (0.10 mole) of triethylbromosilane and 5.8 g. (0.25 g.-atom) of sodium was refluxed for 24 hr. during which time the temperature rose from 160–210°. The excess sodium and sodium bromide were removed by filtration and the residue was distilled *in vacuo* to yield about 7 g. (60% yield) of hexaethyldisilane, b.p. 67–70° (0.5 mm.). Hexaethyldisilane then was purified by gas phase chromatography employing the column described for hexaethyldigermane. The retention time of hexaethyldisilane at 200° (75 ml./min. He flow) was 25.5 min.

Anal. Calcd. for $C_{12}H_{30}Si_2$: C, 62.53; H, 13.12. Found: C, 62.48; H, 13.25.

Triethylsilyltriethylgermane.—A mixture of 19.5 g. (0.10 mole) of triethylbromosilane, 24.0 g. (0.10 mole) of triethylbromogermane, and 5.3 g. (0.23 g.-atom) of sodium was refluxed with stirring under argon. The original pot temperature was 178° and this slowly rose to 225° over a period of 5 days. The mixture was then cooled, taken up in diethyl ether, and filtered to remove excess sodium and sodium bromide. The filtrate was concentrated and distilled *in vacuo* to yield 24 g. of a fraction, b.p. 76–86° (0.50–0.35 mm.). Analysis of this fraction by gas phase chromatography (5% silicone rubber on Chromosorb W) indicated the presence of four components: the first amounting to 4% by weight (retention time, 20.3 min.); the second 28% by weight (retention time, 25.5 min.); the third 27% by weight (retention time, 29.0 min.); and the fourth 42% by weight (retention time, 33.0 min.). The first component was tentatively identified as the cyclic tetramer of diethylsiloxane, $[Et_2SiO]_4$,[9] by infrared analysis and molecular weight determination, the second as hexaethyldisilane, and the fourth as hexaethyldigermane—the latter two having the same retention times as authentic samples of the two compounds. The third component was separated and repurified by gas phase chromatography employing the column

(6) All boiling points are uncorrected but were determined by the same method.

(7) C. A. Kraus and E. A. Flood, *J. Am. Chem. Soc.*, **54**, 1635 (1932).

(8) (a) M. V. George, D. J. Peterson, and H. Gilman, *ibid.*, **82**, 403 (1960); (b) H. Gilman, D. J. Peterson, and D. Wittenberg, *Chem. Ind.* (London), 1479 (1958).

(9) This product whose assignment is tentative was also present in the hexaethyldisilane preparation but not in that of hexaethyldigermane. Accordingly, it is believed to arise either from an impurity in the starting triethylbromosilane or by a catalytic breakdown of the silicone rubber packing.

described for digermane. The separation was conducted at 185° at a flow rate of 450 ml./min. of helium and yielded triethylsilyltriethylgermane of 99.9% purity or better, the retention time being 54.2 min.

Anal. Calcd. for $C_{12}H_{30}SiGe$: C, 52.40; H, 10.99; mol. wt., 275. Found: C, 52.15; H, 10.89; mol. wt., 279 (osmometric).

The other properties of this compound are shown in Table I and are compared with those of hexaethyldisilane and hexaethyldigermane.

Repetition of this experiment with periodic removal of aliquots which were analyzed by gas phase chromatography showed that hexaethyldigermane was formed first, the mixed metal compound second, and the disilane was formed last.

Two subsequent runs were made employing 0.19 mole of triethylbromogermane, 0.19 mole of triethylbromosilane, and 0.48 g.-atom of sodium at 175–230° for 2 days, and 0.23 mole of triethylbromogermane, 0.23 mole of triethylbromosilane, and 0.43 g.-atom of sodium at 175–195° for 8 days. In the first of these runs, 38 g. of high boiling product was obtained consisting of 7% by weight $[Et_2SiO]_4$, 28% by weight $Et_3SiSiEt_3$, 21% by weight $Et_3SiGeEt_3$, and 44% by weight $Et_3GeGeEt_3$. In the second run, 35 g. of high boiling product was obtained consisting of 19% by weight $[Et_2SiO]_4$, 7% by weight $Et_3SiSiEt_3$, 21% by weight $Et_3SiGeEt_3$, and 54% by weight $Et_3GeGeEt_3$.

Attempted Preparation of Hexaethyldisilane.—A mixture of 19.5 g. (0.10 mole) of triethylbromosilane, 50 ml. of tetrahydrofuran and 2.1 g. (0.30 g.-atom) of lithium was refluxed under argon overnight. The slightly colored mixture was then added to diethyl ether, filtered to remove lithium bromide, and distilled to yield several products, b.p. 65–130° (50–0.3 mm.). The infrared spectrum of each of the two major fractions, b.p. 82–90° (0.3 mm.) and 104–115° (0.3 mm.), $n^{25}D$ 1.4465, had strong bands at 9.25 and 10.0 μ, indicative of the presence of C–O–C and Si–O–C groups, respectively. There were no bands indicative of OH groups in the 3-μ region. The molecular weights (ebulliometric in chloroform) were 215 and 250, respectively. The higher boiling fraction had the following analysis consistent with that calculated for 4-triethylsiloxy-*n*-butyl ether.[4]

Anal. Calcd. for $C_{14}H_{32}O_2Si$: C, 64.56; H, 12.39; mol. wt. 260. Found: 64.22; H, 12.99; mol. wt., 250 (ebulliometric).

Attempted Preparation of Triethylsilyltriethylgermane by Cleavage of Hexaethyldigermane.—A mixture of 17.8 g. (0.056 mole) of hexaethyldigermane, 23 g. (0.118 mole) of triethylbromosilane, and 1.1 g. (0.048 g.-atom) of sodium was refluxed for 24 hr. Analysis of an aliquot indicated the presence of a small amount of the disilane with none of the mixed-metal compound present. Two additional increments of 1.1 g. (0.048 g.-atom) of sodium were then added in 24-hr. intervals while continuing to reflux the reaction mixture. Analysis after each of these 24-hr. intervals indicated that the disilane content increased with no change in the digermane content. In no case was there any evidence for the presence of triethylsilyltriethylgermane by gas phase chromatography.

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Chlorination of 2,3-Dimethylpyrazine

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Upon reinvestigation of the reaction of chlorine and 2,5-dimethylpyrazine, Hirschberg and Spoerri[3] found that a rapid, exothermic reaction took place, even in the absence of light, to yield 2-chloro-3,6-dimethylpyrazine. 2-Methylpyrazine was found to undergo a similar reaction to yield 2-chloro-3-methylpyrazine. When the reaction was extended to 2,6-dimethylpyrazine, however, it was found that the reaction proceeded extremely slowly until the solution was irradiated with ultraviolet light. The product of this reaction was shown to be the unstable 2,6-bis-(α-chloromethyl)-pyrazine. Accordingly, it seemed of interest to extend this work to the remaining dimethyl isomer, 2,3-dimethylpyrazine (I). This compound was prepared by a sequence of reactions first described by Gabriel and Sonn[4] in 1907.

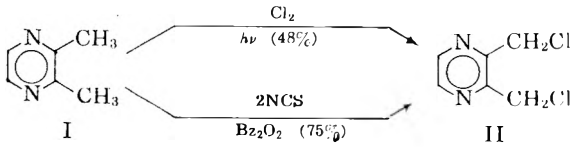
However, in order to obtain high yields of I several modifications of Gabriel's procedure were necessary. The preparation is described in the experimental part. A number of attempts to prepare I according to a recent procedure by Ishiguro and Matsumura[5] gave unsatisfactory yields.

In the manner specified by Hirschberg and Spoerri,[3] chlorine was rapidly bubbled through a solution of I in carbon tetrachloride in the absence of light. After an initial evolution of heat, no precipitate was observed to form. Passage of chlorine was continued for an additional 20 min. after which only a small amount of a white precipitate had formed. The solution was then illuminated with ultraviolet light and the passage of chlorine resumed. This apparently speeded the reaction for within 20 min. a substantial amount of a white solid precipitated. In order to insure completeness of the reaction, the passage of chlorine was continued for an additional 100 min. Examination of the white precipitate showed it to be a hydrochloride of I.

Evaporation of the carbon tetrachloride filtrate left a residual, lachrymatory oil, which polymerized to a tacky solid on standing and which could not be distilled. By analogy with the α-chloromethylpyrazines[3] it seemed that this material was 2,3-bis-(α-chloromethyl)pyrazine (II) and, accordingly, it was treated with an excess of sodium ethoxide in absolute ethanol.

The stable liquid obtained from this alcoholysis exhibited a strong peak in the infrared at 1102 cm.$^{-1}$ consistent with an aliphatic ether.[6] Elemental analysis showed it to be a bisether and, hence, that the oil originally obtained was 2,3-bis-(α-chloromethyl)pyrazine.

In order to verify this, I was treated with two equivalents of N-chlorosuccinimide and a catalytic amount of benzoyl peroxide in carbon tetrachloride. The unstable, lachrymatory oil thus obtained afforded the same bisether previously obtained as shown by a comparison of their infrared spectra.



(1) (a) The work herein reported is based on a thesis submitted by Robert A. Pages in partial fulfillment of the requirements for the degree of Bachelor of Science (Chemistry) at the Polytechnic Institute of Brooklyn, June, 1962; (b) National Science Foundation Undergraduate Summer Research Program participant, 1961.

(2) To whom inquiries should be addressed.

(3) A. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 2356 (1961).

(4) S. Gabriel and A. Sonn, *Ber.*, **40**, 4855 (1907).

(5) T. Ishiguro and M. Matsumura, *Yakugaku Zasshi*, **78**, 229 (1958); *Chem. Abstr.*, **52**, 11862a (1958).

(6) N. B. Colthup, *J. Opt. Sci. Amer.*, **40**, 397 (1950).

For purposes of comparison, the monoethyl ether was also prepared with one equivalent of N-chlorosuccinimide and alcoholysis of the resulting unstable, lachrymatory oil. The stable liquid thus obtained exhibited a strong peak in the infrared at 1100 cm.$^{-1}$ consistent with an aliphatic ether.[6] This was verified by elemental analysis.

Experimental[7]

A. 2,3-Dimethylquinoxaline.—In 2 l. of 2.5% acetic acid, 135 g. of *o*-phenylenediamine (1.25 moles) was dissolved at 65°. A solution of 107.6 g. of biacetyl (1.25 moles) in 750 ml. of water was added, with stirring, over a period of 15 min. The mixture was stirred for an additional 15 min., neutralized with 20% potassium hydroxide, and allowed to stand overnight at 5°. The crude product was filtered, washed with cold water, and recrystallized from aqueous ethanol after treatment with Norit. The product, which crystallizes as the dihydrate, was dried at 60° overnight and was found to weigh 180 g. (91%). It had a melting point of 105.5–106.5° (lit. m.p. 106°).

B. 5,6-Dimethylpyrazine-2,3-dicarboxylic Acid.—2,3-Dimethylquinoxaline (40 g., 0.253 mole) was dissolved in 2 l. of water at 80° in a 3-l. flask fitted with an efficient stirrer and a thermometer. Potassium permanganate (240 g., 1.52 moles) was added in 3–5-g. portions with vigorous stirring at a rate sufficient to maintain the temperature at 85°. The addition required 1.5–2 hr. The reaction mixture was then stirred at 90° for an additional hour. The hot mixture was filtered and the cake of manganese dioxide washed with hot water until the test washings no longer gave a pink color with 1% ferrous sulfate solution. The combined filtrate and washings were evaporated to about 1 l. under reduced pressure and 126 ml. of 37% hydrochloric acid (1.52 moles) cautiously added with stirring. Evaporation under reduced pressure was continued until 500 ml. remained. The mixture was then cooled and the crude diacid–dihydrate removed by filtration. The filtrate was evaporated to dryness under reduced pressure. Fifty milliliters of water was added followed by 750 ml. of acetone and the mixture refluxed 15 min., filtered, and the filtrate evaporated to dryness. The resulting solid was dissolved by refluxing in 750 ml. of acetone, treated with Norit, filtered, and evaporated to dryness to yield the acid as a light tan crystalline solid. The crude product was recrystallized from water after treatment with Norit and dried in a vacuum desiccator over Drierite. The pure product weighed 34 g. (69%) and had a melting point of 192–193° dec. (lit.[8] m.p. 190°); neut. equiv., 98.51 (theoretical 98.08).

C. Derivatives of 5,6-Dimethylpyrazine-2,3-dicarboxylic Acid.

1. **Anhydride.**—Anhydrous acid (4.90 g., 0.025 mole) in 15 ml. of acetic anhydride was heated on a water bath for 4 hr., cooled at 0°, and filtered to yield 2.8 g. of colorless crystals having a melting point of 171–171.5°. Evaporation of the mother liquor followed by treatment with Norit yielded an additional 0.94 g. of anhydride; total yield, 3.74 g. (84%).

Anal. Calcd. for $C_8H_6N_2O_3$: C, 53.94; H, 3.40; N, 15.73. Found: C, 54.00; H, 3.48; N, 15.71.

2. **Methyl Hydrogen Ester.**—One gram of anhydride (0.006 mole) was refluxed in 5 ml. of absolute methanol for 15 min. and evaporated to dryness on a water bath. The residue was recrystallized from benzene–cyclohexane to yield 0.97 g. (82%) of colorless crystals melting at 107–107.5°; neut. equiv., 208.9 (theoretical 210.2).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found; C, 51.38; H, 4.86; N, 13.31.

D. 2,3-Dimethylpyrazine.—Anhydrous 5,6-dimethylpyrazine-2,3-dicarboxylic acid (58.9 g., 0.30 mole) was refluxed in 350 ml. of quinoline, under a stream of nitrogen, until no more carbon dioxide was evolved (approximately 4 hr.). The mixture was then carefully fractionated under vacuum to yield 30.2 g. (93%) of 2,3-dimethylpyrazine (I) boiling at 45–46.5° (11 mm.).

Physical properties: b.p. 155.5–156.5° (lit.[9] 156°); $n^{20}D$ 1.5076; d^{25}_4 1.005.

I was identified by preparation of a picrate, m.p. 149.5–150.5° (lit.[9] 150°).

A methiodide was prepared by a method given by Shriner, Fuson, and Curtin[10] which had m.p. 183–184°.

Anal. Calcd. for $C_7H_{11}N_2I$: N, 11.22. Found: N, 11.21.

E. 2-(α-Chloromethyl)pyrazines. 2-(α-Chloromethyl)-3-methylpyrazine and 2,3-bis(α-chloromethyl)pyrazine (II) were prepared by the reaction of N-chlorosuccinimide with an equimolar quantity of 2,3-dimethylpyrazine (I), using a catalytic amount of benzoyl peroxide (procedure A). In addition, 2,3-bis(α-chloromethyl)pyrazine (II) was also prepared by treatment of I with chlorine in the presence of ultraviolet light (procedure B).

These α-chloromethylpyrazines are unstable, lachrymatory oils, which decompose on standing, and could not be purified by fractional distillation. Accordingly, after isolation, they were immediately used in the preparation of the corresponding pyrazinylmethyl ethyl ethers.

Procedure A. All (α-Chloromethyl)pyrazines.—I (5.4 g., 0.05 mole) in 250 ml. of carbon tetrachloride containing 1 or 2 equivalents of N-chlorosuccinimide and 0.1 g. of benzoyl peroxide was refluxed 12 hr., cooled to 0°, filtered, and the residue washed with two additional 25-ml. portions of carbon tetrachloride. The combined filtrate and washings were evaporated under vacuum at room temperature. The residual oils were immediately used for the preparation of the corresponding ethyl ethers. The yields of these oils ranged from 75–80% (assuming the oils to be pure).

Procedure B. 2,3-Bis-(chloromethyl)pyrazine.—To 250 ml. of carbon tetrachloride was added 10.8 g. of I (0.1 mole). Chlorine was rapidly bubbled in through a sintered glass gas addition tube while the flask was irradiated with ultraviolet light (Burdick-Type QA-250N). A white precipitate formed after only a few minutes. The passage of chlorine was continued for 2 hr. The mixture was then filtered and the residue washed with two 50-ml. portions of fresh carbon tetrachloride. The filtrate and washings were evaporated under reduced pressure leaving 4.0 g. II as a yellow oil which was immediately used in the preparation of the corresponding ethyl ether. A 23% conversion to II was obtained, based on recovery of 5.6 g. I from its hydrochloride. The yield was 48% (assuming the oil to be pure).

F. 2,3-Bispyrazinylmethyl Ethyl Ether.—To 0.12 mole of sodium ethoxide in 200 ml. of absolute ethanol was added 0.035 mole of II (6.2 g.) in 25 ml. of absolute ethanol and the mixture refluxed 12 hr., cooled, filtered, and the residue of sodium chloride washed with several portions of absolute ethanol. The combined filtrate and washings were diluted with 25 ml. of water and concentrated on a water bath until most of the alcohol had been removed. The residual oil was then extracted from the alkaline, aqueous layer with diethyl ether. The ether extracts were dried over anhydrous magnesium sulfate and concentrated on a water bath. The residual oil was then carefully fractionated to yield 1.4 g. (20%) of the bisethyl ether which had a boiling point of 115–116° (10 mm.), $n^{20}D$ 1.4890.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found; C, 61.15; H, 8.31; N, 14.41.

(7) All melting points are corrected. Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(8) K. A. Böttcher, *Ber.*, **46**, 3084 (1913).

(9) Jorre, Dissertation, Kiel, 1897; Beilstein's "Handbuch der organischer Chemie," 4th Ed., Springer Verlag, Berlin, 23, p. 59.

(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 228.

The Cleavage of Aryl Ethers by Alkali Metals in Aliphatic Ether Solvents. Detection by Electron Spin Resonance[1]

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The cleavage of aryl ethers by alkali metals in inert solvents at room temperature was detected by electron

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spin resonance techniques. Some aryl ethers have previously been cleaved by alkali metals,[3] but only under extreme conditions and with no immediate indication of products. In the present research, the cleavage of several types of aromatic ethers was investigated in a variety of inert aliphatic ether solvents employing the alkali metals lithium, sodium, potassium, rubidium, and cesium (Table I). The reaction was first detected in a study of spin exchange in the singly and doubly charged anions of biphenylyl ether.[4]

TABLE I
PRODUCT ANALYSES

Aryl ether	Alkali metal	Products, % ArOH	ArH	ArAr
$(p\text{-}PhC_6H_4)_2O$	Li, Na, K, Rb	60.2	36.0[a]	6.6
$(\beta\text{-}C_{10}H_7)_2O$	Na, K	56.2	42.2[a]	13.8
$(\alpha\text{-}C_{10}H_7)_2O$	Na, K	43.1	6.3[a]	31.9
$(p\text{-}NO_2C_6H_4)_2O$	Na, K, Cs	Negative ion, no cleavage		
$C_6H_5OCH_3$	Na, K	9.7	[c]	[a,b]
$(C_6H_5)_2O$	Na	7.6	[c]	[a,b]

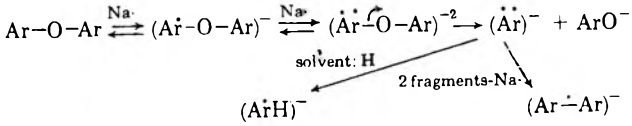
[a] Product detected as negative ion. [b] Incomplete cleavage, yields based on 100% ether initially. Solvents used were 1,2-dimethoxyethane, tetrahydrofuran, tetrahydropyran, and 2-methyltetrahydrofuran. [c] Not detected.

The products of the reaction were, in each case examined, the arylphenol, the aryl hydrocarbon, and small amounts of unidentified high melting neutral material. Product yields and reactivity were greatest with the larger aryl groups—60% *p*-phenylphenol from biphenylyl ether to *ca.* 8% phenol from diphenyl ether. In the case of anisole and diphenyl ether, some unchanged material was recovered. Bis-(*p*-nitrophenyl) ether formed a mononegative ion which failed to cleave and decomposed (losing radical activity) on standing several days. Even the most rigorous conditions, cesium and dimethoxyethane did not succeed in cleaving this ether.[5] Anisole remained completely inert to sodium in tetrahydrofuran, even after standing one week and after subjection to temperatures from −80 to 50°, but reacted readily with potassium in dimethoxyethane. A transient deep yellow color was observed initially in the latter experiment, but, if this species was paramagnetic, it could not be detected, since the immediate formation of biphenyl negative ion covered any other species with its strong signal. Diphenyl thioether (diphenyl sulfide) in dimethoxyethane under treatments similar to those of anisole, yielded no paramagnetic products. The reaction rate depended in some measure upon the solvent in the approximate order dimethoxyethane > tetrahydrofuran > tetrahydropyran ≥ methyltetrahydrofuran[6,7]; however, solvent variation alone did not appear to change significantly the relative product ratios of per cents. The alkali metals were found to be reactive in the order expected: lithium < sodium < potassium < rubidium ≤ cesium.

Several color changes were evident during the reaction stages. In general, the singly charged negative ion was amber or orange, whereas the dinegative ion (detected only with the larger aryl groups) was a greenish color. The color of the product mixture was generally very dark green or blue, owing to the predominant color of the aryl hydrocarbon or the diaryl negative ions.

Stages of reaction were easily followed with e.s.r. signals typical of the compounds under study.[4,8] In the carefully studied case of β-naphthyl ether, increasing reduction of the ether to the orange paramagnetic ion resulted in increasing signal amplitude until the formation of green diamagnetic dinegative ion caused a decrease in signal strength. Further reduction of the mixture resulted in immediate cleavage of the ether and appearance of a strong naphthalene negative ion spectrum. An attempt to produce a paramagnetic negative ion of sodium β-naphtholate resulted only in a diamagnetic and very fluorescent material; therefore, it is not likely that the presence of phenolate anions in the product mixtures would interfere with the hydrocarbon spectra.

Product analysis and the e.s.r. spectra indicate that the reaction proceeds through a heterolytic cleavage of the aryl carbon–oxygen bond of the dinegative ion. During cleavage the two paired electrons are most likely localized in the aryl, rather than the aryloxy, fragment. The aryl fragment may then extract a



hydrogen atom from the solvent or combine with another aryl fragment to form the products obtained. The high-melting neutral products (unidentified) noted earlier are compounds which probably result from combination with aryl fragments of solvent radicals generated by hydrogen atom extraction.

$$(\dot{A}r)^- \xrightarrow{\text{solvent:H}} (\dot{A}rH)^- + (\text{solvent}\cdot)$$

In the cleavage of 1-naphthyl ether only the strong signal of naphthalenide ion was detected in the product mixture; however, product analysis indicated that 1,1′-dinaphthyl was the more abundant product. Consequently, experiment proved that somewhat less of an equivalent of naphthalene added to one equivalent of 1,1′-dinaphthylide ion indeed resulted in exchange of the electrons to naphthalene. Studies are being undertaken to determine the reason for this anomaly, since generally, the larger aryl system possesses the greater electron affinity.[9]

Experimental

General Remarks.—All samples were prepared in a glass apparatus described previously[7] for use in an instrument described earlier.[10] In those experiments in which the major products were separated and examined, 1 g. of sample was used; in those in

(3) P. P. Shorygin, *Ber.*, **57B**, 1627 (1924); *Comp. rend. acad. Sci. URSS.* **14**, 505 (1937) [*Chem. Abstr.*, **31**, 5777 (1937)]; M. Tomita, Y. Inubushi, and H. Niwa, *J. Pharm. Soc. Japan*, **72**, 206 (1952) [*Chem. Abstr.*, **47**, 6428g (1955)]; A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, **76**, 2973 (1954).

(4) D. H. Eargle, Jr., and S. I. Weissman, *J. Chem. Phys.*, **34**, 1840 (1961).

(5) Splitting by cesium (I = 7/2) was detected in the negative ion spectrum, which was much broader (47.8 gauss) than the potassium spectrum (30.9 gauss), but not quite so broad as the spectrum of cesium–nitrobenzene (53.9 gauss).

(6) N. D. Scott, J. F. Walker, and V. L. Hansley, *J. Am. Chem. Soc.*, **58**, 2442 (1936).

(7) D. E. Paul, D. Lipkin, and S. I. Weissman, *ibid.*, **78**, 116 (1956).

(8) N. M. Atherton and S. I. Weissman, *ibid.*, **83**, 1330 (1961); M. G. Townsend, *J. Chem. Soc.*, 51 (1962).

(9) G. J. Hoijtink, in private communication, reports noting this behavior of α-dinaphthyl.

(10) R. L. Ward and S. I. Weissman, *J. Am. Chem. Soc.*, **79**, 2086 (1957).

which the reaction was examined only by means of the e.s.r. signal, samples of 2–3-mg. size were used. The alkali metals, except for lithium, were distilled into the sample tubes under a vacuum of about 10^{-6} torr; lithium metal was carefully melted (with partial reaction with the glass) in a side-arm tube.

Cleavage of β-Naphthyl Ether.—As a typical example, the cleavage by sodium and subsequent work-up of β-naphthyl ether is described. After introduction of β-naphthyl ether (1.00 g., 0.0037 mole) into the sample tube, the system was outgassed and a small chunk (*ca.* 0.2 g.) of freshly cut sodium was distilled three times through constrictions in a side tube, each constriction being sealed off after use. About 4 cc. of dimethoxyethane was distilled into the sample tube (using liquid nitrogen as coolant), and the sample and solvent were thoroughly degassed. The sample tube was then sealed from the vacuum system and shaken two or three times to allow the solution to contact the metal mirror. An orange color immediately developed, which was found to be the color of the mononegative ion. Subsequent shaking caused the mixture to turn a dark blue-green, indicative of the formation of naphthalene negative ion. The mixture was shaken 1 hr. longer, and the sample tube was broken open and the contents exposed to air, whereupon the blue-green color rapidly disappeared. The mixture was neutralized with dilute sulfuric acid and 20 cc. of ether added to it. Extraction of the products was accomplished, first with sodium bicarbonate solution, then with sodium hydroxide, the neutral material remaining unchanged. The acidified bicarbonate extract in this case, as in all others, yielded only a very thin film (after evaporation of the ether solvent) having an odor of aliphatic acids. The acidified sodium bicarbonate extract yielded a white material, which, after sublimation, weighed 0.30 g., m.p. 122°. The melting point upon admixture with authentic β-naphthol was unchanged; yield, 56%. The ether was removed from the neutral material, which was fractionally sublimed. The first and easiest obtained fractions were of an aromatic white material, 0.20 g., m.p. 80–83°, mixture melting point with authentic naphthalene unchanged. Subsequent fractions yielded a white compound, 0.13 g., m.p. 181–183.5 (mixture melting point with β-dinaphthyl unchanged), and a small amount (0.01 g.) of very high-melting material which was not identified. We assume some product loss occurred during the work-up and sublimation procedure; the product yields are all based on pure material recovered.

Acknowledgment.—The author is indebted to Dr. S. I. Weissman and Dr. D. Lipkin for their assistance and guidance in this project and to the U. S. Air Force Office of Scientific Research and Development Command and the Office of Naval Research for support of this work.

The Conversion of 2-Acetoxypulegone to Menthofuran. Terpenes. V.[1]

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Menthofuran, II, has been prepared from isopulegone, I, and from pulegone, Ia, as shown in Diagram I.[4,5,6]

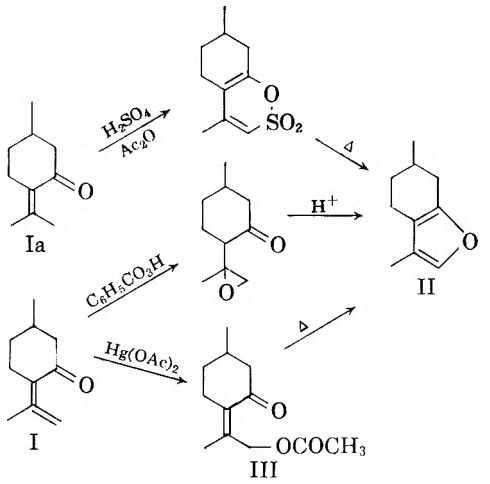
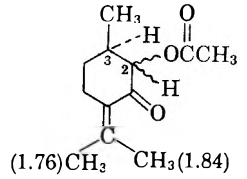


DIAGRAM I

We now report the isolation of optically pure menthofuran as the major product of the pyrolysis of 2-acetoxypulegone, V (Diagram 2). This unusual reaction prompted us to reinvestigate the structure of the product obtained by treating pulegone with mercuric acetate; structure V was assigned to this product by earlier workers.[7] Structure III previously had been assigned to the product obtained by treating isopulegone with mercuric acetate; on pyrolysis III gave menthofuran.

The product isolated on treatment of pulegone with mercuric acetate according to the procedure of Reitsema[7b] was found to have physical properties identical with those previously reported. However, gas chromatography (hydrogen flame detector) showed that it was a mixture containing approximately equal amounts of two components; attempts to separate these two compounds using column chromatography failed. Nevertheless, an examination of the n.m.r. spectrum of the product showed that III was not one of these components, and that the mixture consisted of the *cis* and *trans* isomers of 2-acetoxypulegone, V. The methyl protons of the isopropylidene group in V (*cis* and *trans* isomers) appeared at δ 1.76 (3 protons) and at δ 1.84 (3 protons). In both the *cis* and *trans* isomers the methyl protons of the isopropylidene group *cis* to the carbonyl group would be expected to show a paramagnetic shift compared with the methyl protons *trans* to the carbonyl group (see Diagram 2).[8] Structure III would be expected to show only three protons in this region of its n.m.r. spectrum. The protons of the C-3 methyl group in V ap-



Va *cis* (acetoxy group up)
CH_3 at C_3: δ 0.96; doublet
J = 7 c.p.s.
H at C_2: δ 5.10; doublet,
J = 5.5 c.p.s.
Vb *trans* (acetoxy group down)
CH_3 at C_3: δ 1.05; doublet
J = 5.5 c.p.s.
H at C_2: δ 4.64; doublet
J = 10.5 c.p.s.

DIAGRAM 2.—Position (δ) of protons in n.m.r. spectrum of 2-acetoxypulegone.

(1) Terpenes. IV. Constitution and Absolute Configuration of Eremophilenolide, *Tetrahedron*, in press. Terpenes. III, *Chem. Ind.* (London), 38 (1962). Terpenes. II, *J. Org. Chem.*, **27**, 3535 (1962). Terpenes. I, *ibid.*, **26**, 981 (1961).

(2) Holder of National Science Foundation Summer Fellowship for Graduate Teaching Assistants, Summer, 1962. National Institutes of Health Fellow, 1962–63.

(3) Participant in National Science Foundation College Chemistry Teachers Research Participation Program at Oklahoma State University, Summer, 1962.

(4) W. Treibs, *Ber.*, **70**, 85 (1937).

(5) H. Fritel and M. Fetizon, *J. Org. Chem.*, **23**, 481 (1958).

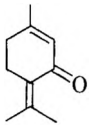
(6) W. Treibs, G. Lucius, H. Kogler, and H. Breslauer, *Ann.*, **581**, 59 (1953).

(7) (a) W. Treibs and H. Bast, *ibid.*, **561**, 165 (1949); (b) R. H. Reitsema, *J. Am. Chem. Soc.*, **79**, 4465 (1957).

(8) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Speetroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

peared as a pair of doublets. The *cis* isomer, Va (see Diagram 2), showed a doublet centered at δ 0.96 (J = 7 c.p.s., 1.8 protons), whereas the *trans* isomer, Vb, showed a doublet centered at δ 1.05 (J = 5.5 c.p.s., 1.2 protons). The proton at C-2 in the *cis* isomer appeared as a doublet centered at δ 5.10 (J = 5.5 c.p.s., 0.6 proton) whereas in the *trans* isomer it appeared as a doublet centered at δ 4.64 (J = 10.5 c.p.s., 0.4 proton). The coupling constants of *cis* 1,2 protons are known to be smaller than the corresponding *trans* isomers.[8] For structure III, one would expect an unsplit signal corresponding to two protons in this region of the n.m.r. spectrum.

Pyrolysis of the mixture of *cis*- and *trans*-2-acetoxypulegone gave essentially optically pure menthofuran, II, in 43% yield. The optical purity of the menthofuran shows that the reaction could not have proceeded *via* intermediate VI, the expected pyrolysis product.



VI

Examination of Dreiding models indicated that in *trans*-2-acetoxypulegone with the cyclohexane ring in a boat conformation, and in *cis*-2-acetoxypulegone with the cyclohexane ring in a chair conformation, the carbonyl group of the acetoxy group can be in close proximity to the hydrogen atoms of one of the methyl groups of the isopropylidene substituent. In the *trans* isomer, this carbonyl can actually approach a hydrogen atom of the isopropylidene group more closely than it can approach the *cis* hydrogen atom at C-3. The route shown in Diagram 3 is suggested.[9]

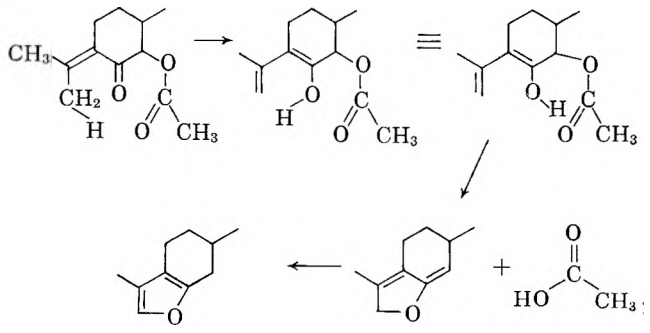


DIAGRAM 3

In view of our findings we decided to repeat the reaction of isopulegone with mercuric acetate to determine if the product was indeed III. Following the procedure previously described[6] a product was obtained which was identical in all respects with the product we obtained from pulegone, namely a mixture of *cis*- and *trans*-2-acetoxypulegone. In addition, the recovered unchanged starting material was found by gas chromatography to be approximately 80% pulegone and 20% isopulegone.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5 spectrophotometer; n.m.r. spectra were determined with the Varian A-60 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as an internal standard (δ = 0). Gas chromatograms, except where noted, were obtained with the Aerograph Hy-Fi gas chromatograph using a hydrogen flame detector and a column $^1/_8$ in. by 5 ft. of 5% SE-30 on acid-washed Chromosorb W, with hydrogen and nitrogen flow rates of 30 ml. per min.

2-Acetoxypulegone.—(+)-Pulegone was obtained by fractional distillation of oil of pennyroyal, and converted to 2-acetoxypulegone as described by Reitsema.[7b] The 2-acetoxypulegone used in the pyrolysis experiment had the following properties: b.p. 110–112° at 1.4 mm. (reported[7] 102° at 4 mm.); $[\alpha]^{25}D$ −14.46° (c 2.31 in ethanol) (reported[7] $[\alpha]^{25}D$ −15.88°); λ_{max}^{EtOH} 252 mμ, ε 6214 (reported[7] λ_{max}^{alc} 252 mμ, ε 6010). Gas chromatography at 170° showed two components in approximately equal amounts with retention times of 5 and 5.3 min.

Pyrolysis of 2-Acetoxypulegone.—A solution of 4.85 g. of 2-acetoxypulegone in 25 ml. of benzene was slowly passed through a 1.5 cm. × 17 cm. Pyrex column packed with $^3/_{32}$-in. glass helices, at 450°; the solution was forced through the column under positive nitrogen pressure. The gas chromatogram, using a thermistor detector, of the benzene eluent showed two components in the ratio of 0.33 to 0.67. The component in smaller amount was very similar in retention time to 3-methylcyclohexanone, and may be 3-methyl-2-cyclohexenone, which could arise by the formation of piperitenone followed by retroaldolization during the course of the pyrolysis. This product was shown not be be thymol by gas chromatographic comparison with an authentic sample. The component of longer retention time and in larger amount was found to be menthofuran. Removal of the benzene at reduced pressure also resulted in the removal of the compound of lower molecular weight, and gas chromatographic analysis showed only the presence of menthofuran with minor impurities (less than 5%). The benzene eluent was found to contain 1.5 g. of menthofuran (43% yield) and no unchanged 2-acetoxypulegone. Charred products remaining on the pyrolysis column presumably accounted for the remainder of the starting material. When the pyrolysis was conducted at temperatures lower than 450° unchanged 2-acetoxypulegone was found to be present according to the gas chromatogram.

The menthofuran had the following properties after distillation: λ_{max}^{EtOH} 220 mμ, ε 5852; $[\alpha]^{25}D$ +87.46° (c 1.87 in ethanol) (reported $[\alpha]^{25}D$ +81°[10a] for natural menthofuran, and $[\alpha]D$ +92 for menthofuran prepared from pulegenol sulfonic ester); the infrared spectrum was identical in all respects with that previously recorded[11]; the n.m.r. spectrum showed the methyl group on the cyclohexane ring as a doublet (J = 5.5 c.p.s.) centered at δ 1.07, the methyl on the furan ring as a doublet (J = 1 c.p.s.) centered at δ 1.85, and the aromatic hydrogen on the furan ring at δ 6.84. The autoxidation product (m.p. 186–187°) and maleic anhydride adduct (m.p. 132–133°) of the isolated menthofuran were identical in melting points to those previously reported.[10a,b]

2-Acetoxypulegone from Isopulegone.—(−)-Isopulegone was pared from isopulegol acetate as follows: a solution of 15.5 g. of isopulegol acetate, 2.4 g. sodium, and 30 ml. of 95% ethanol was refluxed for 4 hr. After cooling, the solution was adjusted to pH 6 with dilute sulfuric acid, and then extracted with ether. The ether extract, after washing with water and drying over anhydrous magnesium sulfate, gave on distillation 8.9 g. (73%) of isopulegol, b.p. 40–41° at 0.1 mm.; ν_{max}^{film} 3450, 1643, 890 cm.$^{-1}$.

A solution of 8.6 g. of isopulegol in 50 ml. dry acetone was cooled in an ice bath and treated with Jones' reagent[12] until the brown color persisted. Water was added and the solution extracted with ether. After washing with water and drying over anhydrous magnesium sulfate, the extract was distilled to give 5.1 g. (60%) of isopulegone, b.p. 52–54° at 0.7 mm.; ν_{max}^{film} 1710, 1643, 891 cm.$^{-1}$; $[\alpha]^{25}D$ +4.33° (c 2.50 in ethanol). This optical rotation indicates the presence of 11% (+)-iso-isopulegone, $[\alpha]D$ +144.4°, and 89% (−)-isopulegone, $[\alpha]D$ −13.5°.[13] The infrared spectrum and gas chromatogram of this product indicated the absence of any pulegone.

(9) We wish to thank the referee for suggesting such a mechanism.

(10) (a) P. Z. Bedoukian, *J. Am. Chem. Soc.*, **70**, 621 (1948); (b) R. B. Woodward and R. H. Eastman, *ibid.*, **72**, 399 (1950).

(11) Y. R. Naves, *Compt. rend.*, **237**, 704 (1953); *Soc. chim. France*, **1954**, 657.

(12) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, **1953**, 2555.

(13) G. Ohloff, J. Osiecki, and C. Djerassi, *Ber.*, **95**, 1400 (1962).

The prepared isopulegone was treated with mercuric acetate as previously described. The acetoxy ketone fraction obtained in 25% yield was found to be identical in infrared and n.m.r. spectra, and in its gas chromatogram with the product obtained from (+)-pulegone. The gas chromatogram of the residue showed only the presence of 80% pulegone and 20% isopulegone.

Reductions with Triphenyltin Hydride

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As part of a continuing study on the scope of hydrogenolyses with triphenyltin hydride we are reporting on the reactions of organo-isocyanates, isothiocyanates, and Schiff bases with triphenyltin hydride.

When phenyl isocyanate or α-naphthyl isocyanate was treated with two equivalents of triphenyltin hydride, the corresponding arylformamides were produced in 40–50% yield. This is distinctly different

$$\mathrm{Ar{-}N{=}C{=}O + 2\ Ph_3SnH \longrightarrow ArNHC(=O)H + (Ph_3Sn)_2}$$

Ar=Ph, α-Naphthyl

from the reaction of isocyanates with lithium aluminum hydride[4] which produces the corresponding N-methylamines. Another advantage of this reaction is that no hydrolysis step is required as in the case of lithium aluminum hydride reactions.

The reaction of phenyl isothiocyanate with triphenyltin hydride takes a different course. From this reaction mixture, hexaphenylditin, and bis-(triphenyltin) sulfide were isolated and identified by mixture melting points with known samples. This indicates that the carbon–sulfur bond is more labile than the carbon–oxygen bond to hydrogenolysis by triphenyltin hydride. In addition to the above products a basic liquid mixture which had a strong odor of an isocyanide was obtained. Infrared spectra indicated the presence of an aryl isocyanide and aromatic amines. Diazotization of the distilled reaction products and treatment with β-naphthol gave an orange product indicating the presence of a primary aromatic amine. Strong, but not completely conclusive, evidence for the identification of the products were the vapor phase chromatographs, using two different columns and three different temperatures, which showed three bands whose retention times in all cases matched those of known samples of aniline, N-methylaniline and phenyl isocyanide.

These reductions of the isothiocyanates by triphenyltin hydride may be contrasted with the reduction with lithium aluminum hydride which reacts with aryl isothiocyanates to give the corresponding N-methylamines.[5]

Since the presence of aniline in the reaction of triphenyltin hydride with phenyl isothiocyanate suggested the presence of a Schiff base as a possible intermediate, benzalaniline was treated with triphenyltin hydride. The product N-phenylbenzylamine was isolated in 35% yield. The low yield of the amine is probably due to decomposition of the hydride by the amine formed. This amine decomposition has been noted by a number of workers.[6] The other product of the reaction was hexaphenylditin, which was identified by mixture melting point with a known sample.

Experimental

α-Naphthyl Isocyanate with Triphenyltin Hydride.—α-Naphthyl isocyanate (3.38 g., 0.02 mole) was added to 14 g. (0.040 mole) of triphenyltin hydride and heated at 80° for 1 hr. Extraction of the cooled, completely solidified, reaction mixture with hot chloroform followed by filtration and cooling afforded a white solid, m.p. 210–220°. An additional crop, m.p. 200–210°, was obtained from the mother liquor. The chloroform was finally removed under vacuum leaving a yellow-white solid, melting at 118–124°. This solid was washed with ethanol leaving behind a white solid, m.p. 220–225°. The ethanol solution was concentrated depositing a white solid, m.p. 190–200°. Water was added to the hot ethanol solution until cloudy, and on cooling a needle-like crystalline product was obtained, m.p. 116–128°. This product was dissolved in hot ethanol (charcoal), and cooled to give a white product, m.p. 123–126°. Recrystallization from benzene–heptane gave 1.43 g. (41%) of colorless α-naphthylformamide, m.p. 137.8–138.5°, whose infrared spectrum was superimposable upon that of known α-naphthylformamide. A mixture melting point with authentic α-naphthylformamide showed no depression (1:1 mixture, m.p. 137.8–138.8°).

The combined solids melting around 200° were recrystallized four times from benzene–heptane to give hexaphenylditin, m.p. 228–231°. A mixture melting point with known hexaphenylditin showed no depression.

Phenyl Isocyanate with Triphenyltin Hydride.—A mixture of 2.4 g. (0.02 mole) of phenyl isocyanate and 15 g. (0.043 mole) of triphenyltin hydride was heated at 100° for 4 hr. On cooling, the reaction mixture solidified. It was extracted overnight with water in a Soxhlet extractor. Distillation of the water *in vacuo* gave a yellow oil, which was recrystallized from ether–pentane to give a product, m.p. 45.4–47.0°. Recrystallization from ether–pentane (charcoal) did not alter the melting point, 1.35 g. (55%). The infrared spectrum was superimposable upon that of known N-phenylformamide and admixture melting point with a known sample of N-phenylformamide showed no depression (1:1 mixture, m.p. 45.6–47.1°).

The hexaphenylditin left after extraction was recrystallized from benzene–heptane to give a product, m.p. 230–231°, showing no depression upon admixture with a known sample of hexaphenylditin.

Phenyl Isothiocyanate with Triphenyltin Hydride.—A mixture of 2.8 g. (0.02 mole) of phenyl isothiocyanate and 28 g. (0.080 mole) of triphenyltin hydride was heated at 90° for 3 hr. Upon cooling, the reaction mixture solidified. It was then heated to 170° under vacuum and the vapors were collected in a flask in a Dry Ice–acetone bath. Vapor phase chromatography of the liquid product, which smelled strongly of an isocyanide, showed three bands which were identified as aniline, N-methylaniline and phenyl isocyanide by comparison with the vapor phase chromatographic behavior of known standards, using two different columns [K-polyethylene glycol (Carbowax 1500), R-polyglycol (Ucon LB-550-X)] and three different temperatures (179°, 189°, 194°) for comparison. The infrared spectrum showed the presence of aromatic amines and an aromatic isocyanide [NH stretch 3450 cm.$^{-1}$ and 3400 cm.$^{-1}$ (shoulder), C—N 1345 cm.$^{-1}$ (primary amine) and 1265 cm.$^{-1}$ (secondary amine), R—N=C 2145 cm.$^{-1}$]. Diazotization of the distilled reaction products and treatment with α-naphthol gave rise to an orange product indicating the presence of a primary aromatic amine.

(1) Taken from a portion of the dissertation submitted to the faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, 1963.

(2) To whom inquiries should be sent.

(3) Sponsored by the U. S. Army Research Office (Durham), whose support we are happy to acknowledge.

(4) R. Wesseley and W. Swoboda, *Monatsh.*, **82**, 621 (1951).

(5) W. Ried and F. Müller, *Chem. Ber.*, **85**, 470 (1952).

(6) (a) A. Stern and E. I. Becker, *J. Org. Chem.*, **27**, 4052 (1962). (b) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *Rec. trav. chim.*, **81**, 853 (1962).

The solid reaction mixture left after the distillation was extracted with hot chloroform and filtered. On cooling it deposited a white solid melting 200–210°. Recrystallization of this solid from chloroform and then from benzene–heptane raised the melting point to 228–231°, which showed no depression on admixture melting point with known hexaphenylditin.

The chloroform filtrate was evaporated *in vacuo* and the resulting yellow solid was washed with ethanol leaving a white solid, m.p. 120–130°, and a yellow ethanol solution. Recrystallization of this white solid from benzene–heptane gave a product melting 143.5–145.0°. A mixture melting point with a sample of known bis-(triphenyltin) sulfide showed no depression.

Benzalaniline with Triphenyltin Hydride.—Benzalaniline (1.81 g., 0.10 mole) was mixed with 10.5 g. (0.030 mole) triphenyltin hydride and heated at 124° for 22 hr. On cooling, the reaction mixture solidified and was extracted with hot methanol. The solid remaining was recrystallized from chloroform and an admixture melting point with hexaphenylditin showed no depression.

The methanol solution was evaporated under vacuum leaving a brownish oil, which was taken up in ether and extracted with 10% hydrochloric acid. Treatment with 10% sodium hydroxide, extraction with ether, drying the ether layer over sodium sulfate, and distillation of the ether left a brownish red oil to which pentane was added. Upon standing in a refrigerator overnight, a solid was obtained, m.p. 32.6–35.3°. Recrystallization from ethanol–water gave 0.65 g. (35%) of colorless product, 35.4–36.5° (lit. 37°).

The **phenylthiourea derivative** was prepared by mixing 0.185 g. of the N-phenylbenzylamine with 0.135 g. of phenyl isothiocyanate and allowing the mixture to stand overnight. Addition of hexane with cooling and scratching gave a white solid with a melting point of 80–83°. Recrystallization from ethanol–water gave colorless crystals, m.p. 104.6–105.6° (lit. 103°).

Multi-nuclear Ferrocenes. I. Biferrocenyl[1a,b]

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In its initial isolation, biferrocenyl (I) was obtained in small yield during distillation of the reaction products produced from treatment of a mixture of lithio- and dilthioferrocene with tri-*n*-hexylbromosilane[2,3]; since publication of a preliminary account of this work,[4] a number of additional reports concerning biferrocenyl have appeared.[5–9] Russian workers prepared biferrocenyl *via* reaction of ammoniacal silver oxide with ferroceneboronic acid,[5,10] and by catalytic pyrolysis of diferrocenylmercury.[6,11] Shechter and Helling[8] have shown that biferrocenyl may be obtained from ferrocenyl Grignard reagents, while still another method for preparation of biferrocenyl parallels the Ullmann procedure for biaryls in that iodoferrocene is heated in the presence of activated copper bronze.[7,9]

Because of the increasing interest in biferrocenyl, and because our spectral data[13] have been used to establish identity of biferrocenyl obtained by various methods,[8,9,12] we wish to report the experimental evidence upon which our original structural assignment to biferrocenyl was based, and present additional evidence in confirmation of that structure.

Initial data (combustion analysis, molecular weight determinations, and infrared C—H stretching absorption)[4] were clearly consistent with the biferrocenyl formulation, and comparison of absorption intensities (absorbance) of the 9- and 10-bands[14] of biferrocenyl with those of ferrocene showed the unsubstituted ring content of the former to be equal to that of the latter (Table I).

TABLE I

9–10-BAND ABSORBANCE OF FERROCENE AND BIFERROCENYL[a]

Molarity	9-Band		10-Band	
× 10^{-3}	Ferrocene	Biferrocenyl	Ferrocene	Biferrocenyl
3.41	0.054	0.061	0.056	0.054
5.08	.082	.076	.082	.076
8.49	.134	.141	.136	.123
11.1	.176	.179	.177	.165
14.1	.222	.218	.223	.200

[a] Measurements carried out in carbon disulfide solution.

The possibility of fortuitous agreement in this case was ruled out by examining similarly the 9–10 infrared absorption of a variety of known ferrocene derivatives (see Experimental). For each compound a Lambert–Beer plot was made of absorbance *vs.* molarity (carbon disulfide solution). Straight line relationships were obtained, while upper limits of concentration were determined for ferrocene, palmitoylferrocene, and hexadecylferrocene. Deviations from linearity for these compounds occurred above concentrations of 14×10^{-3} *M* for the 9-band, and above concentrations of 22×10^{-3} *M* for the 10-band. Working concentrations for all compounds, therefore, were kept below these limits. Difficulties due to base-line variations were overcome by use of the so-called base-line technique introduced by Wright.[15] A more serious limitation, however, lay in the fact that in some cases the 9- and/or the 10-band may be greatly distorted by the close proximity of other absorption. In such cases quantitative use of the 9–10 Rule is not applicable. For this reason the

(1) (a) This research was supported in part by grants from Research Corporation (Frederick Gardner Cottrell Fund) and National Science Foundation (G-24083) for which the authors express sincere gratitude. Grateful acknowledgment is further made to National Science Foundation for an institutional grant which allowed purchase of the n.m.r. spectrometer used in this work; (b) preliminary aspects of this work were presented before the Division of Organic Chemistry, 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959; (c) Department of Chemistry, Bowdoin College, Brunswick, Me.; (d) National Science Foundation Undergraduate Research Participant.

(2) S. I. Goldberg, D. W. Mayo, M. Vogel, H. Rosenberg, and M. Rausch, *J. Org. Chem.*, **24**, 824 (1959).

(3) Formation of biferrocenyl, as described in this work, was first observed in 1957 by D. W. Mayo (Wright Air Development Center technical report 57-62, Part II, February, 1958; ASTIA document no. 150979). Efforts to accumulate additional material for investigation were aided by a subsequent preparation carried out by M. D. Rausch. In that case, tri-*n*-dodecylbromosilane was used instead of the tri-*n*-hexylbromosilane employed in the original and in subsequent runs.

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(6) O. A. Nesmeyanova and E. G. Perevalova, *ibid.*, **126**, 1067 (1959).

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(9) M. D. Rausch, *ibid.*, **26**, 1802 (1961).

(10) The experimental procedures originally reported in ref. 5 have been translated into German and republished [A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Chem. Ber.*, **93**, 2717 (1960)].

(11) Most of the work reported in ref. 6 has been repeated by M. D. Rausch.[12]

(12) M. D. Rausch, *Inorg. Chem.*, **1**, 414 (1962).

(13) Infrared and ultraviolet spectra of biferrocenyl are given in ref. 4.

(14) M. Rosenblum, Doctoral dissertation, Harvard University, 1953; K. L. Rinehart, Jr., K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957); M. Rosenblum and R. B. Woodward, *ibid.*, **80**, 5443 (1958); A. N. Nesmeyanov, L. A. Kazitsyna, B. V. Lokshin, and V. D. Vilchevskaya, *Dokl. Akad. Nauk, SSSR*, **125**, 1037 (1959).

(15) N. Wright, *Ind. Eng. Chem., Anal. Ed.*, **13**, 1 (1941).

9-bands of α-hydroxyethylferrocene and acetylferrocene were found to be unusable, but the 10-band of each gave satisfactory results. Likewise, while the 10-band of *p*-phenoxyphenylferrocene proved to be too distorted by other close-lying absorption, its 9-band gave the expected results.

It was found, not unexpectedly, that in quantitative comparisons of 9–10 absorption of two given ferrocene derivatives (one of which treated as an unknown), a lack of close agreement between absorbance was usually the case. Nevertheless, the ultimate determination—the number of unsubstituted cyclopentadienyl rings—is one for which a relatively large lack of precision may be tolerated. Differences in measured absorbance between compounds which contain an equal number of unsubstituted rings or between compounds which contain a 100% difference in the number of unsubstituted rings (one *vs.* two), fell between 15 and 25%. In no case, except in those with the serious band distortions noted above, was there any difficulty in judging the unsubstituted ring content of the "unknown."

These data, therefore, constituted the basis of our structural assignment to biferrocenyl.[4] Confirmation of that assignment may now be seen in the n.m.r. spectrum obtained from biferrocenyl.[16] The pattern of signals displayed—two symmetrical four-proton triplets (5.82 and 5.68 τ[17], J = 2 c.p.s.) arising from the two equivalent A_2B_2 systems[18] present in I, and a ten-proton signal (6.03 τ) due to the ten equivalent protons in the two unsubstituted rings of I—is typical of that given by a monosubstituted ferrocene.[19]

In view of the known high nucleophilic character of ferrocene, one may expect two directly bonded ferrocene nuclei to exert a mutal shielding effect on all protons present. That this is the case may be seen from the fact that the n.m.r. signal which arises from protons in the unsubstituted rings of biferrocenyl (6.03 τ) appears upfield from that due to the protons in ferrocene itself (5.95 τ). Assignment, therefore, of the higher field triplet (5.82 τ) is made to the α-protons and the lower field triplet (5.68 τ) to the β-protons.

The effect of conjugation between the two ferrocene nuclei of biferrocenyl may be seen from its ultraviolet spectrum.[13] The situation is analogous to the effect of conjugation between two benzene nuclei as seen in the ultraviolet spectra of benzene and biphenyl.[20] Benzene gives rise to a K-band at 202 mμ (log ϵ 3.8), while in biphenyl this band appears at 252 mμ (log ϵ 4.3). A similar bathochromic shift, as well as a similar increase in extinction, was found in a comparison of the ultraviolet absorption of ferrocene—K-band below 220 mμ (log $\epsilon \sim$ 3.7, cyclohexane)—with that of biferrocenyl–absorption shoulder at 257 mμ (log ϵ 4.1, cyclohexane).[21]

(16) N.m.r. spectrum of biferrocenyl [saturated solution in chloroform containing tetramethylsilane (3%, v./v.)], determined with a Varian A-60 spectrometer (room temperature probe).

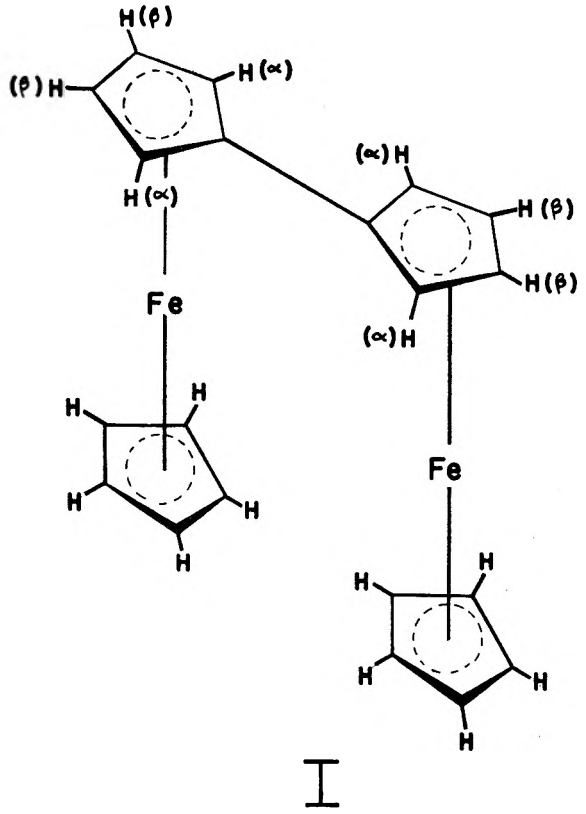
(17) G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

(18) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 92 ff.

(19) See for example the n.m.r. spectrum of *p*-nitrophenylferrocene in, "High Resolution N.M.R. Spectra Catalog," Varian Associates, Palto Alto, Calif.

(20) E. A. Braude in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, Inc., New York, N. Y., 1955.

(21) We are grateful to Prof. K. L. Rinehart, University of Illinois, for calling our attention to this analogy.



I

It is tempting to ascribe the mode of formation of biferrocenyl in this work to a free radical process. Although no direct evidence for participation of ferrocenyl free radicals was obtained, generation of this species *via* thermally induced homolysis of ferrocenyl–silicon bonds[22] was indicated by results of a separate experiment in which ferrocene was formed in 16% yield when pure tri-*n*-hexylsilylferrocene[2] was heated in air to about 250°. While no biferrocenyl was detected in the sublimate of ferrocene obtained, conclusions regarding its formation could not be drawn since the compound, if formed, would not have survived the conditions of the experiment. Other attempts to promote the suspected homolysis of ferrocenyl–silicon bonds, carried out in the absence of air, were not successful. Apparently, a limited amount of air or some other activating agent is required, while in the presence of air, enough for the formation of ferrocene, biferrocenyl is known to suffer decomposition. Homolytic cleavage of arene–silicon bonds also seems to be indicated by the formation of biphenyl during heating of 1,5-bis-(4-biphenylyl)hexamethyltrisiloxane.[23]

In this regard it is pertinent to note that all presently known methods for biferrocenyl production[6–8,12,24] also give rise to ferrocene. While it is true that co-formation of ferrocene and biferrocenyl was not reported in one case[9] which involved heating iodoferrocene in the presence of activated copper

(22) Generation of ferrocenyl free radicals *via* lithio- and dilithioferrocene, analogous to the work with dilithiobiphenyl [G. Wittig and G. Lehmann, *Chem. Ber.*, **90**, 875 (1957)], does not appear to be applicable here since no suitable metal halides were present in the reaction mixtures under discussion. Furthermore, attempts by Prof. P. D. Shaw (University of Illinois, personal communication) to promote coupling of the lithioferrocenes by introduction of various metal halides (*cf.*, Witting and Lehmann, ref. given) were not successful.

(23) R. L. Schaaf and P. T. Kan, Wright Air Development Center technical report 58-187, Part III, 1960, p. 27.

(24) A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **47** (1962).

bronze, Russian workers[7] have noted the formation of ferrocene in this modified Ullmann process. The reaction been repeated several times in this laboratory—each run giving rise to a significant amount of ferrocene in addition to biferrocenyl (Table II), even under conditions slightly milder than those previously reported.[7,9]

TABLE II

PRODUCTS FROM TREATMENTS OF IODOFERROCENE (20 G., 0.064 MOLE) WITH ACTIVATED COPPER BRONZE AT 90° DURING 24 HR. UNDER NITROGEN

	Biferrocenyl[a]		Ferrocene[a]	
Run	Grams	% Yield[b]	Grams	% Yield[b]
1	7.50	63.4	2.80	23.7
2	7.50	63.4	2.90	24.3
3	8.20	69.4	2.50	20.9

[a] Data obtained from purified products. [b] Calculations based on complete conversion of iodoferrocene.

Experimental[25]

Biferrocenyl from Silylferrocenes.—Isolation of biferrocenyl from the complex reaction mixtures obtained from treatment of lithioferrocenes with trialkylbromosilanes may be illustrated by one such procedure in which tri-*n*-hexylbromosilane was used. After preparation of a mixture of lithio- and dilithioferrocene by reaction of ferrocene (18.0 g., 0.097 mole) with *n*-butyllithium (0.71 mole), and then treatment with tri-*n*-hexylbromosilane (35.0 g., 0.096 mole), the reaction mixture was prepared for distillation as previously described.[2] Distillation was carried through collection of a forerun [150–165° (0.2 mm.)] and then collection of tri-*n*-hexylsilylferrocene [184–187° (0.05 mm.)]. At pot temperature of 200–220° (0.05 mm.) biferrocenyl appeared as an orange colored, crystalline sublimate in the column. After all of the material had sublimed and the apparatus was allowed to cool to room temperature, the sublimate was washed out in chloroform solution. Evaporation of the chloroform yielded 170 mg. of crude biferrocenyl (0.11% yield based on 0.097 mole of ferrocene). Initial purification, accomplished by chromatography on alumina and evaporation of the elution solvent, benzene, afforded reasonably pure biferrocenyl. Constant melting material (227.5–229.0°) was obtained, however, only after repeated recrystallizations from benzene–petroleum ether (b.p. 40–50°). Melting range determinations of biferrocenyl were carried out in carefully evacuated capillary tubes since decomposition of the compound (pure or slightly impure) usually started near 200° in the presence of air.

Anal. Calcd. for $(C_{10}H_9Fe)_2$: C, 64.91; H, 4.90; Fe, 30.19; mol. wt., 372. Found: C, 65.03; H, 5.08; Fe, 30.39; mol. wt. (cryoscopic), 385, 389 (camphor), and 397, 361 (naphthalene).

Ferrocene *via* Thermal Decomposition of Tri-n-hexylsilylferrocene.—Tri-*n*-hexylsilylferrocene[2] (5.00 g., 10.7 moles) was slowly heated in a 100-ml. flask fitted with an air condenser. The amber-colored fluid started to darken at about 220°, and decomposition proceeded rapidly near 250°. During the rapid period of the decomposition a mass of orange colored, crystalline material sublimed into the air condenser. The sublimate was collected and shown to be ferrocene (16% yield) by means of comparison of infrared spectra and by admixture melting with authentic material. An ultraviolet spectrum of the sublimate also was found to be identical with that of ferrocene. It did not exhibit any of the intense absorption characteristic of the presence of biferrocenyl.[4]

Similar treatment of another sample of tri-*n*-hexylsilylferrocene except that heating was carried out in an atmosphere of purified nitrogen, merely caused the material to reflux gently with no sign of decomposition.

Biferrocenyl and Ferrocene from Iodoferrocene.[26]—Iodoferrocene (20 g., 0.064 mole), prepared by means of treatment of chloromercuriferrocene[27] with iodine in methylene dichloride solution according to the procedure reported by Shechter and Helling,[8] and activated copper bronze[28] (40 g.) were intimately mixed and placed into a 100-ml. Kjeldahl flask. The flask and contents were flushed with purified nitrogen during 30 min. at room temperature, and then maintained under a slight head of nitrogen during 20 hr. while the system was heated at 90°. Some of the ferrocene formed during the reaction could be seen sublimed on the neck of the flask after several hours. When the reaction mixture had been allowed to cool to room temperature it was extracted with 15-ml. portions of warm benzene until the extracts appeared colorless. Evaporation of the combined extracts *in vacuo* yielded a mass of crystalline material which was dissolved in hot hexane and the resulting solution allowed to cool to room temperature. The initial crop of crystalline material was collected, and the supernatent reduced slightly in volume. This caused a second crop of crystalline material to be deposited which was collected, and again the volume of the supernatent reduced. By repeating this procedure many times it was possible to effect a clean separation between biferrocenyl and ferrocene, the former being less soluble in hexane. Individual crops were each recrystallized from hexane giving, in this representative run, purified biferrocenyl (7.5 g., 63.4%) and purified ferrocene (2.9 g., 24.3%) which each gave rise to infrared and ultraviolet spectra identical to those obtained from respective authentic samples.

TABLE III

COMPOUNDS USED

Compound	9-Band	10-Band
Ferrocene	9.012	9.942
Biferrocenyl	8.986	9.985
m-Tolylferrocene	9.029	9.978
Diferrocenylketone	9.025	9.971
2-Biphenylylferrocene	9.034	9.942
α-Hydroxyethylferrocene	9.036	9.977
Diferrocenylmercury	9.029	9.979
Palmitoylferrocene	9.027	9.976
Hexadecylferrocene	9.036	9.983
Chloromercuriferrocene	9.037	9.990
Trimethylsilylferrocene	9.025	9.975
Benzoylferrocene	9.019	9.963
Benzylferrocene	9.035	9.979
p-Phenoxyphenylferrocene	9.031	9.978
Acetylferrocene	8.996	9.968

Infrared Measurements.—All of the compounds examined (Table III) were samples of analytical purity. Measurements were carried out with a Perkin-Elmer Model 21 double beam recording spectrophotometer, equipped with a sodium chloride prism interchange unit. Absorption intensity data were recorded at the wave lengths given in Table III, with slit settings of 0.0212 and 0.0282 μ at 9 and 10 μ, respectively. Measurements were made from several concentrations (usually four) of each ferrocene derivative in solutions of purified carbon disulfide. The same liquid absorption cell of 1-mm. thickness was used throughout the study. Absorbences were calculated with the use of base lines[15] drawn in each case as nearly parallel as possible to the background radiation of the solvent. Background radiation was checked before and after a series of runs.

(25) All temperature readings are uncorrected. Analysis by the Schwartzkopf Microanalytical Laboratory, Woodside, N. Y. Molecular weight determinations by the Huffman Microanalytical Laboratories, Wheatridge, Colo.

(26) Procedure based upon those previously reported.[7,8]

(27) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Dokl. Akad. Nauk, SSSR*, **97**, 459 (1954).

(28) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., Inc., New York, N. Y., 1948, p. 188.

Preparation of Bicyclo[4.3.1]dec-7-en-10-one

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Although bicyclo[4.3.1]dec-7-en-10-one has not been reported, the preparation of a few derivatives has

been accomplished by alkylation of carbethoxycycloheptanone with either 1,3-dichloro-2-butene or 1-chloro-3-butanone followed by ring closure at the other α-carbon to give 1-carbethoxy-7-methylbicyclo[4.3.1]dec-7-en-10-one and the corresponding acid.[1]

Similarly, 1-carbethoxy-4-methylbicyclo[3.3.1]non-3-en-9-one and its acid, as well as the derivatives of larger carbethoxycycloalkanones, have been prepared.[1] Other bicyclo[3.3.1]nonane derivatives have become available through alkylation of carbethoxycyclohexanone with β-chloropropionaldehyde or β-chloropropionaldehyde diethyl acetal.[2,3]

Substitution of a methyl group for the carbethoxy group has also been shown to permit formation of a substituted bicyclo[3.3.1]nonane system.[4] When, however, the carbethoxy group or the methyl group is not present, cyclization preferentially is accomplished by reaction with the carbonyl group of the cyclic ketone rather than by reaction with the α-hydrogen. 2-(3-Chlorocrotyl)cycloheptanone, for example, gave bicyclo[5.4.0]undec-7-en-9-one,[1] and 2-(3-chlorocrotyl)cyclohexanone gave 45% of $\Delta^{1(9)}$-2-octalone and a trace of 4-methylbicyclo[3.3.1]non-3-en-9-one.[4] Examination of models indicates that the tendency to react with the α-hydrogen on the opposite side of the carbonyl carbon would be enhanced greatly if the 3-chlorocrotyl group is maintained in an axial position. Since, when there is neither a methyl nor a carbethoxy group present on the same α-carbon, the 3-chlorocrotyl group most likely would assume an equatorial position, it is reasonable that cyclization then would take place by reaction with the more accessible carbonyl group if a reaction path is available.

The use of 1,3-dichloropropene instead of 1,3-dichloro-2-butene for the preparation of bicyclic compounds offers the same advantages of an allyl halogen for the alkylation of the carbethoxycyclohexanone together with a vinyl halogen, inert in the initial alkylation but available for the later sulfuric acid-induced cyclization. Furthermore, 2-(3-chloroallyl)cycloheptanone does not have a methyl group available for reaction with the carbonyl group when the carbethoxygroup is absent, and the alternate mechanism of ring closure, therefore, is not available.

That the use of 1,3-dichloropropene is indeed a satisfactory method of preparing bicyclic compounds was established by preparation of the known 1-carbethoxybicyclo[3.3.1]non-3-en-9-one.[2] Once it was demonstrated that the method would work, 2-carbethoxy-2-(3-chloroallyl)cycloheptanone was prepared and stirred with sulfuric acid. Chromatographic analysis of the product mixture before distillation established the presence of a little 2-(3-chloroallyl)-cycloheptanone in addition to higher boiling materials. The heat of the fractional distillation, however, resulted in the formation of a compound not present before distillation. The new compound was identified as bicyclo[4.3.1]dec-7-en-10-one, derived from the loss of the carbethoxy group of the 1-carbethoxybicyclo-[4.3.1]dec-7-en-10-one formed in the cyclization.[5]

The preparation of bicyclo[4.3.1]dec-7-en-10-one from 2-(3-chloroallyl)cycloheptanone, however, proved to be a more economical method.[6] This preparation served both as a proof of structure of the product and as a means of establishing that the product resulted from the decarbethoxylation of 1-carbethoxybicyclo[4.3.1]-dec-7-en-10-one during fractionation, rather than from the cyclization of 2-(3-chloroallyl)cycloheptanone present before, or formed during distillation. The 2-(3-chloroallyl)cycloheptanone was fractionated through the same stainless steel sponge-packed column as the product mixture from the reaction of 2-carbethoxy-2-(3-chloroallyl)cycloheptanone without formation of any bicyclo[4.3.1]dec-7-en-10-one.

The identity of the products of the two methods was established by boiling points, refractive indices, identical gas chromatographic traces individually or mixed, and finally by mixture melting points and infrared spectra of their 2,4-dinitrophenylhydrazones.

Experimental[7]

Starting Materials.—1,3-Dichloropropene was obtained by the method of Hill and Fischer,[8] starting with epichlorohydrin (Eastman White Label) and by careful fractionation of "Flashed D-D" (Shell Chemical Co.). Both sources gave a chromatographically pure material that contained approximately equal quantities of the *cis* and *trans* isomers. Carbethoxycyclohexanone (Arapahoe Chemicals, Inc.) and cycloheptanone (Aldrich Chemical Co.) are available commercially. Carbethoxycycloheptanone was prepared from cycloheptanone and diethyl oxalate[9] (Eastman White Label) and carefully fractionated through a 23 × 1.5-cm. stainless steel sponge packed column to give a chromatographically pure liquid boiling at 105° (3 mm.), $n^{26}D$ 1.4685.

2-Carbethoxy-2-(3-chloroallyl)cyclohexanone.—Carbethoxycyclohexanone (170 g., 1 mole) was added to a hot solution of sodium (23 g., 1 g.-atom) in 700 ml. of absolute alcohol. When the initially formed solid went into solution, 1,3-dichloropropene (111 g., 1 mole) was added to the hot solution, and the mixture was left to reflux overnight. The mixture then was filtered and the alcohol removed by distillation. The residue was taken up in ether, washed with water, and left to dry over magnesium sulfate. Distillation[10] gave 127.9 g. (52.4%) of liquid boiling 146–164° (5 mm). Careful fractionation through the stainless steel sponge-packed column gave a chromatographically pure liquid boiling 148–154° (5 mm.), $n^{25}D$ 1.4471.

Anal. Calcd. for $C_{12}H_{17}ClO_3$; C, 58.90; H, 6.94. Found: C 58.91; H, 6.98.

Bicyclo[3.3.1]non-3-en-9-one-1-carboxylic Acid 2,4-Dinitrophenylhydrazone.—2-Carbethoxy-2-(3-chloroallyl)cyclohexanone (2.4 g.) was carefully laid on the surface of 10 ml. of concentrated sulfuric acid and left to stand at room temperature for 5 days. The mixture then was poured into ice–water and extracted with ether. The ether solution was washed with sodium bicarbonate solution and water and dried over magnesium sulfate. The residue[11] remaining after removal of ether was refluxed overnight with 10% hydrochloric acid. The mixture was then cooled, taken up in ether, and washed with sodium bicarbonate solution.

(1) V. Prelog, P. Barman, and M. Zimmerman, *Helv. Chim. Acta*, **32**, 1284 (1949).

(2) A. C. Cope and M. E. Synerholm, *J. Am. Chem. Soc.*, **72**, 5228 (1950).

(3) A. C. Cope and E. S. Graham, *ibid.*, **73**, 4702 (1951).

(4) S. A. Julia, *Bull. soc. chim. France*, 780 (1954).

(5) This decarbethoxylation was not altogether unexpected in view of similar experiences in the distillation of carbethoxycyclohexanone and carbethoxycycloheptanone in this laboratory and the not unrelated reversal of the condensation of nitromethane with cyclohexanone on distillation, T. F. Wood and R. J. Cadorin, *J. Am. Chem. Soc.*, **73**, 5504 (1951).

(6) Preliminary work with 2-(3-chloroallyl)cyclohexanone indicates a similar course of reaction with the formation of bicyclo[3.3.1]non-3-en-9-one.

(7) Melting and boiling points are not corrected. Microanalyses by Wieler and Strauss, Oxford.

(8) A. J. Hill and E. J. Fischer, *J. Am. Chem. Soc.*, **44**, 2582 (1922).

(9) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

(10) The crude material contains 2-(3-chloroallyl)cyclohexanone.

(11) Chromatographic analysis showed the reaction to be only about half complete. Most chromatographic analyses were done with a homemade unit with a 6-ft. column of Dow-Corning silicone stopcock grease on Johns-Manville Chromosorb at 200° with helium as the carrier gas. Several of the analyses were checked with a Perkin-Elmer vapor fractometer Model 154, using column R, polypropylene glycol.

Evaporation of the ether extract of the acidified sodium bicarbonate solution left a small (about 0.5 g.) residue which was taken up in alcohol and treated with the 2,4-dinitrophenylhydrazine reagent.[12] The resulting 2,4-dinitrophenylhydrazone, recrystallized from alcohol, m.p. 257–259 dec., gave no depression of melting point when mixed with an authentic sample.[13]

2-Carbethoxy-2-(3-chloroallyl)cycloheptanone.—Carbethoxycycloheptanone (31.3 g., 0.17 mole) was added to a hot solution of sodium (3.19 g., 0.17 g.-atom) in 100 ml. of absolute alcohol. After half an hour of heating, 1,3-dichloropropene (18.9 g., 0.17 mole) was added, and the mixture was left to reflux overnight. The usual work up followed by distillation gave 21 g. (47.7%) of colorless liquid boiling at 135–150° (4 mm.). Careful fractionation through the stainless steel sponge-packed column gave a chromatographically pure liquid boiling at 129° (1 mm.), $n^{23}D$ 1.4858.

Anal. Calcd. for $C_{13}H_{19}ClO_3$: C, 60.36; H, 7.34. Found: C, 60.42; H, 7.65.

2-(3-Chloroallyl)cycloheptanone.—Cycloheptanone (112 g., 118 ml., 1 mole) was added to a well stirred mixture of sodium amide (40 g., 1.02 moles) in 500 ml. of anhydrous ether. The mixture was refluxed for 4 hr. and then cooled in ice–water, with nitrogen flowing through the system, and treated with a solution of 1,3-dichloropropene (111 g., 1 mole) in 100 ml. of anhydrous ether. When the initial exothermic reaction had subsided, the mixture was left to reflux overnight. The mixture was then cooled and 500 ml. of water was added. The ether solution was washed with water and dried over magnesium sulfate. Distillation gave 25 g. of unchanged cycloheptanone and 86.8 g. (59.2%) of liquid boiling at 125–130° (10 mm.). Careful fractionation gave a chromatographically pure analytical sample boiling at 96° (2 mm.), $n^{22}D$ 1.4978.

Anal. Calcd. for $C_{10}H_{15}OCl$: C, 64.36; H, 8.04. Found: C, 64.46; H, 8.09.

Bicyclo[4.3.1]dec-7-en-10-one.—(a) 2-Carbethoxy-2-(3-chloroallyl)cycloheptanone (41.6 g., 0.16 mole) was added dropwise with stirring to 50 ml. of concentrated sulfuric acid. After the mixture had been stirred for 1 week at room temperature, the reaction was stopped by the addition of 500 ml. of cold water and the product was taken up in ether. The ether was washed with sodium bicarbonate solution[14] and water and dried over magnesium sulfate. Chromatographic analysis after removal of the ether revealed the presence of a little 2-(3-chloroallyl)cycloheptanone but no bicyclo[4.3.1]dec-7-en-10-one. Fractionation yielded 5.25 g. (21.7%) of bicyclo[4.3.1]dec-7-en-10-one,[15] boiling 100–105° at (4 mm.), $n^{24}D$ 1.5020, 2,4-dinitrophenylhydrazone m.p. 136–138, containing only a trace of 2-(3-chloroallyl) cycloheptanone and 10.9 g. of an inseparable[16] mixture[17] of starting material and 1-carbethoxybicyclo[4.3.1]dec-7-en-10-one boiling at 145–150° (4 mm.), $n^{24}D$ 1.4896.

(b) 2-(3-Chloroallyl)cycloheptanone (49 g., 0.263 mole) was added to 50 ml. of concentrated sulfuric acid and worked up as before. Chromatographic analysis of the product before distillation indicated approximately an equal mixture of unchanged starting material and product. Distillation gave 5.5 g. (14%) of good quality bicyclo[4.3.1]dec-7-en-10-one[18] boiling at 85–91° (2 mm.), $n^{23}D$ 1.5050, 2,4-dinitrophenylhydrazone, m.p. 136–138°. There was no depression of melting point on mixture with the 2,4-dinitrophenylhydrazone obtained from method a.

Acknowledgment.—This research was supported by a grant from The Alfred University Research Foundation.

(12) Shriner and Fuson, "Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, New York, N. Y., 1948, p. 171.

(13) Reported (ref. 2) 259–261°, dec.

(14) Only a trace of gummy material was obtained by acidifying the sodium bicarbonate solution.

(15) Bicyclo[4.3.1]dec-7-en-10-one begins to polymerize after only a few days at room temperature.

(16) With the available fractionating equipment.

(17) No trace of either 2-(3-chloroallyl)cycloheptanone or bicyclo[4.3.1]-dec-7-en-10-one was present in this fraction. A second distillation, with a purposely prolonged total reflux, however, resulted in contamination from both these materials.

(18) An 18.3-g. sample (46.4%) of liquid (of which the 5.5 g. was the best), slightly contaminated with 2-(3-chloroallyl)cycloheptanone, was actually isolated. Greater yields of highly pure product would be possible with better fractionating equipment.

Cyanoethylation of Butadiene Sulfone

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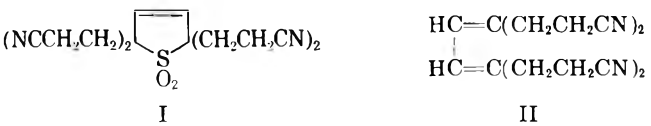
Although cyanoethylation of aryl sulfones[1] and 1,3,5-trimethylene trisulfones[2] has been described, the reaction of butadiene sulfone with acrylonitrile was reported to take another course.[3]

In this last study no definite crystalline addition compounds were found, but instead distillable products which appeared to be low-molecular weight polymers of acrylonitrile and butadiene sulfone. Copolymers of acrylonitrile and cyclic sulfones, containing at least 85% acrylonitrile, also have been claimed.[4]

This paper reports the preparation of a crystalline adduct by the base-catalyzed reaction of butadiene sulfone and four moles of acrylonitrile. It was postulated to be 2,2,5,5-thiophenetetrapropionitrile 1-dioxide (I) on the basis of analysis, infrared spectrum, and chemical behavior. Unlike previous products,[3] our product decomposed at the melting point, with evolution of gas, to form a new crystalline solid. Analysis, infrared and ultraviolet spectra, showed the new compound to be 1,4-tetrakis(2′-cyanoethyl)-1,3-butadiene [better name: 4,7-bis(2′-cyanoethyl)-4,6-decadienedinitrile] (II). The thermal decomposition of I into II constitutes strong evidence of the postulated structures, in view of the known[5] breakdown of simple diene sulfones into 1,3-dienes upon heating.

This two-step procedure provides a new method of preparing 1,4-substituted 1,3-dienes.



I II

Experimental[6]

2,2,5,5-Thiophenetetrapropionitrile-1,1-dioxide (I).—To a solution of 11.8 g. (0.10 mole) of butadiene sulfone (from the Phillips Petroleum Co.), 23.3 g. (0.44 mole) of acrylonitrile, and 50 ml. of acetonitrile was added a mixture of 1 g. of acetonitrile and 2 g. of a 40% solution of benzyltrimethylammonium hydroxide in methanol over a period of 3.5 hr. at 0–10°. The mixture was neutralized with acetic acid and filtered. The product (20% yield) was recrystallized from acetonitrile to give white crystals melting at 209.5–210°, decomposing with the evolution of gas.

Anal. Calcd. for $C_{16}H_{18}N_4O_2S$: C, 58.16; H, 5.49; N, 16.96; S, 9.70. Found: C, 58.40; H, 5.72; N, 17.53; S, 9.57.

Its infrared spectrum showed bands at 2255 cm.$^{-1}$ (nitrile), 1425 cm.$^{-1}$ (–CH_2CN), 1295 and 1130 cm.$^{-1}$ (sulfone), 958 and

(1) H. A. Bruson (to the Resinous Products and Chemical Co.), U. S. Patent 2,435,552 (February 3, 1948).

(2) H. T. Hookway and E. M. Evans (to British Resins Products Ltd.), U. S. Patent 2,468,015 (April 19, 1949).

(3) R. Wegler and H. Lafos (I. G. Leverkusen), 1944; referred to by O. Bayer, *Angew. Chem.*, **61**, 229 (1949).

(4)(a) A. Fournet and H. Lemoine (to Societe des Usines Chimiques Rhone-Poulenc) U. S. Patent 3,017,397 (January 16, 1962); (b) NOTE ADDED IN PROOF.—After this manuscript had been accepted, news of the preparation of compound I was received [Derwent, British Patent, Abstract 3, no. 5, Gp. 1, 2 (February 1, 1963)].

(5)(a) Badische Anilin- and Soda-Fabrik, German Patent 236,386; *Chem. Zentr.*, **II**, 316 (1911); (b) O. Grummitt, A. E. Ardis, and J. Fick, *J. Am. Chem. Soc.*, **72**, 5167 (1950).

(6) Melting points are corrected.

853 cm.$^{-1}$ (distinctive finger-print bands for this material), and 780 and 740 cm.$^{-1}$ (probably *cis* olefin). The expected cyclic olefin band at 1615 cm.$^{-1}$ was very weak.

4,7-Bis(2′-cyanoethyl)-4,6-decadienedinitrile (II).—When 8.9 g. (0.027 mole) of 2,2,5,5-thiophenetetrapropionitrile 1-dioxide was heated at 195–205°, 0.1-mm. pressure, for 4 hr., gas evolved leaving a crystalline solid (90% yield). After recrystallization from acetonitrile it melted at 150–151°.

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04; mol. wt., 266. Found: C, 72.21; H, 6.47; N, 20.72; mol. wt., 253 (thermistor micromethod[7] with acetonitrile as the solvent).

Its infrared spectrum showed bands at 2250 cm.$^{-1}$ (nitrile), 1605 cm.$^{-1}$ (conjugated diene), and 1425 cm.$^{-1}$ (—CH_2CN). There were no sulfone bands at 1295 and 1130 cm.$^{-1}$. The ultraviolet spectrum (in acetonitrile solution) showed bands at 243 mμ (sh, ε 27,500), 247 mμ (ε 28,900), and 255 mμ (sh, ε 20,200). This pattern is typical of a poly-substituted linear conjugated diene.

Acknowledgment. The author wishes to thank Mr. N. B. Colthup, Dr. R. C. Hirt, and Mr. R. G. Schmitt for their interpretation of the infrared and ultraviolet spectra, and Mr. R. J. Francel for his cooperation in the analyses.

(7) A. Wilson, L. Bini, and R. Hofstader, *Anal. Chem.*, **33**, 135 (1961).

The Chloromethylation of 5-Nitrosalicylaldehyde

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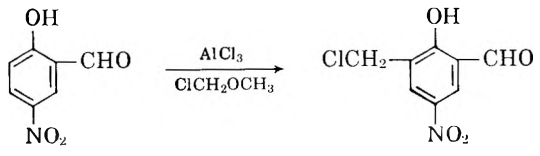
Received December 10, 1962

Recently we have had occasion to prepare 3-chloromethyl-5-nitrosalicylaldehyde. We decided to try the direct chloromethylation of 5-nitrosalicylaldehyde, although the aromatic ring is somewhat inactive. After several unsuccessful conventional reactions,[1] a Friedel–Crafts type reaction with aluminum chloride and chloromethyl methyl ether was tried, although aluminum chloride usually is much too active a catalyst for this type of reaction, yielding diphenylmethane compounds. We now have found that chloromethylation of 5-nitrosalicylaldehyde is accomplished in yields of 90% by employing four equivalents of aluminum chloride (one for each oxygen atom) plus a 10% catalytic excess and by carrying out the reaction in pure chloromethyl methyl ether. Several reactions in chloromethyl methyl ether, with zinc chloride or with only one equivalent of aluminum chloride, yielded only starting material. The success of this reaction may be aided by the noticeable solubility of the salicylaldehyde–aluminum chloride complex in chloromethyl methyl ether. The literature does not mention the application of the halo ether as the solvent and it is possible that other highly oxygenated compounds may be successfully chloromethylated by means of this method.



(1) R. C. Fuson and C. H. McKeever, "Organic Reactions," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 66–71.

Experimental

Into a 2-l, three-necked, round-bottom flask, fitted with a mechanical stirrer, addition tube, 1 Allihn condenser surmounted by a Friedrichs condenser fitted with a calcium chloride drying tube, were placed 95 g. (0.57 mole) of 5-nitrosalicylaldehyde (m.p. 126–127°, Eastman product) and 1 l. of chloromethyl methyl ether (b.p. 58°, Eastman product). To this solution, cooled to 5°, was added with stirring 312 g. of aluminum chloride (2.3 moles) over a 1-hr. period. This slurry was brought to room temperature and then allowed to reflux for 80 hr. until evolution of hydrogen chloride ceased. The viscous solution was cooled to room temperature and then poured with stirring into 3 l. of crushed ice. The resulting brown tar was stirred with ice–water for ~30 min.

$$ClCH_2OCH_3 + H_2O \longrightarrow H_2O + HCl + CH_3OH$$

The brown solid was filtered and the filtrate extracted with ether. The ether extract was dried with sodium sulfate and the ether was removed by evaporation. The brown solid was added to that previously obtained and the product was recrystallized from carbon tetrachloride using charcoal. In this manner 108 g. (89%) of a tan solid (m.p. 89–90°) was obtained. A small portion was recrystallized from hexane (needles), m.p. 90.5–91.5°.

Anal. Calcd. for $C_8H_6ClNO_4$: C, 44.6; H, 2.8; N, 6.5; Cl, 16.5. Found: C, 44.4; H, 2.8; N, 6.6; Cl, 16.7.

An n.m.r. spectrum of the product is in accord with the assigned structure. The compound, run in deuteriochloroform, showed the following bands: one hydroxyl hydrogen at 12.1 p.p.m., one aldehyde hydrogen at 10.1 p.p.m., two aromatic hydrogens at 8.60 p.p.m., and two methylene hydrogens at 4.70 p.p.m. The only band split was that of the aromatic hydrogens, revealing an AB system with a coupling constant of 3 c.p.s., characteristic of aromatic protons in the *meta* position.[2]

(2) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 85.

The Preparation of 1-Aryl-1,2-cyclopropanedicarboximides. An Application of Dimethylsulfoxonium Methylide

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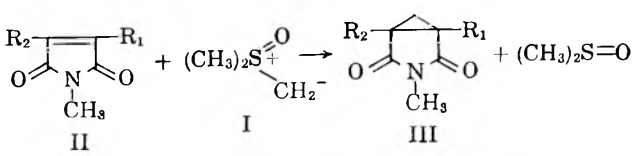
Received January 21, 1963

The interest, in these laboratories, in 1-aryl-1,2-cyclopropanedicarboximides as pharmacologically interesting compounds prompted an investigation of new methods for the preparation of some members of this class of substances.

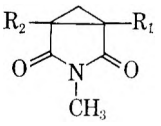
Recently Corey and Chaykovsky[1] have reported on a new synthesis of cyclopropanes based on Michael addition of dimethylsulfoxonium methylide (I) to appropriate α,β-unsaturated ketones. The purpose of this paper is to describe an application of this reaction in which some N-methyl-2-arylmaleimides (II) were the substrates for the action of the ylide. In



(1) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

TABLE I

N-METHYL-1-ARYL-1,2-CYCLOPROPANEDICARBOXIMIDES (III)



	R_1	R_2	M.p., °C.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	C_6H_6	H	55–57[a]	21[b]	$C_{12}H_{11}NO_2$	71.62	5.51	6.96	71.83	5.79	6.62
IIIb	C_6H_6	C_2H_5	113–114[c]	81	$C_{14}H_{15}NO_2$	73.34	6.59	6.11	73.12	6.93	6.03
IIIc	3,4,5-Trimethoxyphenyl	H	136–138[c]	21[c]	$C_{15}H_{17}NO_5$	61.85	5.88	4.81	61.94	6.12	5.01

[a] From alcohol. [b] The low yield was partly the result of difficulty of separation from by-products. In this case, an evaporative distillation and three recrystallizations from alcohol were necessary to bring the compound to analytical purity. [c] Same as in footnote *b*. To achieve purification, repeated fractional crystallizations from alcohol were necessary. The same result could be obtained more conveniently by chromatography of the crude product, using Florisil as adsorbent and benzene and chloroform as the developing and eluting solvents.

the three cases tried the expected 1-aryl-1,2-cyclopropanedicarboximides (III) were formed.

All the reactions were carried out in boiling tetrahydrofuran after first generating I in the same solvent by treating trimethylsulfoxonium chloride with sodium hydride. The results are summarized in Table I.

The evidence for the structure of the cyclopropane products was provided by infrared and ultraviolet spectra, elementary analyses, and unsaturation tests. The infrared spectra of all three compounds, taken in chloroform solution, displayed the typical five-membered cyclic imide doublet at 5.60 and 5.83 μ.[2] A band at 9.74 μ, ascribable to the cyclopropane ring,[3] was present in the spectrum of IIIa and IIIc but absent in that of IIIb. The ultraviolet spectra, taken in methanolic solutions, showed no bands above 220 mμ except for phenyl absorption (IIIa, λ_{max} 250 mμ, ϵ 500; IIIb, λ_{max} 250 mμ, ϵ 690; IIIc, λ_{max} 265 mμ, ϵ 870). The absence of double bonds in all three compounds was also demonstrated by negative tests with bromine in carbon tetrachloride, and potassium permanganate in acetone.

Experimental[4]

Trimethylsulfoxonium Chloride.—This compound was prepared by the method of Kuhn and Trischmann,[5] m.p. 215–216° dec. In spite of extensive purification procedures, and acceptable elementary analyses, the infrared spectrum of this compound, taken on a mineral oil mull, showed bands at 2.78 and 6.22 μ. The intensity of these bands seemed to vary from sample to sample, and in at least one case, they were absent altogether. However, since the reagent gave successful results when used in the reaction, these bands were deemed to be extraneous.

General Procedure for the Preparation of N-Methyl-1-aryl-1,2-cyclopropanedicarboximides.—To a stirred suspension, under nitrogen, of 0.29 g. (0.012 mole) of sodium hydride (from 0.53 g. of a 54.7% oil dispersion) in 150 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added in one lot 1.5 g. (0.012 mole) of trimethylsulfoxonium chloride. As the mixture was heated to reflux, a vigorous evolution of hydrogen ensued. Stirring under reflux was maintained for 45–60 min. and then the N-methyl-2-arylmaleimide (0.012 mole) was added rapidly either as a concentrated tetrahydrofuran solution (10 ml.) or, if insoluble, as a solid in one lot. Following this, the reaction was held at reflux for about 2 hr. and cooled. A few milliliters of absolute alcohol were added to ensure complete destruction of any unchanged sodium hydride and the solvent was removed by distillation at reduced pressure. The invariably dark-colored residue was taken up in 100 ml. of methylene chloride. Alkaline materials were washed out of the solution by three washings with water. The solution was dried ($MgSO_4$) and evaporated to an oily material which usually crystallized after triturating with petroleum ether. This material was then either recrystallized from alcohol or treated as described in Table I.

2-Bromo-N-methyl-2-phenylsuccinimide.—A mixture of 37.8 g. (0.20 mole) of N-methyl-2-phenylsuccinimide,[6] 39.2 g. (0.22 mole) of N-bromosuccinimide, 0.4 g. of benzoyl peroxide, and 800 ml. of carbon tetrachloride was stirred and heated under reflux for 24 hr. and then stored for 16 hr. at room temperature. The nearly theoretical amount (20.8 g.) of succinimide, which floated on top of the solution was filtered and the filtrate was concentrated to about one half volume and cooled in ice. The crystalline product which precipitated (m.p. 107–112°, 49.2 g., 93%) was collected by filtration. Recrystallizations from a mixture of benzene and petroleum ether (b.p. 65–90°) and from aqueous acetone gave colorless crystals, m.p. 110.5–112°.

Anal. Calcd. for $C_{11}H_{10}NO_2Br$: C, 49.26; H, 3.76; N, 5.22; Br, 29.81. Found: C, 49.24; H, 3.80; N, 5.24; Br, 30.04.

N-Methyl-2-phenylmaleimide.—A 7.5-g. (0.028 mole) sample of 2-bromo-N-methyl-2-phenylsuccinimide was dissolved in 75 ml. of anhydrous benzene, and 3 g. (0.03 mole) of triethylamine dissolved in 10 ml. of benzene was added. A precipitate of triethylamine hydrobromide formed immediately and a moderate exothermic effect was noted. The mixture was cooled and allowed to remain at room temperature for 1 hr. The triethylamine hydrobromide was removed by filtration and the benzene filtrate was washed with 0.1 *N* hydrochloric acid and with water, and dried ($MgSO_4$). Concentration at reduced pressure to a small volume and cooling in ice caused the precipitation of yellow needles, m.p. 145.5–148°. The yield was 3.7 g. (71%). A recrystallization from acetone gave pale yellow needles, m.p. 147–148° (lit.[7] m.p. 145–147°). The ultraviolet spectrum showed λ_{max} 222 (ϵ 12,500), 266 (ϵ 9300), and 339 mμ (ϵ 3500).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.37; H, 4.99; N, 7.23.

2-Chloro-3-(3′,4′,5′-trimethoxyphenyl)succinimide.—This compound was prepared by the arylation of maleimide with 3,4,5-trimethoxyphenyldiazonium chloride following a procedure described by Rondestvedt and Vogl.[8] It was obtained as a yellow crystalline product in 27% yield, after recrystallization from acetone, m.p. 207–208° dec.

Anal. Calcd. for $C_{13}H_{14}NO_5Cl$: C, 52.09; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 51.78; H, 4.61; N, 4.70; Cl, 11.68.

2-(3′,4′,5′-Trimethoxyphenyl)maleimide.—A 2-g. (0.0066 mole) sample of 2-chloro-3-(3′,4′,5′-trimethoxyphenyl)succinimide was mixed with 8 ml. of 2,6-lutidine, and the mixture was heated on a steam bath for 30 min. Then 20 ml. of water was added and the crystals were filtered and recrystallized from chloroform to give 1.5 g. (90%) of yellow needles, m.p. 211–213°.

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 58.93; H, 5.44; N, 5.50.

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., J. Wiley and Sons, Inc., New York, N. Y., 1958, p. 221.

(3) L. J. Bellamy, *ibid.*, p. 29.

(4) All melting points were determined in an open capillary tube and are uncorrected. The ultraviolet spectra were taken in methanol on a Cary recording spectrophotometer and the infrared spectra were determined in chloroform with a Perkin-Elmer spectrophotometer (Model 137).

(5) R. Kuhn and H. Trischmann, *Ann.*, **611**, 117 (1958).

(6) Generously supplied by Parke, Davis and Co., Detroit, Mich.

(7) C. A. Miller, U. S. Patent 2,831,867 (1958).

(8) C. S. Rondestvedt and O. Vogl, *J. Am. Chem. Soc.*, **77**, 2313 (1955).

N-Methyl-2-(3′,4′,5′-trimethoxyphenyl)maleimide.—To a well stirred suspension of 2.8 g. (0.01 mole) of 2-(3′,4′,5′-trimethoxyphenyl)maleimide in 75 ml. of freshly distilled tetrahydrofuran (from lithium aluminum hydride), was added 0.24 g. (0.01 mole) of sodium hydride (from 0.45 g. of a 54.7% oil dispersion). There was an immediate evolution of hydrogen which continued briskly as the mixture was brought to reflux. A solution of 7 g. (0.05 mole) of methyl iodide in 10 ml. of tetrahydrofuran was then added to the yellow, boiling, mixture over a 45-min. period, and heating was continued for another 1.75 hr. At the end of this time, the reaction mixture was a dark green color and was neutral to indicator paper. The solvent was distilled at reduced pressure and the residue was dissolved in 75 ml. of chloroform. The chloroform solution was washed twice with water, dried ($MgSO_4$), and evaporated to give 3.1 g. of a deep orange solid. Crystallization from a large volume of hot absolute alcohol in which the material was sparingly soluble (or, from a mixture of ethyl acetate and petroleum ether (b.p. 65–90°)) gave 2 g. (71%) of orange, matted needles, m.p. 155–156°. The ultraviolet spectrum showed λ_{max} 235 (ϵ 13,600), 297 (ϵ 700), and 373 mμ (ϵ 3900).

Anal. Calcd. for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.74; H, 5.71; N, 4.86.

N,5-Dimethyl-3-phenyl-1-pyrazoline-3,4-dicarboximide.—To an ice-cold solution of 8.9 g. (0.048 mole) of N-methyl-2-phenylmaleimide in 150 ml. of methylene chloride was added in one lot a cold, dried (over potassium hydroxide pellets) solution of 0.054 mole of diazoethane in ether.[9] The discharge of the orange-red color was immediate and the final solution retained only a pale yellow color. Evaporation of the solvent and the slight excess of diazoethane gave 11.6 g. (100%) of the crystalline pyrazoline, m.p. 78–85° dec. A sample was purified further by recrystallization from a mixture of methylene chloride and petroleum ether (b.p. 30–60°), giving colorless needles, m.p. 106–107° dec.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.74; H, 5.49; N, 17.43.

N-Methyl-2-ethyl-3-phenylmaleimide.—A 5.1-g. (0.02 mole) sample of the crude pyrazoline (m.p. 78–85° dec.) obtained as described was dissolved in 50 ml. of alcohol and heated on a steam bath for 30 min. There ensued an immediate and rapid evolution of nitrogen. The alcohol was removed by distillation *in vacuo* to give 4.4 g. (100%) of a viscous, colorless oil. This material was subjected to partition chromatography in which the system, *n*-heptane–Methyl Cellosolve, was used. This procedure led to the separation of a major and a minor component. The desired N-methyl-2-ethyl-3-phenylmaleimide was the minor and faster moving component. It was obtained by the evaporation of the solvent in the first peak to give 200 mg. (5%) of solid. Two recrystallizations from aqueous alcohol gave large rhombs, m.p. 69–70°. This compound gave positive tests for unsaturation with bromine in carbon tetrachloride and with potassium permanganate in acetone. The ultraviolet spectrum showed λ_{max} 225 (ϵ 13,500), 260 (ϵ 6000), and 331 mμ (ϵ 1500).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.69; H, 5.74; N, 6.37.

The second and slower moving component, obtained as a colorless, viscous oil, was the main product. This was the expected, N,3-dimethyl-1-phenyl-1,2-cyclopropanedicarboximide. The yield was 4.0 g. (93%).[10] This substance could not be crystallized from solvents, even after an evaporative distillation. It did, however, solidify in part after many days at room temperature. The ultraviolet spectrum showed λ_{max} 255 (ϵ 860) as the only band above 220 mμ. The infrared spectrum showed the characteristic succinimide doublet at 5.62 and 5.82 μ.[2]

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.57; H, 6.42; N, 6.25.

Acknowledgment.—The author wishes to thank Mr. L. Brancone and staff for the microanalyses, Mr. C. Pidacks and staff for the separation work by partition chromatography, and Drs. V. J. Bauer and S. R. Safir for helpful suggestions.

(9) This was prepared from 11.7 g. (0.10 mole) of moist nitrosoethylurea by a procedure analogous to that used for diazomethane (F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(10) The details of this and other associated work will appear in a future publication.

A Convenient Synthesis of 1,2,5,6-Dibenzocyclooctatetraene[1]

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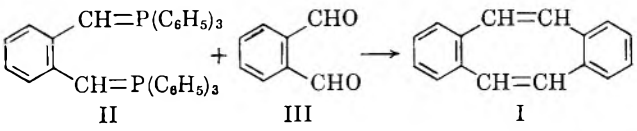
Received January 21, 1963

The Wittig reaction has been applied in several instances for the preparation of cyclic olefins containing five to sixteen carbon atoms and offers a number of advantages over conventional synthetic procedures particularly in the case of larger rings[3]; however, in each of the reported examples, the products have either possessed the *trans* stereochemistry favored by Wittig processes[4] or have been flexible ring systems. In order to determine the limits of applicability of this cyclization procedure, it was of interest to examine a case in which the product was a rigid ring system possessing unfavorable stereochemistry. The model compound chosen for this study was the well characterized 1,2,5,6-dibenzocyclooctatetraene (I),[5–8] for which molecular models indicate a highly rigid *cis* structure,[3a] existing in a tub conformation and incapable of equilibration to a *trans* isomer. The projected synthetic scheme is a simple modification of well established methods,[3a,d] and involves the reaction of the bisylide (II) with *o*-phthaldehyde (III) to form the product (I). The bisylide (II) is readily prepared from *o*-xylylenebis(triphenylphosphonium bromide) (IV) by the action of base.[3d]



II III I

The reaction of III and IV was first attempted under standard Wittig conditions, *i.e.*, in absolute ethanol employing sodium ethoxide as the base for the generation of the ylide (II).[3d] However, in no instance could I be isolated from reactions carried out under these conditions and the presence of only trace amounts was indicated spectrally; only triphenylphospine oxide, III, and polymeric materials were isolated. Since the Wittig reaction under these conditions leads normally to *trans* olefins,[3d,4] it is probably that the reaction of II and III produces initially *trans*-V, which predominantly undergoes intermolecular reaction to form polymer rather than intramolecular ring closure

(1) Supported in part by a grant (G-11280) from the National Science Foundation.

(2) National Science Foundation Undergraduate Research Participant, Summer, 1962.

(3) (a) G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958); (b) K. Dimroth and G. Pohl, *Angew. Chem.*, **73**, 436 (1961); (c) T. I. Bieber and E. H. Eisman, *J. Org. Chem.*, **27**, 678 (1962); (d) C. E. Griffin, K. R. Martin, and B. E. Douglas, *ibid.*, **27**, 1627 (1962); (e) C. E. Griffin and G. Witschard, *ibid.*, **27**, 3334 (1962).

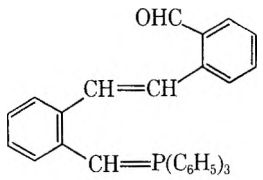
(4) U. Schöllkopf, *Angew. Chem.*, **71**, 260 (1959).

(5) L. F. Fieser and M. M. Pechet, *J. Am. Chem. Soc.*, **68**, 2577 (1946).

(6) A. C. Cope and S. W. Fenton, *ibid.*, **73**, 1668 (1951).

(7) (a) G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Ann.*, **572**, 1 (1951); (b) G. Wittig, G. Koenig, and K. Clauss, *ibid.*, **593**, 127 (1955).

(8) M. Avram, D. Dinu, G. Matescu, and C. D. Nenitzescu, *Chem. Ber.*, **93**, 1789 (1960).



V

to I; the latter process would require *cis* stereochemistry in V.

Recently Shemyakin has shown that the Wittig reaction can be modified to favor the formation of *cis* isomers by conducting the reaction in the presence of a Lewis base and reported that the best results were obtained with lithium bromide or iodide in dimethylformamide.[9] Partial neutralization of the charge on the ylide phosphorus by interaction with the base is postulated as leading to a lessening of the importance of initial ylide–carbonyl dipolar interaction as a determinant in product stereochemistry. Since both of the double bonds to be formed in I are required to be *cis*, the reaction of III and IV was attempted employing conditions similar to those reported by Shemyakin, *i.e.*, the slow addition of a solution of lithium ethoxide in absolute ethanol to a dilute solution of III and IV in dimethylformamide. In this instance, the desired product (I) was isolated from the reaction mixture in 18% yield; since IV can be prepared in 86–89% yield from *o*-xylylene dibromide, an over-all yield of 15–16% of I can be obtained in a two-step process. This yield is comparable to those obtained in the reported four- to five-step procedures.[5-7a]

The successful formation of I by a Wittig procedure indicates that the only probable limitation to effective Wittig cyclization is ring size; the only failures reported to date are in the attempted syntheses of cyclopropenes[3e] and cyclobutenes.[10]

The infrared spectra of samples of I prepared in this study are identical in all respects to the spectrum reported by Wittig[7b] and totally different from that reported earlier by Cope.[6] One of the most prominent features of the spectrum reported by Cope is an intense band at 11.0 μ which is absent in the spectra obtained by Wittig and the present investigators. The ultraviolet spectrum of I shows a single band without fine structure at 239 mμ (ϵ 28,900); Wittig has reported a band at the same wave length of somewhat higher intensity (ϵ 48,000). McEwen and Longuet-Higgins[11] have carried out an LCAO calculation of the electronic transition energies of I; the observed band for I probably corresponds to the calculated $A_1 \rightarrow B_1$ transition at 230 mμ. Because of its high intensity and lack of fine structure, the observed band probably is not related to the calculated forbidden $A_1 \rightarrow A_2$ transition at 239 mμ.

Experimental[12]

o-Xylylenebis-(triphenylphosphonium bromide) (IV) was prepared in 86.5% yield by the reported method.[3d] In the original preparation, IV was reported to have m.p. >340°; however, in subsequent preparations, material decomposing as low as 295° was obtained. The lower melting material was satisfactory in all respects; examination of the infrared spectra of these preparations indicates the melting point depression to be caused by the presence of a trace amount of the monophosphonium salt.[3d]

1,2,5,6-Dibenzocyclooctatetraene (I).—A mixture of 18.1 g. (0.023 mole) of IV and 3.0 g. (0.022 mole) of *o*-phthaldehyde in 400 ml. of dry dimethylformamide (distilled from calcium hydride) was heated to 90° under an atmosphere of dry nitrogen. A solution of 0.059 mole of lithium ethoxide in 100 ml. of absolute ethanol was added to this reaction mixture with rapid stirring over a period of 5 hr. Addition of the basic solution gave a deep orange solution and this color persisted for 4.5 hr. After the addition was completed, the dark reaction mixture was allowed to cool and was diluted with 500 ml. of water. The precipitated material was extracted with ether and the ethereal extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated to give a dark brown oil. This oil was extracted with boiling petroleum ether (60–70°) to effect separation from triphenylphosphine oxide; evaporation of the petroleum ether extracts gave 5.8 g. of a red oil which was chromatographed on a Florisil column (1.25 × 90 cm.). Elution with 1.4 l. of petroleum ether (30–65°) gave 1.8 g. of a pale yellow crystalline solid which was rechromatographed on Florisil (1.25 × 45 cm. column). Twenty-four 10-ml. fractions were collected by elution with petroleum ether (30–65°). Fraction 1 was an oily mixture which failed to crystallize, but fractions 2–24 gave 1.5 g. of a colorless crystalline product on evaporation of solvent; this product was recrystallized from aqueous ethanol to give 0.8 g. (18%) of I, m.p. 109.2–109.4° (lit. m.p. 108.5–109.2°,[7a] 109°,[8] 106.8–108.1°,[5] 106.2–106.9°[6]).

Anal. Calcd. for $C_{16}H_{12}$: C, 94.03; H, 5.92. Found: C, 94.17, 94.11; H 5.80, 5.93.

The ultraviolet spectrum of I in 95% ethanol showed a maximum at 239 mμ (ϵ 28,900). The infrared spectrum was recorded in carbon tetrachloride and acetonitrile and showed bands at the following wave lengths (μ): 3.27 s, 3.32 s, 6.09 w, 6.73 s, 7.01 m, 7.17 m, 8.68 m, 8.97 w, 9.20 m, 9.65 m, 10.42 w, 10.60 m, 11.52 w, 11.98 s, 12.85 vs, 13.42 s, 14.31 s, 14.45 s, 14.87 w.

Treatment of a methanolic solution of I with saturated aqueous silver nitrate gave a colorless precipitate which was recrystallized from ethanol to give the **silver nitrate complex of I**, m.p. 221–222° (lit. m.p. 222°,[9] 214–215°[3a]).

The reaction of *o*-phthaldehyde and IV in refluxing absolute ethanol for 5 hr. employing sodium ethoxide as base was carried out in a manner analogous to the previous experiment. Careful chromatography of the products led to the isolation of triphenylphosphine oxide and the dialdehyde as the only characterizable materials; examination of the infrared spectra of all fractions showed the presence of only trace amounts of I. When the reaction was carried out for a longer period of time (22 hr.), the major portion of the organic material isolated was polymeric in nature, showing aromatic and both *cis* and *trans* olefinic absorptions in the infrared.

(9) M. M. Shemyakin, L. D. Bergelson, and V. A. Vaver, IUPAC International Symposium on Organic Chemistry of Natural Products, Brussels, June 12–15, 1962.

(10) G. Witschard and C. E. Griffin, unpublished results; T. I. Bieber, private communication.

(11) K. L. McEwen and H. C. Longuet-Higgins, *J. Chem. Phys.*, **24**, 771 (1956).

(12) Micronalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Synthesis of 7-Methyl- and 7-Phenylnorbornadiene

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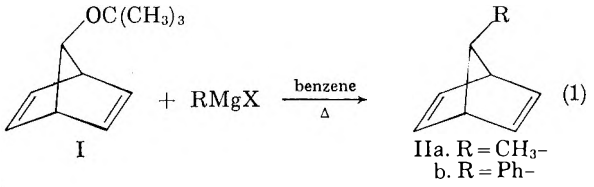
The synthesis of norbornadiene is a relatively straightforward procedure involving the Diels–Alder condensation of cyclopentadiene and acetylene.[1] However, 7-substituted norbornadienes generally are not available by this simple route because the corresponding 5-substituted cyclopentadienes are unstable relative to

(1) J. Hyman, E. Freireich, and R. E. Lidov, U. S. Patent 2,875,256; *Chem. Abstr.*, **53**, 13082 (1959).

their 1 and 2 isomers and at best give a mixture of isomeric products even when generated *in situ*.[2]

7-*t*-Butoxynorbornadiene, prepared by treating norbornadiene with *t*-butyl perbenzoate, has recently proven to be a valuable precursor for the synthesis of several other 7-substituted norbornadienes.[3,4]

We now wish to report the preparation of 7-methyl- and 7-phenylnorbornadiene by treatment of 7-*t*-butoxynorbornadiene with the appropriate Grignard reagent as shown in equation 1.



I

IIa. R = CH_3–
b. R = Ph–

Presumably the reaction could be extended to the synthesis of many alkyl and aryl substituted norbornadienes.

Refluxing the ether (I) with an excess of methylmagnesium iodide in benzene gave a 57% yield of 7-methylnorbornadiene (IIa). Similar treatment of the ether (I) with phenylmagnesium bromide gave 7-phenylnorbornadiene (IIb) in 75% yield. 7-Norbornadienol was not detected among the products; however, it was not rigorously sought. In fact, no other monomeric products were detectable.

The structures of IIa and IIb were established by analysis of their infrared and n.m.r. spectra. Both molecules exhibited the highly characteristic infrared absorptions at 6.5 μ (double bond stretch and at *ca.* 13.6–14.0 μ (*cis* double bond, carbon–hydrogen out-of-plane deformation) indicative of the norbornadiene nucleus.[3] The n.m.r. spectra also were highly characteristic of the norbornadiene nucleus[3] and consistent with the proposed structures. For example, in the 7-methylnorbornadiene spectrum, the methyl group appears as a doublet at $\tau = 9.15$. The bridge hydrogen (7) appears as a complex quartet at $\tau = 7.40$ and the bridgehead hydrogens (1,4) appear as a multiplet at $\tau = 6.82$. In addition, the two pairs of olefinic hydrogens appear as two separate triplets at $\tau = 3.29$ and 3.52 in characteristic fashion.

Several ethers have been cleaved by Grignard reagents to yield analogous hydrocarbons.[5] In most of these examples, at least one moiety was capable of supporting a positive charge. For example, diallyl ether and benzyl ethers are rather easily cleaned to generate hydrocarbons.

The relatively facile cleavage of I is consistent with the stability of the 7-norbornadienyl carbonium ion[4,6] and probably is mechanistically similar to the lithium aluminum hydride reduction of 7-chloronorbornadiene.[7] There is one important exception. The reduction of 7-chloronorbornadiene yielded, in addition to norbornadiene, tricyclo[4.1.0.$0^{3,7}$]heptene-4 as the major product. The corresponding 2-substituted tricyclo[4.1.0.-

III

$0^{3,7}$]heptene-4 (III) was not observed in the reaction of Grignard reagents with I. However, the tricyclic olefins (III) may have been destroyed under the reaction conditions.

Experimental

7-Methylnorbornadiene (IIa).—Following the general procedure of Normant,[8] methylmagnesium iodide was prepared from 57.6 g. (2.4 g.-atoms) of magnesium and 341 g. (2.4 moles) of methyl iodide in 1.5 l. of anhydrous ether. About 1 to 1.5 l. of reagent grade benzene was added in several portions while the ether was removed by distillation. Distillation was continued until the boiling point reached 79°. After the solution was allowed to cool 10–20°, 200 g. (1.22 moles) of 7-*t*-butoxynorbornadiene (I)[3] was added all at once. This mixture was stirred and refluxed for 2.5–3 days. After this time, the excess Grignard was destroyed with about 225 ml. of water and the benzene solution decanted. The solvent was removed at atmospheric pressure with a 24-in. spinning bond distillation column. The product was distilled on the same column to give 74.5 g. (57.6%) of 7-methylnorbornadiene (IIa), b.p. 54.5–55.0° (113 mm.). Infrared (carbon tetrachloride, μ): 3.4 (s), 6.5 (m), 7.6 (s), 13.9 (s). N.m.r. (carbon tetrachloride, τ): 3.29 (3), 3.52 (3), 6.82 (6), 7.40 (4), 9.15 (2), area ratio of 2:2:2:1:3.

Anal. Calcd. for C_8H_{10}: C, 90.50; H, 9.50. Found: C, 90.68; H, 9.43.

7-Phenylnorbornadiene (IIb).—Using the same procedure, 7-phenylnorbornadiene (IIb) was prepared from 14.4 g. (0.6 g.-atom) of magnesium, 94.2 g. (0.6 mole) of phenyl bromide, and 50 g. (0.3 mole) of 7-*t*-butoxynorbornadiene (I) to give 38.9 g. (75.8%) of IIb, b.p. 80–81° (1.7 mm.). This product was about 95% pure. Greater purity was obtained by gas phase chromatography using a 20 ft × 3/8 in. 10% Dow 710 silicone column at 160°. Infrared (neat, μ): 3.2 (m), 6.5 (m), 7.6 (s), 13.5 (m), 13.8 (s), 14.4 (s). N.m.r. (carbon tetrachloride, τ): 2.97 (m), 3.15 (3), 3.5 (m), 6.25 (m), area ratio 5:2:2:3.

Anal. Calcd. for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 93.07; H, 7.41.

(2) R. Vanelli, Ph.D. thesis, Harvard University, 1950.
(3) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).
(4) P. R. Story and M. Saunders, *J. Am. Chem. Soc.*, **84**, 4876 (1962).
(5) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Chap. XV, Prentice-Hall, New York, N. Y., 1954; C. M. Hill, L. Haynes, D. E. Simmons, and M. E. Hill, *J. Am. Chem. Soc.*, **80**, 3623 (1958).
(6) S. Winstein and C. Ordronneau, *ibid.*, **82**, 2084 (1960).
(7) P. R. Story, *ibid.*, **83**, 3347 (1961).
(8) A. Normant, *Bull. soc. chim. France*, (5) **7**, 371 (1940).

Fluorine-Containing Nitrogen Compounds. V. Difluoronitroacetamidines and Difluoronitromethyl-1,2,4-triazoles[1,2]

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The reaction of ammonia or primary or secondary alkylamines with perfluoroalkylnitriles has been shown to afford good yields of stable perfluoroalkylamidines.[3,4] The stability of the perfluoroalkylamidines, as contrasted with their unfluorinated analogs, was attributed to the electronegativity of the fluorocarbon radical.[4]

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.
(2) For paper number IV of this series, see G. C. Shaw, D. L. Seaton, and E. R. Bissell, *J. Org. Chem.*, **26**, 4765 (1961); for paper number III, see E. R. Bissell, *ibid.*, **26**, 5100 (1961).
(3) D. Husted, U. S. Patent 2,676,985 (April, 1954).
(4) W. L. Reilly and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 6032 (1956).

TABLE I

PHYSICAL PROPERTIES AND ANALYSES OF DIFLUORONITROACETAMIDINES AND 3-(DIFLUORONITROMETHYL)-1,2,4-TRIAZOLES

Compound	% Yield[a]	M.p., °C.	d_{25}	$n^{25}D$	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
Ia	63		1.623	1.4491	17.27	17.10	2.17	1.47		
Ia CF_3COOH salt		173–174 dec.			18.98	19.19	1.59	1.42	16.60	16.87
Ib	63		1.451	1.4425						
Ib Hydrobromide		181–182 dec.			15.40	15.26	2.15	2.52	17.96	18.90
Ie	35	34–36	1.345	1.4388						
Ic Hydrobromide		165–167			19.37	18.68	3.25	2.98	16.94	16.83
Id	65		1.374	1.5268	44.65	44.83	3.28	3.18	19.53	20.18
Id Hydrobromide		174–175			32.45	32.50	2.38	2.59	14.19	13.87
Ie	30[b]	91.5–92.5			38.17	38.04	2.14	2.56	14.84	15.54
IIa	86		1.630	1.4480						
IIa Copper chelate		>200			16.52	16.56	0.35	0.58	24.08	24.47
IIb	63		1.572	1.4511						
IIc	40		1.596	1.4546						
IId	60		1.455	1.5172						
IIIa	50	76–77			21.96	21.83	1.23	1.14	23.16[c]	23.02[c]
IIIb	33		1.694	1.4701	26.97	27.12	2.26	1.65		

[a] Based on difluoronitroacetonitrile charged. [b] 90% based on unrecovered nitrile. [c] Fluorine.

Aromatic amines failed to react, presumably because of their low basicity.[4] The unsubstituted perfluoroalkylamidines decomposed smoothly above their melting points with the evolution of ammonia to form 2,4,6-tris(perfluoroalkyl)-1,3,5-triazines.[5]

The present paper describes the reactions of ammonia and primary and secondary amines with a nitrile in which the electronegativity of the alkyl group is further increased over that of the perfluoro compounds by substitution of a nitro group for one of the fluorines. The effect on the reactivity of the nitrile and of the primary addition products and on the course of subsequent reactions is marked.

Like trifluoroacetonitrile, difluoronitroacetonitrile reacted readily with ammonia or primary or secondary alkylamines to form N-substituted difluoronitroacetamidines (I). However, satisfactory yields were obtained only when stoichiometric amounts of the amine were used,

$O_2NCF_2C(:NH)NRR'$ (I)

Ia. R = R′ = H
Ib. R = CH_3, R′ = H
Ic. R = R′ = CH_3
Id. R = phenyl, R′ = H
Ie. R = p-$CF_3C_6H_4$, R′ = H

and low temperatures were required to avoid side reactions. Unlike trifluoroacetonitrile, difluoronitroacetonitrile also formed amidines from amines of low basicity such as aniline (Id) or even *p*-trifluoromethylaniline (Ie), but the reaction rates were lower. The physical properties of the amidines and their derivatives are listed in Table I. The amphoteric nature of difluoronitroacetamidine (Ia) was shown by its formation of both a silver salt and salts with acids such as trifluoroacetic or hydrobromic. The N-substituted amidines also showed evidence of formation of silver salts, but the salts were not obtained in a pure state. Trifluoroacetic acids salts of the substituted amidines were mostly low melting, but the hydrobromides were all crystalline. Two bands in the C=N region of the infrared spectrum of N-methyldifluoronitroacetamidine (Ib) indicate that this compound probably exists as an equilibrium mixture of the two possible tautomeric forms. Single bands in the C=N region of the spectra of the aromatically substituted derivatives (Id and Ie) indicate only one tautomer. Since both Id and Ie show doublets in the NH region, the double bond in these compounds is thought to be conjugated with the aromatic rings.

The amidines combined with a second equivalent of difluoronitroacetonitrile to produce (difluoronitroacetylimino)difluoronitroacetamidines (II) which could also be obtained directly from the nitrile by reaction with one-half equivalent of the amine.

$O_2NCF_2C(:NR)N=C(NR_2')CF_2NO_2$

IIa. R = R′ = H
IIb. R = CH_3, R′ = H
IIc. R = H, R′ = CH_3
IId. R = phenyl, R′ = H

N′ - (Difluoronitroacetylimino)difluoronitroacetamidine (IIa) formed a water-insoluble copper chelate, but this ability was not shown by any of the substituted derivatives. None of the acetyliminoacetamidines formed silver salts.

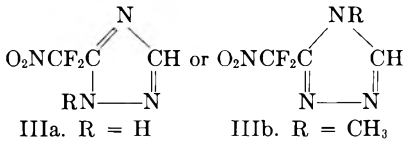
Thermal decomposition of Ia gave difluoronitromethane as the only substantial volatile product. The remainder of the material appeared to be salts and/or polymers similar to those formed by the reaction of the amidine with excess ammonia. Difluoronitromethane, reported here for the first time, is a colorless liquid with a normal boiling point of 43.4° and a freezing point of approximately −120°. Its vapor pressure in the range from 300–800 mm. is given by the equation $\log P_{mm} = 8.0187 - 1626.7/T°_K$. The heat of vaporization calculated[6] from this equation is 7188 cal./mole and the Trouton ratio is 22.7.

Compound IIa showed no tendency to react with a third equivalent of nitrile but decomposed, slowly at room temperature and more rapidly at higher temperatures, to difluoronitromethane and a sublimable, colorless solid melting at 76–77°. The latter was assigned the structure 3 - (difluoronitromethyl) - 1,2,4 - triazole- (IIIa) on the basis of the following evidence. (1) Elementary analysis was consistent with the empirical formula $C_3H_2F_2N_4O_2$. (2) Infrared spectra showed bands corresponding to NH, CH, C=N, NO_2, and CF. (3) The F^{19} nuclear magnetic resonance spectrum in dimethyl sulfoxide solution showed only one unsplit

(5) W. L. Reilly and H. C. Brown, *J. Org. Chem.*, **22**, 698 (1957).

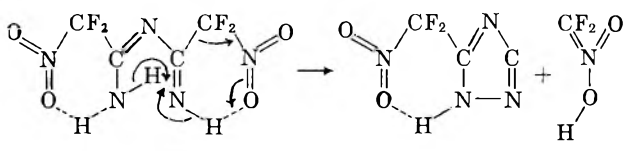
(6) G. W. Thomson, "Physical Methods of Organic Chemistry," Vol. I, Part 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 518.

resonance. The proton spectrum showed two slightly broadened bands at −4.96 and −6.79 p.p.m. with respect to dimethyl sulfoxide. Neither was affected by dilution or by addition of water or pyridine. The higher field band was broadened essentially to the point of disappearance by acidification with dilute hydrochloric acid.[7] (4) The molecular weight as determined by the Rast method in *dl*-camphor was 169 (calcd. 164). (5) The ultraviolet absorption spectrum in aqueous solution showed a maximum at 206 mμ, ϵ_{max} 6300. 1,2,4-Triazole is reported to absorb at 205 mμ, ϵ_{max} 200.[8]



The N - monosubstituted - N - (difluoronitroacetylimino)difluoronitroacetamidines were decomposed to 2(or 4) - substituted - 3 - difluoronitromethyl - 1,2,4-triazoles (IIIb), while the N,N-disubstituted derivative was thermally stable.

The increased reactivity of difluoronitroacetonitrile toward amines (as compared with the perfluornitriles) and the ease of cission of the C–C bond in the novel cyclization of the acyliminoamidines can reasonably be attributed to the higher electronegativity of the nitro compounds. In the ring closure reactions, the large steric requirements of the nitro group probably also play a part. In addition, internal hydrogen bonding between the amino and adjacent nitro groups and between the imino and its adjacent nitro group would be expected to have a pronounced effect on the spacial arrangement of the nitro containing acyliminoamidines and should strongly favor formation of a five-membered ring. A concerted reaction in which difluoronitromethane leaves as the *aci*-nitro acid is readily envisioned and requires migration of only a single proton. The failure of the N,N-disubstituted derivative to cyclize would be expected if such a mechanism were operative. This appears to be the first reported example of the closure of a 1,2,4-triazole ring by the formation of a N–N bond.



Experimental[9]

Difluoronitroacetamidine (Ia).—Difluoronitroacetonitrile[10] (0.02 mole) and ammonia (0.02 mole) were measured by standard vacuum techniques and were condensed by means of liquid nitrogen into an evacuated, 100-ml., Pyrex reaction bulb. The liquid nitrogen bath was then replaced by one of ethylene dichloride slush. After 1 hr. the reaction mixture was allowed to warm to room temperature, and volatile products and unchanged starting materials were pumped off into a liquid nitrogen-cooled trap on the vacuum manifold. The liquid remaining in the bulb was distilled at 80–90° and 5–10 μ to yield 1.79 g. (63%) of slightly yellow liquid. The major infrared absorption bands[11] were at 2.85 (m) (NH_2 asym. stretch), 2.92 (m) (NH_2 sym. stretch), 3.00 (m) (=NH stretch), 3.15 (m), 6.00 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.90 (m), 7.40 (m) (NO_2 sym. stretch), 8.20 (s) (CF), 8.72 (m), 9.60 (m), 9.95 (m), 11.92 (m), and 12.30 (m).

With excess liquid ammonia under reflux at one atmosphere or with a one-to-one ratio at 0°, the yield was only 15–20%. The remainder of the reaction products were mainly nonvolatile, high melting (above 200°), water insoluble solids which are probably mixtures of salts and/or polymers arising from the reaction of the amidine with excess ammonia. Similar solids are formed during thermal decomposition of the amidine.

Silver Salt of Ia.—Silver oxide (0.30 g., 1.29 mmoles) suspended in 1 ml. of dry ether was treated with 0.36 g. (2.59 mmoles) of Ia. Heat was evolved and the brown oxide turned white. The mixture was stirred thoroughly by hand to break up lumps, and the precipitated silver salt was removed by centrifugation, washed twice with 1-ml. portions of ether and vacuum dried at room temperature and 2 μ for 18 hr. The nearly white salt does not melt below 200°, although there is some decomposition at lower temperatures, and darkening occurs gradually at room temperature on exposure to light.

Ia Trifluoroacetate.—The amidine (0.32 g., 2.31 mmoles) was treated for 1 hr. at room temperature with 0.79 g. (6.89 mmoles) of trifluoroacetic acid. Heat was evolved and a white precipitate formed almost immediately. The excess trifluoroacetic acid was removed at room temperature under reduced pressure, and the residue was washed twice with 3-ml. portions of ether and dried at room temperature and 1–2 μ for 20 hr.; m.p. 173–174° dec.

N-Methyl- and N,N-Dimethyldifluoronitroacetamidine(Ib and Ic).—The N-methyl and N,N-dimethyl derivatives were prepared as described. Major infrared absorption bands for Ib were at 2.97 (sh) (NHR stretch), 3.10 (m) (=NH stretch), 3.20 (m) (CH stretch), 6.00 (s) (NC=N asym. stretch), 6.10 (s) (NC=N asym. stretch), 6.33 (s) (NO_2 asym. stretch), 6.60 (sh), 6.90 (vw), 7.10 (w), 7.28 (m), 7.45 (m) (NO_2 sym. stretch), 8.35 (s) (CF), 9.80 (m), 10.40 (w) and 11.92 (m). For Ic they were at 3.05 (m) (=NH stretch), 3.45 (m) (CH stretch), 6.20 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 7.10 (m), 7.40 (m) (NO_2 sym. stretch), 7.87 (w), 8.40 (s) (CF), 9.22 (m), 9.40 (sh), 9.80 (s), 11.40 (m), 12.20 (m), and 13.80 (m).

N-Phenyl- and N-(*p*-Trifluoromethylphenyl)difluoronitroacetamidine (Id and Ie).—The aromatic derivatives were prepared as described except that the amine was measured into the reactor and was frozen in liquid nitrogen prior to evacuation, the reaction temperature was 0°, and the reaction time was 18–24 hr. Major infrared absorption bands for Id were at 2.88 (m) (NH_2 asym. stretch), 2.98 (m) (NH_2 sym. stretch), 3.20 (w) (CH stretch), 5.95 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.75 (m), 7.17 (m), 7.43 (m) (NO_2 sym. stretch), 8.05 (s), 8.50 (s) (CF), 9.35 (w), 9.80 (m), 10.05 (m), 11.00 (w), 11.89 (m), 12.05 (m), 12.80 (m), 13.65 (m), and 14.35. For Ie (KBr pellet) they were at 2.90 (m) (NH_2 asym. stretch), 3.10 (m) (NH_2 sym. stretch), 3.20 (m) (CH stretch), 6.00 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.67 (w), 7.10 (w), 7.25 (w), 7.43 (s) (NO_2 sym. stretch), 8.00 (s), 8.40 (m) (CF), 8.63 (m), 9.00 (s), 9.37 (s), 9.85 (m), 10.10 (m), 11.46 (m), 11.90 (m), 12.02 (m), 12.80 (m), 13.38 (w), and 13.80 (w).

Hydrobromides.—Hydrobromides were prepared by saturating ether solutions of the amidines with hydrogen bromide gas, centrifuging, washing with ether, and drying at room temperature and 5–10 μ for 8–18 hr. The hydrobromides were somewhat hydroscopic and were readily hydrolized in hydroxylic solvents.

N′-(Difluoronitroacetylimino)difluoronitroacetamidine (IIa).

A. From Difluoronitroacetamidine.—Difluoronitroacetamidine (1.19 g., 8.56 mmoles) was treated with 8.83 mmoles of difluoronitroacetonitrile at 0° for 18 hr. Removal of unreacted nitrile and distillation at 100–110° and 5–10 μ yielded 1.25 g. (56%) of slightly yellow liquid. Major infrared absorption bands were located at 2.95 (s) (NH stretch), 3.06 (m) (=NH stretch), 3.2 (sh), 3.48 (w), 3.8 (w), 6.09 (s) (NC=N asym. stretch, 6.30 (s) (NO_2 asym. stretch), 6.59 (s), 7.3 (sh), 7.46 (s) (NO_2 sym.

(7) The proton n.m.r. spectrum of 3-amino-1,2.4-triazole in dimethyl sulfoxide showed two bands at −3.25 and −4.87 p.p.m. with respect to dimethyl sulfoxide. The higher field band was broadened essentially to the point of disappearance by acidification.

(8) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956).

(9) Melting points are corrected; boiling points except for that of difluoronitromethane are not corrected.

(10) I. L. Knunyants and A. V. Fokin, *Dokl. Akad. Nauk, SSSR*, **112**, 67 (1957).

(11) Infrared spectra were taken on a Perkin-Elmer Infracord Model 137 spectrophotometer as liquids unless otherwise noted. The units are microns.

stretch), 8.2 (s) (CF), 8.75 (w), 9.62 (s), 10.03 (m), 11.59 (m), 11.91 (m), 12.30 (s), 12.78 (m), 13.7 (w), and 14.1 (w).

B. **From Difluoronitroacetonitrile.**—Difluoronitroacetonitrile (0.02 mole) and ammonia (0.01 mole) were condensed into an evacuated 150-ml. Pyrex bulb. The bulb then was placed in an ice bath for 18–24 hr. Volatiles were removed on the vacuum manifold, and the liquid product was distilled as before to yield 2.34 g. (86%) of IIa. Its infrared spectrum was identical with that of material prepared from the amidine. If ratios of nitrile to ammonia of greater than two to one were employed, only two equivalents of nitrile were consumed; the remainder could be recovered quantitatively.

Copper Chelate of IIa.—IIa (0.20 g., 1.25 mmole) dissolved in 0.5 ml. of 1,2-dimethoxyethane was shaken with a solution of 0.15 g. (0.66 mmole) of cupric nitrate trihydrate in 1.0 ml. of water. The precipitated, rust-colored solid was removed by centrifugation, washed twice with 0.5-ml. portions of water, and dried at room temperature and 5 μ for 5 hr.; weight 0.17 g. (48%). After one recrystallization from benzene containing a few drops of 95% ethanol, it melted above 200°. It was very soluble in 95% ethanol, forming dark maroon solutions.

N-Methyl- and N,N-Dimethyl-N′-(difluoronitroacetylimino)-difluoronitroacetamidine (IIb and IIc).—IIb and IIc were prepared by method B. Major infrared absorption bands for IIb were at 2.97 (m) (NH stretch), 3.20 (w), 3.45 (w) (CH stretch), 5.93 (s) (NC=N asym. stretch), 6.03 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.55 (m), 6.90 (w), 7.09 (w), 7.40 (m) (NO_2 sym. stretch), 7.65 (w), 8.25 (s) (CF), 8.83 (w), 9.38 (m), 9.80 (m), 10.20 (m), 11.60 (w), 11.90 (m), 12.00 (w), 12.20 (m), 12.35 (m), 12.80 (m), 13.1 (w), and 13.8 (w). For IIc they were at 3.00 (w) (=NH stretch), 3.47 (m) (CH stretch), 6.20 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.70 (m), 7.08 (m), 7.48 (m) (NO_2 sym. stretch), 8.00 (s), 8.20 (s) (CF), 8.45 (w), 8.65 (m), 9.70 (m), 10.20 (m), 11.63 (m), 11.83 (m), 12.03 (w), 12.17 (m), 12.40 (m), and 12.80 (m).

N-Phenyl-N′-(difluoronitroacetylimino)difluoronitroacetamidine (IId).—The phenyl compound was prepared by method B except that the amine was measured into the reactor and was frozen in liquid nitrogen prior to evacuation, and the 0° reaction period was followed by an additional 24 hr. at room temperature. Major infrared absorption bands were at 3.00 (w) (=NH stretch), 6.00 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.80 (m), 7.20 (w), 7.45 (m) (NO_2 sym. stretch), 8.15 (s) (CF), 8.40 (m), 9.40 (w), 9.78 (w), 11.00 (w), 11.90 (m), 12.10 (m), 12.85 (w), 13.2 (w), 13.7 (w), and 14.4 (m).

Difluoronitromethane.—Difluoronitroacetamidine (0.40 g., 2.91 mmoles) was heated for 3 hr. at 95–105° under 400 mm. of helium. Difluoronitromethane (1.77 mmoles, 61%) was collected in a liquid nitrogen-cooled trap atop a short air condenser. Major infrared absorption bands for the vapor were at 3.30 (w), 3.40 (w) (CH stretch), 3.70 (vw), 4.36 (vw), 6.22 (s) (NO_2 asym. stretch), 7.38 (m) (NO_2 sym. stretch), 7.60 (m), 8.55 (s), 10.70 (m), and 12.5 (m). Approximately 50% yields could be obtained by similar thermal decomposition of IIa or IIb. The molecular weight as determined by PVT measurements was 96.4 (calcd. 97.0).

3-Difluoronitromethyl-1,2,4-triazole (IIIa).—IIa (1.68 g., 6.44 mmoles) was heated at 120° for 3 hr. under 400 mm. of helium. The difluoronitromethane which was evolved was collected in a liquid nitrogen-cooled trap atop a short air condenser and amounted to 5.24 mmoles. Heating for an additional 24 hr. at 100–110° under 400 mm. of helium resulted in evolution of an additional 0.21 mmole of difluoronitromethane. Heating the residue at 100–110° at 1 μ caused sublimation of 0.53 g. (50%) of crystalline triazole melting at 73.5–76°. After two recrystallizations from benzene–petroleum ether, it melted at 76–77° (unchanged by sublimation at 100° and 1 μ). The yield was essentially the same if the triazole was prepared directly from difluoronitroacetonitrile without isolation of the intermediate IIa. Major infrared absorption bands (KBr pellet) were at 2.90 (s) (NH stretch), 2.95 (s) (NH stretch), 3.08 (s) (NH stretch), 3.10 (sh), 3.40 (vw) (CH stretch), 3.70 (vw) (NH ammonium type band), 4.10 (vw), 6.03 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.55 (s), 7.00 (w), 7.14 (w), 7.37 (m) (NO_2 sym. stretch), 8.20 (vs) (CF), 9.33 (m), 9.52 (m), 9.70 (m), 10.18 (s), 10.62 (m), 11.59 (m), 11.99 (m), 12.13 (s), 12.78 (s), 13.22 (w), 13.80 (w), and 14.7 (w).

3-Difluoronitromethyl-2(or 4)-methyl-1,2,4-triazole (IIIb).—Difluoronitroacetonitrile (0.02 mole) and methylamine (0.01 mole) were condensed into a 60-ml. evacuated Pyrex bulb. After 20 hr. at 0° the bulb was filled to a pressure of 400 mm. with helium and heated at 100–110° for 7 hr. Difluoronitromethane (5 mmoles, 25% based on nitrile) evolved during the heating was collected in a liquid nitrogen-cooled trap. The liquid remaining in the reaction bulb was distilled at 130–140° and 2–5 μ to yield 1.20 g. (33%) of light yellow liquid. Major infrared absorption bands were at 2.90 (m) (NH stretch), 3.40 (CH stretch), 5.95 (sh) (NC=N asym. stretch), 6.15 (s) (NC=N asym. stretch), 6.30 (s) (NO_2 asym. stretch), 6.55 (m), 6.90 (w), 7.09 (m), 7.41 (m) (NO_2 sym. stretch), 8.10 (s) (CF), 8.85 (w), 9.70 (w), 10.20 (m), 11.60 (w), 12.00 (w), 12.20 (m), and 12.80 (m).

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Addition Compounds of Thiols and 1-Substituted Nicotinamides[1,2]

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van Eys and Kaplan have observed that "the ubiquitous nature of sulfhydryl compounds in biological systems" makes the addition reactions of thiols and diphosphopyridinenucleotide[5] (DPN) and its analogs of "particular interest."[6] The addition of a sulfhydryl enzyme to the 4-position of DPN has been suggested as an intermediate in the oxidation of aldehydes catalyzed by glyceraldehyde-3-phosphate dehydrogenase.[7]

Evidence for the addition of sulfide ion and of thiols to DPN has been adduced from changes in ultraviolet spectra.[6,8]

Wallenfels and Schüly have reported the synthesis of addition compounds of nicotinamide-1-(2,6-dichlorobenzylo) bromide and sulfide ion, benzyl mercaptan, 2-mercaptothiazole, β-phenylethyl mercaptan, ethyl mercaptan, thiocyanate ion, and thiophenol.[9]

In connection with investigations of some model systems for enzymic oxidation and reductions, new adducts of L-cysteine ethyl ester, ethyl thioglycolate, and *n*-propyl mercaptan with nicotinamide-1-(2,6-dichlorobenzylo) bromide have been prepared by addition of the mercaptan in aqueous sodium hydroxide to an aqueous solution of the quaternary bromide. These addition compounds were isolated as crystalline solids and their infrared and ultraviolet spectra were similar to each other.

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(2) Taken from J. M. Kolyer, Ph.D. thesis, University of Pennsylvania, 1960.

(3) Department of Chemistry, Syracuse University, Syracuse, N. Y.

(4) Walter T. Taggart Memorial Fellow, 1959–1960.

(5) Nicotinamide-adenine-dinucleotide.

(6) J. van Eys and N. O. Kaplan, *J. Biol. Chem.*, **228**, 305 (1957).

(7) I. Krimsky and E. Racker, *Science*, **122**, 319 (1955).

(8) H. Terayama and C. S. Vestling, *Biochem. Biophys. Acta*, **20**, 586 (1956); J. van Eys, N. O. Kaplan, and F. E. Stolzenbach, *ibid.*, **23**, 221 (1957).

(9) (a) K. Wallenfels and H. Schüly, *Ann.*, **621**, 86 (1959); (b) K. Wallenfels and H. Schüly, *Angew. Chem.*, **69**, 505 (1957).

The infrared spectra (taken in potassium bromide disks) of these addition compounds of thiols have very strong characteristic absorption at about 1560 cm.$^{-1}$, an absorption which has been attributed to a vinylogous amide group: $>N-C=C-C=O$.[10] Absorption at 1560 cm.$^{-1}$ occurs in 1,4-dihydronicotinamides and also in a compound alleged to be a 1,6-dihydronicotinamide derivative which was obtained by the reduction of nicotinamide-1-(2,6-dichlorobenzylo)bromide with sodium borohydride.[11] The absorption at 1560 cm.$^{-1}$ is much less intense or is absent in typical 1-substituted nicotinamide salts. The infrared spectrum of the addition compound of *n*-propanethiol also differs considerably in other absorption regions from the combined spectra of nicotinamide-1-(2,6-dichlorobenzylo)-chloride and *n*-propanethiol. The infrared spectrum of the mercaptide salt (where the mercaptide ion replaces halide ion) might, to a first approximation, be expected to be the sum of the spectra of nicotinamide-1-(2,6-dichlorobenzylo)chloride and of *n*-propanethiol minus the –SH absorption.

There are points of similarity in the infrared spectra of the adducts and the spectra of both the 1,4- and 1,6-dihydronicotinamides, and it does not seem possible to assign the structure on the basis of these spectra.[12] Some typical spectra are given in the Experimental section.

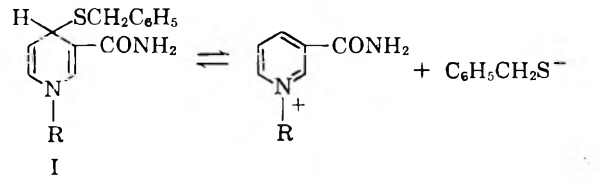
The 1,6-dihydronicotinamide was reported to have maxima in the ultraviolet spectrum at 265 (ϵ 9840) and 355 mμ (ϵ 7450) in methanol, the two maxima being attributed to cross conjugation in excited states.[11] The adducts of thiols and 1-substituted nicotinamides reported previously had one or two maxima in the ultraviolet depending on the solvent or on the concentration; the extinction coefficient for absorption at lower wave length was always greatest.[9a] The lower wave length band was believed to be caused by the dissociation of the addition compounds into the thiolate anion and the quaternary pyridinium ion. The benzyl mercaptan adduct had absorption at 333 mμ in benzene,[2] at 330 mμ in dioxane,[9a] at 316 and 254 mμ in ethanol,[9a] and at 265 mμ in water.[9a] The presence of only one absorption band at 330 mμ in the nonpolar solvents (where dissociation is minimized) may be considered as indicating a 1,4- rather than a 1,6-dihydro structure for the addition compounds; the 1,4-dihydro structure may be preferred on steric grounds.

In solution the addition compounds may exist as charge transfer complexes since the long wave length maximum for the benzyl mercaptan adduct increased from 315 mμ to 330 mμ on going from methanol to dioxane or benzene. However, the ultraviolet maximum for the addition compound of benzyl mercaptan does not shift to longer wave lengths as the polarity of the medium is decreased by changing the solvent from water to ethanol (see Table I). A shift to longer wave lengths as the polarity of the medium is decreased has been suggested as diagnostic of a charge-transfer complex.[13]

The addition compounds are colorless or nearly so. Crude material is generally bright yellow, but the intensity of the color decreases with repeated crystallizations. The original yellow color may be an impurity from the reaction of the nicotinamide salt with hydroxide ion.[14] The addition compound of cyanide ion and nicotinamide-1-(2,6-dichlorobenzylo)bromide is nearly colorless.[9a]

The 1,4-dihydropyridine structure, therefore, is unproved but is analogous to the structures proposed for the addition of cyanide and other substances to 1-substituted nicotinamides.[15] The rather wide melting point of the L-cysteine ethyl ester derivative may indicate that the material obtained is a mixture of position isomers or of mercaptide salt and addition compound.

The adducts are dissociated readily in polar media analogous to the dissociation of cyanide adducts.[16]



I

R = 2,6-dichlorobenzyl

Treatment of addition compound I with hydrogen chloride in chloroform gave the quaternary chloride salt. Treatment of I with a dilute solution of malachite green oxalate in chloroform caused immediate decolorization of the dye. The same behavior was observed in ethanol from which was isolated the addition compound of benzyl mercaptan and malachite green cation. In an analogous reaction, cyanide adducts similar to I transfer cyanide ion to malachite green.[9a]

Experimental

Nicotinamide-1-(2,6-dichlorobenzylo)-bromide.—A mixture of N-bromosuccinimide (10.0 g., 0.056 mole) and 2,6-dichlorotoluene (Aldrich Chemical Co.) (9.0 g., 0.056 mole) in 40 ml. of carbon tetrachloride was refluxed for 31 hr. The solid was removed and the filtrate was fractionally distilled to remove the carbon tetrachloride. Nicotinamide (6.1 g. 0.050 mole) and 25 ml. of absolute alcohol were added, and the solution was refluxed for 12 hr. When the reaction mixture was chilled, the product separated as tan crystals (9.9 g., 48%) and was recrystallized from ethanol–water to give fine white crystals, m.p. 248–249° (lit.[9b] m.p. 245–246°).

Preparation of Thiol Addition Compounds. 1. L-Cysteine Ethyl Ester Adduct.—Nicotinamide-1-(2,6-dichlorobenzylo)-bromide (0.364 g., 0.00101 mole) and L-cysteine ethyl ester hydrochloride (Mann Research Laboratories) (1.99 g., 0.0107 mole) were dissolved in 10 ml. of distilled water. The solution was chilled in an ice bath and stirred while 10% sodium hydroxide solution was added from a buret. After 7.1 ml. had been added, the precipitate did not redissolve on stirring. An additional 0.5 ml. of base was added, and the mixture was stirred briefly.

(10) A. G. Anderson, Jr., and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).

(11) K. Wallenfels and H. Sehüly, *Ann.*, **621**, 106 (1959). [Sodium borohydride reduces the 1-phenylpyridinium ion to 1-phenyl-1,2-dihydropyridine whose structure was proved by proton n.m.r. spectroscopy. M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).]

(12) We wish to thank a referee for suggesting that the infrared spectra might help in establishing a structure.

(13) E. M. Kosower in P. D. Boyer, H. Lardy, and K. Myrbäck, "The Enzymes," Vol. 3, 2nd Ed., Academic Press, New York, N.Y., 1960, p. 183.

(14) A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958).

(15) A. San Pietro, *J. Biol. Chem.*, **217**, 579 (1955); M. B. Yarmolinsky and S. P. Colowick, *Biochim. Biophys. Acta*, **20**, 177 (1956); R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, **206**, 283 (1954); R. M. Burton and N. O. Kaplan, *ibid.*, **211**, 447 (1954).

(16) M. R. Lanborg, R. M. Burton, and N. O. Kaplan, *J. Am. Chem. Soc.*, **79**, 6173 (1957); K. Wallenfels and H. Diekmann, *Ann.*, **621**, 166 (1959).

Filtration gave a white powder (0.033 g., 8%), m.p. 93–102° dec., which was dried over phosphorus pentoxide under reduced pressure; λ_{max} (ethanol) 255 (ϵ 4.9 × 10^3), 315 mμ (ϵ 3.9 × 10^3), λ_{max} (50% ethanol) 268 mμ (ϵ 5.2 × 10^3).

Anal. Calcd. for $C_{18}H_{21}N_3O_3SCl_2$: C, 50.23; H, 4.92; N, 9.76. Found: C, 50.51; H, 4.77; N, 10.11.

When this compound was chromatographed on Whatman no. 1 paper (solvent, 4:1:5 butanol–acetic acid–water) and the chromatogram developed with fresh 1% sodium nitroprusside in 0.05 *N* sodium hydroxide solution both cysteine ethyl ester and cysteine were identified.

2. **Ethyl Thioglycolate Adduct.**—Ethyl thioglycolate (2.6 g., 0.022 mole) in 20 ml. of 5% sodium hydroxide solution was added to nicotinamide-1-(2,6-dichlorobenzylo)-bromide (1.01 g., 0.00279 mole) in 20 ml. of distilled water. After 10 min. the product (0.96 g., 86%) was removed by filtration, washed with water and dried. Recrystallization from ethanol–benzene gave nearly white crystals, m.p. 131–132°; λ_{max} (ethanol) 255 (ϵ 4.1 × 10^3), 316 mμ (ϵ 2.4 × 10^3); λ_{max} (50% ethanol) 267 mμ (ϵ 3.1 × 10^3).

Anal. Calcd. for $C_{17}H_{18}N_2O_3SCl_2$: C, 50.88; H, 4.52; N, 6.98. Found: C, 50.56, 50.64; H, 4.55, 4.67; N, 6.83, 6.87.

When this adduct was chromatographed on paper as described previously, ethyl thioglycolate was identified.

3. ***n*-Propyl Mercaptan Adduct.**—This addition compound was prepared from *n*-propyl mercaptan in the same way as the adduct of ethyl thioglycolate. The crude yellow product was recrystallized from cold ethanol to give a white powder, m.p. 96–98°, λ_{max} (ethanol) 256 (ϵ 4.3 × 10^3), 316 mμ (ϵ 2.7 × 10^3).

Anal. Calcd. for $C_{16}H_{18}N_2OSCl_2$: C, 53.78; H, 5.08. Found: C, 53.91, 54.03; H, 5.13, 5.27.

Ultraviolet Spectra of Benzyl Mercaptan Adduct in Ethanol–Water Mixtures.—The benzyl mercaptan adduct, m.p. 131–132° (lit.[9a] m.p. 131–133°), was prepared by the same method as the ethyl thioglycolate adduct. The effect of the polarity of the medium on the ultraviolet spectrum of this adduct are summarized in Table I.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF BENZYL MERCAPTAN ADDUCT IN ETHANOL–WATER SOLUTIONS

Water, ml.	Ethanol, ml.	Concn. × 10^4 *M*	λ_{max}, mμ	ϵ × 10^{-3}	λ_{max}, mμ	ϵ × 10^{-3}
0	50	1.0	316	4.8	254	7.1
5	45	1.1	315	2.4	257	4.5
10	40	1.5	317	1.6	257	3.9
20	30	1.1	317	0.45	265	3.6
30	20	1.4	317	.14	265	3.8
40	10	0.99	317	.09	265	6.7

Reaction of Benzyl Mercaptan Adduct with Hydrogen Chloride.—The addition compound (*ca.* 0.1 g.) was dissolved in 10 ml. of chloroform, and anhydrous hydrogen chloride was passed through the solution. The white precipitate, m.p. 235° dec., was shown to be nicotinamide-1-(2,6-dichlorobenzylo)-chloride by a mixture m.p. (236°) and by identity of the infrared spectra. Nicotinamide-1-(2,6-dichlorobenzylo)-chloride was prepared by heating a mixture of 2,6-dichlorotoluene (16.1 g., 0.100 mole), sulfuryl chloride (6.8 g., 0.050 mole), and benzoyl peroxide (0.2 g., 0.0008 mole) on the steam bath until gas evolution ceased (1 hour). Nicotinamide (6.1 g., 0.050 mole) and 25 ml. of absolute alcohol were added, and the solution was refluxed for 3 hr. When the reaction mixture was cooled, white crystals (7.8 g., 49%) separated. Two recrystallizations from alcohol–water gave white crystals, m.p. 237–238.5° dec.

Anal. Calcd. for $C_{13}H_{11}N_2OCl_3$: C, 49.16; H, 3.49. Found: C, 48.94, 49.13; H, 3.61, 3.73.

Reaction of the Benzyl Mercaptan Adduct with Malachite Green.—A solution of malachite green oxalate (0.5 g.) in 10 ml. of absolute ethanol was heated gently while the adduct was added, with stirring, until the solution was decolorized (pale green). Filtration gave a pale green solid (0.5 g.) and a green filtrate. The solid was soluble in water and insoluble in alcohol and ether. Two recrystallizations from alcohol–water and decolorization with charcoal gave off-white crystals, m.p. 229–230° dec. Analysis by sodium fusion demonstrated the presence of nitrogen and chlorine and the absence of sulfur. With silver nitrate solution, the compound gave an acid-soluble white precipitate (silver oxalate). It was concluded that the compound was nicotinamide-1-(2,6-dichlorobenzylo)oxalate.

Anal. Calcd. for $C_{28}H_{22}N_4O_6Cl_4$: C, 51.55; H, 3.40. Found: C, 51.54, 51.81; H, 3.45, 3.68.

The green filtrate deposited white fluffy crystals (0.1 g.), m.p. 120–122° dec. This compound was identified as the benzyl sulfide of malachite green by m.m.p. (122°) with an authentic sample. The sulfide was prepared also by the dropwise addition of 6 *N* sodium hydroxide solution to a solution of malachite green oxalate (0.4 g., 0.0004 mole) and benzyl mercaptan (1 ml., 0.009 mole) in 15 ml. of absolute ethanol until the solution was decolorized. A tan solid was removed by filtration, and the filtrate was diluted with 5 ml. of ethanol and allowed to stand for 2 hr. Filtration gave fluffy white crystals (0.08 g., *ca.* 50%), m.p. 121–123° dec. This compound turned green on standing in air.

Anal. Calcd. for $C_{30}H_{32}N_2S$: C, 79.60; H, 7.13. Found: C, 79.51, 79.65; H, 7.07, 7.26.

1-(2,6-Dichlorobenzyl)-1,6-dihydronicotinamide.[11]—Sodium borohydride (0.207 g., 0.00547 mole) was added during 1 min. to a stirred solution of nicotinamide-1-(2,6-dichlorobenzylo)bromide (1.00 g., 0.00276 mole) in 15 ml. of distilled water. The crude product precipitated and was recrystallized by dissolving it in 15 ml. of ethanol, adding 15 ml. of water, and chilling. The bright yellow, fine crystals (0.512 g., 66%), m.p. 161–163° dec. [lit.[11] m.p. >150° (dec.)], were dried over potassium pentoxide. The ultraviolet maxima in ethanol were at 354 mμ (ϵ 4200) and 263 mμ (ϵ 4300) [lit.[11] (methanol) 355 mμ (ϵ 7450), 265 mμ (ϵ 9840)].

Comparisons of Infrared Spectra.—The infrared spectra in $cm.^{-1}$ of the following compounds are given.

n-Propanethiol adduct of nicotinamide-1-(2,6-dichlorobenzylo)-bromide: 3450 m, 3150 m, 2975 m, 1675 s, 1654 s, 1608 m, 1562 s (1590–1535), 1465 w, 1454 m, 1434 m, 1409 m, 1380 m, 1356 m, 1342 m, 1283 m, 1222 m, 1204 m, 1170 m, 1090 m, 1085 m, 1032 w, 957 w, 947 w, 920 w, 875 w, 823 w, 800 w, 776 m, 767 m, 750 m, 737 m, 704 w, 667 w.

1-(2,6-Dichlorobenzyl)-1,4-dihydronicotinamide: 3470–3370 w, 3140 w, 2810 w, 1688 m, 1663–1640 m, 1577 (1610–1540) s, 1435 m, 1380 w, 1360 m, 1338 m, 1300 w, 1280 w, 1207 m, 1161 w, 1085 w, 998 w, 952 w, 867 w, 778 w, 764 w, 713 w.

1-(2,6-Dichlorobenzyl)-1,6-dihydronicotinamide: 3375 m, 3190 m, 2775 w, 1680 m, 1643 s, 1598 s, 1580 s, 1562 s, 1435 s, 1430 s, 1385 s, 1359 m, 1340 w, 1317 m, 1308 w, 1282 m, 1220 m, 1201 m, 1178 w, 1162 w, 1128 w, 1021 w, 979 w, 954 w, 870 w, 777 m, 763 w, 729 w, 707 w.

Nicotinamide-1-(2,6-dichlorobenzylo)chloride: 3500 m, 3380 m, 3290 m, 3080 s (3200–2900), 1688 s, 1617 m, 1578 m, 1563 m, 1497 w, 1466 w, 1447 s, 1411 s, 1390 s, 1366 m, 1320 w, 1275 w, 1202 m, 1185 m, 1133 m, 1118 w, 1088 m, 1027 w, 970 w, 948 w, 895 w, 883 w, 852 w, 834 w, 813 m, 793 w, 778 m, 768 m, 755 m, 708 w, 678 m, 672 m.

n-Propanethiol[17]: 4444 w, 2915 s, 2577 w, 2326 w, 1449 s, 1370 m, 1330 w, 1290 m, 1245 s, 1107 w, 1096 w, 920 m, 901 s, 893 s, 813 s, 790 s, 730 s, 704 m.

(17) Sadtler Standard Spectra, Midget Ed., Sadtler Research Laboratories, Philadelphia, Pa., no. 328 (1962).

The Conjugate 1:4-Addition of Some Acetylenic Grignard Reagents to Cyclohexylidenemalononitrile

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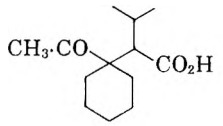
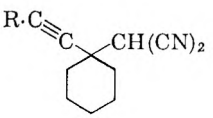
Recently, in another connection, it was found necessary to devise a synthesis of α-(1-acetylcyclohexyl)isovaleric acid (I). By analogy with the well established addition of alkyl Grignard reagents to carbon–carbon

double bonds conjugated with electrophilic groupings,[1] the quaternary center of this acid was produced by the addition of ethynylmonomagnesium bromide[2] to cyclohexylidenemalononitrile to give [1-(1-ethynyl)cyclohexyl]malononitrile (II. R = H). Treatment of II (R = H) with isopropyl iodide in the presence of sodium ethoxide gave the alkylated derivative (III) which was converted into the required γ-ketocarboxylic acid (I) by basic hydrolysis followed by acid-catalyzed decarboxylation.


I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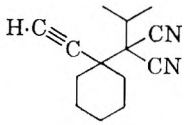
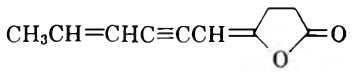

III

A series of such additions[3] then was performed in order to examine this procedure as a general synthetic route to 1,1-disubstituted cyclohexanes. Cyclohexylidenemalononitrile, in the presence of cuprous chloride,[1] was treated with the Grignard reagents of phenylacetylene, 1-octyne, and the tetrahydropyranyl ether of propargyl alcohol and the corresponding [1-(1-alkynyl)-cyclohexyl]malononitriles were isolated in yields ranging from 48% to 17%. When 4-benzoyloxycyclohexylidenemalononitrile was treated with ethynylmonomagnesium bromide, 1-(4-benzoyloxy-1-ethynyl cyclohexyl)malononitrile was obtained as a mixture of the *cis* and *trans* forms.

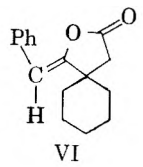
The naturally occurring polyacetylenic acid (IV) is readily transformed at pH 7 into the corresponding γ-enol lactone[4] (V), and this fact suggested that a similar mechanism could account for the unexpected hydration of the triple bond in this series. Alkaline hydrolysis of [1-(1-phenylethynyl)cyclohexyl]malononitrile (II. R = Ph), followed by thermal decarboxylation and treatment with diazomethane, afforded a mixture of the γ-enol lactone (VI) and the keto ester (VII. R = CH_3) which was separated by chromatography on activated alumina.

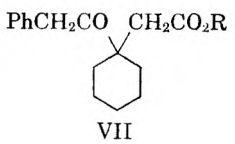
$CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCO_2H$

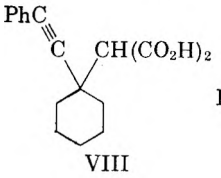
IV

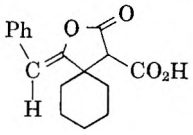

V

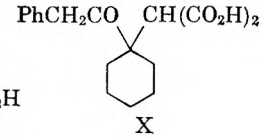
These facts were indicative of the triple bond hydration proceeding *via* the γ-enol lactone (VI) rather than the corresponding δ-enol lactone. The formation of VI and VII (R = H) from the basic hydrolysis and thermal decarboxylation of II (R = Ph), therefore, is envisaged as proceeding through the ethynylmalonic acid (VIII) which would then undergo isomerisation to the related enol lactone (IX). Incomplete hydrolysis of this material would give a mixture of IX and the ketomalonic acid (X), both of which can lose carbon dioxide on heating to furnish the two final products VI and VII (R = H).


VI


VII


VIII


IX


X

Experimental[5]

Cyclohexylidenemalononitrile was prepared in the usual manner[7] by refluxing cyclohexanone (64.5 g.) and malononitrile (40 g.) with ammonium acetate (4.6 g.) and acetic acid (7.5 g.) in benzene. Normal isolation procedure gave the required product (70.4 g.), b.p. 86° (2 mm.), $n^{25}D$ 1.5100.

4-Benzoyloxycyclohexylidenemalononitrile.—A mixture of 4-benzoyloxycyclohexanone (12 g.), malononitrile (3.3 g.), ammonium acetate (0.5 g.), and acetic acid (0.7 g.) in benzene (50 ml.) was heated under reflux for 15 hr. under a Dean and Stark water separator. The cooled reaction mixture was washed with saturated sodium bicarbonate solution and water, dried, and the solvent removed to give **4-benzoyloxycyclohexylidenemalononitrile** which crystallized from methanol in prisms, m.p. 135–136°; ν_{max} (Nujol mull) 1720 cm.$^{-1}$ (benzoate) and 2230 cm.$^{-1}$ (conjugated nitrile).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.15; H, 5.3; N, 10.5. Found: C, 71.95; H, 5.5; N, 10.5.

[1-(1-Ethynyl)cyclohexyl]malononitrile (II. R = H).—A warm solution of ethylmagnesium bromide (from magnesium, 6.0 g.) in dry tetrahydrofuran (200 ml.) was transferred under nitrogen to a dropping funnel and added over 3 hr. to a stirred saturated solution of acetone-free acetylene in tetrahydrofuran (500 ml.). Acetylene was passed through the solution during this addition and for a further hour. Freshly prepared cuprous chloride (5 mole %), followed by cyclohexylidenemalononitrile (7.5 g.) in dry tetrahydrofuran (100 ml.), was added over 3 hr. to the solution of ethynylmonomagnesium bromide held in a nitrogen atmosphere and the reaction mixture then was stirred for 20 hr. at 20°. The Grignard complex was decomposed with saturated ammonium chloride solution and the reaction mixture extracted with ether. The combined ethereal extracts were washed with saturated brine solution, dried, and the solvent removed to give a red oil. An ethanolic solution of the crude product was treated with potassium cyanide (1 g.) in a minimum volume of water and stirred for 4 hr. The reaction mixture then was diluted with water, and isolated in the usual manner by ether extraction. Removal of the solvent followed by fractional distillation of the residual oil gave **[1-(1-ethynyl)cyclohexyl]malononitrile** (4.2 g., 48%), b.p. 74° (0.1 mm.), $n^{25}D$ 1.4824; ν_{max} (liquid film) 3300, 2270, and 2100 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.7; H, 7.0; N, 16.3. Found: C, 76.6; H, 6.75; N, 16.6.

[1-(1-Phenylethynyl)cyclohexyl]malononitrile (II. R = Ph).—Phenylacetylene (10.2 g.) in dry tetrahydrofuran (20 ml.) was added to a stirred solution of ethylmagnesium bromide (from magnesium 2.4 g.) in tetrahydrofuran (250 ml.) and the reaction mixture heated under reflux for 2 hr. The cooled reaction

(1) J. Munch-Peterson, *J. Org. Chem.*, **22**, 170 (1957).

(2) E. R. H. Jones, L. Skattebol, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956).

(3) E. P. Kohler and M. Reimer, *Am. Chem. J.*, **33**, 333 (1905); *Chem. Zentr.*, **1**, 1389 (1905).

(4) P. K. Christiansen, N. A. Sorensen, I. Bell, E. R. H. Jones, and M. C. Whiting, *Festschr. Arthur Stoll*, 545 (1957); I. Bell, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1313 (1958); P. K. Christiansen, *Acta Chem. Scand.*, **11**, 582 (1957).

(5) All melting points were determined on a Kofler hot stage and are corrected. Boiling points are uncorrected. Ultraviolet absorption spectra refer to ethanol solutions and were measured with a Unicam S.P. 500 spectrophotometer. Infrared spectra were determined on the Perkin-Elmer Infracord and Perkin-Elmer 13 spectrophotometers. The alumina used for chromatography was acid washed and activated and graded according to the method of Brockmann and Schodder.[6] Light petroleum refers to the fraction, b.p. 40–60°, unless stated otherwise.

(6) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

(7) A. C. Cope and K. E. Hoyle, *J. Am. Chem. Soc.*, **63**, 733 (1941).

mixture then was treated with cuprous chloride (5 mole %) followed by a solution of cyclohexylidenemalononitrile (7.5 g.) in tetrahydrofuran (25 ml.). After heating under reflux for 4 hr., the Grignard complex was decomposed with a saturated solution of ammonium chloride, extracted with ether, and the combined ethereal extracts washed with water and dried. Removal of the solvent gave a viscous gum which solidified on trituration with light petroleum to give [1-(1-**phenylethynyl**)**cyclohexyl**]**malononitrile** (5 g., 39%), which crystallized from light petroleum in needles, m.p. 62–63°.

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.2; H, 6.5; N, 11.3. Found: C, 82.35; H, 6.4; N, 11.2.

[1-(1-**Octynyl**)**cyclohexyl**]**malononitrile**.—1-Octyne (11 g.) in dry tetrahydrofuran (50 ml.) was added to a solution of ethylmagnesium bromide (from magnesium 2.4 g.) in tetrahydrofuran (85 ml.) and the reaction mixture heated under reflux in an atmosphere of nitrogen for 20 hr. Cuprous chloride (5 mole %) was added to the reaction mixture held at 0°, followed by a slow addition of cyclohexylidenemalononitrile (9.0 g.) in a solution of tetrahydrofuran. The stirred solution was held at room temperature for 18 hr. and then heated under reflux for 8 hr. before being worked up as in the previous experiment. The resultant crude oil was fractionally distilled to give [1-(1-**octynyl**)**cyclohexyl**]**malononitrile** (7.0 g. 44%) as a colorless oil, b.p. 112° (0.1 mm.), $n^{21}D$ 1.4785.

Anal. Calcd. for $C_{17}H_{24}N_2$: C, 79.65; H, 9.45; N, 10.95. Found: C, 79.75; H, 9.45; N, 10.8.

[1-(1-**Tetrahydropyranyloxypropargyl**)**cyclohexyl**]**malononitrile**.—3-Tetrahydropyranyloxy-1-propyne (14 g.) in dry tetrahydrofuran (25 ml.) was added to a solution of ethylmagnesium bromide (from magnesium, 2.4 g.) and the reaction mixture heated under reflux for 8 hr. under nitrogen and then chilled to 0°. Cuprous chloride (5 mole %) then was added followed by a slow addition of cyclohexylidenemalononitrile (9 g.) in tetrahydrofuran (20 ml.) and the reaction mixture stirred for 4 hr. at room temperature and then heated under reflux for 20 hr. The usual work-up procedure gave a dark red viscous liquid which was fractionally distilled to give [1-(1-**tetrahydropyranyloxypropargyl**)**cyclohexyl**]**malononitrile** (3 g. 17%) as a colorless oil, b.p. 140° (0.05 mm.), $n^{21}D$ 1.4920.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.75; N, 9.8. Found: C, 71.6; H, 7.95; N, 10.1.

[1-(4-**Benzoyloxy-1-ethynyl**)**cyclohexyl**]**malononitrile**.—4-Benzoyloxycyclohexylidenemalononitrile (30 g.) in dry tetrahydrofuran (250 ml.) was added to a solution of ethynylmonomagnesium bromide (prepared as in the previous experiment from magnesium 12 g.) and the whole stirred in a nitrogen atmosphere at 4° for 44 hr. Decomposition of the Grignard complex and isolation of the product gave a dark red gum which was adsorbed on alumina (grade I, 900 g.) from benzene–light petroleum (5:1). Elution with the same solvent gave starting material (5 g.) and then elution with benzene afforded [1-(**4-benzoyloxy-1-ethynyl**)**cyclohexyl**]**malononitrile** (4.3 g.), which crystallized from carbon tetrachloride in prisms, m.p. 129–130°; ν_{max} (potassium chloride disk) 3300, 2270, and 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.5; N, 9.6. Found: C, 73.75; H, 5.2; N, 9.8%.

Further elution with benzene–chloroform (4:1) gave the other isomer of [1-(**4-benzoyloxyl-1-ethynyl**)**cyclohexyl**]**malononitrile** (2.6 g.), which crystallized from methanol as prisms, m.p. 177–178°.

Anal. Found: C, 74.2; H, 5.3; N, 9.65%.

[1-(1-**Ethynyl**)**cyclohexyl**]**isopropylmalononitrile** (III).—A solution of [1-(1-ethynyl)cyclohexyl]malononitrile (2.3 g.) and sodium ethoxide (from sodium 0.33 g.) in dry ethanol (20 ml.) was heated under reflux for 3 hr. and chilled to −15°. Isopropyl iodide (2.5 g.) was then added and the reaction mixture again heated under reflux for 16 hr. After removal of most of the ethanol, water was added and the solution extracted with ether and combined ethereal extracts washed with water, dried, and the solvent removed to furnish [1-(1-**ethynyl**)**cyclohexyl**]**isopropylmalononitrile** (0.9 g.), which crystallized from light petroleum in prisms, m.p. 88–89°.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.45; H, 8.45; N, 13.05. Found: C, 78.8; H, 8.35; N, 13.25.

α-(1-**Acetylcyclohexyl**)**isovaleric Acid** (I).—Sufficient ethanol was added to a mixture of [1-(1-ethynyl)cyclohexyl]isopropylmalononitrile (0.6 g.) and 30% aqueous potassium hydroxide solution (25 ml.) to give a homogeneous solution and the whole was then heated under reflux until no more ammonia was evolved. The reaction mixture then was acidified with dilute sulfuric acid and warmed at 100° for 20 min. to effect decarboxylation of the intermediate malonic acid. The cooled solution was thoroughly extracted with ether and the combined ethereal extracts then were washed with water, dried, and the solvent removed to give α-(1-**acetylcyclohexyl**)**isovaleric acid** (0.575 g.), which crystallized from ethyl acetate–light petroleum (b.p. 60–80°) in prisms, m.p. 108–109°.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 69.0; H 9.8. Found: C, 69.15; H, 9.55.

Alkaline Hydrolysis of [1-(1-**Phenylethynyl**)**cyclohexyl**]**malononitrile** (II. **R** = **Ph**).—A mixture of II [R = Ph (2.2 g.)] and 20% aqueous potassium hydroxide solution (100 ml.) was heated under reflux until no more ammonia was evolved. The solution then was acidified, extracted with ether, and the combined ethereal extracts washed with water and dried. Removal of the solvent gave a gum which was heated *in vacuo* at 100° for 2 hr. A portion of the product (1 g.) was esterified with ethereal diazomethane and the resulting ester then adsorbed on alumina (grade III) from light petroleum (b.p. 60–80°). Elution with light petroleum (b.p. 60–80°)–benzene (5:1) yielded the γ-enol lactone VI (0.2 g.), which crystallized from *n*-hexane in needles, m.p. 111–112.5°; ν_{max} (potassium chloride disk) 1800 cm.$^{-1}$ (γ-enol lactone), 1670 cm.$^{-1}$ (enol double bond); λ_{max} 256 mμ (ε 24,000).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5. Found: C, 79.05; H, 7.4.

Further elution with light petroleum (b.p. 60–80°)–benzene (4:1) afforded the keto ester (VII. R = CH_3) as a colorless oil, (0.6 g.), b.p. (bath temp.) 120° (0.05 mm.), $n^{25}D$ 1.5238; ν_{max} (liquid film) 1730 and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.4; H, 8.1. Found: C, 74.2; H, 8.25.

Acknowledgment.—The authors are indebted to Professor R. A. Raphael for many helpful discussions during this work. R. R. gratefully acknowledges a Maintenance Award from the Department of Scientific and Industrial Research.

Anomalous Reduction of Malonic Esters with Lithium Aluminum Hydride

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During the one-step reduction and acetylation of triethyl 1,1,2-ethanetricarboxylate with lithium aluminum hydride and acetic anhydride, 2-methylene-1,4-diacetoxybutane was formed in a 16% yield along with the expected 1,4-diacetoxy-2-(acetoxymethyl)butane in a 52% yield.[3] Since there was no reason to expect elimination of acetic acid from a primary acetate under these conditions, it appeared likely that the unsaturated derivative was formed during the reduction of the substituted malonic ester with lithium aluminum hydride. Dreiding and Hartman[4] showed that certain substituted acetoacetic esters, such as 2-carbethoxycyclohexanone, were reduced through the enolate.

For the reduction of 2-carbethoxycyclohexanone the products were 2-methylenecyclohexanol in a 52%

(1) Office of Naval Research Fellow, 1956–1957; National Science Foundation Fellow, 1957–1959.

(2) Office of Naval Research Fellow, 1951–1954; Union Carbide Fellow, 1954–1955.

(3) W. J. Bailey, W. G. Carpenter, and M. E. Hermes, *J. Org. Chem.*, **27**, 1975 (1962).

(4) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953).

yield, 1-hydroxymethylcyclohexene in a 21% yield, and the expected 2-hydroxymethylcyclohexanol in only an 11% yield. We were able to use all these intermediates to advantage for the synthesis of 3-methylenecyclohexene.[5] The mechanism postulated for this reaction, based partly on the fact that 2-hydroxymethylenecyclohexanone gives the identical products, involves the normal reduction of the ester to the aldehyde, followed by the formation of the corresponding enolate which could undergo attack at either carbonyl group to produce a doubly charged anion which, although stable to further attack by hydride ion, can lose an oxygen ion by analogy with the mechanism for the base-catalyzed dehydration of aldols. One could write a similar mechanism for the reduction of malonic esters. In order to demonstrate that this anomalous reduction would occur with other malonic esters, ethyl methylmalonate was reduced with lithium aluminum hydride to produce, in addition to the expected diol, a 5.2% yield of methallyl alcohol. The methallyl alcohol was identified by vapor phase chromatography and infrared analysis.

Finally as an example that would give an increased opportunity for this anomalous reduction, bimalonic ester, ethyl 1,1,2,2-ethanetetracarboxylate, was reduced as previously described[6] and the forerun from the reductive acetylation was examined carefully. From this reduction was obtained a 15% yield of 2,3-di(acetoxymethyl)-3-butenyl acetate, together with the expected tetraacetate. The structure of this olefin triacetate was proved by pyrolysis to the known 2,3-di(acetoxymethyl)-1,3-butadiene[6] and by independent synthesis by the pyrolysis of 2,3-di(acetoxymethyl)-1,4-diacetoxybutane.

An attempt to isolate 2-phenylallyl alcohol from the reduction of ethyl phenylmalonate failed. It may be that this substituted styrene is formed but is polymerized before isolation.

Experimental[7]

Methallyl Alcohol from Reduction of Ethyl Methylmalonate.—To a slurry of 27.5 g. (0.737 mole) of lithium aluminum hydride and 300 ml. of dry ether in a 1-l., three-necked flask, fitted with a reflux condenser, a dropping funnel, and a stirrer, was added a solution of 75.6 g. (0.435 mole) of ethyl methylmalonate in 100 ml. of ether at a rate such as to maintain gentle reflux of the solvent acid. After the mixture had been heated under reflux for an additional 18 hr., it was poured onto a mixture of ice and dilute hydrochloric acid. The aqueous phase was extracted for 2 days in an exhaustive extractor and the extracts, together with the original ether layer, were dried over anhydrous magnesium sulfate. Distillation of this solution through a 10-in., helix-packed column gave 1.9 g. (5%) of methallyl alcohol, b.p. 112–115°, $n^{25}D$ 1.4228 (reported[8] b.p. 111.5–112°, $n^{25}D$ 1.4232), and 28.1 g. (72%) of 2-methyl-1,3-propanediol, b.p. 90–93° (4 mm.), $n^{25}D$ 1.4436 (reported[9] b.p. 213–214°, $n^{20}D$ 1.4445). Vapor phase chromatography of this sample of methallyl alcohol at 88° on di-*n*-decyl phthalate column gave a single symmetrical peak with the same retention time as that of an authentic sample of methallyl alcohol.

2,3-Di(acetoxymethyl)-3-butenyl Acetate from the Reduction of Ethyl 1,1,2,2-Ethanetetracarboxylate.—To a slurry of 100 g. (2.63 moles) of lithium aluminum hydride in 3 l. of ether was added dropwise a solution of 318 g. (1 mole) of ethyl 1,1,2,2-ethanetetracarboxylate in 3 l. of ether. After 2 l. of *n*-butyl ether had been added, the mixture was heated under reflux for 8 days. Most of the ethyl ether was removed by distillation with the concurrent addition of an additional 2 l. of *n*-butyl ether. After 500 ml. of glacial acetic acid had been added to decompose the excess hydride, followed by the addition of 1000 ml. of acetic anhydride, the mixture was heated under reflux for 6 days. During this period the mixture became so thick that stirring had to be discontinued and an additional 2 l. of *n*-butyl ether was added. The salts were removed from the solution by filtration and the solvent was removed from the filtrate by distillation. Fractionation of the residue through a 10-in. Vigreux column gave a forerun, b.p. 90–115° (0.2–0.4 mm.), and 151 g. (48%) of 2,3-di(acetoxymethyl)-1,4-diacetoxybutane, b.p. 160–165° (1.8 mm.), m.p. 66–68° (reported[6] 67–68°). The forerun, which contained some solid tetraacetate, was filtered and the solid was washed with ether. The combined filtrates were refractionated through a 10-in., helix-packed column to yield 39 g. (15%) of 2,3-di(acetoxymethyl)-3-butenyl acetate, b.p. 107.5–109° (0.2–0.3 mm.), $n^{25}D$ 1.4499 [reported[6] b.p. 138–139° (2 mm.), $n^{25}D$ 1.4518].

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 6.96; sapon. equiv., 86. Found: C, 55.98; H, 7.16; sapon. equiv., 85.

The olefin triacetate produced by the pyrolysis of 2,3-di(acetoxymethyl)-1,4-diacetoxybutane was identical to that prepared by the reductive acetylation of ethyl 1,1,2,2-ethanetetracarboxylate.

Pyrolysis of 2,3-Di(acetoxymethyl)-3-butenyl Acetate.—At a rate of 28 drops per min., 35 g. (0.135 mole) of 2,3-di(acetoxymethyl)-3-butenyl acetate was dropped through the pyrolysis tube heated at 490° while the system was flushed with a slow stream of oxygen-free nitrogen.[6] After an ether solution of the pyrolysate was extracted with water, the organic layer was dried over anhydrous magnesium sulfate. (Titration of an aliquot of the aqueous extracts indicated that 55% of the theoretical amount of acetic acid had been eliminated.) The ether was removed by distillation and the residue was fractionated through a 10-in., helix-packed column to give 10.9 g. (41%) of 2,3-di(acetoxymethyl)-1,3-butadiene, b.p. 61–63° (0.25 mm.), m.p. 62–63° (reported[6] m.p. 63–64°), and 14.1 g. of recovered starting material. A mixture melting point determination of this solid with an authentic sample of the diene-diacetate prepared from the pyrolysis of the tetraacetate[6] showed no depression.

(5) W. J. Bailey and J. C. Goossens, *J. Am. Chem. Soc.*, **78**, 2804 (1956).
(6) W. J. Bailey and W. R. Sorenson, *ibid.*, **78**, 2287 (1956).
(7) The authors are grateful to Mrs. Kathryn Baylouny for the microanalysis.
(8) J. D. Ryan and F. B. Shaw, Jr., *J. Am. Chem. Soc.*, **62**, 3469 (1940).
(9) H. B. Hass, E. T. McBee, and P. Weber, *Ind. Eng. Chem.*, **27**, 1194 (1935).

Reactions of Phenyl-Substituted Methanes and Ethanes with Lithium or *n*-Butyllithium

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The chemistry of triphenylmethyllithium has been studied and reviewed recently by Tomboulain.[1] In that investigation, the organometallic compound was prepared in varying yields by reactions of triphenylmethyl chloride with lithium in a variety of solvents. We are now reporting the preparation of this reagent by the reaction of triphenylmethane with lithium or *n*-butyllithium, as well as by the lithium cleavage of 1,1,1,2-tetraphenylethane in tetrahydrofuran (THF) or in mixtures of diethyl ether and THF. Also reported at this time are some related reactions involving toluene, diphenylmethane, and *sym*-tetraphenylethane.

Although lithium wire in THF had been employed previously in the metalation of fluorene,[2a] 9-phenylfluorene[2a,3] and cyclopentadiene,[2a] and in the cleavage

(1) P. Tomboulain, *J. Org. Chem.*, **24**, 229 (1959).
(2)(a) H. Gilman and R. D. Gorsich, *ibid.*, **23**, 550 (1958); (b) H. O. House and V. Kramar, *ibid.*, **27**, 4146 (1963).
(3) H. Gilman and B. J. Gaj, *J. Am. Chem. Soc.*, **82**, 6326 (1960).

TABLE I

REACTIONS OF LITHIUM DISPERSION WITH PHENYLMETHANES AND -ETHANES[a]

Hydrocarbon, mole	THF, ml.	Temp., °C.	Reaction time, days	Products, %
Ph_2CH_2 (0.1)[b]	100	25	8	Ph_2CH_2 (78)
Ph_2CH_2 (0.1)	150	25	3	Ph_2CHCO_2H (33)[c]; Ph_2CH_2 (54.5)
Ph_2CH_2 (0.05)	50	25	5	Ph_2CHCO_2H (59)[c]; Ph_2CH_2 (22)
$Ph_2CHCHPh_2$ (0.015)[d]	50	65	7	Ph_2CH_2 (12.35); $Ph_2CH(CH_2)_3OH$ (62.2)[e]
Ph_3CCH_2Ph (0.015)	50	65	2	Ph_3CCO_2H (51)
Ph_3CCH_2Ph (0.015)	50	65	4	Ph_3CCO_2H (72.4)
Ph_3CCH_2Ph (0.004)	30	25	6	Ph_3CCO_2H (82.6)

[a] 100% excess of lithium was used in all reactions and all mixtures were carbonated. [b] Lithium sand was employed in this reaction. [c] M.p. 145–147°. [d] Two additional reactions were carried out under comparable conditions, except for reaction times of 2 and 4 days, respectively. Since work-up of the aqueous layer gave no acid, the organic layers of the three reactions were combined and treated in the usual manner. [e] B.p. 135–137° (0.01 mm.), $n^{20}D$ 1.5697, d^{20}_{20} 1.049. *Anal.* Calcd. for $C_{17}H_{20}O$: C, 84.8; H, 8.38; MRD, 75.1. Found: C, 84.75, 84.57; H, 8.63; 8.55; MRD, 75.4. The infrared spectrum of this material has a sharp band at 3356 cm.$^{-1}$, characteristic of the hydroxyl group.

of 9,9-diphenylfluorene,[2a] no reaction occurred with triphenylmethane after five days at room temperature.[2a] Reaction does occur with potassium in 1,2-dimethoxyethane.[2b] The same results were obtained by us when the last-mentioned reaction with lithium and triphenylmethane was repeated during this investigation. When the solution was refluxed for four days, however, a red color developed in the mixture, and a 15.9% yield of triphenylacetic acid was realized subsequent to carbonation after refluxing for an additional fourteen days with stirring.

The yield of acid was not increased to any appreciable extent when lithium sand was employed. However, the use of dispersed lithium in refluxing THF gave triphenylacetic acid in yields ranging up to 72% over a reaction period of seven days. In most of these runs, the stirrer was allowed to rub against the bottom of the flask in order to expose a fresh surface on the metal continuously. In one run where such scraping was not allowed, the yield of acid was only 20.5%. This was considerably lower than the yields obtained after comparable reaction times when rubbing was allowed.

It was also noticed that the yield of triphenylacetic acid varied considerably in the reactions employing a given form of lithium. This variation may possibly have been due to variations in intensity of rubbing by the stirrer, a factor which was difficult to control. The length and variations in induction periods observed for these reactions may also be explained on the same basis. Although care was taken to exclude moisture from these reactions, this induction period was probably due to small amounts of moisture in the system. Once the reactions began, as evidenced by the red color of the organometallic compound, the yields in comparable reactions were of the same order of magnitude. Attempts to effect the metalation with dispersed lithium in diethyl ether or tetrahydropyran both failed, indicating that the basicity of the solvent is a predominant factor in these reactions.

As noted in Table I, lithium sand failed to metalate diphenylmethane after stirring for eight days at room temperature. The reaction of dispersed lithium with this compound at room temperature, however, gave a 33% yield of diphenylacetic acid after three days and a 58% yield after five days. No phenylacetic acid could be detected from the reaction of toluene with lithium dispersion after refluxing for either six or twelve days in THF.

Three reactions of symmetrical tetraphenylethane with lithium dispersion were carried out, but no diphenylacetic acid was isolated after carbonation at various intervals, although several color changes were observed. When the organic layers were combined and distilled, diphenylmethane (12.25%) and an alcohol, which is presumed to be 5,5-diphenyl-1-pentanol (62.2%) were obtained. These reaction mixtures never attained the red colors observed in the reactions of diphenylmethane with lithium.

This solvent cleavage is rather surprising since triphenylmethylsodium does not effect this reaction under reflux conditions unless complexed with triphenyl boron[4] or triphenylaluminum.[5] Also, the reaction of symmetrical tetraphenylethane with potassium in diethyl ether gave diphenylacetic acid subsequent to carbonation.[6] Although a higher temperature was used in the reactions of tetraphenylethane with lithium than in the metalation of diphenylmethane, the failure to observe a red color in the former reaction suggests that a free-radical mechanism may be involved in the formation of 5,5-diphenyl-1-pentanol. Hydrogen abstraction by the radical could also account for the isolation of diphenylmethane from this reaction. In this connection, it is interesting to note that triphenylmethylmagnesium bromide is capable of cleaving THF under reflux conditions, apparently because of the ability of Grignard reagents to coordinate with the solvent.[7]

Unsymmetrical tetraphenylethane similarly was cleaved by lithium, and the mixtures were carbonated to give triphenylacetic acid in yields ranging up to 82.6%. These reaction mixtures did not have the characteristic odor of phenylacetic acid indicating the absence of benzyllithium at the time the mixtures were carbonated. Apparently, the benzyllithium underwent further reaction with the solvent; however, no products derived from it were isolated. Similar results were obtained by Ziegler and Thielmann when potassium was used in an analogous reaction.[6]

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(6) K. Ziegler and F. Thielman, *Ber.*, **56**, 1740, 2453 (1923).
(7) F. R. Jensen and R. L. Bedard, *J. Org. Chem.*, **24**, 874 (1959); see also, J. Eisch and W. Kaska, *Chem. and Ind.* (London), 470 (1961).

TABLE II

METALATION OF PHENYLMETHANES WITH *n*-BUTYLLITHIUM

Compound metalated, mole	BuLi, mole	Solvent, ml. Et_2O:THF	Temp., °C.	Time, hr.	Acid, %	Other products, %
Ph_3CH (0.0204)	0.021	20:50	25	0.25	77.6	...
Ph_3CH (0.0204)	.023	20:50	0	1	51.5	Ph_3CH (37)
Ph_3CH (0.0204)	.022	22:50	25	1	74.0	Ph_3CH (11.6)
Ph_3CH (0.0204)	.03	30:50	0	4	86.5	Ph_3CH (8.2)
$PhCH_3$ (0.19)	.05	50:40	0	1	...	Valeric acid (53.5)[a]
$PhCH_3$ (0.1)	.12	120:50	10	1	...	Valeric acid (48.5)[b]
$PhCH_3$ (0.05)	.075	75:50	25	1	20.7[c]	...
$PhCH_3$ (0.15)	.21	235:80	25	24	24.3[d]	...

[a] B.p. 188–190°, $n^{20}D$ 1.4108. [b] B.p. 187–189°, $n^{20}D$ 1.4112. [c] M.p. 76–77°, from petroleum ether (b.p. 60–70°). [d] M.p. 75–77°, from petroleum ether (b.p. 60–70°).

In Table II, are recorded several reactions of triphenylmethane and toluene with *n*-butyllithium. All of these reactions were carried out in a mixture of diethyl ether and THF since this combination of solvents had previously been shown to be well suited for metalation reactions.[8,9] Apparently, dilution of THF with ether does not decrease the effectiveness of this solvent in facilitating metalation reactions; however, it does stabilize the organometallic compounds, since these reagents are known to be more stable in diethyl ether than in THF.[10] This is also exemplified by the yields of triphenylacetic acid in the reactions recorded in Table II; the best yield was obtained when *ca.* a 50% excess of *n*-butyllithium was employed in a reaction at 0°.

The reactions of toluene with *n*-butyllithium at 0° or 10° failed to give any of the metalated product, whereas stirring at room temperature with an excess of *n*-butyllithium did cause metalation to occur. No indication for the presence of valeric acid was observed after twenty-four hours at room temperature, indicating that the *n*-butyllithium and, undoubtedly, some of the benzyllithium were consumed by a reaction with the solvent. Previously, toluene was metalated in very low yield by *n*-butyllithium in ether solution.[11] These results again indicate the advantage of using THF in metalation reactions. It might be mentioned that metalation of toluene is not the best method for preparing benzyllithium since better yields of this reagent have been obtained by cleavage reactions.[12,13]

Experimental[14]

General Procedure.—The lithium sand used in several reactions was prepared by heating lithium wire in mineral oil to *ca.* 200° and shaking the round-bottomed flask, in which it was contained, very vigorously as it cooled below the melting point of lithium. This was done under an atmosphere of dry, oxygen-free nitrogen. The material was then washed into a separatory funnel with dry benzene and the oil was removed through the stopcock. The finely divided lithium was washed several times with benzene, then with diethyl ether and finally with THF, before being transferred to the reaction flask with dry THF.

The lithium dispersion was kindly supplied by the Lithium Corporation of America, Inc. The material having a particle size of less than 25 μ was dispersed in heavy petrolatum as a 30% dispersion. The petrolatum was removed by washing with benzene and THF before use.

All of the reactions using lithium metal were carried out in three-necked flasks fitted with a mechanical stirrer, reflux condenser, and nitrogen inlet and outlet tube. The stirrer was adjusted so as to fit flush, but not tight against the bottom of the flask. The mixtures were then stirred continuously for the reaction times indicated in the tables and carbonated by pouring through glass-wool into a slurry of Dry Ice and diethyl ether.

In the reactions involving *n*-butyllithium, this organometallic compound was prepared in diethyl ether and added to a solution of the hydrocarbon in tetrahydrofuran. All of these reactions were terminated by carbonation. All products except 5,5-diphenyl-1-pentanol were identified by mixture melting points and infrared spectra if solids, and by their physical constants and infrared spectra if liquids.

Lithium Metal and Triphenylmethane.—A series of runs involving the interaction of triphenylmethane and different physical forms of lithium metal in tetrahydrofuran was carried out, in order to establish optimal reaction conditions. In a typical run, 5.0 g. (0.0204 mole) of triphenylmethane and *ca.* 0.115 g.-atom of lithium metal were stirred (with paddle scraping on the bottom of the flask) together in 50 ml. of tetrahydrofuran. Three types of runs were conducted. First, with cut pieces of lithium wire a 15.9% yield of triphenylacetic acid and a 60% recovery of triphenylmethane were obtained after 18 days at the reflux temperature. Second, with lithium sand the maximum yield of triphenylacetic acid (21.3%) observed was obtained after 9 days of refluxing. Third, with lithium dispersion the maximum yield obtained after 7 days at room temperature was 66% (20.2% of the starting triphenylmethane being recovered). When the reaction was conducted at the reflux temperature over 5–8 days, the yield of triphenylacetic acid ranged from 59–72% and that of recovered triphenyl methane dropped to 15%.

The triphenylacetic acid melted in the range 269–272° and the recovered triphenylmethane melted above 93°.

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(14) All melting and boiling points are uncorrected. Reactions were carried out under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware. The tetrahydrofuran was dried and purified by refluxing over sodium, distilling into lithium aluminum hydride, refluxing over this reagent, then distilling immediately before use under dry nitrogen.

Some Gas-Phase Reactions of Fluoroallyl Halides[1a]

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Miller and his coworkers[2-4] have prepared several highly fluorinated allyl halides and described reactions of these compounds with halide ion. Perfluoroallyl iodide[2b] (I) was prepared by halogen exchange of perfluoroallyl chloride with sodium iodide in acetone solution. The iodine atom in this compound was very reactive and was readily replaced by either bromine or chlorine using the free halogen in the dark at room temperature. Zinc dust in methanol caused replacement of the iodine with hydrogen, and coupling to decafluoro-1,5-hexadiene was effected using zinc dust in anhydrous dioxane.

The high reactivity of the iodine in I suggested that this and similar compounds might be used in the synthesis of polyfluoronitroso compounds. The only olefinic nitroso compound of this type which had been reported was trifluoronitrosoethylene.[5] This compound has been synthesized by the photochemical reaction of trifluoroiodoethylene with nitric oxide in the presence of mercury.

We, therefore, synthesized two polyfluoroallyl iodides in order to convert them into the polyfluoroallyl nitroso compounds. I was prepared by pyrolysing chlorotrifluoroethylene to perfluoroallyl chloride[6] and converting this to the iodide using sodium iodide in acetone.[1] The corresponding 2*H*-tetrafluoroallyl iodide (II) had not been prepared previously. The synthesis was accomplished by preparing 2*H*-tetrafluoroallyl bromide (III) by the dehydrobromination of 1,3-dibromo-1,1,3,3-tetrafluoropropane (IV) which was obtained from the benzoyl peroxide initiated addition of dibromodifluoromethane to 1,1-difluoroethylene.[7] III was converted into II by treatment with sodium iodide in acetone.

A photochemical reaction was carried out in sunlight between I and nitric oxide in the presence of mercury, using a technique described by Barr and Haszeldine.[8] The reaction product was worked up by introduction of oxygen, which converted unchanged nitric oxide into nitrogen dioxide; the latter was removed by reaction with mercury to form mercurous nitrate.[9]

Hexafluoropropene (V) (20%), 3-nitrosopentafluoropropene (34%) (VI), and perfluoroacryloyl fluoride (27.5%) (VII) were obtained. Formation of VI was obviously *via* a simple free radical reaction.

$$CF_2{=}CF{-}CF_2I \longrightarrow CF_2{=}CF{-}CF_2\cdot + I\cdot$$
$$\downarrow NO$$
$$CF_2{=}CF{-}CF_2NO$$

VI was relatively stable in sunlight for the length of time the reaction mixture was irradiated. It was, therefore, unlikely that V or VII resulted from its decomposition. The formation of V and VII was attributed to the presence of mercurous nitrate in the reaction mixture and is discussed later in the article.

The photochemical reaction between II and nitric oxide gave 1,1,3,3-tetrafluoro-3-nitrosopropene (VIII) (24.5%). 2*H*-pentafluoropropene (IX) (38%) and β,β-difluoroacryloyl fluoride (X) (32%) also were formed by reaction between II and mercurous nitrate formed *in situ* during the purification process.

Both VI and VIII had a deep blue color characteristic of monomeric nitroso compounds. VIII was relatively unstable; a sample left in the dark at 25° lost all its blue color after approximately fifteen hours. VI was a little more stable and had to be left for eighty-four hours before all the blue material had decomposed. The mixture of products from the decomposition of either VI or VIII was quite complex. In both cases, there was some solid, high boiling oil and volatile material consisting of several components.

Attention was next turned to the novel reaction between mercurous nitrate and either I or II to form the unsaturated acyl fluorides and fluoropropenes. In most cases, the mercurous nitrate was formed *in situ* from mercury and nitrogen dioxide in the presence of excess oxygen. It was shown in a separate experiment that oxygen itself did not react with I. This made it safe to carry out the reactions with mercurous nitrate in the presence of oxygen, which ensured that all oxides of nitrogen were removed during the reaction, thus giving a cleaner reaction product. The results of these reactions with mercurous nitrate are summarized in Table I.

TABLE I

REACTION OF FLUOROALLYL HALIDES WITH MERCUROUS NITRATE (X = F, H)

Compound	Conversion, %	Yield of $CF_2{=}CX{-}CF_3$, %	Yield of $CF_2{=}CXCOF$, %
$CF_2{=}CF{-}CF_2I$[a,c]	100	13.5	80
$CF_2{=}CFCF_2I$[b]	75	13	70.5
$CF_2{=}CH{-}CF_2I$[a,c]	100	19	76
$CF_2{=}CH{-}CF_2Cl$[a]	90	2	93
$CF_2{=}CF{-}CF_2Cl$[a]	0		
$CF_2{=}CF{-}CF_3$[a]	0		

[a] Reactions carried out with mercurous nitrate formed *in situ* from mercury and nitrogen dioxide. [b] Reaction carried out with commercial mercurous nitrate. [c] A trace of nitroso compound, $CF_2{=}CX{-}CF_2NO$, was also formed.

Table I indicates clearly that reaction of the fluoroallyl halide with mercurous nitrate depends on the reactivity of the halogen used. Obviously the chlorine in $CF_2{=}CF{-}CF_2Cl$ is less reactive than the iodine in $CF_2{=}CF{-}CF_2I$, and it is, therefore, not surprising that the latter reacts with mercurous nitrate to form an acryloyl fluoride whereas the former does not react. We were surprised to find, however, that the other allyl chloride ($CF_2{=}CH{-}CF_2Cl$) reacted readily under the same conditions to form the acryloyl fluoride. The

(1) (a) Halogen, in the sense used in this paper, does not include fluorine; (b) presented at the Annual Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November 1-3, 1962.

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(9) E. Divers and T. Shimidzu, *ibid.*, **47**, 630 (1885).

reason for the lack of reactivity of $CF_2{=}CF{-}CF_2Cl$ compared to that of $CF_2{=}CH{-}CF_2Cl$ must be due to the presence of a fluorine atom on the β-carbon atom. This fluorine atom can exhibit the well known mesomeric effect and back donate nonbonding π-electrons to the olefinic double bond. This would withdraw electron density from the chlorine and make loss of chloride ion as mercury chloride more difficult than in $CF_2{=}CH{-}CF_2Cl$.

The formation of acryloyl fluoride from the reactions of these allyl halides with mercurous nitrate could be by initial formation of mercury halide and an allyl nitrate. It seems reasonable to suppose that the latter could lose nitryl fluoride to form the acyl fluoride. This course of events could also explain the formation of the fluoropropene ($CF_2{=}CX{-}CF_3$) since nitryl fluoride has been reported[10] to be very reactive and a powerful fluorinating agent. It would then either react with allyl halide to form a fluoropropene, or possibly convert some mercurous nitrate to mercurous or mercuric fluoride which could then fluorinate the allyl halide.

$$CF_2{=}CX{-}CF_2Y + HgNO_3 \longrightarrow [CF_2{=}CX{-}CF_2{-}O{-}NO_2] + HgY$$

$$[CF_2{=}CX{-}CF_2{-}O{-}NO_2] \longrightarrow CF_2{=}CX{-}\overset{\overset{O}{\|}}{C}{-}F + NO_2F$$

$$CF_2{=}CX{-}CF_2Y + NO_2F \longrightarrow CF_2{=}CX{-}CF_3 \quad (\text{or } HgF_2)$$

(X = H; Y = I, Cl)
(X = F; Y = I)

Andreades[11] has reported a similar dissociation of a perfluoroalkyl nitrite to an acyl fluoride and nitrosyl fluoride.

$$C_2F_5NO \longrightarrow C_2F_5ONO + \text{other products}$$
$$\downarrow\uparrow$$
$$CF_3COF + NOF$$

The table shows that the ratio of olefin ($CF_2{=}CX{-}CF_3$) to acryloyl fluoride ($CF_2{=}CX{-}COF$) was higher for reaction of an iodide than for a chloride. These data fit our reaction scheme since the more reactive iodide would be fluorinated with nitryl fluoride more readily than the chloride, thus giving a higher yield of the fluoropropene ($CF_2{=}CX{-}CF_3$).

Experimental

Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Schwarzkopf Laboratories, Woodside, N. Y.

1,1,3,3-Tetrafluoro-3-iodopropene.—1,1,3,3-Tetrafluoro-3-bromopropene was prepared as described by Tarrant, Lovelace, and Lilyquist.[7]

1,1,3,3-Tetrafluoro-3-bromopropene (63.5 g., 0.33 mole) and sodium iodide 70 g., 0.466 mole) reacted in acetone (160 ml.) solution for 16 days at room temperature. Solvent was removed by adding water (1000 ml.), separating the two layers, and washing the organic layer with dilute sodium bisulfite (three 25-ml. portions). This organic material was dried over phosphoric anhydride and distilled in a nitrogen atmosphere through a 24-plate spinning band column to give 1.6 g. of recovered 1,1,3,3-tetrafluoro-3-bromopropene, boiling range 34–36°, and 50.6 g. of 1,1,3,3-tetrafluoro-3-iodopropene (64%), boiling range 61–62°, $n^{20}D$ 1.4046.

Anal. Calcd. for C_3HF_4I: C, 15.01; H, 0.42; F, 31.47. Found: C, 15.09; H, 0.60; F, 31.76.

An infrared spectrum showed C=C stretching frequency at 5.73 (m) μ and bands at 7.39 (s), 7.98 (m), 8.30 (m), 9.30 (s), 10.25 (s) and 12.35 (m) μ.

3-Nitroso-1,1,3,3-tetrafluoropropene.—A 2-l. Pyrex flask containing mercury (70 ml.) was evacuated and charged with 3-iodo-1,1,3,3-tetrafluoropropene (4.8 g., 0.02 mole), nitric oxide (1.2 g., 0.04 mole), and mechanically shaken in bright sunshine for 105 min. Oxygen (1.28 g., 0.04 mole) was slowly introduced, and the flask shaken for an additional 30 min. Volatile material was isolated by slowly pumping through two traps cooled in liquid nitrogen. This mixture was separated by large scale v.p.c. (dinonyl phthalate, 25°) into the following three components.

2*H*-Pentafluoropropene, 1.0 g. (38%); an infrared spectrum was identical with that of an authentic sample.

3-Nitroso-1,1,3,3-tetrafluoropropene, 0.7 g. (24.5%).

Anal. Calcd. for C_3HF_4NO: mol. wt., 143. Found: mol. wt., 142.

An infrared spectrum showed C=C and NO stretching absorptions at 5.71 (vs) and 6.29 (m), and bands at 7.30 (s), 7.9 (m), 8.1 (m), 8.9 (ms), 9.7 (w), and 10.5 (m) μ.

β,β-Difluoroacryloyl fluoride, 0.7 g. (32%), b.p. 45.0°.

Anal. Calcd. for C_3HF_3O: C, 32.73; F, 51.83; H, 0.91; mol. wt., 110. Found: C, 32.55; F, 51.60; H, 0.81; mol. wt., 109.

An infrared spectrum showed C=C and C=O stretching frequencies at 5.43 (vs) and 5.81 (vs) and bands at 7.26 (s), 7.85 (m), 8.2 (ms), 9.15 (s), and 10.2 (s).

The nuclear magnetic resonance spectral data[12] on the last two compounds were in agreement with the formulations $CF_2{=}CH{-}CF_2NO$ and $CF_2{=}CH{-}COF$, respectively.

3-Nitrosopentafluoropropene.—Perfluoroallyl iodide was prepared from perfluoroallyl chloride as described by Miller and Fainberg.[1] Perfluoroallyl chloride was prepared by the pyrolysis of chlorotrifluoroethylene as described by Miller.[6]

Perfluoroallyl iodide (5.16 g., 0.02 mole) reacted with nitric oxide (1.2 g., 0.04 mole) and mercury in bright sunshine for 6 hr.

Separation of the products gave perfluoropropene, 0.6 g. (20%), identified by its infrared spectrum and 3-nitrosoperfluoropropene, 1.1 g. (34%).

Anal. Calcd. for C_3F_5NO: C, 22.39; N, 8.70; F, 59.00; mol. wt., 161. Found: C, 22.66; N, 8.60; F, 58.68; mol. wt., 161.

An infrared spectrum showed C=C and NO stretching absorptions at 5.61 (vs) and 6.29 (s) μ, and bands at 7.30 (vs), 7.58 (vs), 8.40 (vs), 9.18 (vs), 10.5 (w), 11.1 (w), and 13.9 (w).

Perfluoroacryloyl fluoride, 0.7 g. (27.5%), b.p. 25.5°.

Anal. Calcd for C_3F_4O: C, 28.13; F, 59.37; mol. wt., 128. Found: C, 28.35: F, 59.12; mol. wt., 128.

An infrared spectrum showed C=C and C=O stretching absorptions at 5.40 (vs) and 5.72 (vs) and bands at 7.3 (s), 7.55 (s), 8.41 (s), 8.50 (sh), 9.50 (ms), and 9.59 (doublet), 9.75 (s) and 9.80 μ (doublet); nuclear magnetic resonance data[13] confirmed the formula $CF_2{=}CF{-}COF$ for this compound.

Reaction of Perfluoroallyl Iodide with Mercurous Nitrate.—A 2-l. flask containing mercurous nitrate (75 g., 0.286 mole) was evacuated and charged with perfluoroallyl iodide (5.16 g., 0.02 mole) and mechanically shaken in the dark for 2 hr. Some brown vapor, obviously nitrogen dioxide, was formed during reaction but only in small amount. Volatile material was isolated by vacuum transfer and separated into 0.29 g. of hexafluoropropene (13%), 1.35 g. of perfluoroacryloyl fluoride (70.5%), and 1.29 g. of recovered perfluoroallyl iodide. The previously white mercurous nitrate turned red during reaction, but the red coating was soluble in acetone. This indicated that it was mercuric iodide.

Reactions between Allyl Halides, Mercury, and Mercurous Nitrate.—Mercurous nitrate was prepared *in situ* from mercury and nitrogen dioxide and oxygen.

Allyl halide (0.02 mole), nitrogen dioxide (1.38 g., 0.03 mole), oxygen (0.96 g., 0.03 mole), and mercury (70 ml.) were shaken together in the dark for 1 hr. in a 2-l. flask. All brown vapor had disappeared after this time, and volatile material was isolated under vacuum and separated into its various components by large scale v.p.c.

The results of these reactions are summarized in Table I.

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Reaction of Perfluoroallyl Iodide with Oxygen.—Perfluoroallyl iodide (5.16 g., 0.02 mole), oxygen (0.64 g., 0.02 mole), nitrogen (0.84 g., 0.03 mole), and mercury (70 ml.) were shaken together in the dark for 1 hr. in a 2-l. flask. The only organic material isolated was 4.7 g. of unchanged perfluoroallyl iodide (91% recovery).

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Ring Conformation in Methyl α- and β-D-Xylothiapyranosides as Demonstrated by Nuclear Magnetic Resonance[1]

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The recent synthesis of sugars in which the ring oxygen is replaced by a sulfur atom[2] makes possible an experimental attack on many interesting questions relative to both chemical and physical–chemical properties of the carbohydrates. However, one question which must be answered before certain other results can be interpreted without ambiguity is that of whether there is a direct effect of this substitution on the ring conformation. The D-xylopyranosides have been shown to exist in the Cl conformation by optical rotatory studies,[3] by stability considerations,[4,5] and by X-ray analysis.[6] It has also been shown in D-xylopyranose tetraacetates that the spin–spin coupling constants observed by n.m.r. are as required for the Cl conformation.[7] The purpose of the present work is to determine if replacement of the ring oxygen by sulfur in D-xylothiapyranose and the methyl D-xylothiapyranosides produces a change in the ring conformation.

The proton magnetic resonance spectra of the various compounds were determined at 60 Mc.p.s. with a Varian A-60 n.m.r. spectrometer using 10–20% by weight solutions of the carbohydrates in deuterium oxide. The assignment of τ values were made by taking the water peak (5.2 τ) as an internal standard. The dihedral angles between the anomeric proton and the proton on the adjacent carbon atom C-2 were calculated from the magnitude of the splitting of the corresponding absorption peak using the modified Karplus equation.[8,9]

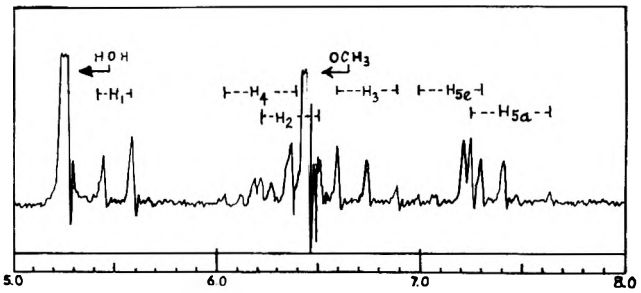

Fig. 1.—N.m.r. spectrum of methyl β-D-xylothiapyranoside in deuterium oxide at 60 Mc., with chemical shifts given in τ values.

It has been shown that the signal due to the anomeric proton of sugars appears at a lower field than that of any of the other carbon-bonded hydrogen atoms.[7,9,10] Further, the signal for an equatorial anomeric proton occurs at a somewhat lower field than for an axial proton. From Table I it is evident that the signal in methyl α-D-xylothiapyranoside appears at a lower field than for the corresponding β-anomer. In all cases the peak corresponding to the anomeric proton is split due to coupling with the proton on C-2. The large values of this coupling constant for methyl β-D-xylopyranoside and methyl β-D-xylothiapyranoside (7.2 and 8.4 c.p.s., respectively) are of the expected order of magnitude for an axial–axial orientation. Similarly the low values for the α-anomers indicate an axial–equatorial situation. The calculated values of the dihedral angles are in reasonable agreement with the expected values for the Cl conformation (60° and 180° for α- and β- anomers, respectively).

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR ANOMERIC PROTONS

	Chemical shifts (τ values)		Coupling constant JH_1H_2, cycles/-sec.	Dihedral angle, deg.
	H_{1e}	H_{1a}		
D-Xylose[a]	4.82	...	2.2	60
	...	5.45	7.2	148
Methyl β-D-xylopyranoside	...	5.62	7.2	148
D-Xylothiapyranose	5.0	...	2.5	57
	...	5.25	8.2	154
Methyl α-D-xylothiapyranoside	5.35	...	2.8	55
Methyl β-D-xylothiapyranoside	...	5.52	8.4	156

[a] Data from ref. 9.

The spectra of both D-xylopyranosides and D-xylothiapyranosides show additional fine structure. The spectrum of methyl β-D-xylothiapyranoside is presented in Fig. 1. The splitting pattern in the region 5.8–6.5 τ has been identified as due to the proton at C-2. This indicates that it is coupled to protons at C-1 and C-3 with J values 8.4 and 8.6, respectively. These large values indicate that the C-2 proton is in axial–axial orientation with the protons at C-1 and C-3. The triplet in the region 6.6–6.9 τ is assigned to the C-3 proton. The splitting pattern shows that the C-3 proton is coupled with

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(4) R. B. Kelly, *Can. J. Chem.*, **35**, 149 (1957).

(5) R. E. Reeves, *Advan. Carbohydrate Chem.*, **6**, 107 (1951).

(6) C. J. Brown, Ph.D. thesis, University of Birmingham, 1939, as quoted by B. Capon and W. G. Overend, *Advan. Carbohydrate Chem.*, **15**, 14 (1960).

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(8) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(9) R. W. Lenz and J. P. Heeschen, *J. Polymer Sci.*, **51**, 247 (1961).

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TABLE II

COUPLING CONSTANTS OF METHYL β-D-THIAXYLOPYRANOSIDE (C.P.S.)

$J_{1a,2a}$	8.4
$J_{2a,3a}$	8.6
$J_{3a,4a}$	8.6
$J_{4a,5e}$	3.3
$J_{4a,5a}$	11.2
$J_{5a,5e}$	13.5

C-2 and C-4 protons with J values of 8.6, which confirms the axial–axial relation between C-2 and C-3 protons and further indicates that the C-3 proton is in axial–axial orientation with the C-4 proton.

The two quartets in the region 7.0–7.7 τ are assigned to the C-5 protons. This is due to the coupling among themselves and with the neighboring proton at C-4. Part of the splitting pattern of the C-4 proton is overlapped by the signals due to the C-2 proton and the methyl hydrogens. This is treated as an ABX-type[11] spectrum, and the values of the various coupling constants which can be deduced from these spectral features are summarized in Table II. The large coupling constant $J_{5e}J_{5a}$ is expected for the interaction of axial and equatorial protons on the same carbon atom.[9] The small J value for the coupling of the equatorial proton on C-5 with the proton on C-4, and the corresponding large value for the coupling of the axial proton on C-5 with this same proton, show beyond a doubt that the proton on C-4 is in an axial orientation.

In summary, the n.m.r. spectra show no evidence for any important alterations in ring conformation due to the replacement of the ring oxygen of D-xylopyranose by sulfur. Furthermore, the spectra of methyl β-D-thiaxylopyranoside are in accord with the Cl ring conformation.

Acknowledgment.—We are indebted to the Corn Industries Research Foundation for financial support of this work.

(11) 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, Chap. 6.

Dipole Moments of Two Nitrogen Analogs of Sesquifulvalene

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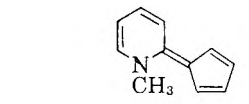
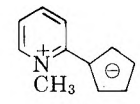
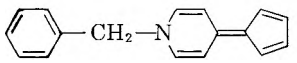
The dipole moments of 1-methyl-2-cyclopentadienylidene-1,2-dihydropyridine (I) and 1-benzyl-4-cyclopentadienylidene-1,4-dihydropyridine (II) are of interest because of possible large contributions of resonance forms with a separation of charge, Ia and IIa, which would cause these molecules to have large dipole moments.[1-5]



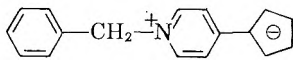
I



Ia



II



IIa

The moment of compound I has not been reported and although that of II has been reported to be 9.7 D.,[1] no experimental details were given. If the electronic polarization was calculated from atomic refraction constants, the reported moment would be high because of the likely exaltation in such a compound.

Results and Discussion

The results are given in Table I. Compound I was sufficiently soluble so solutions up to the usual concentration range of about 1% could be measured and in this range the ϵ_{12}–ω_2 points still fell on a straight line giving no evidence of association. The $P_{E_{20}}$ from the refractive index of the solutions was about 22 units higher than the MRD value, indicating considerable exaltation as expected from this type of compound. The dipole moment of 5.20 ± 0.6 D. gives evidence of approximately a 25% contribution from the forms with a separation of charge Ia and IIa. This calculation was made without taking into account the small moment possessed by the normal forms I and II of the compound since the direction of this small moment is not known with regard to the resultant moment coming mainly from the contribution of the forms with a separation of charge.

Since the solubility of compound II was less than 10 mg. in 10 ml. of benzene, only very dilute solutions could be measured. The density of these solutions was indistinguishable from that of benzene, but dielectric constant differences were significant. More concen-

TABLE I

DIPOLE MOMENTS IN BENZENE AT 25°

1-METHYL-2-CYCLOPENTADIENYLIDENE-1,2-DIHYDROPYRIDINE

ω_2	ϵ_{12}	ν_{12}
0.0	2.2725	1.14025
.0021995	2.3156	1.13935
.0046113	2.3593	1.13830
.0074636	2.4168	1.13726
.0102930	2.4702	1.13636
.0127364	2.5301	1.13532

ϵ_1 = 2.2702 α = 19.9269 ν_1 = 1.14017

β = −0.38057 P_{20} = 3.96391 P_{20} = 623.205

$P_{E_{20}}$ = 69.70 from refractive index of solutions

MRD = 47.75

μ = 5.20 ± 0.06 D.

1-BENZYL-4-CYCLOPENTADIENYLIDENE-1,4-DIHYDROPYRIDINE

0.0	2.2756	1.141947
.00012881	2.2792	1.141947
.00028457	2.2859	1.141947
.00058901	2.2975	1.141947

ϵ_1 = 2.2750 α = 37.9034 ν_1 = 1.14195

β = 0.0 P_{20} = 7.4455 P_{20} = 1736.97

$P_{E_{20}}$ = 108.57 from refractive index of solutions

MRD = 70.07

μ = 8.93 ± 0.18 D.

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(2) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(3) D. N. Kursanov and N. K. Baranetskaya, *Bull. Acad. Sci. USSR*, 341 (1958).

(4) G. V. Boyd, *Proc. Chem. Soc.*, 263 (1960).

(5) J. A. Berson, E. M. Evleth, and Z. Hamlet, *J. Am. Chem. Soc.*, **82**, 3793 (1960).

trated solutions could be made in dioxane, but these were so hygroscopic that it was difficult to get meaningful measurements since in the instrument used some exposure of the solution to the air was unavoidable. The dipole moment of 8.9 ± 0.2 D. was obtained from the three most dilute solutions in benzene. These three points and the one for the solvent fell on a straight line, but the next point at $\omega_2 = 0.00088499$ fell considerably below the line and the next more concentrated solution precipitated slightly and was still further off the line. It is evident that association begins beyond a concentration of about 6 mg. in 10 ml. in this case. The dipole moment calculated from the dioxane solutions came out 8.1 D., but this is probably not so accurate as the value from the benzene solutions. The value of 8.9 D. is smaller than the value of 9.7 D. obtained by the previous workers and this might, in part, be accounted for if they calculated the MR_D value from tables. There is no doubt, however, that this molecule has a high moment. The value of 8.9 D. indicates that there is a contribution of about 27% from forms with a separation of charge, again no account being taken of the moment present in the normal form of the molecule. This is about the same as the contribution of the forms with a separation of charge in compound I.

Experimental

The dielectric constants were measured using a Dipolmeter Model DM 01. The dipole moments were calculated using the method and equation of Halverstadt and Kumler.[2] The dioxane was purified by refluxing with about one-hundredth of its volume of concentrated hydrochloric acid with an exit tube from the reflux condenser leading outdoors, neutralizing and drying with solid potassium hydroxide, refluxing over sodium, and fractionally distilling twice from sodium through a 30-plate column.

Thiophene-free benzene was refluxed over sodium wire and then fractionally distilled from a 30-plate column.

Compound I,[5] orange needles, had m.p. 74–75°; compound II,[3,6] golden yellow plates, decomposed above 200°. The infrared and ultraviolet-visible spectra of these substances were identical with those reported.[3,5,6]

Acknowledgment.—The author wishes to thank Dr. Jerome Berson for suggesting the measurements be made and for supplying pure samples[5,6] of the compounds, and Mr. Thomas Simpson, Jr., for programming the calculations on the 1620 IBM computer.

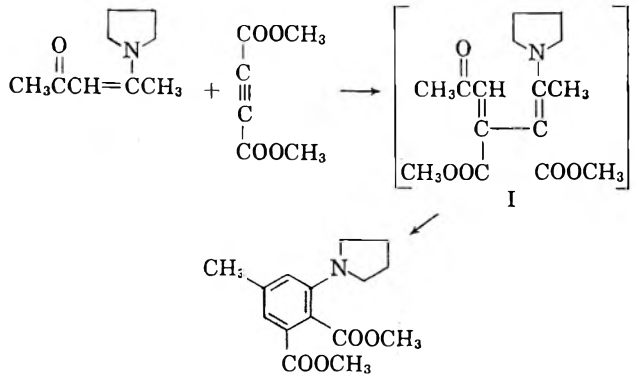
(6) J. A. Berson and E. M. Evleth, *Chem. Ind.* (London), 1362 (1961).

Communication TO THE EDITOR

A Method of Synthesis of the Benzene Ring

Sir:

The introduction by Stork and co-workers in 1954[1] of a new and useful method for the alkylation of carbonyl compounds awakened interest in the chemistry of enamines. A recent interesting new reaction of enamines was cited by Brannock.[2] He indicated that reaction with an acetylenecarboxylic acid ester interposes two carbon atoms between the α and β carbon of the enamine. This reaction, which we had been studying[3] independently, is capable of interesting and useful variations. One of these leads to a new synthesis of the benzene ring under mild conditions. The addition of dimethyl acetylenedicarboxylate to 4-pyrrolidino-3-penten-2-one dissolved in tetrahydrofuran results in a spontaneous reaction (presumably *via* I) with a temperature rise to 90°. The reaction mixture is diluted with water and the solid recrystallized from methanol to give dimethyl-4-methyl-6-pyrrolidinophthalate in 60% yield, m.p. 83–85°. [Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.20. Found: C, 65.25; H, 6.92; N, 5.20. Ultraviolet spectrum in ethanol: λ_{max} 236 mμ (ϵ 16,400), 274 (7,950), and 347 (3,300).] Its structure is demonstrated by the presence of two isolated aromatic protons at 6.94 δ and 6.62 δ with indications of *meta* splitting and a three proton singlet at 2.27 δ due to an aromatic methyl group (A60, tetramethylsilane standard, deuteriochloroform solvent).



(1) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963), and preceding papers.

(2) K. C. Brannock, Abstracts of Papers, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(3) A paper with M. M. Robison and L. Dorfman is in preparation on the reaction of enamines (especially of cyclic ketones) with acetylenecarboxylic acid esters and other dienophiles.

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