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Bridged Polycyclic Compounds. XXIV. The Halogenation of Substituted Norbornyl Radicals[1]

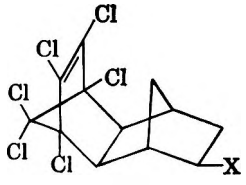
STANLEY J. CRISTOL, LYLE K. GASTON, AND TRENT TIEDEMAN

Department of Chemistry, University of Colorado, Boulder, Colorado

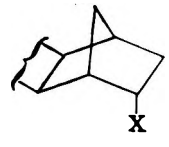
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Various procedures for the preparation of the dihydroaldrinyl radical (IV) and the capture of this radical by halogen donors have been studied. The results suggest that the nature of the radical is independent of its source and that the composition of the mixture of epimers produced depends solely on the halogen donor.

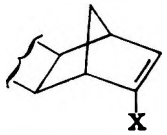
Our interest in the stereochemistry of reactions in bicycloheptane systems has led us to the study of a variety of reactions in which the substituted *exo*- and *endo*-2-norbornyl bromides (Ia and IIa) have been produced.[2,3] We now wish to report some work on the preparation of the related chlorides and iodides (Ib, IIb, Ic, and IIc), the stereochemistry of the reactions leading to them, and some additional work on the bromides.



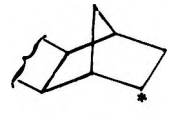
Ia, X = Br
b, X = Cl
c, X = I
d, X = CO_2H
e, X = H
f, X = CO_2Hlg



IIa, X = Br
b, X = Cl
c, X = I
d, X = CO_2H
e, X = H
f, X = CO_2Hlg



IIIa, X = H
b, X = Br
c, X = I



IV

Addition of hydrogen chloride to 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*exo*-*endo*-5,8-dimethanonaphthalene (aldrin, IIIa) with zinc chloride catalysis gave the *exo* chloride (Ib); addition of hydrogen iodide gave the *exo* iodide (Ic). The *exo* structures of these substances was inferred from the syntheses, assuming the usual *exo* addition to norbornenes,[4] and was supported by the observation that mixture melting points of any combinations of Ia, Ib, and Ic were not depressed below that of the lower melting compound of the mixture. Single crystal X-ray diffraction patterns of Ia and Ic were superimposable, thus unequivocally relating the structure of Ic with that of the known Ia.[3,5] The chloride Ib was identical with a sample obtained from Dr. R. E. Lidov, which was produced by the Diels–Alder reaction between hexachlorocyclopentadiene and *exo*-5-chloro-2-norbornene.[6]

Treatment of the silver salt of the acid Id with iodine (Hunsdiecker reaction) gave an 85% yield of a mixture of iodides Ic and IIc in an *exo*–*endo* ratio of 70:30. An identical mixture was obtained in 70% yield by treatment of Id with mercuric oxide and iodine in carbon tetrachloride. Thus the mercuric oxide–halogen procedure[7] has been extended to the formation of alkyl iodides. This procedure is more convenient than the Hunsdiecker reaction, as it avoids the tedious preparation and desiccation of the silver salt. The *endo* iodide (IIc) was separated from the mixture by fractional crystallization.

The *endo* isomers, IIa, IIb,[8] and IIc, did not show melting point depressions when mixed, again indicating structural and crystalline similarities, while mixtures of halide epimers exhibited large melting point depressions. In all the epimeric pairs of halides, the *exo* isomers (I) melted higher than the *endo* isomers (II).

Attempts to prepare *endo*-5-iodo-2-norbornene for Diels–Alder addition to hexachlorocyclopentadiene to form IIc were unsuccessful. Iodine was added to al-

(1) Previous paper in series: S. J. Cristol, J. R. Mohrig, F. P. Parungo, K. Schwarzenbach, and D. D. Tanner, *J. Am. Chem. Soc.*, **85**, 2675 (1963).

(2) S. J. Cristol and L. K. Gaston, *J. Org. Chem.*, **26**, 4672 (1961).

(3) S. J. Cristol, J. R. Douglass, W. C. Firth, Jr., and R. E. Krall, *ibid.*, **27**, 2711 (1962).

(4) See footnote 14 of ref. 3.

(5) The authors are indebted to Dr. Walter M. Macintyre for the X-ray data.

(6) R. E. Lidov, U. S. Patent 2,635,979 (April 21, 1953); *Chem. Abstr.*, **47**, 6596h (1953).

(7) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

(8) C. A. Peri, *Gazz. chim. ital.*, **85**, 1118 (1955).

drin (IIIa) photochemically to give a diiodide, presumably another example of the relatively rare class[9] of vicinal diiodides. Whether this is a *cis* or *trans* isomer was not established. Treatment with base gave the iodoaldrin IIIc. Attempts to hydrogenate the *exo* side of the double bond bearing the iodine atom, as had been accomplished with the bromine analog IIIb,[10] without hydrogenolysis of the iodine–carbon bond, were unsuccessful.

Treatment of the silver salts of Id or of IId with chlorine or with iodine, like that with bromine,[3] gives mixtures of I and II halides whose compositions are independent of the *endo* or *exo* stereochemistry of the starting acid, and which in each case contains approximately 70% of the *exo* isomer and 30% of the *endo* isomer. Kooyman and Vegter[11] have given convincing evidence that the *exo–endo* ratio of products of reaction of a norbornyl radical with halogen donors is increased by increasing steric interactions. It would appear that the dihydroaldrinyl radical (IV) involved in these Hunsdiecker reactions[3] finds the acyl hypohalite (If or IIf), with which it reacts of approximately equivalent steric requirement, independent of the halogen. Presumably the larger van der Waals radius of the heavier halogen is offset by the correspondingly longer covalent bond being developed in the transition state.

Further evidence in support of the Kooyman thesis, that the *endo–exo* ratio is affected solely by the bulk of the halogen donor, is given in the data of Table I.

TABLE I

FREE-RADICAL FORMATION OF ALDRIN HYDROHALIDES

Sources of dihydroaldrin radicals	Halogen donor	Initiation process	% *endo* halide (II) in halide mixture[a]
Id, Ag salt, Cl_2	RCO_2Cl (I)	Heat	30
IId, Ag salt, Cl_2	RCO_2Cl (II)	Heat	31
Id, Ag salt, Br_2	RCO_2Br (I)	Heat	31[b,c]
IId, Ag salt, Br_2	RCO_2Br (II)	Heat	31[b,c]
Id, Ag salt, I_2	RCO_2I (I)	Heat	33
IId, Ag salt, I_2	RCO_2I (II)	Heat	34
Id, HgO, I_2	RCO_2I (?)	Heat	34
$(RCO_2)_2$ *exo*	Br_2	Heat	27[c]
$(RCO_2)_2$ *exo*	$BrCCl_3$	Heat	0[c]
$(RCO_2)_2$ *endo*	$BrCCl_3$	Heat	0[c]
Ie + Cl·	Cl_2	Light	30
Ie + Br·	Br_2	Light	30[d]
Ie + $C_4H_4O_2N$·	N-Bromosuccinimide	Light	16
Ie + CCl_3·	$BrCCl_3$	Benzoyl peroxide	4

[a] Infrared analysis; results are probably accurate to ±4%. [b] Similar results were obtained with mercuric oxide and bromine. [c] See ref. 3. [d] See ref. 2.

Here we have summarized our results with a variety of halogen donors and a variety of sources of the dihydroaldrinyl radical (IV). The radical was formed in various cases by the Hunsdiecker procedure from Id and from IId, by the mercuric oxide–halogen procedure on both acids, by decomposition of both acyl peroxides, and by the attack of halogen atoms, succinimide radicals, and trichloromethyl radicals on dihydroaldrin (Ie). One may note that the fraction of *endo* halide in the halide mixture is, within the limits of accuracy of the infrared analytical technique, independent of the source of the radical species. These data are consistent with the idea that the Hunsdiecker reaction, as well as the other reactions, involves a free-radical chain process.[12]

Skell[13] has recently proposed that the course of bromination of aliphatic compounds with N-bromosuccinimide (NBS) involves the transfer of a bromine atom to the alkyl radical from molecular bromine rather than from a molecule of NBS. This cannot be the case in our experiments with NBS, as the mixture of bromides is clearly different from that obtained with bromine (Table I). Perhaps the radical studied by Skell and co-workers is more selective than the dihydroaldrinyl radical we have investigated. Although we have suggested that, in the experiment with NBS, the radical IV is formed from Ie and a succinimidyl radical, our data do not offer any way to distinguish this from the current suggestions that bromine atoms are the chain carriers in NBS brominations.[14]

Experimental

Preparation of *exo*-2,5,6,7,8,9,9-Heptachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4-*exo*-*endo*-5,8-dimethanonaphthalene (Ib).—To 75 ml. of cold glacial acetic acid, saturated with dry hydrogen chloride, were added 10 g. of fused zinc chloride and 5 g. of aldrin (IIIa, Shell Chemical Co.). The mixture was warmed to room temperature with swirling until solution was complete. On standing at room temperature for 5 days, 4.5 g. (82%) of white crystals precipitated. One recrystallization from benzene gave a solid, m.p. 155–157°. The material was identical (infrared and mixture melting point) with a sample supplied by Dr. R. E. Lidov of the Shell Development Co.[6]

Preparation of 5,6,7,8,9,9-Hexachloro-1,2,3,4,4a,5,8,8a-octahydro-*exo*-2-iodo-1,4-*exo*-*endo*-5,8-dimethanonaphthalene (Ic).—To 90 ml. of glacial acetic acid were added 5.0 g. of aldrin (IIIa), 15 g. of sodium iodide, and 10 ml. of 72% perchloric acid. On standing overnight at room temperature, the solution deposited 4.0 g. of yellow solid. Trituration of this material with acetone gave a white solid, 3.3 g. (49%), m.p. 186–187.5°. Recrystallization from methanol gave material melting below 170°, but which resolidified and melted at 186–187.5°. This process could be repeated several times.

Anal. Calcd. for $C_{12}H_9Cl_6I$: C, 29.32; H, 1.84. Found: C, 29.53; H, 1.81.

Single crystal X-ray diffraction patterns were photographed by Dr. Walter M. Macintyre for Ic and the known *exo* bromide (Ia), using a Supper–Weissenberg camera of radius 57.3 mm. A Norelco diffraction apparatus with molybdenum target was used. The two patterns were superimposable, thus establishing the *exo* configuration of the iodide.

Preparation of 5,6,7,8,9,9-Hexachloro-1,2,3,4,4a,5,8,8a-octahydro-*endo*-2-iodo-1,4-*exo*-*endo*-5,8-dimethanonaphthalene (IIc).—A mixture of 1.00 g. (2.43 mmoles) of 5,6,7,8,9,9-hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4-*exo*-*endo*-5,8-dimethano-*exo*-2-naphthoic acid (Id),[3] 1.20 g. (5.54 mmoles) of red mercuric oxide, and 1.5 g. (5.9 mmoles) of iodine in 50 ml. of reagent grade carbon tetrachloride (poured through a 15 × 1 cm. column of Merck alumina) was heated at reflux in the dark for 4 hr. The mixture was filtered while hot, and the solvent was removed with a stream of warm air. The residue was dissolved in 100 ml. of carbon tetrachloride, slurried with finely ground sodium thiosulfate to remove traces of iodine, filtered, and poured through a 50 × 1

(9) T. S. Peterson and J. Robertson, *J. Chem. Soc.*, **125**, 1526 (1924); A. Fairbanks and D. W. Stevens, *ibid.*, 1973 (1932); M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **79**, 1701 (1957); F. R. Jensen and W. E. Coleman, *J. Org. Chem.*, **23**, 809 (1958).

(10) S. B. Soloway, private communication.

(11) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958).

(12) See ref. 3 for pertinent references.

(13) P. S. Skell, D. L. Tuleen, and P. D. Readio, *J. Am. Chem. Soc.*, **85**, 2850 (1963).

(14) R. E. Pearson and J. C. Martin, *ibid.*, **85**, 354 (1963); G. A. Russell, C. De Boer, and K. M. Desmond, *ibid.*, **85**, 355 (1963).

cm. column of Merck alumina packed in pentane. The column was developed with 200 ml. of pentane, which was removed under vacuum to give 840 mg. (70%) of white solid. Infrared analysis showed this solid mixture was 33–36% *endo* iodide (IIc), and the rest was *exo* iodide (Ic).

Eight grams of material prepared by the foregoing method was triturated with 95% pentane until about 4 g. had dissolved. The pentane-soluble fraction contained most of the *endo* iodide, as judged by absorption peaks at 7.70 and 16.30 μ similar to peaks passessed by the bromo (7.67 and 16.34 μ) and chloro (7.65 and 16.28 μ) analogs. The pentane-soluble material was pouing through Merck acid-washed alumina (with carbon tetra- [illegible] eluent) to remove all traces of carbonyl compounds, slurried with solid sodium thiosulfate to remove iodine, and filtered. Three carefu. fractional crystallizations from pentane gave 2.0 g. of colorless material very rich in *endo* isomer. Two more crystallizations from pentane and three from methanol gave 0.5 g. of pure IIc, m.p. 140–142°.

Anal. Calcd. for $C_{12}H_9Cl_6I$: C, 29.32; H, 1.84. Found: C, 29.37; H, 1.87.

The pentane-insoluble residues are essentially *exo* iodide, which may be purified by crystallization from methanol.

Mixture Melting Points.—Mixture melting points of the aldrin hydrohalides were taken on an electrically heated calibrated brass block. Melting points of pure *exo* chloride (Ib), bromide (Ia), and iodide (Ic) were, respectively, 155–157°, 183–184°, and 186–187°. Melting points of pure *endo* halides IIb, IIa, and IIc were 94–96°, 109–110°, and 140–142°, respectively. For mixture melting point measurements in the *exo* series, a ratio of five parts of the lower melting isomer to one of the higher was used, and, in the *endo* series, a one-to-one mixture was used. Mixture melting points for Ib–Ia, Ib–Ic, and Ia–Ic were 159–162°, 159–164°, and 183–186°, respectively, while those for IIb–IIa, IIb–IIc, and IIa–IIc were 95–98°, 94–98°, and 109–110°, respectively.

Preparation of 5,6,7,8,9,9-Hexachloro-1,2,3,4,4a,5,8,8a-octahydro-2,3-diiodo-1,4-*exo*-*endo*-5,8-dimethanonaphthalene.—A solution of 3 g. of aldrin in 100 ml. of 95% ethanol saturated with iodine was irradiated for 24 hr. with a 300-watt tungsten lamp. The solution was poured into 400 ml. of water and decolorized by slowly adding lump sodium thiosulfate. A trace of mineral acid was also added. The solution was extracted with two 50-ml. portions of chloroform. The combined organic layers were dried with magnesium sulfate, and the solvent was removed. The resulting oil was triturated with methanol until a portion solidified, and 1.17 g. (22%) of white solid, m.p. 137–143°, was separated by filtration. Two recrystallizations from hot 95% ethanol and three from Skellysolve B gave material of m.p. 186–189°. The color of iodine began to appear at 180°, and some softening occurred at 184°. The compound is moderately unstable and light sensitive.

Anal. Calcd. for $C_{12}H_8Cl_6I_2$: C, 23.29; H, 1.30. Found: C, 23.47; H, 1.44.

Preparation of 5,6,7,8,9,9-Hexachloro-1,4,4a,5,8,8a-hexahydro-2-iodo-1,4-*exo*-*endo*-5,8-dimethanonaphthalene (IIIc).—A mixture of 5.0 g. (8.1 mmoles) of the diiodide and 0.46 g. (8.2 mmoles) of potassium hydroxide in 200 ml. of 95% ethanol was slowly warmed to reflux with stirring. At the end of 20 min., solution was complete. Heating at reflux was continued for 30 min.; the solution stood overnight at room temperature and was then poured into water. Organic materials were extracted into chloroform, washed with water, and dried with magnesium sulfate. Evaporation of the solvent gave an oil which on crystallization from 25 ml. of hot methanol gave 3.12 g. (78%) of white crystals, m.p. 110–120°. Recrystallizations from methanol sharpened the melting point to 113–115°. An absorption peak at 6.46 μ indicates the vinyl iodide structure.[15]

Anal. Calcd. for $C_{12}H_7Cl_6I$: C, 29.36; H, 1.44. Found: C, 29.29; H, 1.60.

A mixture of 0.25 g. of IIId, 40 mg. of 10% palladium on charcoal, and 50 ml. of methanol was shaken under 630 mm. of hydrogen for 18 hr. at room temperature. The solution was filtered and the solvent was removed. The infrared spectrum of the residue was essentially that of unchanged starting material.

A mixture of 0.5 g. of IIId, 40 mg. of 10% palladium on charcoal, and 100 ml. of methanol was charged to 39 p.s.i. (gage pressure) with hydrogen and shaken at room temperature for 27 hr. The mixture was filtered and the solvent was removed. The residue possessed an infrared spectrum quite similar to that of dihydroaldrin (Ie), thus establishing the aldrin ring system for IIIc. The residue was poured through a 20 × 1 cm. column of Merck neutral alumina in pentane and washed out with 200 ml. of pentane, which was then distilled. Recrystallization from methanol gave a solid, m.p. 75–77°. A mixture melting point with authentic dihydroaldrin was 75–77°.

Infrared Analysis Procedure.—Analyses of aldrin hydrohalides were done on a Perkin-Elmer Model 137 Infracord equipped with potassium bromide optics, using a differential technique.[2] Sample and reference concentrations were 0.1 *M* for the chlorides and bromides, and 0.08 *M* for the iodides. Tetrachloroethylene, freshly distilled from phosphorus pentoxide, was used as solvent. The cell length was 1.0 mm. The analytical absorption band was at 16.3 μ, characteristic of all *endo* aldrin hydrohalides.

Reaction of *exo* Id Silver Salt[3] with Chlorine.—To 60 ml. of reagent carbon tetrachloride was added 500 mg. (1.01 mmoles) of the silver salt of Id. Ten milliliters of solvent was distilled to ensure dryness, and 1.0 ml. of 1.5 *M* chlorine in dry carbon tetrachloride was added. The mixture was heated at reflux for 2 hr. in the dark and solids were filtered. The filtrate was poured through a 50 × 1 cm. column of Merck acid-washed alumina packed in carbon tetrachloride. The epimeric halides were washed out with 200 ml. of carbon tetrachloride, leaving the carbonyl-containing side products on the column. Evaporation of solvent gave 111 mg. (28%) of a mixture of Ib and IIb. Differential analysis showed that there was approximately 30% of *endo* chloride (IIb).

Reaction of *endo* IId Silver Salt[3] with Chlorine.—Reaction and work-up of 500 mg. (1.01 mmoles) of IId silver salt with 1.5 mmoles of chlorine, exactly as above, gave 175 mg. (44%) of a mixture of Ib and IIb. The *endo* (IIb) chloride content of the mixture lay between the limits 30–33%.

Reaction of *exo* Id Silver Salt with Iodine.—Reaction and work-up of 500 mg. (1.01 mmoles) of Id silver salt with 1 g. (7.9 mmoles) of iodine, exactly as above, gave 441 mg. (89%) of a mixture of Ic and IIc, with the *endo* iodide content between the limits 30–36%.

Reaction of *endo* IId Silver Salt with Iodine.—Reaction and work-up of 500 mg. (1.01 mmoles) of IId silver salt with 1 g. (7.9 mmoles) of iodine, exactly as above, gave 423 mg. (85%) of a mixture of Ic and IIc, with the *endo* iodide content between the limits 33–36%.

Attempted Equilibration of *endo* Chloride (IIb).—*endo* chloride (IIb) (200 mg., 0.5 mmole) and 170 mg. (1 mmole) of silver acetate were placed in 70 ml. of reagent grade carbon tetrachloride, and 10 ml. of solvent was distilled. Two millimoles of chlorine was added in carbon tetrachloride, and the mixture was heated in the dark at reflux for 2 hr., and then filtered; the solvent was removed to give 202 mg. of oil. The infrared spectrum is essentially that of IIb. It has been shown[3] that the corresponding bromides, Ia and IIa, do not rearrange under Hunsdiecker reaction conditions, or under other free-radical conditions.[2]

Chlorination of Dihydroaldrin (Ie).—Dihydroaldrin,[6] 1.835 g. (5.00 mmoles), was dissolved in 50 ml. of carbon tetrachloride, and the vapor volume was swept out with dry nitrogen. Chlorine, 11.2 ml. (STP or 0.5 mmole), was bubbled in at −30°, and the solution was irradiated with a GE AH-4 lamp. The addition took 150 sec. After approximately 1 min., the chlorine color had disappeared. The solvent was removed under reduced pressure and the residue was chromatographed on 160 g. (1.8 × 63 cm. column) of neutral, activity grade I alumina.[16] Starting material that was recovered amounted to 94.9% of the initial amount. The aldrin hydrochloride weighed 79.4 mg. (3.96%), and contained 30 ± 5% *endo* chloride (IIb).

Bromination of Dihydroaldrin (Ie) with N-Bromosuccinimide.—Dihydroaldrin, 1.835 g. (5.00 mmoles), and N-bromosuccinimide, 89.3 mg. (0.514 mmole), were dissolved in 50 ml. of carbon tetrachloride. The flask was irradiated with a 100-watt light bulb for 46 hr. The solvent was removed under reduced pressure, and the residue was chromatographed on 160 g. (1.8 × 62 cm. column) of neutral, activity grade I alumina, as above. The material was put on the column in pentane, in which N-bromosuccinimide and succinimide are virtually insoluble. Starting material recovered amounted to 85.4% of the initial quantity.

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 50.

(16) H. Brockmann and H. Schodder, *Ber.*, **74B**, 73 (1941); see ref. 2 for the detailed chromatographic procedure.

The aldrin hydrobromide portion recovered weighed 128.4 mg. (5.75% yield). Analysis of this material indicated that the mixture contained 16 ± 3% *endo* bromide (IIa).

Bromination of Dihydroaldrin (Ie) with Bromotrichloromethane.—Dihydroaldrin, 1.835 g. (5.00 mmoles), and benzoyl peroxide, 32 mg. (0.124 mmole), were dissolved in 50 ml. of bromotrichloromethane. This solution was heated at 83° for 15 hr. in the dark. The solvent was removed under reduced pressure, and the residue was chromatographed on 160 g. (1.8 × 64 cm. column) of neutral, activity grade I alumina, as above. Fractions 2 through 5 contained 87.0% of recovered starting material. Fractions 6 through 12 contained traces of a colorless oil. Fractions 13 through 30 contained 11.7% of a mixture of aldrin hydrobromides. Differential infrared analysis of this material indicated 4 ± 1% *endo* bromide (IIa).

Acknowledgment.—The authors are indebted to the National Science Foundation for generous support of this work.

Bridged Polycyclic Compounds. XXV. Free-Radical Addition of Benzenesulfonyl Halides to Norbornadiene[1]

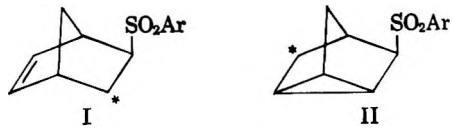
STANLEY J. CRISTOL[2] AND DAVID I. DAVIES[3]

Department of Chemistry, University of Colorado, Boulder, Colorado

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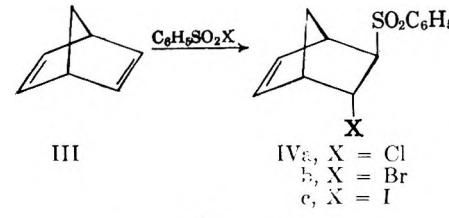
The benzenesulfonyl halides react with norbornadiene under free-radical conditions to give mixtures of *endo*-3-halogeno-*exo*-5-norbornen-2-yl phenyl sulfone (IV) and 5-halogeno-3-nortricyclyl phenyl sulfone (V). The proportion of saturated component decreases along the series (Cl > Br > I). These results combined with dilution experiments provide evidence favoring the two separate intermediates VIII and IX, rather than the nonclassical homoallylic radical (X) as an intermediate.

Some time ago Cristol, Brindell, and Reeder[4] reported that the addition of aryl mercaptans to norbornadiene under free-radical conditions gave a mixture of *exo*-5-norbornen-2-yl aryl thioether *via* 1,2-addition and 3-nortricyclyl aryl thioether *via* homoconjugative addition. Conclusive evidence was provided against the intermediacy of a single nonclassical homoallylic radical and in favor of two separate intermediates. Further work by Cristol and Reeder[5] showed that *p*-toluenesulfonyl chloride added to norbornadiene to give a 1:1 product which was largely saturated, and which, on crystallization, gave a 42% yield of a product which was almost certainly 5-chloro-3-nortricyclyl *p*-tolyl sulfone. The relative completeness of the rearrangement to the nortricyclene ring system was rationalized on the basis of the slow chain transfer of the intermediate radicals with the sulfonyl chloride allowing sufficient time for rearrangement of radical I to II.

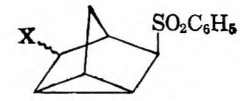


I II

In 1959 McNamara and Skell[6] investigated free-radical addition reactions of benzenesulfonyl halides to reactive olefins and found that, when equimolar quantities of freshly prepared olefin and sulfonyl halide were irradiated for a few minutes with a nonfrosted light bulb, the β-halosulfone addition product, in many cases, crystallized within a few minutes, often in better than 90% yields. In our hands, application of this method to the reaction of benzenesulfonyl chloride with norbornadiene met with only moderate success. If equimolar amounts of reactants were irradiated for several days, the reaction mixture slowly darkened and yielded, on distillation, unchanged benzenesulfonyl chloride, about 10% of the 1:1 addition product, and a large quantity of an intractable black tar. The reaction could proceed to give the following products in the absence of major skeletal rearrangement.



III IVa, X = Cl
b, X = Br
c, X = I



Va, X = Cl
b, X = Br
c, X = I

The product had an infrared absorption band of medium intensity in the 12.3–12.5-μ range characteristic of a nortricyclene structure[7] and did not readily decolorize potassium permanganate in acetone. This indicates that the product is predominantly Va,[8] possibly together with a small amount of IVa.[9] This was confirmed by hydrogenation experiments. Crystallization of the crude 1:1 adduct from methanol gave a pure saturated component, Va, the stereochemistry of the chlorine atom being unknown.

(1) Previous paper in series: S. J. Cristol, L. K. Gaston, and T. Tiedeman, *J. Org. Chem.*, **29**, 1279 (1964).

(2) To whom all inquiries should be addressed.

(3) Shell Development Co. Post-Doctorate Fellow, University of Colorado, 1958–1959.

(4) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Am. Chem. Soc.*, **80**, 635 (1958).

(5) S. J. Cristol and J. A. Reeder, *J. Org. Chem.*, **26**, 2182 (1961).

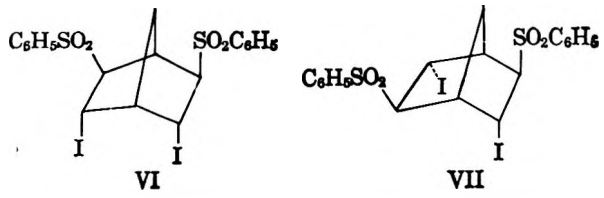
(6) J. H. McNamara and P. S. Skell, Abstracts of Papers, 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959, p. 13L.

(7) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

(8) The stereochemistry of the saturated component Va is unknown, and in the crude 1:1 addition product both of the possible products may be present.

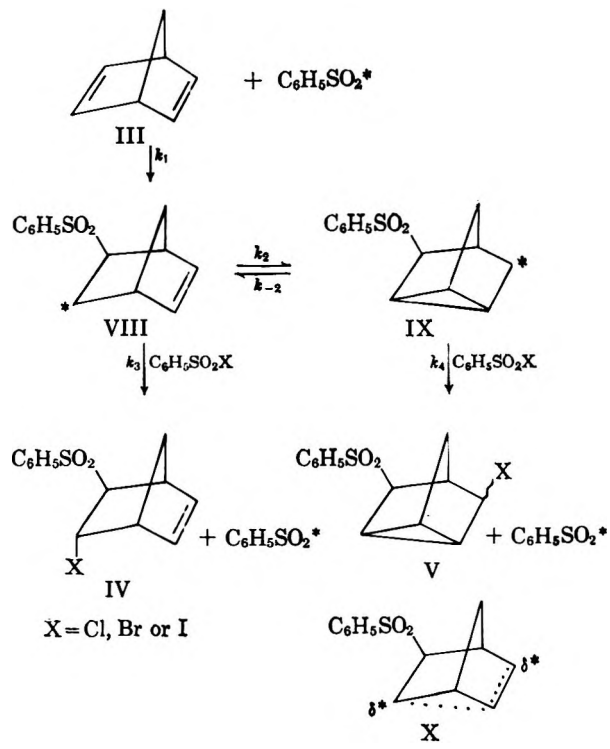
(9) In the unsaturated IVa the benzenesulfonyl and chlorine groups presumably have the *trans* relationship by analogy with the addition product of *p*-toluenesulfonyl chloride to norbornene where a *trans* relationship of sulfur and chlorine groups has been proved.[5]

The reactions of benzenesulfonyl bromide and benzenesulfonyl iodide with norbornadiene were then investigated. An equimolar mixture of norbornadiene and benzenesulfonyl bromide on warming gave over 90% of a 1:1 adduct which consisted of 33% of unsaturated IVb and 67% of Vb. Norbornadiene and benzenesulfonyl iodide reacted vigorously when 1 mole of the iodide was added slowly to 1 mole of norbornadiene. The reaction product was predominantly unsaturated, although a weak absorption band at 12 12.5 μ in the infrared indicated the presence of some saturated material. This was confirmed by subsequent hydrogenation experiments. When norbornadiene was added to benzenesulfonyl iodide, an extremely violent reaction occurred. The product was a high-melting buff-colored solid with correct analysis for a 2:1 adduct of benzenesulfonyl iodide and norbornadiene. It is believed to have the structure VI or VII.



The reaction of the benzenesulfonyl halides with norbornadiene has, most likely, the steps that are shown in Scheme I, which follows, in its chain.

SCHEME I



If this mechanism is correct, and if k_2 and k_{-2} are of the same order of magnitude as $k_3[C_6H_5SO_2X]$, then the following consequences can be predicted. (1) As the nature of X is varied, the ratio of unsaturated IV to saturated V will increase as the tendency to chain transfer (k_3) increases. Thus this ratio should increase as X changes from chlorine to bromine to iodine. (2) As one lowers the concentration of a given halide, the ratio of IV to V will decrease.[10a] On the other hand, if the nonclassical homoallylic radical X were the sole intermediate leading to IV and V isomers, changing the concentration of halide would not affect the ratio of IV to V,[10a] and the effect of varying the nature of X would not necessarily be predictable.

Table I lists the composition of the 1:1 adducts from the various benzenesulfonyl halides and norbornadiene, as estimated by quantitative hydrogenation. It may be noted that the ratio of unsaturated IV to V varies from 0.05 to 5 (neat reactions) as the benzenesulfonyl halide is varied from chloride to iodide,[10b] and that there is an analogous variation in the experiments with reactants dissolved in ten volumes of chlorobenzene. Excepting the benzenesulfonyl chloride experiments, where the yields were very poor, the dilution experiments also are consistent with the proposed mechanism.

In the early work on dilution experiments in the addition of mercaptans to norbornadiene,[4] it was also shown that two intermediates were involved in the free-radical addition reaction. However, the minimum amount of nortricyclyl species found was 60%, so that it was not possible to state with complete assurance that the intermediates were the classical radicals VIII and IX, as the data could be accommodated to the intermediates X and IX. In the present work, where we have now succeeded in trapping the initial intermediate by transfer with benzenesulfonyl iodide before more than 17% has rearranged to the nortricyclyl radical, one may have considerable confidence in excluding X as a product-producing intermediate and in relegating it to the position of a transition state in the rearrangement of VIII to IX.

TABLE I

PROPORTIONS OF IV AND V FORMED IN THE REACTION OF BENZENESULFONYL HALIDES WITH NORBORNADIENE

Type of adduct	Yield, %	IV, %	V, %	IV/V	Hydrogenation time, hr.
Norbornadiene and Sulfonyl Halide in 1:1 Proportions (Neat)					
Norbornadiene + $C_6H_5SO_2Cl$	7.3	5	95	0.05	3
Norbornadiene + $C_6H_5SO_2Br$	90	33	67	0.5	4
Norbornadiene + $C_6H_5SO_2I$	68	83	17	5	48
Norbornadiene and Sulfonyl Halides in 1:1 Proportions, Dissolved in 10 Volumes of Chlorobenzene					
Norbornadiene + $C_6H_5SO_2Cl$	11.4	7	93	0.07	3
Norbornadiene + $C_6H_5SO_2Br$	93	13	87	0.15	5
Norbornadiene + $C_6H_5SO_2I$	72.5	73	27	2.7	48

This conclusion is consistent not only with results in this laboratory, but also with those of other workers on free-radical additions to norbornadiene and other related bridged bicyclic systems, where no evidence could be found in favor of nonclassical homoallylic radicals,[11-14] and it seems possible to state that non-

(10) (a) For a complete discussion of this situation, see ref. 4; (b) the data on the chloride may be unconvincing, in view of the poor yields, but they are consistent with those on the bromide and iodide.

(11) E. S. Huyser and G. Echegaray, *J. Org. Chem.*, **27**, 429 (1962).

(12) M. M. Martin and D. C. DeJongh, *J. Am. Chem. Soc.*, **84**, 3526 (1962).

(13) J. A. Berson and C. J. Olsen, *ibid.*, **84**, 3178 (1962); J. A. Berson, C. J. Olsen, and J. S. Walia, *ibid.*, **84**, 3337 (1962).

(14) H. Hart and F. J. Chloupek, *ibid.*, **85**, 1155 (1963).

classical homoallylic radicals of type X do not exist in the dehydronorbornyl–nortricyclyl series.

Experimental

Reagents.—Norbornadiene supplied by the Shell Development Company was freshly distilled prior to use, b.p. 84° (620 mm.). Benzenesulfonyl chloride was Eastman Kodak reagent grade. Benzenesulfonyl bromide and iodide were prepared, respectively, by the reaction of benzenesulfinic acid with bromine[6] and with iodine.[6,15,16]

Addition of Benzenesulfonyl Chloride to Norbornadiene. A.—Benzenesulfonyl chloride, 115 g. (0.65 mole), and norbornadiene, 60 g. (0.65 mole), were mixed, and a few crystals of benzoyl peroxide were added. The solution was stirred magnetically and irradiated with a 150-watt clear electric light bulb for 56 hr., during which time the solution darkened appreciably. Distillation gave 87 g. of unchanged benzenesulfonyl chloride followed by 12.8 g. (7.3%) of 1:1 adduct as a pale yellow liquid which solidified on standing. An intractable black tar remained in the distillation flask. The crude 1:1 adduct did not decolorize potassium permanganate in acetone, and its infrared spectrum showed absorption of medium intensity in the 12.3–12.5-μ range, characteristic of a nortricyclene structure. Several recrystallizations of a small portion from methanol gave 5-chloro-3-nortricyclyl phenyl sulfone as crystals, m.p. 114–116°.

Anal. Calcd. for $C_{13}H_{13}ClO_2S$: C, 58.08; H, 4.88. Found: C, 57.92; H, 5.00.

B.—A similar reaction with norbornadiene, benzenesulfonyl chloride, and chlorobenzene in the ratio 1:1:10 gave an 11.4% yield of 1:1 adduct, b.p. 180° (0.2 mm.), which was redistilled twice prior to hydrogenation experiments.

Addition of Benzenesulfonyl Bromide to Norbornadiene. A.—Benzenesulfonyl bromide, 6 g. (0.027 mole), was added dropwise to 2.5 g. (0.027 mole) of well-stirred norbornadiene. No reaction appeared to take place, and the solution was irradiated with a 150-watt clear electric light bulb for 27 hr. to give a pale yellow viscous liquid. Distillation afforded no unchanged norbornadiene or benzenesulfonyl bromide, and 7.6 g. (90%) of 1:1 adduct was obtained as a pale yellow, very viscous liquid, b.p. 180° (0.15 mm.), which solidified on standing. The product decolorized dilute potassium permanganate in acetone, and its infrared spectrum showed only medium absorption in the 12.3–12.5-μ range. Several recrystallizations of a portion of the product gave a 5-bromo-3-nortricyclyl phenyl sulfone as white crystals, m.p. 100–105°.

Anal. Calcd. for $C_{13}H_{13}BrO_2S$: C, 49.84; H, 4.19. Found: C, 50.03; H, 4.11.

B.—In a similar reaction with norbornadiene, benzenesulfonyl bromide, and chlorobenzene in ratio 1:1:10, a 93% yield of 1:1 adduct was obtained as a pale yellow liquid, b.p. 186° (0.3 mm.). It was twice redistilled prior to hydrogenation.

Addition of Benzenesulfonyl Iodide to Norbornadiene. A.—To 6.0 g. (0.065 mole) of well-stirred norbornadiene, 17.5 g. (0.065 mole) of benzenesulfonyl iodide was added in small portions. Much heat was evolved, and the reaction was moderated by ice cooling, and then allowed to stand at room temperature overnight to yield a pale yellow semisolid material. The product was boiled with Skellysolve B to remove any unchanged norbornadiene and then boiled with 175 ml. of methanol, the product completely dissolving which indicated the absence of [redacted] adduct. Most of the methanol was removed by distillation and on cooling, 16 g. (68%) of material, m.p. 115–120°, was deposited. The material decolorized potassium permanganate in acetone, indicating the presence of unsaturated material, but the infrared spectrum showed some absorption in the 12.3–12.5-μ region of the infrared, characteristic of a nortricyclene system. A portion of material was recrystallized several times from methanol to give *endo*-3-iodo-*exo*-5-norbornen-2-yl phenyl sulfone as crystals, m.p. 152–153°, which had no absorption at 12.3–12.5 μ in the infrared.

Anal. Calcd. for $C_{13}H_{13}IO_2S$: C, 43.34; H, 3.64. Found: C, 43.69; H, 3.80.

B.—A similar reaction with norbornadiene, benzenesulfonyl iodide, and chlorobenzene in the ratio 1:1:10 gave a 72.5% yield of 1:1 adduct.

C.—Benzenesulfonyl iodide, 51.5 g. (0.19 mole), was placed in a flask equipped with a reflux condenser, and 13.3 g. (0.14 mole) of norbornadiene was added dropwise through the top of the condenser. The mixture was stirred magnetically during the addition. Much heat was evolved and the product was a blackish tarry material. On boiling this with benzene, a solution was obtained which deposited a buff-colored solid on cooling. Several recrystallizations from toluene gave material, m.p. 237°, which would not decolorize potassium permanganate in acetone, and which showed no absorption in the 12.3–12.5-μ region of the infrared.

Anal. Calcd. for $C_{19}H_{18}I_2O_4S_2$: C, 36.32; H, 2.89. Found: C, 36.62; H, 3.04.

Estimation of Unsaturation.—In a typical experiment, 150 mg. of 10% palladium-on-charcoal catalyst was weighed into a hydrogenation flask, 80 ml. of 95% ethanol was added, and the flask was shaken on a quantitative (atmospheric pressure) hydrogenation apparatus for 10–15 min. The flask was detached, and the hydrogen atmosphere in it was removed. Then 0.5–1.5 g. of 1:1 adduct was added to the flask and was washed in with 25 ml. of 95% ethanol. The flask was then shaken on the quantitative hydrogenator until hydrogenation was complete. This took approximately 3, 4–5, and 48 hr., respectively, for the adducts of norbornadiene with benzenesulfonyl chloride, bromide, and iodide. The volume of gas absorbed was corrected to standard conditions by the use of the ideal gas law.

(15) R. Otto and J. Tröger, *Ber.*, **24**, 478 (1891).
(16) P. S. Skell and J. H. McNamara, *J. Am. Chem. Soc.*, **79**, 85 (1957).

Decomposition of Alkyl Hypochlorites. The 4-*t*-Butylcyclohexyl Radical[1]

FREDERICK D. GREENE, CHIN-CHIUN CHU, AND JASJIT WALIA

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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4-*t*-Butylcyclohexyl radical, generated from dimethyl(*cis*- and *trans*-4-*t*-butylcyclohexyl)carbinyl hypochlorite and from *cis*- and *trans*-4-*t*-butylcyclohexanecarbonyl peroxide, reacts with halogen donors (carbon tetrachloride, bromotrichloromethane, alkyl hypochlorite) to yield *cis*- and *trans*-4-*t*-butylcyclohexyl halide (chloride and bromide) in which *cis* halide predominates over *trans* halide by 2:1. Stereospecificity (*cis*–*trans*) *decreases* slightly with decreasing temperature. The results are compared with data on norbornyl systems.

Tertiary alkyl hypochlorites have been shown in a number of cases to undergo decomposition to alkyl halides and carbonyl compounds.[2,3] The sensitivity of decomposition to light, radical sources, and inhibitors points to decomposition by a free-radical chain route. In this report attention is called to the use of hypochlorites for the study of radicals, illustrated here by an investigation of the 4-*t*-butylcyclohexyl radical.

Results

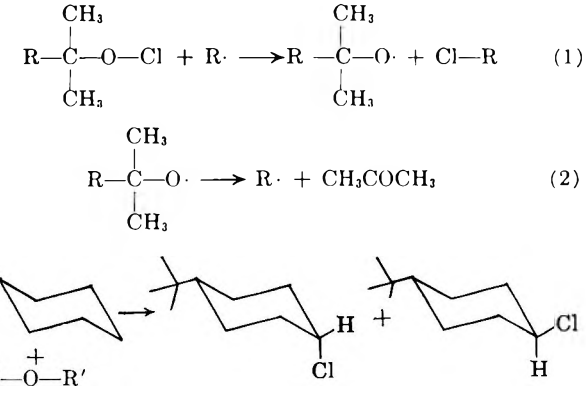
Decomposition of dimethyl(*cis*- or *trans*-4-*t*-butylcyclohexyl)carbinyl hypochlorite in an inert medium by weak irradiation or by heat affords in high yield a mixture of *cis*- and *trans*-4-*t*-butylcyclohexyl chlorides in the ratio of 2:1. Exactly the same ratio of chlorides is obtained from either *cis* or *trans* starting material at all temperatures measured. In control experiments pure *cis* and pure *trans* chloride were observed to be stable to the decomposition conditions and to the conditions of analysis. The data are summarized in Table I.

Assignment of structure to the chlorides is based on the identity with samples prepared from 4-*t*-butylcyclohexanol. Assignment of *cis* stereochemistry to the chloride of shorter retention time on a nitrile silicone column is based on (1) its enhanced ease (in comparison with *trans* isomer) of conversion by base to 4-*t*-butylcyclohexene[4]; (2) location in the n.m.r. spectrum of the C-1 hydrogen at τ 5.63 (*vs.* τ 6.36 for the *trans* isomer)[5]; (3) location in the infrared spectrum of the C–Cl stretching band at 690 cm.$^{-1}$ (*vs.* 725 cm.$^{-1}$ for the *trans* isomer),[6] and a marked similarity in infrared spectra of the *cis* and *trans* chlorides with the corresponding *cis* and *trans* bromides of known configuration.[7]

Decomposition of the diacyl peroxide of *trans*-4-*t*-butylcyclohexanecarboxylic acid has been effected under three sets of conditions: (1) in carbon tetrachloride, (2) in bromotrichloromethane,[8] and (3) in carbon tetrachloride containing bromine. The data are summarized in Table II. Analysis was made for the 4-*t*-butylcyclohexyl chlorides and bromides.[9] In this case also *cis*-4-*t*-butylcyclohexyl chloride is favored over the *trans* isomer, with a slightly larger preference than noted with the hypochlorites. From the decomposition in bromotrichloromethane, *cis* bromide predominates over *trans* bromide by 2:1. Decomposition in carbon tetrachloride containing bromine affords both the chlorides and the bromides. The chlorides are formed in essentially the same ratio as in the absence of bromine. The apparent preference for *trans* bromide is complicated by the instability of the *cis* bromide. In control experiments it was shown that both bromides are somewhat unstable under these experimental conditions and that the *cis* bromide is the less stable of the two (47% destruction of the *cis* isomer under conditions resulting in only 13% destruction of the *trans* isomer).

Discussion

The stability of the hypochlorites in the dark and their sensitivity to light, to initiators, and to inhibitors indicate decomposition by a free-radical chain reaction, in accord with previous data on tertiary hypochlorites.[2,3] The identity of the ratio of *cis*- to *trans*-4-*t*-butylcyclohexyl chloride starting from either *cis* or *trans* hypochlorite is in accord with this view and implicates the 4-*t*-butylcyclohexyl radical as a common intermediate for the two cases. An unexpected feature is the preferential formation of the *cis* (axial) chloride over the *trans* (equatorial) chloride, a pattern that is also found in the decomposition of the *cis*- and *trans*-4-*t*-butylcyclohexanecarbonyl peroxides (Table II). [Although we have not effected the equilibration of these chlorides, control data (see Ex-



(1) Supported in part by the National Science Foundation and by the Atomic Energy Commission under Contract No. AT(30-1)-905. A preliminary report of this work appeared in *J. Am. Chem. Soc.*, **84**, 2463 (1962).

(2) F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.*, **28**, 55 (1963).

(3) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1593, 1597 (1963).

(4) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

(5) (a) A. J. Berlin and F. R. Jensen, *Chem. Ind.* (London), 998 (1960); (b) L. W. Reeves and K. O. Strømme, *Can. J. Chem.*, **38**, 1241 (1960).

(6) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 217.

(7) E. L. Eliel and R. G. Haber, *J. Org. Chem.*, **24**, 143 (1959). We wish to thank Professor Eliel for infrared spectra of the *cis* and *trans* bromides.

(8) Attempts were also made to decompose the hypochlorite in bromotrichloromethane. Although the peroxide gave reproducible results in this solvent, the hypochlorite results were variable and consequently have not been included in this report.

(9) As reported previously [H. H. Lau and H. Hart, *J. Am. Chem. Soc.*, **81**, 4897 (1959)], these are the minor products of decomposition. The major products appear to be more complicated than originally reported and are under reinvestigation.

TABLE I

PRODUCTS FROM THE DECOMPOSITION[a] OF DIMETHYL(*cis*- AND *trans*-4-*t*-BUTYLCYCLOHEXYL)CARBINYL HYPOCHLORITE

Solvent	Concn., *M*	Temp., °C.	Ratio of RCl[b,c] *cis*	Ratio of RCl[b,c] *trans*	Yield of RCl, %
		trans Hypochlorite			
CCl_4	0.37	80	67	33	93
CCl_4	0.40	0	65	35	84
CCl_4	0.37	−30	62	38	68
$CFCl_3$	0.34	0	65	35	99
$CFCl_3$	0.34	−80	58	42	83
CCl_4[d]	0.38	80[d]	66	34	49
		cis Hypochlorite			
CCl_4	0.4	80	67	33	85
CCl_4	0.4	0	65	35	80
CCl_4	0.4	−30	62	38	79
$CFCl_3$	0.28	0	66	34	
$CFCl_3$	0.32	−80	58	42	94
Cyclohexane	0.06	10	67	33	84

[a] Weak irradiation, ref. 21. [b] RCl is 4-*t*-butylcyclohexyl chloride. [c] Precision of ratios, ±0.5%. [d] Thermal decomposition.

TABLE II

PRODUCTS FROM THE THERMAL DECOMPOSITION OF BIS-*trans*-4-*t*-BUTYLCYCLOHEXANECARBONYL PEROXIDE

Solvent	Concn., *M*	Temp., °C.	Ratio of RCl[a] *cis*	Ratio of RCl[a] *trans*	Yield, %	Ratio of RBr[a] *cis*	Ratio of RBr[a] *trans*	Yield, %
CCl_4	0.05	90	73	27	30			
CCl_4[b]	0.18	90	73	27				
CCl_4	0.1	80	73	27	20			
$CBrCl_3$[c]	0.1	80				69	31	
CCl_4[c,d]	0.1	80				37[e]	63	6
CCl_4[f]	0.01	80	(69)[g]	(31)[g]	0.8	40[e]	60	12
CCl_4[h]	0.001	80	(77)[g]	(23)[g]	9	43	57	14

[a] R is 4-*t*-butylcyclohexyl. [b] In this run bis-*cis*-4-*t*-butylcyclohexanecarbonyl peroxide was used. [c] Carried out in amber vessels. [d] Contains bromine, 0.2 *M*. [e] Preferential destruction of *cis* isomer; see description of control data. [f] Contains bromine, 0.02 *M*. [g] Owing to the small yield of RCl, these figures are not so accurate as others. [h] Contains bromine, 0.002 *M*.

TABLE III

EFFECT OF ATOM-TRANSFER AGENT ON *cis*- TO *trans*-4-*t*-BUTYLCYCLOHEXYL HALIDE RATIO FROM 4-*t*-BUTYLCYCLOHEXYL RADICAL AT 80°

Reactant	Solvent	Transfer agent	*cis*–*trans* R–X
Hypochlorite	CCl_4	RO–**Cl**	2:1
Peroxide	CCl_4	Cl_3C–**Cl**	2.7:1
Peroxide	CCl_3Br	Cl_3C–**Br**	2.2:1
Peroxide	CCl_4	Br–**Br**	(~1:1)[a]

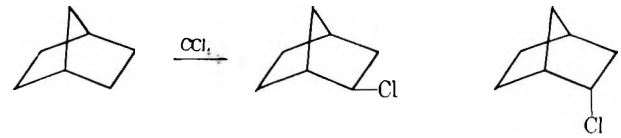
[a] Values uncertain owing to instability of products under reaction conditions (see Table II).

perimental section, Table IV) and data from other systems indicate that chlorine in the axial position is less stable than in the equatorial position.[5b,10] The slightly different *cis*–*trans* product ratio from hypochlorite *vs.* peroxide is probably associated with different halogen donors in the two cases. That the 4-*t*-butylcyclohexyl radical is sufficiently selective to search out good halogen donors is clear from the last three entries of Table II, from which one may estimate that the ΔF^* of the step in which alkyl chloride is formed exceeds by more than 6.5 kcal. the ΔF^* of the alkyl bromide-forming step.

In Table III are summarized the observations bearing on the effect of atom-transfer reagent on the stereospecificity of 4-*t*-butylcyclohexyl radical. Thus *cis* halide is favored over *trans* halide for all of these halogen donors except molecular bromine; for this case, the selectivity appears to be lower but interpretation is obscured by the instability of the products to the reaction conditions.

(10) Ref. 6, p. 236.

Norbornyl Radicals.—A related case in which the stereochemistry of halogen atom transfer to a secondary radical has been examined is the halogenation of norbornane.[11] One notes that the preferential formation of one isomer (*exo*) over the other (*endo*) is considerably greater than in the case of the 4-*t*-butylcyclohexyl system.



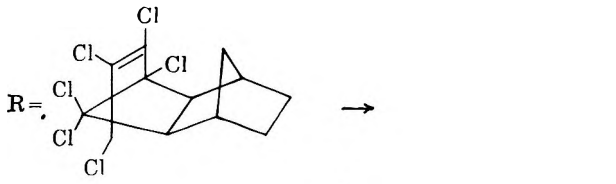
Conditions	Transfer agent	Yield, % *exo*	Yield, % *endo*
hν	Cl–Cl	73	22
$(C_6H_5COO)_2$	Cl_3C–Cl	95	1–5

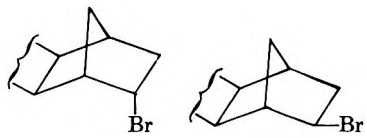
Similar selectivity is also observed with the dihydroaldrinyl radical (**R**).[12]

Hunsdiecker Reactions.—Investigations of the Hunsdiecker reaction and the Cristol–Hunsdiecker reaction (RCOOH–HgO–X_2)[12b] on 2-*exo*-dihydroaldrincarboxylic acid led to an *exo*–*endo* bromide ratio of 70:30, comparable to the low selectivity in the reaction of bromine with the dihydroaldrinyl radical. In a study of the Hunsdiecker reaction with 4-*t*-butylcyclohexanecarboxylic acid,[7] a *trans*–*cis* bromide ratio of 65:35 was reported (total yield of bromides, ~25%). In a

(11) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958).

(12) (a) S. J. Cristol, J. R. Douglass, W. C. Firth, Jr., and R. E. Krall, *J. Org. Chem.*, **27**, 2711 (1962); (b) S. J. Cristol, L. K. Gaston, and T. Tiedeman, *ibid.*, **29**, 1279 (1964).





Composition of RBr fraction,[a] %

Radical source	Transfer agent	*endo*	*exo*
exo-(R–COO)$_2$	Br–Br	30	70
exo-(RCOO)$_2$	Cl_3C–Br	0	100
endo-(RCOO)$_2$	Cl_3C–Br	0	100

[a] Product analysis by infrared method. Results reported as accurate to ±4%.

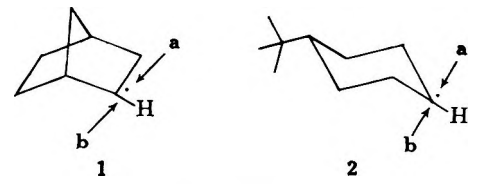
repetition of this experiment, we also observed a predominance of *trans* bromide, but, in view of the low yields and the finding of selective destruction of the *cis* bromide under the conditions of the experiment, further reinvestigation of this Hunsdiecker reaction was discontinued.

Effect of Temperature on *cis*–*trans* Chloride Ratio.—The long chain nature of the decomposition of the hypochlorites of Table I permitted the evaluation of the *cis*–*trans* chloride ratio over a wide temperature range. Although the change is small, it is reproducible and is the same for both reactants. A surprising feature is the *decrease* in selectivity as the temperature is lowered.

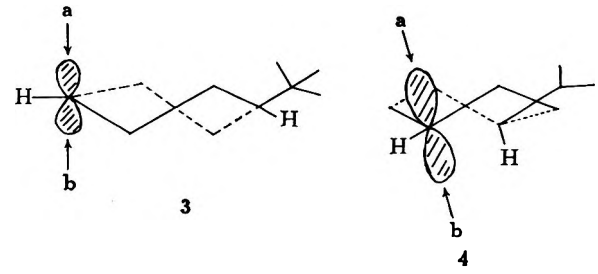
$$\Delta H_{cis}^{*} - \Delta H_{trans}^{*} = 0.3 \text{ kcal./mole}$$
$$\Delta S_{cis}^{*} - \Delta S_{trans}^{*} = +2 \text{ e.u.}$$

Thus the preferential formation of *cis*- over *trans*-4-*t*-butylcyclohexyl chloride in halogen atom abstraction by the 4-*t*-butylcyclohexyl radical is due to a more favorable entropy of activation.

4-*t*-Butylcyclohexyl Radical.—The major feature requiring interpretation in this work is the preference for transfer of an atom to the 4-*t*-butylcyclohexyl radical to form an axial-bonded substituent, compared with the large preference to form an equatorial (*exo*) substituent in transfer to the norbornyl radicals.[11,12] At one point, consideration was given to explanation in terms of radicals pyramidal rather than planar at the carbon holding the odd electron.[13] However, recent evidence from electron paramagnetic resonance (e.p.r.) points strongly to the planar form as the stable geometric array for carbon radicals.[14] (Out of sixteen radicals, acyclic and cyclic including cyclohexyl, that might be expected to have the odd electron in a p-orbital, only cyclopropyl radical showed an α constant [$a_{\alpha\text{-H}}$] outside the range of 21–23 gauss.[13]) The e.p.r. data on cyclohexyl radical also indicate nonequivalence of the β-hydrogens, $a_{\beta\text{-axial H}} = 41$ gauss ($a_{\beta\text{-equatorial H}} = 5$ gauss).[15] The substantial preference for approach from direction **a** over **b** in the 2-norbornyl radical, plus the *decrease* in selectivity with decreasing



temperature in this work make it seem likely that the geometry of the 4-*t*-butycylclohexyl moiety at the transition state for the atom-transfer step which produces *cis* chloride may be appreciably removed from a chair conformation[16] (a point of relevance to other questions of stereochemistry of radical additions to olefins).[17] Two different twist-boat conformations are represented in **3** and **4**. In **3**, atom transfer from directions **a** and **b** appear equally favorable; in **4**, transfer from direction **a** (leading to *cis* product) appears more favorable than transfer from direction **b**. However, the preference for *cis* over *trans* product is energetically a small value ($\Delta F_{trans}^{*} - \Delta F_{cis}^{*} = 0.4$ kcal./mole) and the above consideration is no more than suggestive. It is of interest that 1-hydroxycyclohexyl radicals react with 1-octene to afford product mixtures in which equatorial product predominates.[18a] Also related to this problem are the results of halogenation of 1-chloro- and 1-bromocyclohexane. The ratio of *cis* to *trans* in the 1,4-dihalocyclohexane fraction is less than one when the halogen donor is chlorine and greater than one when the donor is *t*-butyl hypochlorite.[18b]



Experimental

All melting points are corrected; boiling points are uncorrected.

***cis*- and *trans*-4-*t*-Butylcyclohexanecarboxylic Acid.**—The *cis* isomer was obtained by the procedure of Lau and Hart, m.p. 116–118° (lit.[9] m.p. 117–118°), and the *trans* isomer, by the procedure of Tichý, Jonáš, and Sicher, m.p. 174.5–175° (lit.,[19] m.p. 174–175°).

Dimethyl(*cis*- and *trans*-4-*t*-butylcyclohexyl)carbinols were prepared from the corresponding methyl esters by the action of methyl Grignard reagent: *cis* isomer, m.p. 49–50° after recrystallization from acetonitrile (lit.[20] m.p. 49.5–50°); *trans* isomer, m.p. 101.5–102° after recrystallization from acetonitrile (lit.[20] m.p. 103–104°).

(13) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

(14) The strongest evidence for planarity of a radical would appear to lie in the carbon-13 hyperfine interaction constant, to date reported only for methyl radical [M. Karplus and G. K. Fraenkel, *J. Chem. Phys.*, **35**, 1312 (1961)].

(15) Detailed consideration of e.p.r. data on the cyclohexyl radical will appear in a forthcoming publication by R. W. Fessenden and R. H. Schuler.

(16) An alternate explanation has recently been advanced by M. C. R. Symons [*Nature*, **198**, 1196 (1963)]; preferential attack from **b** in **2** is attributed to "electron-rich chlorine" avoiding the region of higher electron density (region **a** was considered of higher electron density based on the greater interaction constant of the radical with the β-axial hydrogens). The suggestion is an interesting one, but we feel that the halogen of hypochlorite or of carbon tetrachloride will be more negative at the transition state than at the ground state and would *prefer* reaction at sites of higher electron density.

(17) For a review of "Stereochemistry of Free Radical Additions to Olefins," see B. A. Bohm and P. I. Abell, *Chem. Rev.*, **62**, 599 (1962); see also D. G. Applequist and N. D. Werner, *J. Org. Chem.*, **28**, 48 (1963).

(18) (a) R. J. Gritter and R. L. Albers, *ibid.*, **27**, 4708 (1962); (b) G. A. Russell, A. Ito, and R. Konaka, *J. Am. Chem. Soc.*, **85**, 2988 (1963).

(19) M. Tichý, J. Jonáš, and J. Sicher, *Collection Czech. Chem. Commun.*, **24**, 3434 (1959).

(20) R. D. Stolow and C. B. Boyce, *J. Org. Chem.*, **26**, 4726 (1961).

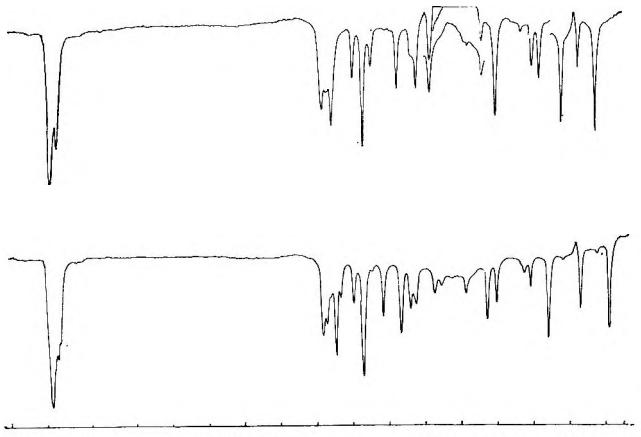


Fig. 1.—4-*t*-Butylcyclohexyl chloride: *trans* isomer (upper curve), *cis* isomer (lower curve). Both spectra were measured in carbon tetrachloride from 3400–900 cm.$^{-1}$ and in carbon disulfide from 900–650 cm.$^{-1}$.

Dimethyl(*cis*- and *trans*-4-*t*-butylcyclohexyl)carbinyl hypochlorites were prepared from the corresponding alcohols by the method described previously[2] in yields of 80–95%.

Decomposition of Hypochlorites (see Table I).—A 0.4 *M* solution of the hypochlorite in the desired solvent, protected from the light by wrapping with aluminum foil, was swept with prepurified nitrogen for 1 hr. at 0° and then irradiated with a weak ultraviolet source[21] for 10 min. The color of the hypochlorite disappeared in 5 min. For decompositions at −30 and +80°, aliquots of hypochlorite solution in test tubes containing glass-enclosed magnet bars, protected from light, were degassed and sealed. The foil-wrapped tubes were placed in a bath at the required temperature for 2-min. warm-up time; the foil was removed and the solution was irradiated[21] with stirring until disappearance of the yellow color. Analysis of products was made by gas–liquid phase chromatography (g.l.p.c.) using XF-1150 (General Electric nitrile silicone fluid) on Chromosorb P or TCEP (1,2,3-tri-β-cyanoethoxypropane). In all runs except those employing Freon 11 (trichlorofluoromethane), the solution from the decomposition was analyzed directly. Quantitative analysis was made by use of cyclohexanone as internal standard by the procedure outlined previously.[2] When Freon 11 was used as solvent, it was evaporated through a Vigreux column, or carbon tetrachloride was added to make a final volume of 2.0 or 5.0 ml. before analysis.

Identification of Products.—In a typical run, a 0.4 *M* solution of hypochlorite in carbon tetrachloride was decomposed at 0°. Analysis of an aliquot on a 20% TCEP column (0.6 × 200 cm.) at 91°, helium pressure 15 p.s.i., showed five peaks: 0.6 min. (carbon tetrachloride), 1.3 min. (acetone), 12.7 and 14.7 min. (*cis*- and *trans*-4-*t*-butylcyclohexyl chlorides), and 26.5 min. (a minor peak, unidentified). Separation of chlorides was improved by use of a 15% XF-1150 column (0.9 × 200 cm.) at 94°, 15 p.s.i., which showed peaks at 59 min. (*cis* chloride) and 69 min. (*trans* chloride). The compound of 59-min. retention time, *cis*-4-*t*-butylcyclohexyl chloride, was collected and redistilled at 0.3 mm. and 80° (bath temp.).

Anal. Calcd. for $C_{10}H_{19}Cl$: C, 68.74; H, 10.96; Cl, 20.30. Found: C, 68.91; H, 10.97; Cl, 20.40.

The infrared spectrum is given in Fig. 1.

A solution of 2.1 g. of a *cis–trans* mixture of chlorides from a decomposition, and 2 g. of potassium hydroxide in 10 ml. of 95% ethanol was heated at reflux for 19 hr. The mixture was poured into water and extracted with petroleum ether (b.p. 30–60°). Washing, drying, and removal of the solvent afforded 1.5 g. of oil; g.l.p.c. analysis showed a peak at 9 min. (4-*t*-butylcyclohexene) and at 69 min. (*trans*-4-*t*-butylcyclohexyl chloride). The latter was collected and redistilled.

Anal. Calcd. for $C_{10}H_{19}Cl$: C, 68.74; H, 10.96; Cl, 20.30. Found: C, 68.62; H, 10.88; Cl, 20.28.

The infrared spectrum is given in Fig. 1.

***cis*- and *trans*-4-*t*-Butylcyclohexyl Chloride.**—To a mixture of 15.6 g. (0.1 mole) of 4-*t*-butylcyclohexanol (a 1:4 *cis–trans* mixture) and 18.5 g. (0.1 mole) of tri-*n*-butylamine in 150 ml. of anhydrous ether at 25° was added with stirring 12 g. (0.1 mole) of thionyl chloride in 50 ml. of anhydrous ether over a period of 1 hr. The mixture was stirred at 25° for 3 hr. and poured onto ice–water; the ether layer was washed with water, dried over magnesium sulfate, and filtered; the ether was removed. Distillation afforded a 7.4-g. fraction (b.p. 48–60° at 10 mm. Redistillation through a 30-cm. spinning platinum band column gave a 3.3-g. fraction (b.p. 60–65° at 12 mm.) of 4-*t*-butylcyclohexene, a 2.9-g. fraction (b.p. 80–85° at 12 mm.) of the isomeric chlorides (largely *cis*), and unchanged alcohol. The chloride fraction, analyzed by g.l.p.c. on an XF-1150 column at 7°, showed peaks at 8.7 (4-*t*-butylcyclohexene), 57.5, and 64.5 min. The 57.5-min. peak was collected; the infrared spectrum was identical with the spectrum of the sample assigned the structure of *cis* chloride obtained from the decomposition of the hypochlorites.

A 2.0-g. sample of a *cis–trans* mixture of the chloride was treated with ethanolic potassium hydroxide, as described above, to destroy the *cis* isomer. The product no longer showed the 57.5-min. peak; the 64.5-min. peak was collected; its infrared spectrum was identical with that of the compound described as *trans*-4-*t*-butylcyclohexyl chloride isolated from the decomposition of the hypochlorites.

***cis*- and *trans*-4-*t*-butylcyclohexyl bromides** were prepared by a published procedure.[7] The separation was effected on an XF-1150 column at 122° and the retention time of *cis* bromide was 45 min., *trans* bromide, 48 min. A sample of pure *cis* bromide was obtained by collection from the column; obtention of pure *trans* was effected by destruction of *cis* isomer by base (see above) followed by g.l.p.c. collection. The infrared spectra of the *cis* and *trans* bromides were identical with those of authentic samples.[7]

4-*t*-Butylcyclohexanecarbonyl Chloride.—A mixture of *trans*- or *cis*-4-*t*-butylcyclohexanecarboxylic acid and an excess of thionyl chloride was allowed to stand at room temperature for 3–4 hr., and the excess thionyl chloride was removed under reduced pressure at ~40–50°. The thionyl chloride used was a commercial product (Eastman Kodak White Label) distilled over linseed oil[22] immediately before use. When the reaction mixture was heated at a higher temperature or unpurified thionyl chloride was used, epimerization took place to an extent of 15%. This was analyzed by g.l.p.c. by converting the acid chlorides to the methyl ester with methanol using the methyl esters prepared from the corresponding acids with diazomethane for reference. Retention times were 19 min. for the *trans* ester and 30 min. for the *cis* ester (TCEP column at 114° and 15 p.s.i.).

***trans*-4-*t*-Butylcyclohexanecarbonyl Peroxide.**—Since some difficulty was experienced in preparation by the published procedure,[9] the following modification is described in detail. To a stirred solution of 3.15 g. (89% purity, *i.e.*, 0.036 mole) of sodium peroxide in 80 ml. of ice–water was added 9.7 g. of 4-*t*-butylcyclohexanecarbonyl chloride (85% *trans* isomer) in 50 ml. of *n*-hexane over a period of 20 min. at −2 to 0°. After stirring at 0° for an additional 2.5 hr., 50 ml. of ether was added to the reaction mixture; the organic layer was washed and dried over calcium chloride at 0°. Filtration and removal of solvent under reduced pressure afforded 5.7 g. of white crystals, m.p. 87–89°, 66% yield. Recrystallization from *n*-hexane gave crystals melting at 88–89°, lit.[9] m.p. 89°. Iodometric analysis gave variable results. The best criteria of purity were the melting point and the infrared spectrum: the characteristic double peak at 1775 and 1800 cm.$^{-1}$ and no other bands in carbonyl absorption region.

***cis*-4-*t*-Butylcyclohexanecarbonyl peroxide** was prepared from the pure *cis* acid chloride by the above procedure, using a temperature of −10 to −5° in 40 and 90% purity, estimated yield from infrared spectrum at 1780 and 1800 cm.$^{-1}$.

Decomposition of *cis*- and *trans*-4-*t*-Butylcyclohexanecarbonyl Peroxide (see Table II).—A sample of the peroxide in the desired solvents was degassed by a nitrogen stream, sealed, and heated at the desired temperature for 15–20 hr. In the runs with bromine, the bromine was added immediately after the degassing step. Dark brown flasks were used for the bromine and the bromotrichloromethane experiments.

(21) Burton Ultraviolet Black Lamp, Model 1910 (a weak ultraviolet source), Burton Manufacturing Co., Santa Monica, Calif.

(22) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 381.

In one run, [illegible] 1.5 mmoles) of the *trans* peroxide was decomposed in 15 [illegible] of carbon tetrachloride. Solvent was removed through a Vigreux column and the residue was chromatographed on 12 g. of activity grade IV alumina (the chlorides were shown to be stable to the isolation procedure), eluting with a 1:2 benzene–petroleum ether mixture. The first 15 ml. afforded 345 mg. of oil. Analysis on an XF-1150 column at 106° showed peak at 16 min. (hexachloroethane), 38 min., and 43 min. Samples of the latter two peaks were collected; the infrared spectra were identical with those of *cis*- and *trans*-4-*t*-butylcyclohexyl chloride, respectively.

A [illegible] sample (2 mmoles) of *trans* peroxide was decomposed in 20 ml. of bromotrichloromethane. The alkyl halide fraction was isolated as described above. Analysis on an XF-1150 column indicated hexachloroethane and *cis*- and *trans*-4-*t*-butylcyclohexyl bromide. The chloride peaks were not present. The bromides were collected by use of a preparative g.l.p.c. column; the infrared spectra were identical with those of authentic samples.

In the peroxide decompositions in carbon tetrachloride with bromine added, the isomeric chlorides and bromides were identified by comparison of retention times.

Control Experiments. A. Stability of *cis*-4-*t*-Butylcyclohexyl Chloride to Hypochlorite Decomposition Conditions.—To a 1.2 *M* solution of diethylisopropylcarbinyl hypochlorite in carbon tetrachloride was added an equal volume of a 0.12 *M* solution of the *cis* chloride in carbon tetrachloride. The solution was swept with nitrogen for 1 hr. and then decomposed by weak ultraviolet light at 0°. Product analysis by g.l.p.c. showed isopropyl chloride, diethyl ketone, diethylisopropylcarbinol, and *cis*-4-*t*-butylcyclohexyl chloride. Quantitative analysis by use of internal standard added after completion of reaction indicated that the amount of the *cis* chloride was unchanged.

B. Behavior of 4-*t*-Butylcyclohexyl Bromides to Peroxide Decomposition Conditions.—In order to test the suitability of cyclohexanecarbonyl peroxide in this control equipment, the peroxide was first decomposed in the absence of added bromide. A solution of 940 mg. of cyclohexanecarbonyl peroxide (purity, 70% by iodometric analysis, 650 mg., 2.5 mmoles) and 1 g. (0.32 ml., 6 mmoles) of bromine in 10 ml. of carbon tetrachloride was heated at 70° for 16 hr. in a brown flask. After cooling, it was washed with sodium thiosulfate solution, 5% sodium bicarbonate solution, and water and dried over magnesium sulfate; the solvent was removed giving 944 mg. of brown oil. Analysis by g.l.p.c. using a TCEP column at 121° had peaks at 5 min. (cyclohexyl bromide), 16 min., and 28 min. (both unidentified). A sample of the *cis*- and *trans*-4-*t*-butylcyclohexyl bromides was added to the product mixture. The retention times for these bromides were 21 and 24 min., respectively, with no interference from either the 16- or the 28-min. peaks.

In another experiment, a 66.2-mg. sample of *cis*-4-*t*-butylcyclohexyl bromide and a 65.9-mg. sample of the *trans* bromide were dissolved in 5 ml. of carbon tetrachloride. To a 4-ml. portion of this solution was added 300 mg. (70% purity, 210 mg., 0.85 mmole) of cyclohexanecarbonyl peroxide and 310 mg. of bromine; carbon tetrachloride was added to a total volume of 100 ml. The solution was heated at 75° for 16 hr. in an amber flask, cooled, washed with sodium thiosulfate solution, 5% sodium bicarbonate solution, and water, and dried over magnesium sulfate. After removal of the solvent under reduced pressure through a Vigreux column, the residual oil was analyzed on an XF-1150 column (*cis* bromide: initial, 53 mg.; final, 28.2 mg.; destruction, 47%; *trans* bromide: initial, 52.7 mg.; final, 45.8 mg.; destruction, 13%).

TABLE IV

CONTROL EXPERIMENTS ON *cis*- AND *trans*-4-*t*-BUTYLCYCLOHEXYL HALIDES

Reactants	Conditions	Results
cis-Br	$BrCCl_3$, 25°, dark	No change (4.5 days)
cis-Br	$BrCCl_3$, 25°, daylight	After 1 day, no *cis*-Br, 33% conversion to *trans*-Br
cis-Cl (0.71) and *trans*-Cl (0.29)	$BrCCl_3$, 25°, dark	No change (6 days)
cis-Cl (0.71) *trans*-Cl (0.29)	$BrCCl_3$, 25°, daylight	30% disappearance of *cis*, 25% increase in *trans* after 3 days; 75% disappearance of *cis*, 50% increase in *trans* after 6 days
trans-Cl	$BrCCl_3$, 25°, daylight	No change (15 days)
cis-Cl	$BrCCl_3$, 25°, daylight	After 3 days, 30% *cis*, 70% *trans* (positive identification by collection from v.p.c.)
cis-Cl	$BrCCl_3$, 25°, daylight 2,6-Di-*t*-butyl-4-methylphenol	No change (6 days)
cis-Cl	CCl_4, Br_2, 25°, dark	No change (5 days)
cis-Cl	CCl_4, Br_2, 25°, daylight	After 3.5 days, 60% *cis*, 40% *trans*
cis-Cl	CCl_4, HBr, 25°, daylight	No change (5 days)

C. Behavior of *cis*- and *trans*-4-*t*-Butylcyclohexyl Halides towards Light, Bromine, and Other Conditions.—The data are summarized in Table IV. Product analyses were made by the procedures described above.

D. Behavior of the Alkyl Halides on Alumina Chromatography.—Chromatography of a 2:1 *cis*–*trans* mixture of 4-*t*-butylcyclohexyl chlorides on activity grade III alumina afforded quantitative recovery; g.l.p.c. analysis showed that the *cis*–*trans* ratio was unchanged.

Chromatography of a sample of *cis*-4-*t*-butylcyclohexyl bromide on activity grade IV alumina afforded 92% recovery. G.l.p.c. analysis showed a small peak corresponding to 4-*t*-butylcyclohexene, a large peak at *cis* bromide, and the absence of the *trans* bromide peak, *i.e.*, a small amount of dehydrobromination of the *cis* bromide but no isomerization to the *trans* isomer.

The Reaction of N-Bromosuccinimide with Bicyclo[2.2.1]-5-heptene-*endo*-*cis*-2,3-dicarboxylic Anhydride[1]

L. H. ZALKOW AND C. D. KENNEDY[2,3]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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N-Bromosuccinimide was found to add to the double bond of bicyclo[2.2.1]-5-heptene-*endo*-*cis*-2,3-dicarboxylic anhydride in the presence of benzoyl peroxide to yield the *cis* adduct, *exo*-5-bromo-*exo*-6-succinimidobicyclo[2.2.1]heptane-*endo*-*cis*-2,3-dicarboxylic anhydride (12). In addition, N-bromosuccinimide rearranges under the conditions of the reaction to give β-bromopropionyl isocyanate.

N-Bromosuccinimide (NBS) has been used extensively as an allylic brominating agent for approximately twenty years.[4] Bloomfield[5a] and Hey[5b] first suggested that this reaction proceeded by a radical chain mechanism, and further support for this postulation was provided by Schmid and Karrer.[6] More recently, Dauben and McCoy[7] reported a very thorough investigation of the reaction of NBS with cyclohexene in carbon tetrachloride. These workers, and the earlier workers, suggest that the succinimidyl radical is generated in an initiation step and then proceeds to abstract an allylic hydrogen atom in the propagation step. Although this mechanism has been widely accepted, another mechanism (Goldfinger mechanism) has been proposed in which succinimidyl radicals are not involved.[8] In the Goldfinger mechanism it is suggested that the function of NBS is simply to provide a constant low concentration of molecular bromine, the molecular bromine being responsible for the allylic bromination. Evidence supporting the Goldfinger mechanism in benzylic brominations with NBS has been recently reported.[9]

If succinimidyl radicals are actually involved in radical brominations with NBS, one might expect such radicals to add to the double bonds under the proper conditions. Walling[10] has suggested that the abstraction of hydrogen atoms by the succinimidyl radical in preference to addition to the double bond is due to the greater bond energy of the N–H bond in the succinimide produced, as compared to the N–C bond which would result from the addition of the succinimidyl radical to the alkene. However, the literature contains a number of examples in which NBS reacts with alkenes to give 1:1 adducts. For example, dihydropyran has been reported to react with NBS to give 2-succinimido-3-bromotetrahydropyran.[11] Methylenecyclobutane forms an adduct with NBS in low yield,[12] and vinylacetonitrile gave a low yield of 3-bromo-4-succinimidobutyronitrile with NBS.[13] In none of these cases, however, is it clear that succinimidyl radicals were involved.

The possible decomposition of other N-haloamides and -imides to yield similar free radicals is likewise not clear. N-Bromophthalimide also adds to dihydropyran in carbon tetrachloride solvent, but in a reverse direction to that observed with NBS.[14] With substituted dihydropyrans, the position of substituents appears to influence the type of products produced.[15] N-Bromotrifluoroacetamide and N-bromotrichloroacetamide add to cyclohexene, but under identical conditions the former gave predominantly ring bromination of toluene, whereas the latter gave side-chain bromination of toluene.[16]

When methylenecyclobutane and cyclohexene were allowed to react with NBS in benzene solution, N-phenylsuccinimide was isolated in each case among the products, but in low yield.[12,17] On the other hand, N-(cyclohepta-2,4,6-trienyl)succinimide was isolated in a high yield in the reaction of cycloheptatriene with NBS.[18] Again, in none of these cases has the existence of the intermediate succinimidyl radical been conclusively established. Succinimidyl radicals do, however, appear to be involved in the propagation step in the formation of *dl*-N-α-methoxy-*p*-nitrobenzylsuccinimide[19] and *dl*-N-α-(*p*-bromophenoxy)benzylsuccinimide[20] by the reaction of NBS with *p*-nitrobenzyl methyl ether and *p*-bromophenylbenzyl ether, respectively. Good yields of the succinimidyl derivatives were obtained by increasing the molar ratio of NBS to the ethers and by removing the molecular bromine produced in the reaction. These observations were considered consistent with the proposed free-radical mechanism.[20]

A study of the reaction of NBS with alkenes in which the only allylic hydrogen atoms are at bridgehead posi-

(1) Taken in part from the dissertation of C. D. Kennedy presented to the Graduate School Faculty of Oklahoma State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1963. A preliminary account of this work was presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962.

(2) Research and Development Department, Continental Oil Company, Ponca City, Okla.

(3) National Defense Education Act Fellow, 1959–1962.

(4) K. Ziegler, A. Spath, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942); C. Djerassi, *Chem. Rev.*, **43**, 271 (1948); T. D. Waugh, "NBS, Its Reactions and Uses," Arapahoe Chemicals, Inc., Boulder, Colo., 1951; L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

(5) (a) G. F. Bloomfield, *J. Chem. Soc.*, 114 (1944); (b) D. H. Hey, *Ann. Rept. Chem. Soc.*, **41**, 184 (1944).

(6) H. Schmid and P. Karrer, *Helv. Chim. Acta.*, **29**, 573 (1946).

(7) H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 4863 (1959); H. J. Dauben, Jr., and L. L. McCoy, *ibid.*, **81**, 5404 (1959).

(8) J. Adam, P. A. Gosselain, and P. Goldfinger, *Nature*, **171**, 704 (1953); F. L. J. Sixma and R. H. Riem, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **B61**, 183 (1958); *Chem. Abstr.*, **53**, 2123*f* (1959); B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, 80 (1961).

(9) G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Am. Chem. Soc.*, **85**, 365 (1963); R. E. Pearson and J. C. Martin, *ibid.*, **85**, 354 (1963).

(10) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 383.

(11) J. R. Shelton and C. Ciadella, *J. Org. Chem.*, **23**, 1128 (1958).

(12) E. R. Buchman and D. R. Howton, *J. Am. Chem. Soc.*, **70**, 2517 (1948).

(13) W. J. Bailey and J. Bello, *J. Org. Chem.*, **20**, 525 (1955).

(14) C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

(15) F. Korte, R. Heinz, and D. Schorb, *Ber.*, **94**, 825 (1961).

(16) J. D. Park, H. J. Gerjovich, W. R. Lycan, and J. R. Lacher, *J. Am. Chem. Soc.*, **74**, 2189 (1952).

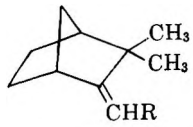
(17) D. R. Howton, *ibid.*, **69**, 2060 (1947).

(18) H. L. Dryden, Jr., and B. E. Burgert, *ibid.*, **77**, 5833 (1955).

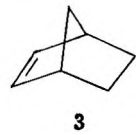
(19) D. G. Markees, *J. Org. Chem.*, **23**, 1490 (1958).

(20) L. L. Braun and J. H. Looker, *ibid.*, **26**, 574 (1961).

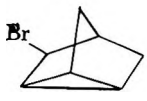
tions of the norbornane-type skeleton should be particularly interesting. In such systems the intermediate bridgehead radicals, if formed, could not be stabilized by resonance since this would be in violation of Bredt's rule,[21] and the reaction might be expected to take a different course from the usual allylic bromination. Roberts and co-workers[22,23] studied the reaction of NBS with two such bicyclic systems, camphene (**1**) and norbornylene (**3**), almost fifteen years ago and the reactions did take an unexpected path. 8-Bromocamphene (**2**) was produced from camphene (**1**),[22] and 3-bromonortricyclene (**4**) was formed from norbornylene (**3**).[23] Recently, bicyclo[2.2.2]octene (**5**) was found to react with NBS to give *endo*-8-bromobicyclo[3.2.1]-2-octene (**6**).[24] All of the bromo compounds **2**, **4**, and **6**



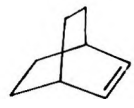
1, R = H
2, R = Br



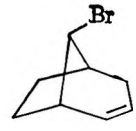
3



4



5

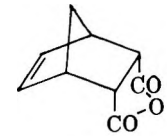


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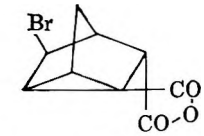
were produced under conditions identical with those used in the normal allylic bromination with NBS, conditions generally assumed to be radical in nature. In each case, succinimide was formed just as in normal allylic brominations.

It is difficult to visualize how **2** and **6** could be formed by a radical mechanism involving the succinimidyl radical in a propagation step. Actually, in the formation of both **2** and **6**, the authors in each case suggested that a bromine atom first adds to the double bond of **1** and **5**, respectively, and in the case of **1** the intermediate then loses a hydrogen atom, and in the case of **5** the intermediate radical rearranges and then loses a hydrogen atom by abstraction. These observations are thus consistent with the Goldfinger mechanism. The formation of **4** could be rationalized by either the Bloomfield–Hey (reaction in which succinimidyl radicals react with the alkene to generate the intermediate substrate radical) or the Goldfinger mechanisms. Of course, **2**, **4**, and **6** could arise by ionic mechanisms. It should be noted that abstraction of a bridgehead hydrogen atom of **5** might have been expected, since the bridgehead hydrogen atoms of bicyclo[2.2.2]octane are abstracted by chlorine atoms eight times more readily than the secondary hydrogen atoms.[25] In norbornyl systems bridgehead radicals are known but they have not been produced by abstraction of the bridgehead hydrogen atoms.[26]

In view of the unusual results obtained in the reaction of NBS with bicyclic alkenes containing only bridgehead allylic hydrogen atoms, we decided to investigate the reaction of NBS with bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic anhydride (**7**). The *endo* anhydride group in **7** would be expected to make formation of a nortricyclene-type product such as **8** difficult because of the steric strain that would be introduced in the formation of the semi-*trans* fused anhydride ring of **8**.



7



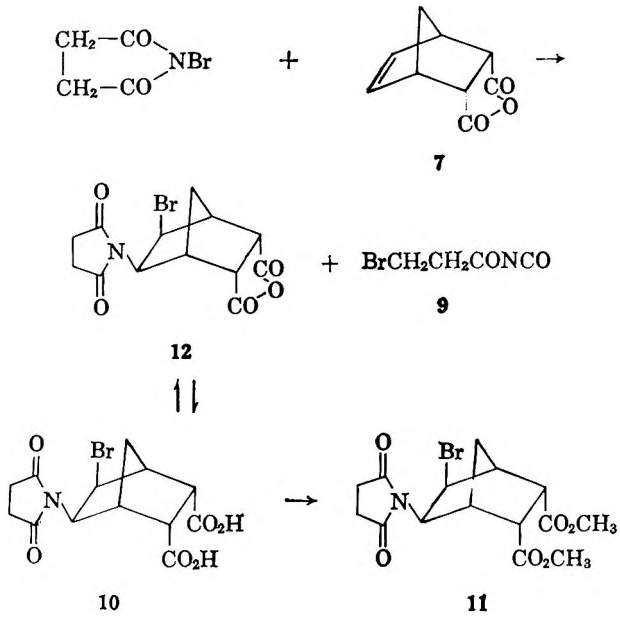
8

The reaction of **7** with NBS was carried out in refluxing carbon tetrachloride in the presence of a catalytic amount of benzoyl peroxide. Identical results were obtained in the presence or absence of light, but no reaction occurred in the absence of benzoyl peroxide, and variation of the amount of benzoyl peroxide used had no effect on the yield of products. No succinimide was produced in the reaction, in contrast to that observed in the reactions of **1**, **3**, and **5** with NBS.

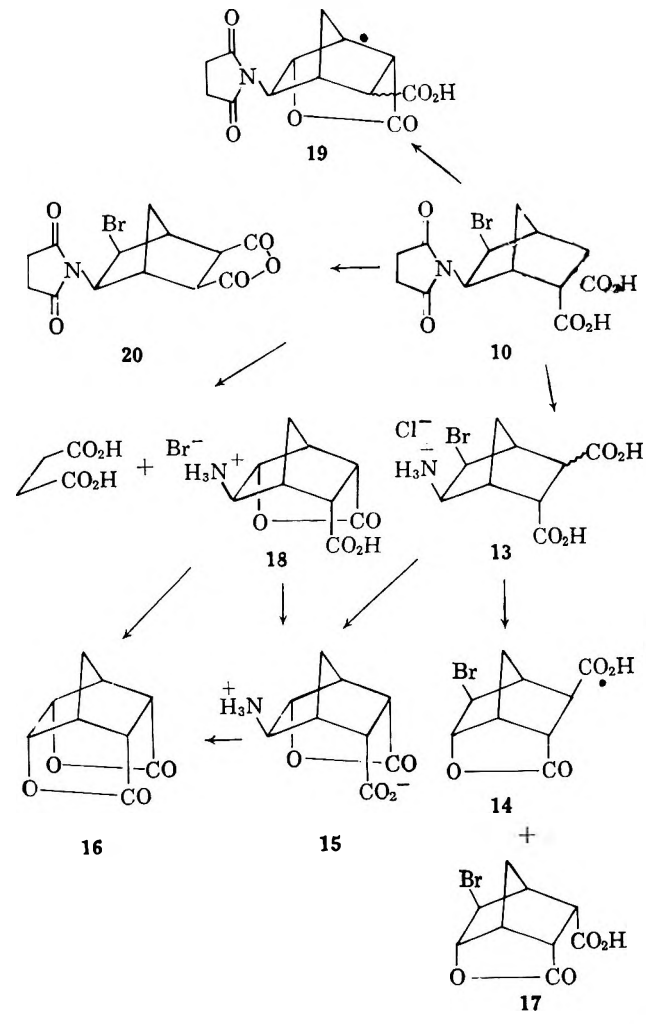
When water was added to the carbon tetrachloride reaction solution, after refluxing, there was a vigorous evolution of carbon dioxide arising from hydrolysis of β-bromopropionyl isocyanate (**9**), produced from NBS in the reaction. By distilling the reaction solution prior to the addition of water, the liquid β-bromopropionyl isocyanate was isolated and, when methanol, rather than water, was added to the carbon tetrachloride solution, crystalline methyl β-bromopropionylcarbamate was isolated in 51% yield (based on starting NBS). β-Bromopropionyl isocyanate has been previously reported to be formed in good yield from NBS in the presence of a free-radical initiator, an unreactive alkene, and in an inert solvent.[27] After the addition of water to the carbon tetrachloride solution, a viscous oil separated from the solution and it yielded a crystalline product **10** after extensive washing with ether. The product **10** could be isolated in two different polymorphic forms which showed different infrared spectra as potassium bromide pellets but identical spectra in dioxane solution, and each gave identical products in all chemical reactions. The infrared spectrum of **10** in dioxane showed strong absorption at ν 1746, 1738, and 1710 cm.$^{-1}$, and elemental analysis showed it to possess the empirical formula $C_{13}H_{14}BrNO_6$. Thus the elements of $C_7H_6BrNO_2$ (NBS or some rearrangement product therefrom) had added to **7** and the anhydride grouping was no longer intact. That **10** was a dicarboxylic acid was shown by preparation of the dimethyl ester **11** ($C_{15}H_{18}BrNO_6$) with diazomethane. The n.m.r. spectrum of **11** clearly showed the presence of the two ester methyl groups at δ 3.58 and 3.68. The n.m.r. spectrum also showed the absence of olefinic protons. The dimethyl ester **11** was isolated in 84% yield based on alkene **7** consumed in the reaction with NBS, but 76% of the alkene did not undergo reaction. Treatment of **10** with acetic anhydride gave an anhydride (**12**) which was reconverted

(21) F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).
(22) J. D. Roberts and E. R. Trumbull, *J. Am. Chem. Soc.*, **71**, 1630 (1949).
(23) J. D. Roberts, E. R. Trumbull, W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).
(24) N. A. LeBel, J. E. Huber, and L. H. Zalkow, *ibid.*, **84**, 2226 (1962).
(25) A. F. Bickel, J. Knotnerus, E. C. Kooyman, and G. C. Vegter, *Tetrahedron*, **9**, 230 (1960).
(26) V. Scholkopf, *Angew. Chem.*, **72**, 147 (1960), and references therein.
(27) (a) H. W. Johnson, Jr., and D. E. Bublitz, *J. Am. Chem. Soc.*, **79**, 753 (1957); (b) J. C. Martin and P. D. Bartlett, *ibid.*, **79**, 2533 (1957); (c) H. W. Johnson, Jr., and D. E. Bublitz, *ibid.*, **80**, 3150 (1958).

SCHEME I



SCHEME II



into **10** with water. The anhydride **12** is apparently the primary product in the reaction of NBS with **7**, but isolation of the diacid **10** from the original reaction mixture was found easier than isolation of the anhydride **12**. (See Scheme I.)

When **10** was refluxed in concentrated hydrochloric acid and the aqueous solution was extracted with ether, succinic acid was obtained. Evaporation of the hydrochloric acid solution gave an amine hydrochloride (**13**) whose infrared spectrum showed ν_{max}^{KBr} 2700–3000, 1720, 1590, 1507, and 1400 cm.$^{-1}$. When **13** was treated with nitrous acid, the known bromolactone acid **14** was obtained. When **13** was passed through a basic ion-exchange column, a lactone zwitterion (**15**) was obtained, which, when treated with sodium nitrite, gave the known dilactone **16**. These data demonstrated that NBS reacted with **7** without skeletal rearrangement of **7** to give an adduct (**12**) in which the succinimidyl group and bromine atom had become attached at C-5 and C-6. In addition, the isolation of the known lactones **14** and **16** under the conditions described showed the bromine atom to be in the *exo* (β) configuration in the adduct **12**. The isolation of **14** and **16** with carboxyl groups of different stereochemistry at C-3 can be explained as follows. The amine hydrochloride **13** is undoubtedly a mixture of the two isomers differing in stereochemistry at C-3. The isomerization of *cis-endo* carboxyl groups to the *trans* arrangement with concentrated hydrochloric acid in such systems is well known.[28] Thus, when the mixture **13** was treated with nitrous acid, the known lactone **14** fortunately crystallized (18% yield), the isomeric lactone **17** remaining in solution. However, when the amine hydrochloride mixture **13** was passed through a basic ion-exchange column, and the product was treated with nitrous acid, the known dilactone **16** was obtained in 50% yield. Under these conditions the isomer of **13** with an *exo* carboxyl group at C-3 would remain on the basic ion-exchange column.

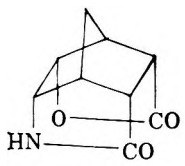
When an aqueous solution of **10** was heated on the steam bath for 3 days, a quantitative yield of succinic acid was obtained from the ether extract. The remaining aqueous solution containing the lactone amine hydrobromide **18** gave the dilactone **16** on the addition of sodium nitrite, whereas passage of the aqueous solution through a weakly basic ion-exchange resin gave **15** in 86% yield. Thus hydrolysis of the succinimido group and lactonization occurred in the hydrolysis of **10** under neutral conditions. (See Scheme II.)

The adduct **10** when refluxed in pyridine gave the lactone **19** in which the succinimido grouping was retained. Heating of **10** gave the anhydride **20**, isomeric with the previously mentioned anhydride **12**, and the same lactone **19** obtained previously as described above. The formation of lactone **19** provides additional evidence for the *exo* configuration of the bromine atom in **10**. The stereochemistry of the carboxyl group at C-2 in **19** cannot be unequivocally assigned on the basis of the evidence at hand.

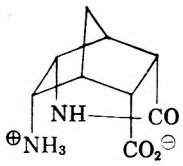
The evidence thus far presented strongly supports the structure depicted for **10** and the stereochemistry indicated at C-2, C-3, and C-5. However, further evidence was sought in order to assign the configuration of the succinimido group at C-6. If the amino group at C-6 in **15** were *endo*, then pyrolysis of this compound would be expected to yield the lactone–lactam **21**, since pyrolysis of **22** has been shown to yield **23**.[29] Since **15** was obtained by the hydrolysis of **10** with water fol-

(28) K. Alder and G. Stein, *Ann.*, **504**, 216 (1933).

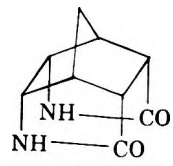
(29) W. S. Worral, *J. Am. Chem. Soc.*, **82**, 5707 (1960).



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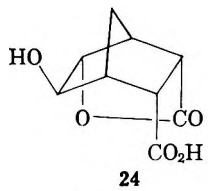


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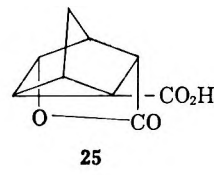


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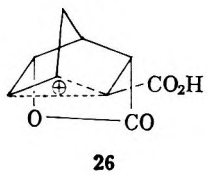
lower by passage through a weakly basic ion-exchange column, the stereochemistry at C-6 in **15** would be expected to be the same as in **10**. Heating of **15** to >310° gave only unchanged **15**. Additional evidence to support the exo configuration at C-6 was provided by the conversion of **15** to **16** with nitrous acid. If the amino group in **15** had been *endo*, then one would expect to isolate, in addition to **16**, either of the known lactones **24** or **25**. Lactone **24** would result from displacement



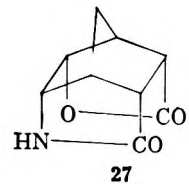
24



25



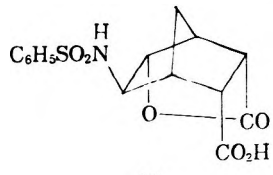
26



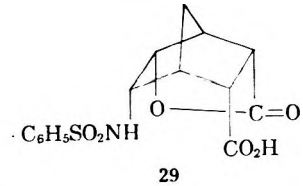
27

of the *endo* diazonium group by water, whereas **25** would be expected from the intermediate nonclassical carbonium ion **26**.[30] The nortricyclene derivative **25** has been reported by acid hydrolysis of **27**, presumably *via* intermediate **26**.[30] Failure to detect either **24** or **25**, when **15** was treated with nitrous acid suggests that the amino group in **15** is *exo* and the diazonium group formed upon treatment with nitrous acid is displaced by the *endo* carboxyl group at C-2. The strongest chemical evidence to support the *exo* configuration of the various substituents at C-6 was provided by conversion of **15** to the benzenesulfonamido derivative **28** which was found to differ from the isomeric derivative **29**.[31] Lactone **29**, on heating at reduced pressure, gave **30**, as expected of the *endo* benzenesulfonamido group at C-6.[31]

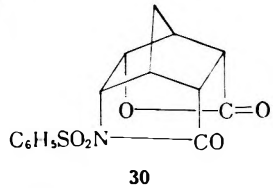
The nuclear magnetic resonance spectra of **15** and **28** also supported the assigned *exo* configuration of the



28



29



30

(30) L. H. Zalkow and C. D. Kennedy, *J. Org. Chem.*, **28**, 852 (1963).
(31) L. H. Zalkow and C. D. Kennedy, *ibid.*, **28**, 3309 (1963).

C-6 substituent.[32] It has been shown that a single *exo* substituent such as is present in **15** and **28** produces nonequivalence in the C-7 protons leading to AB type spin-spin splitting with J = 11–13 c.p.s., whereas in the absence of *exo* substituents such as in **29** and **30**, the C-7 protons give a sharp singlet signal.[32] The observed C-7 signals were as follows: **15**, δ 2.05, 2.38 (J = 13 c.p.s.); **28**, δ 1.84, 2.18 (J = 12 c.p.s.); **29**, δ 1.80; and **30**, δ 2.00. In addition, the n.m.r. spectra of **10**, **11**, and **12** showed that the C-5 and C-6 protons were *cis* ($J_{5,6}$ = 7 c.p.s.) and, therefore, *endo*, since the bromine atom at C-5 has already been shown to be *exo*.[32]

The observation that NBS does not add to **7** in the absence of benzoyl peroxide, and the failure of variation in peroxide concentration to effect the yield of **10** suggests a radical chain mechanism involving succinimidyl radicals as chain carriers. The *cis-exo* addition of NBS is analogous to the formation of *cis-exo*-5,6-dibromobicyclo[2.2.1]heptane-*endo-cis*-2,3-dicarboxylic anhydride in the bromination of **7**.[33] By contrast, the isomer of **7** containing the *cis-exo* anhydride grouping gives the *trans* dibromide on bromination.[34]

Since the rearrangement of NBS to β-bromopropionyl isocyanate (**9**) has been reported to require the presence of an alkene,[27] an attempt was made to determine if the adduct **12** was the precursor of the isocyanate. When **12** was subjected to the original NBS–alkene reaction conditions, no isocyanate was formed and no decomposition of the adduct occurred.

Thin layer chromatography of the crude reaction product failed to show the presence of products resulting from the addition of molecular bromine to the alkene as might have been expected if the NBS had been transformed into succinimide and molecular bromine, as proposed in the Goldfinger mechanism. The failure to isolate succinimide likewise supports this observation.

A referee has pointed out that Ziegler also found that N-bromophthalimide added to an appreciable extent to cyclohexene and he has confirmed this. One of the arguments offered by opponents of the Bloomfield–Hey mechanism has been the inability of workers to isolate bisuccinimidyl arising by coupling of succinimidyl radicals. Some supporters of the mechanism have suggested that this was due to the great instability of bisuccinimidyl.[7] Bisuccinimidyl has now been synthesized and found to be surprisingly stable.[35] Since the submission of this manuscript, additional support of the Goldfinger mechanism has appeared.[36,37]

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5 spectrophotometer and n.m.r. spectra were determined with the Varian A-60 spectrometer using tetramethylsilane as an internal standard (δ = 0). Elemental analyses were performed by Midwest Microlabs, Indianapolis, Ind.

The Reaction of N-Bromosuccinimide (NBS) with Bicyclo[2.2.1]-5-heptene-*endo-cis*-2,3-dicarboxylic Anhydride (7).—In a typical experiment N-bromosuccinimide (8.90 g. of Eastman

(32) L. H. Zalkow and C. D. Kennedy, unpublished results.
(33) J. A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **76**, 4060 (1954).
(34) D. Craig, *ibid.*, **73**, 4889 (1951).
(35) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **85**, 3052 (1963).
(36) P. S. Skell, D. L. Tuleen, and P. D. Readio, *ibid.*, **85**, 2850 (1963).
(37) C. Walling, A. L. Rieger, and D. D. Tanner, *ibid.*, **85**, 3129 (1963).

reagent grade), **7** (8.20 g.), benzoyl peroxide (0.1 g.), and carbon tetrachloride (35 ml.) were refluxed for 2.5 hr. The initially heterogeneous mixture became homogeneous after 0.5 hr. and became turbid after about 1.0 hr. of refluxing. The light brown reaction solution was cooled after the reflux period and worked up either by the addition of water, by the addition of methanol, or by distillation as described below.

Procedure 1.—Water (20 ml.) was added dropwise with stirring to the cooled reaction solution whereupon there was a vigorous evolution of carbon dioxide, identified by the formation of a precipitate on bubbling the gas through a saturated solution of barium hydroxide. After no further evolution of gas could be detected, the mixture was separated into three layers, an aqueous layer (top), a carbon tetrachloride layer (bottom), and a viscous oily layer (middle) in which, on standing 24 hr., crystalline solid formed. After 48 hr. the aqueous and carbon tetrachloride layers were removed. The remaining viscous oil was extensively extracted (ten portions, 20-ml. each) with ether. The ether-insoluble solid was leached twice with 10-ml. portions of acetone. The adduct diacid **10** (0.58 g.) gave m.p. 225–227°, ν_{max}^{KBr} 1772, 1728, and 1688 cm.$^{-1}$ (adduct "A") (Two polymorphic forms of the adduct **10**, "A" and "B," were obtained either as a mixture or one was obtained separately from the other, unpredictably, under presumably identical conditions as described above. Both "A" and "B" gave the same melting point, and the melting point was not depressed on admixture. They differed only in their infrared spectra as KBr pellets.) or 1750, 1700, and 1662 cm.$^{-1}$ (adduct "B").

The ether and acetone solutions from the above extractions were combined and evaporated on a steam bath to give an oily solid and the above extraction procedures were repeated to yield an additional 0.70 g. of **10**, m.p. 224–227° in a second crop, and 0.33 g., m.p. 223–225° in a third crop. The combined yield of **7** was 1.61 g. Both adducts "A" and "B" gave $\nu_{max}^{dioxane}$ 1746, 1738, and 1710 cm.$^{-1}$. Evaporation of the dioxane solutions of adducts "A" and "B" both yielded adduct "B." An analytical sample of adduct "B," m.p. 227–228°, was prepared by recrystallization from a 1:1 ethanol–water solution. The infrared spectrum of adduct "B" did not change on recrystallization.

Anal. Calcd. for $C_{13}H_{14}BrNO_6$: C, 43.31; H, 3.89; Br, 22.23; N, 3.89. Found: C, 43.49; H, 3.97; Br, 22.00; N, 4.10.

The same dimethyl ester **11** was obtained from adducts "A" and "B" by treatment with an excess of ethereal diazomethane. The analytical sample, m.p. 140°, was prepared by recrystallization of the diester from 95% ethanol and drying at 100° and 1 mm. pressure for 5 hr. and had ν_{max}^{KBr} 1775 (weak), 1734, and 1707 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{18}BrNO_6$: C, 46.39; H, 4.68. Found: C, 46.57; H, 4.67.

Procedure 2.—Methanol (20 ml.) was added slowly, with stirring, to the cooled carbon tetrachloride reaction solution. Methyl β-bromopropionylcarbamate (4.75 g., m.p. 133–135°) crystallized on cooling in an ice bath. On partial evaporation of the filtrate, additional carbamate crystallized (0.77 g., m.p. 134–136°). Recrystallization of the carbamate from methanol gave m.p. 138–138.5° (lit.[27] 138–139°); ν_{max}^{KBr} 3250, 3130, 1795, 1755, and 1693 cm.$^{-1}$. An authentic sample prepared as previously described[27a] gave m.p. 136–137° and an identical infrared spectrum.

The filtrate from above was evaporated to give an oil which was hydrolyzed by stirring with a water–acetone solution. Evaporation gave a viscous oil which was treated with 6 g. of diazomethane in ether solution (approx. 100 ml.). One-eighth of this dried (magnesium sulfate) ether solution was allowed to stand at 0° for 2 months. During this time a fraction of dimethyl ester **11** crystallized (0.140 g.), m.p. 140°; ν_{max}^{KBr} 1775 (weak), 1734, and 1707 cm.$^{-1}$. The mother liquor was concentrated *in vacuo* at room temperature to a small volume (approx. 2 ml.) and chromatographed on Merck acid-washed alumina (174 g.) using chloroform as the eluent. The dimethyl ester of bicyclo-[2.2.1]-5-heptene-*endo-cis*-2,3-dicarboxylic acid (0.995 g.; ν_{max}^{film} 1737, 1438, 1367, and 1345 cm.$^{-1}$, identical with the infrared spectrum of an authentic sample prepared by a previously described[38] procedure) was eluted with 400 ml. of chloroform. This diester showed the same single spot as authentic material on thin layer chromatography using ether (R_f 0.8) or ethanol (R_f 0.6) as a solvent. All thin layer chromatograms were run on silica gel, and iodine vapor was used to develop the compounds.

A second fraction (0.378 g.) eluted from the above column chromatograph by an additional 125 ml. of chloroform showed on thin layer chromatography with ether as eluent, one major spot (R_f 0.35) and two minor spots (R_f 0.45). These two spots could be resolved only by allowing the solvent front to move 20 cm rather than the usual 10 cm. Quantitative thin layer chromatography showed that 92% of this fraction, based on recovered material from the preparative thin layer chromatograph, was the adduct diester **11** (0.348 g.). The infrared spectrum and R_f of the adduct diester **11** from thin layer chromatography agreed identically with those of adduct diester **11** prepared as described above. Further elution of the above column chromatograph with chloroform yielded no additional material.

The quantities of materials obtained from the column chromatograph (multiplied by a factor of eight) represent a total of 7.92 g. (38.0 mmoles) of the diester of **7** and 3.9 g. (10.1 mmoles) of the adduct diester **11** recovered by the above sequences from 50 mmoles each of NBS and alkene **7**.

Procedure 3.—The carbon tetrachloride was removed from the cooled reaction solution *in vacuo* (38 mm.) at room temperature. The residue was filtered to remove the precipitated solid and the filtrate was distilled at 25 mm. to yield β-bromopropionyl isocyanate (**9**, 1.25 g., b.p. approx. 69°), identical in infrared spectrum with an authentic sample of the isocyanate prepared as previously described.[27c] The residue remaining after distillation of the isocyanate was extracted with four portions (50-ml. each) of ether, then dissolved in acetone (100 ml.) containing a small amount of concentrated sulfuric acid (2 ml.), and left open to the atmosphere for 6 days during which time the adduct diacid **10** crystallized (0.83 g.), m.p. 226–227°.

Reaction of NBS with Bicyclo[2.2.1]-5-heptene-*endo-cis*-2,3-dicarboxylic Anhydride (7) in the Absence of Radical Initiators. **A.**—N-Bromosuccinimide (17.8 g., 100 mmoles), bicyclic alkene **7** (16.4 g., 100 mmoles, Fisher reagent grade), and carbon tetrachloride (65 ml.) were refluxed for 3 hr. The undissolved solid was allowed to settle and the clear liquid was decanted from the hot solution. The solid which was insoluble in hot carbon tetrachloride was identified as NBS. 13.2 g. (74.5 mmoles), m.p. 170–173° (melting point of starting NBS 171–173°, mixture melting point undepressed; infrared spectra were identical). The combined hot carbon tetrachloride extracts on evaporation to dryness gave the starting alkene **7**, 14.4 g. (88 mmoles), m.p. 165–167° (melting point of starting alkene 170°, admixture with starting alkene gave m.p. 165–169°).

B.—N-Bromosuccinimide (17.8 g., 100 mmoles), bicyclic alkene **7** (16.4 g., 100 mmoles), and carbon tetrachloride (65 ml.) were refluxed for 3 hr. The reaction mixture was allowed to cool and the unchanged starting material was removed by filtration. Water (50 ml.) was added to the filtrate with no sign of reaction, and no reaction products could be isolated. The above carbon tetrachloride remained clear, except for undissolved starting material, for the duration of the reaction period as contrasted to the marked brown color attained when radical initiator was present. A duplicate experiment of the above (no radical initiator present) was refluxed for 12 hr. with no color change

Attempted Elimination of the Bromo and Succinimido Groups from 12 as β-Bromopropionyl Isocyanate.—A mixture of the NBS adduct **12** (2.0 g., m.p. 197–197.5°), benzoyl peroxide (0.05 g.), and 3.7 ml. of carbon tetrachloride was refluxed for 24 hr. The reaction mixture remained heterogeneous during the reflux period, after which the hot mixture was filtered. The starting unchanged anhydride was recovered in quantitative yield. When water was added to the hot filtrate there was no visible evolution of gas.

Attempted Reaction of Bicyclo[2.2.1]-5-heptene-*endo-cis*-2,3-dicarboxylic Anhydride 7 with Carbon Tetrachloride under Free-Radical Conditions.—A mixture of the bicyclic alkene **7** (4.1 g.), benzoyl peroxide (0.262 g.), and carbon tetrachloride (30.8 ml.) was heated at reflux for 18 hr. The mixture became homogeneous after only a few minutes of refluxing, and at the end of the 18-hr. reflux period a viscous brown oil precipitated. The mixture was cooled, 15 ml. of water was added along with enough acetone to keep the mixture homogeneous, and the solution was stirred, open to the atmosphere, for 6 days during which time all of the solvent evaporated. The resulting product was treated with an excess of ethereal diazomethane and the ether solution was dried over anhydrous sodium sulfate, then evap-

(38) K. Alder and W. Roth, *Ber.*, **87**, 161 (1954).

orated on a steam bath to yield an oil. A sample of this oil on thin layer chromatography, using ether as the eluent, showed only the spot (R_f 0.8) for dimethyl bicyclo[2.2.1]-5-heptene-*endo-cis*-2,3-dicarboxylate.

A mixture of the alkene **7** (4.1 g.), benzoyl peroxide (0.050 g.), and 17 ml. of carbon tetrachloride was heated at reflux for 3 hr. This solution was cooled, hydrolyzed, and treated with ethereal diazomethane as above. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield an oil which gave only one spot (R_f 0.8) when chromatographed as above.

***exo*-5-Bromo-*exo*-6-succinimidobicyclo[2.2.1]heptane-*endo-cis*-2,3-dicarboxylic Anhydride (12).**—The same anhydride **12** was obtained from both polymorphic forms "A" and "B" by the following procedure. The diacid **10** (4.00 g., m.p. 225–226°) and acetic anhydride (40 ml.) were heated to reflux, then the mixture was distilled at 45 mm. (approximately 10 ml. remained undistilled). The undistilled residue was cooled and 100 ml. of carbon tetrachloride was added. The solution was decanted and cooled in an ice bath. White needle-like crystals of the anhydride **12** formed in the decanted solution. After air drying, the anhydride (2.23 g.) gave m.p. 197–197.5°; ν_{max}^{KBr} 1850, 1785, and 1707 cm.$^{-1}$. Additional recrystallization from acetic anhydride and carbon tetrachloride did not raise the melting point.

The anhydride **12** (0.25 g.) was hydrolyzed back to the diacid **10** by heating on a steam bath in a mixture of carbon tetrachloride (30 ml.), water (30 ml.), and acetone (5 ml.) until a volume of approximately 30 ml. remained. On cooling, white crystals of the diacid **10** formed which, after air drying, gave m.p. 224–226°. The infrared spectrum of this product indicated that it was a mixture of the two polymorphic forms "A" and "B." Admixture of the diacid obtained by hydrolysis of the anhydride with either pure polymorph "A" or "B" did not depress its melting point.

Concentrated Hydrochloric Acid Hydrolysis of *exo*-5-Bromo-*exo*-6-succinimidobicyclo[2.2.1]heptane-*endo-cis*-2,3-dicarboxylic Acid (10).—A mixture of the adduct diacid **10** (5.000 g., m.p. 225–227°) and concentrated hydrochloric acid (150 ml.) was refluxed for 17.5 hr.; this solution was then continuously extracted with ether for 24 hr. Evaporation of the ether solution yielded succinic acid (1.0 g., m.p. 188.5°, identical in melting point and infrared spectrum with an authentic sample).

Evaporation of the aqueous solution on a rotary evaporator gave **13** (3.91 g.); ν_{max}^{KBr} 2700–3000, 1720, 1590, 1507, and 1400 cm.$^{-1}$. The salt **13** (1.00 g.) dissolved in water (100 ml.) was passed through Amberlite IR-4B (45-g. wet wt. in a column 3 cm. in diameter) in a manner analogous to that described by Meyers and Miller.[39] The column was eluted with 1.0 l. of doubly distilled water. Evaporation of the effluent on a rotary evaporator gave the lactone zwitterion **15** (0.305 g.) which decomposed above 310° but sublimed unchanged at 300° and 38-mm. pressure; ν_{max}^{KBr} 3550, 2700–3000, 1775, 1590, and 1407 cm.$^{-1}$. The further transformation of **15** to the known dilactone **16** is described in the next section.

When sodium nitrite (0.5 g.) was slowly added to **13** (0.500 g.) dissolved in 20% hydrochloric acid (10 ml.) and the solution was heated on a steam bath for 20 min. and then allowed to stand at room temperature, the known bromolactone acid **14** crystallized (0.072 g., m.p. 183.5–184.5°, lit.[40] m.p. 186°) from solution. Admixture with an authentic sample prepared as previously reported[28] did not depress the melting point; ν_{max}^{KBr} 1750 and 1735 cm.$^{-1}$ after drying 8 hr. at 144° and 1-mm. pressure.

Anal. Calcd. for $C_9H_9BrO_4$: C, 41.40; H, 3.47; Br, 30.61. Found: C, 41.22; H, 3.49; Br, 31.50.

Water Hydrolysis of *exo*-5-Bromo-*exo*-6-succinimidobicyclo-[2.2.1]heptane-*endo-cis*-2,3-dicarboxylic Acid (10).—Diacid **10** (1.00 g., m.p. 225–227°) in 50 ml. of distilled water was heated over a steam bath for 3 days. The aqueous solution was then concentrated to a volume of 10 ml. and continuously extracted with ether for 48 hr. Evaporation of the ether extract yielded succinic acid (0.330 g., m.p. 186°). The extracted aqueous hydrolysis solution, which gave a positive silver nitrate test for bromide ion, was passed through Amberlite IR-4B(OH) as previously described[39] (25-g. wet wt. in a column 1.5 cm. in diameter). The column was eluted with 1.0 l. of water, and the effluent was evaporated on a rotary evaporator to yield the lactone zwitterion **15** (0.455 g.). The lactone zwitterion was recrystallized by dissolving it in a minimum amount of hot water and adding four times that volume of an equal mixture of ethanol and ether; the decomposition was ~310°.

When sodium nitrite (0.670 g.) was added to the ether-extracted aqueous hydrolysis solution or to the lactone zwitterion **15** (0.455 g.) dissolved in 10 ml. of 5% hydrochloric acid, the dilactone **16** was formed and crystallized from solution (0.25 g.), m.p. 268°, ν_{max}^{KBr} 1795 and 1770 cm.$^{-1}$. An authentic sample prepared as previously described[41] gave an identical infrared spectrum.

Pyrolysis of *exo*-5-Bromo-*exo*-6-succinimidobicyclo[2.2.1]heptane-*endo-cis*-2,3-dicarboxylic Acid (10).—The diacid **10** (1.0 g., m.p. 225–227°) was heated at 230° for 2 hr. in an open beaker. The melt resolidified after 5 to 10 min. at 230°. The anhydride **20** sublimed on heating this solid at 235° and 35 mm. After 5 hr. 0.095 g. of the anhydride **20** (m.p. 110–111°; ν_{max}^{KBr} 1862, 1780, and 1705 cm.$^{-1}$) was obtained. Resublimation did not raise the melting point.

Anal. Calcd. for $C_{13}H_{12}BrNO_5$: C, 45.63; H, 3.54. Found: C, 45.13; H, 3.93.

The anhydride **20** gave a positive Beilstein test, a neutralization equivalent of 176 when titrated with sodium hydroxide (phenolphthalein end point), and a neutralization equivalent of 334 when titrated with sodium ethoxide in absolute ethanol (phenolphthalein end point); the calculated molecular weight was 342.17.

After sublimation of the anhydride **20** appeared complete, the bath temperature was raised to 280° (35 mm.) and the lactone **19** sublimed (0.070 g.); approx. m.p. 338° with decomposition; ν_{max}^{KBr} 1775, 1728, and 1670 cm.$^{-1}$; this lactone gave a negative Beilstein test.

Anal. Calcd. for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69. Found C, 56.34; H, 4.96.

Preparation of Lactone 19 from 10 under Basic Conditions.—A solution of diacid **10** (1.00 g., m.p. 225–227°) and dry pyridine (10 ml.) was refluxed for 2 hr. The pyridine was then evaporated on a rotary evaporator and the residual oil was dissolved in 5 ml. of water. The aqueous solution was filtered and acidified with 5 ml. of concentrated hydrochloric acid. On standing at room temperature for 6 hr., light amber-colored crystals of the hydrate of lactone **19** formed (0.475 g.); m.p. 265–270° (by raising the temp. 15°/min.); ν_{max}^{KBr} 1767, 1712, and 1697 cm.$^{-1}$. Recrystallization from acetone–water (1:1) did not raise the melting point nor change the color of the crystals. When the lactone hydrate was heated slowly, water of hydration was given off starting at about 252° and, after melting at about 252–257°, resolidification occurred at about 275°. Further heating resulted in sublimation, and the sublimate was identical with **19** obtained as described above.

The same lactone hydrate was obtained but in lower yield by refluxing a solution of diacid **10** (1.55 g.) in aqueous 5% sodium carbonate (30 ml.) for 3 hr. The product was isolated after acidification with excess concentrated hydrochloric acid, continuous extraction of the aqueous solution with ether for 10 days, and evaporation of the ether.

Benzenesulfonation of *endo*-5-Hydroxy-*exo*-6-aminobicyclo-[2.2.1]heptane-*endo-cis*-2,3-dicarboxylic Acid γ-Lactone (15).—The lactone zwitterion **15** (0.204 g. prepared as described above) and benzenesulfonyl chloride (0.183 g.) were stirred in 5% aqueous sodium hydroxide (20 ml.) for 12 hr. at room temperature. The solution was then acidified with concentrated hydrochloric acid and extracted with ether. After drying the ether solution over anhydrous sodium sulfate and evaporation to approximately 5 ml., the benzenesulfonamide **28** crystallized (0.050 g.), m.p. 188–190°. Recrystallization of an analytical sample from ether gave m.p. 194.5–195.5°; ν_{max}^{KBr} 3240, 1780, and 1703 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{15}NO_6S$: C, 53.40; H, 4.48; N, 4.15. Found: C, 53.52; H, 4.49; N, 3.95.

(39) C. Y. Meyers and L. E. Miller, *Org. Syn.*, **32**, 13 (1952).

(40) K. Alder and G. Stein, *Ann.*, **514**, 1 (1934).

(41) A. Winston and P. Wilder, Jr., *J. Am. Chem. Soc.*, **76**, 3045 (1954).

Oxidation of the Fumaric Acid–Methyl Abietate Diels–Alder Adduct with Alkaline Permanganate. Terpenes. VIII[1,2]

L. H. ZALKOW AND D. R. BRANNON

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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The alkaline permanganate oxidation of the fumaric acid–methyl abietate Diels–Alder adduct (IV) a been found to yield three products: an unsaturated γ-lactone (VI), a dihydroxylactone (IX), and a diol (X None of the normal oxidation product, arising by hydroxylation of the C-13 double bond, was detected. The chemical transformations described demonstrate that compounds in this series possessing *cis*-β-C-15,β-C-16 dicarboxyl groups are epimerized with base to the *trans*-α-C-15,β-C-16 dicarboxyl isomers.

Recent work from this laboratory has shown that alkaline permanganate oxidation of maleopimaric acid (I) leads, unexpectedly, to the lactone II in good yield rather than to hydroxylation of the hindered double bond at C-13.[3] The hindered nature of the double bond in I and related compounds was further shown by the results of the ozonolysis of the trimethyl ester of maleopimaric acid (III).[4] In the latter reaction eight products were isolated, all resulting from oxidative attack on the isopropyl group. In a further study of the oxidation of this type of molecule we have investigated the reaction of the fumaric acid–methyl abietate Diels–Alder adduct (IV) with alkaline permanganate.

The starting compound (IV) was prepared by heating methyl abietate and fumaric acid together at 200° in a nitrogen atmosphere. The dienophile, fumaric acid, would be expected to react with the diene, methyl abietate, from the less hindered α (down) side as observed in the reaction of this diene with other dienophiles.[3] However, two products are still possible—one containing an α-C-15 carboxyl group and a β-C-16 carboxyl group and the other containing a β-C-15 carboxyl group and an α-C-16 carboxyl group. The product isolated was shown to be only one of the two possible isomers by its sharp melting point and by the gas chromatograph of its trimethyl ester (V). The chemical transformations described below show unambiguously that the isomer obtained (IV) contains an α-C-15 carboxyl group and a β-C-16 carboxyl group. An identical isomer (IV) was obtained from maleopimaric acid (I) by conversion to ester III, followed by saponification and epimerization with sodium hydroxide.[4] Harris[5] and Silver[6] have previously described the epimerization of maleopimaric acid itself.

Oxidation of IV in alkaline solution with excess permanganate at 10° gave, after acidification and ether extraction, a crude white solid which was esterified with diazomethane and chromatographed on alumina. The infrared spectrum of the first product (IV, m.p. 177–178°) to be eluted from the chromatography column showed a strong band indicative of a γ-lactone at 1775 cm.$^{-1}$ and an ester carbonyl band at 1730 cm.$^{-1}$; its n.m.r. spectrum showed that it was a dimethyl ester which was very similar to VII, the latter having been obtained by permanganate oxidation of maleopimaric acid followed by esterification with diazomethane.[3] That VI was the C-15 epimer of VII was shown by isomerization of II with alkali followed by esterification with diazomethane, in which case a mixture of VI and VII was obtained. Further evidence in support of structure VI was obtained by its ozonolysis to yield ketone VIII. The infrared spectrum showed a γ-lactone carbonyl band and its n.m.r. spectrum showed that the isopropylidene group was no longer present. It is worthwhile noting that under the same conditions VII was unaffected by ozone.[3] The lactone VI has been reported to be formed by the action of lead tetraacetate on IV, although no experimental details were provided.[7] In our hands, the reaction of IV with lead tetraacetate did not give VI, but instead two other products were isolated.[8]

Establishment of the structure of VI and the alkaline epimerization of III to V and of VII to VI show that the stable isomers have α-C-15 and β-C-16 carboxyl groups rather than the reverse arrangement, and the Diels–Alder adduct obtained from fumaric acid and methyl abietate (IV) has this configuration.

Another product (IX, m.p. 123–125°) isolated by chromatography showed hydroxyl absorption at 3500 cm.$^{-1}$, γ-lactone absorption at 1780 cm.$^{-1}$, and ester carbonyl absorption at 1725–1730 cm.$^{-1}$ in its infrared spectrum. The n.m.r. spectrum of IX showed the C-14 proton at δ 4.50. Oxidation of IX with lead tetraacetate gave the same ketone VIII obtained, as mentioned above, from VI. Thus the structure depicted in formula IX can be assigned to the product of m.p. 123–125°. Compound IX undoubtedly arises in the reaction by hydroxylation of intermediate VI (as free acid) and was indeed readily prepared directly from isolated VI, after saponification, by further oxidation with permanganate followed by re-esterification. A comparison of II and VI (after saponification) in their reaction with alkaline permanganate is noteworthy. Further oxidation of II with alkaline permanganate proceeded only with great difficulty and gave a negligible yield of the dihydroxy compound epimeric with IX at C-15.[3] It can therefore be assumed that hydroxylation of VI proceeds from the less hindered side *cis* to the α-carboxy group at C-15 to give a product with the stereochemistry depicted in IX.

(1) We wish to thank the National Science Foundation for financial support of this work through Grant NSF-GP-233. The principal investigator wishes to thank the Research Foundation of the Oklahoma State University for making part of his time available during the academic year for directing this research.

(2) Terpenes. VII: L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, **28**, 2037 (1963).

(3) L. H. Zalkow, R. A. Ford, and J. P. Kutney, *ibid.*, **27**, 3535 (1962).

(4) L. H. Zalkow and N. N. Girotra, *ibid.*, **28**, 2033 (1963).

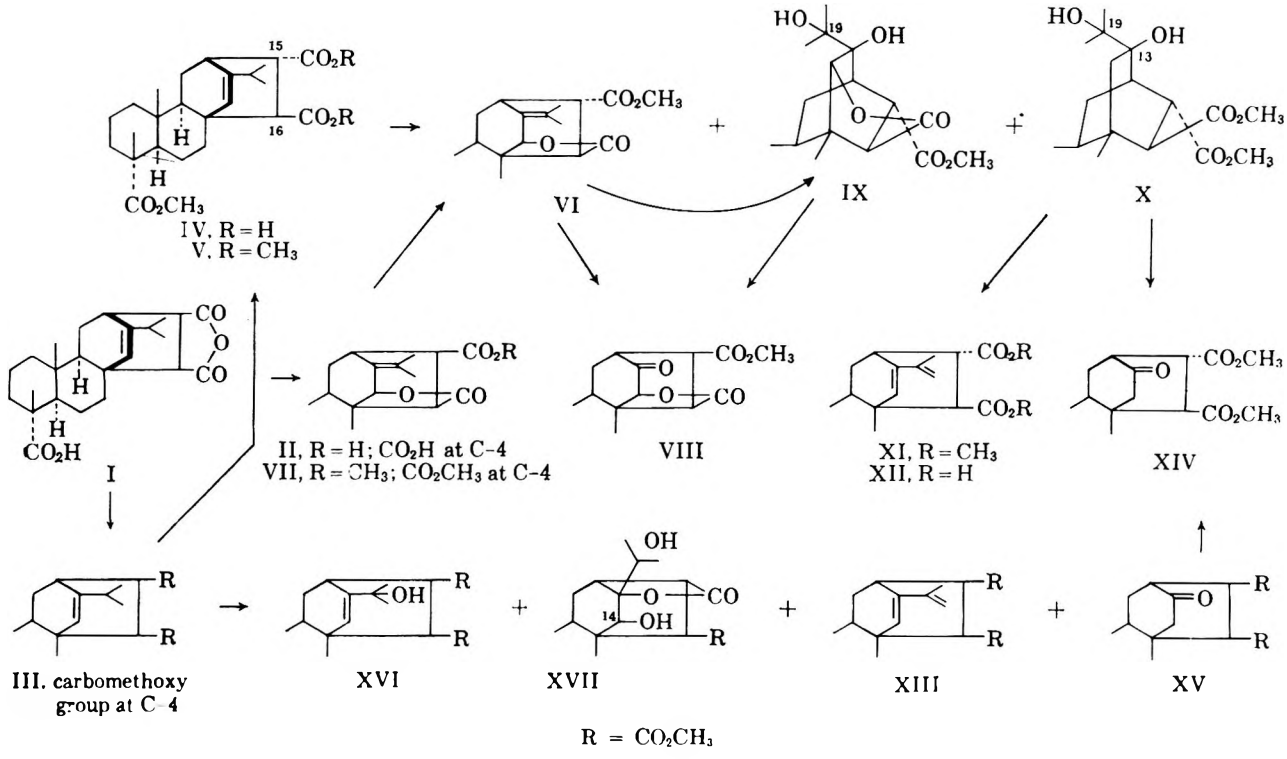
(5) G. C. Harris, U. S. Patent 2,517,563 (1950).

(6) R. P. Silver, U. S. Patent 2,522,586 (1950).

(7) W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963).

(8) L. H. Zalkow and D. R. Brannon, unpublished results, Oklahoma State University.

SCHEME I



The third and final product (m.p. 206–207°) isolated from the permanganate reaction after esterification and chromatography has been assigned structure X on the basis of the following evidence. The infrared spectrum of X showed O–H absorption at 3500 and 3410 cm.$^{-1}$, and carbonyl absorption at 1715 and 1730 cm.$^{-1}$. Its n.m.r. spectrum showed the presence of three carbomethoxy groups and four methyl group singlets. The two singlets at highest field (δ 1.08, 1.13) could be assigned to the C-4 and C-10 methyl groups and the two singlets at next highest field (δ 1.25, 1.32) could be assigned to the two methyl groups flanking the hydroxyl group at C-19 by analogy with XVI, one of the products obtained on the treatment of the trimethyl ester of maleopimaric acid (III) with ozone.[4] That the structure of the product of m.p. 206–207° was X and not that arising by normal hydroxylation of the C-13 double bond in IV was shown by the position of the isopropyl methyl protons in the n.m.r. and by the absence of a signal in the n.m.r. corresponding to the C-14 proton. The latter signal was to be expected at about δ 4.35, the position at which the C-14 proton of XVII appears.[4] Dehydration of X with phosphorus oxychloride in pyridine gave VI. The infrared spectrum of XI showed no hydroxyl absorption and the ultraviolet spectrum showed a strong band at λ_{max} 245 mμ. The C-15 epimer of XI (XIII) showed strong absorption at λ_{max} 240 mμ.[4,9] The n.m.r. spectrum of XI showed the C-10 methyl protons at δ 0.55, thus providing additional evidence for the presence of a C-13 double bond.[4,7] The protons of the methyl group of the isopropenyl group appeared at δ 1.92, whereas the olefinic protons appeared at δ 5.86 and 6.30; both of these observations are clearly consistent with the assigned structure. Treatment of X with lead tetraacetate gave XIV. The latter compound was identified by comparison with an authentic sample, prepared as previously described[4] by isomerization of XV. The stereochemistry of the hydroxyl group at C-13 in X is assigned on the same basis as that for IX as discussed above.

The formation of VI and IX is consistent with a mechanism of the type previously proposed for the formation of II from I.[3] The formation of X is more difficult to rationalize. The C-13,C-14 double bond in IV does not rearrange to the C-13,C-19 position in the presence of alkali and in the absence of permanganate, but it is possible that the migration does occur in the oxidizing medium.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were recorded with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard (δ = 0). Gas chromatographs were run at 280° using a column 0.125 in. × 5 ft. of 5% SE-30 on acid-washed Chromosorb W with a hydrogen flame detector and a hydrogen flow rate of 26 cc./min. and a nitrogen flow rate of 28 cc./min. Thin layer chromatograms were run on 25-μ-thick silica gel-coated glass plates using 5:1 benzene–ethyl acetate as the mobile phase, and detection was by iodine vapors.

Preparation of Fumaric Acid–Methyl Abietate Adduct (IV).—A mixture of 50 g. of commercial methyl abietate (Eastman technical) and 20 g. of fumaric acid was stirred and heated at 200–210° in a nitrogen atmosphere for 3 hr. After washing the viscous yellow reaction mixture several times with hot water, it was poured into 300 ml. of refluxing benzene. The product IV crystallized from the cooled benzene solution in 40% yield. The analytical sample was obtained by recrystallization from glacial acetic acid and gave m.p. 294–295° after drying at 144° (0.1 mm.)[10]; ν_{max}^{KBr} 1730, 1715, and 1960 (weak) cm.$^{-1}$; $[\alpha]_D$ +36° (c 0.004, alcohol).

(9) L. Ruzicka and St. Kaufman, *Helv. Chim. Acta*, **23**, 1346 (1940).

(10) L. H. Zalkow and M. L. Corser, *Proc. Oklahoma Acad. Sci.*, **42**, 190 (1962).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.13; H, 8.40.

The adduct IV was converted into the corresponding trimethyl ester V by treatment with ethereal diazomethane. The triester could not be crystallized but was shown to be homogeneous by gas chromatography, a single peak being obtained in its gas chromatogram with a retention time of 8.7 min. The infrared and n.m.r. spectra of V were identical with those of the product obtained by epimerization of III.[2]

Oxidation of Adduct IV with Alkaline Permanganate.—The adduct IV (10 g.) was added to a solution prepared by dissolving 3 g. of sodium hydroxide in 400 ml. of water. After cooling to 10°, a cold 0.165 *M* aqueous permanganate solution was added to the alkaline solution dropwise until the permanganate color persisted for 3 hr. During the addition of the permanganate solution the reactants were maintained at ≤10°. The precipitated manganese dioxide was removed by filtration and gaseous sulfur dioxide was passed through the aqueous solution until the permanganate color disappeared. Acidification (pH 1) with dilute hydrochloric acid gave 5.5 g. of crude crystalline products, and continuous ether extraction (12 hr.) of the aqueous filtrate gave an additional 2.1 g. of products. The combined products were esterified with ethereal diazomethane and separated by column chromatography as described below.

Isolation of VI.—The crude esterified product (1.58 g.), mentioned above, was chromatographed on 125 g. of Merck acid-washed alumina (activity III) and elution with 15:85 ether–benzene gave 0.320 g. of VI as a gum which was crystallized from isooctane at −40°. Recrystallization from 1:4 water–methanol and drying at 144° (0.1 mm.) gave VI of m.p. 177–178°, positive tetranitromethane test, single peak in gas chromatography with retention time of 9.8 min., single spot in thin layer chromatography with R_f 0.625; ν_{max}^{KBr} 1775 and 1730 cm.$^{-1}$; n.m.r. (carbon tetrachloride) δ 0.70 (3 protons), 1.12 (3), 1.78 (6), 3.62 (3), 3.74 (3), and 4.89 (1).

Conversion of II to VI.—The lactone II (90 mg.) prepared as previously described[3] was refluxed in 10 ml. of a 5% sodium hydroxide solution containing 0.5 ml. of methanol for 4 hr. After removal of the solvent with a rotary evaporator the cooled residue was acidified with dilute hydrochloric acid (pH 1) whereupon a white precipitate was obtained. After filtration, the solid product was treated with ethereal diazomethane, and removal of the ether gave a viscous gum which could not be crystallized. An n.m.r. spectrum of this gummy product showed that it was a mixture of VI and VII by the presence of two peaks at high field, δ 0.70 (C-10 methyl protons in VI) and 0.75 (C-10 methyl protons in VII) and by the presence of peaks at δ 3.62 and 3.74. In VI the two carbomethoxy groups give signals at δ 3.62 and 3.74 whereas in VII only one signal (δ 3.62) is observed for the two carbomethoxy groups. The gummy product after dissolving in 0.5 ml. of methanol was again refluxed with 10 ml. of a 10% potassium hydroxide solution for 60 hr. The n.m.r. spectrum of the product after re-esterification with diazomethane showed the presence of 40% of VI. Thin layer chromatography also showed the presence of VI (R_f 0.625) and VII (R_f 0.583).

Isolation of X.—The second product (X) to be eluted in the chromatography of the esterified oxidation product was eluted in 1:1 ether–benzene, whereupon 0.309 g. was obtained from 1.58 g. of the crude esterified product. This product was crystallized from isooctane and the analytical sample was obtained by recrystallization from methanol, m.p. 206–207° after drying at 100° (0.1 mm.); ν_{max}^{KBr} 3500, 3410, 1715, and 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}O_8 \cdot CH_3OH$[8]: C, 63.85; H, 8.80. Found: C, 63.92; H, 8.56.

Isolation of IX.—The third and final product isolated from the esterified oxidation mixture was eluted from the chromatography column with 99:1 ether–methanol, 0.716 g. being obtained from 1.58 g. of the crude product. Two recrystallizations from isooctane gave the analytical sample, m.p. 123–125°; ν_{max}^{KBr} 3500, 1780, and 1725–1730 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{38}O_8$: C, 65.24; H, 8.01. Found: C, 64.87; H, 8.05.

Preparation of IX from VI.—A solution prepared by dissolving VI (320 mg.) in 10 ml. of 5% potassium hydroxide and 0.5 ml. of methanol was refluxed for 1 hr., then concentrated to 5 ml. with a rotary evaporator. After cooling to room temperature, a 0.165 *M* aqueous potassium permanganate solution was added until an excess of permanganate remained. The precipitated manganese dioxide was removed by filtration and gaseous sulfur dioxide was passed through the solution as previously described. The resulting solution was acidified (pH 1) and continuously extracted with ether for 12 hr. The ether extract was dried over magnesium sulfate, concentrated, and finally treated with ethereal diazomethane. Removal of the ether gave 163 mg. of a gummy residue whose n.m.r. spectrum showed very little of the signal at δ 1.78 arising from the isopropylidene protons thus showing that the double bond had reacted. Chromatography of this residue on 55 g. of Merck acid-washed alumina (activity III) gave 80 mg. of pure IX (m.p. 123–125°) in the 99:1 ether–methanol eluent. The diol IX thus obtained was identical with IX (isolated as previously described) in infrared and n.m.r. spectra and the mixture melting point was undepressed.

Ozonolysis of VI. Preparation of VIII.—A stream of oxygen containing ozone (~3%) was passed through a solution, prepared by dissolving 125 mg. of VI in 15 ml. of glacial acetic acid, at room temperature for 10 hr. Zinc dust (250 mg.) and water (5 ml.) were then added to the acetic acid solution and stirring was continued for 6 hr. After removal of the zinc by filtration the solution was concentrated with a rotary evaporator and then extracted with four 50-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and concentrated to give a resinous solid. Chromatography on 40 g. of Merck acid-washed alumina (activity III) gave 90 mg. of ketone VIII in the 6:4 benzene–ether eluent. The analytical sample was prepared by recrystallization from methanol and gave m.p. 170–172.5°, single spot in thin layer chromatography with R_f 0.580; ν_{max}^{KBr} 1790 and 1730–1740 cm.$^{-1}$; n.m.r. (carbon tetrachloride) δ 0.70 (C-10 methyl protons) and 4.14 (C-14 proton).

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.70; H, 7.26.

Preparation of VIII from IX.—Diol IX (200 mg.) and 275 mg. of dry lead tetraacetate were refluxed in 15 ml. of glacial acetic acid for 24 hr.; an additional 275 mg. of lead tetraacetate was added and refluxing was continued for 36 hr. After removal of the acetic acid on a rotary evaporator, 10 ml. of water was added to the residue and the aqueous solution was extracted with three 20-ml. portions of ether. After drying over magnesium sulfate, the ether was removed to give 160 mg. of brown noncrystalline material which was chromatographed on 9 g. of Merck acid-washed alumina (activity III). Elution with 6:4 benzene–ether gave 80 mg. of VIII, m.p. 168–170°, identical in thin layer chromatography and infrared and n.m.r. spectra with VIII prepared as described above.

Dehydration of X. Preparation of XI and XII.—Diol X (150 mg.) was heated on a steam bath with 2 ml. of phosphorus oxychloride and 5 ml. of dry pyridine for 6 hr. After cooling, 5 ml. of water was cautiously added to the reaction mixture which was then extracted with five 20-ml. portions of ether. The combined ether extract was washed with water, dried over magnesium sulfate, and concentrated to give 110 mg. of noncrystalline residue which was then chromatographed on 10 g. of Merck acid-washed alumina (activity III). Diene XI (75 mg.) was eluted in 9:1 benzene–ether as a viscous gum which could not be crystallized. Thin layer chromatography showed one spot with R_f 0.58; ν_{max}^{film} 1730 and 1745 cm.$^{-1}$; λ_{max}^{EtOH} 235 mμ (log *E* 4.15). The n.m.r. spectrum (carbon tetrachloride) showed signals at δ 0.55 (3 protons), 1.10 (3), 1.92 (3), 3.60 (3), 3.67 (3), 3.74 (3), 5.86, and 6.30.

Preparation of XIV from X.—Diol X (20 mg.) and dry lead tetraacetate (50 mg.) were refluxed in 15 ml. of glacial acetic acid for 12 hr. After removal of the acetic acid with a rotary evaporator, 20 ml. of water was added and the aqueous solution was extracted with three 25-ml. portions of ether. The combined ether extract was washed with water, then dried over magnesium sulfate. Removal of the ether gave a gummy residue which was chromatographed on 8 g. of acid-washed alumina (activity III). Ketone XIV (12 mg.) was eluted in 9:1 benzene–ether and was crystallized from methanol, m.p. 145°. Thin layer chromatography showed one spot, R_f 0.65; XIV thus obtained was identical in all respects with a sample of XIV prepared as previously described.[4]

Studies in the Synthesis of Atisine. Terpenes. X

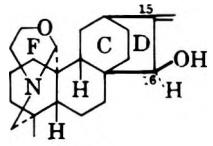
L. H. ZALKOW AND N. N. GIROTRA

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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The carbon skeleton of atisine, a diterpenoid alkaloid, has been synthesized from maleopimaric acid. The latter compound has been prepared from abietic acid, which has been totally synthesized. The compound synthesized is enantiomeric with the isoprenoid portion of the naturally occurring alkaloid.

The synthesis of the diterpenoid alkaloid, atisine (I), has provided a challenge for many workers all over the world. During the past year approximately a dozen



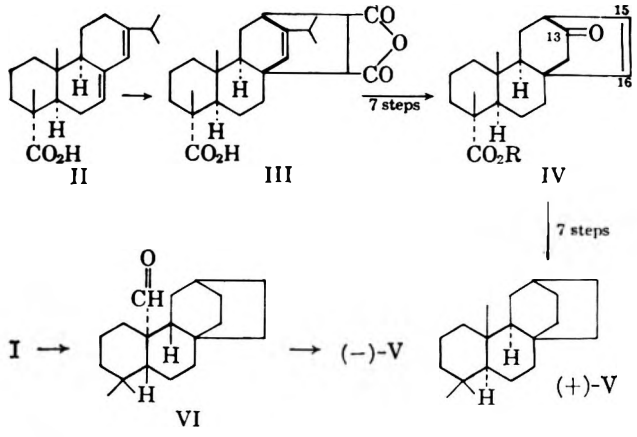
I

publications[1-11] have appeared dealing with various aspects of the synthesis of this interesting compound; Japanese workers[2] have recently reported the first total synthesis of the alkaloid in its racemic form.

The problem involves two distinct phases. One, synthesis of the nitrogen-containing E ring and its subsequent conversion to the oxazolidine F ring, and second, construction of the C–D bicyclo[2.2.2]octane ring system with means of introducing the desired substituents at C-15 and C-16. A number of ingenuous methods have been utilized in the synthetic approaches to the nitrogen-containing E ring, involving classical reactions[2,10,11] and the more modern method of photolysis.[4,9] Likewise, a number of pathways have been offered for the synthesis of the bicyclic C–D ring system. Pelletier and Parthasarathy[5] used the Dieckmann reaction. Bell and Ireland[3] utilized an aldol type condensation, Nagata, *et al.*,[2] used a displacement reaction, and other workers[1,6] have approached the problem *via* the Diels–Alder reaction.

We have previously prepared[7] hydrocarbon (+)-V from maleopimaric acid (III) which in turn has been made by a Diels–Alder reaction between abietic acid (II) and maleic anhydride; abietic acid itself has been totally synthesized.[12,13] Ayer, McDonald, and Iverach[6] likewise synthesized (+)-V by a similar sequence of reactions and, in addition, found that it was, as predicted, enantiomeric with the product obtained by Wolff–Kishner reduction of VI, which had been previously obtained from atisine by Ap Simon, Edwards, and Howe.[14] We now wish to report the conversion of IV, an intermediate obtained in the preparation of V, into XXI, which possesses the entire diterpenoid skeleton of atisine in its correct relative configuration.

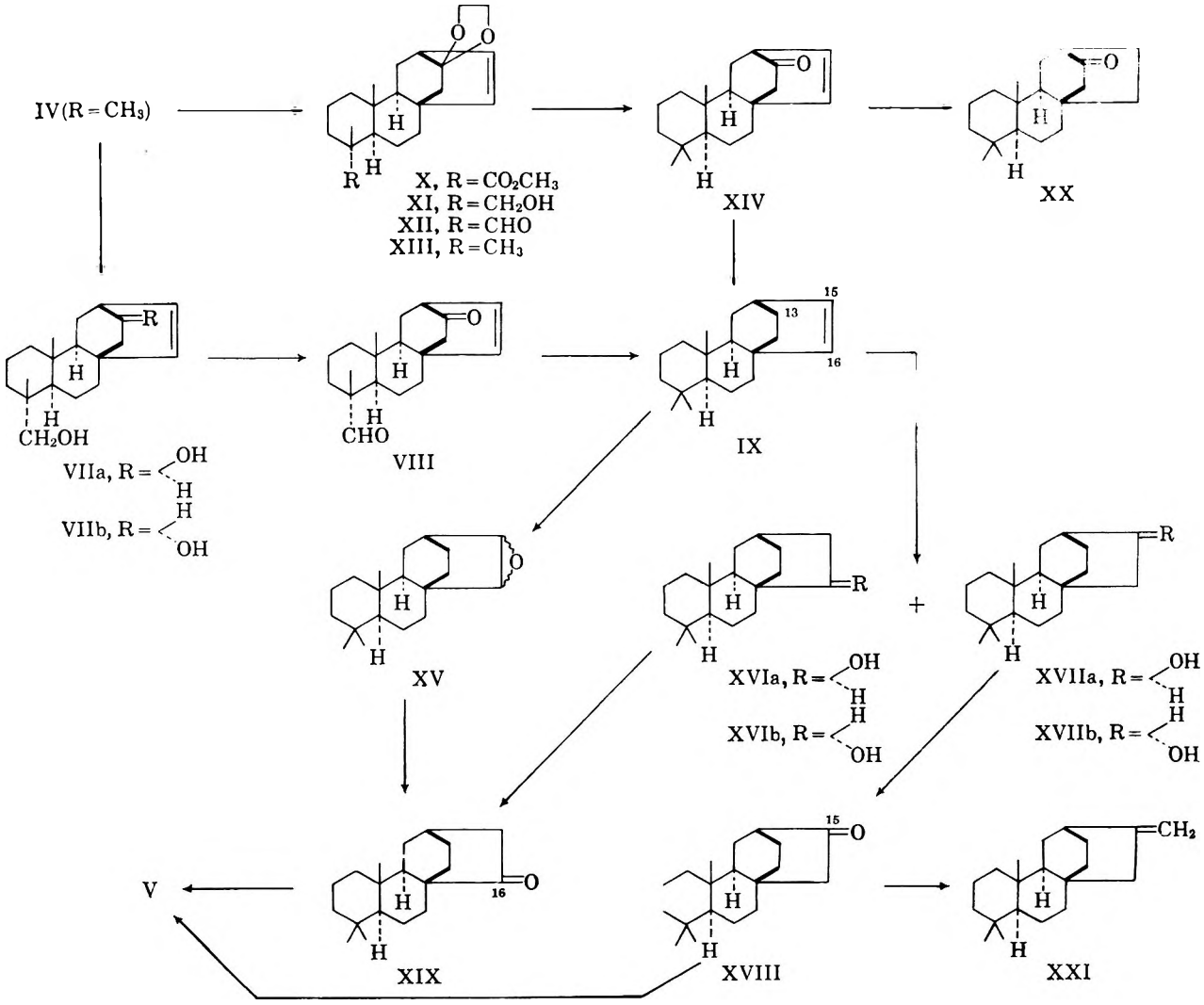
Reduction of keto ester IV with lithium aluminum hydride gave a mixture of alcohols (VIIa and b) which was oxidized directly to give the keto aldehyde VIII. Huang-Minlon[15,16] reduction of VIII gave crystalline alkene IX. The n.m.r. spectrum of IX showed the three methyl-group protons at C-4 and C-10 as sharp



singlets at δ 0.82, 0.87, and 0.96. This is to be contrasted with compounds of this type which contain a double bond at C-13. In such cases the C-10 methyl-group protons appear at δ 0.50.[17] The vinylic protons in IX appeared as three sharp lines at δ 5.92, 5.95, and 6.02. The double bond in IX was hydrated by the Brown hydroboration procedure[18] to yield a mixture of alcohols XVI (a, b) and XVII (a, b) which was treated with chromic anhydride in pyridine. Chromatography of the oxidation product on alumina gave two ketones, A (m.p. 145–146°, λ_{max} 5.78 μ) and B (m.p. 146–148°, λ_{max} 5.81 μ) in a ratio of approximately 4:1, the less abundant isomer B being eluted first. That no skeletal rearrangement had occurred in these transformations was shown by the facile conversion of both ketones A and B to the previously reported hydrocarbon (+)-V by the Huang-Minlon[15,16] procedure. The n.m.r. spectra of ketones A and B were very similar except that in A the methylene protons adjacent to the carbonyl group gave a signal at δ 1.82, whereas in ketone B these protons appeared at δ 2.17. Ketone A gave a positive Cotton effect in its optical rotatory dispersion curve whereas ketone B showed a negative Cotton effect. Although the above information did not allow an unambiguous decision to be made as to

(1) A. A. Othman and N. A. J. Rogers, *Tetrahedron Letters*, 1339 (1963).
(2) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963).
(3) R. A. Bell and R. E. Ireland, *Tetrahedron Letters*, 269 (1963).
(4) W. L. Meyer and A. S. Levinson, *Proc. Chem. Soc.*, 15 (1963).
(5) S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, 205 (1963).
(6) W. A. Ayer, C. E. McDonald, and G. G. Iverach, *ibid.*, 1095 (1963).
(7) L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, **28**, 2037 (1963).
(8) I. Iwai and A. Ogiso, *Chem. Ind.* (London), 1084 (1963).
(9) J. W. Ap Simon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962).
(10) J. A. Findlay, W. A. Henry, T. C. Jain, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 869 (1962).
(11) I. Iwai, A. Ogiso, and B. Shimizu, *Chem. Ind.* (London), 1288 (1962).
(12) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84**, 284 (1962).
(13) A. W. Burgstahler and L. R. Worden, *ibid.*, **83**, 2587 (1961).
(14) J. W. Ap Simon, O. E. Edwards and R. Howe, *Can. J. Chem.*, **40**, 630 (1962).
(15) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(16) Huang-Minlon, *ibid.*, **71**, 3301 (1949).
(17) L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, **28**, 2033 (1963).
(18) H. C. Brown, *et al.*, *J. Am. Chem. Soc.*, **82**, 4233 (1960).

SCHEME I



the structures of isomers A and B, the ratio of products obtained in the hydroboration reaction and subsequent oxidation and the order of elution in chromatography indicated that A possessed the less hindered carbonyl group, *i.e.*, structure XVIII; therefore, B presumably had structure XIX. In order to obtain more information which would be useful in distinguishing between A and B, the isomeric ketone XX, of unequivocal structure, was prepared for comparison purposes.

Keto ester IV was converted to the cyclic ketal X by the usual procedure; the carbomethoxy group at C-4 was converted in turn to a hydroxymethyl group (XI) with lithium aluminum hydride, then to an aldehyde group (XII) by oxidation with chromic anhydride in pyridine, and finally to a methyl group (XIII) by the Huang-Minlon[15,16] procedure. Hydrolysis of the latter compound gave ketoalkene XIV, previously prepared by Ayer, *et al.*,[6] by a different procedure. Huang-Minlon[15,16] reduction of XIV gave the previously described alkene IX, while catalytic reduction of XIV gave the saturated ketone XX, which gave, as previously shown,[6] a positive Cotton effect in its optical rotatory dispersion curve. Unfortunately, it is not possible to use the Octant rule for predicting configuration in these cases since the C–D ring systems possess boat conformations.[19] Using an empirical approach, it can be seen that ketone XVIII possesses a mirror image relationship to ketone XX with regard to the C–D ring system and on this basis the unknown ketone with a negative Cotton effect (B) might be assigned structure XVIII. However, this turned out to be incorrect. During the course of this investigation Bell and Ireland[3] published their synthesis of racemic ketone XVIII by a path which placed the carbonyl function unequivocally at C-15. Comparison of the infrared and nuclear magnetic resonance spectra of racemic XVIII, kindly supplied by Dr. Ireland, with spectra of our ketone A showed that the two were identical, and hence ketones A and B possessed structures XVIII and XIX, respectively. Ketone (+)-XVIII was then converted to alkene XXI by use of the Wittig reagent,[20] thus completing the synthesis of the enantiomeric diterpenoid carbon skeleton of atisine. Bell and Ireland[3] likewise have reported the conversion of racemic XVIII to racemic XXI and succeeded in introducing a hydroxyl group at C-16 of XXI.

Alkene IX was readily converted into epoxide XV. However, when XV was treated with methylmagnesium iodide, the expected introduction of a methyl group at C-15 and/or C-16 did not occur. The product of the Grignard reaction gave, on oxidation with

(19) W. Klyne, *Tetrahedron*, **13**, 40 (1961).

(20) G. Wittig and V. Schöllkopf, *Ber.*, **87**, 1318 (1954).

chromic anhydride in pyridine, the previously obtained ketone XIX. The unexpected preparation of the C-16 alcohol on treatment of epoxide XV with methylmagnesium iodide occurred either by direct reduction of the epoxide or by rearrangement of the epoxide to a C-16 ketone followed by reduction of the latter under the reaction conditions.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were recorded with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard ($\delta = 0$) and carbon tetrachloride as solvent.

Preparation of VII.—A solution of IV (0.5 g.)[7] in 50 ml. of anhydrous ether was added dropwise to a well-stirred suspension of lithium aluminum hydride (0.16 g.) in 25 ml. of anhydrous ether. After the initial reaction was over, the mixture was refluxed for 3 hr. The excess hydride was decomposed by the successive addition of ethyl acetate and water, and the alkaline solution was made acidic with cold 6 *N* hydrochloric acid. The acidic solution was extracted with ether; the ether layer was washed with water, dried over anhydrous magnesium sulfate, and finally evaporated to yield 0.45 g. (m.p. 160–210°) of a mixture of VIIa and b; λ_{max}^{KBr} 2.98, 6.15, 9.38, 9.5, 9.6, 13.9, and 14.36 μ. This mixture was used in the next transformation without further purification.

Preparation of VIII.—A solution of 0.44 g. of VII (a, b) in 15 ml. of anhydrous pyridine was added to a mixture of 1.2 g. of chromic anhydride in 10 ml. of dry pyridine. After stirring for 2 hr. at room temperature, the mixture was poured into ice–water and extracted with ether. The ether extract was successively washed with 5% cold hydrochloric acid and 5% cold sodium hydroxide solution, and then dried over anhydrous sodium sulfate. Removal of the solvent gave 0.42 g. of the crude air-sensitive ketoaldehyde VIII, m.p. 112–118°; λ_{max}^{KB} 3.71, 6.18, 14.12, and 14.7 μ. This was used as such in the following reaction.

Preparation of IX from VIII.—Potassium hydroxide (5 g.) was heated with 5 ml. of 95% hydrazine and 45 ml. of diethylene glycol until it dissolved. The ketoaldehyde VIII (2.69 g.) was added to this solution and the reaction mixture was heated under reflux for 4 hr. Excess hydrazine and water were distilled out until the bath temperature reached 240°. The distillate was saved and the sublimed material was washed out of the condenser with ether. Hydrazine (5 ml.) was added to the residue; refluxing was continued for an additional 12 hr. The reaction mixture, distillate, and ether washings were combined and added to water (250 ml.); the entire mixture was extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of ether yielded 2.3 g. of the crude unsaturated hydrocarbon IX which on elution with petroleum ether (b.p. 60–80°) through 20 g. of neutral alumina yielded 2.04 g. of white crystalline solid, m.p. 82–83°. The analytical sample obtained by recrystallization from methanol had m.p. 84–85°; λ_{max}^{KBr} 6.19, 14.12, and 14.3 μ.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.29; H, 11.70. Found: C, 88.16; H, 11.84.

Preparation of X.—A mixture of IV (3.81 g.), 20 ml. of anhydrous benzene, 2 ml. of freshly distilled ethylene glycol, and 0.03 g. of *p*-toluenesulfonic acid monohydrate was heated at reflux in a flask provided with a Dean–Stark water separator for 20 hr. The cooled mixture was poured into 5% sodium carbonate solution, and the organic layer was washed with water. Drying over anhydrous magnesium sulfate and evaporation of the solvent yielded 4.30 g. of viscous oil which crystallized on the addition of petroleum ether (b.p. 30–60°). Recrystallization from *n*-heptane yielded 4.14 g. (95.3%) of X, m.p. 95–97°. The analytical sample obtained by recrystallization from the same solvent had m.p. 98–99°; λ_{max}^{KBr} 5.8, 6.16, 8.0, 9.02, 9.15, and 14.5 μ; n.m.r. δ 1.03 (3 protons), 1.10 (3), 3.58 (3), 3.77 (4), and 5.85–5.94 (2).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.59; H, 8.94. Found: C, 73.88; H, 8.88.

Preparation of XI.—A solution of 3.8 g. of X in 40 ml. of anhydrous ether was added dropwise to a well-stirred suspension of 0.28 g. of lithium aluminum hydride in 25 ml. of anhydrous ether, and the reaction mixture was refluxed for 5 hr. The excess hydride was decomposed by the successive addition of ethyl acetate and water. After treatment with an excess of 20% aqueous ammonium chloride solution, the ether layer was separated and the aqueous layer was extracted with more ether. The combined ether layers were washed with water, then dried over anhydrous magnesium sulfate. Removal of the solvent yielded 3.49 g. of crude XI which upon crystallization from ether–petroleum ether gave 3.25 g. (92.8%) of material, m.p. 103–105°. The analytical sample was obtained by recrystallization from the same solvent and had m.p. 106–107°; λ_{max}^{KBr} 2.89, 6.17, 9.15, and 14.32 μ; n.m.r. δ 0.73 (3) 1.05 (3), 3.78 (4), and 5.85–5.94 (2).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.85; H, 9.72.

Preparation of XII.—A solution of 2.91 g. of XI in 15 ml. of anhydrous pyridine was added to a mixture of 4 g. of chromic anhydride and 30 ml. of anhydrous pyridine. After stirring at room temperature for 2 hr., the mixture was poured into ice–water and extracted with ether using Super Cel to break the emulsion. The organic layer was washed with water and dried over anhydrous magnesium sulfate; the solvent was evaporated to yield 2.84 g. of crude XII; λ_{max}^{KBr} 3.73, 5.8, 6.15, 9.15, and 14.25 μ. This was subjected to the following reaction without further purification.

Preparation of XIII.—A mixture of 2.76 g. of XII, 40 ml. of diethylene glycol, 6 ml. of 90% hydrazine, and 5 g. of potassium hydroxide was gently heated to dissolve the potassium hydroxide and then refluxed for 4 hr. Excess hydrazine and water were distilled at a bath temperature of 240°; 6 ml. of 90% hydrazine was again added; the reaction mixture was refluxed for an additional 16 hr. The cold mixture was diluted with 250 ml. of water and was extracted with ether. The organic layer was washed with water and, on drying over anhydrous magnesium sulfate followed by evaporation of the solvent, it yielded 2.38 g. of partially crystalline material which on crystallization from methanol yielded 1.4 g. of pure XIII, m.p. 90–90.5°; λ_{max}^{KBr} 6.15, 9.12, and 14.48 μ; n.m.r. δ 0.83 (3), 0.85 (3), 1.00 (3), 3.76 (4), and 5.85–5.94 (2).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.60; H, 10.54.

Preparation of XIV.—Concentrated hydrochloric acid (5 drops) was added to a solution of 1.2 g. of XIII in 15 ml. of methanol, 25 ml. of dioxane, and 5 ml. of water. The solution was stirred at room temperature for 1 hr. and then diluted with water (150 ml.). The aqueous layer was extracted with ether and the extract was washed successively with 5% sodium carbonate solution and water. Drying of the extract over anhydrous magnesium sulfate and evaporation of the solvent yielded 1.05 g. of a crystalline material which upon recrystallization from methanol gave 0.96 g. (93%) of pure XIV, m.p. 119–120°, lit.[6] m.p. 123–124°; λ_{max}^{KBr} 5.81, 6.82, and 14.15 μ; n.m.r. δ 0.83 (3), 0.93 (3), and 6.04–6.10 (2).

Anal. Calcd. for $C_{19}H_{26}O$: C, 83.76; H, 10.36. Found: C, 83.71; H, 10.47.

Preparation of IX from XIV.—A mixture of 10 ml. of diethylene glycol, 2 ml. of 95% hydrazine, and 2 g. of potassium hydroxide was heated until the potassium hydroxide dissolved. To the cooled mixture, 0.8 g. of the keto olefin XIV was added and the solution was refluxed for 28 hr. Water (250 ml.) was added to the cooled reaction mixture, and the solid that precipitated was extracted into ether. The ether extract was washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a crystalline material which on recrystallization from methanol gave 0.6 g. (79%) of an olefin identical in all respects with IX, previously obtained as described above.

Preparation of XX.—A solution of 0.062 g. of XIV in 10 ml. of ethyl acetate was hydrogenated in the presence of 0.010 g. of 10% palladium–charcoal catalyst. The theoretical amount of hydrogen was absorbed within 10 min. The solid product (XX) obtained after the removal of the catalyst and evaporation of the solvent was crystallized from methanol, yielding 0.055 g., m.p. 125–126°, lit.[6] m.p. 126–127°; λ_{max}^{KBr} 5.81 μ; n.m.r. δ 0.80 (3) and 0.87 (3); optical rotatory dispersion run in methanol (*c* 0.055), $[\alpha]_{589\,m\mu}$ +40°, $[\alpha]_{310}$ +649°, and $[\alpha]_{295}$ +231°.

Preparation of XV.—An ethereal solution of monoperphthalic acid (9 ml., 4 mmoles) was added to a solution of 0.92 g. (~3.5 mmoles) of IX in 7 ml. of ether, and the mixture was allowed to

stand for 48 hr. at room temperature. After that interval, 25 ml. of ether was added to the reaction mixture and excess peracid was destroyed by washing the ether layer with an aqueous solution of potassium iodide. The organic layer then was washed, respectively, with sodium thiosulfate, sodium carbonate solution, and water. The ether layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.96 g. of the crude epoxide XV, λ_{max}^{KBr} 11.49 μ. Crystallization from acetone gave 0.42 g. of epoxide which melted over a broad range, 70–112°; n.m.r. δ 0.80 (3), 0.87 (3), 0.95 (3), 2.55 (doublet, J = 5 c.p.s.), and 3.02 (triplet, J = 5 c.p.s.).

Conversion of XV to XIX.—XV (0.52 g.) in 15 ml. of anhydrous ether was added dropwise to an ethereal solution of methylmagnesium iodide (prepared by action of 0.15 ml. of methyl iodide in 5 ml. of dry ether on 0.05 g. of magnesium suspended in 2 ml. of anhydrous ether). The reaction mixture was refluxed for 42 hr., after an initial stirring at room temperature for 2 hr. The complex was hydrolyzed by means of 20% aqueous ammonium chloride solution. The clear ether layer was combined with ether extracts of the aqueous layer and washed with water. The organic layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.54 g. of a semicrystalline alcoholic product, λ_{max}^{Nujol} 2.98 and 9.58 μ. This product was oxidized without further purification.

A solution containing 0.52 g. of the above alcohol in 7 ml. of dry pyridine was added to a mixture of 0.7 g. of chromic anhydride and 6 ml. of dry pyridine, and the reaction mixture was stirred for 8 hr. at room temperature. The mixture was then poured into ice–water and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 0.49 g. of partially crystalline solid (λ_{max}^{film} 5.81 μ) which was suspended in 60 ml. of methanol and 15 ml. of 15% aqueous sodium hydroxide solution, and the resulting mixture was heated at reflux for 8 hr. The cold mixture was diluted with 150 ml. of water and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.34 g. of yellow semicrystalline solid (λ_{max}^{film} 5.81 μ) which was chromatographed over 40 g. of neutral alumina. Elution with 50 ml. of 8.5:1.5 benzene–ether gave 0.114 g. of a ketone (m.p. 144–146°) which after recrystallization from methanol had m.p. 146–148°. This ketone was found to be identical in all respects with XIX prepared as described below.

Preparation of XVI and XVII.—To a well-stirred suspension of 0.21 g. of sodium borohydride in 20 ml. of anhydrous tetrahydrofuran containing 2.2 g. of IX, there was added 1 g. of boron trifluoride etherate in 8 ml. of anhydrous tetrahydrofuran over a period of 1 hr. at room temperature. After stirring for an additional 2 hr. at room temperature, the reaction mixture was heated under reflux for 1 hr. To the cold mixture 4 ml. of 3 N sodium hydroxide followed by 4 ml. of 30% hydrogen peroxide was added slowly. After 1.5 hr. 50 ml. of ether was added to the reaction mixture; the organic layer was separated and washed with water. The ether layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 2.38 g. of a mixture of alcohols XVI and XVII; λ_{max}^{KBr} 2.98, 9.4, and 9.52 μ.

Preparation of XVIII and XIX.—A solution of 2.37 g. of the above alcohol mixture in 30 ml. of anhydrous pyridine was added to a mixture of 3 g. of chromic anhydride and 30 ml. of anhydrous pyridine. The reaction mixture was stirred for 14 hr. at room temperature after which it was poured into ice–water. The aqueous solution was extracted with ether, the extract was washed, respectively, with 5% cold hydrochloric acid and 5% cold sodium hydroxide solution. The organic layer was dried over anhydrous magnesium sulfate and removal of the solvent yielded 2.27 g. of crude ketonic product. Chromatography of the mixture of ketones on alumina and elution with petroleum ether–benzene gave first 0.44 g. of pure XIX (m.p. 146–148°; λ_{max}^{KBr} 5.81 μ; n.m.r. δ 0.85 (3), 0.88 (3), 1.07 (3), and 2.17), then 0.422 g. of a mixture of XVIII and XIX, and finally 1.12 g. of pure XVIII, (m.p. 145–146°; λ_{max}^{KBr} 5.78 μ; n.m.r. δ 0.85 (3), 0.88 (3), 1.02 (3), and 1.82).

Ketone XIX had the following optical rotatory dispersion curve in methanol (c 0.051): $[\alpha]_{589\,m\mu}$ +19.6, $[\alpha]_{342}$ 0°, $[\alpha]_{}$ −1242°, and $[\alpha]_{300}$ −776°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.01. Found: C, 83.18; H, 11.20.

Ketone XVIII had the following optical rotatory dispersion curve in methanol (c 0.051): $[\alpha]_{589\,m\mu}$ +183.2°, $[\alpha]_{308}$ +1145°, and $[\alpha]_{290}$ +760°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.01. Found: C, 82.48; H, 11.16.

Both ketone XVIII and XIX on Huang-Minlon[15,16] reduction gave hydrocarbon V identical in all respects with that previously reported.[17]

Preparation of XXI.—Methyltriphenylphosphonium bromide, 0.6 g. (prepared from methyl bromide and triphenylphosphine),[20] was added to an ethereal solution of n-butyllithium (obtained by addition of 0.21 g. of n-butyl bromide in 5 ml. of anhydrous ether to 0.021 g. of lithium in 5 ml. of ether) under an oxygen-free nitrogen atmosphere. The mixture was stirred for 2 hr. A solution of 0.25 g. of XVIII in 30 ml. of anhydrous ether was added to the mixture and stirring continued for an additional 4 hr. Ether was distilled as anhydrous tetrahydrofuran was added, until most of the ether had been displaced.[21] The reaction mixture was refluxed 6 hr., then allowed to stand at room temperature overnight. The mixture was diluted with 100 ml. of water and extracted with ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate; evaporation of the solvent yielded a gummy mass. Elution of this mixture through neutral alumina (30 g.) with 60 ml. of petroleum ether (b.p. 60–80°) followed by two recrystallizations from methanol yielded 0.220 g. (88.7%) of the olefin XXI, m.p. 57–58°. The analytical sample was obtained by recrystallization from the same solvent and had m.p. 60–61°, lit.[3] (for racemic compound) m.p. 54–55.5°; λ_{max}^{KBr} 3.73, 6.05, 11.3, and 11.45 μ; n.m.r. δ 0.80 (3), 0.83 (3), 0.93 (3), 4.44 (doublet J = 2 c.p.s., one proton), and 4.60 (broad, one proton).

Anal. Calcd. for $C_{20}H_{32}$: C, 88.16; H, 11.83. Found: C, 88.16; H, 11.73.

Acknowledgment.—We gratefully acknowledge support of this investigation by the National Science Foundation (GP-233). We wish to thank Dr. Pierre Crabbé of Syntex, S. A., Mexico D. F., Mexico, for the rotatory dispersion curves. The principal investigator wishes to thank the Research Foundation of Oklahoma State University for making part of his time available during the academic year for directing this research.

(21) F. Sondheimer and R. Mechoulan, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

Erythrina Alkaloids. A Study of the Configurational Interrelationships[1]

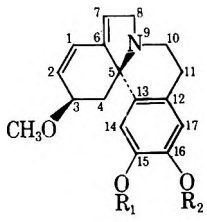
V. BOEKELHEIDE[2] AND MILDRED Y. CHANG[3,4]

Department of Chemistry, University of Rochester, Rochester, New York

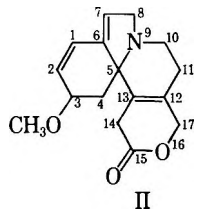
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By the method of molecular rotation differences and by optical rotatory dispersion measurements the aromatic erythrina alkaloids and the erythroidines are shown to have the same configuration at the spiro carbon atom (position 5). Studies directed toward a chemical proof of the configurational interrelationships are described.

The nine known erythrina alkaloids fall into two classes: the aromatic erythrina alkaloids and the erythroidines.[5] The general structure representing most of the aromatic erythrina alkaloids is shown by I and that of β-erythroidine is given by II. α-Erythroidine differs from β-erythroidine in having the aliphatic double bond linking the 13–14- rather than the 12–13-positions, but, since α-erythroidine has been isomerized to β-erythroidine, the configurations at C-3 and C-5 for both α- and β-erythroidine are the same.[6] Likewise, with the exception of erythratine, all of the aromatic erythrina alkaloids have been interrelated and shown to have the same configuration of the spiro carbon atom, C-5.[7] Further, from an X-ray crystallographic study of erythraline hydrobromide[8] and from chemical studies of erysodine and the proof of its structure through synthesis,[9] the relative configurations at C-3 and C-5 are known for the aromatic erythrina alkaloids and the methoxyl and spiro amine groups have a *cis* relationship as shown by I.



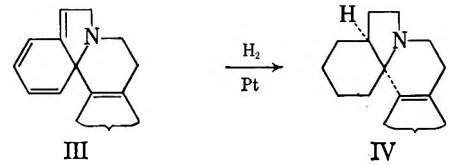
I



II

Thus, for a complete assignment of absolute configurations to essentially all of the erythrina alkaloids only two pieces of information are lacking: (1) a correlation of configuration between the aromatic erythrina alkaloids and the erythroidines, and (2) a determination of the absolute configuration of C-3 or C-5 in one of the alkaloids. The present paper is concerned with the correlation of configuration between the two groups of alkaloids and an accompanying paper describes the determination of the absolute configuration of C-3 in β-erythroidine.[10]

One of the typical reactions encountered in the degradation studies of both the aromatic erythrina alkaloids and the erythroidines was the loss of methanol on treatment with acid to give the corresponding conjugated triene as shown by partial structure III.[11,12] All of the derivatives represented by III have very high negative rotations and on hydrogenation over a platinum catalyst the corresponding saturated derivatives, as represented by partial structure IV, are formed. Since the various molecules represented by structure IV possess only one asymmetric carbon atom, the spiro



III IV

carbon at C-5, and since hydrogenation over platinum leads to a single product which should have the same stereochemistry in each case, all of the requirements for determining the configurational relationships at C-5 by the method of molecular rotation differences[13,14] are met in an ideal fashion. In Table I, the molecular rotations of various examples of both the aromatic erythrina alkaloids and the erythroidines are summarized with regard to those derivatives containing the structural features of III and IV. It is readily apparent that in each case the molecular rotation difference has the same sign and is a large value. Thus, it is safe to conclude that the absolute configuration

TABLE I

MOLECULAR ROTATIONS OF ERYTHRINA DERIVATIVES

Parent alkaloid	Molecular rotation of derivative Structure III	Structure IV	Molecular rotation difference
Erythraline	−2107[a,b]	−95[a]	−2012
Erysodine	−2577[a]	−92[a]	−2485
β-Erythroidine	−1901[c]	−128[c]	−1773
α-Erythroidine	−1952[a,d]	−136[a,e]	−1816

[a] Measured in water. [b] Measured as the hydrobromide. [c] Measured in ethanol. [d] Measured as the perchlorate. [e] This value is for the hexahydrodesmethoxy-β-erythroidine perchlorate which corresponds to the reduction product in this case (see ref. 6).

(1) Paper XVIII in this series. For the preceding communication, see ref. 5.

(2) University of Oregon, Eugene, Ore.

(3) Abstracted from the Ph.D. thesis of M. Y. Chang, University of Rochester, 1959.

(4) Research fellowship grants from the United Cerebral Palsy Association, the Elon Huntington Hooker Fund, the Smith, Kline and French Foundation, Chas. Pfizer and Co., and the Sherman Clarke Fund are gratefully acknowledged.

(5) For a summary of the chemistry of the erythrina alkaloids, see R. H. F. Manske, "The Alkaloids," Vol. VII, Academic Press, New York, N. Y., 1960, Chapter 11.

(6) V. Boekelheide and G. C. Morrison, *J. Am. Chem. Soc.*, **80**, 3905 (1958).

(7) The numbering of the erythrina alkaloids follows that devised earlier as a common numbering for all the erythrina alkaloids [V. Boekelheide and V. Prelog, "Progress in Organic Chemistry," Vol. III, J. W. Cook, Ed., Butterworths, Scientific Publications, London, 1955, Chapter 5].

(8) W. Nowacki and G. F. Bonsma, *Z. Kryst.* **110**, 89 (1958).

(9) V. Prelog, A. Langemann, O. Rodig, and M. Ternbah, *Helv. Chim. Acta*, **42**, 1301 (1959).

(10) V. Boekelheide and G. Wenzinger, *J. Org. Chem.*, **29**, 1307 (1964).

(11) G. L. Sauvage and V. Boekelheide, *J. Am. Chem. Soc.*, **72**, 2062 (1950); V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage, and E. J. Agnello, *ibid.*, **75**, 2550 (1953); V. Boekelheide and M. F. Grundon, *ibid.*, **75**, 2563 (1953).

(12) M. Carmack, B. C. McKusick, and V. Prelog, *Helv. Chim. Acta*, **34**, 1601 (1951).

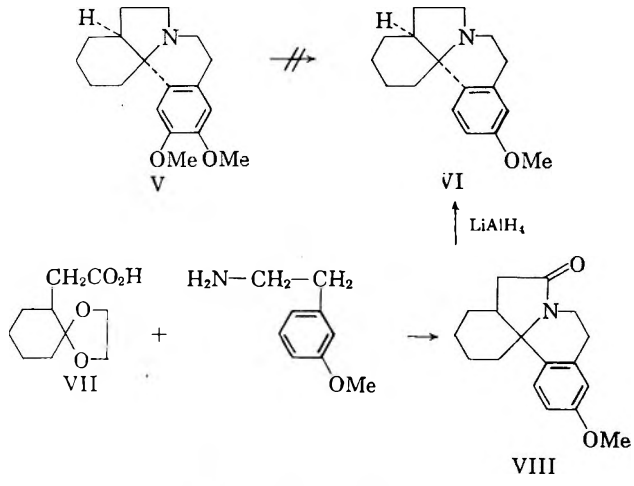
(13) K. Freudenberg, *Ber.*, **66**, 177 (1933).

(14) W. Klyne, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, Chapter 3.

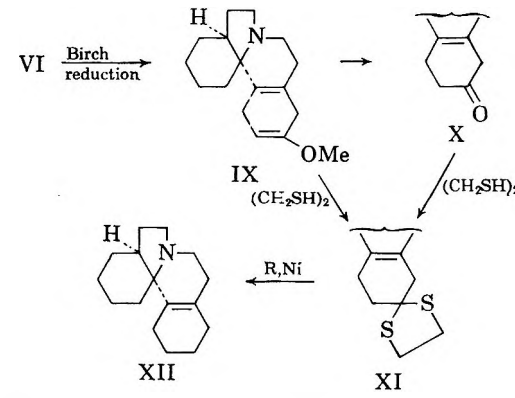
of the spiro carbon, C-5, is the same for both the erythroidines and the aromatic erythrina alkaloids.

Comparison by optical rotatory dispersion was also investigated. In the case of the aromatic erythrina alkaloids, hexahydroapoerysotrine (V) has been a key compound for interrelating the various alkaloids,[12] and its structure has been established by synthesis.[15-17] Mondon has clearly shown through an extension of his earlier synthetic studies that V has the *cis*-octahydroindole ring fusion shown by V.[18,19] The levorotatory enantiomorph of V, which corresponds to the natural series and is commonly designated as (−)-15,16-dimethoxy-*cis*-5,6-erythrinane, has been examined and its optical rotatory dispersion curve is almost superimposable with that of β-tetrahydro-β-erythroidine throughout the region of 320 to 650 mμ (see Experimental).[20] Although no Cotton effect is observed in this region, the close correspondence of the curves and the fairly large rotations observed strongly suggest that the two derivatives must have the same configuration at the spiro carbon atom, C-5, which is in agreement with the conclusions reached previously.

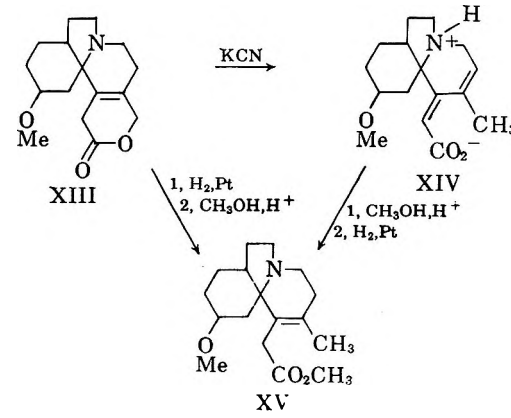
It was of interest to investigate a chemical correlation of the configuration at C-5 as well, both as a complement to the optical method and because of the intrinsic interest in these compounds. 14,15, 16,17-Tetrahydroerythrinane (XII) was the compound chosen for comparison. It was anticipated that the degradation of a member of the aromatic erythrina alkaloids to this compound and the synthetic elaboration of β-erythroidine to this stage would be tasks of comparable difficulty. Since the readily available (−)-15,16-dimethoxyerythrinane (V) has been shown to be identical with hexahydroapoerysotrine and, therefore, has the same configuration at C-5 as the naturally occurring aromatic erythrina alkaloids,[15,17] this was selected as a starting material. However, various attempts to convert it to a monomethoxyerythrinane such as VI were without success. The independent synthesis of VI was then carried out following the Mondon procedure.[16] Condensation of *m*-methoxyphenethylamine with the ketal acid VII occurred smoothly in 70% yield to give VIII which on lithium aluminum hydride reduction led to 16-methoxyerythrinane (VI) in essentially quantitative yield.



Resolution of 16-methoxyerythrinane was readily accomplished using dibenzoyl-L-(+)-tartaric acid. The levorotatory enantiomorph and (−)-15,16-dimethoxyerythrinane were compared through their dibenzoyl-L-(+)-tartrate derivatives and shown to have essentially superimposable optical rotatory dispersion curves. Thus, it is clear that (−)-16-methoxyerythrinane has the same configuration at C-5 as the natural series and so the remaining steps in the degradation to XII were explored. A Birch reduction of racemic 16-methoxyerythrinane proceeded cleanly in 80% yield to the dihydro derivative IX. Acid hydrolysis of IX gave the corresponding ketone X which could be isolated as the picrate but was rather unstable as the free base. Reaction of the ketone X with 1,2-ethanedithiol readily gave the thioketal XI. Later it was found that the enol ether IX was converted directly to the thioketal XI by treatment with 1,2-ethanedithiol and this is a more efficient procedure. Finally, Raney nickel desulfurization of the thioketal XI yielded 14,15,16,17-tetrahydroerythrinane (XII) identical in all respects with the racemic 14,15,16,17-tetrahydroerythrinane prepared previously by independent syntheses.[17]



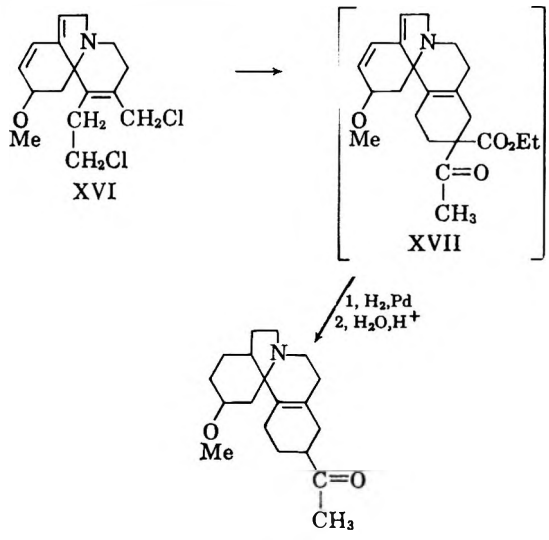
With a route thus available for obtaining optically active 14,15,16,17-tetrahydroerythrinane related to the aromatic alkaloids, attention turned to the conversion of β-erythroidine to an intermediate of the same structure. Although hexahydrodesmethoxy-β-erythroidine is the logical starting material for conversion to XII, the more readily accessible tetrahydro-β-erythroidine (XIII) was employed in the preliminary studies directed toward finding a suitable method for transform-



(15) B. Belleau, *Can. J. Chem.*, **35**, 651 (1957).
(16) A. Mondon, *Angew. Chem.*, **68**, 578 (1956).
(17) V. Boekelheide, M. Müller, J. Jack, T. T. Grossnickle, and M. Chang, *J. Am. Chem. Soc.*, **81**, 3955 (1959).
(18) A. Mondon, *Ann.*, **628**, 123 (1959).
(19) A. Mondon and K. F. Hansen, *Tetrahedron Letters*, [**14**], 5 (1960).
(20) We are indebted to Professor W. C. Wildman for these measurements which were made at the National Heart Institute, Washington, D. C.

ing the δ-lactone ring to a cyclohexene ring. One method investigated for introducing the extra carbon needed was the SN2 displacement of the allylic ester grouping by cyanide ion. However, the expected displacement did not occur; instead, the cyanide ion served as a base effecting elimination with ring opening to give XIV. The structure of XIV is based on spectral data plus its conversion *via* esterification and hydrogenation to a product identical with that obtained by direct hydrogenolysis of XIII followed by esterification.

It has been shown previously that β-erythroidine on reduction with lithium aluminum hydride to the diol followed by reaction with thionyl chloride gives the dichloro derivative XVI.[21] This seemed an attractive starting material and, on treating it with ethyl acetoacetate in *t*-butyl alcohol using potassium *t*-butoxide as catalyst, condensation was effected to give XVII. This product was unstable and difficult to purify. It was, therefore, hydrogenated and then hydrolyzed directly to give the ketone XVIII. However, attempts to remove the acetyl group and to utilize this as a route for the conversion of β-erythroidine to 14,15,16,17-tetrahydroerythrinane have been unsuccessful.



In view of the chemical determination of the absolute configuration of C-3 in β-erythroidine[22] and the recent X-ray crystallographic study of Hanson[23] defining the relative and absolute configurations of dihydro-β-erythroidine hydrobromide, the absolute configurations of both the erythroidines and the aromatic erythrina alkaloids can now be assigned[10] and work directed toward a chemical correlation of the two groups has been terminated.

Experimental[24]

16-Methoxy-8-oxoerythrinane (VIII).—A mixture of 388 mg. of *m*-methoxyphenethylamine hydrochloride[25] and 485 mg. of the ketal acid VII[17] was heated under a nitrogen atmosphere with stirring for 5 hr. The resulting viscous oil was dissolved in chloroform and washed successively with dilute aqueous hydrochloric acid, aqueous sodium carbonate, and then water. The chloroform solution was dried over sodium sulfate and then chromatographed over neutral alumina (Woelm, grade III). Concentration of the eluate gave an oil which crystallized on standing. This was recrystallized from ether to give 393 mg. (70%) of white crystals, m.p. 111–112°, $\gamma_{C=O}$ 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Found: C, 75.08; H, 7.65.

16-Methoxyerythrinane (VI).—A solution of 730 mg. of the lactam VIII in 100 ml. of dry benzene was added with stirring to a boiling solution of 2.0 g. of lithium aluminum hydride in 60 ml. of ether. After the mixture had boiled under reflux for 18 hr., it was cooled and the excess lithium aluminum hydride was destroyed with ethyl acetate. Dropwise addition of a saturated aqueous solution of sodium sulfate was continued until the metallic hydroxides separated as a granular precipitate. The precipitate was removed by filtration and the filtrate was extracted with 5 *N* hydrochloric acid. When the acidic solution was made basic, the oil that separated was extracted with ether and dried; the ether solution was concentrated. Distillation of the residue using a short-path still gave 688 mg. of a light yellow oil, b.p. 115–140° (10^{-2} mm.). This was converted directly to the picrate which, after recrystallization from acetone, melted at 171–173° dec.

Anal. Calcd. for $C_{23}H_{26}N_4O_8$: C, 56.78; H, 5.39. Found: C, 56.77; H, 5.44.

The **resolution** of VI was carried out by adding dropwise a solution of dibenzoyl-L-(+)-tartaric acid in ethyl acetate to a solution of the amine (regenerated from the picrate) in ethyl acetate. The precipitate was recrystallized from acetone several times until its melting point remained constant. It was obtained as white crystals, m.p. 126–127°, $[\alpha]^{26}D$ −91.46° (*c* 1.04, ethanol).

Anal. Calcd. for $C_{35}H_{37}NO_9$: C, 68.28; H, 6.06. Found: C, 68.16; H, 6.01.

In a similar manner treatment of the amine with dibenzoyl-D-(−)-tartaric acid yielded, after recrystallization from acetone, white crystals, m.p. 124–125°, $[\alpha]^{29}D$ +92.61° (*c* 1.04, ethanol).

Anal. Calcd. for $C_{35}H_{37}NO_9$: C, 68.28; H, 6.06. Found: C, 67.98; H, 6.42.

Optical Rotatory Dispersion Studies.[20]—The general comparison of the optical rotatory dispersion curves and the indication of their close correspondence is described in the discussion. This information is presented in Table II for selected points from the curve.

14,17-Dihydro-16-methoxyerythrinane (IX).—To a stirred solution of 620 mg. of 16-methoxyerythrinane (VI) in 55 ml. of anhydrous ether there was added 70 ml. of liquid ammonia followed by 160 mg. of lithium as small pieces. After 10 min., absolute ethanol was added dropwise at such a rate that the blue color was discharged in about 10 min. The ammonia was allowed to evaporate and water was added to the residue. Then, the basic aqueous solution was extracted with ether and the combined ether extracts, after washing with water, were dried over sodium sulfate. Concentration of the ether solution gave a solid which was sublimed at 70–80° (0.1 mm.). This gave 500 mg. (80%) of white crystals, m.p. 84–86°.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.72. Found: C, 78.33; H, 9.58.

The **picrate** of IX was prepared in ethanol and, after recrystallization from acetone, was isolated as yellow crystals, m.p. 157–160° dec.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.55; H, 5.78. Found: C, 56.54; H, 5.97.

14,15,16,17-Tetrahydro-16-oxoerythrinane (X).—Sufficient methanol was added to dissolve 149 mg. of 14,17-dihydro-16-methoxyerythrinane (IX) and then a solution of 500 mg. of oxalic acid dihydrate in 6.5 ml. of water was added dropwise with swirling until the solution became cloudy. The mixture was allowed to stand at room temperature for 1 hr. and then it was cooled in an ice bath and made basic by addition of sodium bicarbonate.

(21) M. F. Grundon, G. L. Sauvage, and V. Boekelheide, *J. Am. Chem. Soc.*, **75**, 2541 (1953).

(22) G. R. Wenzinger and V. Boekelheide, *Proc. Chem. Soc.*, 53 (1963).

(23) A. W. Hanson, *ibid.*, 52 (1963).

(24) Analyses were by A. Smith, T. Montzka, and the Micro-Tech Laboratories. All melting points are corrected.

(25) L. Helfer [*Helv. Chim. Acta*, **7**, 948 (1924)] has previously reported the preparation of *m*-methoxyphenethylamine but gives the melting point of the hydrochloride as 145–146°. Our sample of *m*-methoxyphenethylamine, prepared by the catalytic hydrogenation [K. Kindler, B. Hedemann, and E. Scharfe, *Ann.*, **560**, 215 (1948)] of 3-methoxy-β-nitrostyrene [J. B. Shoesmith and R. H. Connor, *J. Chem. Soc.*, 2232 (1927)] in 61% yield, agreed with Helfer's description in other respects but the hydrochloride melted at 136–137°. (*Anal.* Calcd. for $C_9H_{11}NOCl$: C, 57.60; H, 7.52. Found: C, 57.83; H, 7.43.)

TABLE II. OPTICAL ROTATORY DISPERSION, $[\alpha]_{\lambda}^{25}$

Compound	c	λ[a] 650	589	460	380	320
(+)-15,16-Dimethoxyerythrinane dibenzoyl-D-(−)-tartrate	0.89	+68	+90	+180	+345	+765
(−)-15,16-Dimethoxyerythrinane dibenzoyl-L-(+)-tartrate	0.95	−70	−93	−180	−350	−760
(−)-16-Methoxyerythrinane dibenzoyl-L-(+)-tartrate	0.79	−70	−90	−177	−350	−740
(−)-Tetrahydro-β-erythroidine dibenzoyl-L-(+)-tartrate	0.80	−60	−77	−157	−333	−710

[a] Run in ethanol, λ in mμ.

The basic solution was extracted with ether, the ether extracts were dried, and the solvent was removed under reduced pressure. This left 139 mg. of a yellow oil (carbonyl absorption at 1720 $cm.^{-1}$) which was unstable and purification attempts indicated rapid decomposition. It was, therefore, treated directly with ethanolic picric acid and the resulting solid, after recrystallization from ethanol, gave yellow crystals, m.p. 189–193 dec.

Anal. Calcd. for $C_{32}H_{36}N_4O_8$: C, 55.69; H, 5.52. Found: C, 55.38; H, 5.57.

14,15,16,17-Tetrahydro-16-oxoerythrinane Ethylene Thioketal (XI).—A solution of 130 mg. of X (regenerated from the picrate) in 200 mg. of 1,2-ethanedithiol was cooled in an ice bath and dry hydrogen chloride was bubbled through the mixture. At the end of 3 hr., the mixture was diluted with ether and the whole was made basic with a concentrated aqueous sodium hydroxide solution. The ether layer was separated, dried, and concentrated to give 147 mg. of a clear viscous oil (no carbonyl absorption in the infrared). This was converted directly to the picrate which, after recrystallization from methanol, was obtained as yellow crystals, m.p. 180–182°, liquid crystals, 186–189°. This melting point behavior was reproducible and unchanged by further recrystallization from methanol.

Anal. Calcd. for $C_{24}H_{30}N_4O_7S_2$: C, 52.35; H, 5.49; N, 10.18. Found: C, 52.30; H, 5.31; N, 10.21.

When 165 mg. of IX was treated directly with 1,2-ethanedithiol in the same manner as described above, it was converted in essentially quantitative yield to XI, isolated as the picrate. The picrates from the two preparations were shown to be identical by a mixture melting point determination and by comparison of their infrared spectra.

14,15,16,17-Tetrahydroerythrinane (XII).—An ethanolic solution of 231 mg. of XI containing prepared Raney nickel catalyst was boiled under reflux under 1 atm. of hydrogen for 11 hr. After removal of the catalyst, the solution was concentrated under reduced pressure to give 163 mg. of a colorless oil. This was converted to the picrate which, after recrystallization from ethanol, melted at 152–155°. This was shown to be identical with an authentic sample of the picrate of racemic 14,15,16,17-tetrahydroerythrinane prepared previously[27] by a mixture melting point determination and a comparison of infrared spectra.

Reaction of Tetrahydro-β-erythroidine (XIII) with Potassium Cyanide to Give XIV.[26]—A mixture of 1.05 g. of tetrahydro-β-erythroidine[11b] and 1.0 g. of potassium cyanide was slowly warmed without solvent under a nitrogen atmosphere. The mixture melted and at 160° some effervescence occurred. The temperature was allowed to rise to 200° before the mixture was removed and allowed to cool. It was then extracted with chloroform and examination of the chloroform extract in the infrared indicated the presence of the $\equiv NH^+$, $-OCH_3$, and $-C{=}CCOO^-$ functional groups as required by XIV. For ease of handling, the zwitterion XIV was then converted to the corresponding methyl ester by removing the chloroform and heating the residue with methanolic hydrogen chloride. After removal of the methanol the residue was subjected to chromatography over powdered cellulose using a series of aqueous citrate–phoshate buffers starting at a pH of 6 and extending to a pH of 2.5. The main product was isolated from the eluate at pH 4 by treatment with ammonia and extraction with ether. The ether extract, after drying and concentration, gave a pale yellow oil, b.p. 148–156° (0.003 mm.), R_f (pH 4.0) 0.36. As would be expected for the methyl ester of XIV, the n.m.r. spectrum in deuteriochloroform showed signals at τ 6.22 and 6.72 corresponding to the ester and ether methoxyls, signals at τ 4.15 and 4.35 corresponding to the vinyl protons, and a signal at τ 8.19 corresponding to the allylic methyl protons.

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81; $-OCH_3$, 21.31. Found: C, 69.89; H, 8.75; N, 4.71; $-OCH_3$, 20.89.

The above experiment was repeated but, instead of subjecting the ester to chromatography over powdered cellulose, it was hydrogenated using platinum as a catalyst. This was then followed by purification through countercurrent distribution using chloroform and a citrate–phosphate buffer (pH 4.2) with 40 exchanges. The main product, isolated from tubes 30–38, was obtained as a solid in 47% yield. This, after recrystallization from acetone, gave white crystals, m.p. 135–136°. By a mixture melting point determination and comparison of infrared spectra, this was shown to be identical with XV obtained in the hydrogenolysis experiment following.

Hydrogenolysis of Tetrahydro-β-erythroidine to Give XV.—A solution of 5.0 g. of β-erythroidine hydrochloride in 50 ml. of water containing 600 mg. of platinum oxide catalyst was subjected to hydrogenation at 3-atm. pressure and room temperature for 36 hr. After removal of the catalyst, the solution was made basic and extraction with chloroform. Concentration of the chloroform extract followed by conversion of the residue to its picrate derivative gave yellow crystals, m.p. 213–214°. These were shown to be identical with tetrahydro-β-erythroidine picrate and corresponded to a 22% yield.[27]

The aqueous basic solution was then evaporated to dryness and the residue was taken up in methanolic hydrogen chloride. This solution was boiled under reflux for 4 hr. to convert the acid to the corresponding methyl ester. It was then concentrated, the residue was treated with aqueous ammonia, and the solution was extracted with chloroform. Concentration of the chloroform gave 3.1 g. (68%) of a light tan solid. This, after recrystallization from acetone, yielded white prisms, m.p. 135–136°.

Anal. Calcd. for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.79; H, 8.88; N, 4.90.

16-Acetyl-3-methoxyl-14,15,16,17-tetrahydroerythrinane (XVIII).[28]—To a solution of 440 mg. of potassium in 75 ml. of dry *t*-butyl alcohol there was first added 1.46 g. of ethyl acetoacetate and then dropwise with stirring a solution of 3.53 g. of dichlorodesoxy-β-erythroidinol (XVI)[21] in 200 ml. of dry *t*-butyl alcohol. The solution was boiled under reflux for 20 min. and then, after an additional 440 mg. of potassium in 75 ml. of *t*-butyl alcohol was added, it was boiled under reflux for 6 hr. The precipitate was removed and the solution was concentrated to give 3.99 g. of an oil, which gave a negative Beilstein test for chloride. This oil was dissolved in 330 ml. of ethanol containing 2.5 ml. of concentrated hydrochloric acid and was subjected to hydrogenation using 2.5 g. of a 5% palladium-on-charcoal catalyst at room temperature and atmospheric pressure. After removal of the catalyst and solvent, the residual oil was dissolved in 150 ml. of 3 *N* hydrochloric acid and boiled under reflux for 5 hr. The cooled solution was made alkaline and extracted with benzene and then ether. The combined extracts were washed with water and then concentrated leaving 1.86 g. (58%) of an oil showing a strong carbonyl absorption at 5.85 μ. This was

(26) We thank Dr. K. Butler for working out the experimental details of this reaction.

(27) V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage, and E. J. Agnello, *J. Am. Chem. Soc.*, **75**, 2550 (1953).

(28) We thank Dr. T. T. Grossnickle for working out the experimental details of this reaction.

• treated with ethanolic picrolonic acid to give 2.1 g. of yellow crystals, m.p. 213–215° dec. After recrystallization from ethanol, the picrolonate of XVIII was obtained as yellow crystals, m.p. 216–217° dec.

Anal. Calcd. for $C_{29}H_{37}N_5O_7$: C, 61.36; H, 6.57; N, 12.34. Found: C, 61.32; H, 6.28; N, 12.51.

Regeneration of the free base (XVIII) from the picrolonate followed by distillation using a short-path still gave a pale yellow oil, b.p. 150° (10^{-4} mm.), $[\alpha]^{25}$ +126.0°, $\lambda_{C=O}$ 5.85 μ.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62 $-OCH_3$, 10.23. Found: C, 75.21; H, 9.40; N, 4.51; $-OCH_3$ 10.35.

The Absolute Configurations of the Erythrina Alkaloids[1]

V. BOEKELHEIDE[2] AND GEORGE R. WENZINGER[3,4]

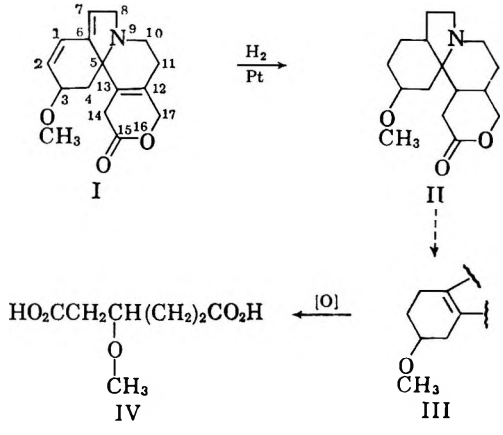
Department of Chemistry, University of Rochester, Rochester, New York

Received July 22, 1963

A degradation of β-erythroidine has been accomplished which allows a correlation between the absolute configuration of the asymmetric atom at C-3 of β-erythroidine and the levorotatory (3*S*)-3-methoxyadipic acid. This combined with other available data allows the assignment of the absolute configuration of β-erythroidine as 3*R*,5*S*. Further, the implications of these results with respect to the other erythrina alkaloids are discussed and absolute configurational assignments are made for these as well.

Although the erythrina alkaloids have been subjected to extensive degradative and synthetic investigations,[5] the relative and absolute configurations of these alkaloids have largely remained as important problems to be settled. In attempting to resolve these questions, we have approached the over-all problem from two points of view. First, the configurational relationships existing among the various erythrina alkaloids have been studied.[1] Secondly, we have undertaken the determination of the absolute configuration of one of the asymmetric atoms of one of the key alkaloids. The combination of data would thus allow complete configurational assignments for all the important erythrina alkaloids. The present communication presents the details of the accomplishment of these objectives.[6]

Of the asymmetric atoms present in the various erythrina alkaloids the most feasible one from the point of view of degradation and ease of correlation with a molecule of known absolute configuration appeared to be the asymmetric carbon at C-3 of β-erythroidine (I). From previous studies,[7,8] it was known that the spiro amine nitrogen is readily removed through a series of Hofmann degradations and by starting with tetrahydro-β-erythroidine (II) such a degradation might yield a derivative having the general features shown by III. Oxidation of III could then yield optically active β-methoxyadipic acid (IV) for which the absolute configuration of each enantiomorph is known[9] because of its role in the elucidation of the absolute configuration of steroids.[10,11]



Preliminary studies on the Hofmann degradation of tetrahydro-β-erythroidine (II), however, led to a mixture of products indicating that, in part, opening of the lactone ring was occurring followed by decarboxylation. To circumvent this the corresponding diol (V) was employed, but in this case the Hofmann reaction was accompanied by some dehydration, leading again to a mixture of products. Treatment of the diol V with phosphoric acid readily converted it to the dihydropyran derivative VI and this now underwent the Hofmann reaction smoothly and cleanly to give VII. The formation of VII being favored in the first step of the Hofmann reaction could be predicted by analogy to the behavior of tetrahydroerythraline[12] as well as from theoretical considerations.[13] The spectral properties of VII are in full accord with this assignment. In the infrared the characteristic absorption bands of a vinyl group are present at 900–915 and at 1000 cm.$^{-1}$. These disappear on hydrogenation. The ultraviolet absorption spectrum of VII has a broad maximum at 238 mμ (log ϵ 3.97) as would be expected.[14] Finally the n.m.r. spectrum of VII shows a clear quartet at τ 2.64 corresponding to the lone internal vinyl hydrogen and a pair of doublets centered at τ 5.07 corresponding to the terminal methylene protons. The approximate coupling constants for the *cis* and *trans* protons are 10.0 and 16.4 c.p.s.

(1) Paper XIX in this series. For the preceding communication, see V. Boekelheide and M. Chang, *J. Org. Chem.*, **29**, 1303 (1964).

(2) University of Oregon, Eugene, Ore.

(3) Abstracted from the Ph.D. thesis of G. R. Wenzinger, University of Rochester, 1960.

(4) Research fellowship grants from Chas. Pfizer and Co., E. I. du Pont de Nemours, the Sherman Clarke Fund, the Elon Huntington Hooker Fund, and the National Science Foundation are gratefully acknowledged.

(5) For a summary of the chemistry of the erythrina alkaloids, see R. H. F. Manske, "The Alkaloids," Vol. VII, Academic Press, New York, N. Y., 1960, Chapter 11.

(6) For preliminary accounts, see G. R. Wenzinger and V. Boekelheide, *Proc. Chem. Soc.*, 53 (1963), and A. W. Hanson, *ibid.*, 52 (1963).

(7) V. Boekelheide and E. J. Agnello *J. Am. Chem. Soc.*, **73**, 2286 (1951).

(8) J. Weinstock and V. Boekelheide, *ibid.*, **75**, 2546 (1954).

(9) M. Viscontini and P. Miglioretto *Helv. Chim. Acta*, **38**, 930 (1955).

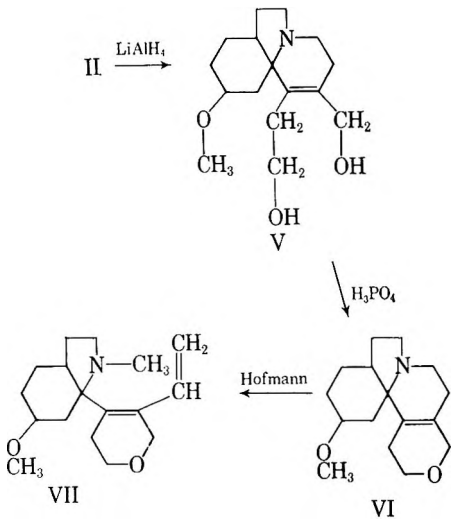
(10) S. Bergstrom, A. Lardon, and T. Reichstein, *ibid.*, **32**, 2 (1949).

(11) K. Brenneisen, Ch. Tamm, and T. Reichstein *ibid.*, **39**, 1233 (1956).

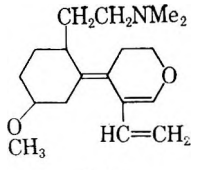
(12) G. W. Kenner, G. H. Khorana, and V. Prelog, *ibid.*, **34**, 1969 (1951).

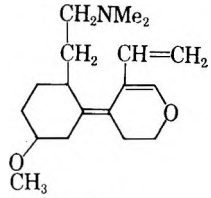
(13) A. C. Cope and E. E. Schweizer, *J. Am. Chem. Soc.*, **81**, 4577 (1959); *cf.* D. V. Banthorpe, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 4054 (1960), and references cited therein.

(14) R. B. Woodward, *J. Am. Chem. Soc.*, **64**, 72 (1942).



The second step in the Hofmann degradation occurred smoothly with VII but did not lead to the desired introduction of a second vinyl group. Instead a mixture of two components resulted and these have been assigned structures VIIIa and VIIIb. This assignment was first deduced on a spectral basis. In the ultraviolet, the mixture of VIIIa and VIIIb showed a broad absorption maximum at 260 mμ (log ε 4.0), indicating a lengthening of the conjugated system. That the additional conjugation was due to an enol ether grouping was suggested by intense absorption in the infrared at 1588 cm.$^{-1}$.[15,16] In confirmation of this VIII was readily hydrolyzed by dilute acid to give a mixture of carbonyl compounds. Although the Hofmann decomposition to give the mixture of VIIIa and VIIIb was not anticipated, it is readily understandable simply as a vinylogous Hofmann reaction. Several eliminations of this type have been noted recently.[17-19]

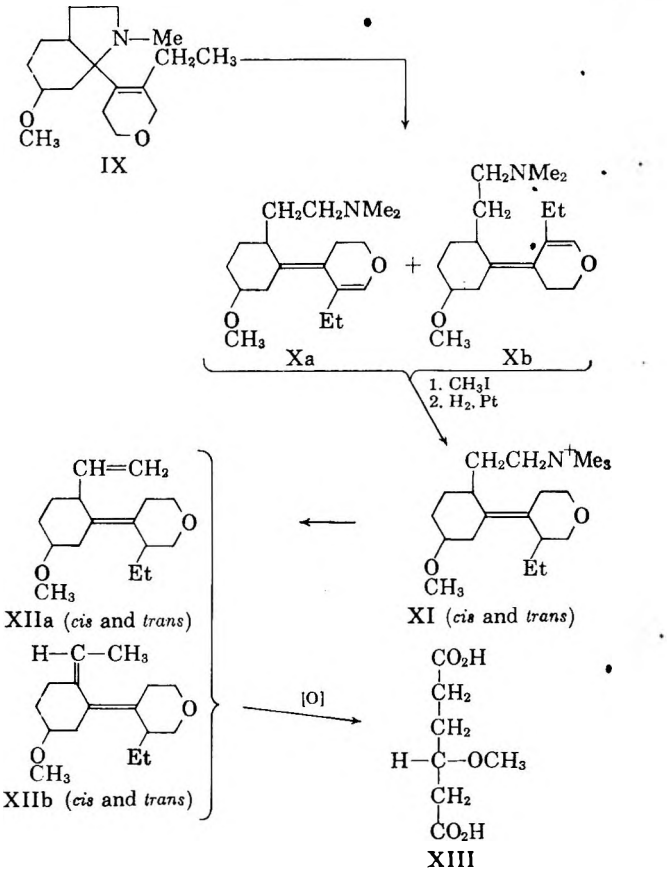

VIIIa


VIIIb

In the hope of altering the course of this Hofmann elimination, VII was first hydrogenated to give IX and then subjected to the Hofmann decomposition. But again, the product proved to be a mixture (Xa and Xb) in which the presence of the enol ether grouping was easily demonstrated. In the n.m.r., there was a signal for the single vinyl proton (τ 3.94) as well as appropriate signals for the other relevant features—the ethyl side chain (triplet, τ 9.09), the methoxyl (singlet, τ 6.72), and the dimethylamino group (6 protons, τ 7.82). The ultraviolet absorption spectrum was essentially the same as that for the mixture of VIIIa and VIIIb. A further Hofmann elimination of X gave products which were apparently aromatic.

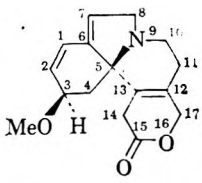
(15) G. D. Meakens, *J. Chem. Soc.*, 4170 (1953).
(16) W. H. T. Davidson and G. R. Bates, *ibid.*, 697 (1960).
(17) H. E. Winberg, F. S. Fawcett, W. E. Mochel, and G. W. Theobald, *J. Am. Chem. Soc.*, **82**, 1428 (1960).
(18) L. A. Errede, *ibid.*, **83**, 949 (1961).
(19) W. von Philipsborn, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **38**, 1067 (1955).

SCHEME I

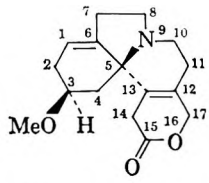


To avoid this, hydrogenation of X was carried out. The difference in rate of reduction of the tri- and tetrasubstituted double bonds is sufficiently large to allow a clean reduction of only the trisubstituted double bond. The resulting mixture was transparent in the ultraviolet and its other spectral characteristics were in keeping with structure XI. A final Hofmann degradation of XI then yielded trimethylamine and a mixture of hydrocarbons (XIIa and XIIb). The spectral characteristics of this mixture showed the presence of both the vinyl and ethylidene groups and, based on their integrated areas in the n.m.r. spectrum, the ratio of XIIa to XIIb is about 65:35. On hydrogenation XII absorbed 1 mole of hydrogen, transforming the vinyl and ethylidene side chains to a common ethyl group and causing the loss of the broad maximum at 240 mμ of the diene system. (See Scheme I.)

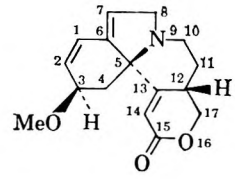
Various attempts to separate the mixture of hydrocarbons represented by XIIa and XIIb, including vapor phase chromatography, were unsuccessful. Therefore, methods of oxidizing the mixture which would lead directly to β-methoxyadipic acid were explored. The most feasible proved to be direct oxidation with acid permanganate. The resulting mixture of acids was separated by countercurrent distribution and the fraction identified as β-methoxyadipic acid was isolated as the crystalline (*S*)-benzylthiuronium salt. The infrared solution spectrum of this derivative was shown to be essentially superimposable with that of an authentic specimen of the (*S*)-benzylthiuronium salt of β-methoxyadipic acid. Although the rotation of our sample from the degradation was low, it was definitely levorotatory and establishes the acid to be (3*S*)-3-



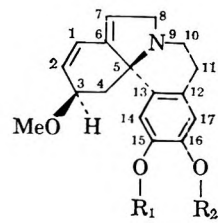
(3*R*,5*S*)-β-Erythroidine



(3*R*,5*S*)-Dihydro-β-erythroidine



(3*R*,5*S*,12*S*)-α-Erythroidine



3*R*,5*S* aromatic erythrina alkaloids
Erysopine, $R_1 = R_2 = -H$
Erythraline, $R_1 = R_2 = -CH_2-$
Erysodine, R_1 or $R_2 = -H$
Erysovine, R_1 or $R_2 = -CH_3$

methoxyadipic acid. This in turn establishes the asymmetric carbon at C-3 in β-erythroidine as having the absolute *R* configuration.

It is possible by a series of logical arguments to deduce the configuration of the spiro carbon at C-5 relative to C-3.[20a] This then leads to the complete assignment of absolute configuration as (3*R*,5*S*)-β-erythroidine. Fortunately, this matter has now been settled beyond question by the recent X-ray crystallographic investigation of dihydro-β-erythroidine hydrobromide by Hanson.[6] These studies established the relative configuration of dihydro-β-erythroidine to be as shown and as predicted for β-erythroidine. In addition Hanson was able to establish the absolute configuration as well and these are 3*R* and 5*S* in verification of the conclusions of the present chemical study.

Although the well-established methods of X-ray crystallography and chemical interrelationship of configuration leave no doubt that the absolute configuration of β-erythroidine is 3*R*,5*S*, Weiss and Ziffer have recently proposed the opposite absolute configuration for β-erythroidine based on arguments from optical rotatory dispersion measurements.[20b] These arguments assume a definable connection between the sign of the Cotton effect and the chirality of the transoid diene chromophore, neglecting contributions from the C-3 and C-5 asymmetric carbons. Although the reasons for the discrepancy in applying the chirality rule to β-erythroidine are not clear, it is apparent that their choice of compounds was unfortunate. Application of their arguments to the corresponding triene, desmethoxy-β-erythroidine, gives an opposite result from that of β-erythroidine. Thus, as we have shown,[1] the sign of the Cotton effect for desmethoxy-β-erythroidine is negative and the deduction using Weiss and Ziffer's arguments about the chirality of the triene lead to an assignment of absolute configuration for desmethoxy-β-erythroidine of 5*S* which then is in agreement with the findings from X-ray crystallography and our present chemical evidence.

It is of interest that the results of the X-ray study also fix the position of the double bond in dihydro-β-erythroidine as being between C-1–C-6 rather than C-6–C-7. In the past there had not been an adequate basis for deciding between these two possibilities although the assignment made to dihydro-β-erythroidine[21] proves to have been correct. The assignments made to the dihydro derivatives in the aromatic series[22,23] probably need to be re-evaluated.

The conversion of α-erythroidine to β-erythroidine establishes that both have the same configuration at C-3 and C-5.[24] Recently, Hill and Schearer have related (+)-O-ethylphenyl 3-tetrahydrofuryl ketone, a degradation product of α-erythroidine,[25] to (+)-methylsuccinic acid.[26] This allows the deduction that C-12 in α-erythroidine has the absolute *S* configuration and allows the formulation of the whole molecule as shown.

In the case of the aromatic erythrina alkaloids, the relative configurations at C-3 and C-5 have been established by chemical interrelationship,[5,23] by X-ray crystallography,[27] and by synthesis.[28] However, the absolute configurations have not been known. In view of the determination of the absolute configuration of the erythroidines and the evidence in the accompanying paper that the configuration at C-5 is the same for both the erythroidines and the aromatic erythrina alkaloids, a total assignment of configuration of the aromatic series can be given as shown. The extension of assignments of absolute configuration from these to the other aromatic erythrina alkaloids is obvious from existing data[5] and requires no further comment.

Experimental[29]

Tetrahydro-β-erythroidinol (V).—A solution of 28.4 g. of tetrahydro-β-erythroidine[21] in a minimum amount of ether was added dropwise to a stirred suspension of 5.75 g. of lithium aluminum hydride in 1.5 l. of anhydrous ether. When addition was complete, the mixture was boiled under reflux for 3 hr. and then stirred at room temperature overnight. The complex was decomposed by the careful addition of a saturated solution of sodium sulfate, causing the separation of a granular precipitate. After removal of the precipitate and concentration of the ether solution, the residual oil was distilled to give 20.7 g. (73%) of a viscous yellow oil, b.p. 180° (0.1 mm.).

Anal. Calcd. for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67. Found: C, 68.45; H, 9.95.

Anhydrotetrahydro-β-erythroidinol (VI).—A solution of 18.8 g. of tetrahydro-β-erythroidinol (V) in 130 ml. of 85% phosphoric acid was heated under an atmosphere of nitrogen at 115° for 7.5 hr. The mixture was then cooled and poured onto ice giving a total volume of about 300 ml. The phosphoric acid was neutralized with potassium carbonate and the oil that separated was

(20)(a) M. Y. Chang, Ph.D. thesis, University of Rochester, 1959; (b) U. Weiss and H. Ziffer, *Experientia*, **19**, 108 (1963). In their paper, Weiss and Ziffer assign β-erythroidine the 5*S* configuration but it is evident that this is the result of a mistake in their use of the Cahn-Ingold-Prelog convention and the logic of their argument as well as their illustration is for a 5*R* assignment.

(21) V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage, and E. J. Agnello, *J. Am. Chem. Soc.*, **75**, 2550 (1953).

(22) M. Carmack, B. C. McKusick, and V. Prelog, *Helv. Chim. Acta*, **34**, 1601 (1951).

(23) V. Prelog, *Angew. Chem.*, **69**, 33 (1957).

(24) V. Boekelheide and G. C. Morrison, *J. Am. Chem. Soc.*, **80**, 3905 (1958).

(25) J. C. Godfrey, D. S. Tarbell, and V. Boekelheide, *ibid.*, **77**, 3342 (1955).

(26) R. K. Hill and W. R. Schearer, *J. Org. Chem.*, **27**, 921 (1962).

(27) W. Nowacki and G. F. Bonsma, *Z. Kryst.*, **110**, 89 (1958).

(28) V. Prelog, A. Langemann, O. Rodig, and M. Ternbah, *Helv. Chim. Acta*, **42**, 1301 (1959).

(29) Microanalyses were by F. Pascher, W. Manser, and Micro-Tech Laboratories.

extracted with ether. The ether solution, after washing with water and drying, was concentrated; the residual oil was distilled to give 14.5 g. (84%) of a nearly colorless oil, b.p. 115° (10^{-4} mm.).

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.88; H, 9.64; N, 5.12.

The picrate of VI formed readily in ethanol and, after recrystallization from the same solvent, melted at 215° dec.

Anal. Calcd. for $C_{22}H_{27}N_4O_9$: C, 53.65; H, 5.73; N, 11.38. Found: C, 53.63; H, 5.69; N, 11.12.

Anhydrotetrahydro-β-erythroidinol Methotetraphenylborate.—A solution of 200 mg. of VI in 15 ml. of methanol was treated with 10 ml. of methyl iodide. The mixture was allowed to stand under nitrogen for 12 hr. Removal of the methanol gave a glass which could not be induced to crystallize. Treatment of the glass with sodium tetraphenylborate following the procedure of Crane[30] yielded a solid which, after recrystallization from an acetone–methanol mixture, gave white crystals, m.p. 215–219°.

Anal. Calcd. for $C_{41}H_{48}BNO_2$: C, 82.40; H, 8.09; N, 2.34. Found: C, 82.64; H, 7.95; N, 2.64.

Des-N-methylanhydrotetrahydro-β-erythroidinol (VII).—To a solution of 12.0 g. of VI in 50 ml. of anhydrous methanol there was added 70 ml. of methyl iodide and the mixture was allowed to stand overnight under nitrogen. Removal of the solvent followed by two washings with ether and decantation left a glass which was dissolved in methanol and passed over an ion-exchange column (Dowex-2, OH^-). The methanol eluate was concentrated and the residual oil was distilled using a short-path still. The Hofmann decomposition began at 120° and the pressure was gradually lowered leading to distillation at 10^{-4} mm. There was collected 10.84 g. of a colorless oil.

Anal. Calcd. for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.64; H, 9.75; N, 5.58.

The picrate of VII was prepared in ethanol and, after recrystallization from the same solvent, gave yellow crystals, m.p. 155–157°.

Anal. Calcd. for $C_{23}H_{30}N_4O_9$: C, 54.54; H, 5.97; N, 11.06. Found: C, 54.61; H, 5.98; N, 11.03.

The **styphnate** of VII was formed in ethanol and, after recrystallization from the same solvent, melted at 135–137°.

Anal. Calcd. for $C_{23}H_{30}N_4O_{10}$: C, 52.87; H, 5.79; N, 10.72. Found: C, 52.84; H, 5.75; N, 10.76.

Des-N-methylanhydrotetrahydro-β-erythroidinol Methotetraphenylborate.—The methotetraphenylborate of VII was prepared in the same manner as that described for the methotetraphenylborate of VI. After recrystallization from an acetone–methanol mixture, it gave white crystals, m.p. 180–182°.

Anal. Calcd. for $C_{52}H_{50}BNO_2$: C, 82.35; H, 8.25; N, 2.29. Found: C, 82.25; H, 8.25; N, 2.62.

Des-N,N-dimethylanhydrotetrahydro-β-erythroidinol (VIIIa and VIIIb).—A solution of 4.51 g. of VII in 20 ml. of methanol was treated with 20 ml. of methyl iodide and allowed to stand under a nitrogen atmosphere for 12 hr. Removal of solvent followed by washing with ether left a glass which was dissolved in methanol and passed over an ion-exchange column (Dowex-2, OH^-). Concentration of the methanol eluate followed by distillation of the residue gave 4.1 g. (86%) of a nearly colorless oil, b.p. 120° (10^{-4} mm.).

Anal. Calcd. for $C_{15}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 73.84; H, 9.75; N, 4.80.

Microhydrogenation of the mixture of VIIIa and VIIIb showed a rapid uptake of 1 mole of hydrogen followed by slower uptake of a further 1.4 moles.

Des-N-methylanhydrohexahydro-β-erythroidinol (IX).—A solution of 822 mg. of VII in 25 ml. of ethanol containing 200 mg. of a pre-reduced Raney nickel catalyst was subjected to hydrogenation at room temperature and atmospheric pressure. There was a rapid uptake of hydrogen corresponding to 90% of theoretical for 1 mole. After removal of the catalyst, the ethanol solution was treated directly with picric acid to give, after recrystallization from ethanol, 800 mg. of yellow crystals, m.p. 173–175°.

Anal. Calcd. for $C_{23}H_{32}N_4O_9$: C, 54.32; H, 6.34; N, 11.02. Found: C, 54.23; H, 6.56; N, 10.47.

Des-N,N-dimethylanhydrohexahydro-β-erythroidinol (Xa and Xb).—A solution of 11.0 g. of IX (regenerated from the picrate) in 30 ml. of methanol was treated with 60 ml. of methyl iodide and the mixture was allowed to stand overnight under a nitrogen atmosphere. After removal of the solvent, the glassy methiodide was washed twice with ether, dissolved in methanol, and passed over an ion-exchange column (Dowex-2, OH^-). The methanol eluate was concentrated and the residual oil was subjected to thermal decomposition using a short-path still. There was collected 10.2 g. (87%) of a nearly colorless oil, b.p. 110–130° (10^{-4} mm.). Microhydrogenation of this oil over Raney nickel showed the uptake of 99% of theoretical for 1 mole of hydrogen.

Anal. Calcd. for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65. Found: C, 73.62; H, 10.65.

Desazaanhydrooctahydro-β-erythroidinol (XIIa and XIIb).—A solution of 11.1 g. of the mixture of Xa and Xb in 30 ml. of methanol was treated with 60 ml. of methyl iodide and allowed to stand overnight under nitrogen. The mixture was concentrated, washed twice with ether, and then redissolved in 50 ml. of methanol. To the solution was then added 30 mg. of Adams catalyst and it was subjected to hydrogenation at room temperature and atmospheric pressure until 1 mole of hydrogen was absorbed. The catalyst was removed and the solution was passed over an ion-exchange column (Dowex-2, OH^-). Concentration of the eluate followed by distillation of the residue using a short-path still gave 7.9 g. (86%) of a colorless oil, b.p. 100–120° (10^{-4} mm.), λ_{max} 240 mμ (log ε 3.91). Microhydrogenation over Adams catalyst gave an uptake of hydrogen corresponding to 96% of theoretical for one double bond. The hydrogenation product was transparent in the ultraviolet and showed no vinyl hydrogens in the n.m.r.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.90; H, 10.59.

Permanganate Oxidation of Desazaanhydrooctahydro-β-erythroidinol (XIIa and XIIb) to Give (3*S*)-3-Methoxyadipic Acid.—A solution of 4.0 g. of the mixture of XIIa and XIIb in 30 ml. of *t*-butyl alcohol was diluted with 40 ml. of water and then cooled to 0°. To this was added dropwise with stirring a solution of 4.0 g. of potassium permanganate in a minimum amount of water. The addition required about 2 hr. The manganese dioxide formed was destroyed by adding concentrated sulfuric acid until the pH was below 7 followed by careful addition of solid sodium bisulfite. The resulting clear solution was concentrated to 150 ml. and then acidified by addition of 30 ml. of glacial acetic acid and 10 ml. of concentrated sulfuric acid. This solution was then cooled to 0° and treated with 10 g. of potassium permanganate over a period of 1.5 hr. with stirring. The manganese dioxide was destroyed by adding sodium bisulfite while the solution was maintained at 0°. The resulting solution was evaporated at room temperature until dry. The solid residue was extracted with five 100-ml. portions of ether. The ether extracts were filtered and then concentrated to give 1.88 g. of a brown oil. The separation of the resulting mixture of acids was carried out by countercurrent distribution using the buffer system of Bergstrom, *et al.*[10] From a forty-tube distribution, tubes 10–19 were found to contain β-methoxyadipic acid, as identified by paper chromatography. The aqueous phase in these tubes was saturated with sodium sulfate and the ether layers were combined. Concentration of the ether gave 580 mg. of an oil. This was converted to the barium salt following Bergstrom, *et al.*,[10] and the barium salt was then treated with (*S*)-benzylthiuronium sulfate. The resulting sticky product was recrystallized three times from acetone containing a drop of methanol to give 45 mg. of crystals, m.p. 136–141°, $[\alpha]^{20}D$ $-0.64 \pm 0.25°$ (58 mg. in 0.747 ml. of methanol).[31]

The infrared spectrum of these crystals in chloroform was essentially identical with that of a similar spectrum of an authentic specimen of the (*S*)-benzylthiuronium derivative of racemic 3-methoxyadipic acid.

(30) F. J. Crane, *Anal. Chem.*, **28**, 1794 (1956).

(31) The pure (*S*)-benzylthiuronium derivative of (−)-3-methoxyadipic acid shows a rotation, $[\alpha]^{18}D$ -1.1 ± 0.3 (*c* 0.5, methanol).

Vinylidene Carbenes by α-Elimination from Haloallenes

H. D. HARTZLER

Contribution No. 935 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

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1-Chloro-3-methyl-1,2-butadiene reacted with potassium *t*-butoxide and olefins to yield dimethylvinylidenecyclopropanes. The relative rates of addition to olefins were found to be the same as those previously obtained with 3-chloro-3-methyl-1-butyne and potassium *t*-butoxide. Dimethylvinylidene carbene is presumed to be a common intermediate. The reported preparation of 3-bromo-1,1-diphenylpropadiene was shown to be erroneous.

Terminal acetylenes with a good leaving group in the γ-position can react with bases by a γ-elimination mechanism to produce vinylidene carbenes as transient intermediates. Vinylidene carbenes have been shown

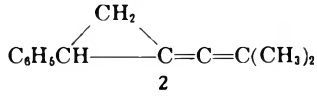
$$R_2C(X)-C\equiv CH + B: \rightleftharpoons H:B + R_2C(X)-C\equiv C^- \longrightarrow [R_2C{=}C{=}C:] + X^-$$

to react with alcohols to form acetylenic ethers,[1] with amines to form acetylenic amines,[2] with olefins to form vinylidenecyclopropanes,[3] with certain acetylide ions to form hexapentaenes,[3] and with bromide ion to form acetylenic bromide (and, possibly, allenic bromide).[4]

This paper describes our work on generation of vinylidene carbenes from haloallenes by α-elimination.

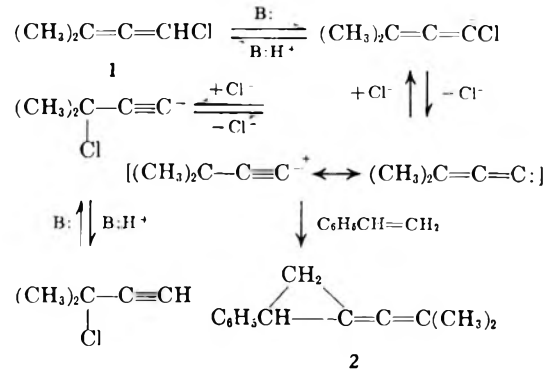
α-Elimination of Haloallenes.—The addition of 1-chloro-3-methyl-1,2-butadiene (1) to a slurry of potassium *t*-butoxide in styrene at 0° gave a rapid, exothermic reaction from which 1-dimethylvinylidene-2-phenylcyclopropane (2) was isolated in greater than 34% yield. Under identical conditions, the vinylidenecyclopropane is formed from the isomeric 3-chloro-3-methyl-1-butyne in 49% yield.[3]

$$\underset{1}{(CH_3)_2C{=}C{=}CHCl} + KO\text{-}t\text{-}Bu + C_6H_5CH{=}CH_2 \longrightarrow$$



2

Although the interconversion of allenic and propargylic compounds is a well-known reaction,[5] it is unlikely that 1 isomerizes to the acetylenic chloride under these conditions. Isomerization of allenic and propargylic systems occurs with Lewis acid catalysis[6] and under conditions of an SN2′ reaction.[7] Isomerization of propargylic and allenic systems could occur in basic systems by a vinylidene carbene mechanism, if a large excess of the common ion is present in solution.[4] The possibility of rearrangement of 1 to the acetylenic chloride by such a mechanism is minimized under our reaction conditions because little chloride ion is in solution in the olefinic solvent and the large excess of olefin employed partitions the intermediate to form cyclopropane.



If the carbene is an intermediate in the reaction, its rates of reactions with olefins should be identical with those determined previously[8] for the same intermediate obtained from the isomeric acetylenic chloride.[9] Relative rates of reaction were determined by competition experiments in which a large excess of an olefin mixture was brought into reaction with potassium *t*-butoxide and 1. Cyclohexene was used as a referent in these reactions and was arbitrarily given a rate of unity. The amounts of the two dimethylvinylidenecyclopropanes that were formed were determined by gas–liquid chromatography under conditions similar to those previously used with the acetylenic chloride.[8] Within experimental error, the relative rates of olefin addition in the two systems are identical. The experimental results are given in Table I.

TABLE I

RELATIVE RATES OF REACTION OF VINYLIDENE CARBENES WITH OLEFINS

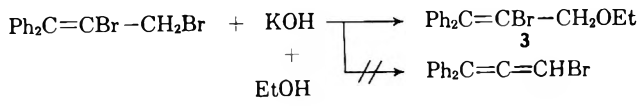
Olefin	log k/k_0 $(CH_3)_2C{=}C{=}C:$[a]	log k/k_0 $(CH_3)_2C{=}C{=}C:$[b]
$(CH_3)_2C{=}C(CH_3)_2$	1.2	1.3
$(CH_3)_2C{=}CHCH_3$	0.69	0.67
$CH_3CH_2(CH_3)C{=}CH_2$	0.62	0.70
	0.00	0.00
$CH_3CH_2CH_2CH_2CH{=}CH_2$	−0.64	−0.60

[a] Carbene generated from $(CH_3)_2C{=}C{=}CHCl$ and potassium *t*-butoxide at −10°. [b] Carbene generated from $(CH_3)_2CCl{-}C{\equiv}CH$ and potassium *t*-butoxide at −10°.[8]

A recent report[10] disclosed the preparation of 1,1-diphenyl-3-bromopropadiene by dehydrobromination of 2,3-dibromo-1,1-diphenylpropene with potassium hydroxide in ethanol. Both the method of preparation

(1) G. F. Hennion and D. E. Maloney, *J. Am. Chem. Soc.*, **73**, 4735 (1951).
(2) G. F. Hennion and K. W. Nelson, *ibid.*, **79**, 2142 (1957).
(3) H. D. Hartzler, *ibid.*, **83**, 4990 (1961).
(4) V. J. Shiner, Jr., and J. W. Wilson, *ibid.*, **84**, 2402 (1962).
(5) A. Favorskii and T. A. Favorskaya, *Compt. rend.*, **200**, 839 (1935); J. H. Ford, C. D. Thompson, and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 2619 (1935).
(6) T. L. Jacobs and W. F. Brill, *ibid.*, **75**, 1314 (1953), and earlier references cited therein.
(7) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *ibid.*, **72**, 3542 (1950).
(8) H. D. Hartzler, *ibid.*, **83**, 4997 (1961).
(9) This would not be true if the carbene is complexed in solution and complexed differently in the two systems. While the former is probably the case, our results indicate the latter is not.
(10) V. I. Pansevich-Kolyada, *J. Gen. Chem. USSR*, **30**, 3854 (1960).

and the reported stability[11] of the bromoallene appeared surprising. The compound was of interest to us since it would be a useful intermediate to diphenylvinylidene carbene. In our hands the reaction gave an 87% yield of 2-bromo-3-ethoxy-1,1-diphenylpropene (**3**), rather



than the allene. The bromo ether has the same melting point reported for the bromoallene. Reaction of the dibromide with collidine in refluxing xylene, potassium *t*-butoxide in dimethyl sulfoxide, and butyllithium in hexane failed to give any of the bromoallene. From the latter reaction there was obtained a 9% yield of the coupling product, 2,5-dibromo-1,1,6,6-tetraphenyl-1,5-hexadiene.

Experimental[12]

1-Chloro-3-methyl-1,2-butadiene (**1**).—This chloroallene was prepared by the method of Jacobs, Teach, and Weiss.[13] The material used in the competition experiments distilled at 50–51° (105 mm.), $n^{25}D$ 1.4744; lit.[17] b.p. 61–62° (175 mm.), $n^{25}D$ 1.4739. Our sample was >98% pure by gas–liquid chromatographic analysis. The n.m.r. spectrum of the chloroallene showed the resonance of the vinyl hydrogen as a septuplet centered at τ 3.92 and the resonance of the methyl hydrogens as a doublet centered at τ 8.14. The coupling constant was ~3 c.p.s. An attempt was made to estimate the acidity of the vinyl hydrogen by measuring the C^{13} coupling constant, but this splitting could not be seen even after decoupling the methyl–vinyl splitting.

1-Dimethylvinylidene-2-phenylcyclopropane (**2**).—A slurry of 12 g. of potassium *t*-butoxide and 40 g. of styrene was stirred under nitrogen at 0°. Compound **1** (10.3 g.) was added dropwise with cooling. After addition, pentane (200 ml.) was added, and the mixture was filtered. Distillation of the filtrate gave 5.75 g. (34%) of **2**, b.p. 68–73° (0.37 mm.), $n^{25}D$ 1.5708; lit.[3] b.p. 78–80° (0.5 mm.), $n^{25}D$ 1.5717–1.5722.

Competition Experiments with 1, Potassium *t*-Butoxide, and Olefins.—The olefins used were Phillips pure grade. Mixtures containing cyclohexene and another olefin (*ca.* 0.2 mole of total olefin) and 1.13 g. of potassium *t*-butoxide were stirred under nitrogen at −10° The allene **1** (1.10 g.) was added dropwise. Five minutes after addition, pentane (50 ml.) was added, and the mixture was filtered through Celite Filter Aid. The filtrates were concentrated under nitrogen and analyzed by gas–liquid chromatography. The column employed was a 2-m. tube packed with 20% triscyanoethylglyceryl ether on firebrick and was operated at 102° (preheat 145°). Retention times were determined with authentic samples.[3] The product ratios were divided by the mole fraction ratios of the starting olefins to give the relative rates of addition. The logarithms of the rate ratios are given in Table I. Duplicate experiments were in agreement within 10%.

2,3-Dibromo-1,1-diphenylpropene.—Crude 1,1-diphenylpropene (106 g., m.p. 41–48°) in 150 ml. of ether was stirred in an ice bath while bromine (88 g.) was added. The solvent was removed under reduced pressure. The residual oil was dissolved in an ethanol–ether mixture and stirred with a solution of 22 g. of sodium hydroxide in 100 ml. of water. The layers were separated, and the ether-soluble product was distilled to give 128 g. (85%) of 2-bromo-1,1-diphenylpropene, b.p. 120–125° (0.5 mm.). The n.m.r. spectrum of the product showed only methyl and phenyl hydrogen.

A mixture of 63 g. of the bromoolefin, 41.4 g. of N-bromosuccinimide, 0.4 g. of benzoyl peroxide, and 200 ml. of carbon tetrachloride was heated at reflux for 3 hr. The succinimide was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue crystallized upon adding ethanol to give 74 g. (91%) of crude dibromide, m.p. 73–78°. Recrystallization from ethanol gave material which melted at 82–83°, lit.[11] m.p. 88–89°. The n.m.r. spectrum of the dibromide showed the resonances of the phenyl hydrogen at τ 2.74 and 2.78 and the methylene hydrogen at τ 5.68. The intensity ratio was 5:1.

2-Bromo-3-ethoxy-1,1-diphenylpropene (**3**).—A solution of 10 g. of potassium hydroxide in 30 ml. of ethanol was added to a stirred mixture of 10 g. of 2,3-dibromo-1,1-diphenylpropene in 40 ml. of ethanol. The mixture was heated at 70° for 30 min. Water (100 ml.) was added, and the product was extracted with ether. Distillation gave 6.75 g. of **3**, b.p. 126° (0.4 mm.). Crystallization from ethanol gave pure **3**, m.p. 62.4–63.4°, lit.[11] m.p. 60–61° for the bromoallene.

Anal. Calcd. for $C_{17}H_{17}BrO$: C, 64.4; H, 5.40; Br, 25.2. Found: C, 64.6; H, 5.32; Br, 25.3.

The infrared spectrum of **3** showed the presence of both saturated and unsaturated CH, conjugated C=C (6.15 μ), aromatic and C–O absorption (9.0 μ). There was no allenic absorption. The n.m.r. spectrum of **3** showed the resonances of the unsplit methylene at τ 5.70, the methylene of the ethoxy group (quartet) centered at τ 6.45, and the methyl triplet centered at τ 8.77.

2,5-Dibromo-1,1,6,6-tetraphenyl-1,5-hexadiene.—A solution of 17.6 g. of 2,3-dibromo-1,1-diphenylpropene in 100 ml. of ether was stirred at −5° while a solution of butyllithium in hexane (34 ml., 0.05 mole) was added. After 15 min., water was added, and the organic product was taken up in ether. Evaporation of the ether left a viscous oil. A crystalline solid (1.33 g.) was obtained when the residue was dissolved in 80 ml. of boiling methanol. Recrystallization from ethanol gave the pure diene (1.27 g., 9%), m.p. 167–168°.

Anal. Calcd. for $C_{30}H_{24}Br_2$: C, 66.2; H, 4.44; Br, 29.4; mol. wt., 544. Found: C, 66.6; H, 4.67; Br, 29.0; mol. wt. (b.p. in benzene), 585, 547.

In addition to the aromatic hydrogens, the n.m.r. spectrum showed the unsplit methylene at τ 7.05 with an intensity one-fifth that of the aromatic hydrogen. The infrared spectrum showed the absorption of the conjugated olefin and was completely consistent with the assigned structure.

Acknowledgment.—We thank Mrs. Adah Richmond for her invaluable assistance with the gas–liquid chromatographic analyses.

(11) The corresponding chloroallene has never been isolated because of its very rapid dimerization. T. Nagase, *Sci. Papers Inst. Phys. Chem. Res.*, **55**, 165, 172 (1961); P. D. Landor and S. R. Landor, *Proc. Chem. Soc.*, 77 (1962).

(12) Melting points and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer, n.m.r. spectra on a Varian A-60 spectrometer, and ultraviolet spectra on a Cary Model 14 spectrometer.

(13) T. L. Jacobs, E. G. Teach, and D. Weiss, *J. Am. Chem. Soc.*, **77**, 6254 (1954).

Highly Selective Lithium–Amine Reducing Systems. The Selective Reduction of Aromatic Compounds by Lithium in Mixed Amine Solvents[1a]

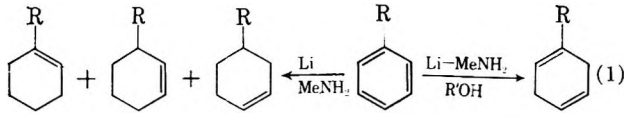
ROBERT A. BENKESER, RAM K. AGNIHOTRI, MERWYN L. BURROUS, EDWIN M. KAISER, JEAN M. MALLAN, AND PATRICK W. RYAN

Richard B. Wetherill Chemical Laboratories, Purdue University, West Lafayette, Indiana

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Changes in the primary amines normally employed as solvents for reducing aromatic compounds with lithium have a marked effect upon product composition. Systematic variation of the solvent from methyl- to ethyl- to *n*-propylamine caused a gradual increase in the percentage of 1-alkyl cyclohexenes obtained from the reduction of alkyl benzenes. The effect was even more dramatic when the primary amine was diluted with a secondary amine like dimethylamine or morpholine. Addition of these secondary amines not only provided much greater selectivity in the reduction, but at the same time lowered the over-all volatility of the solvent system, affording greater ease of handling. The equilibrium isomer distributions of methyl- and *t*-butylcyclohexene were determined. From the results it is deemed unlikely that the monoolefins produced in these reductions are isomerized to any appreciable extent under the conditions of the reaction. Rather, the final product composition seems determined by the nature and concentrations of the cyclohexadiene precursors.

In the previous paper in this series,[1b] it was shown that the addition of alcohol to a solution of lithium in methylamine has a profound effect on the reducing properties of this system. Normally, aromatic hydrocarbons are reduced selectively to monoolefins (tetrahydro products) by the lithium–amine reagent.[2] In the presence of an alcohol, however, two equivalents of lithium (based on aromatic) dissolved in methylamine will reduce aromatic compounds quite selectively to the dihydro stage.



(1)

When carried out under these conditions the reaction resembles the celebrated Birch reduction.

In this paper we report the effect of variations in the amine solvents on the course of the reduction whereby some light is thereby cast on the mechanism of these reductions.

As was reported earlier,[3] certain low molecular weight aliphatic amines are effective solvents in the reduction of aromatic hydrocarbons by lithium. In order to assess the relative merits of various amine solvents, a detailed study was made of the reduction of toluene, isopropyl- and *t*-butylbenzene in methyl-, ethyl-, and *n*-propylamine. All reactions were carried out at −7°, the boiling point of methylamine. The results of these experiments are listed in Table I. Two things are immediately apparent from the data. (1) The ratio of the 1-olefin relative to the 3- and 4-olefin increases as the alkyl group of the amine becomes larger. (2) The rate of reduction of the hydrocarbons decreases (as evidenced by the recovery of aromatic) as the molecular weight of the amine increases. Particularly in the case of *n*-propylamine, the direct reaction of the metal with the solvent to form hydrogen and amide begins to compete successfully with the reduction of the aromatic.

TABLE I

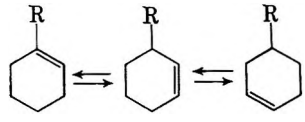
REDUCTION OF ALKYL BENZENES IN METHYL-, ETHYL-, AND *n*-PROPYLAMINE AT −7°

	Product composition (% 1-olefin)[a,b]		
Aromatic compound	$MeNH_2$	$EtNH_2$	$n\text{-}PrNH_2$
Toluene	59[c,d]	61 (13)	75 (14)
Isopropylbenzene	47	58 (3)	73 (35)
t-Butylbenzene	42	56 (1)	77 (35)

[a] The values listed are the percentage of the 1-olefin relative to the total olefinic content. The difference between the value given and 100% represents the percentage distribution of the 3- and 4-olefins except in those cases where aromatic was recovered. [b] The values in parentheses represent the amount of aromatic recovered. [c] The values in this table represent an average value of two trials. None of the olefin percentages differed by more than 2% in these trials. [d] All analyses in this table were by v.p.c. Either a Perkin-Elmer Model 154C equipped with a 12-ft. column packed with β,β′-oxydipropionitrile on C-22 firebrick or an Aerograph A-110-C equipped with a 14-ft. column was used.

In many cases, ethylamine becomes the solvent of choice where great selectivity is desired.

It is unlikely that the increase in 1-olefin observed when the solvent is varied from methyl- to *n*-propylamine (Table I) can be attributed to varying base strengths of the solvent, since the latter is almost identical in the case of these three amines. On the other hand, the steric bulk of the three amines is definitely increasing as the alkyl substituent is varied from methyl to *n*-propyl. This may be an important factor in determining product ratios, since these amines are functioning as the protonating agent for the anion intermediates. It seemed possible that, as the reaction became slower owing to employment of a bulky solvent like *n*-propylamine, more time would be provided for the establishment of an equilibrium between the monoolefinic products.[4] If this equilibrium were slow in establishment, it seemed reasonable that a bulky pro-



(2)

(1) (a) This is paper VIII in a series entitled "Reduction of Organic Compounds by Lithium in Low Molecular Weight Amines"; (b) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963).

(2) R. A. Benkeser, R. K. Agnihotri, and M. L. Burrous, *Tetrahedron Letters*, **16**, 1 (1960).

(3) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1954).

(4) A. P. Krapcho and A. A. Bothner-By [*ibid.*, **81**, 3658 (1959)] have shown that the rate of reduction of benzene by lithium in ammonia and alcohol is roughly twenty-seven times as fast when ethanol rather than *t*-butyl alcohol is employed.

TABLE II

REDUCTIONS OF AROMATIC COMPOUNDS TO MONOOLEFINS IN MIXED AMINE SOLVENTS

Aromatic	Amine solvents (ml.)	1-Alkylcyclohexenes,[a,b] %	3- + 4-alkylcyclohexenes, %
(1) Toluene	$MeNH_2$ (100) Me_2NH (100)	69 (60)	30[c] (40)
(2) Toluene	$MeNH_2$ (100) Me_2NH (400)	76 (60)	24 (40)
(3) Cumene	$MeNH_2$ (45) n-$PrNH_2$ (300)	56 (46)	44 (54)
(4) Cumene	$MeNH_2$ (100) i-$PrNH_2$ (100)	65 (46)	19[c] (54)
(5) Cumene	$MeNH_2$ (50) Morpholine (150)	88 (46)	12 (54)
(6) Cumene	$H_2N(CH_2)_2NH_2$ (75) Morpholine (100)	87 (76)	12[c] (19[c])
(7) Cumene	$MeNH_2$ (50) Me_3N (200)	48 (46)	51 (54)
(8) Cumene	$MeNH_2$ (75) Et_2O (75)	50 (46)	50 (54)
(9) Cumene	$MeNH_2$ (75) t-Octylamine (75)	53 (46)	45[c] (54)
(10) Cumene	$EtNH_2$ (150) Me_2NH (160)	85 (73)	15 (27)
(11) Cumene	$EtNH_2$ (200) Me_3N (100)	68 (73)	32 (27)
(12) t-Butylbenzene	$EtNH_2$ (200) Me_2NH (220)	80 (70)	13[d] (30)
(13) t-Butylbenzene	$H_2N(CH_2)_2NH_2$ (100) Morpholine (200)	86 (70)	14 (22)[e]
(14) Biphenyl	$MeNH_2$ (75) Morpholine (150)	92 (49)	8 (36)[e]
(15) Naphthalene	$EtNH_2$ (250) Me_2NH (250)	80[h]	20[i]
(16) β-Phenylethanol	$EtNH_2$ (150) Morpholine (150)	88 (83)[f]	12 (9)[c,g]
(17) Acetophenone	$MeNH_2$ (200)	70[e]	
(18) Acetophenone	$H_2N(CH_2)_2NH_2$ (200)	34[e]	
(19) Acetophenone	$H_3N(CH_2)_2NH_2$ (100) Morpholine (200)	55[e]	

[a] The values in parentheses are the isomer distributions observed when only the pure primary amines were used as solvent. [b] The percentages given represent the isomer distributions obtained. [c] Saturated compound made up the remainder of the product. [d] The remainder of the product recovered was aromatic. [e] Reduction in methylamine was carried out by using 6 equiv. of lithium; 4 equiv. of lithium was used in ethylenediamine and ethylenediamine–morpholine. Reduction carried out in 67 ml. of methylamine and 134 ml. of morpholine with 6 equiv. of lithium resulted in a 90% yield of product. The product referred to in each of these entries is methyl-1-cyclohexenylcarbinol. [f] The product referred to is β-(1-cyclohexenyl)ethanol. [g] The products referred to here are the β-(3- and 4-cyclohexenyl)-ethanols. [h] The product here was $\Delta^{9,10}$-octalin. [i] This product was $\Delta^{1,9}$-octalin.

tonating agent might provide more time for the anion intermediates to rearrange to the most thermodynamic form in which the alkyl group is situated on the double bond.

In order to test this hypothesis, the reductions were attempted in mixtures of primary and secondary amines (see Table II). It was indeed found that the addition of secondary amines like dimethylamine and morpholine to the primary amine solvents usually had a profound effect in increasing the percentage of 1-olefin formed.[5] Certain primary amines like isopropylamine and t-octylamine seemed to have some effect also, but tertiary amines (*e.g.*, trimethylamine) and diethyl ether seemed to have have little influence. This discovery has extreme significance in the utilization of the lithium–amine reducing agent as a tool in organic syntheses. As will be noted in Table II the employment of secondary amine diluents permits one to carry out reductions with the lithium–amine reagent in a much more selective fashion. Thus the yield of 1-isopropylcyclohexene was practically doubled when the reduction was carried out in a 3:1 (v./v.) morpholine–methylamine system (entry 5, Table II). The same was true of 1-cyclohexylcyclohexene from the reduction of biphenyl (entry 14, Table II). Likewise the yield of $\Delta^{9,10}$-octalin from the reduction of naphthalene was increased from 52 to 80% by the addition of dimethylamine. The other product (20%) in this reduction was $\Delta^{1,9}$-octalin.

In a few cases the addition of a secondary amine had only a negligible effect on the isomer ratio of the products. In the reduction of β-phenylethanol in ethylamine, the addition of morpholine increased the proportion of β-(1-cyclohexenyl)ethanol from 83 to 88%. On the other hand, when the same reduction was carried out in pure methylamine only 70% of β-(1-cyclohexenyl)-ethanol was obtained. This points again to the greater selectivity which is usually achieved in ethylamine compared to methylamine. In almost every case studied thus far, the addition of secondary amines had a salutary effect in increasing the proportion of 1-olefin. An additional advantage to the mixed amine systems is that the volatility of the solvent system is diminished making for greater ease of handling.

It is particularly interesting that at least a small amount of the primary amines like methyl- or ethylamine or ethylenediamine is needed for the reduction to proceed at any appreciable rate. This is vividly illustrated in Table III which lists the isomer distributions

TABLE III

REDUCTION OF CUMENE IN VARIOUS DILUTIONS OF METHYLAMINE–DIMETHYLAMINE

Solvent composition (volume % dimethylamine in methylamine)	1-Isopropylcyclohexene,[a] %	3- + 4-Isopropylcyclohexene,[a] %
33[b]	55	45
50[c]	68	32
80[d]	77	23
93[e]	82	18
96[f]	Dihydro products + cumene	
100[g]	No reduction	

[a] These percentages represent the olefin distribution in the product. [b] Cumene (0.1 mole) and 0.44 g.-atom of lithium used in 100 ml. of Me_2NH and 200 ml. of $MeNH_2$. [c] Cumene (0.1 mole) and 0.44 g.-atom of lithium used in 200 ml. of Me_2NH and 200 ml. of $MeNH_2$. [d] Cumene (0.1 mole) and 0.44 g.-atom of lithium used in 800 ml. of Me_2NH and 200 ml. of $MeNH_2$. [e] Cumene (0.05 mole) and 0.2 g.-atom of lithium used in 350 ml. of Me_2NH and 25 ml. of $MeNH_2$. [f] Cumene (0.1 mole) and 0.4 g.-atom of lithium used in 160 ml. of Me_2NH and 8 ml. of $MeNH_2$. [g] Cumene (0.05 mole) and 0.22 g.-atom of lithium used in 150 ml. of Me_2NH.

(5) We wish to emphasize that, while we were led to try the secondary amine diluents as a result of considerations regarding steric hindrance to protonation, their success does *not necessarily* prove the validity of this hypothesis. It is entirely possible that the secondary amines exert their influence by an entirely different mechanism. Indeed, there are certain difficulties associated with the concept of steric hindrance to protonation by the secondary amines of which we are well aware. In this paper we are simply reporting the reasoning process which prompted us to try diluting the primary amine solvents with other additives.

obtained in the reduction of cumene as the volume per cent of methylamine–dimethylamine was systematically varied. Two things are apparent from the data. First, the percentage of 1-olefin increases as the quantity of dimethylamine increases, and secondly the limit is reached at about 93% dimethylamine. In pure dimethylamine, very little reduction occurs. Similarly, reduction in pure isopropylamine and pure morpholine was found to proceed very slowly or not at all. At least small amounts of the low molecular weight aliphatic amines seem essential in these reductions to solubilize some of the lithium metal. The lithium appears to be quite insoluble in secondary and branched chain amines.

In order to ascertain whether the addition of secondary amines was permitting equilibration of the isomeric olefins as depicted in eq. 2, the equilibrium distribution of the methylcyclohexenes and *t*-butylcyclohexenes was determined. This was accomplished by equilibrating pure 1-methyl- and 4-methylcyclohexene as well as pure 1-*t*-butyl- and 4-*t*-butylcyclohexene and mixtures of varying composition. The results are listed in Table IV. The most favorable conditions for equilibration was found to be refluxing the olefins in glacial acetic acid containing catalytic quantities of *p*-toluenesulfonic acid. An average value taken from Table IV

TABLE IV
EQUILIBRATION OF METHYL- AND *t*-BUTYLCYCLOHEXENES

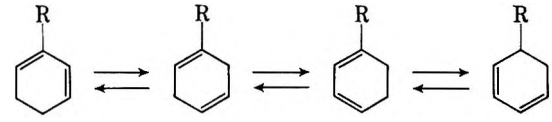
Original composition, %	Reflux time, hr.	Final composition, %
1-Methylcyclohexene, 100	96	1-Methylcyclohexene,[a] 91
1-Methylcyclohexene, 100	113	1-Methylcyclohexene, 94
4-Methylcyclohexene, 100	122	1-Methylcyclohexene, 77
1-Methylcyclohexene, 70	96	1-Methylcyclohexene, 84
4-Methylcyclohexene, 30		
1-Methylcyclohexene, 88	163	1-Methylcyclohexene, 93
4-Methylcyclohexene, 12		
t-Butylcyclohexene, 100	184	1-*t*-Butylcyclohexene, 76
		3-*t*-Butylcyclohexene, 14
		4-*t*-Butylcyclohexene, 10
4-*t*-Butylcyclohexene, 100	238	1-*t*-Butylcyclohexene, 67
		3-*t*-Butylcyclohexene, 17
		4-*t*-Butylcyclohexene, 16
1-*t*-Butylcyclohexene, 75		1-*t*-Butylcyclohexene, 79
3-*t*-Butylcyclohexene, 18	167	3-*t*-Butylcyclohexene, 13
4-*t*-Butylcyclohexene, 7		4-*t*-Butylcyclohexene, 8
1-*t*-Butylcyclohexene, 39		1-*t*-Butylcyclohexene, 72
3-*t*-Butylcyclohexene, 36	24	3-*t*-Butylcyclohexene, 13
4-*t*-Butylcyclohexene, 18		4-*t*-Butylcyclohexene, 6
t-Butylcyclohexane, 7		*t*-Butylcyclohexane, 9

[a] This value shows the percentage of 1-olefin relative to total olefin. On prolonged refluxing small amounts of aromatic and unknown were observed.

would be 91–94% 1-methylcyclohexene at equilibrium and 76–79% 1-*t*-butylcyclohexene. As might have been predicted, the results indicate that a methyl group imparts greater thermodynamic stability to 1-methylcyclohexene than does a *t*-butyl group in the same relative position.

It will be noted from Table II (entry 13), that an ethylenediamine–morpholine solvent mixture results in an 86% distribution of 1-*t*-butylcyclohexene. This value lies above the equilibrium value obtained for this isomer as listed in Table IV, and would thus cast serious doubt upon the importance of eq. 2 under actual reduction conditions.

To test further the possibility that equilibration of the type shown in eq. 2 was occurring during the reductions, an attempt was made to isomerize 4-methylcyclohexene (an isomer we have shown to be thermodynamically unstable relative to 1-methylcyclohexene) in the presence of lithium methylamide in methylamine. After 6 hr., which might be considered an average time for lithium–amine reduction, little or no isomerization had occurred. Hence, it is our current belief that the monoolefins produced in the lithium–amine reductions are formed under essentially *nonisomerizing conditions*.[6] The isomer distribution of monoolefins must thus be predetermined by the nature and concentrations of the precursors, which, upon reduction, produce the monoolefins. These precursors are very likely cyclohexadienes, that are in a rapid and mobile equilibrium.



Future papers in this series will take up the nature and importance of these cyclohexadienes in determining the final olefin composition.

Experimental

General Procedure for the Reduction of Aromatic Compounds in Mixed Amine Solvents.—Five equivalents of lithium were added to a solution of the aromatic compound in the mixed amine solvent. After the metal had disappeared, the amines were evaporated. Water and ether were added, and the ethereal extracts were dried and distilled. When the primary amine solvent boiled above room temperature (*e.g.*, ethylenediamine), water and ether were added immediately after the metal disappeared with no attempt being made to remove the solvents. The ethereal layer was then neutralized with dilute hydrochloric acid before drying and distilling. The results of all of the reductions run in mixed amine solvents are listed in Table II. The following procedure for the reduction of biphenyl can be taken as typical of this method.

Reduction of Biphenyl in Methylamine–Morpholine.—In a 500-ml. flask was placed 15.4 g. (0.1 mole) of biphenyl in a solvent consisting of 75 ml. of methylamine and 150 ml. of morpholine. A total of 7.7 g. (1.1 g.-atoms) of lithium was added to this solution and was entirely consumed after stirring at room temperature for 12 hr. After the methylamine was evaporated, water was added slowly to the cooled flask. The ethereal extracts were neutralized with dilute hydrochloric acid. Distillation of the ethereal extracts gave 7.9 g. of liquid (48%) along with a small amount of unreduced biphenyl. See Table II for analysis of the distillate.

Analyses of Olefin Mixtures.—All olefin mixtures encountered were analyzed by vapor phase chromatography. Retention times were compared with those of authentic samples prepared by unequivocal methods described below.

Since considerable efforts were expended to obtain pure, authentic samples for comparison, the boiling points and refractive indices of these olefins have been included in Table V, along with the literature values when these were available.

Preparation of Authentic Monoolefins.—All 1-alkylcyclohexenes were prepared by the dehydration of the alkylcyclohexanol with iodine as described by Mosher.[7] The alcohols were prepared by treating cyclohexanone with the appropriate Grignard reagent. Table V lists the physical properties of these alkenes.

The 3-alkyl cyclohexenes were all prepared by a method described by Biggerstaff, *et al.*[8] Table V lists the physical constants of these alkenes.

(6) It is likely, however, that some isomerization can and does occur when these reductions are carried out in ethylenediamine at elevated temperatures [L. Reggel, S. Friedman, and I. Wender, *J. Org. Chem.*, **23**, 1136 (1958)].

(7) W. A. Mosher, *J. Am. Chem. Soc.*, **62**, 552 (1940).

(8) W. R. Biggerstaff, *et al.*, *J. Org. Chem.*, **19**, 934 (1954).

TABLE V

PHYSICAL CONSTANTS OF PURE SAMPLES OF ALKYL CYCLOHEXENES

Compound	B.p., °C.	$n^{20}D$
1-Methylcyclohexene[b]	108 [109][a]	1.4500 [1.4497][a]
3-Methylcyclohexene[c]	102 [104]	1.4439 [1.4445]
4-Methylcyclohexene[d]	102 [102–103]	1.4419 [1.4418]
1-Ethylcyclohexene[e]	134–136 [134–136]	1.4570 [1.4576]
3-Ethylcyclohexene[f]	132–133 [133]	1.4510 [1.451]
4-Ethylcyclohexene[g]	132 [133]	1.4491 [1.449]
1-Isopropylcyclohexene[h]	155 [155–157]	1.4576 [1.4594]
3-Isopropylcyclohexene[i]	152 [150]	1.4552 [1.4542]
4-Isopropylcyclohexene[j]	155 [150–152]	1.4543 [1.4560]
1-*t*-Butylcyclohexene[g]	170 [173]	1.4623 [1.4638]
3-*t*-Butylcyclohexene[k]	170 [66 (23 mm.)]	1.4595 [1.4593]
4-*t*-Butylcyclohexene[l]	172 [172]	1.4589 [1.4587]
1-Cyclohexylcyclohexene[m]	112 (16 mm.) [88 (4 mm.)]	1.4945 [1.4916]
3-Cyclohexylcyclohexene[n]	109 (13 mm.)	1.4941
4-Cyclohexylcyclohexene[o]	233 [236]	1.4922

[a] The value in brackets represents the literature values. [b] K. Auwers and P. Ellinger, *Ann.*, **387**, 200 (1912). [c] G. Egloff, "Physical Constants of Hydrocarbons," Vol. II, Reinhold Publishing Corp., New York, N. Y., 1940, p. 327. [d] R. T. Arnold, G. G. Smith, and R. M. Dodson, *J. Org. Chem.*, **15**, 1256 (1950). [e] O. Wallach, *et al.*, *Ann.*, **360**, 48 (1908). [f] S. W. Ferris, "Handbook of Hydrocarbons," Academic Press, Inc., New York, N. Y., 1955, p. 33. [g] See footnote *f*, p. 50. [h] See footnote *f*, p. 42. [i] A. Berlande, *Bull. soc. chim. France*, 9, 644 (1942). [j] H. Pines, R. C. Olberg, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **74**, 4872 (1952). [k] W. R. Biggerstaff, A. P. Menditto, and I. Yokoyama, *J. Org. Chem.*, **19**, 934 (1954). [l] See footnote *c*, p. 343. [m] F. K. Signaigo and P. L. Cramer, *J. Am. Chem. Soc.*, **55**, 3326 (1933). [n] *Anal.* Calcd. for $C_{12}H_{20}$: C, 87.8; H, 12.2. Found: C, 87.53; H, 12.42. [o] W. Schrauth and K. Gorig, *Ber.*, **56**, 1900 (1923).

The 4-alkylcyclohexenes were prepared by the sequence: 4-alkyl phenol → 4-alkyl cyclohexanol → 4-alkyl cyclohexyl acetate → 4-alkyl cyclohexene. The final pyrolysis step was patterned after that described by Bailey.[9] Table V lists the physical constants of these alkenes.

Equilibration of Methyl- and *t*-Butylcyclohexenes (Table IV).—The following isomerizing conditions were studied.

A. **Alumina at 350°.**—Passing an olefinic mixture over an alumina column at 350° caused considerable aromatization. When the temperature was lowered to 220°, little change in composition occurred on several consecutive passes through the column.

B. ***p*-Toluenesulfonic Acid.**—This catalyst proved more efficient and effective than alumina. The olefin was refluxed under nitrogen in acetic acid with a trace of *p*-toluenesulfonic acid. Periodically, about 2 ml. of material was withdrawn, neutralized with excess 10% sodium hydroxide solution, and taken up in 2 ml of ether. The organic layer was analyzed on a Fisher–Gulf partitioner equipped with a 12-ft. β,β′-oxdipropionitrile on C-22 firebrick column operated at 75–85° and at 20 p.s.i.

As noted in Table IV, the amount of 1-methylcyclohexene present in an equilibrium mixture of the methylcyclohexenes was 91–93%. An equilibrium mixture of the *t*-butylcyclohexenes contained 76–79% of the 1-olefin.

In one of the isomerization trials a material balance was calculated. When starting with 15.9 g. of a mixture containing 39% 1-*t*-butylcyclohexene, 11.0 g. of material containing 74% 1-*t*-butylcyclohexene was recovered. Thus the actual amount of 1-olefin increased from 6.2 g. to 8.05 g.

General Directions for the Reductions of Alkylbenzenes in Primary Amines at −7° (Table I).—In each instance lithium wire was added to a solution of alkylbenzene in the amine. The reaction flask was immersed in a cooling bath held at −5 to −9° in the case of ethyl- and *n*-propylamine. Stirring was continued until the lithium had been consumed. With methyl- and ethylamine as solvents, the amine was evaporated before hydrolysis. With *n*-propylamine, water was added directly to the reduction mixture when the metal was completely consumed. At no time during the reductions in *n*-propylamine did the solvent become blue throughout. A blue color was discerned intermittently around the pieces of reacting lithium. The results of these reductions are listed in Table I.

Attempted Isomerization of 4-Methylcyclohexene by Lithium Methylamide.—Lithium methylamide was generated by the reduction of 7.8 g. (0.1 mole) of benzene with 2.8 g. (0.4 g.-atom) of lithium in 200 ml. of methylamine. After all the lithium was gone, 9.6 g. of a mixture of 97% 4-methylcyclohexene and 3% 1-methylcyclohexene was added. After the mixture was stirred for 6 hr., the amine was evaporated. After work-up, an analysis showed 95% 4-methylcyclohexene and 5% 1-methylcyclohexene.

Acknowledgment.—The authors are grateful to the National Institutes of Health and the National Science Foundation for fellowship aid which made this work possible.

(9) W. J. Bailey and C. King, *J. Org. Chem.*, **21**, 858 (1956).

Stereochemistry of the Deamination of Aziridines[1a,b]

RONALD D. CLARK AND GEORGE K. HELMKAMP

Department of Chemistry, University of California, Riverside, California

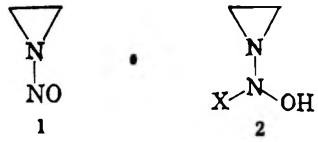
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The reaction of stereoisomers of 2,3-dimethylaziridine with nitrosating agents such as 3-nitro-N-nitrosocarbazole, nitrosyl chloride, and methyl nitrite results in the formation of nitrous oxide and 2-butene with greater than 99% stereoselective deamination. At temperatures below −20°, a yellow intermediate was isolated that exhibited infrared, ultraviolet, and n.m.r. spectra characteristic of an N-nitrosoaziridine. The *trans*-dimethyl intermediate decomposed in a first-order rate with a half-life of 11 min. in methanol at −15°, and it formed nitrous oxide and *trans*-2-butene. The yellow product could be isolated as an oil and purified by low temperature chromatography on Florisil. Certain other nitrosoaziridines, including *cis*-dimethyl, methyl, ethyl, and tetramethyl, were less stable, but nitrosoaziridine itself was more stable. The deamination of aziridines with nitrosyl chloride also led to the formation of aziridine hydrochlorides that were stable at −78°. Although the salts tended to polymerize at higher temperatures, they could be converted to stable derivatives by exchanging anions with silver 2,4,6-trinitrobenzenesulfonate.

Preliminary to a study of the cleavage of nitrogen–carbon single bonds and the synthesis of various β-substituted amines, we have investigated the possibility that N-nitroso derivatives of selected aziridines might be sufficiently stable for isolation and study. It had been shown by Bumgardner, McCallum, and Freeman[2] that aziridine was deaminated readily by 3-nitro-N-nitrosocarbazole to yield ethylene and nitrous oxide. They proposed that the mechanism of the reaction involved either formation of the nitrosamine (1) or a

(1) (a) Supported in part by Cancer Research Funds of the University of California; (b) abstracted in part from the Ph.D. thesis of R. D. Clark, University of California, 1963.

(2) C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, **83**, 4417 (1961).



related intermediate (2). Very recently, Rundel and Müller[3] reported the preparation of an ethereal solution of N-nitrosoaziridine (1), from the low temperature reaction of aziridine with nitrosyl chloride.

We now wish to report that the reaction of 2,3-dimethylaziridine with nitrosyl chloride, 3-nitro-N-nitrosocarbazole, or methyl nitrite led to nitrous oxide and 2-butene with a very high degree of stereospecificity. Furthermore, a yellow intermediate whose properties were consistent with those expected for the N-nitroso derivative was isolated and purified by low temperature chromatography. Analogous intermediates were formed from other alkyl-substituted aziridines.

Stereochemical Course of Deamination.—The reaction of 2,3-dimethylaziridines with nitrosyl chloride was carried out in carbon tetrachloride solution. For the comparable reaction with 3-nitro-N-nitrosocarbazole, refluxing benzene was used according to the procedure of Bumgardner, *et al.*[2] The yields in the two reactions were compable (Table I) if it was assumed that one

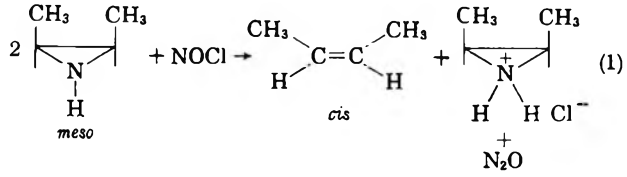
TABLE I

YIELD OF OLEFIN FROM ALKYL AZIRIDINES AND NITROSATING AGENTS

Compound	Yield, %
Aziridine	40[a]
2-Methylaziridine	57–71[b]
2-Ethylaziridine	53[b]
meso-2,3-Dimethylaziridine	43–53[c]
	43–53[b]
dl-2,3-Dimethylaziridine	19–38[c]
	37–53[b]
2,2,3,3-Tetramethylaziridine	27[d]

[a] As reported by Bumgardner, *et al.*[2] [b] Using nitrosyl chloride. [c] Using 3-nitro-N-nitrosocarbazole. [d] Using nitrosyl chloride in *p*-xylene.

additional equivalent of aziridine was consumed by the acid formed in the nitrosyl chloride reaction (eq. 1). Such a salt was isolated as a crystalline by-product.



(1)

It polymerized exothermically and gave a water-soluble product at room temperature. A similar polymerization was noted by Jones, *et al.*,[4] in the addition of anhydrous hydrogen chloride to aziridine in ether.

The stereochemical course of the deamination reactions was followed by the use of *meso*- and *dl*-2,3-dimethylaziridine. The results are shown in Table II.

The stereoisomeric 2,3-dimethylaziridines were prepared from the corresponding 2-butenes *via* the epoxides

(3) W. Rundel and E. Müller, *Ber.*, **96**, 2528 (1963).

(4) G. D. Jones, A. Langsjoen, Sister M. M. C. Neumann, and J. Zomlefer, *J. Org. Chem.*, **9**, 125 (1944).

TABLE II

STEREOSPECIFICITY OF THE DEAMINATION OF 2,3-DIMETHYLAZIRIDINES

Isomer	Reagent	Product butene, % *cis*	Product butene, % *trans*	Starting butene,[a] % *cis*	Starting butene,[a] % *trans*
cis	NOCl	99.1	0.9	99.9	0.1
trans	NOCl	0.3	99.7	1.0	99.0
cis	3-Nitro-N-nitroso-carbazole	99.6	0.4	99.9	0.1
trans	3-Nitro-N-nitroso-carbazole	0.5	99.5	1.0	99.0
trans	Methyl nitrite	<10[b]	>90[b]	1.0	99.0

[a] The sequence involved 2-butene → epoxide → aziridine → [nitrosoaziridine] → 2-butene. [b] The reaction mixture exploded and only a trace of product was recovered.

by a series of five steps.[5,6] Since both the *trans* epoxide and the *trans*-imine have lower boiling points than the *cis* isomers, it can be assumed that during their purification some of the *cis* contaminant was removed. This would account for the increase in purity of the product butene compared with the starting butene in the complete synthetic cycle (Table II). On the other hand, it would have been more difficult to effect purification of the higher boiling components in the *cis* series. Thus the increase of *trans* contaminant concentration during the cycle was not necessarily related to the deamination reaction. The deamination was most certainly better than 99% stereospecific.

It was observed by Bumgardner[7] that the treatment of *cis*-2,3-diphenylaziridine with N-nitroso-3-nitrocarbazole in refluxing benzene yielded a mixture of stilbenes containing about 10% of the *trans* isomer. The presence of *trans* isomer was accounted for by stilbene isomerism rather than from a nonstereospecific deamination mechanism because isomerization of *cis*-stilbene occurred to about the same extent under the reaction conditions.

Isolation of N-Nitrosoaziridines.—When the nitrosyl chloride reaction was carried out with *trans*-2,3-dimethylaziridine in a Dry Ice–acetone bath, a bright yellow solution was formed which was stable for several weeks at that temperature. However, when the solution was allowed to warm to room temperature, there was rapid disappearance of the yellow color and concomitant production of nitrous oxide and *trans*-2-butene. In order to isolate the colored intermediate, the nitrosation reaction was carried out in methyl ether at Dry Ice temperature, the reaction solution was decanted to separate the solid by-product, and the solvent was removed at −35 to −40° on a rotary evaporator. The oily residue was further purified by dissolving it in butane and chromatographing it on Florisil at about −50°. The solvent was again removed by evaporation at low temperature and pressure to give a product that was considered to be essentially pure.[8]

Rundel and Müller[3] carried out their nitrosation reaction using aziridine in ether at −60° with triethylamine to remove the hydrogen chloride produced.

(5) C. E. Wilson and H. J. Lucas, *J. Am. Chem. Soc.*, **58**, 2396 (1936).

(6) F. H. Dickey, W. Fickett, and H. J. Lucas, *ibid.*, **74**, 944 (1952).

(7) C. L. Bumgardner, private communication.

(8) Decomposition of the intermediate was sufficiently exothermic that it became violent if the temperature was allowed to approach ambient. Because of this, no attempts were made to obtain data on molecular weight or elemental analyses.

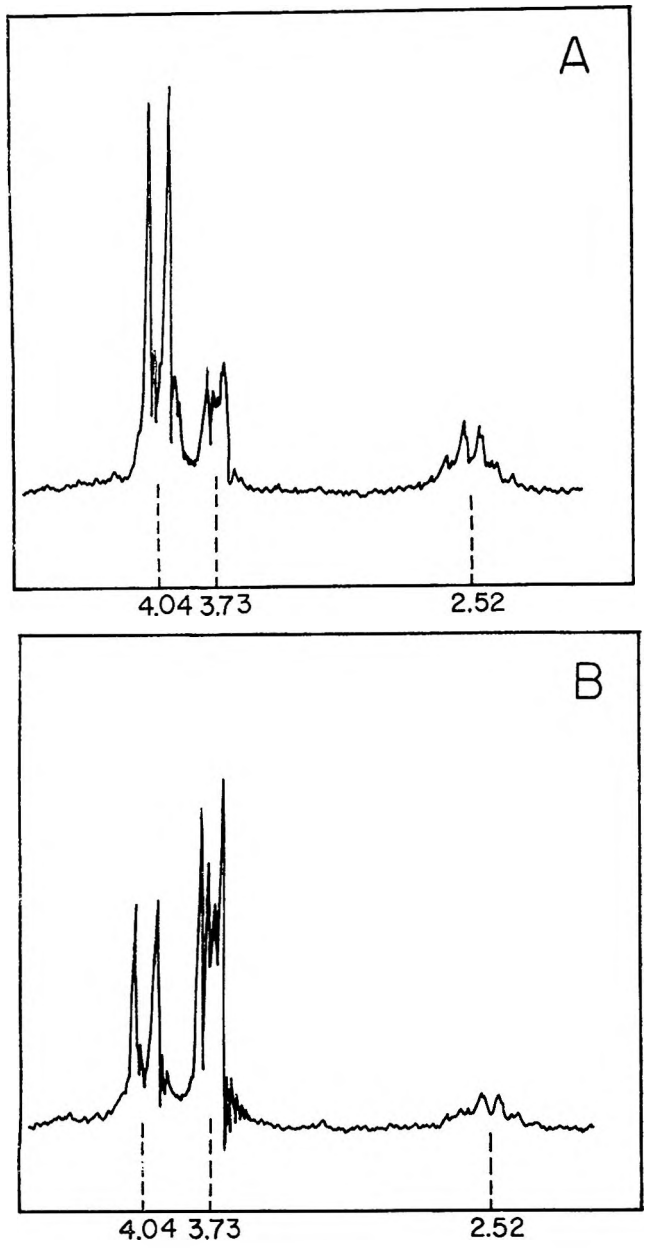


Fig. 1.—Proton n.m.r. spectra of *trans*-2,3-dimethyl-N-nitrosoaziridine in methylene chloride at −22°; shifts in p.p.m. upfield from the solvent: A, fresh sample with trace of 2-butene decomposition product at 3.73 p.p.m.; and B, same sample after more extensive decomposition.

Their evidence for the nitroso intermediate was based on its ultraviolet spectrum and largely unsuccessful attempts to isolate a stable derivative. Although we have also been unsuccessful so far in isolating a stable, solid derivative, we have additional evidence for the nitrosamine structure based on infrared, n.m.r., and ultraviolet spectroscopy.

The infrared spectrum of the yellow intermediate from *trans*-2,3-dimethylaziridine was obtained in carbon tetrachloride by warming the solution just above the melting point of the solvent and passing it through a standard 0.5-mm. sodium chloride cell. A continuous flow of solution was maintained so that fresh, cold material was always present in the cell. Spectra obtained in this manner were compared with those from the solution after it had been allowed to come to room temperature. With one minor exception, the peaks in the "warm" spectrum could be identified as belonging to carbon dioxide, nitrous oxide, and the appropriate 2-butene. The one extraneous peak occurred at 6.16 μ, and, since it also occurred in the "cold" spectrum, it was assumed to result from an impurity. The "cold" spectrum showed no N–H or O–H bands, but it did show peaks at 6.72, 6.95, and 7.62 μ related to the nitroso group and a peak at 9.60 μ related to the N–N group, in agreement with the values reported for dialkyl nitrosamines.[9] A peak at 8.25 μ was taken as evidence that the aziridine ring was still intact.[10] A peak expected at about 11.5 μ, assigned to the aziridine ring,[10] was not observed, but it was also absent in the spectrum of *trans*-2,3-dimethyl-N-methylaziridine.

The proton n.m.r. spectra[11] at −22° of the intermediate from *trans*-2,3-dimethylaziridine and its decomposition products are shown in Fig. 1. Methylene chloride was used as the solvent and internal standard. In a freshly prepared sample (Fig. 1A), two bands were observed at 2.52 and 4.04 p.p.m. upfield from the solvent and were attributed to the intermediate. The band at 4.04 p.p.m. was split into a doublet by about 5 c.p.s. and was assigned to the methyl protons. The second band, at 2.52 p.p.m., was assigned to the ring protons. It was expected that the band from these protons would be split into a quartet by the methyl group. In addition, further splitting by the *trans* proton, to give a more complex spectrum, was possible. Six peaks were easily distinguished, indicating that the splitting was more complex than that due only to the methyl group, and that the two ring protons were not identical. A very similar spectrum was observed for *trans*-2,3-dimethylaziridine, with the methyl doublet occurring at 4.3 p.p.m. and the multiplet at 3.8 p.p.m. The areas of the peaks in either case were in the ratio of 3:1. The third band (Fig. 1), at 3.73 p.p.m., was due to the methyl protons of *trans*-2-butene. The vinyl protons were masked by the solvent. As the intermediate decomposed, this peak slowly increased in magnitude while the other two peaks decreased (Fig. 1B). After the sample was warmed and the yellow color had disappeared, the butene peak was the only one remaining. Assignment of this peak was verified by comparing the shift and splitting with that of a known sample of *trans*-2-butene under the experimental conditions.

The n.m.r. spectrum of the unsubstituted nitrosoaziridine showed a single sharp peak at 2.70 p.p.m. that disappeared completely when the sample was warmed. No product peak was observed, and it was assumed that it was masked by the solvent.

The visible and ultraviolet spectra were similar to those reported for nitrosoaziridine.[3] Except for a shift in the position of maxima and somewhat less fine structure, they were also quite comparable with those of dimethylnitrosamine.[12] The ratio of intensities of the $n\rightarrow\pi^*$ band (457 mμ) and the $\pi\rightarrow\pi^*$ band (254 mμ) was about 1:100 as estimated by dilution technique. It was impossible to determine values for absorbancy because of the instability of the compound.

(9) R. N. Haszeldine and B. J. H. Mattinson, *J. Chem. Soc.*, 4172 (1955).
(10) H. T. Hoffman, Jr., G. E. Evans, and G. Glockler, *J. Am. Chem. Soc.*, **73**, 3028 (1951).
(11) Spectra were obtained with a Varian Associates V-4300 spectrometer operating at 56.4 Mc.
(12) W. S. Layne, H. H. Jaffé, and H. Zimmer, *J. Am. Chem. Soc.*, **85**, 435 (1963).

Electrochemical reduction of the yellow intermediate could be observed by polarographic means. At −25° half-wave potentials of −1.20 v. and −1.65 v. *vs.* a mercury pool were observed in ethyl ether–methanol (50% by volume) containing 0.25 *M* lithium chloride. Both waves were found to diminish with time and disappeared completely when the solution had been warmed sufficiently for the discharge of the yellow color. Large scale constant potential reduction failed to yield any significant amount of reduced product because the rate of decomposition of the nitroso compound was too rapid.[13]

An attempt was made to obtain some thermodynamic values from the polarographic data. At −15° the decomposition was followed by maintaining a constant potential of −1.5 v., but at lower temperatures (−20°, −25°, and −30°) the polarograph was placed on a 10-min. cycle. Periodic degassing was required to prevent the formation of a maximum in the polarographic wave, presumably caused by the build-up of gaseous products in the solution. The activation energy was found to be approximately 16 kcal./mole and the entropy of activation about −13 e.u. It was impossible to correlate these data closely with the rates obtained spectrophotometrically because of the use of mixed solvent and the presence of lithium chloride.

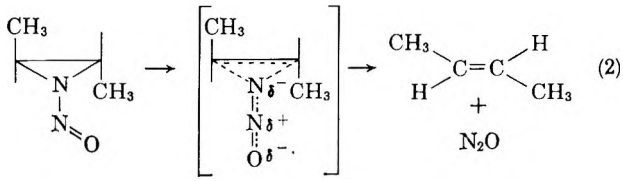
In general agreement with the data of Rundel and Müller,[3] the rate of decomposition of the intermediate was found to be first order. Additionally, in the spectrophotometric determination of rates in pure solvents, it was also observed that a tenfold increase in rate occurred when the solvent was changed from pentane to dimethylformamide (Table III).

TABLE III

RATE OF DECOMPOSITION OF *trans*-2,3-DIMETHYL-N-NITROSOAZIRIDINE IN VARIOUS SOLVENTS AT −15°

Solvent	$k_1 \times 10^2$, min.$^{-1}$	Approximate half-life, min.
Pentane	1.2 ± 0.3	58
Ethyl ether	1.8 ± 0.3	38
Methanol	6.3 ± 0.4	11
Dimethylformamide	13 ± 4	5

Since the reaction was first order in nitrosamine, and product formation was stereospecific, it seemed likely that the transition state involved a concerted cleavage of the two C–N bonds (eq. 2). The charge



(2)

separation related to the incipient formation of the nitrous oxide molecule could account for a small-to-moderate solvent dependence of reaction rates. In contrast, in the desulfurization of 2,3-dimethylthiirane with triphenylphosphine[14] in which a similar concerted bond cleavage was postulated, the observed change of rate with change in solvent was very small.

Maximum thermal stability among the various substituted nitrosoaziridines was observed with the *trans*-dimethyl isomer. The corresponding *cis*-dimethyl isomer decomposed so rapidly that it could not be purified at −35 to −40°. The methyl, ethyl, and tetramethyl intermediates were also less stable than the *trans*-dimethyl intermediate. However, the unsubstituted material was more stable, having a half-life in ethyl ether at −15° of about 256 min., compared to about 38 min. for the *trans* isomer.

The decomposition of *trans*-2,3-dimethyl-N-nitrosoaziridine was found to be catalyzed by acids. Although the compound was stable for long periods of time at −78°, the presence of a small amount of sulfuric acid induced a noticeable rate of decomposition. Better solvation in the transition state through hydrogen bonding or more formal protonation would be expected in the presence of acids. Such interactions have been proposed[12,15] as an explanation for the effect of acids on the spectra of dialkyl nitrosamines.

Isolation of Aziridine Salts.—The aziridine hydrochlorides formed from the reaction of aziridines with nitrosyl chloride were isolated as crystalline solids after the nitrosamines were separated. Although they appeared to be stable indefinitely at −78°, all except the salt of tetramethylaziridine polymerized exothermically when allowed to warm to room temperature. A similar polymerization was reported for the hydrochloride formed from aziridine and anhydrous hydrogen chloride in ether.[4] On the other hand, the hydrochloride of 2,2-dimethylaziridine, isolated in 90% yield from an ether solution at −77°, was found to be stable in dry air at room temperature for several days.[16] This hydrochloride, shown to be a monomer by quantitative conversion to the known picrate, polymerized to a water-soluble polymer at its melting point of 54–56°.[16]

The yield of polymer in the nitrosyl chloride reaction was usually somewhat greater than 100% based on the previously suggested stoichiometry. Up to 94% of the original aziridine was accounted for in the specific case of 2-methylaziridine, where 71% propene and 117% polymer were isolated. The excess material in the polymer was probably a complex mixture of side products formed by ring cleavage and diazotization of the resulting amine.

The unstable hydrochlorides of aziridine and 2-methylaziridine were converted to stable derivatives by treating them with an acetonitrile solution of silver 2,4,6-trinitrobenzenesulfonate.[17] After the precipitated silver chloride was removed by filtration, the aziridine trinitrobenzenesulfonate was precipitated by the addition of ether. The hydrochloride could not be converted directly to the trinitrobenzenesulfonate with the acid because the resulting product was unstable, probably owing to hydrogen chloride trapped in the product.

Structure proof for the aziridinium salts was based on syntheses by independent routes. The trinitrobenzenesulfonates were prepared directly by the reaction of the aziridine with trinitrobenzenesulfonic

(13) That an intermediate of type **2**, where X = Cl, was not present in the original solution was shown by the absence of any precipitate when the solution was treated with silver nitrate.

(14) D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, **82**, 4736 (1960).

(15) W. S. Layne, H. H. Jaffé, and H. Zimmer, *ibid.*, **85**, 1816 (1963).

(16) L. B. Clapp, private communication; data from the Ph.D. thesis of V. B. Schatz, Brown University, 1954.

(17) The authors are indebted to D. J. Pettitt for providing the silver 2,4,6-trinitrobenzenesulfonate.

acid or indirectly by forming the hydrochloride at low temperatures and converting this with silver trinitrobenzenesulfonate. Salts from all sources were found to have identical infrared spectra, melting points, and mixture melting points. Furthermore, the materials had the expected elemental analyses for a simple salt and the correct molecular weight for a monomeric species.

Experimental

Aziridines.—Aziridine was donated by the Dow Chemical Company, Midland, Mich. The 2-methylaziridine and 2-ethylaziridine were purchased from Interchemical Corporation, 67 West 44th Street, New York 36, N. Y. Stereospecific *cis*- and *trans*-2,3-dimethylaziridine were prepared from the corresponding 2-butene isomers *via* the epoxide.[5,6] The 2,2,3,3-tetramethylaziridine was prepared according to the method of Closs and Brois.[18]

***trans*-2,3-Dimethyl-N-nitrosoaziridine.**—A solution of 3.30 g. (0.0503 mole) of nitrosyl chloride in 50 ml. of methyl ether was added slowly and with stirring to 7.1 g. (0.100 mole) of freshly distilled *trans*-2,3-dimethylaziridine in 100 ml. of the same solvent in a bath at −78°. After about 2 hr. at this temperature, when the precipitated aziridine hydrochloride had settled, the yellow solution was separated by decantation. The residue was washed with several 25-ml. portions of cold methyl ether. The solvent in the combined ethereal solutions was removed in a rotary evaporator at 25-mm. pressure and −35 to −40°. Ther esidual oil was dissolved in a small amount of butane and placed on a Florisil chromatographic column kept at about −50°. Methanol at about −50° was continuously circulated through a jacket surrounding the column, and a vacuum jacket surrounded the entire working length of the apparatus. The yellow material was eluted with butane containing a small amount of methyl ether and collected in a cold receiver. The purified product was reisolated by evaporation of the solvent as previously described.

Deamination of Aziridines.—As an example of a typical deamination procedure, 7.1 g. (0.10 mole) of freshly distilled *cis*-2,3-dimethylaziridine in 75 ml. of carbon tetrachloride was placed in a 300-ml. flask containing (a) an addition funnel and (b) a reflux condenser connected in series with two Dry Ice traps. A solution of 3.3 g. (0.050 mole) of nitrosyl chloride in 50 ml. of carbon tetrachloride was added with stirring. Both solutions were kept just above the freezing point of the solvent during this period of about 15 min. After the yellow solution was slowly allowed to warm to room temperature, it was refluxed for 2 hr. The yield of butene, determined volumetrically in the liquid phase and based on the stoichiometry of eq. 1, was 43–53%. The distribution of butene isomers was determined by chromatography with a 15-ft. column of Dow 11 silicone oil on firebrick. No other low-boiling hydrocarbon products were detected. Nitrous oxide was isolated by adding a liquid nitrogen trap to the collection system, and it was identified by chromatography on a 6-ft. silica gel column.

Reaction of 2-Methylaziridine with 2,4,6-Trinitrobenzenesulfonic Acid.—A solution of 5.7 g. (0.10 mole) of 2-methylaziridine in 50 ml. of acetonitrile was added to 35 g. (0.12 mole) of 2,4,6-trinitrobenzenesulfonic acid dissolved in a minimum quantity of acetonitrile. The product was precipitated by the addition of anhydrous ether. Recrystallization from acetonitrile–ether yielded 30 g. (86%) of a white solid. The melting point of the product was highly dependent on the rate of heating and the degree of preheating; when the oil bath was preheated to 150° and the rate of heating was about 10°/min., the material decomposed at 173–174°.

Anal. Calcd. for $C_9H_{10}N_4O_9S$: C, 30.86; H, 2.88; N, 16.00; mol. wt., 350. Found: C, 30.90; H, 2.74; N, 15.95; mol. wt. (crystalline material), 352 ± 3.[19]

Aziridinium 2,4,6-Trinitrobenzenesulfonate.—The aziridinium trinitrobenzenesulfonate was prepared in the same manner as the 2-methylaziridinium salt. The product decomposed sharply at 189° when the bath was preheated to 175° and the rate of heating was about 10°/min.

Anal. Calcd. for $C_8H_8N_4O_9S$: C, 28.58; H, 2.40; N, 16.66; mol. wt., 336. Found: C, 28.90; H, 2.75; N, 16.79; mol. wt., 350 ± 6.[19]

Reaction of Aziridine Hydrochlorides with Silver 2,4,6-Trinitrobenzenesulfonate.—A small amount of an aziridine hydrochloride was dissolved in cold acetonitrile and added to an excess of silver 2,4,6-trinitrobenzenesulfonate in the same solvent. In the absence of excess silver salt the solution turns deep red. The solution was filtered to remove silver chloride, and the product was precipitated by the addition of anhydrous ethyl ether. Recrystallization from acetonitrile–ether yielded a product identical with that described above for the direct preparation of the salt.

Kinetic Procedure.—Samples of consistent (but unknown) concentration of the nitrosamines were prepared by adding small amounts of the yellow oil to the cold solvent in a spectrophotometer cell until the absorbancy of the solution was very near unity at 450 mμ. The cell, which had a jacket for circulation of coolant, and which was protected from moisture condensation by an air space isolated by pairs of quartz windows, was quickly brought to the temperature of the kinetic run (as determined by a thermocouple in the nitrosoaziridine solution). The decompotion was followed spectrophotometrically at the indicated wave length.

The addition of pellets of potassium hydroxide to a solution used for kinetic measurement had no effect on the rate of decomposition. Hence it was assumed that separation of nitrosoaziridine from aziridine salt in the synthetic procedure had been complete and no acid catalysis was involved during the rate studies.

Acknowledgment.—The authors wish to express their appreciation to Dr. C. L. Bumgardner for his helpful discussion of the problem and for his generosity in providing his stereochemical data on the stilbene system. We are also indebted to Dr. L. B. Clapp for his data on 2,2-dimethylaziridine hydrochloride, to Mr. J. F. Sebastian and Mr. M. P. Schweizer for n.m.r. spectra, and to Mr. E. T. Seo for assistance in making polarographic measurements.

(18) G. L. Closs and S. J. Brois, *J. Am. Chem. Soc.*, **82**, 6068 (1960).

(19) Determined with a Mechrolab Model 301A osmometer using acetonitrile solvent and dimethylamine trinitrobenzenesulfonate as a standard.

Studies in Ozonolysis. IV. Steric Effects in Determining the Existence of the Molozonide[1]

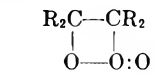
FRED L. GREENWOOD

Contribution No. 318, Department of Chemistry, Tufts University, Medford, Massachusetts

Received December 17, 1963

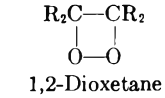
Ozonation of alkenes in ether solution at −112° followed by treatment with isopropyl Grignard reagent at this temperature gave propene, propane, and 2-propanol as reaction products. From various alkenes the following additional products were obtained: *trans*-2-pentene gave *threo*-pentane-2,3-diol and minor amounts of 3-methyl-2-butanol and 2-methyl-3-pentanol; *trans*-3-hexene gave *dl*-hexane-3,4-diol and a minor amount of 2-methyl-3-pentanol; 1-pentene gave pentane-1,2-diol, 2-methyl-1-propanol, and 2-methyl-3-hexanol; *cis*-2-pentene gave 3-methyl-2-butanol and 2-methyl-3-pentanol, but no α-diol; *cis*-3-hexene gave 2-methyl-3-pentanol, but no α-diol. The products from the *trans* alkenes and 1-pentene indicate that a stable molozonide, assumed to be a 1,2,3-trioxolane, resulting from the stereospecific *cis* addition of ozone to the carbon–carbon double bond was formed. Such a species would appear not to have been formed in the reaction of ozone with the *cis* alkenes. The various alcohols are assumed to have been formed by reaction of ozonide with the Grignard reagent. These data may be explained by the steric interaction between two *cis* alkyl groups and the lone pair orbitals on the oxygen atoms of the molozonide being so great as to prohibit a stable structure, whereas, when the two alkyl groups are *trans*, the steric interactions are markedly diminished and a stable molozonide may be formed.

From the fact that a monomeric ozonide could not be converted to the polymeric ozonide, Staudinger[2] concluded that these materials must be secondary reaction products which arise from a primary reaction product. This primary product was called a molozonide, and it was formulated as the following.



Molozonide

The reason for this formulation was simply that Staudinger also was interested in autoxidation of alkenes, and he was trying to correlate ozonation and autoxidation. There were many similarities between these two reactions; the initial product of autoxidation was believed to be a moloxide which was formulated as a 1,2-dioxetane; hence the molozonide was formulated as indicated above. Staudinger postulated that this molozonide could rearrange to the ozonide, it could polymerize, it could revert to reactants, or it could fragment to carbonyl compounds, carboxylic acids, and ketone diperoxide.



1,2-Dioxetane

In the years following Staudinger's postulation of a molozonide there were attempts to obtain evidence for this species. One of the more careful studies was that reported by Pummerer and Richtzenhain,[3] but they could find no evidence for an α-diol, which would be the expected reduction product of the molozonide. It was not until 1960 that some firm evidence for the existence of the molozonide appeared. Criegee and Schröder[4] reported the results of some experiments with *cis*- and *trans*-di-*t*-butylethylene, and these results clearly showed that the *trans* alkene gave a molozonide which was stable at −75° but which rearranged at a somewhat higher temperature to the ozonide. The *cis* alkene–ozone reaction gave no evidence of the formation of a molozonide. It was stated that one could say nothing about why the molozonide could be isolated in the case of the *trans* alkene, and that similar experiments with related alkenes were unsuccessful in detecting the existence of a molozonide.

While another facet of the alkene–ozone reaction was pursued, it was decided to carry out ozonations at a temperature below −75°, which, by and large, had been the lowest temperature employed to that time. At the conclusion of the ozonation of a relatively concentrated solution of 3-octene in *n*-pentane at −95°, white crystals were present. These crystals exhibited the behavior observed earlier by Criegee and Schröder[4] for their molozonide; *i.e.*, on warming to −85° the reaction mixture underwent a mild eruption, the crystals disappeared, and the temperature of the solution was −65°. In a second ozonation of 3-octene in *n*-pentane at −95° the ozonation mixture was treated at −95° with isopropyl Grignard reagent. From this reaction mixture was obtained *n*-butylisopropylcarbinol, ethylisopropylcarbinol, and a high-boiling residue which gave a positive test for α-diol with periodic acid. These results indicated that it might be advantageous to examine the ozonation at a low temperature of some simple alkenes, and Criegee and Schröder's results indicated it might be worthwhile to examine *cis* and *trans* alkenes.

Since the molozonide of simple alkenes would appear to be an unstable species, in experiments designed to detect it one should use as low a temperature as possible. The boiling point of ozone is reported as −112°. It was considered injudicious to introduce liquid ozone into an alkene solution, hence a temperature of −112° was used for the ozonations and the treatment of the ozonation mixture with isopropyl Grignard reagent. The ozonations were carried out in dilute ether solution to avoid separation of solid material on addition of the Grignard reagent. The reaction mixture was refluxed until the evolution of gas ceased. In every case this gas contained propene and propane. Hydrolysis of the reaction mixture was effected with aqueous ammonium chloride, and the mixture refluxed to obtain propane as a measure of the excess Grignard reagent. The liquid reaction products were separated by distillation into low-boiling and high-boiling (when present)

(1) Presented at the Southwest Regional Meeting, American Chemical Society, Houston, Texas, Dec. 5–7, 1963.

(2) H. Staudinger, *Ber.*, **58**, 1088 (1925).

(3) R. Pummerer and H. Richtzenhain, *Ann.*, **529**, 33 (1937).

(4) R. Criegee and G. Schröder, *Chem. Ber.*, **93**, 689 (1960).

materials. The low-boiling material was a mixture of alcohols, and the high-boiling material, when obtained, was primarily α-diol. Considerable isopropyl alcohol was present in the low-boiling material from each experiment.

From *trans*-2-pentene was obtained a good yield of *threo-dl*-pentane-2,3-diol and smaller amounts of methylisopropylcarbinol and ethylisopropylcarbinol. Authentic *threo-* and *erythro*-pentane-2,3-diol were completely separated by vapor phase chromatography (v.p.c.) on a phenyldiethanolamine succinate (PDEAS) column. The diol from the alkene by v.p.c. gave a *threo*-diol peak which exhibited no evidence of a shoulder; hence this *threo*-diol would appear to be free of the *erythro* isomer. Identity of the *threo*-diol was verified by the preparation of a bis-3,5-dinitrobenzoate. The two carbinols are assumed to arise by reaction of the Grignard reagent with a small amount of the ozonide present in the ozonation mixture. *trans*-3-Hexene gave a respectable yield of *dl*-hexane-3,4-diol and a minor amount of ethylisopropylcarbinol. This carbinol supposedly arose from reaction of a small amount of ozonide with the Grignard reagent. Since the phenyldiethanolamine succinate column effectively separated *threo-* and *erythro*-pentane-2,3-diol, it was assumed that the column could separate *dl-* and *meso*-hexane-3,4-diol. The diol from the hexene by v.p.c. gave a *dl* peak which had no evidence of a shoulder; hence this *dl*-diol would appear to be free of the *meso* isomer. Verification of the *dl*-diol was made by the preparation of a bis-3,5-dinitrobenzoate. 1-Pentene gave rise to isobutyl alcohol and *n*-propylisopropylcarbinol, supposedly by interaction of the ozonide and the Grignard reagent, and pentane-1,2-diol. The identity of the diol was confirmed by the preparation of a bisphenylurethane.

cis-2-Pentene gave good yields of methylisopropylcarbinol and ethylisopropylcarbinol, and *cis*-3-hexene gave a good yield of ethylisopropylcarbinol. In neither case could any α-diol be detected.

One would expect propene from the reaction of ozonized alkene and isopropyl Grignard reagent, for the reaction of di-*t*-butyl peroxide with Grignard reagents has been reported[5] to give an alkene from the Grignard reagent. Isopropyl alcohol and propane, also, would be expected reaction products, for *t*-butyl hydroperoxide on reaction with the Grignard reagent has been reported[6] to give an alkane and an alcohol corresponding to the Grignard reagent. In the present experiments it is difficult to understand the large amount of propane formed unless one assumes that the ozone was reacting to some extent with the ether to form an active hydrogen-containing compound. Indeed, ether cooled to −112° did react avidly with ozone. That not all of the ozone introduced into the alkene–ether solution was reacting with the alkene is indicated by material balance calculations. In each experiment the identified products account for about 80% of the carbon in the reactants, whereas the products account for but 65–70% of the ozone introduced into the reaction mixture. One way of explaining this low oxygen balance would be for some of the ozone to effect an oxidation of the ether and lose some oxygen in the process.

To rule out the possibility of any of the α-diol found in the above-described experiments having been formed by the Grignard reagent effecting condensation of an aldehyde, propionaldehyde and isopropyl Grignard reagent were subjected to the same reaction conditions and work-up procedure as used in the ozonation experiments. A surprisingly large amount (0.72 g. from 3.73 g. of aldehyde) of high-boiling material was obtained, but this material gave a negative test for α-diol with periodic acid.

The experiments with *trans*-2-pentene, *trans*-3-hexene, and 1-pentene indicate that there was a stable species which resulted from the stereospecific *cis* addition of ozone to the carbon–carbon double bond, and this species was stable at a temperature where it would react with the isopropyl Grignard reagent. In the case of *cis*-2-pentene and *cis*-3-hexene, it is clear that, if a species resulting from *cis* addition of ozone was formed, it was not stable at a temperature where it would react with the Grignard reagent. This *cis* addition species is the molozonide, and it is formulated as a 1,2,3-trioxolane. In such a structure the valence orbitals of each oxygen atom will assume a tetrahedral arrangement. This means that each oxygen atom will have an orbital containing a lone pair of electrons projecting above the trioxolane ring and such an orbital projecting below the plane of the ring. These orbitals will have some space requirement, and the question is "how much?".

Barton and Cookson[7] by analogy with some carbanion chemistry made the suggestion that piperidine should exist predominantly in that conformation with the hydrogen atom on the nitrogen atom in an axial position. Aroney and LeFèvre[8] concluded from dipole moment studies with piperidine that the space requirement for a lone pair orbital appeared to exceed that of a covalently bound hydrogen atom. Later, from some studies on N-methylpiperidine they[9] concluded that the lone pair orbital must have a space requirement approaching that of a methyl group. If one accepts the more modest space requirement for the lone pair orbital, one can simulate a model for a trioxolane by constructing a model for cyclopentane in which the hydrogen atoms on three contiguous carbon atoms represent the space requirement of the lone pair orbitals of the oxygen atoms in a trioxolane. If in such a model one places two ethyl groups or a methyl and an ethyl group in a *cis* configuration, one finds the alkyl groups can be fitted into the model but they are permitted almost no rotational freedom.

At present the working hypothesis is that a molozonide will not be stable if a methyl and an ethyl or any pair of larger alkyl groups are in a *cis* configuration; the steric interactions between the alkyl groups and the lone pair orbitals do not permit a stable molecule. In a molozonide of *trans* configuration the steric interactions are considerably diminished, and such a structure is stable. Hence, a *trans* alkene on ozonation will form a molozonide as an intermediate: if the temperature at which the ozonation is carried out is low enough, the molozonide will be stable; if the temperature is

(5) T. W. Campbell, W. Burney, and T. L. Jacobs, *J. Am. Chem. Soc.*, **72**, 2735 (1950).

(6) S.-O. Lawesson and N. C. Yang, *ibid.*, **81**, 4230 (1959).

(7) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(8) M. Aroney and R. J. W. LeFèvre, *Proc. Chem. Soc.*, 82 (1958).

(9) M. Aroney and R. J. W. LeFèvre, *J. Chem. Soc.*, 3002 (1958).

too high, the molozonide will not be stable and will rearrange to the more stable ozonide. A *cis* alkene on ozonation will not form a molozonide, but will form the ozonide directly.

Experimental

Chemicals.—***n*-Pentane** (pure grade, Phillips Petroleum Co.) was treated with excess ozone at −40°; the pentane was entrained with a stream of nitrogen and extracted successively with aqueous potassium iodide, aqueous sodium thiosulfate, and water. Finally, it was filtered through a pad of phosphorus pentoxide.

Ethyl ether (analytical reagent, anhydrous, Mallinckrodt) was stored over sodium ribbon.

Propionaldehyde (Matheson Coleman and Bell) was distilled under a nitrogen atmosphere through a spinning-band column (7-mm. i.d. × 600 mm.), b.p. 47.7° (758 mm.), n^{25}D 1.3600.

Isopropyl bromide (Matheson Coleman and Bell) was distilled through a Fenske column (20-mm. i.d. × 760 mm.), b.p. 60° (759 mm.).

3-Octene was prepared by a Boord synthesis, b.p. 122.8° (748 mm.), n^{25}D 1.4112.

1-Pentene (research grade, Phillips Petroleum Co.) was distilled through a spinning-band column under a nitrogen atmosphere, b.p. 29.8° (757 mm.).

***cis*- and *trans*-2-pentene** and ***cis*- and *trans*-3-hexene** were API standard samples (Carnegie Institute of Technology).

1,2-Pentanediol was prepared from 1-pentene by the method of Emmons, *et al.*,[10] b.p. 70° (0.7 mm.), n^{25}D 1.4372; lit.[10] b.p. 78–80° (0.3 mm.), n^{20}D 1.4400.

***erythro-dl*-Pentane-2,3-diol** was prepared from *trans*-2-pentene by the method of Emmons, *et al.*,[10] b.p. 52° (1 mm.), n^{25}D 1.4406; lit.[11] b.p. 93.5° (13 mm.), n^{20}D 1.4431.

***threo-dl*-Pentane-2,3-diol** was prepared from *cis*-2-pentene by the method of Emmons, *et al.*,[10] b.p. 54° (1 mm.), n^{25}D 1.4335; lit.[11] b.p. 88.5° (13 mm.), n^{20}D 1.4370.

Ozonation Procedure.—An ozonizer[12] operating at an oxygen flow rate of 13.0 l./hr. produced an ozone–oxygen solution containing 1.5–2.0 vol. % of ozone. The ozone concentration remained constant during each ozonation. The ozone–oxygen solution was bubbled into the alkene solution which was cooled to the appropriate temperature until the desired amount of ozone had been introduced.

Ozonation of 3-Octene.—Ozone (18.0 mmoles) was introduced into a solution of 2.24 g. (20.0 mmoles) of 3-octene in 40 ml. of *n*-pentane which was cooled to −95° (frozen acetone bath). At the conclusion of the ozonation white crystals were present. A thermometer was placed directly into the reaction mixture and it was allowed to warm. At a temperature of −85° the reaction mixture underwent a mild eruption; after the eruption the solution temperature was −65° and the crystals had disappeared. The crystals would appear to be molozonide, and their behavior paralleled that observed by Criegee and Schröder[4] in an experiment with *trans*-di-*t*-butylethylene.

Reaction of Ozonized 3-Octene with Isopropyl Grignard Reagent.—At the conclusion of the addition of 38.0 mmoles of ozone to a solution of 4.48 g. (40.0 mmoles) of 3-octene in 100 ml. of *n*-pentane which was cooled to −95°, no crystals were present. The reaction mixture was purged with nitrogen for 0.75 hr. The reaction flask was fitted with a stirrer, dropping funnel, and thermometer well. During the dropwise addition of 200 ml. of 2.2 *M* isopropylmagnesium bromide the temperature of the reaction mixture was not permitted to rise above −90°. At the conclusion of the addition considerable solid material had separated. After standing overnight the reaction mixture was refluxed for 0.5 hr. Gas (presumably propene) which decolorized bromine–water was evolved during the reflux period. After hydrolysis of the reaction mixture with aqueous sulfuric acid and ether extraction of the aqueous layer, the combined extracts and organic layer was dried over sodium sulfate.

After removal of the ether and pentane through the Fenske column the residue was distilled through a spinning-band column at 1 mm. to effect a separation of the more volatile from the less volatile material. The residue (0.86 g.) gave a positive test for α-glycol with periodic acid. The more volatile material was distilled through the spinning-band column to give 1.54 g. (15.1 mmoles) of 2-methyl-3-pentanol, b.p. 52° (29 mm.), n^{25}D 1.4148 [authentic alcohol,[13] b.p. 52° (31 mm.), n^{25}D 1.4148, 3,5-dinitrobenzoate m.p. 89.4–90.2°], 2.25 g. (17.3 mmoles) of 2-methyl-3-heptanol, b.p. 83° (29 mm.), n^{25}D 1.4240 [lit.[14] b.p. 76° (20 mm.), n^{25}D 1.4246], and various intermediate fractions.

Reaction of Ozonized *trans*-3-Hexene with Isopropyl Grignard Reagent.—A solution of 3.20 g. (38.0 mmoles) of *trans*-3-hexene in 400 ml. of ether was cooled to −112° (frozen ether bath) and 1.73 g. (36.1 mmoles) of ozone was added. Nitrogen was passed through the reaction mixture for 1 hr. to purge it of oxygen. The reaction flask was fitted with a stirrer, dropping funnel, and thermometer well. During the addition of 300 ml. of 1.14 *M* (342 mmoles) isopropylmagnesium bromide the temperature of the reaction mixture did not rise above −110°. After standing overnight, the reaction mixture was refluxed for 15 min. During reflux gas that decolorized bromine–water was evolved. The reaction flask was cooled and the mixture was hydrolyzed with aqueous sulfuric acid. The aqueous layer was extracted in a continuous extractor with alcohol-free ether, the combined ether solutions were dried over sodium sulfate, and the ether was removed through the Fenske column. The residue was distilled through a spinning-band column to give a forerun containing an uncertain amount of isopropyl alcohol. That this forerun contained isopropyl alcohol was verified by the preparation from it of isopropyl 3,5-dinitrobenzoate, m.p. and m.m.p. 121.8–122.2°. Also obtained were 1.25 g. (12.2 mmoles) of 2-methyl-3-pentanol, b.p. 56° (31 mm.), n^{25}D 1.4138–1.4148, 3,5-dinitrobenzoate m.p. and m.m.p. 87.2–88.6° (lit.[13] *vide supra*); and 2.05 g. (17.3 mmoles) of *dl*-hexane-3,4-diol, b.p. 69–72° (3 mm.), n^{25}D 1.4275–1.4415, bis-3,5-dinitrobenzoate m.p. 166.2–167.4° (lit. n^{20}D 1.4412,[15] bis-3,5-dinitrobenzoate[16] m.p. 167–168°).

Reaction of Ozonized *cis*-3-Hexene with Isopropyl Grignard Reagent.—An experiment with 3.09 g. (36.7 mmoles) of *cis*-3-hexene, 1.67 g. (34.8 mmoles) of ozone, and 300 ml. of 1.13 *M* (339 mmoles) isopropylmagnesium bromide was carried out as described above. After removal of ether the residue gave a negative test for α-glycol with periodic acid. Distillation of the residue through the spinning-band column gave 1.31 g. (21.8 mmoles) of isopropyl alcohol, b.p. 71–81° (759 mm.), n^{25}D 1.3750–1.3755, 3,5-dinitrobenzoate m.p. and m.m.p. 122.6–123.2°; and 4.80 g. (47.0 mmoles) of 2-methyl-3-pentanol, b.p. 52.0–52.2° (31 mm.), n^{25}D 1.4130–1.4138, 3,5-dinitrobenzoate m.p. and m.m.p. 86.8–87.7° (lit.[13] *vide supra*). The 0.44 g. of distillation residue gave a negative test for α-glycol.

General Procedure for Reaction of Ozonized Alkenes with Isopropyl Grignard Reagent.—A solution of the alkene (*ca.* 40 mmoles) in 400 ml. of ether was cooled to −112° and 95% of the theoretical amount of ozone was added. After standing for 30 min. while the oxygen of the ozonizer was displaced with nitrogen, the reaction mixture was purged of oxygen by bubbling nitrogen through it for 1 hr. The reaction flask was fitted with a stirrer, dropping funnel, thermometer well, and outlet tube which was connected to a Dry Ice–alcohol-cooled trap which was protected with a mercury trap. During the dropwise addition of a known amount of Grignard reagent the temperature of the reaction mixture did not rise above −110°. During a 2-day period the reaction mixture warmed to 10°, and nothing had condensed in the Dry Ice–alcohol-cooled trap. The dropping funnel was replaced by a reflux condenser which was connected to a gas-collecting bottle containing saturated salt solution. The outlet tube was sealed and the reaction mixture refluxed until no more gas was evolved (1 hr.). This gas was analyzed by v.p.c. (Wilkens Aerograph Model A-110-C, 20-ft. dimethylsulfolane column) and by mass spectrometry.[17] The reaction mixture was cooled to −15° with a salt–ice bath. It is necessary to keep a record of the nitrogen dissolved by the reaction mixture during this cooling. After hydrolysis by the addition of saturated, aqueous ammonium chloride, the reaction mixture was refluxed until the evolution of

(10) W. D. Emmons, A. S. Pagano, and J. P. Freeman, *J. Am. Chem. Soc.*, **76**, 3472 (1954).

(11) H. van Risseghem, *Bull. soc. chim. France*, 1661 (1959).

(12) F. L. Greenwood, *Ind. Eng. Chem., Anal. Ed.*, **17**, 446 (1945).

(13) Prepared from propionaldehyde and isopropyl Grignard reagent.

(14) G. L. Dorough, H. B. Glass, T. L. Gresham, G. B. Malone, and E. E. Reid, *J. Am. Chem. Soc.*, **63**, 3100 (1941).

(15) E. von Rudloff, D. E. Stuetz, and H. F. Bauer, *Can. J. Chem.*, **35**, 315 (1957).

(16) W. G. Young, S. J. Cristol, and F. T. Weiss, *J. Am. Chem. Soc.*, **65**, 1245 (1943).

(17) The author indebted to the Texas Research Laboratories, Beacon, N. Y., for the mass spectrometric analyses.

gas ceased (0.75 hr.). This gas was twice led through concentrated sulfuric acid to remove the ether, and the amount of the residual gas was a measure of the excess Grignard reagent. The addition of a small amount of sulfuric acid to the reaction mixture was necessary to break the emulsion. The aqueous layer was placed in a continuous extractor with alcohol-free ether. The combined ether solutions were dried over sodium sulfate, and the ether was removed through the Fenske column.

The residue was distilled *in vacuo* from a Claisen flask with a Vigreux distilling arm, first at 5 mm. to obtain the more volatile material and then at 0.1 mm. to obtain the high-boiling material. The more volatile material was a mixture of alcohols which was analyzed by v.p.c. (5% cyanosilicone on hexamethyldisilazane-treated Chromosorb W column). The composition (wt. %) of the mixture was calculated from the relative peak areas. The composition of known mixtures of isopropyl alcohol and 2-methyl-3-pentanol which was determined in this manner agreed within 2–3% of the known concentrations. This more volatile material was distilled through a small spinning-band column (7-mm. i.d. × 200 mm.); each fraction was subjected to v.p.c.; and the various alcohols were verified by comparison of their infrared spectra[18] with those of authentic alcohols. The high-boiling material was subjected to v.p.c. (30% phenyldiethanolamine succinate on hemamethyldisilazane-treated Chromosorb W column) to identify the diol, and the composition (wt. %) of the material calculated from the relative peak areas. The identity of the diol was verified by the preparation of a derivative.

trans-**2-Pentene**.—Alkene used was 3.08 g. (43.9 mmoles); ozone introduced, 41.7 mmoles; and Grignard reagent reacted, 155 mmoles. Refluxing the ozonation mixture gave 28.9 mmoles of propene and 54.7 mmoles of propane. The more volatile material (3.01 g.) contained isopropyl alcohol, 30.1 mmoles; 3-methyl-2-butanol, 8.2 mmoles; and 2-methyl-3-pentanol, 5.4 mmoles. The high-boiling material (2.68 g.) contained 23.2 mmoles of *threo-dl*-pentane-2,3-diol and 10 wt. % of unidentified material. The phenyldiethanolamine succinate column effected a complete separation of authentic *threo*- (smaller retention time) and *erythro*-pentane-2,3-diol. Since the *threo*-diol peak of the v.p.c. curve of the high-boiling material did not have a shoulder, one may conclude that little, if any, *erythro*-diol was in the reaction mixture. The high-boiling material gave the bis-3,5-dinitrobenzoate of *threo-dl*-pentane-2,3-diol, m.p. and m.m.p. 159.5–161.4°; lit.[19] m.p. 160.5°. After distillation of the high-boiling material a residue of 0.23 g. remained.

cis-**2-Pentene**.—Alkene used was 3.04 g. (43.4 mmoles); ozone introduced, 41.2 mmoles; and Grignard reagent reacted, 157 mmoles. Refluxing the ozonation mixture gave 22.2 mmoles of propene and 43.2 mmoles of propane. The more volatile material (6.36 g.) contained isopropyl alcohol, 25.1 mmoles; 3-methyl-2-butanol, 27.5 mmoles; and 2-methyl-3-pentanol, 23.1 mmoles. High-boiling material (0.57 g.) was obtained, but it gave a negative α-glycol test and v.p.c. showed it to contain no pentane-2,3-diol. Hence, no diol was formed in this reaction. A residue of 0.18 g. remained after the high-boiling material was collected.

trans-**3-Hexene**.—Alkene used was 3.36 g. (39.9 mmoles); ozone introduced, 37.9 mmoles; and Grignard reagent reacted, 133 mmoles. Refluxing the ozonation mixture gave 28.2 mmoles of propene and 48.4 mmoles of propane. The more volatile material (2.80 g.) contained isopropyl alcohol, 32.9 mmoles; and 2-methyl-3-pentanol, 7.5 mmoles. The high-boiling material (2.99 g.) contained 16.4 mmoles of *dl*-hexane-3,4-diol and 35% of unidentified material. Since the phenyldiethanolamine succinate column separated *threo*- and *erythro*-pentane-2,3-diol, it was assumed that it would separate *dl*- and *meso*-hexane-3,4-diol. The diol peak in the v.p.c. curve of the high-boiling material had no indication of a shoulder; hence *meso*-diol is assumed to be absent. A residue of 0.67 g. remained after the high-boiling material was collected.

cis-**3-Hexene**.—Alkene used was 3.24 g. (38.5 mmoles); ozone introduced, 36.6 mmoles; and Grignard reagent reacted, 130 mmoles. Refluxing the ozonation mixture gave 16.2 mmoles of propene and 24.3 mmoles of propane. The more volatile material (6.65 g.) contained isopropyl alcohol, 26.0 mmoles; and 2-methyl-3-pentanol, 49.5 mmoles. No high-boiling material could be obtained, and a distillation residue of 0.37 g. remained. All of the products gave a negative α-glycol test; hence no diol was formed in this reaction.

1-Pentene.—Alkene used was 3.02 g. (43.1 mmoles); ozone introduced, 40.9 mmoles; and Grignard reagent reacted, 148 mmoles. Refluxing the ozonation mixture gave 23.4 mmoles of propene and 50.3 mmoles of propane. The low-boiling material (4.56 g.) contained isopropyl alcohol, 19.9 mmoles; isobutyl alcohol, 15.1 mmoles; and 2-methyl-3-hexanol, 18.2 mmoles. The high-boiling material (1.38 g.) contained 29% of unidentified material and 9.4 mmoles of pentane-1,2-diol. This material gave the bisphenylurethane of pentane-1,2-diol, m.p. and m.m.p. 106.4–108.8°; lit.[20] m.p. 108–110°. A distillation residue of 0.23 g. remained.

An experiment in which isobutylmagnesium bromide was used gave similar results, *mutatis mutandis*.

Reaction of Propionaldehyde with Isopropyl Grignard Reagent.—To rule out the possibility of any of the diol found in the above-described experiments having been formed by condensation of an aldehyde, 3.73 g. (64.2 mmoles) of propionaldehyde in 400 ml. of ether was treated with 90.0 mmoles of Grignard reagent under the same conditions as those used for the reaction of the ozonized alkenes with the Grignard reagent. There were obtained 52.4 mmoles of 2-methyl-3-pentanol and 0.72 g. of distillation residue. Neither of these materials gave a positive test for α-glycol.

Reaction of Ether with Ozone.—Ether (50 ml.) was cooled to −112° and ozonized. After 30 min. the ether was retaining 75% of the ozone passed into it.

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(18) Infrared spectra were obtained with a Perkin-Elmer Model 21 infrared spectrograph.

(19) H. J. Lucas, M. J. Schlattter and R. C. Jones, *J. Am. Chem. Soc.*, **63**, 22 (1941).

(20) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **83**, 589 (1929).

Stereochemical Studies on 6,7-Substituted Derivatives of Estra-3,17β-diol

O. WINTERSTEINER, M. MOORE, AND ALLEN I. COHEN

The Squibb Institute for Medical Research, New Brunswick, New Jersey

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In an attempt to establish conclusively the configurations tentatively assigned[1] to the epimeric 6-hydroxyestra-3,17β-diols IIa and IIIa, 6β-hydroxy-7α-bromoestradiol 3,17-diacetate (Va) was prepared from 6-dehydroestradiol diacetate (IV) with N-bromoacetamide and converted *via* the 7α-bromo 6-ketone VIa to its 6α-epimer VIIa. On removal of the bromine atom by catalytic hydrogenation the latter bromohydrin gave as expected 6α-hydroxyestradiol 3,17-diacetate (IIc). However, IIc was also the main product obtained in this reaction from the 6β-hydroxy-7α-bromo isomer Va, while the expected 6β-hydroxyestradiol 3,17-diacetate (IIIc) was formed in small amounts only. The cause of this anomaly is obscure, as no inversion occurs when 6β-hydroxyestradiol diacetate is treated in the same manner. That Va is correctly formulated as the *trans* diaxial bromohydrin follows *inter alia* from its convertibility with anhydrous base to 6β,7β-oxidoestradiol diacetate (IXa). This epoxide reacts abnormally in steric regard in that on reduction with lithium aluminum hydride it yields the equatorial alcohol, 7β-hydroxyestradiol (XIb), and on hydrolysis the 6ξ,7β-glycol (tentatively formulated as the 6α,7β-diequatorial glycol XIVa), whereas the 6α,7α-epoxide X is opened to the normal diaxial 6β,7α-glycol XIIa. The n.m.r spectra of the fully acetylated compounds bearing 7α-substituents or hydrogen only at C-7 indicate that ring B in these is in the hemichair form, while in those with a 7β-acetoxy group (XIc and XIVb) it appears to assume a more planar conformation intermediate between hemichair and boat.

In a previous publication[1] we described the preparation from 6-ketoestradiol diacetate (Ia) of the 6-epimeric 6-hydroxy-17β-estradiols and their triacetates. The higher melting triol (m.p. 249–251°, triacetate m.p. 144–145°) was tentatively assigned the 6α-configuration (IIa) and the lower melting triol (m.p. 191–195°, triacetate m.p. 176–178°) the 6β-configuration (IIIa) on the basis of the stereochemical criteria then available. The objective of the work reported in the present paper was originally to adduce conclusive proof for these assignments. To this end we explored the reaction of 6-dehydroestradiol diacetate (IV)[2] with N-bromoacetamide in the hope that the resulting bromohydrin would be the 6β-hydroxy-7α-bromo isomer, which was then expected to yield, on reductive removal of the bromine and acetylation, the 6β-triol triacetate IIIb. The reaction of IV with N-bromoacetamide proceeded smoothly to give in almost quantitative yield a bromohydrin (m.p. 186–187°), which indeed carried the new hydroxyl group at C-6, since on Jones oxidation[3] it afforded a bromo ketone exhibiting ultraviolet absorption characteristics similar to those of 6-ketoestradiol diacetate (Ia). The same bromo ketone was also obtained as the sole product when Ia was brominated in acetic acid containing a small amount of hydrobromic acid. The carbonyl stretching vibration band in the infrared spectrum appears at 5.91 μ, while that of the parent ketone Ia is located at 5.94 μ. In the spectra of the corresponding 17-monoacetates the positions of these bands are 5.92 and 5.96 μ, respectively (measurements on chloroform solutions; in Nujol mulls considerably higher values for Δ, namely 5.95 → 5.90 μ for the diacetates, and 6.01 → 5.93 μ for the 17-monoacetates, were observed). These hypsochromic shifts, corresponding to +8 and +11 cm.$^{-1}$, respectively, on the frequency scale, are smaller than those usually associated with the introduction of an equatorial bromine atom in the α-position of saturated cyclic ketones (average +20 cm.$^{-1}$).[4] In view of these ambiguous results, and since there was no assurance that the above shift rule derived from measurements on unconjugated ketones[4] would hold for the α-tetralone system of Ia, recourse was taken to optical rotatory dispersion measurements.[5] The curves of Ia and of the derived bromo ketone in dioxane were rather similar in that they both showed a positive Cotton effect with peaks of moderate amplitudes at 357 mμ, respectively (*cf.* Experimental). The smallness of the bathochromic shift and the *decrease* in amplitude ([α] 2013 → 1833°; [α] of peaks 553 → 576°) in going from Ia to the bromo ketone seemed to indicate that the bromine substituent was equatorial rather than axial.[6] Examination of the n.m.r. spectra of the two ketones, however, led to the opposite conclusion. The spectrum of the bromo ketone exhibits a doublet at τ 5.50 (J = 2 c.p.s.) which is absent in that of Ia and hence must represent the 7-proton coupled with the axial 8β-proton. The small value of J indicates a dihedral angle between these two protons of not less than 60° and not more than 120°.[7] Now, the scale models of Ia with ring B in either the hemichair or the hemiboat form show that the only one of the four dihedral angles in question which falls into this range is ϕ (7βH–8βH, hemichair) $\cong$ 75°, meaning that the bromine atom must be α and axial in a hemichair. Since this conclusion is also supported, as will appear farther below, by chemical evidence relating to the reactions of the bromohydrin, the bromo ketone must be formulated as VIa, and the bromohydrin, on the basis of the rule of diaxial addition and of the chemical findings mentioned, as the 6β-hydroxy-7α-bromo stereoisomer Va.

It is clear from the above facts that the generalizations regarding the changes in peak positions and amplitude of O.R.D. curves following the introduction

(1) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **81**, 442 (1959).

(2) S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *ibid.*, **72**, 4531 (1950).

(3) K. Bowden, I. M. Heilbron, E. R. H. Jones, and C. L. Weston, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(4) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(5) These measurements were carried out in the laboratory of Dr. Franz Sondheimer, Syntex S. A., Mexico City, who informed us that he had independently prepared the bromo ketone VIa from the enol acetate of Ia and determined the infrared spectra and O.R.D. curves of the two ketones. The measurements were then repeated on our samples in two different solvents. We are greatly indebted to Dr. Sondheimer for putting these data at our disposal for publication.

(6) C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *ibid.*, **80**, 1216 (1958).

(7) H. Conroy, "Advances in Organic Chemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960, p. 311; see ref. 25 also.

of an axial α-bromine substituent in conformationally rigid cyclohexanones[6] do not hold for the α-tetralone system present in Ia. This is not surprising, as these generalizations, and their extension in the "axial halo ketone rule,"[6] were not meant, and in fact have never been shown, to apply even to transoid α′-halo-α,β-unsaturated octalones, the closest analogs that could be substituted in this context for the bromo ketone VIa.

Since VIa was obtained from Ia by bromination in the presence of hydrobromic acid, it should be the thermodynamically more stable isomer. Attempts to prepare the epimeric 7-bromo ketone by bromination in the presence of sodium acetate, that is, under conditions of kinetic control, failed, as only VIa could be isolated, although in smaller yield than in the runs with excess hydrobromic acid. This was also the case in equilibration experiments in which VIa was treated with hydrobromic acid at room temperature, and even when a solution of the bromo ketone in acetic acid containing 5% *p*-toluenesulfonic acid was heated under reflux for 24 hr.[8] All that happened in the latter reaction was the loss of the 3-acetyl group, so that the product isolated was 7α-bromo-6-ketoestradiol 17-monoacetate (VIb). It must be concluded from these results that the 7α-bromo compound, as the thermodynamically favored isomer, preponderates under conditions of kinetic control as well. It is of interest in this connection that 3β-acetoxy-7α-bromo-6-ketocholestane, the infrared[9] and ultraviolet[10] spectra of which leave no doubt about the axial character of its bromine substituent, is quite stable in acetic acid containing hydrobromic acid at 90° (the conditions under which it is formed from the 5α-bromo isomer),[11] and that its 7β-epimer is unknown.

In various attempts to remove the bromine atom of the bromohydrin Va or its triacetate Vb with zinc in ethanol, these compounds remained either unchanged or reverted to 6-dehydroestradiol diacetate. Reduction with Raney nickel appeared unpromising since Iriarte, *et al.*,[12] had found that the use of this reagent on 6α,7α-oxidoestradiol and 6α,7α-dihydroxyestradiol resulted in hydrogenolysis at both C-6 and C-7 with the formation of estradiol. Of the catalytic hydrogenation experiments carried out with noble metal catalysts, only that with palladium on calcium carbonate in ethanol was successful in the sense that the bromine was eliminated quantitatively after the uptake of 1 mole of hydrogen. There was obtained in about 50% of the theoretical yield a compound, m.p. 140–142°, $[\alpha]_D$ +53°, which had the composition and spectral properties of a 6-hydroxyestradiol 3,17-diacetate, and on oxidation with chromium trioxide gave 6-ketoestradiol diacetate. However, the triacetate it yielded on acetylation was not the expected 6″β″-hydroxyestradiol triacetate, m.p. 178°, but slightly impure (m.p. 140°) 6″α″-hydroxyestradiol triacetate. In later hydrogenation runs the diacetate always turned up in form of a lower melting polymorphous modification melting at 128–129°. This was also the case in experiments in which the crude product was subjected to thin layer chromatography on acid-washed alumina; in addition the chromatogram yielded small amounts of estradiol diacetate and 17-monoacetate, and of a triol diacetate, m.p. 160°, which was subsequently identified as 6″β″-hydroxyestradiol 3,17-diacetate.

It proved possible to secure the 3,17-diacetates of the 6-epimeric 6-hydroxyestradiols by modifying the conditions originally employed for the preparation of the two epimeric triols from 6-ketoestradiol diacetate. Thus, by conducting the reduction with sodium borohydride at 0° for only 15 min.,[13] and chromatographing the crude product, the lower melting modification of 6″α″-hydroxyestradiol 3,17-diacetate was obtained in good yield together with a smaller amount of the 17-monoacetate; and 6″β″-hydroxyestradiol 3,17-diacetate, m.p. 162°, was the sole product when ethyl acetate was substituted for ethanol as the solvent in the catalytic reduction of the ketone with platinum oxide as the catalyst.

While this work was in progress, Breuer, Knuppen, and Pangels[14] succeeded in bringing about incontrovertible proof for the configuration at C-6 of the 6-hydroxyestradiols by correlating them with the 6-epimeric 6-hydroxyandrostenediones by means of the aromatizing placental enzyme of Ryan.[15] The results showed that our tentative assignments were correct. The triol diacetate (m.p. 142°), which is the main product in the reductive debromination of the bromohydrin, is thus indeed 6α-hydroxyestradiol 3,17-diacetate (IIc), and the diacetate (m.p. 162°), formed only in small amounts in that reaction, is the 6β-epimer IIIc.

Since at the time when this work came to our attention the configuration of the bromohydrin Va was still in question, it appeared from the result of the reductive debromination experiment (formation from Va of 6α-hydroxyestradiol 3,17-diacetate as the main product) that the bromohydrin was either the 6α-hydroxy-7α-bromo-*cis* isomer VIIa, or the diequatorial 6α-hydroxy-7β-bromo isomer VIII. The former could conceivably have arisen from IV *via* a 6α,7α-bromonium ion passing into a 6-carbonium ion, which then added hydroxyl ion from the less hindered α-side. This would parallel the behavior of certain β-substituted styryl oxides,[16] stilbene oxides,[17] and indene oxides,[18] which undergo ring opening by aqueous acids or hydrohalides predominantly or exclusively with retention of configuration at the reacting benzylic carbon atom. Alternatively, an initially formed 6β,7β-bromonium ion may have by the same mechanism produced the diequatorial isomer VIII.

Chemical proof that the stereochemistry of the bromohydrin, m.p. 187°, is correctly represented by Va rather than by VIIa or VIII was obtained as follows.

(8) Using these conditions G. P. Mueller and W. F. Johns [*J. Org. Chem.* **26**, 2403 (1961)] were able to effect the conversion of 3-methoxy-17α-bromoestra-1,3,5(10)-trien-16-one to its 17β-epimer.

(9) E. J. Corey, *J. Am. Chem. Soc.*, **76**, 175 (1954).

(10) E. Cookson, *J. Chem. Soc.*, 282 (1954).

(11) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *ibid.*, 801 (1937).

(12) J. Iriarte, H. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6105 (1958).

(13) In this manner 6-ketoestrone acetate could be reduced to 6α-hydroxyestradiol 3-monoacetate (personal communication by Professor H. Breuer, Bonn).

(14) H. Breuer, R. Knuppen, and G. Pangels, *Nature*, **190**, 720 (1961); *Biochem. Biophys. Acta*, **65**, 1 (1962).

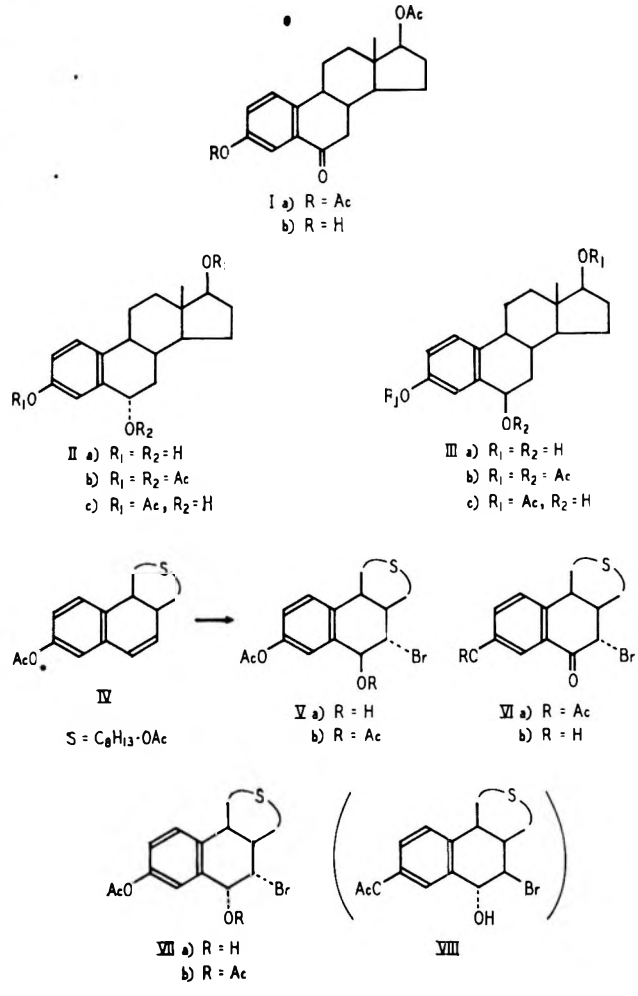
(15) K. J. Ryan, *J. Biol. Chem.*, **234**, 268 (1959).

(16) R. Kuhn and F. Ebel, *Ber.*, **58**, 919 (1925); H. Wasserman and N. E. Aubrey, *J. Am. Chem. Soc.*, **78**, 1726 (1956).

(17) J. Boeseken and G. Eisen, *Rec. trav. chim.*, **47**, 694 (1928); J. Boeseken and G. C. C. Schneider, *J. prakt. Chem.*, **131**, 285 (1931); J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956).

(18) J. Boeseken, *Rec. trav. chim.*, **41**, 199 (1922).

SCHEME I



On reduction with sodium borohydride in methanol (15 min., 0°) the bromo ketone VIa afforded in excellent yield and as the sole product a new bromohydrin diacetate (m.p. 170–172°), which was further characterized by conversion to the triacetate (m.p. 228–230°). The highly stereospecific character of this reaction (and of Ia → IIc) is noteworthy insofar as, in contrast, 3β-acetoxy-7α-bromo-6-ketocholestane on reduction by this agent gives rise to a mixture of the 6-epimeric alcohols.[19] On short treatment with potassium *t*-butoxide in *t*-butyl alcohol at room temperature, the bromohydrin (m.p. 172°) yielded 6-keto-estradiol diacetate (Ia), showing that the two ring B substituents are *cis* to each other, and consequently *trans* in its 6-epimer, the bromohydrin (m.p. 187°) obtained from 6-dehydroestradiol diacetate. The conclusion that the latter bromohydrin is the diaxial 6β-hydroxy-7α-bromo isomer Va (rather than the diequatorial isomer VIII), and the bromohydrin (m.p. 172°) is, therefore, the 6α-hydroxy-7α-bromo isomer VIIa, rests on the formation from the former on treatment with potassium *t*-butoxide of the 6β,7β-epoxide which depending on conditions is obtained either as the 3,17-diacetate IXa or the 17-monoacetate IXb.

That the oxiran ring in these compounds is β-oriented follows from two facts. (1) The diacetate (m.p. 126°) was not identical with the 6α,7α-oxidoestradiol diacetate X (m.p. 169°) which Iriarte, Ringold, and Djerassi[12] had obtained with perphthalic acid from 6-dehydroestradiol diacetate and had reduced with lithium aluminum hydride to 7α-hydroxyestradiol (XIa). (2) Application of the latter reaction to the new oxidoestradiol diacetate (m.p. 126°) gave 7β-hydroxyestradiol (XIb), identical with the triol resulting from the reduction of 7β-hydroxyestrone[20,21] with sodium borohydride. It should be noted that this result, while proving that the parent oxide is the β,β isomer, is anomalous, since the reduction of steroid expoxides normally leads to the axial alcohol, and hence in the present case should have yielded 6β-hydroxyestradiol (IIIa). Obviously, the partial positive charge on the benzylic atom directs the hydride ions delivered by the reducing agent to this site.

The hydrolysis of the oxide IXa by acid (perchloric acid in boiling aqueous ethanol) likewise took a sterically abnormal course. The hydrolysis product was amorphous and hence had to be characterized as the tetraacetate (m.p. 217°, $[\alpha]_D - 1°$). Had the opening of the oxiran ring taken the normal course, this compound should be the tetraacetyl derivative of the diaxial *trans* glycol, 6β,7α-dihydroxyestradiol tetraacetate (XIIb), and hence should be identical with the tetraacetate derivable from the 6α,7α-oxidoestradiol diacetate X of Iriarte, *et al.* Since the Syntex authors had not studied the hydrolysis of X [although they did assign the 6β,7α-dihydroxyestradiol 3,17-diacetate structure XIIa—erroneously, as will be shown further below—to a crystalline product (m.p. 88°) they had isolated from the mother liquors of X], we prepared the oxide by their procedure and subjected it to hydrolysis with perchloric acid. In this case the hydrolysis product itself, a 6,7-dihydroxyestradiol 3,17-diacetate (m.p. 171°), was crystalline, and on acetylation yielded a new tetraacetate (m.p. 136°, $[\alpha]_D$ +68°). There can be no doubt that these compounds are, respectively, the 3,17-diacetate XIIa and tetraacetate XIIb of 6β,7α-dihydroxyestradiol, the isomer formed by normal *trans* diaxial opening of the oxide X, for the following reasons. (1) As already mentioned, X is reduced by lithium aluminum hydride to the normal product, the axial alcohol 7α-hydroxyestradiol. (2) Iriarte, *et al.*,[12] found that when 6α,7α-dihydroxyestrone, prepared from 6-dehydroestrone with osmium tetroxide, was treated with methanolic hydrogen chloride, it was isomerized to its 6-epimer, the *trans* diaxial glycol 6β,7α-dihydroxyestrone (XIIc), also obtained from 6α,7α-oxidoestrone by acid hydrolysis, and hence configurationally analogous to XIIa and b in the estradiol series. Since this unusual inversion must have involved, as the Syntex authors suggest, the intermediary formation of a carbonium ion at the benzylic carbon atom, there can be no doubt that the glycol formed on hydrolysis of 6α,7α-oxido-

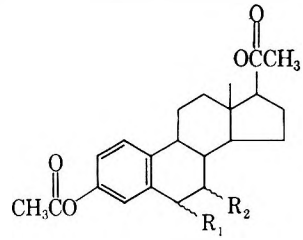
(19) D. R. James and C. W. Shoppee, *J. Chem. Soc.*, **1954**, 4224.

(20) W. H. Pearlman and O. Wintersteiner, *J. Biol. Chem.*, **132**, 605 (1940).

(21) The 7-configurations of the two epimeric 7-hydroxyestrones and of 7α-hydroxyestradiol (XIa) were inferred by Iriarte, *et al.*,[12] from the fact that 7β-hydroxyestrone had been prepared by Pearlman and Wintersteiner[20] by catalytic reduction of 7-hydroxy-6-dehydroestrone diacetate (enol acetate of 7-ketoestrone acetate) in which catalyst approach was assumed by the Syntex authors to have occurred from the α-side. The possibility that this may not be so when, as in estrogens, the 19-methyl group is absent was not considered. However, our n.m.r. data on 7β-hydroxyestradiol triacetate (Table I) leave no doubt about the correctness of the above configurational assignments.

TABLE I

N.M.R. SPECTRA OF FULLY ACETYLATED DERIVATIVES OF 6-HYDROXY-, 6-HYDROXY-7-BROMC-, AND 6,7-DIHYDROXYESTRADIOLS

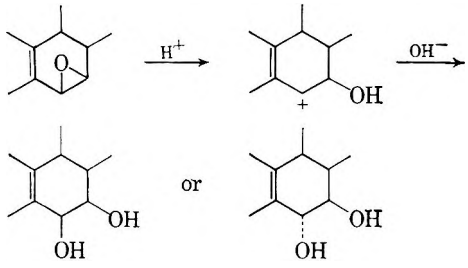


Compound	R_1	R_2	τ Values for CH_3COO— C-3	C-6	C-7	C-17	C-6 H, τ[a]	C-7 H, τ[a]	C-18 CH_3, τ
IIb	α-OAc		7.73	7.88		7.96	3.98 (d, d, 8.5, 5.5)		9.18
IIIb	β-OAc		7.73	7.95		7.95	3.99 (d, ~3)		9.14
VIIb	α-OAc	α-Br	7.69	7.72		7.95	3.93 (d, ~4)	5.23 (d, 4)	9.14
Vb	β-OAc	α-Br	7.69	7.95		7.95	3.85 (d, ~2)	5.72 (d, ~2)	9.11
XIIIb	α-OAc	α-OAc	7.72	7.89	7.96	7.97	3.95 (d, 4)	4.51 (d, 4)	9.16
XIIb	β-OAc	α-OAc	7.73	7.93	7.95	7.97	4.13 (d, 2)	4.89 (m)	9.13
XIc		β-OAc	7.73		7.98	7.96	7.16 (d, 7)		
							6.97 (d, 6.5)	4.93 (m)	9.16
XIV[b]	α-OAc	β-OAc	7.72	7.94	7.94	7.95	3.97 (d, 6)	4.78 (m)	9.16

[a] Number of peaks in parentheses, J in c.p.s., s = singlet, d = doublet, m = multiplet.

estrone and, consequently, XIIa and b are correctly formulated as the *trans* diaxial 6β,7α isomers.

The Syntex authors also applied the osmium tetroxide reaction to 6-dehydroestradiol and thus obtained 6α,7α-dihydroxyestradiol (XIIIa), the tetraacetate XIIIb of which melts at 229° and has $[\alpha]_D$ +17°. Clearly, then, the tetrol tetraacetate (m.p. 217°) obtained from the 6β,7β-oxide IX, since it is different from the two tetraacetates XIIb and XIIIb having the 7α-configuration, must have the β-configuration at C-7, and, therefore, must be derived either from the diequatorial 6α,7β- or the axial–equatorial 6β,7β-glycol. The latter could have arisen by the carbonium ion mechanism shown below which is analogous to the one postulated by Cookson and Hudec[22] to explain the conversion by acid of 3β-phenyl-2α,3α-oxidocholestane to 3β-phenyl-2α,3α-dihydroxycholestane.



The same mechanism could, of course, be invoked for the formation of the 6α,7β-dihydroxy isomer since in the second step the hydroxyl ion could just as well, or perhaps even more readily, add from the unhindered α-side. Alternatively, it could be assumed that ring B in the oxide exists in the boat conformation, in which case likewise, as in the formation of diequatorial 17α-hydroxy-16β-bromo derivative in the reaction of 3α-acetoxy-11,17α-diketo-D-homo-5β-androstane 16α,17α-oxide with hydrobromic acid,[23] the diequatorial 6α,7β-glycol would result.

(22) R. C. Cookson and J. Hudec, *Proc. Chem. Soc.* 24 (1957).

(23) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956); N. L. Wendler, *Chem. Ind.* (London), 1662 (1958).

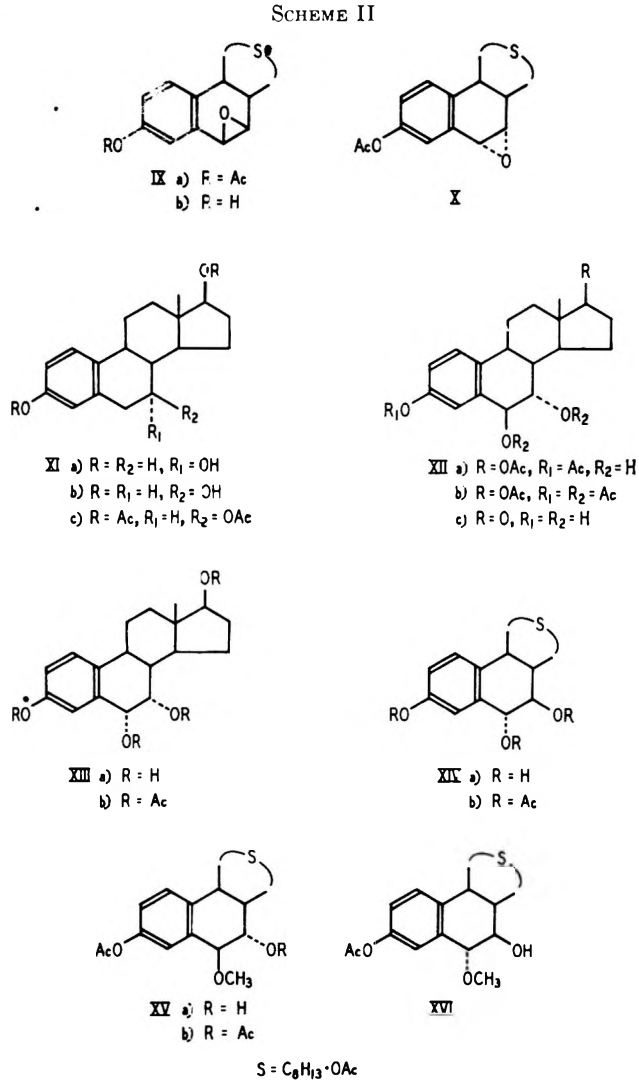
We were unable to resolve this question by chemical means, but from a consideration of the coupling constants for protons 6 and 7 and of the chemical shift of the 6-acetoxy signal in the n.m.r. spectra of the tetraacetate in question (see Table I and discussion) have come to favor the 6α,7β-configuration for this hydrolysis product, and hence tentatively write it as XIVa, and its tetraacetate (m.p. 217°) as XIVb.

One of the unsuccessful attempts to establish the configuration of the 6-acetoxy group in the tetraacetate (m.p. 217°) involved the perchloric acid-catalyzed methanolysis of both the 6α,7α-oxide X and the 6β,7β-oxide IXa. It was reasoned that in both cases the methanolysis would take the same steric course as hydrolysis; *i.e.*, replacement of the oxidic linkage by methoxyl ion would in both compounds occur at the benzylic C-6 atom. Thus X would give rise to the diaxial isomer, 6β-methoxy-7α-hydroxyestradiol 3,17-diacetate (XVa), and IXa either to the diequatorial isomer, 6α-methoxy-7β-hydroxyestradiol 3,17-diacetate (XVI), or to the latter's 6-epimer, 6β-methoxy-7β-hydroxyestradiol 3,17-diacetate. Oxidation of the two methanolysis products should then lead either to the same 7-ketone or to two different 7-ketones, depending on whether the methanolysis product of IXa (and hence also the tetraacetate, m.p. 217°) has the 6β- or the 6α-configuration.

The methanolysis product of the 6α,7α-oxide X, undoubtedly representing the diaxial 6β-methoxy-7α-hydroxy isomer XVa, turned out to be identical with the compound (m.p. 88°), which, as has been mentioned by Iriarte, *et al.*,[12] had been obtained from methanolic mother liquors of X and erroneously assumed to be the glycol XIIa. [We had likewise encountered it in this source, but then found that on acetylation it formed a triacetate (XVb) instead of a tetraacetate, and that it contained methoxyl.]

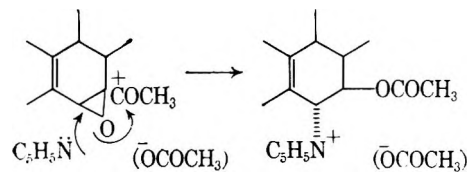
The methanolysis product (m.p. 178°) obtained in the same manner from the 6β,7β-oxide IXa can then be formulated, on the basis of the configurations suggested by the n.m.r. data for the tetraacetate (m.p. 217°), as the diequatorial isomer XVI. (See Scheme II.)

SCHEME II



The two methanolysis products XVa and XVI were subjected to chromic acid oxidation under a variety of conditions. In no case, however, could the 7-ketone be obtained, either as such or in the form of a crystalline derivative, from either substance. It is possible that this failure has its cause in the tendency of the incipient 7-keto group to enolize towards C-6, the partial positive charge on this carbon atom being reinforced by the electron-withdrawing effect of the O-methyl group, facilitating the formation of the enolic double bond and ultimately resulting in the loss of the O-methyl group from the enol ether formed when acidic conditions prevailed.

It is noteworthy that the 6β,7β-oxide IX deviates from other steroid epoxides also in its purely chemical behavior. It was, for instance, not possible to convert the 17-monoacetate IXb into the 3,17-diacetate IXa by acetylation with acetic anhydride and pyridine, because it was transformed by these reagents (but not by pyridine alone) to water-soluble, highly polar products which are in all probability 7β-acetoxy-6-pyridinium acetates formed by the concerted mechanism shown below (or the equivalent 6-carbonium ion mechanism). The conversion of IXb into IXa can be effected, however, with acetic anhydride alone. Furthermore, the oxide is readily hydrolyzed by water near neutrality, as shown by the following observations. When the



trans-bromohydrin Va was dissolved in aqueous methanol containing 1% potassium carbonate, it rapidly eliminated bromine ion and yielded after neutralization with acetic acid an amorphous product having the composition and spectral properties of a dihydroxyestradiol 17-monoacetate (XIVa) which on acid-catalyzed acetylation afforded the tetraacetate XIVb (m.p. 217°) in good yield. The amorphous monoacetate XIVa convertible to the tetraacetate XIVb was also obtained when in the preparation of the oxide IX from the *trans*-bromohydrin Va with potassium *t*-butoxide, 1 equiv. (in respect to the latter) of acetic acid was added prior to working up the reaction mixture with ether and water. Lastly, all attempts to convert the oxide IX to a bromohydrin by treatment with hydrobromic acid in acetic acid or dioxane were unsuccessful. Under the usual conditions for bromohydrin formation (acetic acid, 1 hr. at room temperature) almost no bromide ion was consumed, and the oxide appeared to remain intact, as shown by the formation of water-soluble products from the recovered material after acetylation in pyridine. When the reaction time was extended to 24 hr., some reaction did occur in acetic acid, but the only crystalline product which could be isolated by chromatography from the material acetylated with acetic anhydride and sodium acetate was a small amount of impure tetrol tetraacetate XIVb (m.p. 207°, identified by infrared spectrum). Clearly hydrolysis or acetolysis had supervened over bromohydrin formation.

There remains the question why 6β-hydroxy-7α-bromoestradiol diacetate (Va) yielded on catalytic hydrogenation with palladium–calcium carbonate as the main product 6α-hydroxyestradiol 3,17-diacetate (IIc) and only a small amount of its 6-epimer IIIc. Numerous attempts were made to eliminate the bromine atom from Va as the triacetate Vb by other reductive procedures, catalytic and chemical. In no case, however, was either IIc or IIIc or the corresponding 17-monoacetates encountered at all. In the catalytic hydrogenation experiments, hydrogen uptake was generally sluggish and often incomplete, and the prevailing reaction was usually hydrogenolysis at both C-6 and C-7, resulting in the formation of estradiol diacetate and leaving some of the bromohydrin unattacked. This was also the course of events when the triacetate Vb was hydrogenated in the presence of palladium–calcium carbonate.

The hydrogenation with palladium–calcium carbonate of the 6-epimeric bromohydrin, 6α-hydroxy-7α-bromoestradiol diacetate (VIIa), proceeded with far less facility than with Va, presumably because catalyst approach from the rear was impeded by the 6α-hydroxy group. It did afford, however, though in poor yield (since some starting material always remained unattacked) the expected product, 6α-hydroxyestradiol 3,17-diacetate (IIc), thus confirming the configurational proof of Breuer, *et al.*[14]

In view of the possibility that 6β-hydroxyestradiol diacetate (IIIc) might be the primary product formed in the catalytic reduction with palladium–calcium carbonate of the *trans*-bromohydrin Va, and then be epimerized to the quasi-equatorial isomer IIc, the diacetate IIIc was subjected for 8 hr. to the conditions of the hydrogenation experiment, except that 1 equiv. of hydrobromic acid was added at the start. However, save for estradiol diacetate formed by hydrogenolysis, only IIIc was recovered. It appears, therefore, that the inversion of the 6β-hydroxy group of Va is dependent on the simultaneous reductive removal of the 7-bromine atom.

Nuclear Magnetic Resonance Spectra.—In all but one (XIV) of the compounds measured the configurations of the 6- and/or 7-substituents have been established by chemical means. It was then of interest to ascertain by means of n.m.r. measurements[24] how these substituents affect the conformation of ring B.

Conformational assignments have been made[25] from a study of n.m.r. spectra, particularly from a consideration of the proton–proton coupling constants arising from the spin interaction of protons on adjacent carbon atoms. The quantitative relationship between the dihedral angle and the magnitude of the coupling constant J proposed by Karplus[25] and modified by Williamson and Johnson[25] has been used by Tadanier and Cole[25] for the assignment of the B-ring chair conformation and the configuration of the 6-substituent of the epimeric 6-acetoxy-17-ethylenedioxy-3α,5α-cycloandrostanes.

The pertinent data are shown in Table I. The epimeric 6-hydroxyestradiol triacetates IIb and IIIb will be considered first. It is evident from the fact that the spectrum of the 6α-epimer IIb is of the ABX type and that of the 6β-epimer IIIc of the AX type, and furthermore from the much larger coupling constant of the 6β-proton of IIb as compared with that of the 6α-proton in IIIb, that the 6-acetoxy group in IIb and IIIb must be quasi-equatorial and quasi-axial, respectively, and that consequently ring B in both epimers must be in the hemichair form.[26] (If ring B were in the boat form, the values of the coupling constants would be reversed for the two compounds.) This conclusion is furthermore supported by the differences in the chemical shift of the 6-acetoxyl groups in the two epimers, the deshielding effect of the benzene ring on the equatorial 6α-acetoxy group of IIb being responsible for the larger downfield shift observed with this epimer.

Similar relationships in regard to the magnitude of the coupling constants of the 6-protons and the chemical shifts of the 6-acetoxy signals were obtained with the 6-epimeric bromohydrin triacetates Vb and VIIb and the tetrol tetraacetates XIIIb and XIIb,[27] and it, therefore, appears that in those compounds ring B is also in the hemichair form.

The C-6 protons of 7β-hydroxyestradiol triacetate (XIc) appear as four equal intensity peaks between 167 and 185 c.p.s. downfield of the internal reference. Since the ratio, $J_{AB}/(\delta_B - \delta_A)$, is approximately one, the AB spectrum would appear as two intense inner peaks and two weak outer peaks. At the concentration used, the first-order assignment of the coupling pattern is that of an AX and BX spectrum. The coupling constants of the 6-protons with the 7α-proton in XIc are 6.5 and 7 c.p.s., corresponding to dihedral angles of approximately 35 and 130°.[28] These angles cannot be well accommodated in either the ring B hemichair or the boat form of XIc, and suggest that ring B in this compound assumes a more planar conformation intermediate between these forms.

In the tetrol tetraacetate XIVb, the only other compound with a 7β-substituent, the configuration of the 6-acetoxy group is not known. However, a case of sorts can be made for this group having the α-configuration on the following grounds. The position of the signal for this group (τ 7.94) conforms with those for the axial 6β-acetoxy groups in IIIb, Vb, and XIIb, and hence would indicate that this group, too, is β and axial, provided ring B in XIVb is in the hemichair form. However the dihedral angles (39 or 128°) calculated from the coupling constant $J_{6\xi\text{-H}-7\beta\text{-H}} = 6.0$ c.p.s. do not agree with those measured on the model for 6α-H to 7α-H in the hemichair (165°), nor for 6β-H to 7α-H in the boat (75°) (in which latter case the 6-acetoxy group would, of course, be α-oriented but likewise axial). Rather, the coupling constant indicates, as with XIc, that ring B is in a conformation intermediate between hemichair and boat, and, when this form is approximated in the model (with 6α–7α = 30°, or 6β–7α = 145°), it appears that a 6α-acetoxy group would have somewhat more axial character and, therefore, be less deshielded by the aromatic ring A than a 6β-acetoxy group. We, therefore, tentatively assign to this group in XIVb the α-configuration.

Experimental

The melting points were taken in open Pyrex glass capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semimicrotube, with chloroform as the solvent, unless indicated otherwise. The ultraviolet spectra were measured in absolute ethanol in a Cary self-recording instrument, Model 11 M. The infrared spectra were determined on Nujol mulls in the Perkin-Elmer double beam self-recording spectrophotometer, Model 21. The characteristics of the infrared bands are expressed in the text as follows: (s) strong, (m) medium, (l) low, (vl) very low, (br) broad, (sh) shoulder. The analytical samples were dried at 110° (2 mm.) unless indicated otherwise.

6α-Hydroxyestradiol 3,17-Diacetate (IIc).—6-Ketoestradiol diacetate (1 g.) was dissolved in reagent methanol (400 ml.),

(24) The spectra were obtained with a Varian Associates Model A-60 n.m.r. spectrometer of samples dissolved in deuteriochloroform containing tetramethylsilane as an internal reference and were run by A.I.C.

(25)(a) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Am. Chem. Soc.*, **80**, 2237 (1958); (b) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961); (c) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (d) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962).

(26) The coupling pattern and the magnitude of the coupling constant of the 6α-proton of IIIb are similar to those of the 6α-proton of 6β-acetoxy-17-ethylenedioxy-3α,5α-cycloandrostane assigned the chair conformation by Tadanier and Cole.[25d] The corresponding 6α-acetoxy derivative and IIb show similar coupling patterns of the 6β-proton but different values of the coupling constants because the B-ring of IIb is more planar than that of the 3α,5α-cycloandrostane derivative.

(27) Williamson and Johnson[25b] found that the 2β-proton signal in 2α-bromocholestan-3-one exhibits the same coupling constants as in the 2α-acetoxy derivative. It should be also noted that the greater chemical shift of the 6α-acetoxy group in the *cis*-bromohydrin triacetate VIIb reflects additional deshielding by the 7α-bromine atom.

(28) The dihedral angles calculated from the equation of Karplus[25c] for the compounds of this series should be regarded as approximations in the sense recently stressed by this author [*J. Am. Chem. Soc.*, **85**, 2870 (1963)], and hence conclusions regarding gross deviations from the normal hemichair conformation of ring B are justified only if the differences between the calculated angles and the normal angles are large, as in the case of XIc and XIVb.

magnetically stirred, and cooled to 0°. A solution of sodium borohydride (1 g.) in reagent methanol (100 ml.) cooled to 0° was added dropwise under anhydrous conditions. After 15 min. the reaction mixture was acidified to about pH 5 with cold 10% acetic acid and diluted with water (1.5 l.). The mixture was extracted with three portions of ether. The combined ether extracts were washed with sodium bicarbonate and twice with water. Chromatography of the residue of the dried ether solution on acid-washed alumina yielded slightly impure 6α-hydroxyestradiol diacetate (482 mg.) in the 1:3 ether–benzene eluates. After two crystallizations from ethyl acetate–hexane the compound (334 mg.) melted at 128–129.5°; $[\alpha]^{21}D$ +64° (*c* 0.987); λ_{max}^{alc} 267 mμ (ε 760), 275 (644), 263 sh (658); λ_{max}^{Nujol} 2.90 (m), 5.67 (s), 5.85 (s), 8.20 (s) μ.

Anal. Calcd. for $C_{22}H_{28}O_5$ (372.4): C, 70.94; H, 7.58. Found: C, 70.97; H, 7.59.

6β-Hydroxyestradiol 3,17-Diacetate (IIIc).—A solution of 6-ketoestradiol diacetate (410 mg.) in ethyl acetate (20 ml.) was added to pre-reduced platinum dioxide (250 mg.) in ethyl acetate (23 ml.) and shaken with hydrogen at atmospheric pressure. When the uptake of hydrogen ceased (1.17 equiv.) the catalyst was removed by filtration and the solution was evaporated to dryness *in vacuo*. The residue crystallized from ethyl acetate–hexane as plates (341 mg.) which melted at 161–162°; $[\alpha]^{21}D$ +5° (*c* 1.008); λ_{max}^{alc} 267mμ (ε 502), 275 (450), 215 sh (9700); λ_{max}^{Nujol} 2.86 (m), 5.64 (s), 5.83 (s), 7.94 (s) μ.

Anal. Calcd. for $C_{22}H_{28}O_6$ (372.4): C, 70.94; H, 7.58. Found: C, 70.58; H, 7.87

6β-Hydroxy-7α-bromoestradiol 3,17-Diacetate (Va).—To a solution of 6-dehydroestradiol diacetate[29] (101 mg.) in pure peroxide-free dioxane (5 ml.) and 0.5 *N* perchloric acid (0.63 ml.), solid N-bromoacetamide (50 mg.) was added with stirring in the dark over a period of 2 min. After 40 min. 5% sodium sulfite solution (0.24 ml.) was added with stirring until the iodide starch reaction was negative. Water was added and the turbid mixture was extracted with chloroform (50 ml.). The residue (164 mg.) from the washed and dried chloroform solution crystallized from 90% methanol as rods (80 mg.; m.p. 186–187°); $[\alpha]^{20}D$ +9.9° (*c* 1.069); λ_{max}^{alc} 268 mμ (ε 585), 276 (570); λ_{max}^{Nujol} 2.87 (m), 5.61 (m), 5.82 (m), 7.84 (s) μ.

Anal. Calcd. for $C_{22}H_{27}O_5Br$ (451.4): C, 58.55; H, 6.03; Br, 17.71. Found: C, 58.44; H, 5.88; Br, 18.19.

The **triacetate Vb** obtained from the diacetate by acetylation in pyridine formed hairlike crystals from dilute methanol which melted at 164–165°; $[\alpha]^{20}D$ +83° (*c* 1.011); λ_{max}^{alc} 268 mμ (ε 720), 276 (656), 214 sh (11,720), 263 sh (562); λ_{max}^{Nujol} 5.69, 5.74, 5.78 (triplet, s), 8.10 (s) μ.

Anal. Calcd. for $C_{24}H_{29}O_6Br$ (493.4): C, 58.42; H, 5.92. Found: C, 58.57; H, 5.67.

6-Keto-7α-bromoestradiol Diacetate (VIa). A. From 6β-Hydroxy-7α-bromoestradiol 3,17-Diacetate (Va).—A stirred solution of 6β-hyroxy-7α-bromoestradiol diacetate (45 mg.) in reagent acetone (6 ml.) was treated dropwise with 1 ml. of 0.402 *N* chromic acid in dilute sulfuric acid and acetone.[3] After 10 min., the excess chromium trioxide was destroyed with 95% ethanol and the reaction mixture was diluted with water. The acetone and ethanol were removed *in vacuo* and the resulting precipitate was filtered off and washed well with water. Two crystallizations from methanol yielded small needles (27 mg.), m.p. 172–174°; $[\alpha]^{21}D$ −15° (*c* 0.798); λ_{max}^{alc} 212 mμ (ε 20,500), 258 (10,790), 307 (2283); λ_{max}^{Nujol} 5.67 (s), 5.76 (s), 5.90 (s), 8.02 (s) μ.

Anal. Calcd. for $C_{22}H_{25}O_5Br$ (449.3): C, 58.80; H, 5.61. Found: C, 59.06; H, 5.90.

B. From 6-Ketoestradiol Diacetate (Ia).—To a solution of 6-ketoestradiol 3,17-diacetate (248 mg.) in glacial acetic acid (15 ml.) 0.65 *M* bromine in acetic acid (2 drops) was added. The yellow color faded out on the addition of 1 drop of 32% hydrobromic acid. A total of 1.08 ml. (5% excess) of bromine solution was added dropwise. The reaction mixture was diluted with water and extracted twice with chloroform. The chloroform was then washed with water, sodium bicarbonate, and again with water. The residue from the sodium sulfate-dried chloroform after three crystallizations from methanol melted at 171–172; $[\alpha]^{19}D$ −16° (*c* 1.033). The spectral characteristics were identical with those of the specimen prepared from Va.

Anal. Calcd. for $C_{22}H_{25}BrO_5$ (449.3); C, 58.80; H, 5.61. Found: C, 58.70; H, 5.73.

The **17-monoacetate VIb** of the bromo ketone was obtained when a solution of the diacetate (102 mg.) and *p*-toluene sulfonic acid (204 mg.) in acetic acid (4 ml.) was heated under reflux in an atmosphere of nitrogen for 14 hr. After the addition of water, the product was isolated by extraction with ether–benzene. The residue from the extract (95 mg.) after two crystallizations from dilute methanol yielded needles (63 mg.), m.p. 158–160°; $[\alpha]^{20}D$ −21° (*c* 1.031); λ_{max}^{alc} 216 mμ (ε 16,890), 261 (8880), 336 (1700), 316 sh (1640); λ_{max}^{Nujol} 2.95 (m), 5.64 (m), 5.77 (s), 5.84 (s), 5.93 (s), 8.07 (s) μ.

Anal. Calcd. for $C_{20}H_{23}O_4Br$ (407.3): C, 58.97; H, 5.69. Found: C, 58.82; H, 5.98.

For **6-keto-7α-bromoestradiol diacetate**, O.R.D. in dioxane (*c* 0.05525) showed $[\alpha]_{700-626}$ −20, $[\alpha]_{450}$ −60, $[\alpha]_{378}$ +576, $[\alpha]_{333}$ −1257, $[\alpha]_{325}$ −494°.

For **6-ketoestradiol diacetate**, O.R.D. in dioxane (c 0.06075) showed $[\alpha]_{600}$ −30, $[\alpha]_{468}$ −60 (broad trough), $[\alpha]_{370}$ +488, $[\alpha]_{365}$ +430, $[\alpha]_{357}$ +553, $[\alpha]_{317.5}$ −1460, $[\alpha]_{310}$ −824°.

6α-Hydroxyestradiol 3,17-Diacetate (IIc) from 6β-Hydroxy-7α-bromoestradiol 3,17-Diacetate (Va).—A solution of 6β-hydroxy-7α-bromoestradiol diacetate (305 mg.) in 95% ethanol (19 ml.) was added to a suspension of hydrogenated 5% palladium on calcium carbonate (303 mg.) in 95% ethanol (11 ml.). The hydrogen uptake ceased after 6 hr. when the equivalent of 1 mole had been consumed. The catalyst was filtered off and the ethanol was removed *in vacuo*. The residue was dissolved in chloroform, washed twice with water, and dried over sodium sulfate. After the removal of the solvent *in vacuo*, the residue (241 mg.) was twice recrystallized from ethyl acetate–hexane, yielding 113 mg., m.p. 140–141°; $[\alpha]^{21}D$ +53° (c 0.754); λ_{max}^{alc} 268 mμ (ε 705), 276 (660), 261 sh (562); λ_{max}^{Nujol} 2.88 (s), 5.69 (s), 5.88 (s), 7.90 (m) μ.

Anal. Calcd. for $C_{22}H_{28}O_5$ (372.4): C, 70.94; H, 7.58. Found: C, 71.16; H, 7.73.

Acetylation of the diacetate IIc in anhydrous pyridine and acetic anhydride gave the triacetate IIb, identical with an authentic sample by mixture melting point, rotation, and infrared spectrum. Oxidation of IIc (33 mg.) in acetone with Jones reagent yielded 6-ketoestradiol diacetate (Ia, 21 mg.), m.p. 173–174°; λ_{max}^{alc} 248 mμ (ε 10,000), 300 (2045). Admixture with an authentic sample did not depress the melting point.

In another debromination experiment conducted under the same conditions on Va (153 mg.), the crude reaction product was chromatographed on a thin layer of Woelm neutral alumina, grade V. The chromatogram was developed with 24:1 chloroform–ethyl acetate. Short irradiation with an ultraviolet lamp served to locate the bands; elution was effected with 1:9 methanol–ethyl acetate. The material eluted in the first band just behind the front (29 mg.) was inhomogeneous and was, therefore, rechromatographed. The second band contained 6β-hydroxyestradiol diacetate (16 mg.) identified by its melting point, 158–160°, and its infrared spectrum; from the third band 56 mg. of the lower melting polymorphous modification of 6α-hydroxyestradiol diacetate, m.p. 128–130°, was obtained after purification. On rechromatography of the first band on Woelm neutral alumina in which chloroform alone was used for development, estradiol 3,17-diacetate was isolated as the main product. A small amount of estradiol 17-monoacetate[30] was also present. For identification the 17-monoacetate was prepared by treating the 3,17-diacetate with potassium carbonate in 90% methanol.

When the triacetate Vb of the *trans*-bromohydrin was hydrogenated in 95% EtOH with 5% palladium on calcium carbonate as the catalyst and then chromatographed, only estradiol 3,17-diacetate could be isolated.

6α-Hydroxy-7α-bromoestradiol 3,17-Diacetate (VIIa).—A solution of 6-keto-7α-bromoestradiol 3,17-diacetate (32 mg.) in methanol (15 ml.) was cooled to 0° and treated dropwise under anhydrous conditions with a chilled solution of sodium borohydride (33 mg.) in methanol (6 ml.). After 15 min., the reaction mixture was acidified to about pH 5 with 10% acetic acid and diluted with cold water (60 ml.). Extraction with ether in the usual way yielded 32 mg. of residue which after two crystallizations from ethyl acetate–hexane was obtained as long narrow plates (19 mg.) melting at 170–171°; $[\alpha]^{20}D$ +29° (*c* 0.771);

(29) The 6-dehydroestrone from which 6-dehydroestradiol diacetate was prepared was obtained from Dr. Earl Chamberlin of the Merck Sharp and Dohme Research Laboratories through the good offices of the Cancer Chemotherapy National Service Center. We wish to thank Dr. Chamberlin for the generous gift of 10 g. of this compound.

(30) K. Miescher and C. Scholz, *Helv. Chim. Acta*, **20**, 263 (1937).

λ_{max}^{alc} 267 mμ (ε 610), 275 (570); λ_{max}^{Nujol} 3.94 (m), 5.66 (s), 5.80 (s), 8.03 (s) μ.

Anal. Calcd. for $C_{22}H_{27}O_5Br$ (451.4): C, 58.55; H, 6.03. Found: C, 58.62; H, 5.92.

The triacetate VIIb prepared from VIIa by acetylation in pyridine formed small prisms from methanol melting at 228–230°; $[\alpha]^{20}D$ +68° (*c* 1.114); λ_{max}^{alc} 267 mμ (ε 580), 275 (560), 217 sh (10,840); λ_{max}^{Nujol} 5.69 (s), 5.74 (s), 5.78 (s), 8.10 (s) μ.

Anal. Calcd. for $C_{24}H_{29}O_6Br$ (493.4): C, 58.42; H, 5.92. Found: C, 58.30; H, 5.84.

Debromination of 6α-Hydroxy-7α-bromoestradiol 3,17-Diacetate (VIIa).—A solution of 6α-hydroxy-7α-bromoestradiol 3,17-diacetate (103 mg.) in 90% ethanol (10 ml.) was added to a suspension of hydrogenated 5% palladium on calcium carbonate (106 mg.) in 90% ethanol (2 ml.) and was shaken with hydrogen at atmospheric pressure. The hydrogen uptake ceased after 6 hr. when only 0.6 equiv. of 1 mole had been consumed. The catalyst was removed by filtration and the solution was evaporated to dryness *in vacuo*. A chloroform solution of the residue, after being washed and dried, yielded 95 mg. which was chromatographed on a thin layer of Woelm neutral alumina, grade V, and developed with 24:1 chloroform–ethyl acetate. The infrared spectrum and optical rotation of the main fraction (37 mg., m.p. 125–127°) were identical with those of 6α-hydroxyestradiol 3,17-diacetate (IIc), and in mixture with an authentic sample the melting was not depressed. The second crystalline compound obtained proved to be some unattacked starting material.

Conversion of 6α-Hydroxy-7α-bromoestradiol 3,17-Diacetate (VIIa) to 6-Ketoestradiol 17-Monoacetate (Ib).—A solution of 6α-hydroxy-7α-bromoestradiol 3,17-diacetate (58 mg.) in anhydrous *t*-butyl alcohol was treated with 0.45 *M* potassium *t*-butoxide in *t*-butyl alcohol (1.14 ml.). After 5 min. ether (40 ml.) was added and the reaction mixture was washed twice with water and dried over sodium sulfate. The residue (39 mg.) crystallized from 95% ethanol as diamond-shaped plates, m.p. 280–283°, which were identified as 6-ketoestradiol 17-monoacetate (Ib) by analysis and comparison (infrared, mixture melting point) with an authentic sample. The latter was obtained by treating 6-ketoestradiol 3,17-diacetate (Ia, 65 mg.) with 1% potassium bicarbonate in 90% aqueous methanol (5.5 ml.) for 1 hr. at room temperature and isolating the product by ether extraction. The ether residue (38 mg.) was thrice crystallized from 95% ethanol and then melted at 284–287°; $[\alpha]^{20}D$ −18° (*c* 0.997, dioxane); λ_{max}^{alc} 221 mμ (ε 20,920), 256 (8840), 327 (3090); λ_{max}^{Nujol} 2.96 (m), 5.76 (s), 6.01 (s), 6.21 (m), 8.01 (s) μ.

Anal. Calcd. for $C_{20}H_{24}O_4$ (328.4): C, 73.14; H, 7.37. Found: C, 73.34; H, 7.41.

6β,7β-Oxidoestradiol Diacetate (IXa).—6β-Hydroxy-7α-bromoestradiol 3,17-diacetate (200 mg.) was dissolved in dry *t*-butyl alcohol (5 ml.) and treated at room temperature with freshly prepared 0.31 *M* potassium *t*-butoxide in *t*-butyl alcohol (2.14 ml.). After 15 min. ether (200 ml.) was added and the mixture was washed twice with water and then dried over sodium sulfate. The glassy residue (167 mg.) crystallized from dilute methanol as rods which melted at 124–126°; $[\alpha]^{19}D$ −61° (*c* 0.858); λ_{max}^{alc} 272 mμ (ε 736), 278 (791), 215 sh (6510), 287 sh (354); λ_{max}^{Nujol} 5.64 (s), 5.78 (s), 7.97 (s), 8.06 (s) μ.

Anal. Calcd. for $C_{22}H_{26}O_5$ (370.4): C, 71.33; H, 7.08. Found: C, 71.23; H, 6.91.

The 17-monoacetate IXb of the β-oxide was obtained in the above reaction when the potassium *t*-butoxide was not limited to 1.5 mole equiv. and also when in the work-up water was added before ether. This product crystallized from methanol as rectangular plates, m.p. 183–186; $[\alpha]^{20}D$ −37° (*c* 0.44); λ_{max}^{alc} 244 mμ (ε 6430), 286 (2265); λ_{max}^{Nujol} 2.97 (m), 5.83 (s), 7.83 (s) μ.

Anal. Calcd. for $C_{20}H_{24}O_4$ (328.4): C, 73.14; H, 7.37. Found: C, 73.26; H, 7.63.

When an attempt was made to acetylate the 17-monoacetate IXb in anhydrous pyridine and acetic anhydride, only a small amount of an amorphous product could be recovered by ether extraction, the remainder, probably 6-pyridinium salts, staying in the aqueous phase. However, the diacetate IXa was readily obtained when the monoacetate was allowed to stand in acetic anhydride overnight, and the mixture was worked up in the usual way by ether extraction. The residue from the washed and dried ether solution on crystallization from methanol melted at 124–125°, and its infrared spectrum was identical with that of the diacetate.

7β-Hydroxyestradiol (XIb). A. From 6β,7β-Oxidoestradiol Diacetate (IXa).—A solution of 6β,7β-oxidoestradiol diacetate (100 mg.) in dry tetrahydrofuran (6 ml.) was added slowly to a mixture of a saturated ether solution of lithium aluminum hydride (2 ml.) and tetrahydrofuran (20 ml.) which was then heated under reflux for 6 hr. Excess lithium aluminum hydride was destroyed by adding ethyl acetate dropwise and the reaction mixture was distributed between ethyl acetate (100 ml.) and water (100 ml.). Hydrochloric acid (2 *N*) was added to dissolve the flocculent precipitate in the water before the layers were separated. The residue (75 mg.) from the washed and dried ethyl acetate crystallized from a minimum amount of methanol and ethyl acetate yielding plates (44 mg.) melting at 237–238°; $[\alpha]^{21}D$ +38° (*c* 0.863, in absolute ethanol); λ_{max}^{alc} 281 mμ (ε 2050), 220 sh (6200); λ_{max}^{Nujo} 2.91, 2.99 (doublet, m) μ.

Anal. Calcd. for $C_{18}H_{24}O_3$ (288.4): C, 74.97; H, 8.39. Found: C, 74.92; H, 8.49.

The triacetate XIc obtained by acetylating the triol with anhydrous pyridine and acetic anhydride in the usual manner crystallized from acetone–hexane as small needles, m.p. 171–173°; $[\alpha]^{20}D$ +60°; λ_{max}^{KBr} 5.69 (s), 5.78 (s), 8.02 (s) μ.

B. From 7β-Hydroxyestrone.—A solution of sodium borohydride (60 mg.) in water (3 ml.) was added dropwise to a stirred solution of 7β-hydroxyestrone (30 mg.) in methanol (9 ml.). After 3 hr. at room temperature, the excess sodium borohydride was decomposed with 10% acetic acid, and water (15 ml.) was added. Two extractions with ethyl acetate (40 ml.), which was washed with water and dried, yielded the crude triol which after recrystallization from ethyl acetate (22 mg.) melted at 239–240°, and was found to be identical with the specimens obtained from the oxide IXa by comparison of the infrared spectra.

6β,7α-Dihydroxyestradiol 3,17-Diacetate (XIIa).—6α,7α-Oxidoestradiol diacetate[12] (X, 30 mg.) was dissolved in 50% aqueous acetone (20 ml.) containing a drop of 70% perchloric acid and was heated under reflux for 15 min. The residue obtained by evaporation *in vacuo* of a washed and dried ethyl acetate extract of the diluted reaction mixture was twice crystallized from ethyl acetate–hexane and yielded 17 mg., m.p. 170–171°; $[\alpha]^{20}D$ +16° (*c* 0.622, dioxane); λ_{max}^{alc} 267 mμ (ε 570), 275 (550), 215 sh (9430); λ_{max}^{Nujol} 2.92 (s), 5.65 (s), 5.86 (s), 7.93 (s) μ.

Anal. Calcd. for $C_{22}H_{28}O_6$ (338.4): C, 68.02; H, 7.27. Found: C, 68.02; H, 7.26.

The tetraacetate XIIb was prepared by the acetylation of the diacetate XIIa in anhydrous pyridine and acetic anhydride at room temperature overnight. The small rods from dilute ethanol melted at 134–136°; $[\alpha]^{21}D$ +68° (*c* 0.311), λ_{max}^{alc} 269 mμ (ε 737), 276 (690), 214 sh (12,300); λ_{max}^{Nujol} 5.68 (m), 5.77 (s), 8.05 (s) μ.

Anal. Calcd. for $C_{26}H_{32}O_8$ (472.5): C, 66.08; H, 6.83. Found: C, 66.29; H, 6.72.

6α,7β-Dihydroxyestradiol Tetraacetate (XIVb). A. From 6β,7β-Oxidoestradiol Diacetate.—A solution of 6β,7β-oxidoestradiol diacetate (21 mg.) in 50% aqueous ethanol (5 ml.) containing a drop of 70% perchloric acid was boiled under reflux for 15 min. After the addition of water the reaction mixture was extracted with ethyl acetate and subsequently washed with dilute sodium bicarbonate solution and water. The amorphous residue was acetylated in 0.1 ml. of anhydrous pyridine and 0.2 ml. of acetic anhyride at 90° for 1 hr. The reaction mixture, worked up in the usual manner, yielded 24 mg. which crystallized from ethyl acetate–hexane as small rods and melted at 215–216°; $[\alpha]D$ −1° (*c* 0.791). The ultraviolet and infrared spectra were identical with those of the 6α,7β-dihydroxyestradiol tetraacetate obtained from 6β-hydroxy-7α-bromoestradiol 3,17-diacetate as described below.

B. From 6β-Hydroxy-7α-bromoestradiol 3,17-Diacetate (Va) *via* 6α,7β-Dihydroxyestradiol 17-Monoacetate (XIVa).—A solution of 6β-hydroxy-7α-bromoestradiol diacetate (45 mg.) in methanol (2 ml.) was flushed with nitrogen and then was treated with 10% aqueous potassium carbonate (0.2 ml.) which had previously been flushed with nitrogen. After 1 hr. glacial acetic acid (2 drops) was added and the mixture was diluted with water. The noncrystallizable residue (33 mg.) obtained by evaporation *in vacuo* of a washed and dried ether extract consisted largely of the tetrol 17-monoacetate XIVa as shown by the following data: $[\alpha]^{22}D$ +30° (*c* 0.613); λ_{max}^{alc} 282 mμ (ε 2150); λ_{max}^{Nujol} 2.98 (m), 5.83 (s), 8.00 (s) μ.

Anal. Calcd. for $C_{20}H_{26}O_5$ (346.4): C, 69.34; H, 7.57. Found: C, 69.36; H, 7.58.

A solution of the above monoacetate (64 mg.) and *p*-toluenesulfonic acid hydrate (96 mg.) in acetic acid (3.6 ml.) and acetic anhydride (1.25 ml.) was allowed to stand at room temperature overnight. The reaction mixture was poured onto crushed ice

and dilute sodium carbonate solution and then extracted with ether. The residue (78 mg.) from the washed and dried ether was twice crystallized from ethyl acetate–hexane, yielding small rods, m.p. 216–217°; $[\alpha]^{21}D$ −2° (*c* 0.578, dioxane); λ_{max}^{alc} 267 mμ (ε 780), 276 (723), 260 sh (595); λ_{max}^{Nujol} 5.63, 5.68, 5.75 (triplet, s), 8.05 (s) μ.

Anal. Calcd. for $C_{26}H_{32}O_8$ (472.5): C, 66.08; H, 6.83. Found: C, 65.76; H, 6.78.

The monoacetate XIVa was also obtained as the sole product when in the preparation of 6β,7β-oxidoestradiol diacetate glacial acetic acid equivalent to the moles of potassium *t*-butoxide was added at the beginning of the work-up.

6β-Methoxy-7α-hydroxyestradiol 3,17-Diacetate(XVa).—6α,7α-Oxidoestradiol diacetate (32 mg.) was dissolved in reagent methanol (10 ml.) containing 70% perchloric acid (0.04 ml.). After about 10 min. at room temperature, the reaction mixture was neutralized with a saturated solution of sodium bicarbonate. The methanol was removed *in vacuo* and the residue from a washed and dried chloroform extract crystallized on standing in dilute methanol as small needles, m.p. 83–88°; $[\alpha]^{21}D$ +25° (*c* 0.777, dioxane); λ_{max}^{alc} 267 mμ (ε 620), 275 (580); λ_{max}^{Nujol} 2.95 (m), 5.67 (s), 5.77 (s), 8.07 (s) μ.

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.5): OCH_3, 7.71. Found: OCH_3, 7.79.

When the methanolic mother liquor of 6α,7α-oxidoestradiol diacetate (X) was allowed to stand at room temperature for several days and the solid obtained by removal of the methanol was chromatographed, the main product proved to be 6β-methoxy-7α-hydroxyestradiol 3,17-diacetate. Its melting point, rotation, and spectral data were identical with those of the methanolysis product of the oxide.

Triacetate XVb.—6β-Methoxy-7α-hydroxyestradiol 3,17-diacetate (50 mg.) was acetylated in anhydrous pyridine and acetic anhydride in the usual manner. The reaction product was recrystallized twice from ethyl acetate–hexane yielding fine rods (41 mg.), m.p. 182–183°; $[\alpha]^{21}D$ −9° (*c* 0.867); λ_{max}^{alc} 267 mμ (ε 613), 275 (564), 263 sh (503); λ_{max}^{Nujol} 5.63 (s), 5.74 (s), 8.04 (s) μ.

Anal. Calcd. for $C_{25}N_{32}O_7$ (444.5): C, 67.55; H, 7.26. Found: C, 67.56; H, 7.37.

6α-Methoxy-7β-Hydroxyestradiol 3,17-Diacetate XVI.—6β,7β-Oxidoestradiol diacetate (43 mg.) was dissolved in reagent methanol (15 ml.) containing 70% perchloric acid (0.053 ml.). After about 10 min. at room temperature, the reaction mixture was neutralized with a saturated solution of sodium bicarbonate. The methanol was removed *in vacuo* and the residue (42 mg.) from the washed and dried chloroform extract was twice crystallized from ethyl acetate–hexane yielding small needles, m.p. 177–178°; $[\alpha]^{20}D$ −18° (*c* 0.775, dioxane); λ_{max}^{alc} 267 mμ (ε 563), 273 (527); λ_{max}^{KBr} 2.94 (m), 5.57 (s), 5.77 (s), 8.06 (s) μ.

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.5): C, 68.63; H, 7.51; OCH_3, 7.71. Found: C, 68.82; H, 7.79; OCH_3, 7.35.

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Microbial Hydroxylation of Estrone and Estradiol in the 6β-, 7α-, and 15α-Positions

ALLEN I. LASKIN, PAUL GRABOWICH, BARBARA JUNTA, CAROL DE LISLE MEYERS, AND JOSEF FRIED[1]

The Squibb Institute for Medical Research, New Brunswick, New Jersey

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Estrone and estradiol have been converted into their 7α- and 15α-hydroxy derivatives by microorganisms of the genera *Glomerella* and *Aspergillus*, and to 6β-estradiol by *Mortierella alpina*. 15α-Hydroxyestrone and 15α-hydroxyestradiol are new compounds of low estrogenic potency.

The stereospecific hydroxylation of steroidal substrates by microbial enzymes has during the past decade developed into one of the most important and widely employed reactions in steroid chemistry. It has been applied to a large variety of substrates particularly those possessing the pregnane and androstane skeleton, and with very few exceptions all available positions of the steroid nucleus have been hydroxylated by this elegant procedure.[2] There is one important class of steroids, however, that is only sparsely represented in the literature in connection with this reaction and these are the phenolic estrogens. Only two reports have appeared,[3,4] both presenting evidence for the 16α-hydroxylation of estrone and estradiol. This limited measure of accomplishment is surely not due to a lack of interest in the hydroxylation of the estrogenic hormones, but, to judge from our own experience, a reflection of the tendency of these phenolic steroids to suffer multiple enzymic attack thereby giving rise to difficultly separable mixtures. The present report, therefore, represents the result of considerable effort involving a large variety of organisms.

The organisms destined for further exploration were selected on the basis of paper chromatographic evidence for complete utilization of the substrate and the formation of substantial amounts of hydroxylated products. They belong to the genera *Glomerella*, *Aspergillus*, and *Mortierella*. The organisms were grown in flasks which were vigorously shaken to promote maximum growth, then transferred to a fresh growth medium, to which the steroid had been added, and allowed to grow under the same conditions. Samples were taken at intervals and analyzed for the degree of conversion by paper chromatography. The fermentations were terminated when all the substrate had disappeared. The steroid metabolites were then recovered from the filtered broth by extraction with chloroform and methyl isobutyl ketone, and the individual components were isolated after chromatography on alumina. It soon became evident that when the time of fermentation was extended from 2 to 7 days the organisms, in addition to hydroxylating estrone, also caused partial reduction of the 17-keto group, thus producing the corresponding hydroxylated estradiol derivatives. The reverse was true when estradiol was used as a substrate. This complicated the isolation process leading to twice as many metabolites as positions hydroxylated. Thus, *Glomerella fusarioides* (ATCC 9552) furnished at least

(1) The Ben May Laboratory for Cancer Research, University of Chicago, Chicago 37, Ill.

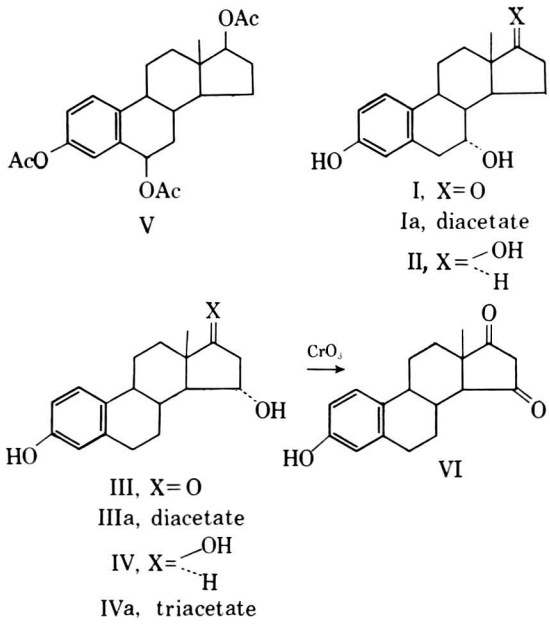
(2) For a most recent review on this subject with citations of earlier review papers, *cf.* C. Tamm, *Angew. Chem.*, **74**, 225 (1962).

(3) K. A. Kita, J. L. Sardinas, and G. M. Shull, *Nature*, **190**, 627 (1961).

(4) B. F. Stimmel, T. E. Bucknell, and V. Notchev, *Federation Proc.*, 115 (1960).

(5) J. Iriarte, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6105 (1958).

four products, the known 7α-hydroxyestrone (I)[5] and 7α-hydroxyestradiol (II),[5] as well as two new metabolites shown in the sequel to be 15α-hydroxyestrone (III, m.p. 226–230°, $[\alpha]_D$ +197° in ethanol) and 15α-hydroxyestradiol (IV, m.p. 248–250°, $[\alpha]_D$ +163° in dioxane). The same products were obtained using *Glomerella glycines* (ATCC 3422) and the morphologically unrelated *Aspergillus carneus* (Centraalbureau voor Schimmelcultures, Baarn, Holland).



15α-Hydroxyestrone was further characterized as the diacetate and 15α-hydroxyestradiol as the triacetate. The location of the newly introduced hydroxyl group became evident upon examination of the spectra of the diketone VI prepared by chromic acid oxidation of either III or IV. Its ultraviolet spectrum in methanolic potassium hydroxide showed an intense peak at 277 mμ (ε 15,000), and the infrared spectrum exhibited peaks at 5.66 and 5.78 μ (in addition to benzenoid absorption) in close harmony with the data reported by Bernstein, *et al.*,[6] for 15-ketoandrostenedione ($\lambda_{max}^{alc\ KOH}$ 277 mμ (ε 19,700), λ_{max}^{KBr} 5.66 and 5.76 μ). Additional and most convincing evidence for the presence of a 1,3-diketone system was derived from the n.m.r. spectrum, which exhibited a singlet representing two protons at τ 7.03, characteristic of a methylene group flanked by two carbonyl groups.[7] The fact that this peak integrates to two protons indicates that VI must be completely in the diketone form, a finding that is supported by the failure of VI to give a coloration with ferric chloride and by the ultraviolet spectrum in neutral medium, which is essentially identical with that of estrone. Having established the position of the newly introduced hydroxyl group, its orientation follows from the strongly positive molecular rotation contribution of that group in both 15-hydroxyestrone (ΔM_D +141° in dioxane) and 15-hydroxyestradiol (ΔM_D +249° in alcohol).[8] For the 15-ketone VI we propose the C–D *cis*-fused 14β-structure since it is recovered unchanged on treatment with base under conditions that will readily isomerize 15-keto steroids[9] and related *trans*-indanones[10,11] to their *cis* isomers. Moreover, the negative rotation contribution of the 15-keto group in VI (ΔM_D −226° in methanol) rather than a positive increment as in 15-ketoprogesterone (ΔM_D +53° in chloroform)[9] lends additional support to the *cis* fusion of rings C and D.[12]

The isomerization of the *trans*- to the *cis*-indanone could only have occurred under the slightly acidic conditions of the Jones oxidation. Such a reaction, although not previously encountered under these conditions, is not unanticipated, in view of the fact that Dreiding models indicate a greater strain in the *trans*-fused 15,17-diketone system than is known to exist in the corresponding *trans*-fused monoketones. Relief of that strain by enolization of the 15-keto group towards C-14 would, therefore, be expected to occur more readily in the present case.

The capacity of microorganisms of the genus *Glomerella* to effect hydroxylation of steroidal substrates is not confined to the phenolic estrogens. *Glomerella* species including *G. fusarioides* have been reported to hydroxylate cortexolone and related substrates in the 11α-position.[13] To rationalize this shift in the locus of hydroxylation with the change in substrate, we wish to point to the fact that carbon atoms 15, 14, 13, and 18 occupy the same positions relative to each other as carbon atoms 11, 9, 10, and 19. On the premise then that the presence of the latter arrangement of carbon atoms is instrumental in directing enzymic attack to C-11, its absence in the ring A aromatic steroids might be expected to shift the attack to the terminus of the related sequence, namely, C-15.

Fermentation of estrone with *Mortierella alpina* (ATCC 8979)[14] gave in moderate yield the known 6β-hydroxyestradiol,[15] isolated as the triacetate. It is interesting to note in this connection that 6β-hydroxyestradiol has been isolated by Breuer, *et al.*,[15b] from incubates of estradiol with rat liver microsomes.

7α-Hydroxyestrone and 15α-hydroxyestradiol had, respectively, 1/3000 and 1/1000 the uterotrophic

(6) (a) S. Bernstein, L. I. Feldman, W. S. Allen, R. H. Blank, and C. E. Linden, *Chem. Ind.* (London), 111 (1956); (b) S. Bernstein, M. Heller, L. I. Feldman, W. S. Allen, R. H. Blank, and C. E. Linden, *J. Am. Chem. Soc.*, **82**, 3685 (1960).

(7) The signal for the methylene protons in the analogous cyclopentene-3,5-dione [C. H. DePuy and E. F. Zawesky, *ibid.*, **81**, 4920 (1959)] is at τ 7.10: private communication from Professor DePuy.

(8) The molecular rotation contributions for the hydroxyl group in 15α- and 15β-hydroxyandrostenedione in methanol are ΔM_D +107 and −71°, respectively (*cf.* ref. 6). These values are in good agreement with those for the 15-hydroxy derivatives of progesterone [J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progr. Hormone Res.*, **11**, 157 (1955)] and of cortexolone (ref. 6).

(9) C. Djerassi, L. B. High, J. Fried, and E. F. Sabo, *J. Am. Chem. Soc.*, **77**, 3673 (1955).

(10) J. F. Biellman, D. Francetić, and G. Ourisson, *Tetrahedron Letters*, **18**, 4 (1960).

(11) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **84**, 4356 (1962).

(12) The related 15-ketoandrostenedione described by Bernstein, *et al.* (ref. 6a,b), shows a very similar ΔM_D for the 15-keto group (−194°). It is more than likely, therefore, that both compounds possess rings C and D in *cis* fusion. The possibility that an enol form could cause the observed negative rotation contribution as discussed by Bernstein, *et al.* (*cf.* footnote 14 in ref. 6b), is ruled out in our case by the n.m.r. and ultraviolet data.

(13) F. Carvajal, U. S. Patent 2,985,563 (1961).

(14) *Mortierella* species including *M. alpina* have been claimed to effect 6β-hydroxylation of progesterone [L. I. Feldman, N. E. Rigler, A. J. Shay, and B. E. Nielsen, U. S. Patent 3,060,101 (1962)] and 1-hydroxylation of 9α-fluorohydrocortisone [L. I. Feldman, N. E. Rigler, and A. J. Shay, U. S. Patent 2,462,423 (1961)].

(15) (a) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **81**, 442 (1959); (b) H. Breuer, R. Knuppen, and G. Pangels, *Nature*, **190**, 720 (1961); *Biochim. Biophys. Acta*, **65**, 1 (1962).

activity of estradiol benzoate in the immature female mouse assay.[16]

Experimental

All melting points are uncorrected in capillaries. Rotations are in chloroform unless otherwise specified. Ultraviolet spectra were determined on a Cary 11 spectrometer, infrared spectra on a Perkin-Elmer 21 spectrometer, and n.m.r. spectra on a Varian A-60 spectrometer in deuteriochloroform solution with tetramethylsilane as internal standard. The following paper chromatographic systems were used to determine the progress of the fermentations. The toluene–propylene glycol system of Zaffaroni, *et al.*,[17] was used for determination of residual substrate. For separation of the products, a modification of the B5 system of Bush[18] was used, in which the ratio of benzene–methanol–water was 1:1:1, and the procedure was carried out at room temperature instead of at 30–38°.

Fermentation of Estrone with *Glomerella fusarioides* (ATCC 9552).—Surface growth from each of five 3-week agar slant cultures of *Glomerella fusarioides* (ATCC 9552) (the slant containing nutrient medium A–glucose, 10 g.; Difco yeast extract, 2.5 g.; K_2HPO_4, 1 g.; agar, 20 g.; and distilled water to 1 l.) was suspended in 2.5 ml. of an 0.01% sodium lauryl sulfate aqueous solution. One-milliliter portions of the suspension were used to inoculate ten 250-ml. conical flasks (each containing 50 ml. of sterilized nutrient medium B–dextrose, 10 g.; cornsteep liquor, 6 g.; $NH_4H_2PO_4$, 3 g.; Difco yeast extract, 2.5 g.; $CaCO_3$, 2.5 g.; and distilled water to 1 l.) After 5 days of incubation at 25° with continuous rotary agitation (280 cycles per min., 2-in. radius), 10% (v./v.) transfers were made to one-hundred 250-ml. conical flasks each containing 50 ml. of fresh sterilized medium B. To each flask was added 0.25 ml. of a sterile solution of the steroid in N,N-dimethylformamide (60 mg./ml.) so that the concentration of steroid was 300 μg./ml. After 48 hr. of further incubation, the contents of the flasks were pooled and filtered through a Seitz clarifying pad. The flasks, mycelium, and pad were washed with successive 50-ml. portions of warm water.

The combined filtrate and washings (5300 ml.) were extracted with three 1-l. portions of chloroform, and the combined chloroform extracts were washed with water and evaporated to dryness *in vacuo*. The resulting crude residue (654 mg.) on trituration with ethyl acetate furnished 290 mg. of a residue, which on recrystallization from methanol furnished 153 mg. of 7α-hydroxyestrone (I), m.p. 260–262°; $[\alpha]^{23}D$ +111° (*c* 0.42, 95% ethanol), +117° (dioxane); λ_{max}^{alc} 281 mμ (ε 2380); in 2.5% KOH in methanol λ_{max} 297 mμ (ε 2980); λ_{max}^{Nujol} 2.92, 5.80, 5.98, 6.15, 6.27, and 6.63 μ; lit.[5] m.p. 260–262°, $[\alpha]D$ +124° in dioxane.

Anal. Calcd. for $C_{18}H_{22}O_3$ (286.36): C, 75.49; H, 7.74. Found: C, 75.71; H, 7.81.

The ethyl acetate mother liquors from which most of the 7α-hydroxyestrone had been removed were evaporated to dryness *in vacuo* and taken up in chloroform; the resulting crystals were removed by filtration. Concentration of the mother liquors produced crystalline material (275 mg.), which on recrystallization from ethyl acetate produced an additional 16 mg. of 7α-hydroxyestrone melting at 257–258°. Evaporation of the ethyl acetate mother liquors to dryness and crystallization of the residue from chloroform–ethyl acetate furnished 15α-hydroxyestrone (III, 73 mg.), which after additional recrystallization from the same solvent mixture had m.p. 228–230°; $[\alpha]^{23}D$ +197° (*c* 0.49, 95% ethanol); λ_{max}^{alc} 281 mμ (ε 2290); in 2.5% KOH in methanol λ_{max} 297 mμ (ε 3030); λ_{max}^{Nujol} 3.00, 5.78, 6.19, 6.29, and 6.66 μ.

Anal. Calcd. for $C_{18}H_{22}O_3$ (286.36): C, 75.49; H, 7.74. Found: C, 75.38; H, 7.39.

7α-Hydroxyestrone 3,7-Diacetate (Ia).—Fifty milligrams of 7α-hydroxyestrone was acetylated with 0.5 ml. of acetic anhydride in 0.5 ml. of dry pyridine at room temperature for 18 hr. Evaporation of the reagents furnished 65 mg. of crude material, which on recrystallization from ether–hexane gave 44 mg. of pure 7α-hydroxyestrone diacetate (Ia), m.p. 135–137°; $[\alpha]^{23}D$ +51° (*c* 0.46); lit.[5] m.p. 140–141°, $[\alpha]D$ +65° in chloroform.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.05; H, 6.92.

The infrared spectrum of this sample was identical with that of an authentic sample of 7α-hydroxyestrone diacetate, kindly supplied by Dr. H. Ringold.

15α-Hydroxyestrone 3,15-Diacetate (IIIa).—Sixty-two milligrams of 15α-hydroxyestrone was acetylated as described above. The crude residue (78 mg.) was recrystallized from ether–hexane and gave 48 mg. of pure 15α-hydroxyestrone diacetate (IIIa), m.p. 142–143°; $[\alpha]^{23}D$ +201° (*c* 0.64); λ_{max}^{Nujol} 5.65, 5.73, 6.20, 6.68, and 7.95 μ.

Anal. Calcd. for $C_{22}H_{26}O_5$ (370.43): C, 71.33; H, 7.08. Found: C, 71.13; H, 7.26.

15α-Hydroxyestradiol (IV).—To a solution of 43 mg. of 15α-hydroxyestrone in 4.5 ml. of methanol was added 45 mg. of sodium borohydride. The reaction mixture was allowed to remain at room temperature for 1 hr., diluted with water, and acidified with glacial acetic acid; the methanol was evaporated *in vacuo*. The resulting suspension was extracted with ethyl acetate; the ethyl acetate extract was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue on recrystallization from ethyl acetate furnished pure 15α-hydroxyestradiol (IV, 37 mg.), m.p. 248–250°; $[\alpha]^{23}D$ +163° (*c* 0.48, dioxane); λ_{max}^{Nujol} 2.90, 3.00, 3.15, 6.15, 6.30, and 7.65 μ.

Anal. Calcd. for $C_{18}H_{24}O_3$ (288.37): C, 74.97; H, 8.39. Found: C, 74.91; H, 8.26.

15α-Hydroxyestradiol 3,15,17-Triacetate (IVa).—Acetylation of 15α-hydroxyestradiol with pyridine and acetic anhydride as described above gave the crystalline triacetate, which after recrystallization from acetone–hexane had the following properties: m.p. 154–156°; $[\alpha]^{23}D$ +128° (*c* 0.60); λ_{max}^{alc} 257 mμ (ε 770), 266 mμ (ε 755); λ_{max}^{Nujol} 5.65, 5.76, 6.23, 6.32, 6.70, and 8.02 μ.

Anal. Calcd. for $C_{24}H_{30}O_6$ (414.48): C, 69.54; H, 7.30. Found: C, 69.39; H, 7.32.

15-Keto-14β-estrone (VI).—To a solution of 48 mg. of 15α-hydroxyestrone (IV) in 2 ml. of acetone was added 1.3 ml. of a solution containing 20 mg. of chromium trioxide and 32 mg. of concentrated sulfuric acid per milliliter of 90% aqueous acetone. The mixture was allowed to remain at room temperature for 30 min., following which excess chromium trioxide was reduced by the addition of a few drops of methanol. Chloroform and water were added; the chloroform layer was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue (35 mg.) was dissolved in 4 ml. of ethyl acetate and 4 ml. of hexane and chromatographed on 2 g. of silica gel. Elution with the same solvent mixture (50 ml.) furnished crystals which after recrystallization from acetone–hexane afforded the 15-keto-14β-estrone (VI), m.p. 193–195°; $[\alpha]^{23}D$ +79° (*c* 0.30), +69° (*c* 0.46, methanol); λ_{max}^{alc} 279 mμ (ε 2750), shoulder at 245–250 mμ (ε 3100); in 2.5% KOH in methanol λ_{max} 240 mμ (ε 8300), 277 mμ (ε 15,000); λ_{max}^{KBr} 2.98, 5.66, 5.78, 5.91 (acetone of crystallization), 6.20, 6.31, and 6.64 μ; n.m.r., τ 8.93 (s, 19-Me), 7.81 (s, three protons, acetone), 7.18 (two protons, 14-CH and 9-CH), 7.03 (s, two protons, 16-CH_2), and 3.38, 3.30, and 2.82 (one proton each, aromatic CH).

Anal. Calcd. for $C_{18}H_{26}O_3$ (284.34): C, 76.03; H, 7.09. Found: C, 76.04; H, 7.03.

Fermentation of Estrone with *Glomerella glycines* (ATCC 3422).—Following the fermentation procedure described above but substituting a culture of *Glomerella glycines* (ATCC 3422) for the *G. fusarioides*, supplying 80 flasks of the fermentation medium with 500 μg./ml. of steroid instead of 300 μg./ml., and carrying out the final incubation stage for 24 hr. instead of 48 hr., there was obtained a combined filtrate and washings possessing a volume of 5020 ml. This solution was extracted with three 1.6-l. portions of chloroform, and the combined chloroform extracts were filtered and evaporated to dryness *in vacuo*. The resulting residue (390 mg.) on trituration with ethyl acetate furnished 134 mg. of crystalline material, which on recrystallization from the same solvent gave 107 mg. of pure 7α-hydroxyestrone (I). The ethyl acetate mother liquors from the trituration of the crude residue were taken to dryness and triturated with chloroform. The solid residue which weighed 158 mg. was dissolved in ethyl acetate and chromatographed on a column of 8 g. of neutral alumina. Ethyl acetate (500 ml.) eluted crystalline material which after having been triturated with chloroform and recrystallized from ethyl acetate–chloroform furnished pure 15α-hydroxyestrone (III), m.p. 228–230°, identical in all respects with the material obtained by fermentation with *Glomerella fusarioides*.

Extended Fermentation of Estrone with *Glomerella glycines* (ATCC 3422).—Following the general procedure described above, but carrying out the final incubation stage for 7 days instead of

(16) The authors appreciate the cooperation of Dr. L. J. Lerner and his associates in performing these assays.

(17) A. Zaffaroni, R. B. Burton, and E. H. Keutman, *Science*, **111**, 6 (1950).

(18) I. E. Bush, *Biochem. J.*, **50**, 370 (1952).

48 hr. in ten 2-l. flasks each containing 500 ml. of medium B supplied with 500 μg. of steroid per milliliter, the combined filtrate and washings had a volume of 6000 ml. This solution was extracted with three 3-l. portions of chloroform and the combined chloroform extracts were filtered and evaporated to dryness *in vacuo*. Fractional crystallization of the resulting residue (706 mg.) from ethyl acetate gave as the most insoluble component 43 mg. of 15α-hydroxyestradiol (IV) melting at 248–250° and identical in all respects with the material described above. This was followed by several fractions melting at about 252–256° which on recrystallization from ethyl acetate gave 85 mg. of 7α-hydroxyestrone (I), m.p. 258–260°.

An additional amount of 15α-hydroxyestradiol was obtained by extraction of the chloroform-extracted broth with two 1-l. portions of methyl isobutyl ketone. Evaporation of these extracts furnished 110 mg. of crystalline material which on crystallization from methanol furnished 55 mg. of 15α-hydroxyestradiol melting at 247–249°.

Fermentation of Estradiol with *Aspergillus carneus* (Baarn).—Surface growth from a 3-week agar slant culture of *Aspergillus carneus* (Baarn), the slant containing nutrient medium A, was suspended in 2.5 ml. of a 0.01% sodium lauryl sulfate aqueous solution. One-milliliter portions of the suspension were used to inoculate two 250-ml. conical flasks, each containing 50 ml. of the sterilized nutrient medium B. After 72 hr. of incubation at 25° with continuous rotary agitation (280 cycles per min., 2-in. radius), 10% (v./v.) transfers were made to twelve 250-ml. conical flasks each containing 50 ml. of fresh sterilized medium B. These were incubated under the conditions described above for 4 days, after which another 10% (v./v.) transfer was made to 100 additional 250-ml. flasks containing 50 ml. of fresh sterilized medium B. The estradiol was supplied by adding to each flask 0.25 ml. of a sterile solution of the steroid in N,N-dimethylformamide (100 mg./ml.) so that the concentration of steroid was 500 μg./ml. After 5 days of further incubation, the contents of the flasks were pooled and filtered through a Seitz clarifying pad. The flasks, mycelium, and pad were washed with successive 50-ml. portions of warm water.

The combined filtrate and washings (4250 ml.) were extracted with three 1-l. portions of methyl isobutyl ketone. The combined extracts were evaporated to dryness leaving 1.57 g. of a semicrystalline residue. This material was triturated with chloroform and the crystalline residue (1.25 g.) was triturated again with acetone. Recrystallization from acetone and finally from 95% ethanol produced pure 15α-hydroxyestradiol (IV), m.p. 246–248°. The combined mother liquors obtained in the above triturations with chloroform and acetone were evaporated to dryness *in vacuo* and treated with ethyl acetate. This produced 425 mg. of crystals consisting mainly of 7α-hydroxyestradiol (II) contaminated by a small amount of 7α-hydroxyestrone (I) as well as a mother liquor, which was concentrated to a volume of 10 ml. for chromatography as described below. To separate the two components, the material was recrystallized from 95% alcohol which furnished 44 mg. of 7α-hydroxyestrone (I) identified by its infrared spectrum. The mother liquors were evaporated to dryness and recrystallized from ethyl acetate furnishing 75 mg. of pure 7α-hydroxyestradiol, m.p. 255–257°, lit.[5] m.p. 254–260°.

Anal. Calcd. for $C_{18}H_{24}O_3$ (288.37): C, 74.97; H, 8.39. Found: C, 75.18; H, 8.39.

The infrared spectrum of this sample was identical with that of an authentic specimen.

The ethyl acetate mother liquor (10 ml.) described above was chromatographed on 32 g. of acid-washed alumina. Elution of the column with ethyl acetate (350 ml.) furnished 210 mg. of crystalline material which after recrystallization from acetone–ether yielded 50 mg. of 7α-hydroxyestrone (I). Continued elution with ethyl acetate–acetone 1:1 (250 ml.) gave an additional 25 mg. of 7α-hydroxyestrone. Subsequent elution with 350 ml. of ethyl acetate–acetone 1:1 and with acetone (300 ml.) furnished 210 mg. of crude crystals which on recrystallization from acetone yielded 28 mg. of pure 15α-hydroxyestradiol (IV), m.p. 248–250°.

6β-Hydroxylation of Estrone by *Mortierella alpina* (ATCC 8979).—Surface growth from a 3-week agar slant culture of *Mortierella alpina* (ATCC 8979), the slant containing nutrient medium A, was suspended in 2.5 ml. of a 0.01% sodium lauryl sulfate aqueous solution. One-milliliter portions of the suspension were used to inoculate two 250-ml. conical flasks, each containing 50 ml. of the sterilized nutrient medium B. After 48 hr. of incubation at 25° with continuous rotary agitation (280 cycles per min., 2-in. radius), 10% (v./v.) transfers were made to twelve 250-ml. conical flasks each containing 50 ml. of fresh sterilized medium B. These were incubated under the conditions described above for 48 hr., after which another 10% (v./v.) transfer was made to 100 additional 250-ml. flasks containing 50 ml. of fresh sterilized medium B. The estrone was supplied by adding to each flask 0.25 ml. of a sterile solution of the steroid in N,N-dimethylformamide (100 mg./ml.) so that the concentration of steroid was 500 μg./ml. After 5 days of further incubation, the contents of the flasks were pooled and filtered through a Seitz clarifying pad. The flasks, mycelium, and pad were washed with successive 50-ml. portions of warm water.

The combined filtrate and washings (6000 ml.) were extracted with three 2-l. portions of methyl isobutyl ketone; the extracts were washed with water and evaporated to dryness *in vacuo*. The residual oily material, 3.5 g., was dissolved in benzene (100 ml.) and chromatographed on 60 g. of neutral alumina. The column was washed successively with 400-ml. portions of benzene–ethyl acetate (1:1) and ethyl acetate, and these eluates were discarded. Subsequent elution with methanol produced 600 mg. of dark brown noncrystalline material which contained the desired 6β-hydroxyestradiol. For further purification it was dissolved in 50 ml. of ethyl acetate and chromatographed on 24 g. of neutral alumina. Elution with ethyl acetate (800 ml.) produced mainly nonpolar material which was discarded. Elution with 200 ml. of ethyl acetate–acetone (3:1), 200 ml. (1:1), 1 l. of acetone, and finally with 200 ml. of methanol furnished amorphous material which consisted essentially of 6β-hydroxyestradiol as shown by paper chromatography. The fractions were combined and acetylated with 2 ml. of dry pyridine and 2 ml. of acetic anhydride. Evaporation of the reagents left a crystalline residue which after several recrystallizations from ether–hexane furnished 40 mg. of pure 6β-hydroxyestradiol triacetate (V), m.p. 173–175°, $[\alpha]^{23}D$ +57° (*c* 0.45, chloroform); lit.[15] m.p. 176–178°, $[\alpha]D$ +53° in chloroform.

Anal. Calcd. for $C_{24}H_{30}O_6$ (414.48): C, 69.54; H, 7.30. Found: C, 69.61; H, 7.23.

The infrared spectrum of this substance was identical with that of an authentic sample of 6β-hydroxyestradiol triacetate kindly furnished by Dr. O. P. Wintersteiner.

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The Epimeric *syn*-Bicyclo[3.2.1]octane-2,8-diols[1]

NORMAN A. LEBEL[2] AND LANGLEY A. SPURLOCK[3]

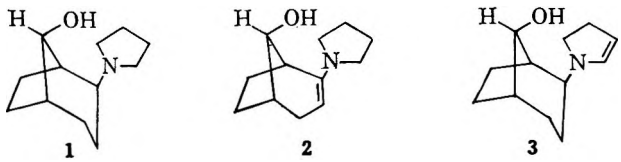
Department of Chemistry, Wayne State University, Detroit 2, Michigan

Received December 26, 1963

The isomeric *syn*-8-hydroxybicyclo[3.2.1]octan-2-one and *exo*(axial)-2-hydroxybicyclo[3.2.1]octan-8-one have been obtained by unique oxidative degradations of known intermediates. Reduction of these ketols with sodium borohydride afforded *endo*(equatorial)-*syn*-bicyclo[3.2.1]octane-2,8-diol and *exo*(axial)-*syn*-bicyclo-[3.2.1]octane-2,8-diol, respectively. The reaction sequence from 2-methyl-2-aza-3-oxatricyclo[3.3.2.^{4,8}0^{1,5}]decane to the *exo-syn* diol represents a simple, versatile synthetic application of the intramolecular nitrone–olefin addition.

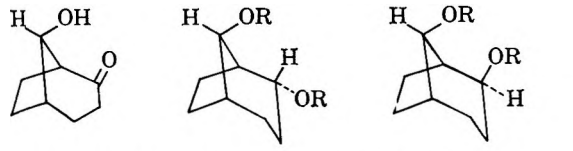
In the course of investigations of synthetic routes to bicyclo[3.2.1]oct-2-en-8-yl derivatives,[4] several observations were made which provided the basis for a stereospecific synthesis of *exo-syn*- and *endo-syn*-bicyclo[3.2.1]-octane-2,8-diol. At the risk of undue prolificacy, we have chosen to report these results because they provide a rather striking illustration of the utility of intramolecular nitrone–olefin cyclizations for synthetic and structural studies.

Mercuric acetate oxidation[5] of the *syn*-amino alcohol **1**[4] gave, in poor yield, an unstable enamino alcohol (**2**) which could not be easily purified (the presence of **3** in the product mixture is conceivable, though no indication of its presence was found). Hydrolysis of the



1 **2** **3**

product afforded the crystalline *syn*-bicyclo[3.2.1]octan-8-ol-2-one (**4**) whose stereochemistry is confirmed by establishment of the *syn* configuration for the 8-hydroxyl substituent of its precursor.[4] Reduction of ketol **4** with sodium borohydride gave a major diol **5a** as evidenced by the excellent yield of a sharp melting

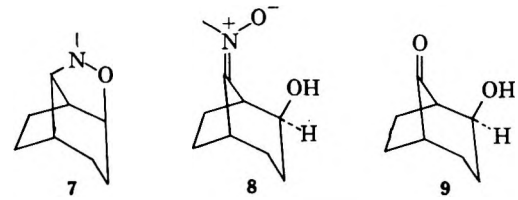


4 **5a**, R = H; **b**, R = *p*-$NO_2C_6H_4C(=O)$– **6a**, R = H; **b**, R = *p*-$NO_2C_6H_4C(=O)$–

product, and the preparation of a bis-*p*-nitrobenzoate (**5b**). The hydroxyl group at C-2 was assigned the *endo*(equatorial) configuration because of the established preference for hydride reductions of unhindered ketones to give thermodynamically more stable equatorial alcohols,[6] and/or possible complexation of the reducing species with the *syn*-8-hydroxyl group.[7] Moreover, the physical properties of **5a** were distinctly different from those reported[8] for *exo*(axial)-*syn*-bicyclo-[3.2.1]octane-2,8-diol (**6a**).

It was noted that some confusion had existed in the literature as to the structure of diol **6a**. Initially, a synthesis of *trans*-bicyclo[2.2.2]octane-2,3-diol was reported,[9] but later the product obtained by employment of the same procedure was assigned as **6a**.[8] We repeated the preparation of **6a** *via* formolysis of bicyclo[2.2.2]-octene oxide.[8] Again a single, sharp-melting diol was isolated. This product (**6a**) gave a negative periodate test as expected for a 1,3-diol; however, like its epimer **5a**, it failed to show appreciable reaction with *p*-nitrobenzaldehyde. The diols **5a** and **6a** were different compounds as shown by infrared spectra, mixture melting point, and comparison of bis-*p*-nitrobenzoates.

The assignment of **6a** as *exo-syn*-bicyclo[3.2.1]octane-2,8-diol seems unambiguous in view of the detection of intramolecular hydrogen bonding[8]; however, we can now provide an interesting degradative sequence which supports this assignment and which promises to have additional, valuable application. The condensation of Δ^4-cycloheptene carboxaldehyde and N-methylhydroxylamine has been reported to produce the tricyclic isoxazolidine **7** in good yield.[10] Oxidative cleavage of **7** could be effected with peracetic acid.[11] The product was a semisolid oil which could not be purified. It was assigned the hydroxynitrone structure **8** (stereochemistry uncertain) on the basis of its infrared spectrum and by analogy with the results of other studies.[11] The acidic hydrolysis of **8** further verified the proposed



7 **8** **9**

structure, as *exo*-bicyclo[3.2.1]octan-2-ol-8-one (**9**) was the only neutral product isolated. The ketol **9** was found to be quite unstable to base; for example, sodium bicarbonate washing of an ether solution of the hy-

(1) This work was supported by a generous grant from the National Science Foundation.

(2) Alfred P. Sloan Foundation Fellow, 1961–1965.

(3) U. S. Public Health Predoctoral Fellow, 1961–1963.

(4) N. A. LeBel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964).

(5) For a summary of references dealing with the mercuric acetate oxidations of tertiary amines, see N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(6) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

(7) An examination of Dreiding models indicates that steric hindrance to hydride attack at C-2 in ketol **4** is quite similar in magnitude for both *exo* and *endo* directions. The cited effect, coupled with the greater thermodynamic stability of **5a** over its C-2 epimer (**6a**), could easily account for the nearly exclusive production of **5a**.

(8) H. M. Kwart and G. C. Gatos, *J. Am. Chem. Soc.*, **80**, 881 (1958).

(9) H. M. Walborsky and D. F. Loncrini, *ibid.*, **76**, 5396 (1954).

(10) N. A. LeBel, G. M. J. Slusarczuk, and L. A. Spurlock, *ibid.*, **84**, 4360 (1962).

(11) The scope, mechanism, and other applications of this interesting reaction will be reported elsewhere.

drolysis material resulted in the isolation of only viscous oil instead of the crystalline product. This is undoubtedly the result of a facile retro-aldol condensation of **9**, and supplied supporting evidence for the β-hydroxy ketone structure. The infrared spectrum of **9** showed a typical split carbonyl absorption (1742 and 1748 cm.$^{-1}$) similar to that reported for bicyclo[3.2.1]octan-8-one.[12]

Reduction of **9** with sodium borohydride provided a striking confirmation of structure for the three reaction sequences employed. The product was, as in the reduction of the isomeric ketol **4**, a single diol. Identical infrared spectra, melting points and mixture melting point with the diol from formic acid treatment of bicyclo[2.2.2]octene oxide, and a comparison of bis-*p*-nitrobenzoate derivatives confirmed the structure of both compounds as *exo-syn*-bicyclo[3.2.1]octane-2,8-diol (**6a**). That reduction of **9** should take place preferentially from the side of the two-carbon bridge was anticipated from results obtained with bicyclo[3.2.1]-octan-8-one itself[12] and several analogs.[4,12,13]

The observation that the *exo-syn* diol **6a** did not form a *p*-nitrobenzilidine derivative under normal conditions might be considered unusual. This result is, however, not surprising when consideration is taken of the relative geometry of C-2 and C-8 substituents in this bicyclic ring system. The oxygen–oxygen bond distance is somewhat shorter in compound **6a** than in the corresponding *exo-syn*-bicyclo[2.2.1]heptane-2,7-diol as evidenced by hydrogen bonding studies[8] and by formation of slightly more stable cuprammonium complex.[8] However, the latter complex prefers an O–Cu–O bond angle close to 90°. Introduction of a carbon atom between the two oxygens *via* an equilibrium reaction (to form an additional bridged six-membered heteroring) is unfavorable because additional strain would be introduced into the over-all skeleton.[14]

Experimental[15]

2-N-Pyrrolidylbicyclo[3.2.1]oct-2-en-8-ol.—A solution of 9.75 g. (0.05 mole) of amino alcohol **1**[4] and 75 g. (0.24 mole) of mercuric acetate in 200 ml. of 5% aqueous acetic acid was heated with stirring on a steam bath for 2 hr. Precipitation was apparent after 20 min. The precipitate was removed by filtration and was washed with 5% aqueous acetic acid solution. The combined filtrate and washings were saturated with hydrogen sulfide, and the precipitate of mercuric sulfide was removed by filtration. The filtrate was made basic with potassium carbonate. A layer of ether was added, and the solution was saturated with potassium carbonate. The layers were separated and the aqueous layer was extracted with two more portions of ether. The extracts were dried and concentrated affording 1.70 g. (18%) of crude enamino alcohol (**2**). No attempt was made at further purification.

syn-**Bicyclo[3.2.1]octan-8-ol-2-one** (**4**).—The crude enamino alcohol **2** was dissolved in 60 ml. of 10% hydrochloric acid. The solution was boiled for a few minutes to remove hydrogen sulfide and was then allowed to stand on the steam bath for 30 min. The cooled solution was saturated with sodium chloride and was continuously extracted with ether. After drying, concentration of the extract gave 1.5 g. of crude material which could be sublimed at 125° (100 mm.) to give 1.05 g. (66%) of pure hydroxy ketone (**4**), m.p. 197–198°; infrared spectrum (CCl_4): 3600, 3413, 1712, 1163, 1147, and 1087 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.30; H, 8.82.

The **2,4-dinitrophenylhydrazone** crystallized from absolute ethanol as orange needles, m.p. 163–165° dec.

endo-syn-**Bicyclo[3.2.1]octane-2,8-diol** (**5a**).—To 0.400 g. (2.8 mmoles) of **4** in 20 ml. of absolute methanol was added 0.109 g. (2.9 mmoles) of sodium borohydride, and the solution was stirred for 3 hr. at 15–20°. One milliliter of water followed by 2 ml. of 15% potassium hydroxide were added, and the mixture was concentrated to a volume of approximately 10 ml. Water (15 ml.) was again added and the resulting suspension was continuously extracted with ether. The extract was dried and concentrated to give 0.412 g. of crude alcohol which was crystallized by dessication. Recrystallization from ether afforded 0.363 g. (90%) of pure diol, m.p. 250.2–251.0°; infrared spectrum ($CHCl_3$): 3610, 3413, 1088, 1071, 1024, and 1006 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.64; H, 9.69.

The **bis-*p*-nitrobenzoate** (**5b**) was crystallized from chloroform–ether, m.p. 191.2–191.8°.

Anal. Calcd. for $C_{22}H_{20}N_2O_8$: C, 60.00; H, 4.58; N, 6.36. Found: C, 59.82; H, 4.71; N, 6.27.

exo-**Bicyclo[3.2.1]octan-2-ol-8-one** (**9**).—To 1.00 g. (6.5 mmoles) of isoxazolidine **7** stirred at 0° was added dropwise 1.24 g. (6.6 mmoles) of 40% peracetic acid. The temperature was not allowed to rise above 5°. The solution was stirred for 2 hr. at 0° and then was neutralized with sodium bicarbonate. Ether (10 ml.) and 10 ml. of 1% hydrochloric acid were added; and the resulting mixture was stirred vigorously for 1 hr. The ether layer was separated, dried, and concentrated, giving 0.415 g. of crude material. The crude hydroxy ketone was sublimed at 115–120° (100 mm.) and was recrystallized from a mixture of ether and pentane affording 0.365 g. (40%) of pure material, m.p. 179.5–180.2°; infrared spectrum (CCl_4): 3390, 1748, 1742, 1285, 1080, and 990 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.67; H, 8.66.

The **2,4-dinitrophenylhydrazone** was crystallized from absolute ethanol as orange plates, m.p. 113–115° dec.

In a separate experiment, 0.40 g. (2.6 mmoles) of **7** in 2 ml. of chloroform was treated with a solution of 0.40 g. (2.9 mmoles) of perbenzoic acid in 8.9 ml. of chloroform. The mixture was stirred for 18 hr. and was then washed with saturated sodium bicarbonate solution, dried, and concentrated. The yellow semisolid (0.797 g.) could not be purified without excessive decomposition. The presence of hydroxynitrone **8** was confirmed by the infrared spectrum (mull): 3322 and 1170 cm.$^{-1}$.

exo-syn-**Bicyclo[3.2.1]octane-2,8-diol** (**6a**).—By a procedure similar to that employed with the isomeric ketol **4**, 0.070 g. (0.5 mmole) of **9** was treated with 0.125 g. (3.3 mmoles) of sodium borohydride in 6 ml. of methanol. The product was recrystallized from ether–pentane giving 0.065 g. (92%) of pure diol, m.p. 267.0–268.0° (lit.[8] m.p. 255–257°); infrared spectrum ($CHCl_3$): 3610, 3401, 1182, 1087, 1045, 993, and 928 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.36; H, 9.82.

The **bis-*p*-nitrobenzoate** was crystallized from chloroform–ether, m.p. 220.0–220.5°.

Anal. Calcd. for $C_{22}H_{20}N_2O_8$: C, 60.00; H, 4.58; N, 6.36. Found: C, 60.00; H, 4.72; N, 6.21.

2,3-Epoxybicyclo[2.2.2]octane.—The epoxide was prepared from bicyclo[2.2.2]octene and peracetic acid[16] in 85% yield, m.p. 189–191°, lit.[16] m.p. 190–192°.

exo-syn-**Bicyclo[3.2.1]octane-2,8-diol.**—The diol was prepared from the epoxide and formic acid in 61% yield, m.p. 267–268°, lit.[8] m.p. 255–257°. Mixture melting point with diol **5a** was 255–258°, and that with diol **6a** was 267–268°.

The **bis-*p*-nitrobenzoate** was prepared and was crystallized from chloroform–ether, m.p. 219.5–220.5°. A mixture melting point with bis-*p*-nitrobenzoate **5b** showed 174–177°, and with **6b** was 219.5–220.5°.

(12) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Am. Chem. Soc.*, **82**, 4299 (1960).

(13) C. S. Foote and R. B. Woodward, *Tetrahedron*, in press.

(14) For example, the tetrahydrooxazine formally derived from condensation of formaldehyde and *exo-syn*-8-[N-methylamino]bicyclo[3.2.1]-octan-2-ol is very unstable to hydrolytic conditions (L. A. Spurlock, unpublished observations).

(15) Melting points are corrected and boiling points are uncorrected. Analyses were by Midwest Microlabs, Inc., Indianapolis, Ind. Infrared spectra were obtained with a Beckman Instruments, Inc., Model IR-4, or a Perkin-Elmer Corp. Infracord spectrometer, both with sodium chloride optics.

(16) H. M. Walborsky, M. E. Baum, and A. A. Youssef, *J. Am. Chem. Soc.*, **83**, 988 (1961).

Attempted Preparation of *exo-syn*-Bicyclo[3.2.1]octyl-2,8-*p*-nitrobenzylidine Acetal.—To a solution of 0.220 g. (1.45 mmoles) of *p*-nitrobenzaldehyde in 2.5 ml. of dry benzene was added 0.200 g. (1.40 mmoles) of diol **6a** and a catalytic amount of *p*-toluenesulfonic acid. The solution was heated at reflux for 8 hr., and then the solvent was removed *in vacuo*. The resulting yellow semicrystalline mass was triturated with ether until most of the yellow color was removed. The residual solid was recrystallized from ethanol–ether, affording 0.175 g. (88%) of starting diol **6a**, m.p. 265–268°.

The Mannich Reaction with 2-Methylcyclopentanone and 2-Methylcyclohexanone[1a]

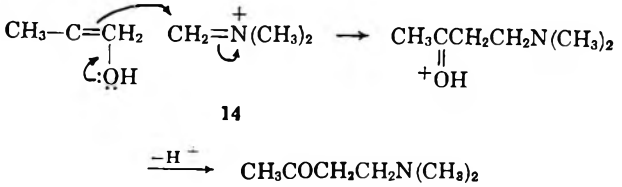
HERBERT O. HOUSE AND BARRY M. TROST[1b]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received November 19, 1963

The Mannich reaction of dimethylamine and formaldehyde with 2-methylcyclopentanone yields 2-dimethylaminomethyl-2-methylcyclopentanone (**15**). The corresponding reaction with 2-methylcyclohexanone yields a mixture of structurally isomeric amino ketones **5** and **16** in which 2-dimethylaminomethyl-2-methylcyclohexanone (**16**) is the predominant product. These orientations are contrary to what has previously been reported for the Mannich condensation with these ketones.

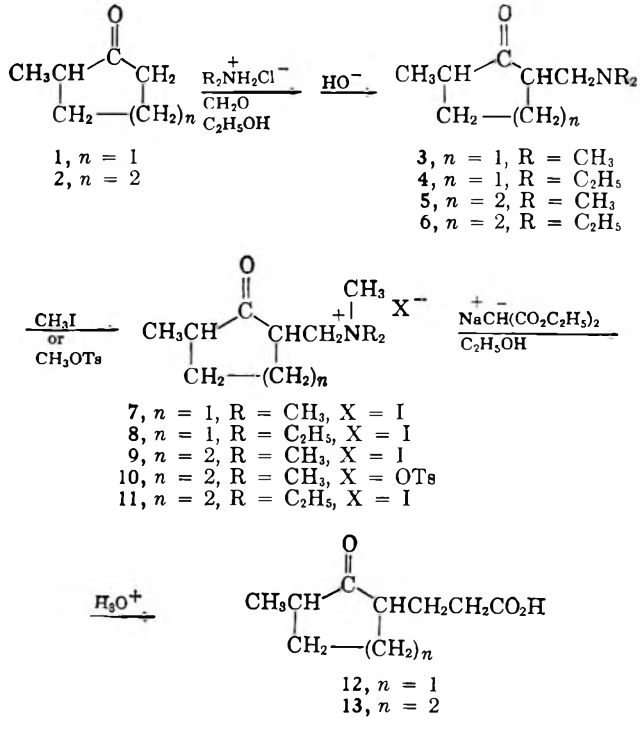
As part of a study of the Michael reaction we wished to prepare an authentic sample of 2-(2-carboxyethyl)-5-methylcyclopentanone (**12**) and elected to follow a synthetic path (see Chart I) analogous to that previously employed[2] for the corresponding cyclohexanone derivative **13**. Both of these preparative procedures were intended to make use of the reported[3] Mannich condensations of 2-methylcyclopentanone (**1**) and 2-methylcyclohexanone (**2**) at the less highly substituted position to form Mannich bases **4** and **6**. Although the reported orientation in these two Mannich condensations has been widely accepted as correct,[2-4] the current view that Mannich reactions in slightly acidic media involve an electrophilic attack of an imminium salt such as **14** on the enol form of the ketone[5] is difficult to reconcile with the reported[3] orientation since the



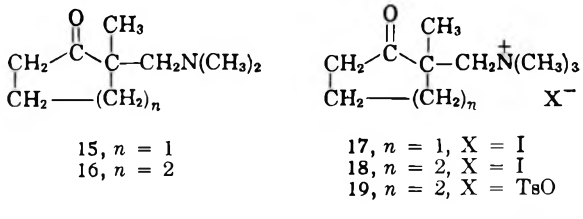
more highly substituted enols of 2-methylcyclopentanone and 2-methylcyclohexanone are expected to be the more stable.[6]

Our initial attempt to prepare acid **12** utilized the previously described[3] Mannich base derived from 2-methylcyclopentanone (**1**), diethylamine hydrochloride, and formaldehyde. Neither the previous investigators nor we were able to obtain the base (reported to be **4**) or its methiodide (reported to be **8**) as crystalline solids. From the reaction of this crude methiodide with diethyl sodiomalonate as previously described,[2] we were unable to isolate any of the desired keto acid **12**, only a small amount of methylmalonic acid being recovered.

CHART I



The Mannich reaction was, therefore, repeated with dimethylamine hydrobromide to form a Mannich base which readily yielded a crystalline methiodide in an over-all yield of 89%. However, the n.m.r. spectrum (see Experimental) of this crystalline product left no doubt that it was not the methiodide **7** but rather had structure **17**. The n.m.r. spectrum of the original Mannich base indicated that at least 80% of this material had structure **15** and not **3**. Thus, our earlier failure to prepare the keto acid **12** was not surprising.



(1) (a) This research has been supported in part by Grant No. RG-8761 from the National Institutes of Health; (b) National Science Foundation Predoctoral Fellow, 1963–1964.

(2) (a) R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.*, **73**, 724 (1951); (b) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

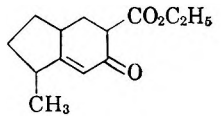
(3) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(4) (a) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); (b) B. Reichert, "Die Mannich Reaktion," Springer-Verlag, Berlin, 1959; (c) R. Jacquier, M. Mousseron, and S. Boyer, *Bull. soc. chim. France*, 1653 (1956).

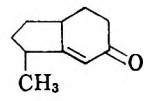
(5) (a) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); (b) T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

(6) H. O. House and V. Kramar, *ibid.*, **28**, 3362 (1963).

The previous experimental data[3] which had led to the assignment of structure **4** to the Mannich condensation product consisted of the conversion of the crude methiodide (reported to be **8**) to a liquid product, thought to be **20**, in 18% yield. Further transformation



20

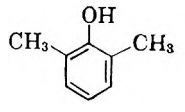


21

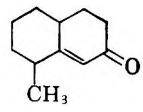
of this liquid product led to a mixture of materials from which a crystalline semicarbazone and a crystalline 2,4-dinitrophenylhydrazone were isolated in unstated yield. These crystalline materials were believed to be derivatives of the unsaturated ketone **21**. Thus, even if one accepts the fact that the liquid product was pure and had structure **20**, these earlier data require that 18% of the Mannich base have the assigned structure **4**.

This finding made the corresponding report[3] that the Mannich condensation of methylcyclohexanone (**2**) with diethylamine and formaldehyde yields **6** open to suspicion in spite of the fact that this report has been accepted by others.[2,4] Repetition of this reaction with dimethylamine hydrochloride produced, in 58% yield, a Mannich base whose n.m.r. spectrum (see Experimental) indicates the presence of approximately 30% of the Mannich base **5** and 70% of the Mannich base **16**. In previous studies[2] the crude methiodide or methotosylate of this Mannich base had been used for the preparation of keto acid **13**; the yield of the crude ester (a mixture of the ethyl ester of keto acid **13** and the corresponding malonic ester) corresponded to a yield of less than 42%.[2a] Partial separation of the mixture of methiodides obtained from the Mannich base afforded fractions, m.p. 190–192° dec. and 160–163° dec., which were thought[2b] to be the crude diastereoisomers of structure **9**. We have now measured the n.m.r. spectra of these samples and find the fraction, m.p. 190–192° dec., to be the pure methiodide **18** while the fraction, m.p. 160–163° dec., is a mixture of methiodide **9** and **18**. The crude Mannich base from 2-methylcyclohexanone (**2**) had also been converted[2b] to a mixture of crude methotosylates from which a small sample of a pure isomer, m.p. 141–142°, thought to be one of the diastereoisomers of structure **10** was isolated. The n.m.r. spectrum (see Experimental) of this material has established that this sample has structure **19**.

The experimental evidence[3] which had previously led to the assignments of structures **6** and **11** to the Mannich base and the corresponding methiodide derived from 2-methylcyclohexanone (**2**) consisted of the conversion of the crude Mannich base to 2,6-dimethylphenol (**22**) in unstated yield and the conversion of the crude methiodide to a liquid product, assigned structure



22

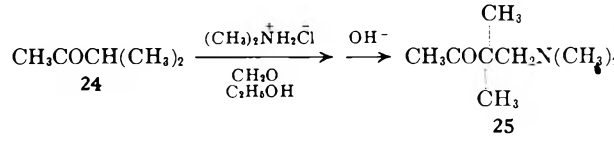


23

23, in 60% yield. This liquid product was converted to several crystalline derivatives, but again no yields were stated. Consequently, no data permitting a reliable estimate of the homogeneity of this initial liquid product **23** are available.

Since the mechanism of the Mannich reaction has been suggested[5b] to change for reactions carried out in neutral or basic solution rather than the usual acidic conditions, we have also examined the reaction of 2-methylcyclohexanone with formaldehyde and free dimethylamine. The n.m.r. spectrum of the resulting Mannich base indicates the presence of about 65% of **16** and 35% of **5**. Thus, at least for ketone **2**, the proportion of structurally isomeric bases obtained in the Mannich reaction do not differ appreciably when the free amine is employed rather than the amine hydrochloride.

Consequently, we conclude that both 2-methylcyclohexanone (**2**) and 2-methylcyclopentanone (**1**) undergo predominant Mannich condensation at the most highly substituted position, contrary to previous claims in the literature, but in accord with the result to be expected on mechanistic grounds. It is also appropriate to note that 3-methyl-2-butanone (**24**), contrary to an



24 **25**

earlier report,[4c] has also been found[7] to yield primarily, if not exclusively, the more highly substituted Mannich base **25**. These results suggest that certain previous reports[4] that Mannich reactions with unsymmetrical ketones occur at the less highly substituted position should be viewed with suspicion until rigorous structural evidence is provided.

Experimental[8]

Mannich Reaction of 2-Methylcyclopentanone (1).—A mixture of 7.89 g. (0.0805 mole) of 2-methylcyclopentanone, 3.22 g. (0.107 mole of formaldehyde) of paraformaldehyde, 10.00 g. (0.0795 mole) of dimethylamine hydrobromide, and 5 ml. of ethanol was heated on a steam bath overnight and then cooled. The resulting semisolid mixture was made basic by the addition of cold (0°) aqueous sodium hydroxide and then extracted with ether. After the ethereal solution had been dried and concentrated, 11.12 g. (90%) of the crude Mannich base **15** remained as a yellow liquid. To a solution of 9.72 g. (0.063 mole) of this crude amino ketone in 50 ml. of benzene was added, dropwise and with stirring, 9.50 g. (0.067 mole) of methyl iodide. After the resulting mixture had been allowed to stand in the refrigerator for 3 days, the crude methiodide **17** was collected and recrystallized from an ethanol–petroleum ether mixture to separate 18.2 g. (89% based on the starting dimethylamine) of the pure methiodide **17** as white needles, m.p. 196–196.5° dec. The product has infrared absorption[9] at 1730 cm.$^{-1}$ (cyclopentanone C=O) and n.m.r.[10] singlets at δ 3.74 (2H, CCH_2N^+), 3.36 (9H, CH_3N^+), and 1.30 (3H, CH_3C), as well as complex absorption attributable to three methylene groups in the region δ 2.1–3.1.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.40; H, 6.79; I, 42.73. Found: C, 40.25; H, 6.72; I, 42.74.

(7) M. Brown and W. S. Johnson, *J. Org. Chem.*, **27**, 4706 (1962).

(8) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin-Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(9) Determined as a suspension in a potassium bromide pellet.

(10) Determined as a solution in deuterium oxide.

From a comparable reaction employing 3.99 g. (0.041 mole) of 2-methylcyclopentanone, 1.61 g. (0.054 mole of formaldehyde) of paraformaldehyde, 5.00 g. (0.040 mole) of dimethylamine hydrobromide, and 5 ml. of ethanol, distillation of the crude basic product separated 4.5 g. (73%) of the Mannich base **15**, b.p. 43–45° (0.3 mm.), $n^{23}D$ 1.4562. The mass spectrum of the product exhibits a molecular ion peak at *m/e* 155; the sample has infrared absorption[11] at 1730 cm.$^{-1}$ (cyclopentanone C=O). The n.m.r. spectrum[11] of this sample has a singlet at δ 2.13 (NCH_3) superimposed on a complex series of peaks in the region δ 1.5–2.5 and a singlet at δ 0.83 (CH_3C). A broadening at the base of the last mentioned singlet and several very small peaks in the region of δ 0.9–1.2 suggests that the major product **15** may be contaminated by a small amount (less than 20%) of one or both of the stereoisomeric Mannich bases **3**, containing a $CH_3CH<$ function, whose n.m.r. C-methyl signals could appear as a pair of doublets. A solution of the Mannich base **15** in deuterium oxide containing 20% deuterium chloride exhibited n.m.r. peaks at δ 3.39 (2H singlet, $CCH_2N^+D<$) and 1.22 (3H singlet, CH_3C) with complex absorption in the region δ 1.6–2.8 and two peaks at δ 2.92 and 2.98 (6H, $CH_3N^+D<$). The presence of two peaks for the N-methyl signal in the salt suggests that the dimethylammonium grouping exists in a preferred conformation with respect to the asymmetric C-2 position of the cyclopentanone ring. As was the case for the n.m.r. spectrum of free base **15**, the n.m.r. singlet at δ 1.22 attributable to the C-methyl group has a slight broadening at the base suggesting the presence of a small amount of the salt of either one or both of the amino ketones **3**.

Mannich Reaction of 2-Methylcyclohexanone (2). A. With Dimethylamine Hydrochloride.—A mixture of 9.0 g. (0.080 mole) of 2-methylcyclohexanone, 3.42 g. of an aqueous solution containing 37% (0.040 mole) of formaldehyde, and 3.26 g. (0.040 mole) of dimethylamine hydrochloride was refluxed for 15 min. and then diluted with water and saturated with sodium chloride. After the resulting mixture had been extracted with ether, it was made basic with potassium hydroxide and extracted with ether. The resulting basic extract was dried, concentrated, and distilled to separate 3.95 g. (59%) of the Mannich base (a mixture of **5** and **16**), b.p. 48–50° (0.15 mm.), $n^{23}D$ 1.4638 [lit. 71° (1.3 mm.),[2a] 62–63° (0.7 mm.),[2b] $n^{20}D$ 1.4650,[2a] $n^{25}D$ 1.4639[2b]]. The mass spectrum of the product exhibits a molecular ion peak at *m/e* 169; the material has infrared absorption[11] at 1710 cm.$^{-1}$ (C=O). The n.m.r. spectrum of a solution of this Mannich base in deuterium oxide containing 20% deuterium chloride exhibits, apart from complex absorption in the region δ 1.7–2.7, a singlet at δ 3.33 (CCH_2N^+D), a singlet at δ 2.98 (CH_3N^+D), and a singlet at δ 1.39 (CH_3C) attributable to the salt of the amino ketone **16**. In addition there is a small peak at δ 2.87 ($CH_3N^+D<$) and two doublets centered at δ 0.98 (J = 6.5 c.p.s.) and 1.22 (J = 7 c.p.s.) corresponding to the C-methyl signal from the $CH_3CH<$ grouping in the two stereoisomeric salts derived from the amino ketones **5**. From the relative areas under these C-methyl peaks, we estimate the Mannich base to contain approximately 70% of the amino ketone **16** and 30% of the amino ketones **5**. The n.m.r. spectrum[11] of the free base has single peaks at δ 2.36 ($CCH_2N<$), 2.13 ($CH_3N<$), and 0.97 (CH_3C). In the n.m.r. spectrum of the free base, the singlet C-methyl peak at δ 0.97 partially obscures the small C-methyl doublets in the region δ 0.85–1.0.

B. With Dimethylamine.—Into a mixture of 6.0 g. (0.053 mole) of 2-methylcyclohexanone and 2.16 g. of an aqueous solution containing 37% (0.027 mole) of formaldehyde was distilled 1.22 g. (0.027 mole) of dimethylamine. An exothermic reaction occurred as the amine was added. The resulting mixture was refluxed for 10 min. and then cooled, poured into dilute aqueous hydrochloric acid, and extracted with ether. The aqueous layer was made basic with potassium hydroxide and again extracted with ether. After the basic, ethereal extract had been dried and concentrated, distillation of the residue separated 2.7 g. (59%) of the Mannich base (a mixture of **5** and **16**), b.p. 50–52° (0.2 mm.), $n^{26}D$ 1.4645. This sample, which has infrared absorption practically identical with the infrared absorption of the previous sample, has comparable n.m.r. absorption except that the C-methyl doublets are slightly more intense. From the areas under the C-methyl peaks we estimate that the sample contains about 35% of **5** and 65% of **16**.

N.m.r. Spectra of the Quaternary Salts Derived from the Mannich Base of 2-Methylcyclohexanone.—The previously described[2] methiodide, m.p. 190–192°,[2b] exhibits three n.m.r.[12] singlets at δ 3.81 (2H, CCH_2N^+), 3.22 (9H, CH_3N^+), and 1.42 (3H, CH_3C) as well as complex absorption in the region δ 1.7–2.9 and should be assigned structure **18** rather than the previously[2] assigned structure **9**. The methiodide sample, m.p. 160–163°,[2b] is apparently a mixture of approximately equal amounts of **18** and one of the diastereoisomers of structure **9**, since the n.m.r.[12] C-methyl absorption consists of a singlet at δ 1.42 and a doublet (J = 6.5 c.p.s.) centered δ 0.99. The previously described[2b] crude methotosylate, m.p. 120–145°, has C-methyl peaks in the n.m.r.[12] indicating the presence of **19** (about 65%, singlet at δ 1.32) and one of the diastereoisomers of **10** (about 35%, doublet, J = 6.5 c.p.s., centered at δ 0.97). The one pure isomer, m.p. 141–142°,[2b] isolated from the mixture has the structure **19** rather than the previously assigned structure **10**. The n.m.r. spectrum[12] has two doublets (J = 9 c.p.s. for each) centered at δ 7.37 and 7.74 (4H, aryl CH) as well as singlets at δ 3.69 (2H, CCH_2N^+), 3.12 (9H, CH_3N^+), 2.38 (3H, aryl CH_3), and 1.32 (3H, CH_3C), and complex absorption in the region δ 1.5–2.8.

(11) Determined as a solution in carbon tetrachloride.

(12) Determined as a solution in deuterium oxide.

Preparation of Perhydronaphthalene-1,8-dione from 1,4,4aβ,5,8,8aβ-Hexahydronaphthalen-5α-ol-1,4-dione Acetate

IRVING ALLAN KAYE AND RICHARD S. MATTHEWS[1]

Department of Chemistry, Brooklyn College, The City University of New York, Brooklyn 10, New York

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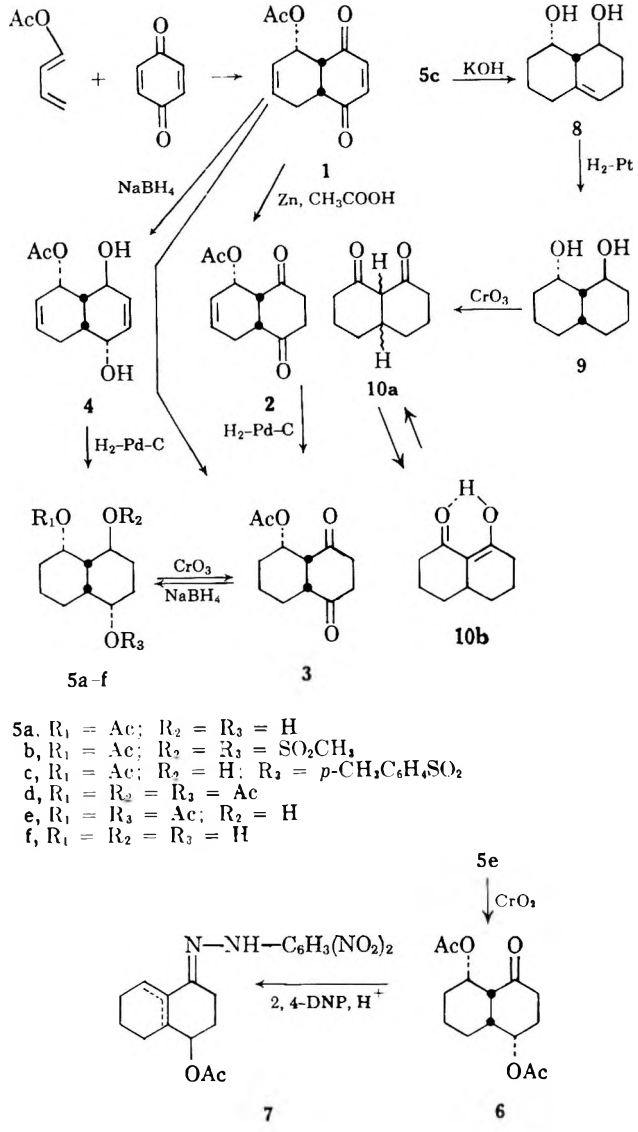
Perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-acetate (**5a**) was prepared by a two-step reduction from 1,4,4aβ,5,8,8aβ-hexahydronaphthalen-5α-ol-1,4-dione acetate (**1**). The triol monoacetate (**5a**) was selectively tosylated in the 1-position and the tosyl group was eliminated with base. The 1,2,3,5,6,7,8,8aβ-octahydronaphthalene-1β,8α-diol (**8**) formed was hydrogenated and then oxidized to perhydronaphthalene-1,8-dione (**10a**). A new synthesis of 2-*n*-butyrylcyclohexanone (**14a**) is described wherein the diketone was prepared from 2-(1-hydroxy-*n*-butyl)cyclohexanone (**11a**). The n.m.r. spectra of these 1,3-diketones indicate that the decalindione (**10a**) is completely enolized in chloroform solution at room temperature, while its flexible monocyclic analog (**14a**) is only 77% enolized. Intermediate between these two values is the enolization (87%) of the bicyclic analog, perhydroindane-1,7-dione (**15a**).

Interest in this laboratory has been focused recently on the preparation of β-diketones which can give rise only to *cis* enols and in which the distance between the carbonyl groups is fixed and determined by the geometry of the molecule. In a previous communication[2] two methods were described for the preparation of a

(1) National Science Foundation Undergraduate Research Participant, 1961–1962.

(2) I. A. Kaye and R. S. Matthews, *J. Org. Chem.*, **28**, 325 (1963).

CHART I



5a, R_1 = Ac; R_2 = R_3 = H
b, R_1 = Ac; R_2 = R_3 = SO_2CH_3
c, R_1 = Ac; R_2 = H; R_3 = p-$CH_3C_6H_4SO_2$
d, R_1 = R_2 = R_3 = Ac
e, R_1 = R_3 = Ac; R_2 = H
f, R_1 = R_2 = R_3 = H

compound of this type, perhydronaphthalene-1,8-dione (decalin-1,8-dione, **10a**). The diketone was prepared by a modification of the procedure of Stetter and Milbers[3] and also by the Jones oxidation[4] of a mixture of perhydronaphthalene-1,8-diols formed by hydrogenating 8-hydroxy-1-tetralone in the presence of a supported rhodium catalyst. At the time of the publication of Stetter and Milbers' preparation of this compound,[3] we had made considerable progress in synthesizing the diketone by an entirely different route. This procedure is outlined in Chart I and forms the subject of this report.

1,4,4aβ,5,8,8aβ-Hexahydronaphthalen-5α-ol-1,4-dione acetate[5] (**1**) was formed on heating a mixture of 1-acetoxy-1,3-butadiene[6] and p-benzoquinone. This stereochemistry is consistent with assigned products obtained in reactions of dienophiles with 1-substituted 1,3-butadienes[7] and is supported by the fact that only one product was obtained in high yield, that relatively mild conditions were employed in the condensation, and that the reaction proceeded at a rate rapid enough to afford little opportunity for the kinetically favored *cis* ring-fused adduct to isomerize to the *trans* form.

The tetrahydro derivative, perhydro(4aβ,8aβ)naphthalen-5α-ol-1,4-dione acetate (**3**), was obtained by hydrogenating the Diels–Alder adduct (**1**) in the presence of palladium–carbon. Alternatively it could be prepared by catalytic reduction of 1,2,3,4,4aβ,5,8,8aβ-octahydronaphthalene-5α-ol-1,4-dione acetate (**2**), which was formed in excellent yield by reducing **1** with zinc in acetic acid solution.[8] From the combined mother liquors of several preparations of the dihydro compound (**2**), which had been subjected to prolonged heating, there was obtained a small amount of a higher melting isomer. Since Sarett, *et al.*,[9] have shown that *cis*-1,4-diketodecalins are readily transposed to the *trans* isomers in the presence of alkaline alumina, and Hückel[10] has found that *cis*-α-decalone isomerizes slowly to the *trans* form at room temperature, it seems probable that the by-product is one of the *trans*-decalin isomers.[11]

With sodium borohydride at 0° the tetrahydro compound (**3**) was converted in good yield to the triol monoacetate (**5a**). That no change in the stereochemistry of the ring fusion had occurred was demonstrated by the formation of the starting diketone (**3**) on oxidation of the product (**5a**) with chromium trioxide–pyridine.[12] The nonequivalence of the two hydroxyl groups in the reduction product was revealed by the isolation of a monotosylate derivative from a reaction with p-toluenesulfonyl chloride at 0°. The hindrance to esterification is in large measure due to the bulk of the reagent, since, under the same conditions, reaction with methanesulfonyl chloride afforded the dimesylate. A scale model of the product (**5a**) suggested that, if both hydroxyl groups were equatorial, the 4-hydroxyl should be hindered by the equatorially oriented 5-acetate. An alternate possibility was an axial orientation for only one of these two substituents. In view of the hindrance at the equatorial 4-position and the fact that reduction with sodium borohydride follows "steric control" to give axial epimer[13] in proportion to the amount of hindrance at the carbonyl site, the possibility existed

(3) H. Stetter and U. Milbers [*Chem. Ber.*, **91**, 977 (1958)] found, by ultraviolet spectroscopic measurements, that perhydronaphthalene-1,8-dione in ethanol at room temperature is completely enolized.

(4) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(5) W. Flaig [*Ann.*, **568**, 1 (1950)] obtained this product, m.p. 64°, in unstated yield by heating the reactants in acetic acid solution. The stereochemistry of the compound was not described.

(6) W. J. Bailey and R. Barclay, Jr., *J. Org. Chem.*, **21**, 328 (1956).

(7) (a) D. Craig, *J. Am. Chem. Soc.*, **72**, 1678 (1950); (b) D. Craig, J. J. Shipman, and R. B. Fowler, *ibid.*, **83**, 2885 (1961); (c) K. Alder and M. Schumacher, *Ann.*, **565**, 148 (1949); (d) P. A. Robbins and J. Walker, *J. Chem. Soc.*, 3249 (1956); (e) A. Alberola, M. Lora-Tamayo, J. L. Soto, and M. Soto, *ibid.*, 3941 (1962); (f) M. F. Ansell and G. C. Culling, *ibid.*, 2908 (1961); (g) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(8) W. Albrecht, *Ann.*, **348**, 31 (1905).

(9) L. H. Sarett, R. M. Lukes, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandegrift, and G. E. Arth [*J. Am. Chem. Soc.*, **74**, 1393 (1952)] obtained both of the two possible *trans* forms from 5α-methyl-6-ethoxy-1,2,3,4,4aβ,5,8,8aβ-octahydronaphthalene-1,4-dione.

(10) W. Hückel, *Ann.*, **441**, 1 (1925).

(11) Since only one product was obtained under presumably equilibrium conditions, it seems likely that this is 1,2,3,4,4aα,5,8,8aβ-octahydronaphthalen-5α-ol-1,4-dione acetate, in which the acetoxyl group is equatorially oriented. P. A. Robbins and J. Walker [*J. Chem. Soc.*, 642 (1952)] also obtained a small amount of a higher melting compound on reducing an acetic acid solution of their Diels–Alder adduct with zinc dust. They, too, assumed that their by-product had been formed by an isomerization at one of the ring junction hydrogens.

(12) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(13) (a) H. J. Loewenthal, *Tetrahedron*, **6**, 269 (1959); (b) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

that the less reactive hydroxyl was at the 4α (axial) position.

Evidence that the 4-hydroxyl group was indeed the hindered group was obtained in the following manner. When heated with excess acetic anhydride–pyridine at 95° for eight minutes,[14] the triol monoacetate (**5a**) afforded a diacetate (**5e**) in good yield. Oxidation of the triol diacetate (**5e**) with chromium trioxide–pyridine[12] yielded the keto diacetate (**6**). On heating this compound with 2,4-dinitrophenylhydrazine in methanol containing acid, there was obtained a red dinitrophenylhydrazone whose ultraviolet spectrum and elementary analysis indicated that it was the derivative of an α,β-unsaturated ketone (**7**).[15] This ready loss of the elements of water is characteristic of β-ketols and their esters.

If the hindered 4-hydroxyl were axially oriented, then removal of the 5-acetyl group should not alter its chemical reactivity. The opposite should be true in the case of an equatorial 4-hydroxyl. This hypothesis was tested using the saponification and acetylation techniques of Beyler and Sarett.[14] On heating the triacetate (**5d**) prepared from the triol monoacetate (**5a**) and acetyl chloride, in refluxing aqueous methanolic potassium carbonate for exactly ten minutes, the triol (**5f**) was obtained. A hindered acetate group would have been expected to resist hydrolysis under these conditions.[14] Presumably the equatorial ester groups at the 1- and 5-positions were quickly saponified and, with removal of the hindering 5-acetyl moiety, the equatorial 4-acetate was then also cleaved rapidly. The ready triacetylation of the triol (**5f**), by heating with excess acetic anhydride–pyridine at 95° for eight minutes,[14] contrasts with the behavior of the triol monoacetate (**5a**) and supports the contention that the 4-hydroxyl is equatorially oriented and hindered by the nearby 5-acetate group.

Two other procedures for the synthesis of the triol monoacetate, perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-acetate (**5a**), were explored, but neither was so satisfactory as the palladium-catalyzed hydrogenation of the Diels–Alder adduct (**1**). The product could be obtained in low yield by hydrogenating the diketo acetate (**3**), in the presence of ruthenium–carbon,[16] or by palladium-catalyzed hydrogenation of 1,4,4aβ,5,8,8aβ-hexahydronaphthalene-1α,4β,5α-triol 5-acetate (**4**). The latter was prepared in low yield by reducing the adduct (**1**) with sodium borohydride at 0°; at a higher reaction temperature an isomer of **4** was obtained.[17]

Advantage was taken of the ease with which the tosyl grouping is eliminated, when the tosylate (**5c**) is treated with nucleophilic reagents, to remove the 1-substituent. Accordingly, the unsaturated diol (**8**), 1,2,3,5,6,7,8,-8aβ-octahydronaphthalene-1β,8α-diol, was prepared by dissolving the tosylate (**5c**) in methanol containing potassium hydroxide. When **8**, in the form of its diacetate, was hydrogenated in acetic acid in the presence of platinum, a saturated diol was obtained in moderate yield. This method of reduction has been shown to be highly stereoselective in introducing both hydrogens from the same side of the molecule and to cause little, if any, isomerization of the unhydrogenated cycloalkene.[18] Consideration of a molecular model of the unsaturated diol (**8**) indicates that the introduction of hydrogen can best be accommodated from the less hindered side of the molecule containing the 8aβ-hydrogen to give perhydro(4aβ,8aβ)naphthalene-1β,8α-diol (**9**). The two hydroxyl groups in this configuration should both be equatorial and, indeed, the lack of hindrance at these functions was demonstrated by the ease with which they were both acetylated under the conditions of the "standard acetylation procedure" of Beyler and Sarett.[14] By contrast, the unsaturated diol (**8**), one of whose hydroxyls is axially oriented, was incompletely acetylated under these conditions[14] and yielded a mixture of the diacetate and the two isomeric monoacetates.

The diol (**9**) was oxidized by the method of Jones[4] to perhydronaphthalene-1,8-dione (**10a**), whose infrared spectrum was identical with that of a sample prepared by the method of Stetter and Milbers.[3] 2-*n*-Butyrylcyclohexanone (**14a**), a flexible monocyclic analog of this bicyclic diketone (**10a**),[19] was prepared similarly from 2-(1-hydroxy-*n*-butyl)cyclohexanol (**13**), whose method of preparation is outlined in Chart II. The latter was synthesized to provide a model for investigating the conditions necessary for effecting the oxidation of the 1,3-diol (**9**) to the 1,3-diketone (**10a**).[20]

In preparing the precursor (**11a**) of **13** by the mixed aldol condensation reaction, a small amount of a ketodiol by-product was isolated.[21] A distinction among the three likely structures for this compound, 2-(1,3-dihydroxy-2-ethyl-*n*-hexyl)cyclohexanone (**12a**), 2,2-bis(1-hydroxy-*n*-butyl)cyclohexanone (**12b**), and 2,6-bis(1-hydroxy-*n*-butyl)cyclohexanone (**12c**), was made by observing that the product formed by acid-catalyzed dehydration absorbed at 254 mμ. This absorption is in good agreement with the latter formula (**12c**), since the cross-conjugated ketone thus formed would be expected to have an absorption peak in the vicinity of that (245

(14) R. Beyler and L. Sarett, *J. Am. Chem. Soc.*, **74**, 1406 (1952). With a compound of structure very similar to **5a**, but with a methyl at the 5-position instead of an acetate group, the 4-hydroxyl, under these conditions, resisted acetylation while the 1-hydroxyl was easily esterified. When subjected to their standard potassium carbonate saponification conditions, their diacetate (analogous to **5d**, but with a methyl at the 5-position), unlike our triacetate (**5d**), was selectively saponified only at the 1-position.

(15) Migration of the initially formed double bond at the 8,8a-position to the 4a,8a-position would be expected. M. I. Bowman, C. C. Ketterer, and A. U. Chamberlain [*J. Org. Chem.*, **18**, 905 (1953)] report an absorption maximum of 381 mμ (log ϵ 4.4) for an ethanolic solution of Δ^9-1-octalone.

(16) Hydrogenations in the presence of ruthenium–carbon are reputed to effect reduction of carbonyl groups without hydrogenating olefinic bonds. This was apparently confirmed in one of our experiments wherein the dihydro adduct **2** was found to absorb exactly 2 moles of hydrogen in methanol in the presence of this catalyst. Similar reduction of the Diels–Alder adduct **1** resulted in the uptake of 3 moles of hydrogen indicating that the olefinic bond in the enedione system was reduced under these conditions.

(17) This isomer may be 1,4,4aβ,5,8,8aα-hexahydronaphthalene-1α,4β,5α-triol 5-acetate; *cf.* ref. 12.

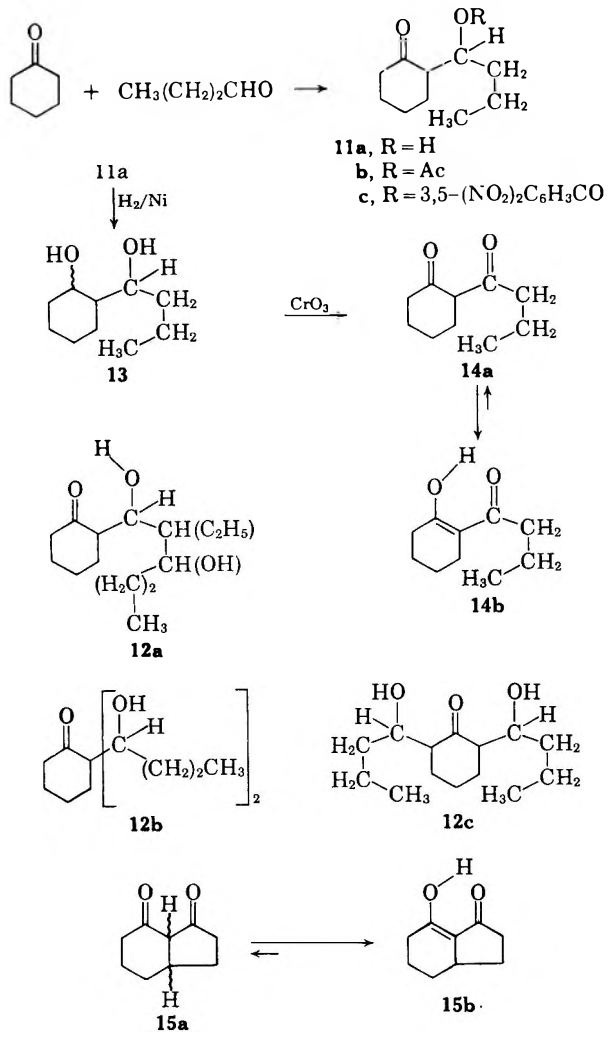
(18) (a) S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 3082 (1960); (b) J.-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **83**, 3874 (1961).

(19) Some of the physical properties of **10**, **14**, and **15** are under investigation by Dr. L. Magnusson, Dr. C. Postmus, Jr., and Dr. C. Craig at the Argonne National Laboratory.

(20) The diol **12**, as well as 2-ethyl-1,3-hexanediol, was also used in trial reactions which explored the conditions necessary for the preparation of benzylidene acetals of 1,3-diols. These experiments are described in the Experimental section. A sample of 2-ethyl-1,3-hexanediol was generously contributed by the Union Carbide Chemicals Co.

(21) Since the ketodiol was apparently formed under equilibrating conditions, the product presumably has the *cis* configuration; *cf.* B. Rickborn, *J. Am. Chem Soc.*, **84**, 2414 (1962). F. A. Fries and F. Broich [German Patent 956,948 (January 24, 1957); *Chem. Abstr.*, **53**, 7056 (1959)] prepared the ketol **11a** and some of its congeners by a similar process. They also found that a higher boiling product, which they did not investigate, was formed.

CHART II



mμ) shown by the α,β-unsaturated ketone obtained from 2-(1-hydroxy-*n*-butyl)cyclohexanone (**11a**).[22] The monosubstituted product (**12a**) would have given rise to a conjugated dienone absorbing at about 296 mμ[22]; from the unsymmetrically disubstituted cyclohexanone (**12b**) water would not have been eliminated readily nor would a product absorbing strongly in the ultraviolet have been formed.

Intercomparison of the intensities of the hydroxylic proton (at 16.37 p.p.m.) and combined ring proton signals, in the nuclear magnetic resonance[23] spectrum of perhydronaphthalene-1,8-dione (**10a**), indicates that, in chloroform solution at room temperature, the compound is completely enolized.[3] A similar comparison, in the case of the n.m.r. spectrum of perhydroindane-1,7-dione (**15a**) in the same solvent (the hydroxylic proton signal was also observed at 16.37 p.p.m.), leads to an enolization value of 86.9%. In the spectrum of the monocyclic analog of perhydronaphthalene-1,8-dione (**10a**), 2-*n*-butyrylcyclohexanone (**14a**), a comparison of its hydroxylic proton signal (at 16.28 p.p.m.) with that of its methyl protons indicates that the compound is 76.7% enolized. The exchange of the hydrogen-bonded proton from one oxygen to the other in the β-dicarbonyl system has been considered as a factor contributing to the stabilization of the enol.[24] Such stabilization would apparently be greatest in the case of 1,2,3,4,4a,5,6,7-octahydronaphthalen-8-ol-1-one (**10b**) because of the equivalence of the two enolic forms, whereas in each of the other two diketones (**14a** and **15a**) one of the two enolic structures possible in each case (**14b** and **15b**) would be expected to be more stable.[25]

(22) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 18–21.

(23) For a discussion on the application of n.m.r. to the determination of the position of equilibrium in systems capable of exhibiting keto–enol tautomerism, *cf.* F. C. Nachod and W. D. Philips, "Determination of Organic Structures by Physical Methods," Vol. 2, Academic Press, New York, N. Y., 1962, p. 454. Difficulties in accurate area intercomparisons give rise to some uncertainty regarding the absolute accuracy of results obtained by this method.

Experimental[26]

Materials.—Redistilled cyclohexanone, b.p. 154–155°, *n*-butyraldehyde, b.p. 73–76°, and benzaldehyde, b.p. 179°, which had been distilled and stored under nitrogen, were used in the aldol condensation and acetal preparations. Pyridine and benzene were dried for several days over calcium hydride before use in reactions requiring anhydrous solvents. The Raney nickel catalyst, employed in the preparation of the diol (**13**), was obtained commercially,[27] as was the 10% palladium–carbon catalyst.[28] The nickel was washed with distilled water, isopropyl alcohol, and ethyl acetate in succession and then stored for several days under ethyl acetate until used. The acetone employed as solvent in the Jones oxidation had been refluxed for several hours over, and then distilled from, potassium permanganate. 1-Acetoxy-1,3-butadiene was prepared in 57% yield, b.p. 56.0–57.5° (37 mm.), by the procedure of Bailey and Barclay.[6]

1,4,4aβ,5,8,8aβ-Hexahydronaphthalen-5α-ol-1,4-dione Acetate (1).—The preparation of this compound was studied rather extensively and our optimum conditions are described. A vigorous exothermic reaction resulted on heating to reflux a solution of 86.3 g. of 1-acetoxy-1,3-butadiene[6] and 75.7 g. (0.70 mole) of *p*-benzoquinone in 70 ml. of carbon tetrachloride and 250 ml. of isopropyl ether. This was moderated by occasional immersion in an ice bath and then left at room temperature until spontaneous ebullition ceased. The reaction mixture was next heated under reflux for 1 hr. and then diluted to a volume of 1400 ml. with hot isopropyl ether. The clear yellow solution was decanted from a small amount of black tar, which seemed to have been formed by the decomposition of the *p*-benzoquinone, and left to cool slowly. It was seeded when its temperature had dropped to 37°. After standing at room temperature for several hours longer, it was left overnight at 0°. The large pale yellow hexagonal crystals were separated by filtration and washed three times with ice-cold isopropyl ether. In addition to this first crop of 1, which weighed 125.8 g. (80.4%) and melted at 64.5–66.5°, a second crop, weighing 14.8 g. (9.5%) and melting at 62–64°, was obtained by concentrating the filtrate to a volume of 250 ml. A solution of 2.4 g. of the higher melting product in 100 ml. of refluxing isopropyl ether deposited 1.49 g. of almost white rhombohedra on cooling to 0°; m.p. 66–66.5°[5]; λ_{max} 221 and 335.5 mμ (log ε 4.01 and 2.86, respectively), λ_{min} 269 mμ (log ε 2.11); $\lambda_{max}^{CCl_4}$ 5.76 (s, acetate C=O), 5.83 (s), 5.89 (s), 5.95 (s), 6.06 (w, sh, unconjugated C=C), 7.34 (m, CH_3), and 8.20 μ (s, acetate C–O st.).

The instability of the adduct to heat, acids, bases, and alumina is not unprecedented.[11,12]

(24) L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957).

(25) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(26) *Cf.* footnote 26 of ref. 2 for information relative to the determination and reporting of melting and boiling points, infrared and ultraviolet absorption spectra, and calculated and experimental elementary analyses. Ultraviolet spectra were measured in 95% ethyl alcohol. The n.m.r. spectra were determined with a Varian A-60 spectrometer operating at 60 Mc. on solutions of the samples in deuteriochloroform. The spectra were calibrated in p.p.m. downfield from internal tetramethylsilane. Alcoa F-20 alumina, activity I, was used in the chromatographic separations. Thin layer chromatograms were conducted on Merck Kieselgel G; ether was used as the developing solvent. The spots were visualized either by exposure to iodine vapor or by spraying with potassium permanganate solution.

(27) A sample of No. 28 Raney active nickel catalyst in water was generously supplied by the Raney Catalyst Co., Inc., Chattanooga, 2, Tenn.

(28) Purchased from Englehard Industries, Inc., Newark, 2, N. J.

1,2,3,4,4aβ,5,8,8aβ-Octahydronaphthalen-5α-ol-1,4-dione Acetate (2).—The reduction of the conjugated olefinic bond in 1 was carried out by a modification of the procedure of Albrecht[8] which exposed the starting material and product to a minimum amount of heating. The product (2) was stable at room temperature for long periods of time, but was stored at 4° since it had been noted that **3** decomposed after several months at room temperature.

Zinc dust was added in about 5-g. portions to a stirred solution of 76.5 g. (0.344 mole) of 1,4,4aβ,5,8,8aβ-hexahydronaphthalen-5α-ol-1,4-dione acetate (1) in 300 ml. of glacial acetic acid. The reaction flask was immersed in an ice bath during the addition, which was controlled so as to maintain a reaction temperature of 21–27°. After 96 g. of zinc dust had been added, further addition produced no immediate rise in temperature; a total of 101 g. of the metal was added over a 20-min. period. The mixture was stirred at room temperature (26–32°) for 18 hr. longer, then diluted with 1800 ml. of acetone and filtered through a layer of a diatomaceous earth. The filtrate was evaporated to dryness *in vacuo* below 30°. The tan solid which remained was dissolved, for the most part, in 150 ml. of boiling acetone. A small amount of zinc acetate was removed by filtering the mixture through a layer of a diatomaceous earth. The filtrate was evaporated to dryness at room temperature in a current of air and the residue was dissolved in 100 ml. of hot isopropyl alcohol. The hot solution was chilled immediately in an ice bath and left at 0° overnight after seeding. The colorless product which precipitated was separated by filtration, washed with cold isopropyl alcohol, air-dried at room temperature, and then dried *in vacuo*. The dihydro compound (2) weighed 63.9 g. (83.6%), m.p. 112.5–114.5°. Another recrystallization from the same solvent raised the melting point to 113.5–114.5°. A second crop of crystalline product was obtained by concentrating the mother liquors to a volume of about 25 ml. After recrystallization from isopropyl alcohol, an additional 2.89 g. (3.7%), m.p. 104–106.5°, was obtained. The infrared spectrum of a Nujol mull showed absorption at 5.78 (s, ester C=O st.), 5.84 (s, C=O st.), 7.67 (m, C=O), and 8.03–8.13 μ (s, acetate C–O st.).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; O, 28.80. Found: C, 65.24; H, 6.49; O, 28.69.

From the combined filtrates of several previous preparations, in which the product had been subjected to prolonged heating in carbon tetrachloride and acetone, there was obtained a small amount of an isomeric product. This was much more insoluble in isopropyl alcohol than **2** and, after crystallization from this solvent, melted (evac.)[26] at 176–177°. Its infrared absorption spectrum in Nujol was similar to, but not identical with, that of **2**; strong absorption was evident at 5.76, 5.84, and 8.10–8.27 μ and weak absorption was apparent at 6.05 μ (shoulder). No absorption was visible in the 2.0–3.4-μ region.

Anal. Found for $C_{12}H_{14}O_4$: C, 64.69; H, 6.13; O, 28.93.

On hydrogenation in ethyl acetate over 10% palladium–carbon,[28] a reduction product was obtained in low yield which melted (evac.) at 177.0–179.5°, after crystallization from isopropyl alcohol.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.32.

Perhydro(4aβ,8aβ)naphthalen-5α-ol-1,4-dione Acetate (3).—A mixture of 110.1 g. (0.50 mole) of 1,4,4aβ,5,8,8aβ-hexahydronaphthalen-5-α-ol-1,4-dione acetate (1), 2.0 g. of 10% palladium–carbon,[28] and 150 ml. of ethyl acetate was hydrogenated at room temperature and an initial pressure of 40 p.s.i. After 3.5 hr., hydrogen was no longer absorbed. The mixture was filtered through a layer of a diatomaceous earth, and the yellow filtrate was evaporated to dryness at room temperature in a current of air. A solution of the residue in 185 ml. of boiling isopropyl ether was left overnight at 0°. The crude product, weighing 75.5 g. and melting at 85–95°, was recrystallized from the same solvent. The clusters of white needles which precipitated were air-dried to constant weight and then dried further at 0.1 mm. for several hours, yielding 65.7 g. (58.5%), m.p. 97.5–99.5°. Recrystallized again from isopropyl ether, the product melted at 99.5–100°; λ_{max} 285–286.5 mμ (ε 40); $\lambda_{max}^{CCl_4}$ 5.75 (ester C=O st.), 5.84 (C=O st.), 8.15 and 8.19 μ (ester C–O st.), all with strong bands.

Anal. Found for $C_{12}H_{16}O_4$: C, 64.34; H, 7.27.

The tetrahydro compound (**3**), m.p. 95–96°, could also be obtained in lower yield by catalytic hydrogenation of 1,2,3,4,4aβ,5,8,8aβ-octahydronaphthalen-5α-ol-1,4-dione acetate (2) over palladium–carbon or by oxidation of perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-acetate (**5a**) with chromic anhydride–pyridine,[12] m.p. 97.5–99.5°. Each of these products gave no depression in melting point on admixture, and gave an infrared spectrum identical with that of **3**.

1,4,4aβ,5,8,8aβ-Hexahydronaphthalen-1α,4β,5α-triol 5-Acetate (4).—A solution of 3.80 g. of sodium borohydride in 40 ml. of methanol was added dropwise to a stirred chilled suspension of 11.0 g. (0.05 mole) of the Diels–Alder adduct (1) in 45 ml. of methanol at a rate such that the reaction temperature was maintained below +5°. This required 45 min. when the reaction vessel was chilled in an ice–salt mixture. Stirring was continued for 1 hr. longer, during which period the reaction flask was chilled in an ice bath. An ice-cold solution of 12 ml. of acetic acid in 650 ml. of ice–water was added, and the mixture was extracted several times with methylene chloride. The extracts were decolorized with charcoal and the solvent then was removed; the oil which remained was triturated with isopropyl ether. The white powder, which was thus formed, weighed 1.37 g. Three recrystallizations from isopropyl ether gave **4** as clusters of needles whose melting point was constant at 106–108.5°; $\lambda_{max}^{CHCl_3}$ 2.84 (m, shoulder), 2.91 (m), 5.78 (s), 6.06 (w, shoulder), and 8.01–8.31 μ (s).

Anal. Found for $C_{12}H_{16}O_4$: C, 64.25; H, 7.36.

When the sodium borohydride reduction of the adduct 1 was conducted at reflux temperature, a very small amount of an isomeric product[17] was obtained which melted at 146–147°, after five recrystallizations from isopropyl ether; $\lambda_{max}^{CHCl_3}$ 2.82 (w, shoulder), 2.96 (m), 5.80 (s), 6.05 (w), and 8.10 μ (s).

Anal. Found for $C_{12}H_{16}O_4$: C, 64.06; H, 7.26.

On hydrogenating the lower melting isomer (**4**) at atmospheric pressure in the presence of palladium–carbon, 2 moles of hydrogen were absorbed. A crystalline product was isolated which melted at 130–137° and gave an infrared spectrum identical with that of perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-acetate (**5a**). The higher melting isomer also absorbed 2 moles of hydrogen but formed a colorless oil whose infrared spectrum differed from that of **5a** mainly in the fingerprint region.

Perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-Acetate (5a).—A solution of 9.5 g. (0.25 mole) of sodium borohydride in 100 ml. of methanol was added dropwise over a period of 40 min. to a mixture of 57.1 g. (0.255 mole) of perhydro(4aβ,8aβ)naphthalen-5α-ol-4-dione acetate (**3**) in 400 ml. of methanol, immersed in a bath at −20°, at a rate such that a reaction temperature below 4° was maintained. A clear colorless solution was formed after a portion of the hydride solution had been added. After all the sodium borohydride solution had been added, the solution was left in an ice bath for 75 min. A considerable volume of hydrogen was evolved during this period. While maintaining the reaction temperature at 2 to 4°, a mixture of 30 ml. of glacial acetic acid and 70 ml. of water was added over a 15-min. period. The solution was evaporated *in vacuo* and a small amount of water which remained was removed by azeotropic distillation with ethylene chloride. The ethylene chloride solution was concentrated to a volume of 100 ml., after which 200 ml. of boiling isopropyl ether was added, and the mixture was left overnight at 0°. The hard crust which precipitated was broken up, separated by filtration, and washed well with cold isopropyl ether. The white powder, after drying in air and then at 0.1 mm. for several hours, weighed 44.1 g. (76%), m.p. 138–143.5°. After two recrystallizations from isopropyl ether, compound **5a** melted at 145–146°; λ_{max}^{Nujol} 2.94 (s), 5.78 (s), and 8.03 μ (s).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.11; H, 8.95.

From a mixture of 673 mg. (3 mmoles) of (**3**), 200 mg. of 5% ruthenium–carbon,[28] and 25 ml. of methanol, which had been hydrogenated at 765 mm. and 28°, there was obtained, after recrystallization from ethyl acetate, 140 mg. of the triol monoacetate (**5a**), m.p. 139–144°. On admixture with pure product obtained by sodium borohydride reduction, a melting point of 141–144° was observed. The infrared spectra of the two samples were identical.

Perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol (5f).—A solution containing 8.76 g. of potassium hydroxide and 11.41 g. (0.05 mole) of the triol monoacetate (**5a**) dissolved in a mixture of 25 ml. of distilled water and 250 ml. of methanol was heated under reflux for 1 hr. After adding a mixture of 6.5 ml. of glacial acetic acid and 100 ml. of benzene, the solution was evaporated on a steam bath in a current of air, and the last traces of water were removed by azeotropic distillation with benzene. The residue

remaining after removing the benzene was suspended in refluxing chloroform, and the mixture was filtered through a layer of a diatomaceous earth. The solvent was removed and the residue was crystallized from acetone–isopropyl ether. The air-dried triol (**5f**) weighed 7.96 g. (86%), m.p. 139–144.5°. After two recrystallizations from acetone, the product melted at 144.5–146°. No absorption was apparent in the carbonyl region of its infrared spectrum; a Nujol mull showed strong broad absorption at 3.14 μ (H-bonded OH) and strong bands at 9.39, 9.56, and 9.63 μ.[29]

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.49; H, 9.49.

The triol (**5f**), m.p. 137–142°, was also obtained from the triacetate (**5d**) by the controlled saponification procedure of Beyler and Sarett.[14] No depression in melting point was observed on admixture with product obtained by the potassium hydroxide saponification of the triol monoacetate. Both samples in Nujol gave identical infrared absorption spectra.

Perhydro(5aβ,8aβ)naphthalene-1α,4β,5α-triol Triacetate (5d).—A solution of 500 mg. (2.19 mmoles) of perhydro(4aβ,8aβ)-naphthalene-1α,4β,5α-triol 5-acetate (**5a**) in 7 ml. of acetyl chloride was heated under reflux for 3 hr. and the solution then was evaporated on a steam bath in a current of air. On crystallization from methanol there was obtained 430 mg. (63%) of the triacetate, m.p. 120–122°. One recrystallization from isopropyl ether narrowed the melting point range to 121–122°; λ_{max}^{Nujol} 5.77 (s) and 8.07 μ (s, broad); there was no absorption in the 2.00–3.40-μ region.

Anal. Calcd. for $C_{16}H_{25}O_6$: C, 61.52; H, 7.75. Found: C, 61.44; H, 7.69.

The triacetate, m.p. 120.5–122°, was also prepared from the triol (**5f**), in 72% yield, by the method of Beyler and Sarett.[14]

Perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 1,5-Diacetate (5e).—The diacetate was obtained in 61% yield, m.p. 161–162.5°, from the triol monoacetate (**5a**) by the acetylation procedure of Beyler and Sarett.[14] On recrystallization from isopropyl ether, the product melted at 162–163°; λ_{max}^{Nujol} 2.91 (s), 5.78 (s, shoulder), 5.84 (s), and 8.06 μ (s).

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.24; H, 8.32.

Perhydro(4aβ,8aβ)naphthalene-1α,5α-diol-4-one Diacetate (6).—From 1.00 g. (3.70 mmoles) of perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 1,5-diacetate (**5e**) and 1.09 g. of chromic oxide in 15 ml. of pyridine, there was obtained[12] 905 mg. (91%) of the ketone **6** after crystallization from isopropyl ether, m.p. 144.5–146°. After another crystallization from this solvent, the product melted at 145–146.5°; λ_{max}^{Nujol} 5.74 (s, shoulder) and 5.82 μ (s). In one preparation a higher melting form was isolated, m.p. (evac.) 179–180°, m.m.p. 147–154.5°. The infrared spectra of the two forms were identical.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.44; H, 7.44.

The **2,4-dinitrophenylhydrazone** melted (evac.) at 193–194°, λ_{max} 384 mμ (log ε 4.34),[15] after crystallization from methanol.

Anal. Calcd. for $C_{18}H_{20}N_4O_6$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.83; H, 5.00; N, 14.44.

Perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-Acetate Dimesylate (5b).—From the reaction of 3.66 g. (0.016 mole) of the triol monoacetate (**5a**) with 5.3 ml. of methanesulfonyl chloride in 12 ml. of pyridine at 0° for 96 hr., there was obtained 4.88 g. (79%) of the dimesylate, m.p. 119–120°, after crystallization from acetone–isopropyl ether. The melting point depended on the rate of heating, on the temperature at which the capillary tube was inserted into the bath, and the length of time in the bath. In its infrared spectrum, no absorption was apparent in the 2.0–3.3-μ region; λ_{max}^{KBr} 7.46 (s) and 8.50 μ (s, $-OSO_2-$).

Anal. Calcd. for $C_{14}H_{24}O_8S_2$: C, 43.73; H, 6.29; S, 16.68. Found: C, 44.18; H, 5.93; S, 16.52.

Perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-Acetate 1-Tosylate (5c).—The tosylate was prepared by treating 1.37 g. (0.006 mole) of perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-acetate (**5a**) with 3.45 g. of *p*-toluenesulfonyl chloride in 7 ml. of pyridine at 0° for 19 hr. The product, crystallized from isopropyl ether, weighed 2.02 g. (88%) and melted at 113–114°; λ_{max} 2.82 (m, OH), 7.30 (s, CH_3), 7.44 (s), and 8.57 μ (s, $-OSO_2-$), (as a mull in hexachlorobutadiene). The melting point, like that of the dimesylate, varied with the manner in which it was determined.

Anal. Calcd. for $C_{19}H_{26}O_6S$: C, 59.67; H, 6.85; S, 8.38. Found: C, 59.89; H, 7.06; S, 8.52.

1,2,3,5,6,7,8,8aβ-Octahydronaphthalene-1β,8α-diol (8).—The crude tosylate (**5c**), from the reaction of 2.74 g. (0.012 mole) of (**5a**) with 6.90 g. of *p*-toluenesulfonyl chloride in 14 ml. of pyridine, was dissolved in 150 ml. of hot methanol. A solution of 7.2 g. of potassium hydroxide in 15 ml. of hot water was added to the hot yellow solution which was then left at room temperature for 7 hr. The solution was concentrated *in vacuo* to a small volume and extracted with benzene. Evaporation of the dried (over sodium sulfate), decolorized (with charcoal) benzene extract left a white solid which was crystallized from isopropyl ether–hexane, weighing 1.27 g. (63%), m.p. 112–113°. After two further recrystallizations from isopropyl ether, the compound melted at 114–114.5°; λ_{max}^{Nujol} 3.14 (s, H-bonded OH) and 9.89 μ (s). The n.m.r. spectrum exhibited multiplets centered at 5.77 p.p.m. (1H, vinyl C–H) and at 4.45 p.p.m. (2H, carbinol C–H), a broad peak centered at 3.30 p.p.m. (2H, OH) which was shifted on acidification with trifluoroacetic acid, and a complex series of peaks in the region 1.50–2.50 p.p.m. (11H, saturated C–H). The compound gave a yellow color with tetranitromethane. Its thin layer chromatogram showed only one spot.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.54.

The thin layer chromatogram of the crude product, obtained by heating 63.0 mg. of the unsaturated diol **8**, 0.8 ml. of pyridine, and 0.5 ml. of acetic anhydride in a boiling water bath for exactly 8 min.,[14] showed a spot whose R_f was identical with that of the diol **8**, another spot whose high R_f was the same as that of the diacetate, and two more intense spots of intermediate R_f.

Perhydro(4aβ,8aβ)naphthalene-1β,8α-diol (9).—The diacetate of the unsaturated diol **8** was prepared by heating under reflux a mixture of 900 mg. of **8** and 13 ml. of acetyl chloride for 3 hr. The solution was then evaporated *in vacuo*. The residue showed no absorption in the infrared in the 2.0–3.4-μ region, but absorbed strongly at 5.79 and 8.13 μ. To a solution of this viscous, slightly colored oil in 25 ml. of acetic acid was added 121 mg. of platinum oxide,[28] and the mixture hydrogenated at room temperature and at atmospheric pressure. In about 1 hr., 110% of the theoretical amount of hydrogen was absorbed; thereafter no further absorption was apparent. After removing the catalyst and acetic acid, the pleasant smelling oil which remained was saponified by heating under reflux for 2 hr. a solution in 75 ml. of methanol with 3 g. of potassium hydroxide dissolved in 5 ml. of water. Most of the methanol was removed on a steam bath in a current of air, and the product was extracted with copious amounts of hot benzene. The oil which remained, after evaporating the dried and decolorized benzene solution, crystallized quickly and was recrystallized from hexane. The clusters of small white needles weighed 555 mg. (61%) and melted at 115–116.5°. On recrystallization from the same solvent, the diol melted at 115.5–117°; λ_{max}^{Nujol} 2.95 (s, broad), 9.60 (s, broad), and 9.72 μ (s). No vinylic proton absorption was apparent in the n.m.r. spectrum. It gave no color with tetranitromethane and only one spot on thin layer chromatography.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.24; H, 10.58.

The compound had the correct analysis when dried *in vacuo* at 80° and 2 mm. just prior to analysis. The diol apparently hydrates readily, for a dried sample, which had been exposed to air for some time, gave a low carbon analysis.

The thin layer chromatogram of the crude product, obtained from the reaction of a solution of 65.1 mg. of the saturated diol (**9**) in 0.8 ml. of pyridine with 0.5 ml. of acetic anhydride at 100° for exactly 8 min.,[14] showed the absence of any starting material, a strong spot whose R_f was identical with that of 1,2,3,5,6,7,8,-8aβ-octahydronaphthalene-1β,8α-diol diacetate (diacetate of **8**), and a faint spot whose R_f was intermediate between those of the two monoacetates of the unsaturated diol **8**.

Perhydronaphthalene-1,8-dione (10a) [1,2,3,4,4a,5,6,7-Octahydronaphthalen-8-ol-1-one (10)].—This product was prepared from perhydro(4aβ,8aβ)naphthalene-1β,8α-diol (**9**) by the Jones oxidation,[3] as described in a previous publication,[2] and was isolated in 67% yield as its copper chelate. The infrared spectrum of a Nujol mull of the salt was superimposable on that of a sample prepared by the method of Stetter and Milbers.[2,3] It was decomposed by stirring a suspension in 4 *N* sulfuric acid–pentane

(29) E. L. Eliel and C. A. Lukach, [*J. Am. Chem. Soc.*, **79**, 5986 (1957)] reported that the equatorial hydroxyl in *trans*-2-methylcyclohexanol absorbed at 9.39, 9.50, and 9.63 μ in contrast with an axial hydroxyl which absorbed at 9.83, 10.23, and 10.60 μ.

mixture until two clear layers were formed. After crystallization from pentane at −70°, the white crystals melted at 54–55.5°. On admixture with the authentic diketone,[2] no depression in melting point was observed; the infrared spectra of Nujol mulls of the two samples were identical. In the n.m.r. spectrum, the enolic hydroxylic signal was observed as a sharp singlet at 16.37 p.p.m. (1H). The absorption of the hydrogens on the carbon adjacent to the carbonyl group overlapped that of the allylic protons; these were observed as a series of peaks in the region 2.17–2.66 p.p.m. (5H). When the intensity of this absorption was compared with that of the hydroxylic proton, an enolization value of 98% was obtained. The remaining cyclic protons were evident as a complex series of peaks in the region of 0.88–2.12 p.p.m. (8H). A comparison of the intensity of the hydroxylic proton absorption with that of the combined ring protons leads to a value of 100% enolization.

The n.m.r. spectrum of perhydroindane-1,7-dione[2] exhibited an enolic hydroxyl signal, also as a sharp singlet at 16.37 p.p.m., and a complex series of peaks in the region 0.83–2.93, due to the cyclic protons. Comparison of the intensities of these signals indicated that the compound is 86.9% enolized in chloroform solution.

2-(1-Hydroxy-*n*-butyl)cyclohexanone (11a).[21]—A solution of 36.1 g. (0.50 mole) of *n*-butyraldehyde in 115 ml. of cyclohexanone was added dropwise over a period of 3 hr. to a stirred mixture of 300 ml. of cyclohexanone (total amount employed was about 3.40 moles) and 6.7 ml. of 10% aqueous sodium hydroxide. The rate of addition was controlled so as to maintain a reaction temperature of 18–21°. The mixture was then stirred 4 hr. longer, at a reaction temperature of 20–23°, after which 1.57 g. of tartaric acid and a few drops of alcoholic phenolphthalein were added. The pink color of the indicator was discharged after a few minutes of stirring. Anhydrous sodium sulfate was added, and the mixture was stirred for 0.5 hr. After separating the drying agent by filtration and washing it with ether, the combined filtrates were distilled *in vacuo*. A fraction was collected at 79–83° (0.06 mm.), $n^{25}D$ 1.4720–1.4723, and weighed 49.4 g. (56%). A sample, redistilled for analysis, had b.p. 61.0–61.5° (0.03 mm.) and $n^{28}D$ 1.4703. The infrared spectrum of the neat liquid showed absorption bands at 2.86 (m, broad, OH st.), 5.87 (s, H-bonded C=O st.), and 7.62 μ (m, C=O).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.37; H, 10.42.

A solution of the ketol in 95% ethanol containing a trace of concentrated hydrochloric acid absorbed at 245 mμ (ε 3800) (calculated[22] for 2-butylidenecyclohexanone: 242 mμ).

2,6-Bis(1-hydroxy-*n*-butyl)cyclohexanone.—In preparations of 2-(1-hydroxy-*n*-butyl)cyclohexanone (**11a**) which were distilled very slowly *in vacuo* the amount of high-boiling residue increased considerably at the expense of ketol.[21] Since the distillation was performed in the presence of excess tartaric acid, it is presumed that a retroaldol condensation occurred and was followed by an aldol condensation of the product **11a** with the liberated *n*-butyraldehyde.[21]

In one run there was isolated a viscous oil, b.p. 126–130° (0.03 mm.), $n^{26}D$ 1.4918, which crystallized on long standing. After two recrystallizations from hexane, the melting point of the white crystals remained constant at 100.5–101.5°. In the infrared spectrum of a Nujol mull, strong peaks were observed at 3.00 (broad, OH) and 5.87 μ (C=O).

Anal. Calcd. for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81; O, 19.81. Found: C, 69.55; H, 10.57; O, 20.07.

A solution of the ketodiol in 95% ethanol containing a trace of concentrated hydrochloric acid absorbed at 254 mμ (ε 3850).[22]

2-(1-Hydroxy-*n*-butyl)cyclohexanone Acetate (11b).—The product from the reaction of 17.0 g. (0.10 mole) of 2-(1-hydroxy-*n*-butyl)cyclohexanone (**11a**) and 35 ml. of acetic anhydride in 50 ml. of pyridine distilled at 77–79° (0.02 mm.), $n^{27}D$ 1.4645–1.4655, and weighed 16.1 g. (76%). The analytical fraction was collected at 77.5–78° (0.02 mm.), $n^{27}D$ 1.4648; λ_{max}^{neat} 5.76 (s), 5.84 (s), and 8.11 μ (s).

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.42. Found: C, 68.06; H, 9.42.

2-(1-Hydroxy-*n*-butyl)cyclohexanone 3,5-Dinitrobenzoate (11c).—Since 1,3-ketols undergo elimination readily, a modification of the procedure of Brewster and Ciotti,[30] for the esterification of similarly sensitive alcohols, was employed. The crude product **11c**, from 1.70 g. (0.01 mole) of the ketol **11a**, after filtration and washing with cold water followed by isopropyl ether, was a white powder which weighed 1.91 g. (52%), m.p. 93–105°. Recrystallized twice from isopropyl ether, the ester showed a constant melting point at 104.5–106°; λ_{max}^{Nujol} 5.75 (s), 5.80 (s), 5.85 (s), 6.13 (m), 6.44 (s), and 7.82 μ (s).

Anal. Calcd. for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 56.03; H, 5.75; N, 7.94.

2-(1-Hydroxy-*n*-butyl)cyclohexanol (13).—A mixture of 51.1 g. (0.30 mole) of 2-(1-hydroxy-*n*-butyl)cyclohexanone (**11a**), 75 ml. of ethyl acetate, and 80 ml. of a settled Raney nickel suspension in ethyl acetate was hydrogenated at room temperature, under an initial pressure of 55 p.s.i., for 22 hr. After removing the catalyst and the solvent, the residual oil was distilled *in vacuo*. The product, b.p. 96–99° (0.1 mm.), $n^{23}D$ 1.4778–1.4781, weighed 36.7 g. (80%). The analytical sample had b.p. 97.2–98.2°, $n^{23}D$ 1.4780; λ_{max}^{neat} 3.00 (s, broad), 9.51 (s), and 9.75 μ (s).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.65; H, 11.78.

2-Ethyl-1,3-hexanediol *m*-Nitrobenzylidene Acetal.—A mixture of 14.6 g. (0.10 mole) of 2-ethyl-1,3-hexanediol, 15.1 g. of *m*-nitrobenzaldehyde, 50 mg. of *p*-toluenesulfonic acid monohydrate, and 160 ml. of dry benzene was heated under reflux, using a Dean–Stark water trap, for 2 hr. When the mixture had cooled, it was washed once with saturated aqueous sodium bicarbonate, dried over anhydrous potassium carbonate, and stripped of solvent *in vacuo*. The product, collected at 138.5° (0.02 mm.), $n^{22}D$ 1.5257–1.5259, weighed 17.6 g. (63%). A middle fraction, $n^{22}D$ 1.5257, was submitted for analysis.

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.30; H, 7.69; N, 5.05.

Small-Scale Preparation of Benzylidene Acetals of 1,3-Glycols.—A mixture of 1.0 to 10.0 mmoles of the 1,3-diol with an equivalent amount of benzaldehyde or its *m*- or *p*-nitro derivative was heated for 4–8 hr. in 75 ml. of benzene in the presence of 15 mg. of *p*-toluenesulfonic acid monohydrate.[31] The volume was slowly reduced to 20–30 ml. during this heating period. The cooled solution was washed in succession with 25-ml. portions of saturated aqueous sodium bisulfite, water, and saturated aqueous sodium bicarbonate (three times), dried over anhydrous sodium sulfate, and stripped of solvent *in vacuo*. The crude acetals, obtained in this fashion in almost quantitative yield, showed, in the infrared, no carbonyl or hydroxyl bands. The following absorption peaks were found in the spectra of the benzylidene and *m*- and *p*-nitrobenzylidene 1,3-glycol acetals[32] studied in this and a related investigation[2]: 6.15–6.17 (w, *m*-NO_2), 6.19–6.23 (m, *p*-NO_2), 6.24–6.25 (w, broad, C_6H_5), 6.28–6.30 (w, *m*-NO_2), 6.66–6.75 (w-m), 6.79–6.90 (m), 7.99–8.06 (w-m), 8.19–8.29 (w-m), 8.52–8.65 (m), 8.73–8.96 (s), 9.01–9.10 (s), 9.14–9.21 (s, absent in *m*-NO_2), 9.53–9.75 (m-s, usually broad, 2 bands were occasionally found in this region), 14.19–14.25 (s, *m*- and *p*-NO_2), and 14.34–14.36 μ (m-s, C_6H_5). In addition, the nitrobenzylidene derivatives absorbed strongly at 6.51–6.58 (asym. NO_2 st.) and 7.41–7.44 μ (sym. NO_2 st.); the *p*-nitrobenzylidene acetals showed an additional strong peak at 9.81–9.86 μ.

2-Ethyl-1,3-hexanediol *p*-nitrobenzylidene acetal was obtained in crystalline form from a hexane solution of the crude product, obtained in the above manner. On recrystallization from hexane, an acetal melting at 64–65.5° was obtained.

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58. Found: C, 64.72; H, 7.40.

On chromatographing a petroleum ether (b.p. 30–60°) solution of the crude product, obtained by this method from 2-(1-hydroxy-*n*-butyl)cyclohexanol (**13**) and *p*-nitrobenzaldehyde on alumina, three products were obtained. The first was eluted with 1:19 benzene–petroleum ether, the second with 1:9 and 1:4 benzene–petroleum ether, and the third with 1:1 benzene–petroleum ether and pure benzene. The infrared spectra of all three were similar, differing somewhat in the fingerprint regions of their spectra.

(30) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

(31) The amount of *p*-toluenesulfonic acid used in this preparation was rather critical; in smaller preparations where less than this amount was employed, no reaction occurred.

(32) L. J. Bellamy ("The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 116) states that four bands in the 8.33–10.00-μ region have been regarded as specific for the C-O-C-OC grouping. Y. Klibansky and D. Ginsburg [*J. Chem. Soc.*, 1293 (1957)] found ethylenedioxy ketal bands at 8.45, 8.64, and 9.12–9.23 μ. C. W. Shoppee, R. E. Lack, and A. V. Robertson, [*ibid.*, 3610 (1962)] associated peaks at 9.18, 9.35, and 9.73 μ with the C-O-C bond. H. R. Warner and W. E. M. Lands [*J. Am. Chem. Soc.*, **85**, 60 (1963)] found that their aliphatic ethers showed strong absorption near 9.10 μ and weaker absorption at 8.54, 8.70, and 8.89 μ.

All three showed absorption characteristic of *p*-nitrobenzylidene acetals. The third fraction crystallized on standing and was recrystallized twice from hexane. The large yellow crystals of **2-(1-hydroxy-*n*-butyl)cyclohexanol *p*-nitrobenzylidene acetal** melted at 62–63°.

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59. Found: C, 67.03; H, 7.57.

The crude benzylidene acetals derived from 2-(1-hydroxy-*n*-butyl)cyclohexanol (**13**) and perhydro(4a,β,8aβ)naphthalene-1β,8α-diol (**9**), as well as the *p*-nitrobenzylidene acetal of the latter, obtained by this general procedure, showed infrared absorption characteristic of these acetals but could not be obtained crystalline, even after chromatographic fractionation on alumina.

2-(*n*-Butyryl)cyclohexanone (14a).—The copper salt of the diketone was prepared in 55% yield, m.p. 135–140°, by the Jones oxidation[2] of 2-(1-hydroxy-*n*-butyl)cyclohexanone. This was recrystallized once from hexane, m.p. 151–152°,[33] and then decomposed by stirring for several hours with a mixture of methylene chloride and 4 *N* sulfuric acid. The product **14a**, collected at 131–132° (20 mm.), $n^{32}D$ 1.4928–1.4932, was obtained in 79% yield (from recrystallized copper salt). In the infrared spectrum of the neat liquid, absorption peaks were evident at 3.20 (w, shoulder), 3.79 (w), 5.82 (m, shoulder), 5.86 (m), 6.25 (s, broad), 7.06 (m), and 9.38 μ (m). The n.m.r. spectrum exhibited a singlet at 16.28 p.p.m. (OH), a multiplet centered at 2.38 p.p.m. (allylic protons and hydrogens on the carbons adjacent to the carbonyls), a triplet centered at 0.98 p.p.m. (CH_3, J = 7 c.p.s.), and a broad signal centered at 1.72 p.p.m. (remaining cyclic and acylic protons).

The copper salt was also obtained, in 53% yield, by oxidation[2] of the diol **13**. Recrystallized to constant melting point from hexane, the compound was obtained as gray-green plates possessing a silvery luster, m.p. 153–154.5°,[33] λ_{max}^{Nujol} 6.35 μ (s, C=O st.).

(33) This compound has previously been prepared by the condensation of a butyric ester or anhydride with cyclohexanone. J. T. Adams and C. R. Hauser [*J. Am. Chem. Soc.*, **67**, 284 (1945)] reported b.p. 133–134° (20 mm.) for the diketone and m.p. 156–157° for its gray copper salt.

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Steroids. CCLI. Lead Tetraacetate Oxidation of 17β-Hydroxy-5α-androst-1-en-3-one Acetate[1]

STEPHEN KAUFMANN

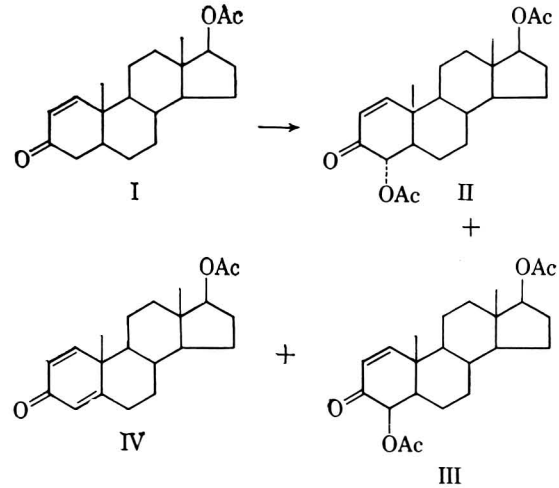
The Research Laboratories of Syntex, S. A., Apartado 2679, Mexico, D. F., Mexico

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Oxidation of 17β-hydroxy-5α-androst-1-en-3-one acetate (I) with lead tetraacetate gave a mixture of 4α,17β-dihydroxy-5α-androst-1-en-3-one diacetate (II), 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III), and 17β-hydroxyandrosta-1,4-dien-3-one acetate (IV). Alkaline hydrolysis of II and III resulted in the formation of 4-hydroxytestosterone. Proof for the assignment of the steric configuration of the epimeric 4-acetoxy groups in II and III has been presented.

The reaction of ring A α,β-unsaturated keto steroids with lead tetraacetate has been studied in the past. The most important representatives of this group, the Δ^4-3-keto steroids have been subjected to the oxidation with this reagent by several investigators.[2,3] It has been established that oxidation results mainly in the introduction of an acetoxy group into the 2α- and 2β-positions and the formation of the corresponding $\Delta^{1,4}$-3-ketone to a lesser degree. More recently,[4] the lead tetraacetate oxidation of 17β-acetoxy-5α-estr-1(10)-en-2-one has been described, which yields a mixture of epimeric 3-acetoxy compounds.

In analogy, we have investigated the behavior of a Δ^1-3-keto steroid with lead tetraacetate, whereby attack on C-4 could be expected. As a suitable compound, we selected the acetate of 17β-hydroxy-5α-androst-1-en-3-one (I), the Δ^1 isomer of testosterone acetate. In accordance with expectations, the 4α,-17β-dihydroxy-5α-androst-1-en-3-one diacetate (II) and 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III) could be isolated from the reaction mixture together with the $\Delta^{1,4}$-3-ketone (IV). The less soluble β isomer (III) was separated by direct crystallization, whereas the α isomer (II) and the doubly unsaturated ketone (IV) could be obtained only by chromatography of the mother liquors. It is significant that the yield of IV is considerably higher (about 20%) than that obtained by lead tetraacetate oxidation of testosterone acetate,[3] probably because of the easier removal of the



(1) Steroids CCL: J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, in press.

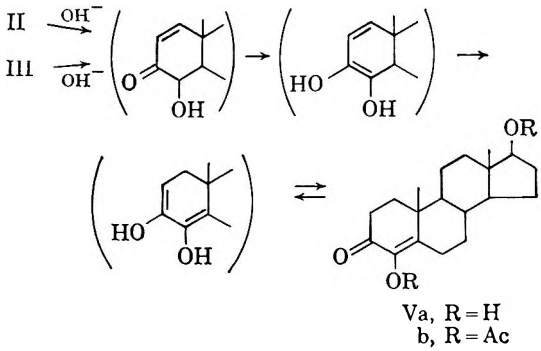
(2) (a) G. Erhart, M. Ruschig, and W. Aumüller, *Angew. Chem.*, **52**, 363 (1939); (b) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944); (c) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

(3) R. L. Clarke, K. Dobriner, A. Mooradian, and C. M. Martini, *ibid.*, **77**, 661 (1955).

(4) J. Fishman, *J. Org. Chem.*, **28**, 1528 (1963).

5α-hydrogen in comparison to the secondary hydrogens at C-1.

The structures of II and III have been established through alkaline hydrolysis, whereby both compounds are converted to the known 4-hydroxytestosterone (Va). Under these conditions, the Δ^1 double bond shifts through different enol intermediates, which can be formulated as follows.



Va, R = H
b, R = Ac

The configuration of the 4-acetoxy group has been determined in compound II as α and in compound III as β, on the basis of molecular rotation changes relative to the parent compound I (see Table I). It was

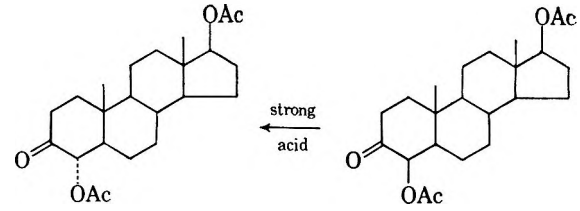
TABLE I

Compound	MD	ΔMD	A	B
I	+148.8			
II	+126.8	−22		
III	+396.9	+248	+113	+135
17β-Hydroxy-5α-androstan-3-one acetate	+86.3			
VI	−102.2	−188.5		
VII	+261.3	+175.0	−6.7	+181.7

first pointed out by Barton and Klyne[5] and later by Stokes and Bergmann[6] that displacement of a hydrogen on C-4 by a hydroxy or acetoxy group in the α-position has a negative contribution to the optical rotation, whereas substitution in the isomeric β-position is followed by an increase in rotation. Following the reasoning of Stokes and Bergman,[6] if the vicinal effect is represented by "A" and the contribution of the new asymmetric center by "B", the α-substitution changes the molecular rotation by "A − B" and the β-substitution by "A + B". The calculated "A" and "B" values for compounds II and III and for VI and VII are shown in Table I.

Further proof for the α-position of the 4-acetoxy group in II has been obtained by hydrogenating the latter to the known[7] 4α,17β-dihydroxy-5α-androstan-3-one diacetate (VI) with palladium–charcoal catalyst. Under the same conditions, compound III is transformed into the β isomer, 4β,17β-dihydroxy-5α-androstan-3-one diacetate (VII). Compound VII is unstable in strong acidic medium (acetic acid and hydrobromic acid) and is isomerized to the more stable 4α-acetoxy compound VI. The chair conformation of ring A favors the equatorial configuration of the substituents on C-4. It is remarkable that the Δ^1-unsaturated analog III remains unchanged by treatment with *p*-toluenesulfonic acid or potassium acetate in acetic acid, which means that the β isomer is thermodynamically as stable as the α isomer.[8]

The ΔMD values (Table I) of VI and VII compared with the parent compound 17β-hydroxy-5α-androstan-3-one acetate are in good agreement with the theory. The "B" values for II and III (+135) and for VI and VII (+181.7) are of the same magnitude, as should be expected on the basis of the rules given by Stokes and Bergmann.[6] On the other hand, it is interesting to note that the vicinal effect on "A" of the $-\overset{O}{\overset{\|}{C}}CH_2-$ moiety is negative and the one of $-\overset{O}{\overset{\|}{C}}CH{=}CH-$ positive.



VI VII

The ultraviolet absorption of compound III shows a λ_{max} at 235 mμ, whereas the α isomer II has the same λ_{max} (at 230 mμ) as the parent compound I. The bathochromic shift caused by the β-substitution confirms the fact that the latter is accompanied by strain in ring A.

Experimental[9]

4α,17β-Dihydroxy-5α-androst-1-en-3-one Diacetate (II), 4β,-17β-Dihydroxy-5α-androst-1-en-3-one Diacetate (III), and 17β-Hydroxyandrosta-1,4-dien-3-one Acetate (IV).—A solution of 20 g. of 17β-hydroxy-5α-androst-1-en-3-one acetate (I) in 800 ml. of glacial acetic acid was heated on the steam bath and 24 g. of lead tetraacetate was added in a 6-g. portion every hour. The heating was continued for an additional hour and the reaction mixture was concentrated under vacuum to dryness. Water (4 l.) was added and the oily precipitate was extracted with several portions of methylene chloride. The organic layer was washed with water and with dilute sodium hydroxide solution, and dried with anhydrous sodium sulfate; the solvent was evaporated to dryness. The residual gummy material (21 g.) was dissolved in 200 ml. of methanol. Water was added until crystallization started, which was completed after standing and yielded 2.5 g. of 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III). Recrystallization from methanol yielded 2.1 g. of pure product, m.p. 242–244°, $[\alpha]D$ +102.3°; $\lambda_{max}^{C_2H_5OH}$ 235 mμ (log ε 4.05); $\lambda_{max}^{CCl_4}$ 3.42, 5.70, 5.90, 7.30, and 8.16 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 71.10; H, 8.30. Found: C, 71.15; H, 8.31.

The mother liquors of III were concentrated to dryness and the oily residue (18 g.) was chromatographed on 500 g. of silica gel. Elution with benzene–ethyl acetate (9:1) gave in the first fractions an oily material which crystallized after addition of ether. Two recrystallizations from methanol yielded 0.85 g. of pure 4α,17β-dihydroxy-5α-androst-1-en-3-one diacetate (II), m.p. 191–192°, $[\alpha]D$ +32.7°; $\lambda_{max}^{C_2H_5OH}$ 230 mμ (log ε 3.95); $\lambda_{max}^{CCl_4}$ 3.42, 5.69, 5.84, 7.27, and 8.10 μ.

(5) D. H. R. Barton and W. Klyne, *Chem. Ind.* (London), 755 (1948).

(6) W. M. Stokes and W. Bergmann, *J. Org. Chem.*, **17**, 1194 (1952).

(7) R. Gardi, P. P. Castelli, and A. Ercoli, *Tetrahedron Letters*, 499 (1962).[11]

(8) On the contrary, 2β-hydroxytestosterone diacetate is epimerized to 2α-hydroxytestosterone diacetate by refluxing with potassium acetate in acetic acid solution.[4]

(9) All melting points are corrected. Optical rotations were measured in chloroform, ultraviolet absorption spectra in 95% ethanol, and infrared absorption spectra in carbon tetrachloride. We are indebted to Dr. C. Zapata and his staff for these determinations. Microanalyses were performed by Dr. G. M. Maciak (Midwest Microlab, Inc., Indianapolis, Ind.).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.02; H, 8.30.

Continued elution with benzene–ethyl acetate (9:1) yielded a crystalline material (3.9 g.) which after recrystallization from methanol proved to be identical with 17β-hydroxyandrosta-1,4-dien-3-one acetate (IV) by mixture melting point comparison with an authentic sample. The melting point was 152–153°, $[\alpha]D$ +32°; $\lambda_{max}^{C_2H_5OH}$ 244 mμ (log ε 4.18); lit.[10] m.p. 151–152°, $[\alpha]D$ +28°.

4-Hydroxytestosterone (Va).—A solution of 1 g. of 4α,17β-dihydroxy-5α-androst-1-en-3-one diacetate (II) in 50 ml. of methanol was treated with 5 ml. of a 20% sodium hydroxide solution. The mixture was heated under reflux for 1 hr. The slightly yellow solution was poured into water, acidified with hydrochloric acid, and extracted with ether. The ether solution, after drying, was concentrated to a small volume, whereby the 4-hydroxytestosterone (Va) crystallized. After recrystallization from methanol–water, 0.45 g. of pure product was obtained, m.p. 216.5–218°, $\lambda_{max}^{C_2H_5OH}$ 278 mμ (log ε 4.076), lit.[11] m.p. 222–223°.

In the same way, 4-hydroxytestosterone was obtained by saponification of 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III).

Diacetate (Vb).—The diacetate was obtained in the usual way by acetylation with acetic anhydride–pyridine at room temperature. It melted at 168.5–169.5°, $[\alpha]D$ +96.5°, $\lambda_{max}^{C_2H_5OH}$ 246 mμ (log ε 4.135); lit.[11] m.p. 170–172°, $[\alpha]D$ +105°, $\lambda_{max}^{C_2H_5OH}$ 246 mμ (log ε 4.19). There was no depression of melting point by admixture with an authentic sample of 4-hydroxytestosterone diacetate.

4β,17β-Dihydroxy-5α-androstan-3-one Diacetate (VII).—A solution of 1 g. of 4β,17β-dihydroxy-5α-androst-1-en-3-one diacetate (III) in 150 ml. of ethyl acetate was hydrogenated under 30-p.s.i. pressure with 0.1 g. of 5% palladized charcoal catalyst. After 1 hr. the catalyst was separated by filtration and the filtrate was concentrated to dryness. The crystalline residue was recrystallized from ether–hexane to give 0.85 g. of pure 4β,17β-dihydroxy-5α-androstan-3-one diacetate (VII), m.p. 166–169.5°, $[\alpha]D$ +67°; $\lambda_{max}^{CCl_4}$ 3.63, 5.76, 7.29, and 8.20 μ.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 70.63; H, 8.70.

4α,17β-Dihydroxy-5α-androstan-3-one Diacetate (VI). A. From 4α,17β-Dihydroxy-5α-androst-1-en-3-one Diacetate (II).—Hydrogenation of 0.5 g. of compound II in the above-described manner and crystallization from ether–hexane gave 0.3 g. of pure 4α,17β-dihydroxy-5α-androstan-3-one diacetate (VI), m.p. 197.5–198°, $[\alpha]D$ −26.2°; $\lambda_{max}^{CCl_4}$ 3.43, 5.74, 7.27, and 8.10 μ; lit.[7] m.p. 196.5–197.50, $[\alpha]D$ −24°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 70.76; H, 8.68.

B. From 4β,17β-Dihydroxy-5α-androstan-3-one Diacetate (VII).—A solution of 1 g. of VII in 50 ml. of glacial acetic acid was treated with a saturated solution of 1 ml. of hydrobromic acid in glacial acetic acid. The mixture was left to stand overnight, after which it was poured into water and extracted with ether. The ether solution was washed to neutrality, dried, and concentrated to dryness. Recrystallization of the residue from ether–hexane afforded 0.82 g. of 4α,17β-dihydroxy-5α-androstan-3-one diacetate (VI), m.p. 197.5–198°, $[\alpha]D$ −24.7°.

The products obtained by methods A and B were identical by infrared spectral comparison and no depression was observed in the mixture melting point.

(10) H. H. Inhoffen, G. Zühlsdorff, and Huang-Minlon, *Ber.*, **73**, 451 (1950).

(11) B. Camerino, B. Patelli, and A. Vercellone, *J. Am. Chem. Soc.*, **78**, 3541 (1956).

Reaction of Nitrosyl Chloride with Steroid 5-Enes.[1] Nuclear Magnetic Resonance as a Stereochemical Tool in Steroids

ALFRED HASSNER AND CLAYTON HEATHCOCK[1d]

Department of Chemistry, University of Colorado, Boulder, Colorado

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Steroid 5-enes, on treatment with an excess of nitrosyl chloride, give 5α-chloro-6β-nitro steroids in good yield. These nitrochloro adducts are transformed by pyridine into the corresponding 6-nitro-5-enes. The latter are reduced stereospecifically by sodium borohydride to 6α-nitro 5α-steroids. 6β-Nitro-5α-chlorocholestan-3β-ol acetate reacts with chromous chloride in methanolic hydrochloric acid to give 6-oximino-5α-methoxycholestan-3β-ol acetate. It is shown that the half-width of a band in the n.m.r. may be correlated with the conformation of the proton giving rise to the band. Thus, equatorial protons give rise to a narrow band (5–12 c.p.s.), while axial protons give a broad band (15–30 c.p.s.).

It has been shown by Closs and Brois that olefins may be transformed *via* their nitrosyl chloride adducts into aziridines.[2] In connection with our interest in the preparation of steroidal aziridines,[3] we investigated the reaction of nitrosyl chloride with some steroid 5-enes. Although nitrosyl chloride has been widely used in the terpene field,[4] it had apparently found no application in steroids.[5]

Cholesteryl acetate (**1a**) reacts with excess nitrosyl chloride at 0° in methylene chloride or carbon tetrachloride to give in 85% yield a crystalline product, m.p. 142–143°, for which structure **2a** is suggested on the basis of elemental analysis and characteristic nitro absorption bands in the infrared (1559, 1370, 864, and 640 cm.$^{-1}$).[5,6] Furthermore, the ultraviolet spectrum of **2a** in neutral and basic medium is very similar to that of nitrocyclohexane. On treatment with pyridine at room temperature, **2a** is transformed into the known 6-nitrocholesteryl acetate (**4a**).[5,6] Methanolic hydrochloric acid converts the acetate **2a** into the corresponding alcohol **3a**. Similar transformations are observed with 5-androsten-3β-ol-17-one acetate (**1b**), methyl 3β-acetoxy-5-cholenate (**1c**), and 5-pregnen-3β-ol-20-one formate (**1d**). The 5α,6β-configuration in **2a** has been assigned largely because ready elimination of

(1)(a) Nitro Steroids. II. Paper I: A. Hassner and J. M. Larkin, *J. Am. Chem. Soc.*, **85**, 2181 (1963). (b) This investigation was supported in part by Public Health Service Grant CY-4474, from the National Cancer Institute. (c) Presented in part before the Division of Organic Chemistry at the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964. (d) National Science Foundation Fellow, 1961–1963.

(2) G. Closs and S. J. Brois, *J. Am. Chem. Soc.*, **82**, 6068 (1960).

(3) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 393 (1963).

(4) For a review of nitrosyl chloride chemistry, see L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951).

(5) After the present work was essentially complete, however, the work of Tanabe and Hayashi appeared in print.[6] These workers describe the preparation of compounds **2a**, **2b**, **3a**, **4a**, and **4b** in the same manner as that described here.

(6) K. Tanabe and R. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 1177 (1962).

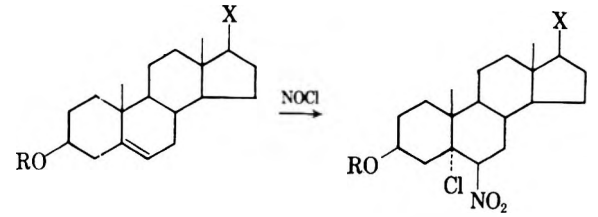
NO_2Cl from **2a** by zinc dust is consistent with diaxially disposed groups.[6] This assignment is now corroborated for compounds **2a–d** and **3a–d** by means of n.m.r. spectra (see below).

Ogloblin has recorded examples of isolation in low yield of nitro compounds in nitrosyl chloride additions to olefins,[7,8] but there seems to be no previously reported case in which a nitro compound is the only product observed in such a reaction. When cholesteryl acetate (**1a**) was treated with one molar equivalent of nitrosyl chloride, a mixture of starting olefin and nitrochloro compound **2a** was obtained. Exclusion of oxygen did not alter the results of the addition reaction. Nitryl chloride reacts with cholesteryl acetate to yield a mixture of products which is difficult to separate and which consists only in part of nitro steroids. Since it is known that nitroso alkanes readily are oxidized to nitro compounds,[4,9] products **2** most likely arise by oxidation of the initially formed nitroso chloride by nitrosyl chloride.[10]

With regard to the mode of addition of nitrosyl chloride to steroid 5-enes, one expects attack at the 6-position by NO^+ or $NO\cdot$ to give an intermediate tertiary carbonium ion or free radical, respectively. Whereas ionic additions to steroid 5-enes generally proceed by attack of the electrophile from the α-side,[11] the products from the NOCl addition contain the nitro group in the less stable axial 6β-configuration. This is compatible with a stereoelectronically controlled axial approach of NO^+. The fact, however, that free-radical addition of hydrogen bromide[12] to cholesterol yields 6β-bromocholestan-3β-ol[13] suggests that the addition of nitrosyl chloride might proceed by a free-radical *trans* addition.[14] The determination of the precise mechanism involved is still under investigation.

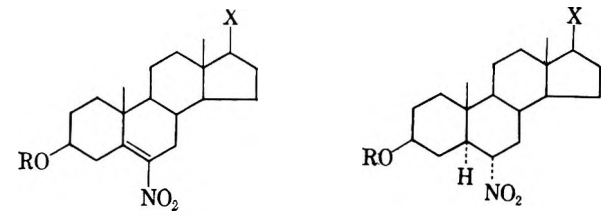
Several attempts (*i.e.*, catalytic reductions with palladium or platinum, stannous chloride, or ferrous sulfate) to reduce the nitrochloro adduct **2a** to the corresponding chloro amine were unsuccessful. Zinc dust or iron dust in refluxing glacial acetic acid regenerated cholesteryl acetate (**1a**). The reluctance of the nitro group to be reduced is in accord with the assignment to it of an axial configuration.

On treatment of **2a** with chromous chloride in methanolic hydrochloric acid, there is obtained a substance, $C_{30}H_{51}NO_4$, which was assigned structure **5**. In the infrared, **5** shows absorption characteristic of an oxime (3450 and 1655 cm.$^{-1}$); its diacetate shows bands for an oxime acetate[15] (1785 and 1640 cm.$^{-1}$). The n.m.r. spectrum shows a sharp singlet at τ 6.90 (OCH_3). Therefore, the nitro group in **2a** has been reduced to the oxime stage, while the chlorine has been solvolyzed by



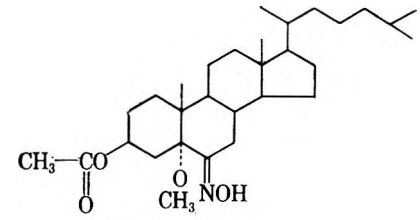
1a, R = $COCH_3$; X = C_8H_{17}
b, R = $COCH_3$; X = O
c, R = $COCH_3$; X = $CH(CH_3)$-$CH_2CH_2CO_2C_2H_5$
d, R = CHO; X = $COCH_3$

2a, R = $COCH_3$; X = C_8H_{17}
b, R = $COCH_3$; X = O
c, R = $COCH_3$; X = $CH(CH_3)$-$CH_2CH_2CO_2C_2H_5$
d, R = $COCH_3$; X = $COCH_3$
3a, R = H; X = C_8H_{17}
c, R = H; X = $CH(CH_3)$-$CH_2CH_2CO_2C_2H_5$
d, R = H; X = $COCH_3$



4a, R = $COCH_3$; X = C_8H_{17}
b, R = $COCH_3$; X = O
c, R = $COCH_3$; X = $CH(CH_3)$-$CH_2CH_2CO_2C_2H$

6a, R = $COCH_3$; X = C_8H_{17}
b, R = $COCH_3$; X = $OCOCH_3$
c, R = $COCH_3$; X = $CH(CH_3)$-$CH_2CH_2CO_2C_2H_5$
d, R = $COCH_3$; X = $CH(OCOCH_3)CH_3$
7a, R = H; X = C_8H_{17}
b, R = H; X = OH
c, R = H; X = $CH(CH_3)$-$CH_2CH_2CO_2C_2H_5$
d, R = H; X = $CH(OH)CH_3$



5

methanol. Since the 3α-proton appears as a band at τ 5.17 with a band width at half-height of 24 c.p.s. (see discussion below), it is axial and the A–B ring junction is *trans*. It follows that the methoxy group is 5α.

We found that reduction of 5α-chloro-6β-nitro steroids, *i.e.*, **2a**, or of 6-nitro steroid 5-enes with sodium borohydride in ethanol leads in a stereospecific manner to 6α-nitro 5α-steroids. Thus, 6-nitrocholesteryl acetate (**4a**) is converted in 85% yield to 6α-nitrocholestan-3β-ol (**7a**). No detectable amount of any other diastereomer is produced in this reaction. Oxidation of **7a** by the Jones reagent[16] leads to 6α-nitrocholestan-3-one (**8a**). Nitro alcohol **7a** is also produced by base-catalyzed hydrolysis of 6α-nitrocholestan-3β-ol acetate[17] (**6a**), which is formed in 49% yield in the reaction of 6β-nitro-5α-chlorocholestan-3β-ol acetate (**7**) with sodium

(7) K. A. Ogloblin, *Zh. Obshch. Khim.*, **27**, 2541 (1957); **28**, 3245 (1958).
(8) K. A. Ogloblin and A. A. Potekhin, *ibid.*, **31**, 2438 (1961).
(9) W. E. Noland and R. Libers, *Tetrahedron*, **19**, 23 (1963).
(10) That the 6-nitroso steroid would have to be oxidized to the 6-nitro compound before it is able to tautomerize to an oxime is indicated by the well-known[4] fact that oximes are oxidized by NOCl not to nitro but to α-chloronitroso or α-chloronitro compounds.
(11) For instance in the hypobromous acid addition to steroid 5-enes [M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **84**, 1496 (1962)].
(12) In contrast with ionic addition of DCl which leads to 6α-deuterio-5α-chloro steroids (C. W. Shoppee, private communication).
(13) C. W. Shoppee and R. Lack, *J. Chem. Soc.*, 4864 (1960).
(14) A recent postulate of *cis* addition of NOCl to norbornene [J. Meinwald, Y. C. Meinwald, and T. N. Baker, *J. Am. Chem. Soc.*, **85**, 2513 (1963)] is based on the assumption that NO^+ or NOCl would approach from the least hindered side which does not seem to be the case with steroid 5-enes.
(15) A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, **27**, 1760 (1962).
(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(17) This compound is practically identical by infrared with 6α-nitrocholestan-3β-ol acetate synthesized independently from the 6-ketoxime by G. D. Meakins and E. R. H. Jones. We are grateful to these authors for informing us of their results prior to publication.

borohydride in ethanol. This latter reaction probably proceeds *via* the initial formation of nitro olefin **4a**, which is reduced in the normal manner to give nitro acetate **6a**.[18]

In a similar manner, 6-nitro-5-androsten-3β-ol-17-one acetate (**4b**) is reduced by sodium borohydride to 6α-nitroandrostane-3β,17β-diol (**7b**) in 64% yield. Nitrodiol **7b** was characterized as diacetate **6b** and by oxidation to 6α-nitroandrostane-3,17-dione (**8b**). Methyl 6-nitro-5-cholenate (**4c**) is likewise reduced by sodium borohydride in ethanol, with concomittant ester interchange in the side chain, to give a mixture of ethyl 6α-nitro-3β-acetoxy-5α-cholanate (**6c**) and ethyl 6α-nitro-3β-hydroxy-5α-cholanate (**7c**) in 76% yield. Alcohol **7c** is converted by acetic anhydride in pyridine to the acetate **6c**. 6-Nitro-5-pregnen-3β-ol-20-one formate (**4d**), on borohydride reduction, gives in 92% yield crude nitrodiol (**7d**) as a mixture of the C-20 epimers. Crystallization of this mixture from methanol–water gave one of the pure epimers, m.p. 247–248.5°, which was also characterized as its diacetate derivative (**6d**).

Since hydride reduction of nitro compounds to amides sometimes proceeds with inversion,[19] we chose n.m.r. spectra instead of reduction to amines for the assignment of stereochemistry at C-5 and C-6 on compounds **6**–**7**. These are assigned the 5α- and 6α-configuration because the half-width (20–25 c.p.s.) of the bands for the C-3 and C-6 protons in the n.m.r. indicate them to be axial protons (see discussion below).

The reduction of 6-nitro steroid 5-enes probably occurs by a Michael addition of hydride to the α,β-unsaturated nitro system with formation of the anion of the *aci*-nitro compounds. Protonation and equilibration then gives the thermodynamically more stable equatorial epimer (6α).[20] The initial stereospecificity of the reaction at C-5 indicates that the hydride prefers to attack from the α-side, giving the more stable *trans* A–B ring junction. This is in accord with results obtained in the sodium borohydride reduction of 3-keto-4-androstenes where 5α-androstan-3-ols are the products.[21] Reductions of nitro olefins and even of nitro benzenes with sodium borohydride have been reported.[22,23] Schechter and co-workers have shown that nitro olefins may be reduced by metal hydrides to give the corresponding nitro alkanes.[22] They found, however, that a major product, and indeed sometimes the only product, was the dimer or higher polymer formed by Michael addition of the initially formed *aci*-nitro anion to the nitro olefin. In the case of 6-nitro steroid 5-enes, this competing dimerization reaction evidently does not take place, probably for steric reasons.

Nuclear magnetic resonance has recently been successfully employed in differentiation of isomers in steroids.[24–26] Chemical shift differences between epimers are generally not great and in many cases both isomers are required for conclusive assignments to be made. The fact, that diaxial vicinal coupling constants are much greater than diequatorial or axial–equatorial ones,[25] also can be used to assign configurations to steroidal epimers. In general, when an electronegative substituent is attached to the steroid framework, the geminal proton is found downfield in the unobscured region of the spectrum. However, such a proton will usually be adjacent to several others and will give rise to a broad band in which the number of closely spaced lines due to spin–spin coupling are not readily discernible. The width of such a band, measured at one-half its height (referred to as the half-width and symbolized by $W^{1/2}$), will reflect the magnitude of the vicinal coupling constants. Thus, an axial proton, split by adjacent axial ($J \sim 9$ c.p.s.) and equatorial protons ($J \sim 2$ c.p.s.), should give rise to a much wider band than an equatorial proton split by adjacent axial ($J \sim 2$ c.p.s.) and equatorial protons ($J \sim 2$ c.p.s.). The utility of half-widths in assignment of stereochemistry has been pointed out recently in a number of cases, mainly in hydroxy and acetoxy cyclohexanes with a rigid skeleton.[24–27] Anomalies have also been reported.[27]

In order to further test the general applicability of this simple technique in assigning stereochemistry in steroids, the spectra of over forty steroids with various functional groups (equatorial and axial) have been obtained. The steroids tested had the cholestane, coprostane, androstane, cholanic acid, or pregnane skeleton. The following functional groups were present at C-2: OH, OAc, NH_2, NHAc, NCO, $NHCO_2CH_3$, and I; at C-3: OH, OAc, $OCOC_6H_5$, OCHO, NH_2, NHAc, I, Cl, and NO_2; at C-4: OH; at C-5: OH, OCH_3, and Cl; at C-6: OH, OAc, and NO_2; at C-7: OAc; at C-12: OAc. Fig. 1A–F shows partial spectra of some compounds examined. Inspection of the results reveals that *the half-width of the bands due to equatorial protons is 5–10 c.p.s., while that for axial protons is 15–30 c.p.s.* Often it is not necessary to measure the exact band width, since a visual inspection reveals the configuration (see Fig. 1). It should be pointed out that the equatorial hydrogen geminal to the axial $NH–COCH_3$ or $NHCO_2CH_3$, in 2β-acetamido-3α-acetoxy- and 3α-acetamido-2β-acetoxycholestanes or in 3β-(N-carbomethoxy)-

(18) These results suggest that the sodium borohydride reduction of 17-bromo-17-nitro steroids to 17-nitro steroids reported recently [A. A. Pachett, F. Hoffmann, F. F. Giarrusso, H. Schwam, and G. E. Arth, *J. Org. Chem.*, **27**, 3823 (1962)] also proceeds by elimination of H–Br followed by hydride reduction of the 17-nitro 16-olefin.

(19) H. Shechter, N. Kornblum, and L. Fishbein, *J. Am. Chem. Soc.*, **77**, 6266 (1955); S. J. Cristol, Abstract of the XVIIIth National Organic Chemistry Symposium, Columbus, Ohio, June 1963, p. 21.

(20) Although protonation of the anion of *aci*-nitro groups generally leads to axial nitro compounds, equilibration in base gives the more stable equatorial isomer [*cf.* A. Bowers, M. B. Sanchez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3702 (1959); H. E. Zimmerman and T. E. Nevins, *ibid.*, **79**, 6559 (1957)].

(21) F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. Ind.* (London), 1482 (1954).

(22) H. Shechter, D. E. Ley, and E. B. Roberson, *J. Am. Chem. Soc.*, **78**, 4984 (1956).

(23) T. Severin and M. Adam, *Ber.*, **96**, 448 (1963).

(24) (a) G. Slomp and B. R. McGarvey, *J. Am. Chem. Soc.*, **81**, 2200 (1959); (b) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962); (c) A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962); (d) K. L. Williamson and W. J. Johnson, *ibid.*, **83**, 4623 (1961).

(25) R. U. Lemieux, R. K. Kulling, H. J. Bernstein, and W. G. Schneider, *ibid.*, **79**, 1005 (1957); **80**, 6098 (1958).

(26) R. C. Tweit, A. H. Goldkamp, and R. M. Dodson, *J. Org. Chem.*, **26**, 2856 (1961); R. C. Tweit, R. M. Dodson, and R. D. Muir, *ibid.*, **27**, 3654 (1962); R. C. Tweit, *ibid.* **27**, 2693 (1962); K. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963); S. G. Levine, N. H. Endy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963).

(27) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).

amino-3α-iodocholestane, gives rise to broader bands (13–17 c.p.s.) than expected. That this is due to additional coupling with the N–H can be shown by the fact that the signal for the N–H appears as a doublet (J = 6–7 c.p.s.).

Whereas the chemical shift, *e.g.*, for the axial hydrogen geminal to a hydroxy or an acetoxy group at C-3, varies considerably with the structure of the rest of the steroid molecule[28] and is of use only if both epimers are available, the half-width of such a proton (15–25 c.p.s.) allows a clear distinction between an axial and an equatorial configuration in all cases studied.

The use of this technique for assigning stereochemistry to a number of 6-nitro steroids is illustrated. The spectra of the 6-nitro-5-chloro 3β-alcohols (**3**) and their acetates (**2**) all show a band in the region from τ 5.22 to 5.37, with a half-width of 5–7 c.p.s. In each case this narrow band is accompanied by a broad band ($W^{1/2}$ 21–24 c.p.s.) which appears in the region τ 4.5–4.7 in the acetates and τ 5.6–5.8 in the free alcohols. These spectra are similar to that of 3β,6β-diacetoxycholestan-5α-ol. It is readily apparent that the compounds have one axial and one equatorial functional group. The narrow band in the τ 5.3 region may be assigned to the C-6 proton, geminal to the nitro group, since it is not shifted appreciably in going from the alcohol to its acetate. The broad band in each spectrum is then assigned to the 3α-hydrogen. The shift in this band of *ca.* 1 p.p.m. between the alcohols and their acetates is of the expected order of magnitude. Therefore the correct configuration for these compounds is the one which has the nitro group axial (6β) and the oxygen function equatorial and β, thus fixing the A–B ring junction as *trans*. This case is especially interesting, since it enables us to use the band-width of the C-3 proton resonance to establish the configuration at C-5.

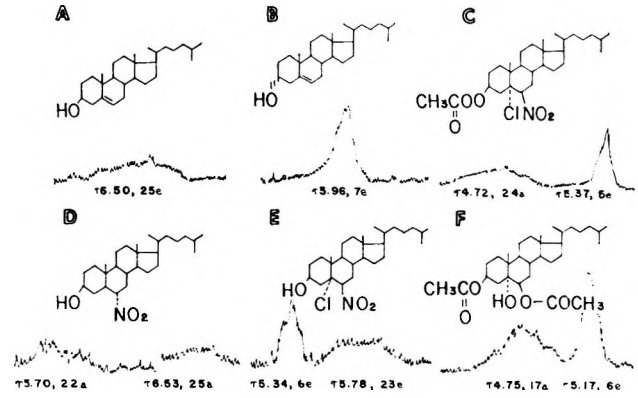


Fig. 1.—Determination of configuration in steroids by means of nuclear magnetic resonance. The first number below each peak is the chemical shift in τ units. The second number is the width of the band at half-height ($W^{1/2}$) in c.p.s., and the letter a (axial) or e (equatorial) denotes the configuration of the proton responsible for the band. There are two errors in this figure: A should read τ 6.50, 25a; E should read τ 5.34, 6e, and τ 5.78, 23a.

Experimental[29]

Nitrosyl Chloride Addition to Steroid 5-Enes. General Procedure.—Nitrosyl chloride (from a cylinder of the compressed gas, or freshly prepared) was passed into methylene chloride or carbon tetrachloride (25–100 ml.) at 0° until the solution had a deep burgundy color. This gave a 10–15% solution. The steroid olefin (5–10 g.) or a solution of the olefin in carbon tetrachloride was added. The solution was kept for 2–24 hr. at 0 to −16° in the dark. The excess of nitrosyl chloride and the solvent were removed *in vacuo* and the product was crystallized.

6β-Nitro-5α-chlorocholestan-3β-ol Acetate (2a).—From 4.93 g. of cholesteryl acetate (1a) there was obtained 5.1 g. of product, m.p. 132–136°. Crystallizations from ether–methanol and from methanol brought the melting point to 142–143°, lit.[8] m.p. 141–142°; ν_{max} 1750 (C=O), 1559 and 1370 (NO_2), 1240 and 1036 cm.$^{-1}$ (acetate). The n.m.r. spectrum, in carbon tetrachloride, has a broad band ($W^{1/2}$ 24 c.p.s.) at τ 4.72 (C-3 H, axial), a narrow band ($W^{1/2}$ 5 c.p.s.) at 5.37 (C-6 H, equatorial), and methyl peaks at 8.97 (C-19, singlet), 9.14 (C-26 and C-27, doublet, J = 6.5 c.p.s.), and 9.28 (C-18, singlet). **2a** had λ_{max} 283 mμ (ε 50) and λ_{min} 264 mμ (ε 39). In 0.1 *N* methanolic potassium hydroxide, λ_{max} changed to 265 mμ (ε 1440) immediately and to 275 mμ (ε 3320) after 24 hr.

Anal. Calcd. for $C_{29}H_{48}ClNO_4$: C, 68.26; H, 9.50; Cl, 6.95; N, 2.75. Found: C, 68.35, 68.12, 68.23, 68.13; H, 9.39, 9.64, 9.67, 9.41; Cl, 7.16; N, 2.67.

6β-Nitro-5α-chloroandrostan-3β-ol-17-one Acetate (2b).—From 7.23 g. of **1b** there was obtained 7.41 g. of white prisms, m.p. 220–225° dec., and 1.44 g., m.p. 209–221° dec. Crystallizations from benzene–hexane raised the melting point to 227–230° dec., lit.[6] m.p. 209–210°; ν_{max} 1740, 1548, 1360, 1240, and 1023 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}ClNO_5$: C, 61.23; H, 7.34; Cl, 8.61. Found: C, 61.12; H, 7.58; Cl, 8.67.

Methyl 6β-Nitro-5α-chloro-3β-acetoxycholenate (2c).—From 5.0 g. of methyl 3β-acetoxy-5-cholenate (**1c**) 4.45 g. (75%) of **2c** was obtained, m.p. 160–161.5°, which on further recrystallization from acetone–hexane melted at 165–167°; ν_{max} 1738, 1550, 1362, 1250, 1163, and 1036 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}ClNO_6$: C, 63.32; H, 8.27; Cl, 6.92. Found: C, 63.52; H, 8.35; Cl, 6.88.

6β-Nitro-5α-chloropregnan-3β-ol-20-one Formate (2d).—5-Pregnen-3β-ol-20-one formate (**1d**, 20.0 g.) was converted to 15.95 g. of product, m.p. 155–158°, which on crystallization from acetone–hexane melted at 160–161°; ν_{max} 1723 (C-17, =O), 1700 (formate C=O), 1552 and 1353 (NO_2), and 1170 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{22}H_{32}ClNO_5$: C, 62.03; H, 7.57; Cl, 8.32. Found: C, 62.08; H, 7.65; Cl, 8.54.

6β-Nitro-5α-chlorocholestan-3β-ol (3a).—A solution containing 1.22 g. of nitrocholoro acetate **2a** and 10 ml. of 4.8 *N* hydrochloric acid in 100 ml. of methanol was refluxed for 2 hr. and then allowed to stand overnight at room temperature. The resulting precipitate was filtered off and air-dried. The product weighed 930 mg. and melted at 95–101°, lit.[6] m.p. 98–104° (the melting point was not improved by repeated recrystallization from methanol); ν_{max} 3400 (O–H), 1552 and 1362 cm.$^{-1}$ (NO_2). The n.m.r. spectrum in CCl_4–$CDCl_3$ has bands at τ 5.33 (C-6 H, $W^{1/2}$ = 7 c.p.s., equatorial), 5.78 (C-3 H, $W^{1/2}$ = 20 c.p.s., axial), and methyl peaks at 8.98 (C-19, singlet), 9.12 (C-26 and C-27, doublet, J = 6.5 c.p.s.), and 9.27 (C-18, singlet).

Methyl 6β-nitro-5α-chloro-3β-hydroxycholanate (3c) was prepared in a similar manner from nitrochloro acetate **2c**. The yield of crude alcohol, m.p. 109–112°, was 87%. After recrystallization from methanol–water, the substance melted at 113–115°; ν_{max} 3500 (OH), 1725 (C=O), 1550 and 1360 (NO_2), 1162 (ester), 1062 and 1035 cm.$^{-1}$ (C–O).

Anal. Calcd. for $C_{25}H_{40}ClNO_5$: C, 63.90; H, 8.58. Found: C, 63.90, 63.82; H, 8.56, 8.62.

6β-Nitro-5α-chloropregnan-3β-ol-20-one (3d) was prepared in the same manner from the nitrochloro acetate **2d**. This material was also obtained, in 65% yield, when compound **2d** (5.0 g.), ethylene glycol (5 ml.), *p*-toluenesulfonic acid (100 mg.), and benzene (110 ml.) were refluxed under a water separator for 22 hr. in an attempt to prepare the 17-ethylenedioxy derivative. The crude material melted at 184–189°. The infrared spectrum has

(28) For instance the axial 3α-H appears at τ 6.33 in cholestan-3β-ol, 5.58 in cholestan-3β,6β-diol, 5.27 in 7-cholesten-3β-ol, and 6.60 in 5-androsten-3β-ol-17-one.

(29) All melting points are uncorrected and were determined on a Fisher-Johns melting block. Infrared spectra were determined in potassium bromide pellets on a Perkin-Elmer 21 infrared spectrometer and nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer on dilute solutions (*ca.* 10% by weight) in carbon tetrachloride or deuteriochloroform with tetramethylsilane as an internal standard. Chemical shifts were taken as the geometrical center of the band concerned and are expressed on the τ scale. Microanalyses were performed by A. Bernhardt, Muelheim, Germany.

peaks at 3500 (OH), 1697 (C=O), 1542 and 1360 (NO_2), 1086, 1060, and 1040 cm.$^{-1}$ (C–O).

Anal. Calcd. for $C_{21}H_{32}ClNO_4$: C, 64.45; H, 7.87. Found: C, 64.37; H, 8.03.

Methyl 6-Nitro-3β-acetoxy-5-cholenate (4c).—A solution of 1.0 g. of the nitrochloro acetate **2c** in 10 ml. of anhydrous pyridine was kept at room temperature for 6 hr. The solvent was removed under reduced pressure at 50°, leaving a semisolid. This material was partitioned between 20 ml. of water and 20 ml. of ether. The aqueous layer was extracted with another 20 ml. of ether, and the combined ether extracts were washed with 5% sulfuric acid (20 ml.) and water (20 ml.). From the dried ethereal solution there was obtained white prisms, m.p. 151–153°, in 67% yield. Recrystallization from methanol raised the melting point to 154–155°; ν_{max} 1745 (C=O), 1520 and 1360 (NO_2), 1235 and 1160 (ester bands), and 1036 cm.$^{-1}$ (C–O).

Anal. Calcd. for $C_{27}H_{41}NO_6$: C, 68.18; H, 8.69; N, 2.95. Found: C, 68.05; H, 8.66; N, 2.92.

6-Nitrocholesteryl acetate (4a) [m.p. 103–105°, lit.[30] m.p. 104°; ν_{max} 1518 cm.$^{-1}$, lit.[30] 1518 cm.$^{-1}$; λ_{max} 262 mμ (ε 1920), lit.[30] 258 mμ (ε 1940)] was obtained from **2a** in the same manner.

6-Nitro-5-androsten-3β-ol-17-one acetate (4b) was prepared as described for **4c**. The product recrystallized from ethanol melted at 221–223°, lit.[8] m.p. 215–216°; ν_{max} 1743 (C=O), 1527, 1518, and 1362 (NO_2), 1240 (ester), and 1028 cm.$^{-1}$ (C–O).

6-Nitro-5-pregnen-3β-ol-20-one Formate (4d).—From 5.0 g. of compound **2d** in 40 ml. of anhydrous pyridine there was obtained 4.39 g. (96%) of **4d**, m.p. 213–214°. Crystallization from methanol furnished an analytical sample, m.p. 216–218°; ν_{max} 1730 (C-17, =O), 1698 (formate C=O), 1515 and 1353 (NO_2), and 1168 cm.$^{-1}$ (ester band).

Anal. Calcd. for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.97; H, 7.97; N, 3.55.

6-Oximino-5α-methoxycholestan-3β-ol 3-Acetate (5).—Sodium dichromate dihydrate (5.96 g.) was dissolved in 100 ml. of 6 *N* hydrochloric acid. Zinc dust (10 g.) was added and allowed to react under a blanket of nitrogen. This chromous chloride solution was added in one portion to a refluxing solution of 2.0 g. of compound **2a** in 100 ml. of methanol. The reaction mixture turned green immediately, and a white solid separated. After refluxing under nitrogen for 5 min., the slurry was cooled and then filtered. The air-dried product weighed 1.80 g. and melted at 185–197°. Upon crystallization from methanol–water, there was obtained 875 mg. of the oxime, m.p. 222–224°. Two additional crystallizations, from methanol–water and acetone–water, raised the melting point to 231–234°; ν_{max} 3450 (OH), 1720 (C=O), 1655 (C=N), 1270 (ester band), and 1060 cm.$^{-1}$ (C–O). The n.m.r. spectrum, in CCl_4, had peaks at τ 1.12 (OH), 5.17 (C-3 H, $W^{1/2}$ = 24 c.p.s., axial), 6.90 (OCH_3), 8.01 (acetate CH_3), 9.13 (C-19, singlet), 9.13 (C-26 and C-27, doublet, J = 6.5 c.p.s.), and 9.36 (C-18, singlet).

Anal. Calcd. for $C_{30}H_{51}NO_4$: C, 73.57; H, 10.50. Found: C, 73.70; H, 10.33.

Oxime **5** (170 mg.) was converted to its acetate by treatment with acetic anhydride and pyridine at room temperature for 18 hr. Work-up from ether and crystallization from methanol–water gave 80 mg. of 6-oximino-5α-methoxycholestan-3β-ol diacetate, m.p. 130.5–132°; ν_{max} 1785 (C=O of acetoxime), 1735 (C=O of 3-acetate), 1640 (C=N), 1260 and 1235 cm.$^{-1}$ (ester bands).

Sodium Borohydride Reduction of Nitro Steroids. General Procedure.—To a solution of nitro olefin **4** or of nitrochloro steroid **2** or **3** in absolute ethanol there was added sodium borohydride (*ca.* one-fifth the weight of the nitro compound). The solution was kept at room temperature for *ca.* 24 hr. and then was poured into water. The resulting suspension was extracted with ether. The oil, obtained from the washed ether extracts on evaporation, was chromatographed on Woelm neutral alumina activity grade I.

6α-Nitrocholestan-3β-ol Acetate (6a).—From 4.0 g. of 6β-nitro-5α-chlorocholestan-3β-ol acetate (**2a**) was obtained 3.57 g. of an oil which on chromatography gave 1.84 g. of **6a** eluted with 50:1 hexane–ether to pure ether. Crystallization from methanol gave 1.6 g. of product, m.p. 132–134°. The analytical sample melted at 134–136°; ν_{max} 1750 (C=O), 1553, and 1372 (NO_2), 1243 (ester), 1028 cm.$^{-1}$ (C–O).

The n.m.r. spectrum (in CCl_4) shows bands at τ 5.5 (C-6 H, $W^{1/2}$ 22 c.p.s., axial), 5.75 (C-3 H, $W^{1/2}$ 20 c.p.s., axial), 8.10 (acetate methyl singlet), 9.10 (C-19, singlet), 9.14 (C-26 and C-27, doublet, J = 6 c.p.s.), and 9.35 (C-18, singlet).

Anal. Calcd. for $C_{29}H_{49}NO_4$: C, 73.22; H, 10.38. Found: C, 72.82; H, 10.43.

6α-Nitrocholestan-3β-ol (7a).—From 3.0 g. of nitro olefin **4a** and 450 mg. of sodium borohydride there was obtained 2.33 of alcohol **7a** eluted with 19:1 ether–methanol, crystallizing as white needles, m.p. 76–82°. The analytical sample, prepared by two recrystallizations from methanol, melted at 76–82°; ν_{max} 3430 (O–H), 1545 and 1370 (NO_2), 1057, and 962 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{47}NO_3$: C, 74.78; H, 10.92; N, 3.23. Found: C, 74.94; H, 10.76; N, 3.14.

The n.m.r. spectrum in CCl_4 has bands at τ 5.70 (C-6 H, $W^{1/2}$ 22 c.p.s., axial), 6.53 (C-3 H, $W^{1/2}$ 25 c.p.s., axial), 9.12 (C-19, singlet), 9.14 (C-26 and C-27, doublet, J = 6.5 c.p.s.), and 9.34 (C-18, singlet). The infrared spectrum of this material was identical with that of a sample obtained on mild basic hydrolysis of 6α-nitro-3β-cholestanyl acetate (**6a**).

6α-Nitroandrostane-3β,17β-diol (7b) was obtained in 64% yield, melting at 115–125°, by reduction of 6-nitro-5-androsten-3β-ol-17-one acetate (**4b**). Recrystallizations from methanol–water, acetone–hexane, and benzene gave long white needles, m.p. 105–113°; ν_{max} 3300 (OH), 1540 and 1370 (NO_2), 1060, 960, and 935 cm.$^{-1}$.

The n.m.r. spectrum in CCl_4 or $CHCl_3$ shows absorption bands at τ 2.68 (benzene of solvation, six protons by integration), 5.56 (C-6 H, $W^{1/2}$ 25 c.p.s., axial), 6.41 (C-3 H and C-17 H, $W^{1/2}$ 25 c.p.s., axial), 9.11 (C-19), and 9.27 (C-18).

Anal. Calcd. for $C_{19}H_{31}NO_4 \cdot C_6H_6$: C, 72.25; H, 8.98; N, 3.37. Found: C, 71.88; H, 8.97; N, 3.66.

Ethyl 3β-Acetoxy-6α-nitro-5α-cholanate (7c).—Sodium borohydride reduction of methyl 3β-acetoxy-6-nitro-5-cholenate (**4c**, 975 mg.) gave 915 mg. of clear oil which was chromatographed on 20 g. of alumina. Fractions 3 and 4 (9:1 benzene–ether to 4:1 benzene–ether) gave 99 mg. (10%) of ethyl 3β-acetoxy-6α-nitro-5α-cholanate (**7c**), m.p. 114–117°. Fractions 8 and 9 (49:1 ether–methanol) gave 592 mg. (66%) of oily ethyl 3β-hydroxy-6α-nitro-5α-cholanate (**6c**) which could not be induced to crystallize. Its infrared spectrum had bands at 3400 (OH), 1730 (C=O), 1548 and 1370 (NO_2), 1240, 1030, and 965 cm.$^{-1}$.

The crude alcohol **6c** was acetylated by heating on a steam bath for 20 min. with acetic anhydride and pyridine. The product weighed 585 mg. (60%) and melted at 107–109°. Recrystallization from methanol–water gave pure **7c**, m.p. 116–117°; ν_{max} 1740 and 1728 (C=O), 1543 and 1370 (NO_2), 1240, 1023, and 960 cm.$^{-1}$. The n.m.r. spectrum has bands at τ 5.4 (C-3 H and C-6 H, $W^{1/2}$ 35 c.p.s., axial), 5.81 (CH_2 of ethyl group, quartet, J = 7 c.p.s.), 7.96 (acetate methyl), 8.73 (CH_3 of ethyl group, triplet, J = 7 c.p.s.), 9.08 (C-19), and 9.31 (C-19).

Anal. Calcd. for $C_{27}H_{43}NO_6$: C, 68.40; H, 9.23. Found: C, 68.89; H, 9.40.

6α-Nitro-5α-pregnane-3β,20-diol (7d).—Reduction of 2.75 g. of nitro olefin **4d** gave a mixture of epimeric diols weighing 2.37 g. (96%) that melted at 198–215°. Recrystallization of 510 mg. of this crude material from methanol–water gave one of the epimers, 318 mg., m.p. 247–248.5°. The analytical sample melted at 246–247.5°; ν_{max} 3300 (OH), 1545 and 1373 (NO_2), 1051, 1032, and 968 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 68.92; H, 9.73; N, 3.93.

6α-Nitro-5α-pregnane-3β,20-diol Diacetate (6d).—Crude diol **7d** (1.3 g., m.p. 198–215°) was acetylated with acetic anhydride in pyridine at room temperature to yield 515 mg. of material which crystallized from methanol, m.p. 168–175°. Two recrystallizations from acetone–hexane provided an analytical sample of **6d**, m.p. 177–179°; ν_{max} 1735 (C=O of acetate), 1548 and 1371 (NO_2), 1240, 1075, 1026, 970, and 768 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.75; N, 3.12. Found: C, 66.92; H, 8.93; N, 3.30.

On acid-catalyzed hydrolysis, in 2.4 *N* methanolic hydrochloric acid at reflux for 30 min. diacetate **13**, m.p. 177–179°, gave in 90% yield the diol **7d**, m.p. 240–247°, identified by its infrared spectrum.

6α-Nitrocholestan-3-one (8a).—A solution of 817 mg. of the nitro alcohol **7a** and 300 mg. of sodium dichromate dihydrate in 20 ml. of glacial acetic acid was heated briefly to 60° and then allowed to stand at room temperature for 18 hr. Water was added and after 24 hr. a white solid was obtained by filtration.

(30) G. E. Anagnostopoulos and L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 532 (1954).

It weighed 790 mg. (97%) and melted at 121–126°. Crystallization from ethanol raised the melting point to 138–140°; ν_{max} 1725 (C=O), 1550 and 1370 (NO_2), 1410, and 960 cm.$^{-1}$. The n.m.r. spectrum in CCl_4 shows bands at τ 5.65 (C-6 H, $W^{1/2}$ 25 c.p.s., axial), 8.94 (C-19, singlet), 9.14 (C-26 and C-27, doublet, J = 6.5 c.p.s.), and 9.32 (C-18, singlet).

Anal. Calcd. for $C_{27}H_{45}NO_3$: C, 75.13; H, 10.51; N, 3.25. Found: C, 75.33; H, 10.49; N, 3.42.

Nitro ketone **8a** was also obtained by oxidation of nitro alcohol **7** with 8 *N* chromic acid in acetone (Jones reagent); it gave a yellow 2,4-dinitrophenylhydrazone, m.p. 184–186° after recrystallization from methanol–acetone.

6α-Nitroandrostane-3β,17β-diol Diacetate (6b).—Acetylation of 140 mg. of diol **8** in 4 ml. of acetic anhydride and 1 ml. of pyridine at room temperature for 12 hr. gave 120 mg. (68%) of diacetate **6b**, m.p. 183–186°. Two crystallizations from methanol–water furnished the analytical sample, m.p. 187–189°; ν_{max} 1730 (acetate C=O), 1545 and 1370 (NO_2), 1238, 1025, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{35}NO_6$: C, 65.53; H, 8.37; N, 3.32. Found: C, 65.43; H, 8.38; N, 3.51.

6α-Nitroandrostane-3,17-dione (8b).—A solution of 200 mg. of the nitrodiol **7b** in 5 ml. of glacial acetic acid was treated with 200 mg. of chromium trioxide in 5 ml. of 80% aqueous acetic acid. After 12 hr. at room temperature the solution was poured into ice water, made basic with sodium hydroxide, and then just neutralized with 10% hydrochloric acid. The crude dione which precipitated weighed 80 mg. and melted at 235–240°. Two crystallizations from aqueous methanol furnished **8b**, m.p. 244–246°. The infrared spectrum showed peaks at 1740 (C-17, =O), 1712 (C-3, =O), 1560, 1537, 1376, and 778 cm.$^{-1}$ (NO_2).

Anal. Calcd. for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.32; H, 8.29; N, 4.41.

The Preparation of Thiones in the Presence of Anhydrous Hydrogen Fluoride

R. M. ELOFSON, LESLIE A. BAKER, F. F. GADALLAH, AND R. A. SIKSTROM

Contribution No. 244 from the Research Council of Alberta, Edmonton, Alberta, Canada

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A rapid and facile preparation of aromatic and aliphatic thials and thiones or their polymeric forms is outlined. The method consists of the reaction of the corresponding aldehyde or ketone with hydrogen sulfide in the presence of anhydrous hydrogen fluoride. The scope and limitations of the reaction are described. The results are formulated on the basis of an optimum acid-catalyst concentration in accordance with that demonstrated for many other aldehyde and ketone reactions.

In the course of an electrochemical study on aromatic thiones in this laboratory it became necessary to prepare a number of thiones with a wide range of appended substituents. Thiones have previously been prepared in a number of ways depending on the availability and reactivity of the starting materials. *p,p'*-Dimethoxythiobenzophenone can be prepared from thiophosgene and anisole by the Friedel–Crafts reaction.[1] Michler's thione, $[(CH_3)_2NC_6H_4]_2C{=}S$, has been best prepared by treating auramine with hydrogen sulfide.[2] However, it can also be made by the reaction of Michler's ketone with P_2S_5.[3] *p*-Dimethylaminothiobenzophenone has been made by the action of hydrogen sulfide on the corresponding anil.[4] In a few cases sulfur changes a methylene group to a thiocarbonyl[5] as in the preparation of Michler's thione from *p,p'*-dimethylaminodiphenylmethane.

The most widely used method of preparation of thials and thiones depends upon the conversion of an aldehyde or ketone to the corresponding thio compound by hydrogen sulfide in the presence of alcoholic hydrogen chloride.[6] By this method all aliphatic ketones and all aldehydes can be converted to the corresponding thio derivatives which can only be isolated in the form of their dimeric, trimeric, or polymeric derivatives. Aromatic ketones are less reactive but this method has been successfully used to prepare thiobenzophenone, α-naphthylphenylthione, *p*-phenylthiobenzophenone, *p*-methylbenzothione,[7] and thiofluorenone.[8]

$$Ar_2CO + H_2S \underset{\longleftarrow}{\xrightarrow{C_2H_5OH,\ HCl}} Ar_2C{=}S + H_2O \qquad (1)$$

According to eq. 1 the reaction is reversible and considerable difficulty is encountered in preparing pure materials. In an attempt in this laboratory to force Michler's ketone to react directly with hydrogen sulfide, the ketone was dissolved in liquid anhydrous hydrogen fluoride and the cooled solution was treated with hydrogen sulfide. This resulted in an almost quantitative yield on Michler's thione. The scope and limitations of this reaction is the subject of this paper.

The original selection of liquid anhydrous hydrogen fluoride as a medium for the reaction was based on a number of considerations. This material is a good dehydrating agent, an acidic catalyst, and a good solvent for ketones, all of which would be favorable for thione formation. Unlike some other possible materials, such as sulfuric acid, hydrogen fluoride is neither an oxidizing nor a reducing reagent.

Experimental results with formaldehyde, benzaldehyde, acetone, Michler's ketone, and 3,3'-dinitrobenzophenone fully confirmed expectations. When hydrogen sulfide was passed into chilled solutions of the aldehydes or ketones in anhydrous hydrogen fluoride, quantitative yields of the trimeric thials and of the thiones were obtained.

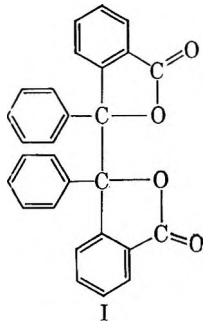
When the reaction was attempted on benzophenone, much less satisfactory results were obtained. Initially, upon passing hydrogen sulfide into a solution of benzophenone in anhydrous hydrogen fluoride, very little thione was produced. However, if the temperature was allowed to rise and most of the hydrogen fluoride was allowed to evaporate, a blue solution was obtained which was shown by spectrophotometric analysis to contain about 60% thione and 40% ketone. Similar results were obtained with *p*-methylbenzophenone, but with α-naphthylphenyl ketone only about 10% conver-

(1) L. Gattermann, *Ber.*, **28**, 2869 (1895).
(2) T. S. Fehrmann, *ibid.*, **20**, 2844 (1887); D. S. Tarbell and V. P. Wystrock, *J. Am. Chem. Soc.*, **68**, 2110 (1946).
(3) Badische Anil-u Sodafabuk, German Patent 3,8074 (1886).
(4) C. Reddelien and H. Danilof, *Ber.*, **54**, 3142 (1921).
(5) R. Mohlen, M. Heinze, and R. Zimmermann, *ibid.*, **35**, 375 (1902).
(6) H. Staudinger and H. Freudenberger, *ibid.*, **61**, 1576 (1928); *Org. Syn.*, **11**, 94 (1931).
(7) R. W. Bost and B. O. Cosby, *J. Am. Chem. Soc.*, **57**, 1404 (1935).
(8) E. Campaigne and W. B. Reid, Jr., *ibid.*, **68**, 769 (1946).

sion could be demonstrated. In order to get satisfactory yields of pure products from benzophenone and related compounds, it was found necessary to add an alcohol to the reaction mixture. By judicious selection of a suitable ratio of alcohol to hydrogen fluoride, a solution of the ketone could be obtained from which the thione could be precipitated in quite pure form by addition of hydrogen sulfide. Optimum results with benzophenone were obtained with a mixture of 40% hydrogen fluoride and 60% methanol, whereas *n*-butyl alcohol in the same proportions produced the best results with α-naphthylphenyl ketone. Detailed directions for reaction of a number of typical carbonyl compounds are given in the Experimental section.

In general, the reaction of carbonyl compounds with hydrogen sulfide in the presence of hydrogen fluoride is much faster than the reaction in ethanolic hydrogen chloride. Only one compound that has been investigated, xanthone, failed to react under at least one of the experimental conditions described, but the products obtained with various other compounds show the limitations of the reaction. Fluorenone reacts rapidly in anhydrous hydrogen fluoride to produce quantitative yields of the dimeric form of thiofluorenone. Little if any of the monomer is produced unless methanol and short reaction times are used. Since the monomer can be isolated quite readily from the reaction in ethanol and hydrogen chloride, the new method is plainly inferior if it is desired to inhibit dimerization.[9]

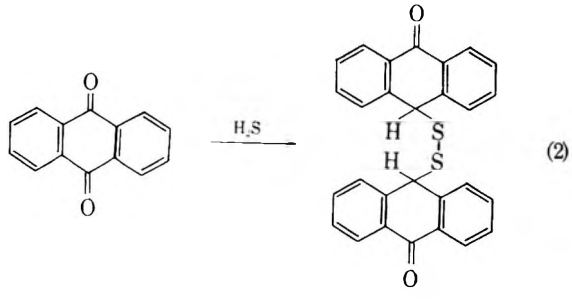
While *p*-carboxybenzophenone was converted without difficulty to the corresponding thione, *o*-carboxybenzophenone was converted in significant yield to the dimeric dilactone I.



I

While no evidence of reduction of nitro groups in nitrobenzophenones by hydrogen sulfide was observed in anhydrous hydrogen fluoride, addition of boron trifluoride to the reaction medium resulted in the production of amines which were not investigated further.

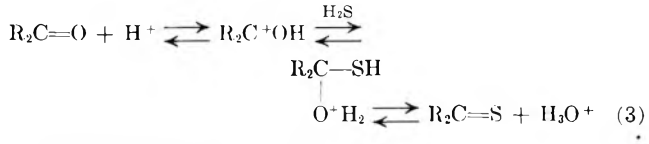
Anthraquinone dissolved in anhydrous hydrogen fluoride reacted rapidly with hydrogen sulfide to produce a yellow material which is believed to be the dianthrone disulfide according to eq. 2. This material has an average sulfur content of about 12% corresponding to a disulfide. All fractions have a carbonyl absorption at 1662 (KBr); anthrone, 1660; and anthraquinone, 1690 cm.$^{-1}$. It dissolves in strong alkali to produce a red solution which is readily oxidized by hydrogen peroxide to anthraquinone and sulfate and by air to anthraquinone and sulfide. Molecular weight measurements in sulfolane[10] gave values up to 450 indicative of dimerization. No reaction between anthraquinone and hydrogen sulfide was observed in ethanolic hydrogen chloride.



(2)

Discussion

The reaction of hydrogen sulfide with ketones in the presence of hydrogen fluoride involves the nucleophilic attack of hydrogen sulfide on the protonated ketone[11] according to eq. 3.



(3)

In the case of aldehydes, aliphatic ketones, Michler's ketone, and 3,3′-dinitrobenzophenone, the reaction goes smoothly indicating that anhydrous hydrogen fluoride is able to protonate ketones such as the latter two which do not react with hydrogen sulfide in alcohol and hydrochloric acid. However, the failure of simple aromatic ketones to react satisfactorily with the reagent without the addition of diluents and of xanthone to react at all, required comment.

According to eq. 3, if the positive charge is delocalized or centered elsewhere in the molecule, reaction would be inhibited. The failure of xanthone to react under all conditions tried is attributed to the predominance of a salt in which the positive charge is centered at the rings instead of at the ketonic carbon.[12]

In the case of benzophenone, another factor may be operating. Benzophenone protonates readily under all conditions described here, but presumably the delocation of charge depletes the positive charge on the carbonyl so that not enough charge persists on this carbon to react with hydrogen sulfide present. Since the hydrogen sulfide would also be largely protonated in anhydrous hydrogen fluoride, addition of methanol should favor the formation of thione by releasing more hydrogen sulfide from its protonated form and thus encourage nucleophilic attack on the protonated carbonyl. The negative substituents in 3,3′-dinitrobenzophenone and Michler's ketone preserve enough charge on the carbonyl carbon of these compounds to react without addition of methanol.

These postulates were checked by the addition of sodium fluoride and boron trifluoride to the reaction medium containing benzophenone and anhydrous hydrogen fluoride. Sodium fluoride, which lowers the acidity of hydrogen fluoride,[13] caused a rapid development of a blue color indicative of thione formation in

(9) See also J. H. Wood and R. W. Bost, *J. Am. Chem. Soc.* **59**, 1011 (1937).

(10) J. C. Wood, S. E. Moschopedis, and R. M. Elofson, *Fuel*, **40**, 193 (1961).

(11) Y. Nomura and Y. Takeorich, *J. Chem. Soc. Japan*, 1743 (1960); E. Campaigne, "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, p. 141.

(12) D. Cook, *Can. J. Chem.*, **39**, 1184 (1961).

(13) E. L. Macken, A. Hofstrau, and J. H. van der Waals, *Trans. Faraday Soc.*, **54**, 66 (1958).

the presence of hydrogen sulfide. Boron trifluoride, in contrast, known to increase the acidity of anhydrous hydrogen fluoride,[13] inhibited development of a blue color until evaporation of most of the hydrogen fluoride. This concept of an optimum acidity for thione formations accords with the findings of Jenek[14] for reaction of ketones with nitrogen bases. The optima were shown to be due to opposing effects of general acid catalysis and decrease in concentration of the attacking free nitrogen base due to conversion to the conjugate acid at low pH. Because of the greater acidity of hydrogen sulfide, the optimum acidity for thione formation is much greater than for semicarbazone formation.

Experimental

Anhydrous hydrogen fluoride was obtained in cylinders from the Mathieson Co., East Rutherford, N. J., and was used without purification. Hydrogen sulfide was obtained in cylinders from the same source and also was used directly.

Small scale runs of less than 5 g. may be carried out in polyethylene graduates, whereas larger runs are best carried out in polyethylene erlenmeyer flasks. Hydrogen fluoride–methanol mixtures containing crystals can be filtered directly through Whatman No. 1 filter paper using polyethylene Büchner funnels. Anhydrous hydrogen fluoride can be best handled by evaporation of most of the acid before pouring into a solution of bicarbonate. The use of rubber gloves, safety glasses, and shields is mandatory.

More sensitive thiones such as benzothione should be protected from light and air by standard methods. Solvent extracts should be dried as quickly as possible to prevent hydrolysis. Some thiones can be usefully purified by chromatography over Florisil[15] (Floridin Co., Talahassee, Fla.). Some procedures are described briefly below.

Michler's Thione.—Michler's ketone (2 g.) was dissolved in 30 ml. of anhydrous hydrogen fluoride cooled in Dry Ice and acetone to about −10 to −20°. Hydrogen sulfide was passed into the solution for 2 hr. while the temperature was allowed to become ambient. The solution was poured with care into 5% sodium bicarbonate; the thione was taken up in chloroform, washed with sodium bicarbonate, and dried over sodium sulfate. The thione was recrystallized either from a small volume of chloroform or from a mixture of chloroform and hexane. The yield of nearly pure material was quantitative. The recrystallized material had m.p. 208–209°, lit.[16] m.p. 202–204° for Michler's thione.

3,3′-Dinitrobenzothione.—*p,p′*-Dinitrobenzophenone (5 g.) was dissolved in 40 ml. of anhydrous hydrogen fluoride cooled to −30°. Hydrogen sulfide was passed into the solution for 2 hr. while the temperature was allowed to become ambient. A 4-g. sample of crystals was obtained, m.p. 131.5–132.5°.

Anal. Calcd. for $C_{13}H_8N_2O_4S$: S, 11.11. Found: S, 10.85.

Trithiobenzaldehyde.—Benzaldehyde (5 g.) was dissolved in 30 ml. of anhydrous hydrogen fluoride cooled to −40°. Hydrogen sulfide was passed through the solution until the temperature became ambient and most of the hydrogen fluoride evaporated. The resulting solution was poured into sodium bicarbonate solution and extracted with hexane. The extract was dried over potassium hydroxide pellets and evaporated to produce a quantitative yield of the B form of trithiobenzaldehyde, m.p. 225–227°, lit.[17] m.p. 226°.

Trithiane.—Paraformaldehyde (5 g.) was dissolved in 30 ml. of anhydrous hydrogen fluoride cooled to −40°. Hydrogen sulfide was passed into the solution and the temperature was allowed to rise to room temperature. After most of the hydrogen fluoride had evaporated, the residue was poured into sodium bicarbonate solution and filtered, yielding 6.5 g. of trithiane, m.p. 212–215°, lit.[18] m.p. 216°, without further crystallization.

Dianthrone Disulfide.—Anthraquinone (5 g.) was dissolved in 30 ml. of anhydrous hydrogen fluoride cooled to −20°. Hydrogen sulfide was passed into the solution overnight while the temperature was allowed to become ambient. The residue was poured into sodium bicarbonate solution and extracted with chloroform. The chloroform extract was washed with sodium bicarbonate solution and dried over sodium sulfate. Upon evaporation of the chloroform, a yellow to orange solid was produced, m.p. 151–155° (indefinite). The material, crystallized from benzene–hexane mixtures, produced a variety of fractions, some with m.p. 174–175°. The crude material had a sulfur content of about 10–12%. Work is continuing on characterization of this material.

Benzothione.—Two grams of benzophenone was dissolved in 20 ml. of anhydrous hydrogen fluoride. A 30-ml. sample of absolute methanol was added to the solution, cooled to −20°, while hydrogen sulfide was passed into the reaction medium. Brilliant blue crystals were formed which, after 1.5 hr. of reaction, were filtered cold, washed with cold methanol, and sealed *in vacuo* in a glass tube, yielding 1.5 g. The nearly pure crystals had m.p. 50–52° and were shown to be free of benzophenone by lack of carbonyl absorption in the infrared. Somewhat higher yields can be obtained by using more concentrated solutions of benzophenone but coprecipitation of benzophenone results in a somewhat impure product.

***p,p′*-Dimethoxybenzothione.**—Five grams of dimethoxybenzophenone was dissolved in 20 ml. of anhydrous hydrogen fluoride and 20 ml. of methanol. The solution was cooled to −30°, and hydrogen sulfide was passed in overnight. The excess hydrogen fluoride was removed at the water pump. The residue was extracted with hexane, washed with sodium bicarbonate, and dried over sodium sulfate. The hexane was removed and the material, recrystallized from absolute ethanol, yielded 4.7 g., m.p. 116–118°, lit.[7] m.p. 115° for dimethoxybenzothione.

α-Naphthylphenylthione.—α-Naphthylphenyl ketone (2.6 g.) was dissolved in 15 ml. of anhydrous hydrogen fluoride at −20°. To this solution was added 25 ml. of *n*-butyl alcohol. Hydrogen sulfide was passed into the solution for 1 hr. and the temperature was allowed to rise slowly. A 2.0-g. sample of blue crystals was filtered off, m.p. 112°, lit.[7] m.p. 110° for α-naphthylphenylthione.

***p*-Dimethylaminobenzothione.**—*p*-Dimethylaminobenzophenone (10 g.) was dissolved in 100 ml. of anhydrous hydrogen fluoride and 100 ml. of absolute methanol. Hydrogen sulfide was passed into the solution for 4 hr. while the temperature was allowed to become ambient. The reaction mixture was poured into sodium bicarbonate solution, extracted with chloroform, and dried over sodium sulfate. Addition of carbon tetrachloride yielded 9.5 g. of dark red, nearly black crystals, m.p. 86°, lit.[4] m.p. 86° for *p*-dimethylaminobenzothione.

3,3′-Diphenyl-3,3′-diphthalidyl.—*o*-Carboxybenzophenone (2 g.) was dissolved in 35 ml. of anhydrous hydrogen fluoride and 18 ml. of methanol. Hydrogen sulfide was passed through the reaction mixture while 30 ml. of additional methanol was added over a period of 2 hr. White crystals formed which were removed by filtration from the slightly blue solution. These crystals weighed 0.5 g. and had a m.p. of 243–247°. The material was recrystallized from benzene, m.p. 258–260°, lit.[19] m.p. 265° for 3,3′-diphenyl-3,3′-diphthalidyl; C=O stretch in carbon tetrachloride, 1782 cm.$^{-1}$.

Acknowledgment.—The authors are indebted to Dr. H. W. Habgood of this laboratory for many helpful discussions in preparation of the manuscript and to Dr. J. C. Wood for the molecular weight determinations.

(14) W. P. Jenek, *J. Am. Chem. Soc.*, **81**, 475 (1959).

(15) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *ibid.*, **79**, 712 (1957).

(16) D. S. Tarbell and V. P. Wystrack, *ibid.*, **68**, 2110 (1946).

(17) A. H. Ford-Moore, R. A. Peters, and R. W. Wakelin, *J. Chem. Soc.*, 1754 (1949).

(18) H. Brintzinger, H. Koddebusch, K. E. Kling, and G. Jung, *Ber.*, **85**, 455 (1952).

(19) F. Ullmann, *Ann.*, **291**, 17 (1896).

Preparation and Rearrangement Reactions of 2-Methylsulfinylindanedione-1,3. The Mechanism of the New Ninhydrin Synthesis•

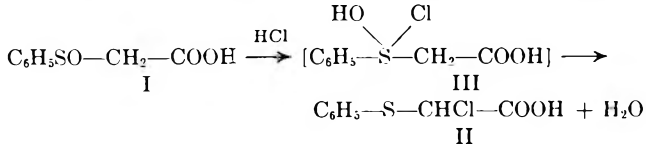
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General Electric Research Laboratory, Schenectady, New York

Received December 6, 1963

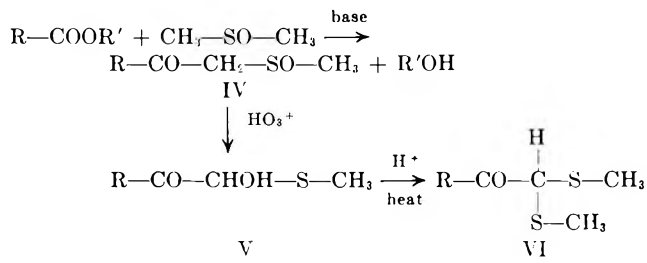
Diethyl phthalate condenses with methylsulfinyl carbanion to give 2-methylsulfinylindanedione-1,3. This new β-keto sulfoxide undergoes acid-catalyzed rearrangement reactions (Pummerer reactions) with various nucleophiles leading to 2-substituted 2-methylmercaptoindanediones. The rearrangement of 2-methylsulfinylindanedione-1,3 into 2-hydroxy-2-methylmercaptoindanedione-1,3 has been followed by ultraviolet spectroscopy. The exhibition of two isosbestic points in the course of the reaction suggests that we are dealing with a true rearrangement rather than with a cleavage and recombination process. A mechanism of probable generality for acid-catalyzed reactions of β-keto sulfoxides is proposed.

The Pummerer Reaction.—Pummerer found that phenylsulfinylacetic acid (I) is cleaved by warm dilute mineral acids to form thiophenol and glyoxylic acid.[1] Combination of the cleavage products can lead to the phenylthioacetal of glyoxylic acid.[2] Treatment of phenylsulfinylacetic acid with gaseous hydrogen chloride yields α-chlorophenylmercaptoacetic acid (II).[1] For its formation, Pummerer assumed an *intramolecular* rearrangement *via* the hypothetical intermediate III.

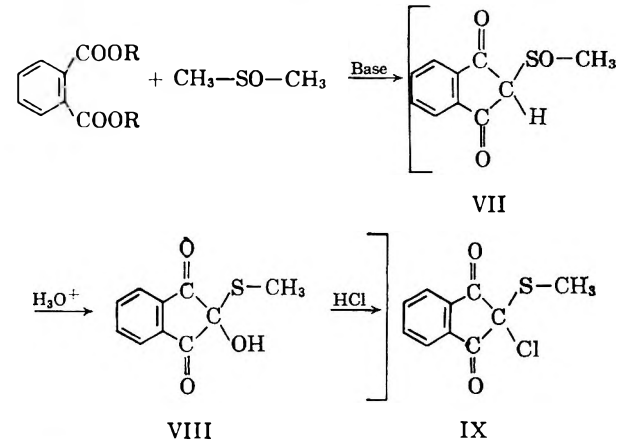


Upon treatment with acetic anhydride, phenylsulfinylacetic acid yields α-acetoxythioglycolic acid.[2] This reaction was later studied by Horner and Kaiser and found to be a general reaction between sulfoxides and acid anhydrides.[3] The mechanism of this reaction has recently been substantiated by means of a tracer study.[4]

Interest in the Pummerer reaction was renewed when β-keto sulfoxides became easily available by base-catalyzed condensation of dimethyl sulfoxide with esters and the observation was made that ω-methylsulfinylacetophenone rearranged smoothly into the hemithioacetal of phenylglyoxal (V) at room temperature in the presence of acid.[5] No chemical evidence was found that at any time during the reaction the cleavage products, methanethiol and phenylglyoxal, were present. Furthermore, it was found that the methylthioacetal of phenylglyoxal (VI) only resulted from decomposition of the hemithioacetal under drastic conditions. A recently proposed cleavage–recombination mechanism[6] for the Pummerer reaction thus appears rather unlikely.



The base-catalyzed condensation of dimethyl sulfoxide with diethyl phthalate, followed by acidification of the reaction mixture with hydrochloric acid, yields 2-chloro-2-methylmercaptoindanedione-1,3 (IX), which upon hydrolysis gives ninhydrin.[7a] The reaction sequence proposed involved a step in which the OH group in the "normal" rearrangement product VIII would be substituted by treatment with hydrochloric acid to yield IX. This appeared at the time reasonable since the conversion of α-hydroxy thioethers into α-chloro thioethers is well known.[8] Attempts to isolate the intermediates VII and VIII had previously been unsuccessful because no information about the chemistry of 2-methylsulfinylindanedione-1,3 (VII) was available. We now wish to report the synthesis of both VII and VIII.



Results[9]

We have finally succeeded in preparing 2-methylsulfinylindanedione-1,3 (VII) by base-catalyzed condensation of dimethyl sulfoxide with diethyl phthalate.[10] In its crystalline state (m.p. 111°) it is stable.

(1) R. Pummerer, *Ber.*, **42**, 2282 (1909).

(2) R. Pummerer, *ibid.*, **43**, 1401 (1910).

(3) L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959).

(4) S. Oae, T. Kitao, S. Kawamura, and Y. Kitaoka, *Tetrahedron*, **19**, 817 (1963).

(5) H.-D. Becker, G. J. Mikol, and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3410 (1963).

(6) W. J. Kenney, J. A. Walsh, and D. A. Davenport, *ibid.*, **83**, 4019 (1961).

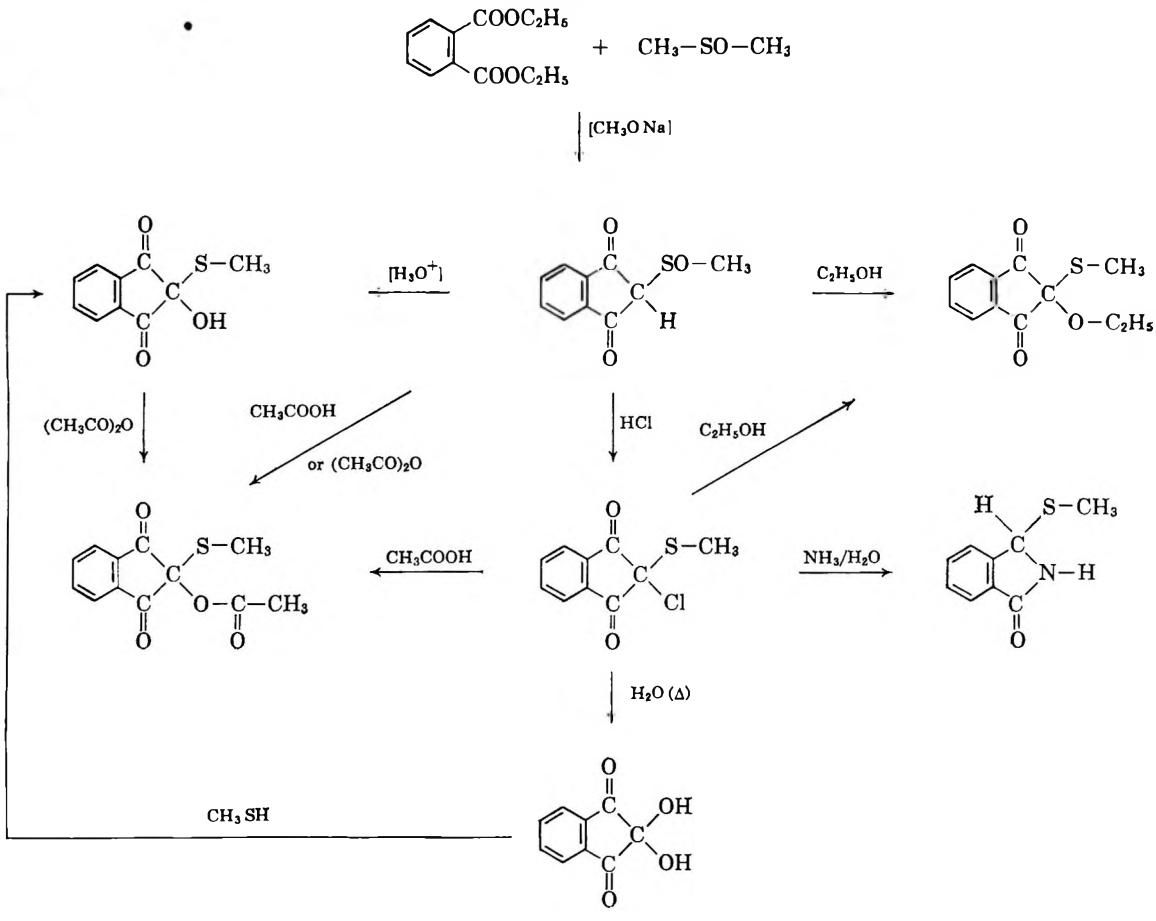
(7) (a) H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963); (b) H.-D. Becker and G. A. Russell, *ibid.*, **28**, 1896, 1897 (1963).

(8) See, *e.g.*, A. Schöberl and A. Wagner, "Methoden der Organischen Chemie," Vol. 9, E. Müller, Ed., Houben-Weyl, 1955, p. 204.

(9) See Scheme I.

(10) Base-catalyzed reaction of diethyl phthalate with dimethyl sulfone in dimethyl sulfoxide solution yields the recently described[7b] stable 2-methylsulfonylindanedione-1,3 in 50% yield if sodium methoxide is used as base. Application of potassium *t*-butoxide as base in dimethyl sulfoxide results in the condensation of 2 moles of dimethyl sulfone per mole of diethyl phthalate, yielding a compound, $C_{12}H_{12}O_5S_2$. Details will be published later.

SCHEME I



Its isolation, however, was complicated by the extreme facility with which VII underwent rearrangement in solution. It was found to be a most interesting representative of the group of β-keto sulfoxides since it underwent the Pummerer reaction with a variety of nucleophiles to yield α-substituted thioethers. In dilute aqueous solution, VII is completely ionized. A 10^{-2} *M* solution has a pH of 2; a 10^{-3} *M* solution, a pH of 3. A saturated aqueous solution has a pH of 1.8 which, during a 24-hr. period, changes to pH 2.5. The unidentified high melting product isolated from this reaction possessed a molecular weight suggestive of a trimer, which indicates that VII underwent intermolecular condensation reactions, perhaps with its own anion (VIIa).

We found that treatment of VII with *strong* hydrochloric acid indeed yielded 2-chloro-2-methylmercaptoindanedione-1,3. Acetic anhydride converted VII smoothly into 2-acetoxy-2-methylmercaptoindanedione-1,3. This substance, however, was also formed by treatment of VII with acetic acid. We made this observation originally when we attempted to condense VII with diphenylcarbinol in the presence of acetic acid, a reaction which has been described for 2-nitroindanedione-1,3.[11a,b] In the presence of ethanol, 2-methylsulfinylindanedione-1,3 was converted into 2-ethoxy-2-methylmercaptoindanedione-1,3. The rearrangement products were also obtained by nucleophilic substitution reactions of 2-chloro-2-methylmercaptoindanedione-1,3 with acetic acid and with ethanol, respectively.[12] The product of the reaction of VII with acetic anhydride was shown, furthermore, to be identical with the acetylation product of 2-hydroxy-2-methylmercaptoindanedione.

Treatment of 2-methylsulfinylindanedione-1,3 with *dilute* hydrochloric acid yielded 2-hydroxy-2-methylmercaptoindanedione-1,3 (VIII). We have prepared VIII also by an independent method from triketohydrindene hydrate and methanethiol. *This hemithioketal could not be converted into the 2-chloro-2-methylmercaptoindanedione-1,3 (IX) by treatment with hydrochloric acid.* This clearly indicates that IX must be a direct rearrangement product of 2-methylsulfinylindanedione-1,3 (VII).

We have studied the rearrangement of VII into VIII spectroscopically. This was possible despite the very small differences in the ultraviolet spectra of undissociated VII and VIII, but, since VII is a strong acid, we actually observed the spectrum of its anion (VIIa) in aqueous solution. Addition of 75 ml. of 10^{-2} *N* hydrochloric acid to 25 ml. of a 10^{-4} *M* solution of VII shifted the equilibrium to the side of the undissociated

(11) (a) G. Vanag, "Cyclic β-Diketones" (in Russian), G. Vanag, Ed., Riga, 1961, p. 127. The author is indebted to Dr. Oškaja, Riga, for sending a copy of this book. (b) *Cf.* also Z. Eckstein, K. Oracz, and B. Rudnicka, *Roczniki Chem.*, **37**, 249 (1963).

(12) When we extended our work to the substitution reaction of 2-chloro-2-methylmercaptoindanedione with ammonia, we found that rather drastic changes in the molecule occurred. The formation of 2-arylaminoindanedione-1,3 from 2-halo-2-methylindanedione-1,3 and amines had been described in the literature [G. Ya. Vanag and Ya. Ya. Ozol, *Zh. Obsch. Khim.*, **32**, 1436 (1962)]. Treatment of 2-chloro-2-methylmercaptoindanedione-1,3 with aqueous ammonia did not lead to the 2-amino derivative, but yielded 3-methylmercaptophthalimidine. Its structure is supported by C, H, N, S analysis and infrared and n.m.r. data. Its formation probably involves a decarboxylation reaction, since ring-opening reactions of triketohydrindene hydrate in base are known [see, *e.g.*, D. J. McCaldin, *Chem. Rev.*, **60**, 39 (1960)].

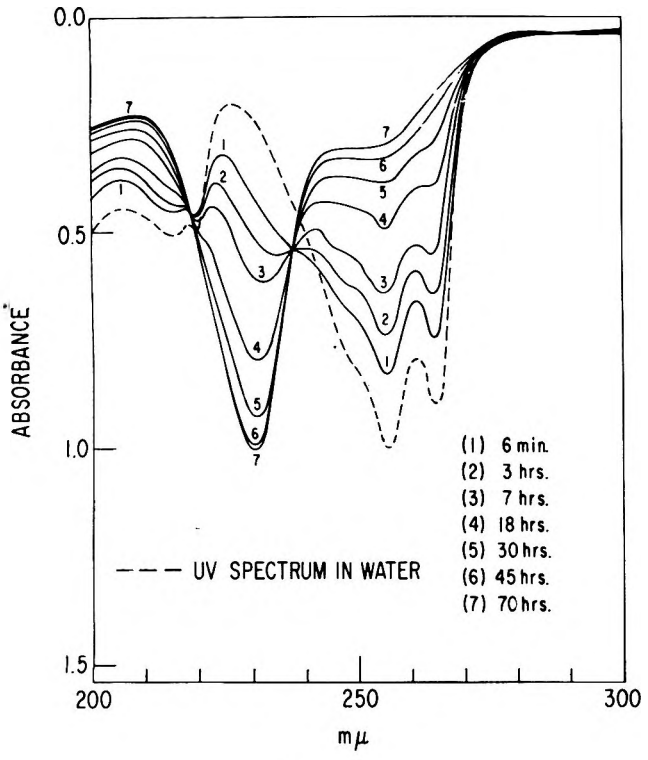


Figure 1.

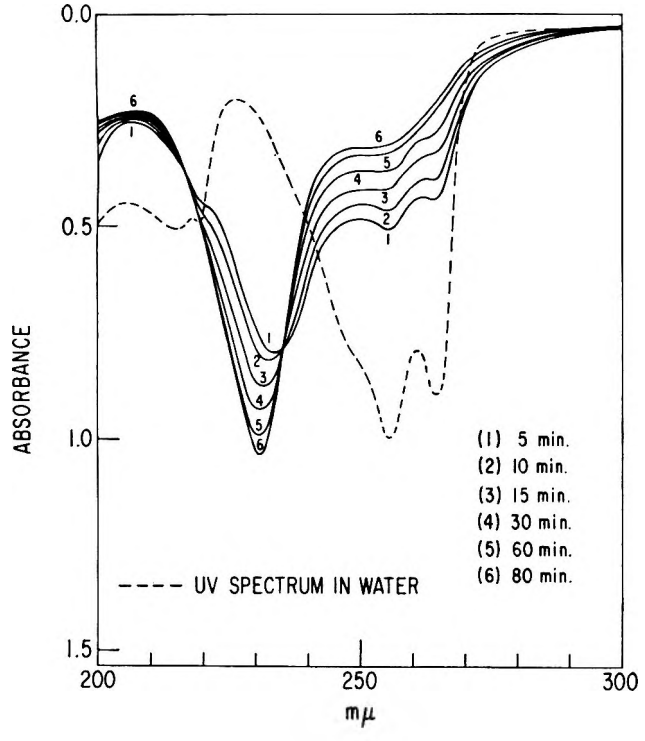
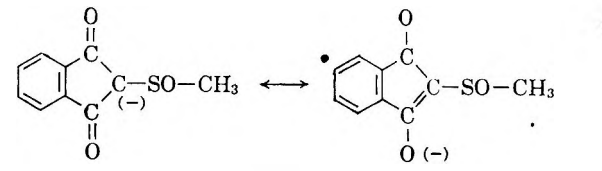


Figure 2.

indanedione derivative, as indicated by the slight change in its spectrum (Fig. 1). The absorbance of the anion at 256 and 265 mμ decreases immediately from 1.0 and 0.9, to 0.85 and 0.75, respectively. Spectroscopic observation over 70 hr. revealed that anion VIIa slowly disappears. The new maximum formed at 231 mμ corresponds to that of a 2.5×10^{-5} *M* solution of 2-hydroxy-2-methylmercaptoindanedione (in hydrochloric acid). Two isosbestic points which are exhibited in the course of the reaction prove that we are

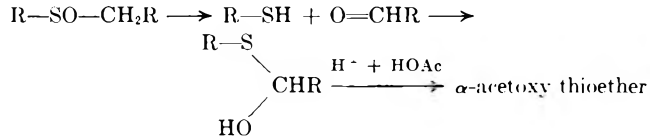


VIIa

dealing with a rearrangement reaction in which only two absorbing species are present in detectable amounts. Since VII is in equilibrium with its anion VIIa, the ultraviolet spectrum of this mixture can be considered as that of one species. When a 10^{-4} *M* solution of VII (25 ml.) was diluted with 75 ml. of 5×10^{-2} *N* hydrochloric acid, absorbance of the anion at 256 mμ (265) dropped from 1.0 (0.9) to0.45 (0.37); a new maximum appeared immediately at 234 mμ (Fig. 2). This originally appeared rather discouraging for the spectroscopic investigation of the rearrangement reaction. However, we noted that the rapid increase of the absorbance of this maximum was connected with a slight shift of the maximum to 231 mμ, and the curves exhibited two isosbestic points. Thus, the maximum at 234 mμ appears to be that of an equilibrium favoring undissociated VII.

Discussion

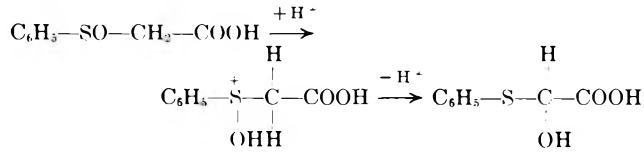
The main feature of a mechanism recently proposed for the Pummerer reaction was the direct cleavage of the sulfinyl compound into a mercaptan and a carbonyl fragment followed by recombination to form the α-substituted thioether.[6] The results were obtained under the rather drastic reaction conditions shown.



Our chemical and spectroscopic results are in disagreement with this mechanism. We did not find it possible to substitute the hydroxy group in the hemithioketal (VIII) under the conditions of reaction.

The cleavage–recombination mechanism appears even less likely by the finding that the rearrangement of sulfoxides of pyrimido[5,4-*b*][1,4]thiazines is subject to acid and base catalysis leading to different α-substituted thioethers.[13] Their formation was explained with the reaction of the nucleophilic media with the easily formed and stable 4,1-azathionium ion.

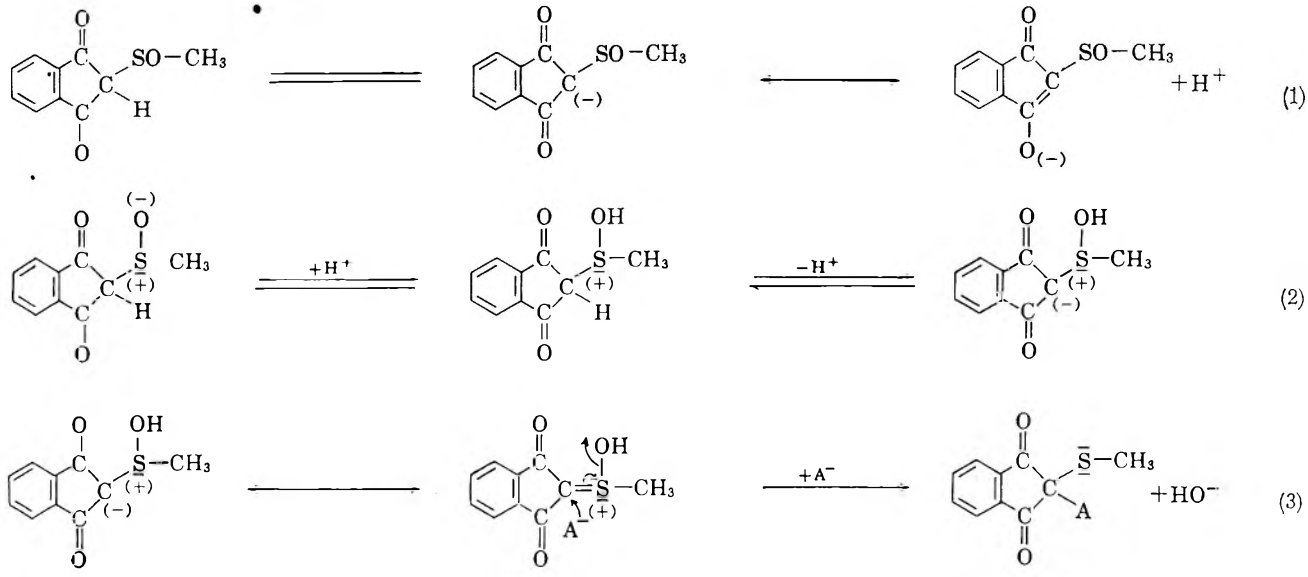
Recently evidence has been presented for an *intramolecular* mechanism of the rearrangement of phenylsulfinylacetic acid into the hemiphenylmercaptal of glyoxylic acid.[14] We have found that the hemithio-



ketal (VIII) is formed in aqueous solution, while other 2-substituted 2-methylmercaptoindanediones are

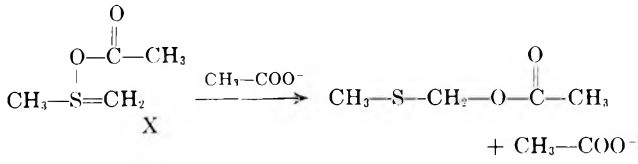
(13) E. F. Schroeder and R. M. Dodson, *J. Am. Chem. Soc.*, **84**, 1904 (1962).
(14) D. Walker and J. Leib, *Can. J. Chem.*, **40**, 1242 (1962).

MECHANISM A



formed in other solvents and are not formed *via* the α-hydroxy thioethers.[15]

Of particular importance for the understanding of the rearrangement of sulfoxides were the results obtained in an O^{18} tracer investigation recently reported.[4] The earlier proposed[3] cyclic *intramolecular* mechanism for the conversion of dimethyl sulfoxide into α-acetoxymethyl methyl sulfide could not be supported by this study. The new mechanism suggested involves an *intermolecular* nucleophilic attack on an intermediate (X) by acetate ions.



A similar mechanism for the conversion of dimethyl sulfoxide into monochloro dimethyl sulfide has been proposed earlier.[16]

The results obtained in the present investigation show that the acid-catalyzed rearrangement of VII involves a nucleophilic attack of a reactive intermediate by the solvent. As the spectroscopic data of the conversion of VII into VIII reveal, the reaction is higher than first order in hydrogen ions. This indicates that formation of a reactive intermediate requires protonation of the sulfinyl group in VII. Our results cannot be explained, however, by an *intramolecular* rearrangement of this protonated species. Mechanism A which is in agreement with both our chemical and spectroscopic data involves the sequence (eq. 1–3, where A^- = OH^-, Cl^-, CH_3COO^-, or $C_2H_5O^-$), in which protonation of the sulfinyl group is followed by formation of the reactive intermediate which undergoes attack by nucleophiles such as HO^-, Cl^-, CH_3COO^-, or $C_2H_5O^-$, leading to the various 2-substituted 2-methylmercapto-indanediones described in the present work.[17] The mechanism should be applicable to acid-catalyzed rearrangement reactions of β-keto sulfoxides in general. Recent results indicate that sulfinyl compounds other than β-keto-substituted ones can undergo quite different acid-catalyzed rearrangement reactions.[18]

Experimental[19]

Dimethyl sulfoxide was dried over calcium hydride and freshly distilled under vacuum. Sodium methylate was a commercial product.

2-Methylsulfinylindanedione-1,3 (VII).—To a suspension of 5.4 g. of sodium methoxide (0.1 mole) in 75 ml. of dimethyl sulfoxide placed under nitrogen in a 250-ml. round-bottom flask equipped with a magnetic stirring bar, distillation head, and receiver was slowly added 5 ml. of diethyl phthalate (0.025 mole). The stirred yellow reaction mixture was kept at room temperature at ~1-mm. pressure for 24 hr. The solvent was then removed completely by distillation for 1 hr. at a bath temperature of 65°. The yellow-colored semisolid residue was dissolved in 30 ml. of ice–water to which a mixture of 10 ml. of concentrated hydrochloric acid and 90 ml. of water was added slowly until the pH of the reaction mixture was about 5–6. Then 200 ml. of chloroform was added to the aqueous layer and the rest of the hydrochloric acid solution was added under quick shaking of the reaction mixture. The yellow chloroform solution was separated immediately, the extraction quickly was repeated three times, and the combined chloroform solutions were filtered and evaporated *in vacuo*. The yellow oily residue obtained crystallized quickly after addition of ether. The yield was 2.6 g. (50%) of 2-methylsulfinylindanedione-1,3, m.p. 105°. Purification by precipitation from chloroform by adding ether raised the melting point to 110–111°.

Anal. Calcd. for $C_{10}H_8O_3S$ (mol. wt., 208.16): C, 57.69; H, 3.87; S, 15.4. Found: C, 57.70; H, 3.90; S, 15.7.

2-Hydroxy-2-methylmercaptoindanedione-1,3 (VIII). A. From Ninhydrin.—Ninhydrin (2 g., 11 mmoles) was suspended in 15 ml. of absolute ethanol in a 25-ml. erlenmeyer flask and a stream of methanethiol was bubbled through for 45 min. The ninhydrin went completely into solution with evolution of heat. Evaporation of the solvent at room temperature gave 2 g. of VIII

(15) Boiling of 2-methylsulfinylindanedione-1,3 (VII) in inert solvents (chloroform) leads to high-melting materials not further investigated. Since rearrangement of VII in the presence of its own anion results in the formation of water, it is possible that 2-hydroxy-2-methylmercaptoindanedione VIII) is formed (see below). Also, simple heating of VII yields a product which exhibits an OH peak in its infrared spectrum. The infrared spectrum, however, is not identical with that of VIII.

(16) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

(17) According to these considerations, catalytic amounts of water should be sufficient to convert β-keto sulfoxides into α-hydroxy thioethers, and this indeed has been found. Crude or impure samples of keto sulfoxides rearrange in the solid state,[5,18] making the reaction *appear intramolecular*.

(18) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **85**, 1896 (1963).

(19) All melting points are taken on a Fisher-Johns apparatus and are not corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

as light yellow crystals of m.p. 120° (85%). Recrystallization from a mixture of hot ethanol and petroleum ether raised the melting point to 121–123°.

Anal. Calcd. for $C_{10}H_8O_3S$ (mol. wt., 208.16): C, 57.69; H, 3.87; S, 15.4. Found: C, 57.66; H, 3.86; S, 15.4.

B. From 2-Methylsulfinylindanedione-1,3 (VII).—VII (100 mg., 0.48 mmole) was dissolved in 40 ml. of water. Then 60 ml. of 0.5 *N* hydrochloric acid was added and the colorless (slightly cloudy) solution was extracted twice after 15 min. with 75 ml. of chloroform. The yellowish-colored chloroform solution was evaporated *in vacuo* yielding a yellow oil which rapidly crystallized. The yield was 90 mg. (90%), m.p. 121°; mixture melting point with the substance obtained under A showed no depression.

2-Chloro-2-methylmercaptoindanedione-1,3 (IX). A.—The direct preparation from diethyl phthalate and dimethyl sulfoxide has been described previously.[7a]

B. From 2-Methylsulfinylindanedione-1,3 (VII).—VII (70 mg.) was dissolved in 2 ml. of 10% sodium carbonate solution. The yellow colored solution was then added to a mixture of 2 ml. of concentrated hydrochloric acid and 3 ml. of water, giving a colorless precipitate. The yield was 50 mg. (66%) of IX, m.p. 64–65°; mixture melting point with authentic[7a] IX showed no depression.

2-Acetoxy-2-methylmercaptoindanedione-1,3. A. From 2-Chloro-2-methylmercaptoindanedione-1,3.—2-Chloro-2-methylmercaptoindanedione-1,3 (300 mg., 1.3 mmoles) was dissolved in 5 ml. of glacial acetic acid and refluxed for 3 hr. The reaction mixture was then poured into a Petri dish. Evaporation of the solvent at room temperature gave 275 mg. of 2-acetoxy-2-methylmercaptoindanedione-1,3 (83%), m.p. 138°.

Anal. Calcd. for $C_{12}H_{10}O_4S$ (mol. wt., 250.20): C, 57.60; H, 4.03; S, 12.79. Found: C, 57.59; H, 4.15; S, 12.84.

B. From 2-Methylsulfinylindanedione-1,3 (VII) and Acetic Acid.—VII (100 mg., 0.48 mmole) was dissolved in 25 ml. of acetic acid and kept at 50° for 20 hr. The originally yellow-colored solution had turned almost colorless. Evaporation of the solvent under vacuum gave a slightly yellow-colored oil which gave colorless crystals upon addition of little methanol. The yield was 85 mg. (71%), m.p. 136–137°; mixture melting point with 2-acetoxy-2-methylmercaptoindanedione-1,3 obtained under A showed no depression. In concentrated solutions of VII in acetic acid, a higher melting product not further investigated was formed.

C. From 2-Methylsulfinylindanedione-1,3 (VII) and Acetic Anhydride.—VII (100 mg., 0.48 mmole) was dissolved in 3 ml. of acetic anhydride. The reaction mixture was kept at 50° for 15 hr. Evaporation of the solvent at room temperature gave 90 mg. of colorless 2-acetoxy-2-methylmercaptoindanedione-1,3 (75%), m.p. 136–138°; mixture melting point with authentic sample from procedure A gave no depression.

D. From 2-Hydroxy-2-methylmercaptoindanedione-1,3 (VIII) and Acetic Anhydride.—VIII (500 mg., 2.4 mmoles) was dissolved in 5 ml. of pyridine and 5 ml. of acetic anhydride. The reaction mixture was refluxed for 5 min. The dark solution yielded 450 mg. (75%) of 2-acetoxy-2-methylmercaptoindanedione-1,3 as colorless crystals, m.p. 138°, after evaporation of the solvents at room temperature and washing of the residue with cold methanol; mixture melting point with authentic sample obtained under A showed no depression.

2-Ethoxy-2-methylmercaptoindanedione-1,3. A. From 2-Chloro-2-methylmercaptoindanedione-1,3 (IX).—One gram of 2-chloro-2-methylmercaptoindanedione-1,3 (IX) was dissolved in 5 ml. of absolute ethanol and refluxed for 3 hr. Evaporation of the solvent at room temperature gave a yellow oil which crystallized after 5 days. The substance was recrystallized from hot ethanol, yielding 950 mg. (91%) of 2-ethoxy-2-methylmercaptoindanedione-1,3, m.p. 65–66° (yellowish prismatic needles).

Anal. Calcd. for $C_{12}H_{12}O_3S$ (mol. wt., 236.22): C, 61.01; H, 5.12; S, 13.55. Found: C, 60.83; H, 5.16; S, 13.77.

B. From 2-Methylsulfinylindanedione-1,3.—VII (100 mg., 0.48 mmole) was dissolved in 10 ml. of absolute ethanol and kept at 55° for 12 hr. Evaporation of the solvent at room temperature gave 60 mg. (52%) of crystalline 2-ethoxy-2-methylmercaptoindanedione-1,3, m.p. 63–64°; mixture melting point with authentic sample obtained under A showed no depression.

Reaction of 2-Chloro-2-methylmercaptoindanedione-1,3 (IX) with Ammonia.—IX (200 mg., 0.9 mmole) was dissolved in 3 ml. of ether. Addition of 6 ml. of 15% aqueous ammonia solution and shaking for a few minutes caused precipitation of colorless crystals (aqueous layer was brown colored). The reaction mixture was kept in an open beaker for 1 hr. and then filtered. The yield was 100 mg. (63%) of 3-methylmercaptophthalimidine, m.p. 156°. Recrystallization from hot methanol raised the melting point to 158°.

Anal. Calcd. for C_9H_9NOS: C, 60.33; H, 5.06; N, 7.82; S, 17.82; mol. wt., 179.16. Found: C, 60.55; H, 5.03; N, 7.88; S, 17.89; mol. wt.,[20] 166.

Ultraviolet Spectra.—The ultraviolet spectra were taken on a Perkin-Elmer recording instrument (Model 202). The solutions were prepared by diluting a 10^{-4} *M* aqueous solution of 2-methylsulfinylindanedione-1,3 to a molarity of 2.5×10^{-3} with 10^{-2} and 5×10^{-2} *N* hydrochloric acid, respectively.

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(20) Thermoelectric measurement was made in dioxane.

Structure and Reactivity. I. The Oximation Rates of Some Straight-Chain and Monomethyl-Substituted Alkanones

PAUL G. KLETZKE

606 North 17th Street, La Crosse, Wisconsin

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The oximation rates have been determined for 65 straight-chain and monomethyl-substituted alkanones. The methyl ketones are the most reactive of the straight-chain ketones studied, followed by the ethyl ketones. The propyl and higher ketones have the same rate. A methyl group on the first carbon adjacent to the carbonyl group lowers the rate the most as compared to the corresponding straight-chain compounds. This decreased rate is observed to a smaller degree if the methyl group is on the second carbon, while a methyl group on the third carbon has no effect on the rate.

The rate of oxime formation of various alkanones has been the subject of a number of investigations.[1-8] However, no systematic or extended study has been reported. This paper reports the oximation rates of 65 alkanones at 20°. These compounds have been selected in such a manner that the oximation rate is defined with a high degree of probability for all of the theoretically possible structurally isomeric straight-chain and monomethyl-substituted alkanones up to and including fifteen carbon atoms.

The early investigators generally worked with equilibrium mixtures, as nothing was added to remove the hydrogen chloride liberated during the formation of the oxime. Bryant and Smith[5] found pyridine to be a satisfactory base for this purpose, thus driving the reaction to completion. These investigators used this fact to devise a generally useful method for the quantitative estimation of carbonyl groups.[5] Their method, slightly modified, has been found satisfactory for determining the oximation rates reported in this paper.

The results are shown in Table I. The methyl ketones (**1**–**9**) are the most reactive, followed by the ethyl ketones (**10**–**16**). In both series the rate becomes constant with the third and second member, respectively. The *n*-propyl and higher ketones (**17**–**27**) have the same rate. The above order of reactivity holds true for all of the branched homologous series shown in Table I, the isopropyl ketones (**28**–**34**) serving as an example. *sec*-Butyl (**35**–**40**), 1-methylbutyl (**41**–**46**), and higher 1-methylalkyl ketones have the same rate, as 1-methylheptyl ethyl ketone (**47**) has the same rate as the corresponding lower members (**36** and **42**). With the exception of their methyl ketones, the isobutyl (**49**–**52**) and the isopropyl ketones have the same rate. The identity of their rates was confirmed by testing several pairs of ketones simultaneously, **29** with **49**, and **31** with **51**. In both cases the color changes were identical. The 2-methylbutyl ketones (**53**–**56**) are slightly less reactive than the corresponding isobutyl ketones, the higher homolog (**57**) being of the same order of reactivity. The isopentyl[9] (**58**–**60**) and isohexyl ketones (**62**–**64**), as well as several of their homologs (**61** and **65**), have the same rate as the corresponding straight-chain ketones.

The above results are in general agreement with previous studies on the oximation rate of ketones. From a consideration of the work of Petrenko-Kritschenko and co-workers[1,3] together with their own results, Ruzicka and Buijs[4] concluded that the *n*-alkyl methyl ketones have the same oximation rate while the symmetrical di-*n*-alkyl ketones have a lower but otherwise identical rate. Pringsheim and Gorgas[10] found that 2-pentanone forms the oxime more rapidly than 3-pentanone. Bryant and Smith[5] and Vavon and co-workers[7,8] found that a methyl group or groups adjacent to the carbonyl group results in a lower oximation rate.

The results are also compatible with a variety of rate studies on other groups.[11] As indicated above, in a given homologous series the methyl and ethyl ketones are the most reactive, followed by the propyl and higher ketones. This same order of reactivity has been observed with the *n*-alkyl halides in their reaction with sodium phenoxide,[12] sodium eugenoxide,[13] sodium guaiacoxide,[14] sodium *m*-4-xylyloxide,[15] sodium benzyloxide,[16] piperidine,[17] sodium thiocyanate,[18] and potassium iodide.[19] The observation that the thirty-carbon myricyl chloride[19] has the same order of reactivity as the lower chlorides suggests that the conclusions on oximation rates reported in this paper may be extended to higher ketones.[20] The isobutyl and isopentyl halides[12,13,17] have lower rates while isohexyl bromide[18] has the same rate as the normal bromide. Asinger and Eckoldt[21] determined the rate of reaction between cyclohexylamine and the 1-, 2-, 3-, 4-, 5-, 7-, and 8-bromohexadecanes. The 3- to 8- had the same rate; the 2-isomer had twice the rate while the 1-isomer had one-hundred times the rate of the 3- to 8-isomers. Asinger

(1) P. Petrenko-Kritschenko and S. Lordkipanidze, *Ber.*, **34**, 1702 (1901).
(2) A. W. Stewart, *J. Chem. Soc.*, 410 (1905).
(3) P. Petrenko-Kritschenko and W. Kantscheff, *Ber.*, **39**, 1452 (1906).
(4) L. Ruzicka and J. B. Buijs, *Helv. Chim. Acta*, **15**, 8 (1932).
(5) W. M. D. Bryant and D. M. Smith, *J. Am. Chem. Soc.*, **57**, 57 (1935); S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 28–30.
(6) A. R. Poggi, R. Biffoli, and C. Stella, *Gazz. chim. ital.*, **77**, 536 (1947); *Chem. Abstr.*, **42**, 3335 (1948).
(7) G. Vavon and P. Anziani, *Bull. soc. chim. France*, 2026 (1937).
(8) G. Vavon and D. Ivanoff, *Compt. rend.*, **177**, 453 (1923).
(9) The ketones were prepared from 4-methylpentanoic acid obtained from isobutyl bromide through the malonic ester synthesis. Ketones prepared from commercial isopentyl bromide always gave longer reaction times, presumably due to the presence of 2-methylbutyl bromide as an impurity.
(10) H. Pringsheim and A. Gorgas, *Ber.*, **57**, 1561 (1924).
(11) The following literature survey is not intended to be complete.
(12) D. Segaller, *J. Chem. Soc.*, 1154 (1913).
(13) S. S. Woolf, *ibid.*, 1172 (1937).
(14) J. A. Mitchell, *ibid.*, 1792 (1937).
(15) P. J. Hardwick, *ibid.*, 141 (1935).
(16) P. C. Haywood, *ibid.*, 1904 (1922); L. J. Goldsworthy [*ibid.*, 1102 (1926)] pointed out that sodium ethoxide is actually the reactive alkoxide present.
(17) S. M. McElvain and J. Semb, *J. Am. Chem. Soc.*, **53**, 690 (1931).
(18) T. I. Crowell, *ibid.*, **75**, 6046 (1953).
(19) J. B. Conant and R. E. Hussey, *ibid.*, **47**, 476 (1925).
(20) Attempts to determine the oximation rates of 12-tricosanone and 18-pentatriacontanone were unsuccessful owing to their insolubility in methanol.
(21) F. Asinger and H. Eckoldt, *Ber.*, **76**, 579 (1943).

TABLE I

OXIMATION RATES OF SOME ALKANONES

Compound no.	Ketone	Preparation: Method	Preparation: R of R-MgBr	0.5 N NaOH required, ml.	Second-order velocity constants for: 25% reaction	50% reaction	90% reaction	$k_{av.}$
1	2-Propanone[a]			15.0			250.0	250.0
2	2-Butanone[a]			15.0			107.4	107.4
3	2-Pentanone[a]			14.9			68.2	68.2
4	2-Hexanone	A	Butyl	15.0			68.2	68.2
5	2-Heptanone[a]			14.9			68.2	68.2
6	2-Octanone[a]			14.8			68.2	68.2
7	2-Nonanone	A	Heptyl	14.8			68.2	68.2
8	2-Decanone	A	Octyl	15.0			68.2	68.2
9	2-Heptadecanone[a, b]			14.8			68.2	68.2
10	3-Pentanone[a]			14.8		24.4	20.8	22.6
11	3-Hexanone	A	Propyl	15.0	15.74	15.50	15.65	15.6
12	3-Heptanone[a]			14.9	15.74	15.50	15.65	15.6
13	3-Octanone	A	Pentyl	14.8	15.74	15.50	15.65	15.6
14	3-Nonanone	A	Ethyl	15.0	15.74	15.50	15.65	15.6
15	3-Decanone	A	Heptyl	14.8	15.74	15.50	15.65	15.6
16	3-Pentadecanone	B	Dodecyl	13.8	15.74	15.50	15.65	15.6
17	4-Heptanone	A	Propyl	15.0	10.46	10.65	9.63	10.2
18	4-Octanone	A	Butyl	15.0	10.46	10.65	9.63	10.2
19	4-Nonanone	A	Pentyl	15.0	10.46	10.65	8.94	10.0
20	4-Decanone	A	Propyl	15.0	10.46	10.65	8.94	10.0
21	4-Pentadecanone	B	Propyl	14.7	10.46	10.65	8.94	10.0
22	5-Nonanone	A	Butyl	15.0	10.46	10.65	8.94	10.0
23	5-Decanone	A	Pentyl	15.1	10.46	10.65	8.94	10.0
24	5-Pentadecanone	A	Decyl	14.7	10.46	10.65	8.94	10.0
25	6-Pentadecanone	B	Pentyl	14.5	10.46	10.65	8.94	10.0
26	7-Pentadecanone	A	Octyl	14.8	10.46	10.65	8.94	10.0
27	8-Pentadecanone	B	Heptyl	14.6	10.46	10.65	8.94	10.0
28	3-Methyl-2-butanone[a]			14.8		24.4	25.0	24.7
29	2-Methyl-3-pentanone	A	Ethyl	15.1	1.74	1.67	1.42	1.61
30	2-Methyl-3-hexanone	A	Propyl	15.1	1.16	1.09	0.947	1.066
31	2-Methyl-3-heptanone	A	Butyl	15.1	1.16	1.09	0.977	1.076
32	2-Methyl-3-octanone	A	Pentyl	15.1	1.16	1.09	0.977	1.076
33	2-Methyl-3-nonanone	A	Hexyl	14.9	1.16	1.09	1.01	1.09
34	2-Methyl-3-tridecanone	A	Decyl	14.9	1.16	1.14	1.14	1.15
35	3-Methyl-2-pentanone	A	*sec*-Butyl	15.1	8.98	9.0	7.82	8.60
36	4-Methyl-3-hexanone	A	*sec*-Butyl	15.1	0.55	0.51	0.466	0.509
37	3-Methyl-4-heptanone	A	*sec*-Butyl	15.1	0.35	0.33	0.298	0.326
38	3-Methyl-4-octanone	A	*sec*-Butyl	15.1	0.35	0.33	0.298	0.326

and co-workers[22] studied the alkaline hydrolysis of the acetates and benzoates of 1-, 2-, 3-, and 4-octanol. The acetate rate ratios were 30:4:1.4:1 and the benzoate ratios 3.9:3.1:1:1. Similar results were obtained by Dorough and co-workers[23] in the acylation of the same octanols with acetic acid in sealed tubes and acetic anhydride in acetone. These same investigators also used the same reagents to determine the acylation rates of a number of methylheptanols. A methyl group adjacent to the hydroxyl group always resulted in a lower rate. Norris and Cortese[24] determined the reaction rate of a number of alkanols with *p*-nitrobenzoyl chloride in ether. Methanol was the most reactive, followed by ethanol. *n*-Propyl alcohol and higher normal alkanols had the same rate. The rates of the 2-, 3-, and 4-alkanols paralleled the oximation rates of the corresponding ketones shown in Table I. The 2-methyl-1-alkanols had the same rate, comparable to **49**, **54**, and **57** in Table I. The 3- and 4-methyl 1-alkanols had the same rate as the normal alkanols.

(22) F. Asinger, G. Geiseler, and G. Mueller, *Ber.*, **93** 2491 (1960).

(23) G. L. Dorough, H. B. Glass, T. L. Gresham, G. B. Malone, and E. E. Reid, *J. Am. Chem. Soc.*, **63**, 3100 (1941).

(24) J. F. Norris and F. Cortese, *ibid.*, **49**, 2640 (1927).

Experimental

Preparation of Ketones.—Unless otherwise indicated, the ketones were prepared by the following two methods.

Method A.—A Grignard reagent (see Table I) was treated with an aldehyde and the resulting carbinol was oxidized to the corresponding ketone with a sodium dichromate–sulfuric acid mixture according to Sandborn.[25] The carbinol yields were 50 to 72%, and the ketone yields were 61 to 83%.

Method B.—A Grignard reagent (see Table I) was converted to the cadmium dialkyl which was treated with an acid chloride according to the procedure of Cason and Prout.[26] Yields were 47 to 68%.

Ethyl 3-Hydroxy-3-Methylnonanoate.[27]—Seventy-three grams (3 g.-atoms) of magnesium metal turnings and 1 g. of U.S.P. mercuric chloride were placed in a 3-l. three-necked flask equipped with a stirrer, reflux condenser, and addition funnel. The flask was swept with dry nitrogen for 10 min. before covering the metal with 450 ml. of sodium-dried ether. The stirrer was started and 20 ml. of a mixture of 384 g. (3 moles) of 2-octanone and 380 g. (3.1 moles) of ethyl chloroacetate in 900 ml. of ether was added. The mixture was stirred and warmed until the reaction started. After the reaction became vigorous, the stirrer was stopped and

(25) L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 340.

(26) J. Cason and F. S. Prout, *Org. Syn.*, **28**, 75 (1948).

(27) This method is the procedure of J. Colonge and D. Joly [*Ann. chim.* (Paris), [11]**18**, 306 (1943)] for the preparation of ethyl 3-ethyl-3-hydroxypentanoate.

TABLE I (*Continued*)

Compound no.	Ketone	Preparation: Method	Preparation: R of R-MgBr	0.5 *N* NaOH required, ml.	Second-order velocity constants for: 25% reaction	50% reaction	90% reaction	*k*, av.
39	3-Methyl-4-nonanone[c]	B	Pentyl	14.7	0.40	0.348		0.374
40	3-Methyl-4-decanone[d]	B	Hexyl	14.9	0.35	0.33		0.34
41	3-Methyl-2-hexanone	A	Methyl	15.1	8.98	9.0	7.82	8.60
42	4-Methyl-3-heptanone	A	Ethyl	15.1	0.55	0.51	0.453	0.504
43	5-Methyl-4-octanone	A	Propyl	15.1	0.35	0.33	0.28	0.321
44	4-Methyl-5-nonanone[e]	A	Butyl	15.1	0.35	0.33	0.298	0.326
45	4-Methyl-5-decanone[f]	B	Pentyl	14.6	0.35	0.32	0.274	0.315
46	4-Methyl-5-undecanone[g]	B	Hexyl	14.6	0.33	0.30	0.271	0.30
47	4-Methyl-3-decanone	B	Ethyl	14.7	0.55	0.51	0.496	0.519
48	4-Methyl-2-pentanone[a]			15.1	12.5	11.4	11.4	11.8
49	5-Methyl-3-hexanone	A	Isobutyl	15.1	1.74	1.67	1.65	1.69
50	2-Methyl-4-heptanone	A	Isobutyl	15.1	1.16	1.09	1.04	1.096
51	2-Methyl-4-octanone	A	Isobutyl	15.1	1.16	1.09	1.04	1.096
52	2-Methyl-4-undecanone[h]	B	Isobutyl	14.6	1.16	1.14	1.08	1.126
53	4-Methyl-2-hexanone	B	Methyl	14.9	10.4	10.0	10.4	10.3
54	5-Methyl-3-heptanone	B	Ethyl	14.7	1.49	1.35	1.36	1.40
55	6-Methyl-4-octanone	B	Propyl	14.8	0.87	0.835	0.79	0.832
56	3-Methyl-5-undecanone[i]	B	Hexyl	14.7	0.87	0.835	0.736	0.814
57	5-Methyl-3-undecanone[j]	B	Ethyl	14.6	1.49	1.35	1.33	1.39
58	5-Methyl-2-hexanone[a]			15.1			68.2	68.2
59	6-Methyl-3-heptanone	B	Ethyl	14.8	15.74	15.50	15.65	15.6
60	2-Methyl-5-dodecanone[k]	B	Heptyl	14.7	10.46	11.4	10.4	10.8
61	6-Methyl-3-dodecanone[l]	A	3-Methylnonyl	14.7	15.74	15.50	15.65	15.6
62	6-Methyl-2-heptanone	B	Methyl	15.1			68.2	68.2
63	7-Methyl-3-octanone	B	Ethyl	14.5	15.74	15.50	15.65	15.6
64	8-Methyl-4-nonanone[m]	B	Propyl	14.6	10.46	10.0	8.93	9.79
65	7-Methyl-3-tridecanone[n]	B	Ethyl	14.7	15.74	15.50	15.65	15.6

[a] Commercially available. [b] Ketone was dissolved in 100 ml. of pyridine-indicator solution with warming and cooled, and 25 ml. of hydroxylamine hydrochloride solution was added. [c] New compound, b.p. 94–96° (20 mm.). Calcd. for $C_{10}H_{20}O$: CO, 17.9. Found: CO, 17.4. [d] New compound, b.p. 113–115° (25 mm.). Calcd. for $C_{11}H_{22}O$: CO, 16.4. Found: CO, 16.2. [e] New compound, b.p. 189–190° (745 mm.). Calcd. for $C_{10}H_{20}O$: CO, 17.9. Found: CO, 17.9. [f] New compound, b.p. 110–112° (23 mm.). Calcd. for $C_{11}H_{22}O$: CO, 16.4. Found: CO, 15.9. [g] New compound, b.p. 133–135° (34 mm.). Calcd. for $C_{12}H_{24}O$: CO, 15.2. Found: CO, 14.7. [h] New compound, b.p. 122–124° (20 mm.). Calcd. for $C_{12}H_{24}O$: CO, 15.2. Found: CO, 14.7. [i] New compound, b.p. 123–125° (20 mm.). Calcd. for $C_{12}H_{24}O$: CO, 15.2. Found: CO, 14.8. [j] New compound, b.p. 123–125° (24 mm.). Calcd. for $C_{12}H_{24}O$: CO, 15.2. Found: CO, 14.7. [k] New compound, b.p. 144–146° (28 mm.). Calcd. for $C_{17}H_{36}O$: CO, 14.1. Found: CO, 13.7. [l] New compound, b.p. 137–139° (22 mm.). Calcd. for $C_{13}H_{26}O$: CO, 14.1. Found: CO, 13.7. [m] New compound, b.p. 85–87° (12 mm.). Calcd. for $C_{10}H_{20}O$: CO, 17.9. Found: CO, 17.3. [n] New compound, b.p. 154–156° (22 mm.). Calcd. for $C_{14}H_{28}O$: CO, 13.2. Found: CO, 12.8.

the reaction was moderated with a bath of cold water. After the initial reaction was over, the remainder of the mixture was added with stirring as rapidly as possible with external cooling. About 45 min. was required. After the addition was complete, the cooling bath slowly was removed and the mixture finally was refluxed for 1 hr. on the steam bath. The mixture was allowed to cool and was poured onto a mixture of 1800 g. of cracked ice, 600 ml. of water, and 90 ml. of concentrated sulfuric acid. The ether layer was separated, washed once with dilute sulfuric acid, once with dilute aqueous potassium bicarbonate, dried with anhydrous potassium carbonate, and distilled. A fraction boiling at 136–138° (14 mm.) was collected. Two runs gave yields of 538 g. (83%) and 555 g. (83.5%).

Ethyl 3-Methyl-2-nonenoate.—Phosphorus pentoxide (1170 g.) was placed in a 5-l. three-necked flask equipped with a stirrer and reflux condenser. Dry, thiophene-free benzene (2 l.) was added and the mixture was heated to boiling with stirring. Ethyl 3-hydroxy-3-methylnonanoate (1 kg.) was added in 250-g. lots at 0.5-hr. intervals. As the dehydration proceeded, the mixture became viscous and stirring became impossible. The mixture was gently refluxed for a total of 4 hr., the stirrer being turned by hand at frequent intervals. The flask was allowed to cool and the benzene solution was decanted and distilled. A fraction, b.p. 122–128° (14 mm.), was collected. Most of the material boiled at 122–123° (14 mm.); yield was 747 g. (81.5%).

Ethyl 3-Methylnonanoate.[28]—The ethyl 3-methyl-2-nonenoate was reduced over platinum oxide (Engelhard Industries) in methanol at 40–50-lb. pressure. The ester boiled at 123–125° (26 mm.), yielding 95%.

(28) J. Cymerman, I. M. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 144 (1944).

3-Methylnonanoic Acid.—Ethyl 3-methylnonanoate (100 g., 0.5 mole) and 60 g. of sodium hydroxide dissolved in 250 ml. water were placed in a 2-l. three-necked flask equipped with a stirrer and reflux condenser. The mixture was refluxed with stirring for 2 hr. Water (250 ml.) was added and the alcohol was distilled, finally, under reduced pressure. The residue was allowed to cool, acidified with dilute sulfuric acid, extracted with ether, and distilled. A fraction boiling at 155–157° (21 mm.) was collected; yield was 75 g. (87%).

3-Methyl-1-nonanol.—Lithium aluminum hydride (35 g.) was dissolved in 1000 ml. of sodium-dried ether in a 5-l. three-necked flask equipped with a stirrer, reflux condenser, and addition funnel. Ethyl 3-methylnonanoate (294 g., 1.47 moles) dissolved in 500 ml. of ether was added drop by drop with stirring, and the mixture was stirred for 1 hr. after the addition was complete. Water (200 ml.) was then added drop by drop and the mixture was stirred for 15 min. after the addition was complete. The mixture was poured onto crushed ice and acidified with dilute sulfuric acid. The ether layer was separated, dried over anhydrous potassium carbonate, and distilled. A fraction boiling at 121–123° (20 mm.) was collected; yield was 211 g. (91%).

3-Methyl-1-bromononane.—3-Methyl-1-nonanol (211 g., 1.3 moles) was placed in a 1-l. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel. The flask was cooled to −5° with a Dry Ice–acetone bath and 400 g. of phosphorus tribromide was added drop by drop with stirring, the temperature being kept at −5 to 5°. After the addition was complete, the mixture was stirred for 1 hr. at 0–5° and then allowed to stand overnight. The mixture was poured into ice water, extracted with ether, dried over anhydrous potassium carbonate, and distilled. A fraction boiling at 109–111° (18 mm.) was collected; yield was 230 g. (78%).

5-Methylundecanoic Acid.—3-Methyl-1-bromononane (110 g., 0.5 mole) and 120 g. (0.75 mole) of diethyl malonate were placed in a 2-l. three-necked flask equipped with a stirrer and reflux condenser; *t*-butyl alcohol[29] (250 ml.) was added. The equivalent of 0.5 mole of a sodium hydride–mineral oil dispersion was added with stirring as rapidly as the refluxing allowed. The mixture was refluxed with stirring for 15 hr. The *t*-butyl alcohol was removed by distilling under reduced pressure on the water bath with stirring. Water was added to the cooled residue to dissolve the sodium bromide. The ester layer was separated and distilled to 110° (20 mm.) to remove low boiling material. The residue was hydrolyzed according to Vliet, Marvel, and Hsueh.[30] After the 3-hr. heating period with sulfuric acid was completed, the mixture was allowed to cool and the top layer was taken up in ether. The ether was distilled and the decarboxylation was completed. The cooled residue was dissolved in a solution of 20 g. of sodium hydroxide dissolved in 750 ml. of water and extracted twice with ether; the ether extracts were discarded. The aqueous solution was acidified with dilute sulfuric acid, the top layer was separated, and the water layer was extracted twice with ether. The top layer and ether extracts were combined and distilled. A fraction boiling at 174–175° (16 mm.) was collected; yield was 74 g. (74%).

Analysis and Rate Determinations—A modified method[3] of Bryant and Smith[5] was used. A Fisher constant temperature water bath was used. Temperature was controlled with a "JUMO" thermoregulator with a rated sensitivity of 0.005°, purchased from the Scientific Glass Apparatus Co., Bloomfield, N. J. The bath thermometer had a range of 0–100°, graduated in 0.1°. Mallinckrodt Analytical Reagent chemicals were used.

Preparation of Reagents.—The pyridine-indicator solution was prepared by placing 0.25 ml. of a 4% solution of bromophenol blue in methanol in a 1-l. volumetric flask. Pyridine (20 ml.) was added and the mixture was diluted with methanol. Final volume adjustment was made in the constant temperature bath at 20°.

The hydroxylamine hydrochloride solution was prepared by dissolving 42.000 g. of hydroxylamine hydrochloride in 160 ml. of distilled water in a 1-l. volumetric flask, and the solution was diluted with methanol. Final volume adjustment was made at 20°.

The 0.5 *N* sodium hydroxide was prepared by dissolving 20.5 g. of sodium hydroxide pellets in 100 ml. of distilled water. The solution was cooled and diluted with 900 ml. of methanol. The cloudy solution was allowed to stand overnight and the clear solution was decanted. The solution was standardized against 0.5 *N* hydrochloric acid using phenolphthalein as indicator. The normality was always adjusted to within 0.25% of 0.5 *N*.

Determination of the Volume of 0.5 *N* Sodium Hydroxide Required for Complete Reaction.—One-hundred milliliters of pyridine-indicator solution (cooled to 20° in the water bath) and 25 ml. of hydroxylamine hydrochloride solution (cooled to 20°) were pipeted into nine 250-ml. erlenmeyer flasks. One of the flasks was set aside as a blank. The calculated amount of ketone required to react with one-half of the hydroxylamine hydrochloride present was weighed out in a 12 × 35 mm. shell vial to the nearest milligram. The vial was transferred to the flask with forceps; the flask was stoppered, shaken, and allowed to stand 24 hr. or longer at room temperature. The yellow solution was titrated with 0.5 *N* sodium hydroxide to a color match with the blank against a white background illuminated with a 30-watt double tube fluorescent desk lamp.[32] As the end point was approached, the alkali was added in 0.1-ml. portions until the sample displayed a distinctly darker blue color than the blank. The buret reading less 0.1 ml. was taken as the end point. Results are shown in Table I. The results of this titration may be used to calculate the per cent purity of the ketones[5] and also may serve as a method of analysis for the twelve new ketones recorded in Table I.

Determination of the Time Required for 25, 50, and 90% Oximation—The water bath was equipped with a readily removable 9.5 × 18.5 cm. tray made of wire screen. This tray supported a 9 × 18 cm. piece of white glass (milk glass). The tray was illuminated with a 30-watt double tube fluorescent desk lamp.[32] The volume (25, 50, or 90%) of 0.5 *N* sodium hydroxide found necessary for complete reaction was added from a buret to a 250-ml. erlenmeyer flask containing the pyridine-indicator and hydroxylamine hydrochloride solutions. The solution became a deep blue. The flask was placed on the tray in the water bath together with another flask containing only the pyridine indicator and hydroxylamine hydrochloride solutions, the latter flask serving as a color blank. While the flasks were cooling to bath temperature, the calculated amount of ketone required to react with one-half of the hydroxylamine hydrochloride present was weighed out in a small crucible to the nearest milligram. The crucible was transferred to the flask with forceps and the time was noted while swirling the flask to mix the contents. As the end point was approached, the tray was momentarily lifted from the water bath to make color comparisons. As the color change is gradual, a time interval was taken. The first value of the interval was the time the solution was a slightly darker blue color than the blank, while the second value was the time the solution was a slightly paler blue color than the blank. The midpoint of the interval was the time used for calculating the reaction velocity constants. The number of identical rate constants recorded in Table I indicates only that the end points occurred within the same time interval.

The sodium chloride present in the above test solutions did not have an appreciable effect on the rate. Two ketones, 2-methyl-3-heptanone and 3-methyl-4-heptanone, were tested for 90% reaction as described above, while in comparison runs the alkali was added just before the end point. Good color matches were always observed.

The test solutions to which alkali has been added are stable. An alkaline test solution that was allowed to stand for 14 hr. at room temperature before the ketone was added gave the same results as the solutions treated as above.

Calculation of the Second-Order Reaction Velocity Constants.—The calculated hydroxylamine hydrochloride concentrations are 0.11738, 0.11410, and 0.109238 *M* for 25, 50, and 90% reaction, respectively. The corresponding ketone concentrations are one-half the above amounts or 0.05869, 0.05705, and 0.054619 *M*. Time is expressed in minutes.

Comparative Oximation Rates of Pairs of Ketones.—The required volumes of 0.5 *N* sodium hydroxide were added to two flasks containing the pyridine-indicator–hydroxylamine hydrochloride solution and the flasks placed on the tray in the water bath. The ketones were weighed out in separate crucibles and simultaneously added to the flasks. The color changes in the two flasks were compared with each other to and past the end point.

(29) The *t*-butyl alcohol was used without further treatment.

(30) E. B. Vliet, C. S. Marvel, and C. M. Hsueh, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 416.

(31) Methanol was used as the solvent instead of ethanol; 42 g. of hydroxylamine hydrochloride per liter was used instead of 35 g. per liter.

(32) A white background and uniform illumination was found necessary for obtaining reproducible results.

The Electrolytic Hydroxylation and Acetoxylation of Diaryl Alkenes

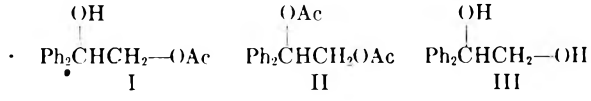
FRANK D. MANGO AND WILLIAM A. BONNER

The Department of Chemistry, Stanford University, Stanford, California

Received January 13, 1964

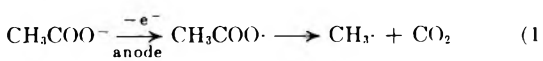
When sodium acetate in acetic acid was electrolyzed in the presence of 1,1-diphenylethylene, the latter was converted into a mixture of 2-*O*-acetyl-1,1-diphenylethylene glycol (I) and its corresponding diacetate (II). The mechanism of this novel electrolytic hydroxylation and acetoxylation reaction was investigated stereochemically by conducting similar electrolyses in the presence of *trans*-stilbene. Under anhydrous conditions, this diaryl alkene afforded mainly *meso*-1,2-di-*O*-acetyl-1,2-diphenylethylene glycol (IX). In moist acetic acid *trans*-stilbene yielded *threo*-1-*O*-acetyl-1,2-diphenylethylene glycol (VIII) and a mixture of the epimers of 1,2-diphenyl-1-propyl acetate (X). None of the epimeric *erythro*-1-*O*-acetyl-1,2-diphenylethylene glycol (VII) was obtained from *trans*-stilbene in either experiment. These results exclude an epoxide mechanism for the formation of such electrolytically produced hydroxylation and acetoxylation products, and are in accord with a mechanism involving an intermediate cyclic 1,2-acetoxonium ion which is formed stereoselectively at the electrode surface.

Recently we have reported the isolation of the skeletally unrearranged product, 2-*O*-acetyl-1,1-diphenylethylene glycol (I), from the Kolbe electrolysis of a

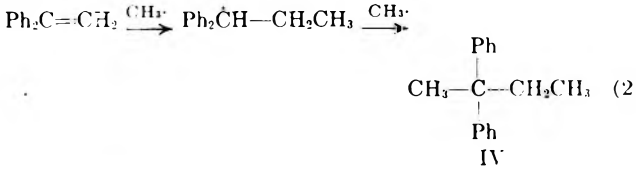


mixture of sodium acetate and sodium 3,3-diphenylpropanoate.[1] It was suggested that the monoacetate I might have arisen as a result of the intermediate formation of 1,1-diphenylethylene during the electrolysis, since it is well known that olefins are formed, often in good yield, during Kolbe electrolyses of aliphatic monobasic acids.[2] The experimental testing of this hypothesis and its extention to include other aryl-substituted alkenes is the subject of the present paper.

When 1,1-diphenylethylene was slowly added dropwise to an electrolyzing solution of sodium acetate in glacial acetic acid, two esters could be isolated on chromatographic separation of the crude electrolysis product. The first of these (16% of crude product) was 1,2-di-*O*-acetyl-1,1-diphenylethylene glycol (II), and the second (46%) was the previously encountered monoacetate I. The structures of these esters followed from microanalytical and n.m.r. data and from the facts that II could be readily hydrolyzed to the known 1,1-diphenylethylene glycol (III) and that the latter glycol could be monoacetylated to produce I. When the above experiment was repeated with the modification that the 1,1-diphenylethylene was added in a single batch to the electrolyzing medium, a complex mixture resulted. From this, a small amount (2.3%) of what appeared to be 2,2-diphenylbutane (IV) was the only homogeneous product isolated. The formation of IV may be rationalized as shown in eq. 1 and 2.

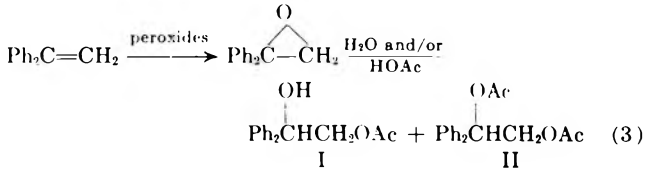


(1)



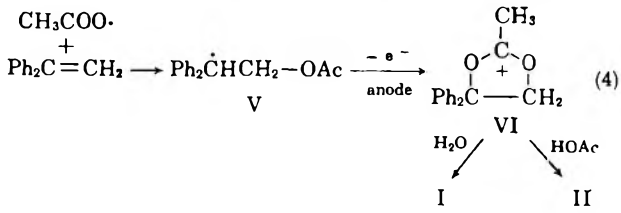
(2)

Attention was next turned to the mechanism of formation of the electrolytic hydroxylation and acetoxylation products, I and II. Two paths appeared as *a priori* possibilities. The first involved epoxidation of the 1,1-diphenylethylene by electrolytically produced peroxides or peracids, followed by acetolysis and acetylation of the intermediate epoxide (eq. 3). The



(3)

presence of peroxides and peracids during Kolbe electrolyses has been documented,[3-4] particularly at low temperatures, and these intermediates have been postulated as being involved in the mechanism of the Kolbe reaction.[7] The second mechanism involved addition of an acetoxy radical to the 1,1-diphenylethylene to give the resonance-stabilized benzhydryl radical V, whose subsequent anodic oxidation might produce the cyclic acetoxonium ion VI. The latter would in turn be capable of solvolysis to the observed products I and II (eq. 4). The first step in this mechanism has prec-



(4)

edent in the known addition of acetoxy and methyl radicals to conjugated dienes[8] and to aromatic nuclei[9,10] under electrolytic conditions, and in the initiation of vinyl polymerization by electrolyzing solutions of carboxylic acids.[11]

(1) W. A. Bonner and F. D. Mango, *J. Org. Chem.*, **29**, 430 (1964).

(2) M. J. Allen, "Organic Electrode Processes," Reinhold Publishing Corp., New York, N. Y., 1958, p. 102.

(3) F. Fichter and R. Zumbrunn, *Helv. Chim. Acta*, **10**, 869 (1927).

(4) F. Fichter and H. Buess, *ibid.*, **18**, 445 (1935).

(5) G. Hallie, *Rec. trav. chim.*, **57**, 152 (1938).

(6) E. Denina, G. Ferrero, and F. S. de Paolini, *Gazz. chim. ital.*, **68**, 443 (1938).

(7) See ref. 1, p. 97 ff.

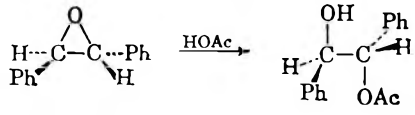
(8) W. B. Smith and H. G. Gilde, *J. Am. Chem. Soc.*, **81**, 5325 (1959); **83**, 1355 (1961).

(9) T. Hayashi and C. L. Wilson, Abstracts of Papers, 126th National Meeting of the American Chemical Society, New York, N. Y., 1954, p. 78-O.

(10) L. F. Fieser, R. C. Clapp, and W. H. Daudt, *J. Am. Chem. Soc.*, **64**, 2052 (1942).

(11) W. B. Smith and H. G. Gilde, *ibid.*, **82**, 659 (1960).

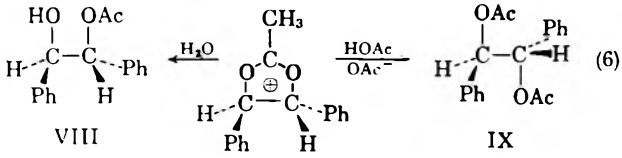
It appeared reasonable to suppose that the stereochemistry of such electrolytic hydroxylations might provide criteria for distinguishing between the two postulated mechanisms in eq. 3 and 4. Our working hypotheses were the following. If *trans*-stilbene were electrolytically hydroxylated *via* the epoxidation mechanism 3, the intermediate epoxide would in all probability undergo *trans* opening to form the inversion product,[12a] *erythro*-1-*O*-acetyl-1,2-diphenylethylene glycol (VII) (eq. 5), although *cis* opening to give the *threo*-



(5)

VII

epimer VIII or ring opening to give both VII and VIII could not be theoretically excluded.[12b] If the acetoxonium ion solvolysis mechanism 4 were applicable to *trans*-stilbene, however, electrolysis under moist conditions should, by analogy with the findings of Winstein,[13] produce a monoacetate of retained configuration, *threo*-1-*O*-acetyl-1,2-diphenylethylene glycol (VIII), whereas electrolysis in anhydrous acetic acid should afford[13] a diacetate of inverted configuration, *meso*-1,2-di-*O*-acetyl-1,2-diphenylethylene glycol (IX) (eq. 6). For comparison purposes, authentic samples of the products

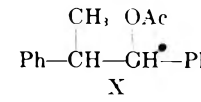


(6)

VIII IX

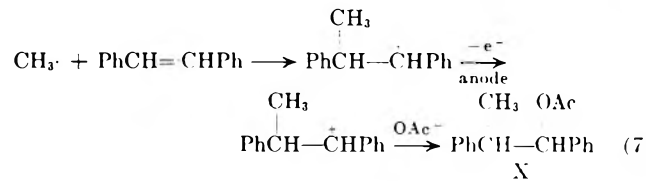
anticipated from each mechanism were synthesized independently. The *threo*-monoacetate VIII was prepared by the action of silver acetate and iodine[14] on *trans*-stilbene. The *erythro*-monoacetate VII and the *meso*-diacetate IX were obtained by the partial acetylation of *meso*-hydrobenzoin, prepared in turn by the sodium borohydride reduction of benzil.[15] *dl*-1,2-Di-*O*-acetyl-1,2-diphenylethylene glycol was obtained by acetylation of the above *threo*-monoacetate VIII.

Sodium acetate was electrolyzed in acetic acid containing *trans*-stilbene under anhydrous conditions, and the crude product was subjected to chromatographic separation. The pure products which could be characterized consisted of the *meso*-diacetate IX, a small quantity of the *threo*-monoacetate VIII, and a small quantity of *erythro*-1,2-diphenyl-1-propyl acetate (X, see below). None of the *erythro*-monoacetate VII was noted, although this was sought specifically using thin layer chromatography. The electrolysis was then repeated in acetic acid containing added water. Chromatographic separation of the crude product afforded primarily the *threo*-monoacetate VIII, small quantities of *dl*-1,2-di-*O*-acetyl-1,2-diphenylethylene glycol (by acetylation of VIII), and none of the *erythro*-epimer



X

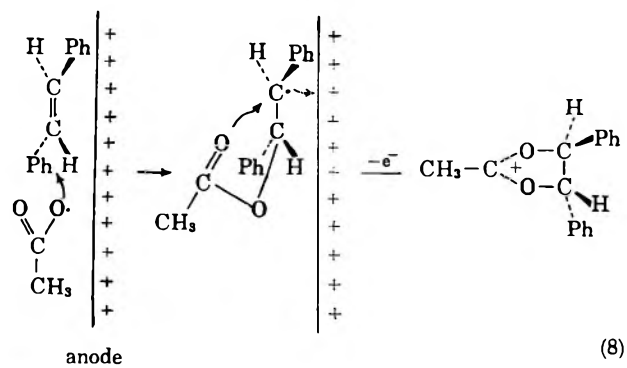
VII. In addition, considerable quantities of a mixture of *erythro*- and *threo*-1,2-diphenyl-1-propyl acetate (X) were isolated. It appeared probable that the latter ester arose by the reaction sequence illustrated in eq. 7.



(7)

Since in the above electrolyses only the *threo*-monoacetate VIII was isolated and none of the *erythro*-epimer VII could be found, it was deemed essential to be certain that *erythro*-VII could not be converted into *threo*-VIII under the electrolysis conditions employed. An acetic acid solution of sodium acetate was accordingly electrolyzed in the presence of the *erythro*-monoacetate VII, and the crude product was examined for the *threo*-epimer VIII. None of the latter acetate was formed, and the *erythro*-epimer VII was recovered unchanged, except for a small amount of additional acetylation. Thus the *threo*-monoacetate VIII appeared to be an *original* product of the electrolysis in the presence of *trans*-stilbene and not to have been formed in any secondary process. These observations, involving the electrolysis of sodium acetate in the presence of *trans*-stilbene under anhydrous and moist conditions, are fully in accord with the predictions of mechanism 6, and appear to preclude the intervention both of the epoxide mechanism 5 and any alternative mechanism incapable of operating in a highly stereoselective manner.

The intimate details of the mode of formation of the cyclic acetoxonium intermediates in mechanism 4 and 6 are not completely clear at present. The addition of anodically produced acetoxy radicals to stilbene molecules in the bulk solution would appear unlikely, since Swarc[16] has estimated the acetoxy radical lifetime to be only 10^{-9}–10^{-10} second, and has suggested that such radicals react only in their original "cage" and not in the surrounding solution. If the *trans*-stilbene were adsorbed on the anode surface, however, it could conceivably be close enough to an acetoxy "cage" for the latter radical to add to it (eq. 8). Such anodic adsorption of dienes has been proposed by Smith and Gilde[8] to explain the stereochemistry of the addition products



(8)

(12) (a) S. Winstein and R. B. Henderson, "*Heterocyclic* Compounds," Vol. 1, R. Elderfield, Ed., John Wiley and Sons, New York, N. Y., 1950, p. 27–32; (b) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 757 (1959).

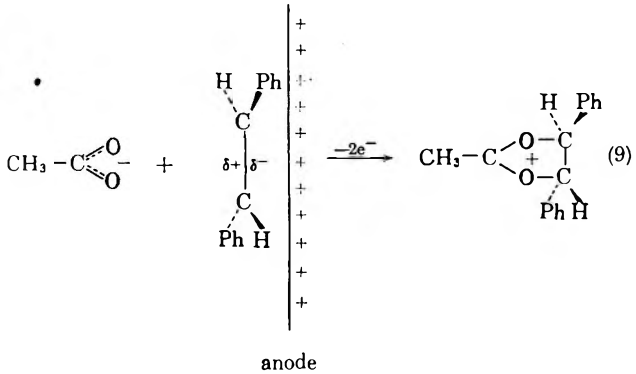
(13) S. Winstein, H. V. Hess, and R. E. Buckles, *J. Am Chem. Soc.*, **64**, 2796 (1942); S. Winstein and R. M. Roberts, *ibid.*, **75**, 2297 (1953).

(14) R. B. Woodward and F. V. Brutcher, Jr., *ibid.*, **80**, 209 (1958).

(15) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1955, p. 175.

(16) L. Herk, M. Feld, and M. Swarc, *J. Am. Chem. Soc.*, **83**, 2998 (1961).

of electrolytically produced radicals to conjugated dienes, and the fact that such addition products were found only in the anode compartment. Examples of the adsorption of uncharged aromatic compounds on electrode surfaces have also been reported,[17-20] and it has been proposed[18] that the adsorption of aryl amines on positively charged surfaces results from interactions between the π-electrons of the flatly held aromatic system and the metal. We presently have only preliminary experimental evidence that *trans*-stilbene is adsorbed on the anode surface during the above Kolbe electrolyses. When sodium acetate in acetic acid was electrolyzed in a cell powdered by a square wave generator (1 c.p.s.), the decay curve pattern (oscilloscope screen) resulting from interruption of the applied potential was significantly altered when *trans*-stilbene was present. These studies, however, are as yet incomplete. Another mechanism whereby the acetoxonium intermediate in eq. 6 might arise electrolytically from *trans*-stilbene is shown in eq. 9. Here the anodically adsorbed



olefin, polarized by the electrode as shown, is directly attacked at the positively polarized portion of its π-electron cloud by acetate ion, two electrons are expelled directly into the anode, and the acetoxonium intermediate is formed in one direct step. We have no experimental data, however, which distinguish between the two-step mechanism 8 and the one-step mechanism 9. Regardless, either process, each involving anodically adsorbed *trans*-stilbene, generates stereoselectively the required cyclic intermediate of eq. 6. So far as we are aware, electrolytic hydroxylations and acetoxylations of the above sort involving aryl-substituted alkenes have not been previously reported.

Experimental

Electrolysis of Sodium Acetate with 1,1-Diphenylethylene.—The electrolysis cell used in the following experiments was that which we have described earlier,[1] and the conditions for the following electrolyses were maintained as closely as possible to those described in our previous study.[1] Approximately 800 mg. of 1,1-diphenylethylene was added dropwise, at the rate of 1 drop per 10 min., to an electrolyzing (0.3 amp.) solution of sodium acetate (1.6 g.) in acetic acid (25 ml.). After about 4 hr. the crude product (*ca.* 0.7 g.), isolated as described earlier, was chromatographed on 50 g. of silicic acid using benzene, gradually enriched in ether, as eluant. Evaporation of the first 100 ml. of eluent left 35 mg. of clear oil, shown by its infrared spectrum to be unchanged 1,1-diphenylethylene. The next 300 ml. of eluent yielded 100 mg. of oil which appeared to be a mixture of starting material and the component in the next fraction. The next 400 ml. of eluent yielded 129 mg. of crystalline material. One recrystallization from a mixture of *n*-hexane and benzene yielded a white solid, m.p. 145–148°. The reported melting point for 1,1-di-*O*-acetyl-1,1-diphenylethylene glycol is 145–146°.[21] The infrared spectrum of the crystalline solid showed a strong carbonyl stretching band at 1731 cm.$^{-1}$, and three bands in the ester C–O stretching region at 1231, 1246, and 1252 cm.$^{-1}$. A 10-mg. portion of the crystalline material was hydrolyzed in alcoholic potassium hydroxide. The crude hydrolysis product, recrystallized from a mixture of *n*-hexane and benzene, had m.p. 119–121.5°. A mixture of this material with authentic 1,1-diphenylethylene glycol (m.p. 120–122°) showed no melting point depression (120–122°), and the infrared spectra of the two glycol samples were identical. The 1,1-di-*O*-acetyl-1,1-diphenylethylene glycol represented approximately 16% of the crude product. The final 500 ml. of eluent from the above chromatographic separation of the crude electrolysis product yielded 330 mg. of thick oil which crystallized on standing. This was recrystallized from a mixture of *n*-hexane and benzene, affording white crystals, m.p. 91–92.5°. The infrared spectrum showed an O–H stretching band at 3500 cm.$^{-1}$, a carbonyl stretching band at 1725 cm.$^{-1}$, and a strong band in the ester C–O stretching region at 1236 cm.$^{-1}$. The n.m.r. spectrum (Varian A60 n.m.r. spectrometer, tetramethylsilane internal standard, $CDCl_3$ solvent) contained a sharp band at 3.0, which shifted on warming, another band at 4.66, and a third at 1.98 p.p.m. A multiplet of bands appeared in the aromatic proton region between 7.15 and 7.5 p.p.m. This spectrum was consistent with 2-*O*-acetyl-1,1-diphenylethylene glycol, where the hydroxyl proton absorbed at 3.0, the identical methylene protons at 4.66, and the three acetate methyl protons at 1.98 p.p.m. This monoacetate had an identical infrared spectrum and showed no mixture melting point depression with a sample of the 2-*O*-acetyl-1,1-diphenylethylene glycol prepared below. The product represented approximately 46% of the crude material obtained from the above electrolysis.

The electrolysis was repeated using approximately 2 g. of 1,1-diphenylethylene, which was added in one batch to the electrolyzing solution of sodium acetate. Electrolysis was continued for approximately 8 hr., whereupon the crude product was isolated as before. The thick oil was chromatographed on 100 g. of silicic acid using a mixture of petroleum ether (b.p. 66–70°) and benzene (1:4) as eluent. The first 200 ml. of eluent yielded 70 mg. of clear liquid, which appeared to be homogeneous on thin layer chromatography. Its infrared spectrum showed no absorption bands attributable to functional groups. The hydrocarbon was purified by rechromatographing on neutral alumina (10 g.) using benzene–ether (100:2) as eluent. Evaporation of the first 25 ml. of eluent left 50 mg. of thin oil, presumably 2,2-diphenylbutane.

Anal. Calcd. for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.04; H, 8.68.

The remaining chromatography of the crude electrolysis product afforded various fractions of oily material from which little crystalline material separated. Thin layer chromatographic examination of these fractions indicated them to be impure, and to contain components in addition to the ones noted in the original electrolysis. Further attempts to obtain pure components from these fractions were abandoned.

1,1-Diphenylethylene Glycol.—This material was prepared, for comparison with the above electrolysis products, by the addition of dilute aqueous potassium permanganate to a chilled ethanol solution of 1,1-diphenylethylene, after the procedure of Clark and Owen.[22] The crude crystalline product was recrystallized from a mixture of *n*-hexane and benzene, affording sharp needles, m.p. 120–122. The reported melting point for 1,1-diphenylethylene glycol is 121°.[23]

2-*O*-Acetyl-1,1-diphenylethylene Glycol.—A few milligrams of the above 1,1-diphenylethylene glycol was treated with an excess of acetic anhydride in an equal volume of pyridine, and the resulting solution was allowed to stand at room temperature for 4 hr. The solution was treated with sufficient water to engender cloudiness and chilled; the crystalline material was collected. The product, recrystallized from a mixture of *n*-hexane and benzene, had m.p. 93–93.5°

(17) M. A. Loshkarev and A. Kryukova, *Zh. Anal. Khim.*, **6**, 166 (1951).
(18) J. O'M. Bockris, *Z. physik. Chem.* (Leipzig), **215**, 1 (1960).
(19) M. A. Gerovich, *Dokl. Acad. Nauk SSSR*, **105**, 1278 (1955).
(20) E. Blomgren and J. O'M. Bockris, *J. Chem. Phys.*, **63**, 1475 (1959).
(21) S. Winstein and F. H. Seabold, Jr., *J. Am. Chem. Soc.*, **69**, 2916 (1947).
(22) M. F. Clark and L. N. Owen, *J. Chem. Soc.*, 315 (1949).
(23) P. Weidenkoff, *Ber.*, **39**, 2063 (1906).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.97; H, 6.32.

Electrolysis of Sodium Acetate with *trans*-Stilbene under Anhydrous Conditions.—Anhydrous glacial acetic acid was obtained by distilling the acid from acetic anhydride after a mixture of the two had been heated under reflux for 12 hr. Anhydrous conditions were maintained during the electrolysis, conducted otherwise as above, by sealing the electrolysis cell from the atmosphere with a calcium chloride tube. A magnetically stirred, ice-cooled, solution of anhydrous glacial acetic acid (20 ml.) and sodium acetate (2 g.) containing *trans*-stilbene (2 g., dried in a vacuum over phosphorus pentoxide) was electrolyzed (0.2 amp.) during a period of 29 hr. The electrolysis mixture was then evaporated to dryness under reduced pressure and the residue was added to a mixture of ether and water (100 ml., 1:1) and shaken vigorously. The ether layer was washed with water, dilute aqueous sodium bicarbonate, and again with water, then was dried and evaporated, leaving approximately 1.5 g. of crude product. The thin layer chromatogram (silica gel G), using ether and benzene (3:10) as eluent, showed three principal spots and three minor ones. The crude product was chromatographed on 100 g. of silicic acid using solvent mixtures of increasing polarity from 5% ligroin in benzene, through benzene, to 10% ether in benzene. Fractions (50-ml. each) were collected and evaporated to dryness under reduced pressure. The residues were examined by thin layer chromatography, and combined on the basis of their thin layer chromatographic behavior.

The first combined fraction (750 mg., 57.9%) gave a thin layer chromatogram displaying two spots with R_f values identical with those of 1,2-di-*O*-acetyl-1,2-diphenylethylene glycol and 1,2-diphenyl-1-propyl acetate, respectively. A portion (625 mg.) of the solid fraction was recrystallized from a mixture of benzene and *n*-hexane yielding first 40 mg. of white solid, m.p. 120–127°, and finally an additional 54 mg. of white solid, m.p. 87–97°. Both products were found to be mixtures by thin layer chromatographic examination. The solid having m.p. 120–127° was hydrolyzed by the procedure described above. The crude hydrolysis product was recrystallized from a mixture of *n*-hexane and benzene to yield 10 mg. of a white solid, m.p. 134–135°. The infrared spectrum of this solid was identical with that of authentic *meso*-hydrobenzoin (m.p. 135–136.5°).

The second combined fraction (172 mg., 13.3%) gave a thin layer chromatogram displaying two spots, the principal one corresponding in position and hue to that of 1,2-di-*O*-acetyl-1,2-diphenylethylene glycol. The product was recrystallized twice from petroleum ether (b.p. 56–70°), affording fine needles, m.p. 133–135°. The reported melting point for *meso*-1,2-di-*O*-acetyl-1,2-diphenylethylene glycol (IX) is 136–138°.[24] A mixture melting point of the above sample with an authentic specimen of the *meso*-diacetate IX (m.p. 135–136.5°) was 134–136.5°, and the infrared spectra of the two samples were identical.

Thin layer chromatographic examination of the third combined fraction (162 mg., 12.5%) revealed the presence of at least four components, one of which was the above *meso*-diacetate IX. The fourth combined fraction (211 mg., 16.3%) gave a thin layer chromatogram indicating again the presence of at least four components. One of the four spots on the chromatogram was identical in position and the hue with that of *threo*-1-*O*-acetyl-1,2-diphenylethylene glycol (VIII). No evidence of the presence of the epimeric *erythro*-monoacetate VII was found. These two epimers were found to separate cleanly upon thin layer chromatography, but that portion of the chromatogram which would contain the *erythro*-monoacetate spot was blank. All attempts to crystallize the *threo*-monoacetate from the original cuts making up this combined fraction failed, but one of these fractions, thought to be richest in the *threo*-epimer, afforded a small amount of waxy solid whose infrared spectrum was similar to that of the *threo*-monoacetate VIII, but contained one extraneous band in the methyl C–H stretching region at 2960 cm.$^{-1}$. We estimate that the *threo*-monoacetate VIII was present to the extent of less than 5% in the crude electrolysis product.

Electrolysis of Sodium Acetate with *trans*-Stilbene under Moist Conditions.—To an electrolyzing (0.4 amp.) glacial acetic acid solution (20 ml.) of *trans*-stilbene (2.7 g.) and sodium acetate (1 g.) was added dropwise over a period of 9 hr. 1.2 g. of water. The crude, partially crystalline electrolysis product (3.6 g.) was chromatographed on 100 g. of silicic acid in the manner described above, yielding three fractions after recombination as above on the basis of thin layer chromatography.

The first of these (1496 mg., 47.6%) was partially crystalline. It was recrystallized from ethanol and then from a mixture of *n*-hexane and benzene to yield a product having m.p. 105–106° and showing no mixture melting point depression with an authentic sample of *erythro*-1,2-diphenyl-1-propyl acetate (X, m.p 103–105°). The infrared spectra of the two samples were superimposable. Although some of the original fractions comprising this combined fraction were oils, their thin layer chromatograms contained single, sharply defined spots, identical in position and hue with those of either *threo*- or *erythro*-1,2-diphenyl-1-propyl acetate. The infrared spectra of these oils were almost identical with that of a mixture of the two epimers.

A thin layer chromatogram of the second combined fraction (343 mg., 10.9%) revealed the presence of four components. The principal one had a spot identical in position and hue with that of either *dl*- or *meso*-1,2-di-*O*-acetyl-1,2-diphenylethylene glycol. This material partially crystallized on prolonged standing and was recrystallized from a mixture of *n*-hexane and benzene, yielding a few milligrams of white solid, m.p. 90–110°. The thin layer chromatogram of this solid contained a single, cleanly defined spot, identical in position with that of 1,2-di-*O*-acetyl-1,2-diphenylethylene glycol. The infrared spectrum of the crude solid differed only slightly, with a few variations in band intensities and slight band shifts, from the spectrum of *dl*-1,2-di-*O*-acetyl-1,2-diphenylethylene glycol. The reported melting point for this racemic diacetate is 114–116°.[25] The diester represented less than 6% of the crude electrolysis product.

The third combined fraction (1306 mg., 41.5%) gave a thin layer chromatogram showing at least four spots. The principal spot was identical in all respects with that of *threo*-1-*O*-acetyl-1,2-diphenylethylene glycol (VIII). The crude material was rechromatographed on 100 g. of silicic acid using benzene as eluant. The first 900 ml. of eluent contained none of the monoacetate, and was discarded. The next 600 ml. of eluent left a thick oil (1124 mg.) which crystallized readily on seeding with a sample of authentic *threo*-monoacetate VIII. The thin layer chromatogram of this material contained one principal spot, identical in position with that of the *threo*-monoacetate, and two minor spots. The portion of the chromatogram corresponding to a spot for the *erythro*-monoacetate VII was blank. A portion (227 mg.) of the above crystalline material was recrystallized from a mixture of *n*-hexane and benzene, yielding 143 mg. of white solid, m.p. 85–87°. Its mixture melting point with authentic *threo*-1-*O*-acetyl-1,2-diphenylethylene glycol (m.p. 86–88°) was undepressed (85–87°), and the infrared spectra of the two samples were identical. The *threo*-monoacetate VIII represented approximately 20% of the crude electrolysis product.

Electrolysis of Sodium Acetate in the Presence of *erythro*-1-*O*-Acetyl-1,2-diphenylethylene Glycol.—This experiment was undertaken to establish whether or not the *erythro*-monoacetate VII, not found in the product mixtures from the above electrolyses, could survive the conditions of the reaction. The electrolysis was carried out as described above. A glacial acetic acid solution (20 ml.) of sodium acetate (1 g.) containing 0.57 g. of a mixture of *meso*-hydrobenzoin, the *erythro*-monoacetate VII, and the *meso*-diacetate IX was electrolyzed (0.4 amp.) for a period of 5 hr., after which a 2-ml. portion of the electrolysis mixture was withdrawn and evaporated to dryness in a vacuum desiccator over potassium hydroxide. The thin layer chromatogram of the residue contained spots corresponding to the *erthro*-monoacetate VII and the *meso*-diacetate IX, but did not contain a spot corresponding to *meso*-hydrobenzoin or to the *threo*-monoacetate VIII.

***threo*-1-*O*-Acetyl-1,2-diphenylethylene Glycol (VIII).**—The method used to prepare an authentic sample of the *threo*-monoacetate VIII was essentially that of Woodward and Brutcher.[14] A slurry of glacial acetic acid (100 ml.) containing *trans*-stilbene (5 g., m.p. 122–123°) and silver acetate (9.5 g.) was placed in a three-neck flask equipped with a reflux condenser, stirrer, and thermometer. Finally powdered iodine (6.7 g.) was added to the reaction mixture in small portions with vigorous stirring over a period of 30 min. at room temperature. When all of the iodine had been consumed, aqueous glacial acetic acid (10 ml., acid–water, 25:1) was added, and the reaction mixture was heated at 90–95° for 3 hr. with vigorous stirring, whereupon it was cooled, treated with an excess of sodium chloride, and filtered free

(24) S. Winstein, *J. Am. Chem. Soc.*, **68**, 119 (1946).

(25) F. A. A. Elhafez and D. J. Cram, *ibid.*, **75**, 339 (1953).

of insoluble salts. There were washed with hot benzene, and the filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in ether (100 ml.) and the solution was washed with dilute ammonium hydroxide and with water. Evaporation of the dried ether solution left 6.5 g. (97.5%) of thick oil which crystallized on standing. After two recrystallizations from a mixture of *n*-hexane and benzene, the desired pure *threo*-monoacetate VIII was obtained as white crystals, m.p. 86–88°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.93; H, 6.21.

***dl*-1,2-Di-*O*-acetyl-1,2-diphenylethylene Glycol.**—A pyridine solution (5 ml.) of the above *threo*-monoacetate VIII (0.45 g.) was treated with 5 ml. of acetic anhydride, and the resulting solution was allowed to stand at room temperature for a period of 12 hr. The mixture was then evaporated under reduced pressure, yielding 0.5 g. of solid residue, m.p. 100–105°. After two recrystallizations from a mixture of *n*-hexane and benzene, the pure *dl*-diacetate was obtained, m.p. 116–117°. The reported melting point is 114–116°.[26]

***erythro*-1-*O*-Acetyl-1,2-diphenylethylene Glycol (VII) and *meso*-1,2-Di-*O*-acetyl-1,2-diphenylethylene Glycol (IX).**—The starting material, *meso*-hydrobenzoin, was prepared by the sodium borohydride reduction of benzil after the procedure of Fieser.[15] One recrystallization of the crude product from dilute ethanol yielded sufficiently pure product, m.p. 135–136.5°.

A pyridine solution (10 ml.) of *meso*-hydrobenzoin (1.1 g.) and acetic anhydride (0.6 ml., 1.2 equiv.) was allowed to stand at room temperature for a period of 2 hr., whereupon sufficient water was added to engender cloudiness. On standing in the cold room for 12 hr., a white solid crystallized from the turbid solution. The crystals were collected and the filtrate was acidified with dilute hydrochloric acid and extracted three times with ether. The extracts were washed with water, dried, and evaporated, affording 0.5 g. of thick oil. The original white solid (0.3 g., m.p. 128–131°) was recrystallized from a mixture of *n*-hexane and benzene, yielding white needles, m.p. 135–136.5°. The reported melting point for *meso*-1,2-di-*O*-acetyl-1,2-diphenylethylene glycol is 136–138°.[24] The crude oil extracted from the above aqueous filtrate was chromatographed on 100 g. of silicic acid using benzene, gradually enriched in ether, as eluent. The first 600 ml. of eluent was discarded. Evaporation of the next 700 ml. of eluent left 0.39 g. of white solid. This was recrystallized from a mixture of *n*-hexane and benzene, affording the pure *erythro*-monoacetate VII, m.p. 90–92°. The infrared spectrum showed a strong O–H stretching band at 3380 cm.$^{-1}$ in addition to two typical ester bands at 1732 (C=O) and 1239 cm.$^{-1}$ (C–O).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.27; H, 6.43.

1,2-Diphenyl-1-propyl Acetate (IX).—1,2-Diphenyl-1-propanol was prepared in the customary manner by the action of phenylmagnesium bromide (20% excess) on hydratropaldehyde. The thin layer chromatogram of the crude product displayed two spots, with no spot corresponding to starting aldehyde, and its infrared spectrum showed an O–H stretching band at 3420 cm.$^{-1}$, and no carbonyl bands. The crude 1,2-diphenyl-1-propanol (10 g.) was added to a mixture of pyridine (10 ml.) and acetic anhydride (10 ml.), and the resulting solution was stirred at room temperature for a period of 18 hr., then was treated with an excess of chilled dilute sulfuric acid, extracted with ether, and processed in the usual fashion. The crude acetylation product was a thick oil, 11.4 g., which partially crystallized on standing. It was recrystallized once from petroleum ether (b.p. 66–70°), affording sharp rectangular crystals, m.p. 103–105°. The reported melting point for *erythro*-1,2-diphenyl-1-propyl acetate is 109–110°, and that for the *threo*-epimer is 38–39°.[25]

(26) D. Swern, G. Billen, T. Findley, and J. Scanlan, *J. Am. Chem. Soc.*, **67**, 1786, (1945).

Chlorination of Furfural in Concentrated Hydrochloric Acid

YOSHIKAZU HACHIHAMA, TOSHIYUKI SHONO, AND SATORU IKEDA

Department of Chemical Technology, Faculty of Engineering, Osaka University, Osaka, Japan

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Treatment of furfural with manganese dioxide or chlorine in hydrochloric acid to produce mucochloric acid yielded two unknown crystalline materials, one as an intermediate of the reaction and the other as a by-product. The intermediate was identified as β-chloro-β-formylacrylic acid and the by-product as α-chlorocrotonolactone.

When furfural is treated with manganese dioxide or chlorine gas in concentrated hydrochloric acid, the major product is mucochloric acid (III) which is the raw material for the synthesis of dichloromaleic acid.

Mucochloric acid has been produced by a variety of methods,[1,2] such as by the action of chlorine on furoic acid, treatment of furoic acid in hydrochloric acid with manganese dioxide, treatment of β,γ-dichlorofuroic acid with an excess of bromine water or with nitric acid, and by reaction of furfural with the reagents mentioned in the first paragraph. The mechanisms of these reactions are very complex since the process involves chlorination, oxidation, and opening of the furan ring. In this article, two unknown crystalline compounds were isolated, one from the initial stage of the reaction of furfural with manganese dioxide in hydrochloric acid and the other from the reaction of furfural with manganese dioxide or chlorine, and their structures were determined.

The reaction of furfural with manganese dioxide in concentrated hydrochloric acid is the most convenient way to prepare mucochloric acid on a laboratory scale A yield of nearly 75% was obtained by the method of Yanagida.[3]

In this process, the reaction can be considered to take place in two steps, the first below and the second above 10°. If the reaction is interrupted after the first step and extracted with ether, and the ether extract is distilled at reduced pressure, colorless crystals of m.p. 53–55° are obtained (compound A). If the reaction is allowed to proceed to completion, the mucochloric acid is separated by filtration, and the mother liquors are ether extracted, evaporation of the ether and distillation of the residue (105–115° at 4 mm.) yields a colorless liquid that crystallizes on standing, m.p. 25–27° (compound B). However, treatment of furfural with chlorine in hydrochloric acid is more convenient to obtain compound B in high yield.

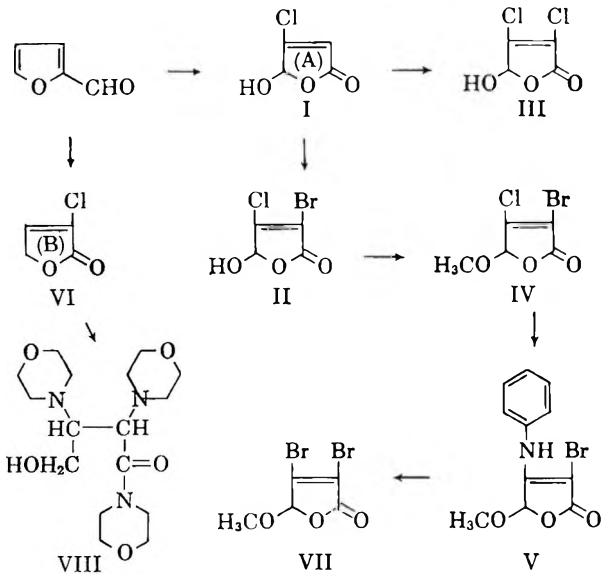
Elementary analysis of compound A agreed with formula $C_4H_3O_3Cl$. Its infrared spectrum resembled that of mucochloric acid which exists not as the open-chain α,β-dichloro-β-formylacrylic acid but in the ring structure (III). The spectrum had bands at 1625

(1) D. T. Mowry, *J. Am. Chem. Soc.*, **72**, 2535 (1950).

(2) A. P. Dunlop and E. Sherman, U. S. Patent 2,821,553 (1958).

(3) M. Yanagida, *J. Pharm. Soc. Japan*, **72**, 1383 (1952).

SCHEME I



(C–C double bond), at 1760 (lactone carbonyl), and at 3290 cm.$^{-1}$ (hydroxyl). Carboxylic acid bands were absent. Compound A was converted to mucochloric acid with manganese dioxide in concentrated hydrochloric acid at 60–80°. From these results, the compound was presumed to be the ring form of α- or β-chloro-β-formylacrylic acid.

Hill[4] and Prins[5] reported the oximes (m.p. 150°) which may be derived from α- or β-chloro-β-formylacrylic acid; however, their proof of the position of the chlorine atom may be questionable.

To determine the position of the chlorine atom, the compound was brominated to yield colorless crystals, m.p. 122–123°. The chloro–bromo compound gave a pseudo methyl ester, m.p. 37–38°. The ester was treated with aniline by the method of Wasserman[6] to form a monoanilino derivative, m.p. 115–117°, which gave no depression in melting point upon admixture with an authentic specimen of α-bromo-β-anilino-γ-methoxycrotonolactone[6] (V), and whose carbon–hydrogen analysis agreed with formula V. From these results, the structure of compound A was determined to be the cyclic form of β-chloro-β-formylacrylic acid (I). According to Kuh and Shepard,[7] β-bromo-α-chloro-β-formylacrylic acid is obtained by bromination of furfural followed by chlorination, which shows that the β-position of β-formylacrylic acid is more reactive toward halogenation than the α-position. These results are confirmed by the present work.

The elementary analysis of compound B, which was obtained as a by-product in the reaction of furfural with manganese dioxide or chlorine in concentrated hydrochloric acid to produce mucochloric acid, agreed with that calculated for $C_4H_3O_2Cl$. Its infrared spectrum showed bands at 1625 (C–C double bond) and 1775 cm.$^{-1}$ (carbonyl group) and had no hydroxyl bands. The spectrum corresponded to that of α-chlorocrotonolactone over the whole wave-length range. Compound B reacted with morpholine to produce the trimorpholino derivative (VIII), which was also produced from authentic α-chlorocrotonolactone.[8] From this evidence, the structure of compound B is deduced to be that of α-chlorocrotonolactone (VI).

(4) Hill and Allen, *Am. Chem. J.*, **19**, 665 (1897).

(5) H. J. Prins and H. G. Haring, *Rec. trav. chim.*, **73**, 479 (1954).

(6) H. H. Wasserman and F. M. Precopio, *J. Am. Chem. Soc.*, **76**, 1242 (1954).

(7) E. Kuh and L. Shepard, *ibid.*, **75**, 4597 (1953).

Experimental

β-Chloro-β-formylacrylic Acid (I).—A round-bottom four-necked flask fitted with an efficient agitator, a dropping funnel, and a thermometer was charged with 1 l. of concentrated hydrochloric acid (35%) and cooled to 0° in a salt–ice mixture. A mixture of 80 g. of freshly distilled furfural and 320 g. of finely powdered manganese dioxide was added in small portions over a period of 3 hr. while the temperature was maintained below 10°. The reaction mixture was stirred at room temperature for 0.5 hr. and then was extracted with ether in a continuous extractor. After drying (sodium sulfate) and removal of the ether, 92 g. of a light yellow liquid was obtained. This was distilled *in vacuo* (120–150° at 1 mm.) and recrystallized from benzene yielding colorless crystals (85 g.) of m.p. 53–55°. Its molecular weight was 135 by cryoscopy in dioxane.

Anal. Calcd. for $C_4H_3O_2Cl$: C, 35.7; H, 2.23; Cl, 26.4; mol. wt., 134.5. Found: C, 35.84; H, 2.39; Cl, 26.22; mol. wt., 135.

Preparation of Mucochloric Acid (Yanagida's Method).—In the preceding procedure, after the reaction mixture attained room temperature and was stirred for 0.5 hr., it was heated with stirring to 60° in a water bath and an additional 140 g. of manganese dioxide was added in small portions while the temperature was raised to 80°. After the final addition, the reaction temperature was raised to 100° and was held there until the black color of the mixture changed to a red-brown. The reaction mixture was decanted while hot into a beaker and was allowed to cool. The crystals that formed were filtered and recrystallized from water to yield colorless crystals of mucochloric acid, m.p. 125°.

Mucochloric Acid (III) from I.—Five grams of I was suspended in 50 ml. of concentrated hydrochloric acid and 5 g. of manganese dioxide was added at room temperature. The reaction flask was heated slowly to 60° with stirring while an additional 20 g. of manganese dioxide was added over a period of an hour. The mixture then was heated at 95° for 0.5 hr., decanted into a beaker, and allowed to cool. Colorless crystals (2 g.), m.p. 125–126.5°, were obtained after recrystallization from water. They did not depress the melting point of an authentic sample of mucochloric acid.

Bromination of I.—A four-neck round-bottom flask fitted with an efficient agitator, a dropping funnel, and a thermometer was charged with 12 g. of I and 50 ml. of water and was heated to 60–70°; 16 g. of bromine was added over a period of an hour. After cooling, filtration, and recrystallization from water, 16 g. of α-bromo-β-chloro-β-formylacrylic acid (II), m.p. 122–123°, was obtained.

Methylation of II.—The esterification was carried out by heating 11.5 g. of II with 60 ml. of methanol and 10 drops of 98% sulfuric acid. Lachrymatory crystals (8 g.) of the pseudo methyl ester, α-bromo-β-chloro-γ-methoxycrotonolactone (IV), were obtained, m.p. 37–38°, after recrystallization from petroleum ether (b.p. 35–70°).

α-Bromo-β-anilino-γ-methoxycrotonolactone (V).—A cold solution of 1.74 g. of aniline in 4 ml. of methanol was added to 2 g. of IV in 4 ml. of methanol, and the resulting solution was placed in the refrigerator overnight. The dropwise addition of water with stirring to the cold solution caused an oil to separate which gradually solidified to a light yellow solid. After several recrystallizations from methanol, colorless crystals were obtained, m.p. 115–117°.

Anal. Calcd. for $C_{11}H_{10}O_3BrN$: C, 46.41; H, 3.64. Found: C, 46.48; H, 3.55.

In a similar manner, mucobromic acid was converted to the pseudo methyl ester (VII), m.p. 48.5–49.5°, and then to the β-anilino derivative (V) which was identical in melting point with the one derived from IV and gave no depression upon admixture with it.

α-Chlorocrotonolactone (VI).—The reaction was run in a five-neck 300-ml. round-bottom flask fitted with an efficient agitator,

(8) Y. Hata, *J. Chem. Soc. Japan*, **79**, 1531 (1958).

reflux condenser, dropping funnel with a capillary stem, gas feed tube, and a thermometer. It is important that the capillary of the dropping funnel always remains below the surface of the reaction mixture.

The flask was charged with 250 ml. of 35% hydrochloric acid and cooled to 0°. A 1:2 mixture of chlorine and air (v./v.) was passed through the liquid at a rate of 2 l./min. Forty grams of furfural was added dropwise below 5° from the dropping funnel. After the addition, the reaction mixture was colorless. It was then heated slowly with stirring to 85° over a period of 2 hr. and kept at this temperature for 1.5 hr. The mixture then was cooled to room temperature to yield 14 g. of crystalline mucochloric acid. The mother liquors were extracted with ether, and the ether extract was vacuum distilled to yield 21 g. of a colorless liquid, b.p. 105–115° (4 mm.). This crystallized on standing and had a melting point of 25–27° after recrystallization from water.

Anal. Calcd. for $C_4H_3O_2Cl$: C, 40.50; H, 2.53; Cl, 29.92. Found: C, 40.96; H, 2.55, Cl, 29.94.

Trimorpholino Derivative of VI (VIII).—A mixture of 4 ml. morpholine and 0.8 g. of VI in 40 ml. of dry ether was refluxed for 6 hr. and allowed to stand overnight. The resulting white precipitate was separated and extracted with 50 ml. of dry acetone. Concentration of the acetone extract yielded 500 mg. of white crystals, m.p. 157–158°, after recrystallization from acetone and benzene.

Anal. Calcd. for $C_{16}H_{29}O_5N_3$: C, 55.96; H, 8.51; N, 12.24. Found: C, 55.38; H, 8.58; N, 11.96.

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Some New Reactions and Derivatives of Azulene[1]

ARTHUR G. ANDERSON, JR., DONALD J. GALE, RICHARD N. MCDONALD, ROBERT GRIFFIN ANDERSON,[2] AND ROBERT C. RHODES[3]

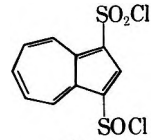
Department of Chemistry, University of Washington, Seattle 5, Washington

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In the course of our studies on the chemistry of azulene[4] a number of new reactions and derivatives of azulene have been found which did not prove pertinent to subsequent papers. These collected results are reported.

The facile reaction of azulene with mercuric chloride to form a bis(chloromercuri)azulene had been observed earlier,[5] but the derivative was very insoluble in organic solvents and attempts to establish the positions occupied by the chloromercuri groups through displacement reactions were unsuccessful (except for the formation of 1-acetylazulene in low yield). The analogous reaction with mercuric acetate has been found to give a diacetoxymercuri derivative (1) in high yield. Treatment of an acetic acid solution of 1 with iodine gave 1,3-diiodoazulene and provided evidence that the dimercuri compounds were, as expected, 1,3 substituted. Reaction of 1 with bromine or nitryl chloride, however, resulted in oxidative decomposition, and treatment with N-bromosuccinimide or N,N-dibromomethylhydantoin gave an unstable red oil which was not characterized. Warming a mixture of acetic anhydride and 1 in acetic acid formed 1-acetylazulene in 34% yield but no 1,3-diacetylazulene. This was unexpected, as no azulene was obtained when 1 was exposed to 85% phosphoric acid for several hours.[6]

Reaction of azulene with sulfur trioxide–dioxane adduct and then basification gave a red solid. That this material, which was not obtained analytically pure, was sodium 1-azulenesulfonate was indicated by the absorptions at 8.5, 8.95, 9.37, and 9.57 μ[7] in its infrared spectrum: its reaction with nitric acid and acetic anhydride to give 1,3-dinitroazulene[8a]; and the formation of azulene-1-sulfonyl-3-sulfinyl dichloride (2) from the reaction of the free acid with excess thionyl chloride. Attempts to isolate the free 1-azulenesulfonic acid afforded hygroscopic maroon needles. These results are similar to those obtained by Treibs and Schroth[8b] in the analogous sulfonation of guaiazulene and the preparation of a number of derivatives of the guaiazulenesulfonic acid.



2

The direct introduction of a cyano group onto benzenoid aromatic nuclei by Lewis acid-catalyzed reactions with cyanogen bromide is well known.[9] It has been found, however, that uncatalyzed reactions with thiophene[10] and furan[11] gave the α-bromo rather than the cyano substitution products. We have examined the stannic chloride-catalyzed reaction of cyanogen bromide with azulene, and the results obtained differ appreciably from those reported by Treibs[12] while our studies were in progress. The addition of azulene to one equivalent of preformed cyanogen bromide–stannic chloride complex in ether gave a 36% (94% net) yield of 1-cyanoazulene. When the same procedure was used but with a tenfold excess of cyanogen bromide–stannic chloride, there were obtained two different products: 1,3-dibromoazulene (16%) and a new substance which showed absorption at 567 mμ and a sharp band at 4.54

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(2) National Science Foundation Predoctoral Fellow, summer, 1959; National Institutes of Health Fellow, 1959–1961.

(3) National Institutes of Health Fellow, 1961–1963.

(4) (a) A. G. Anderson, Jr., and L. L. Replogle, *J. Org. Chem.*, **28**, 262 (1963); (b) A. G. Anderson, Jr., R. G. Anderson, and T. S. Fujita, *ibid.*, **27**, 4535 (1962), and preceding papers.

(5) A. G. Anderson, Jr., E. J. Cowles, J. J. Tazuma and J. A. Nelson, *J. Am. Chem. Soc.*, **77**, 6321 (1955).

(6) The 1,3-bis(chloromercuri)azulene was readily converted to azulene (66%) by this reagent.[5]

(7) N. B. Colthup, *J. Opt. Soc. Am.*, **40**, 397 (1950).

(8) (a) The electrophilic displacement of groups from the 1-position of azulene is well known [see, for example, A. G. Anderson, Jr., and R. N. McDonald, *J. Am. Chem. Soc.*, **81**, 5669 (1959)]; (b) W. Treibs and W. Schroth, *Ann.*, **586**, 202 (1954).

(9) P. Karrer and E. Zeller, *Helv. Chim. Acta*, **2**, 482 (1919); **3**, 261 (1920).

(10) W. Steinkopf, *Ann.*, **430**, 78 (1923).

(11) A. H. Klopp and G. F. Wright, *J. Org. Chem.*, **4**, 142 (1939).

(12) W. Treibs, *Ber.*, **92**, 606 (1959).

TABLE I

REACTION OF AZULENES WITH CYANOGEN BROMIDE AND STANNIC CHLORIDE[a]

Procedure	Ratio of reactants, moles: Azulene	CNBr	$SnCl_4$	Yield of products, %[a]: Azulene	1-CN	1-Br-3-CN	1,3-DiBr	1-Br
I[b]	1	10	10			49.2	16.1	
I	2	15	15			38.9	17.0	
I	1	1	1	61.7	36 (94)			
I[c]	1	10	10	38.7		21.3	Trace	25.1
II[b]	1	10	10			33.1	5.8	
II	1	1	1	62.5	36 (96)			
II	1	1	4	61.0	36 (93)			
	1-Br							
II	1	1	1					94.6
II	1	10	10			38	42.8	
	1-CN							
I	1	10	10		No reaction			
II	1	10	10		No reaction			
	1,3-DiBr							
I	1	10	10		No reaction			

[a] Figures in parentheses are per cent net yields. [b] See text for description of procedures. [c] Reaction quenched after 1.5 hr.

μ. These data and the elemental analyses corresponded to those of 1-bromo-3-cyanoazulene,[13] and this structure was confirmed by the formation of the same substance from the reaction of 1-bromoazulene with cyanogen bromide–stannic chloride.

The marked difference in the products from the two experiments (no 1-cyanoazulene was formed in the run with excess cyanogen bromide–stannic chloride) led to further investigation. Two procedures were followed and the ratio of reactants was varied in each. In procedure I the cyanogen bromide–stannic chloride complex was preformed and the azulene was added to this. In procedure II the azulene and cyanogen bromide were dissolved in ether and to this was added the stannic chloride. The results obtained are summarized in Table I. It is seen that the use of a large excess of cyanogen bromide and stannic chloride formed only 1,3-dibromo- (6–17%) and 1-bromo-3-cyanoazulene (33–49%) with both procedures. Both procedures, however, gave only 1-cyanoazulene (36%) when the azulene–cyanogen bromide ratio was 1:1. The formation of 1-cyanoazulene and 1,3-dibromoazulene *via* normal electrophilic substitution was expected, but the complete dependence of the nature of the products on the molar ratio of reactants was quite otherwise.

In view of our previous observations that electron-withdrawing groups on the 1-position deactivated the azulene ring to the electrophilic introduction of a second substitutuent,[4] it seemed likely that the 1-bromo-3-cyano compound was formed *via* 1-bromoazulene. It was demonstrated that the latter was indeed an intermediate by stopping one run after about one-sixth of the usual time. The reaction mixture was found to contain a 25% yield of 1-bromoazulene, 21% of the 1-bromo-3-cyano product, and a trace of the 1,3-dibromo compound. Therefore, it appeared that under these conditions the sole initial reaction was the bromination of the azulene, but that the cyanation of the 1-bromoazulene formed was the preferred mode of the second reaction. The matter is not quite so clear-cut as this, however, since a run starting with 1-bromoazulene gave approximately equal amounts of the cyano and bromo disubstitution products. That the bromocyano compound did not arise from the bromination of 1-cyanoazulene or by a displacement on the dibromoazulene was shown by the finding that the latter compounds were inert to an excess of cyanogen bromide and stannic chloride. The inertness of 1-bromoazulene to a molar equivalent of cyanogen bromide and stannic chloride was also observed and thus the 1-cyanoazulene produced from azulene under these conditions could not have been formed *via* 1-bromoazulene. No satisfactory explanation was found for the change in products caused by the change in molar ratios of reactants.

The reaction of azulene at the 4-position with alkyl and aryl lithium compounds was established by Hafner and co-workers.[14] These reactions gave a dihydroazulene which was readily aromatized to the 4-substituted azulene. Stafford, *et al.*,[15] identified the red oil product from azulene and sodium amide as 4-aminoazulene solely on the basis of the similarity of its absorption spectra with those of 4-methoxyazulene. The direct formation of 4-aminoazulene seemed reasonable,[16] and verification of this result was sought. Heating azulene and sodium amide in tetrahydrofuran afforded an unstable red oil. The shift in the visible region (λ_{max} of principal absorption at 510 mμ) and a peak in the N–H region at 3.0 μ were indicative of a 4-aminoazulene, but the substance could not be obtained analytically pure. However, it formed a crystalline, stable, acetyl derivative which had the expected composition and spectral properties and was thus very probably N-acetyl-4-aminoazulene.

Melville[17] first observed that an azulene and sodium would react to form a substance insoluble in hexane. More recently Weissman and co-workers[18] have studied the reaction of naphthalene and sodium in tetrahydrofuran and found that carbonation of the product formed two isomeric dihydronaphthoic acids. Treatment of a solution of azulene in tetrahydrofuran with sodium caused the color of the solution to change from blue to

(13) The calculated λ_{max} in the visible is 571 mμ based on the additivity of the effects of the two groups in the 1- and 3-positions [see A. G. Anderson, Jr., and B. M. Steckler, *J. Am. Chem. Soc.*, **81**, 4941 (1959), and references therein].

(14) K. Hafner, C. Bernhard, and R. Müller, *Ann.*, **650**, 35 (1961); K. Hafner and H. Weldes, *ibid.*, **606**, 90 (1957).

(15) W. H. Stafford, J. P. Ward, and D. H. Reid, *Chem. Ind.* (London), 1258 (1955).

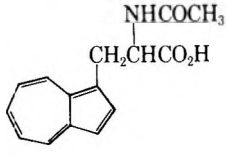
(16) 2-Aminopyridine results directly from the reaction of pyridine and sodium amide, while an alkyl lithium and pyridine form a dihydro addition product.

(17) J. Melville, *J. Am. Chem. Soc.*, **55**, 3288 (1933).

(18) D. E. Paul, D. Lipkin, and S. I. Weissman, *ibid.*, **78**, 116 (1956).

red-brown, and carbonation of the mixture gave a red acidic product from which was obtained methyl 1-azuloate in 7.7% yield and a small yellow fraction. Reaction of the latter with chloranil gave 0.8% of methyl 1-azuloate as the only azulenic product.

1-Bromo-3-acetylazulene was obtained in good yield from the reaction of 1-acetylazulene with N-bromosuccinimide. Treatment of 1-azulylmethyltrimethylammonium iodide with the sodium salt of ethyl acetamidocyanoacetate and hydrolysis of the product gave α-acetamido-β-(1-azulyl)-propionic acid (**3**). Attempts to convert this to the free amino acid were unsuccessful.



3

Experimental[19]

1,3-Bis(acetoxymercuri)azulene.—To a stirred solution of 512 mg. (4.0 mmoles) of azulene in 25 ml. of methanol was added 3.828 g. (12.0 mmoles) of mercuric acetate in 75 ml. of methanol. After about 5 min. the solution became light yellow-green and a metallic blue precipitate formed. The precipitate was collected by filtration, washed with methanol (several times) and then with ether, and dried under vacuum for 4 hr. The product (2.36 g., 91%) did not melt at 360° and was soluble only in acetic acid and dimethyl sulfoxide. An acetic acid solution showed λ_{max} in mμ (D^{20a}) at 270 (1.73), 275 (1.85), 280 (1.85), 339 (0.20), and 620 (1.0).

Anal. Calcd. for $C_{14}H_{12}Hg_2O_4$: C, 26.04; H, 1.86; Hg, 62.15. Found: C, 26.02; H, 1.78; Hg, 62.08.

1,3-Diiodoazulene from 1,3-Bis(acetoxymercuri)azulene.—To a solution of 1.215 g. (1.6 mmoles) of 1,3-bis(acetoxymercuri)azulene in 300 ml. of acetic acid was added 1.219 g. (4.8 mmoles) of iodine in 100 ml. of acetic acid. The mixture was stirred for 4 hr. and poured into 1.6 l. of water; the blue material was extracted with 300-, 100-, 100-, and then 50-ml. portions of dichloromethane. The combined extracts were washed with two 500-ml. portions of water, dried over calcium chloride, and evaporated to dryness in an air stream. The residue was chromatographed on an alumina column and elution with petroleum ether (b.p. 30–60°) separated most of the excess iodine from the blue fraction. The residue from the latter was rechromatographed with 1:1 petroleum ether–dichloromethane as the eluent and yielded 130 mg. (21.3%) of green needles which were identical (ultraviolet, visible, and infrared spectra) with an authentic sample.[20b]

Anal. Calcd. for $C_{10}H_6I_2$: C, 31.61; H, 1.59. Found: C, 31.67; H, 1.61.

1-Acetylazulene from 1,3-Bis(acetoxymercuri)azulene.—A solution of 200 mg. (0.305 mmole) of 1,3-bis(acetoxymercuri)-azulene in 10 ml. of acetic acid and 5 ml. of acetic anhydride was heated on a steam bath for 2.5 hr., then cooled, and added to 150 ml. of water. The aqueous mixture was extracted with 100- and 50-ml. portions of dichloromethane, and the combined extracts were washed with 200 ml. of water and dried over calcium sulfate. The solvent was removed, and the residue was chromatographed on an alumina column. Petroleum ether was used as the eluent until the reaction of acetic anhydride with the alumina ceased, and thereafter petroleum ether–dichloromethane (2:1) was used. A small blue band was followed by a lavender band, and several small colored bands remained near the top of the column. Removal of the solvent from the lavender eluate left 18 mg. (34.4%) of a maroon oil which was identified (visible and infrared spectra) as 1-acetylazulene.[5]

Reaction of Azulene with Sulfur Trioxide–Dioxane Adduct.—A solution of 50 mg. (0.39 mmole) of azulene in 5 ml. of dry 1,2-dichloroethane was added dropwise to a cooled (ice bath), stirred suspension of sulfur trioxide–dioxane adduct prepared by passing sulfur trioxide (generated by warming an excess of Sulfan B) into 5 ml. of dry 1,2-dichloroethane and 2 ml. of dry dioxane until a small amount of the white complex was visible. The orange-red mixture was stirred for 15 min. and then poured into water. The mixture was made alkaline with sodium carbonate, and the aqueous layer then was separated and filtered. Evaporation of the filtrate to dryness, extraction of the red residue with hot ethanol, and removal of the solvent from the violet alcoholic solution left 40 mg. of red solid which did not melt up to 300°. The peaks in the infrared spectrum (8.5, 8.95, 9.37, and 9.57 μ) were those expected for sodium 1-azulenesulfonate.[7]

The salt was treated with 10 ml. of a solution prepared by adding 1 ml. of concentrated nitric acid to 25 ml. of acetic anhydride at 0° and an emulsion formed. One drop of concentrated nitric acid was added, and the emulsion broke as the color of the solution changed to orange. After 5 min., the mixture was poured into water, the whole was extracted with dichloromethane, and the organic extracts were dried over sodium sulfate. Removal of the solvent left orange needles, m.p. 262–263°, which were identical (mixture melting point, ultraviolet and visible spectra) with an authentic sample of 1,3-dinitroazulene.[5]

Azulene-1-sulfonyl-3-sulfinyl Dichloride.—Azulene (100 mg., 0.78 mmole) and sulfur trioxide–dioxane adduct were allowed to react as described above and then were filtered to remove excess adduct. (The isolation of hygroscopic maroon needles, which were presumed to be 1-azulenesulfonic acid, could be accomplished by concentration of the filtrate). To the filtrate was added 3 ml. of thionyl chloride, and the mixture was heated under reflux for 40 min. The solution, the color of which had become green, was cooled and poured into water; the whole was extracted with dichloromethane. The combined organic extracts were washed with water and saturated salt water, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from petroleum ether–dichloromethane gave yellow-brown crystals, m.p. 115–129° dec., which on recrystallization amounted to 112 mg. (46%) of golden needles, m.p. 117–125° dec. A chloroform solution showed λ_{max} in mμ (D^{20a}) at 238 (0.69), 297 (1.62), 321 (0.29), 365 (0.38), and 466 (1.5).

Anal. Calcd. for $C_{10}H_6Cl_2O_3S_2$: C, 38.84; H, 1.96; Cl, 22.93. Found: C, 38.90; H, 2.34; Cl, 23.10.

Reaction of Azulene with Cyanogen Bromide. Procedure I.—Anhydrous stannic chloride was added dropwise with cooling and stirring to cyanogen bromide in dry ether under a dry nitrogen atmosphere. A white precipitate separated, and the mixture was stirred at room temperature for 10 min. Azulene then was added, and the mixture was stirred overnight and then worked up as described below for the preparation of 1-bromo-3-cyanozulene.

Procedure II.—Anhydrous stannic chloride was added dropwise with stirring and cooling under a dry nitrogen atmosphere to a solution of azulene and cyanogen bromide in dry ether. The mixture was stirred overnight at room temperature and worked up as described below for the preparation of 1-bromo-3-cyanoazulene.

1-Bromo-3-cyanozulene. A. From Azulene by Procedure I.—Azulene (0.256 g., 2 mmoles) was treated with cyanogen bromide (2.12 g., 20 mmoles) and stannic chloride (5.2 g., 20 mmoles) according to procedure I. After 24 hr., 10 ml. of 5% hydrochloric acid was added and the separated organic layer was washed with water, 5% sodium bicarbonate, and then water. The residue from the dried (sodium sulfate) solution was chromatographed on a column of acid-washed alumina. Elution with *n*-hexane gave a blue fraction from which was obtained 92 mg. (16.1%) of green needles, m.p. 89–90°, which were identical (mixture melting point, absorption spectra) with an authentic sample of 1,3-dibromoazulene. A very small green band was eluted next with 2:5 dichloromethane–*n*-hexane, and the main product was removed as a purple fraction by a 1:1 mixture of these solvents. The residue from the purple solution formed purple needles, m.p. 162–165°, which after recrystallization from *n*-hexane amounted to 0.228 g. (49.2%) and melted at 167–168.5°. A dichloromethane solution showed λ_{max} in mμ (D^{20a}) at 236 (0.70), 285 (0.79), 291 (1.07), 297 (1.01), 303 (1.38), 373 (0.22),

(19) Melting points were taken on a calibrated Fisher-Johns apparatus and are uncorrected. Visible and ultraviolet absorption spectra were recorded with a Cary Model 11S or 14 spectrophotometer. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer. Elementary analyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England; Dr. Alfred Bernhardt, Mulheim (Ruhr), Germany; Elek Microanalytical Laboratory, Los Angeles, Calif.; or Mr. B. J. Nist and Mr. C. H. Ludwig and Miss K. Schwarz, Miss A. Kuo, and Miss L. Ho.

(20) (a) *D* represents optical density. (b) A. G. Anderson, Jr., and B. M. Steckler, *J. Am. Chem. Soc.*, **81**, 4941 (1959).

and 567 (1.24) with a shoulder at 598 (1.12). The infrared spectrum showed a peak attributed to the nitrile group at 4.54 μ.

Anal. Calcd. for $C_{11}H_6BrN$: C, 56.71; H, 2.60; N, 6.06. Found: C, 56.88; H, 2.81; N, 5.78.

B. From Azulene by Procedure II.—Azulene (0.256 g., 2 mmoles), cyanogen bromide (2.12 g., 20 mmoles), and stannic chloride (5.2 g., 20 mmoles) were allowed to react according to procedure II, and the reaction mixture was worked up as described in A. There was obtained 33 mg. (5.8%) of 1,3-dibromoazulene and 0.153 g. (33.1%) of 1-bromo-3-cyanoazulene which were identical to the products in A.

C. From 1-Bromoazulene by Procedure I.—1-Bromoazulene (0.16 g., 0.77 mmole) was treated with cyanogen bromide (0.82 g., 7.7 mmoles) and stannic chloride (2.02 g., 7.7 mmoles) according to procedure I. After 24 hr., the reaction mixture was worked up as described in A. From the *n*-hexane eluate was obtained 94 mg. (42.7%) of 1,3-dibromoazulene, and from the 1:1 dichloromethane–*n*-hexane eluate was isolated 68 mg. (38%) of 1-bromo-3-cyanoazulene which were identical with the products in A.

1-Cyanoazulene. Procedure I.—Azulene (0.256 g., 2 mmoles), cyanogen bromide (0.212 g., 2 mmoles), and stannic chloride (0.522 g., 2 mmoles) were allowed to react according to procedure I, and the reaction mixture was worked up as described for 1-bromo-3-cyanoazulene. The crude product was chromatographed on an acid-washed alumina column. Elution with *n*-pentane removed 0.158 g. (61.7%) of unchanged azulene, and then dichloromethane removed a reddish fraction from which was obtained 0.11 g. (36%, 94% net) of 1-cyanoazulene as maroon needles, m.p. 50–51°, which were identical (mixture melting point, absorption spectra) with an authentic sample.

Procedure II.—Azulene (0.256 g., 2 mmoles), cyanogen bromide (0.25 g., 2.36 mmoles), and stannic chloride (0.67 g., 2.56 mmoles) were allowed to react according to procedure II, and the reaction mixture was worked up as described above for 1-bromo-3-cyanoazulene. Chromatography of the crude product on an acid-washed alumina column gave 0.16 g. (62.5%) of unchanged azulene and 0.11 g. (36%, 96% net) of 1-cyanoazulene, m.p. 50–51°, which was identical with an authentic sample.

Incomplete Reaction of Azulene and Cyanogen Bromide–Stannic Chloride.—Azulene (0.256 g., 2 mmoles), cyanogen bromide (2.12 g., 20 mmoles), and stannic chloride (5.2 g., 20 mmoles) were allowed to react according to procedure I, except that the reaction was quenched by the addition of water after 1.5 hr. The reaction mixture was worked up as described for 1-bromo-3-cyanoazulene, and the crude product was chromatographed on a column of acid-washed alumina. Elution with *n*-pentane removed a blue fraction and from the fractional sublimation (room temperature and 0.2-mm. pressure) of the residue from this were obtained azulene (99 mg., 38.7%), 1-bromoazulene (0.104 g., 25.1%), and a trace of 1,3-dibromoazulene which were identical with authentic samples of these compounds. A 1:1 *n*-pentane–dichloromethane solvent eluted a purple band from which was obtained 99 mg. (21.3%) of 1-bromo-3-cyanoazulene which was identical with an authentic sample.

N-Acetyl-4-aminoazulene.—A solution of 512 mg. (4 mmoles) of azulene and 200 mg. (5 mmoles) of sodium amide in 200 ml. of pure, dry tetrahydrofuran was heated under reflux for 24 hr. under anhydrous conditions. The mixture was cooled, treated with 2 ml. of water, and the solvent was removed under reduced pressure. Nitrogen was admitted to the flask, then 200 ml. of ether, and 100 ml. of water. The mixture was shaken and filtered. The separated ethereal solution was washed with two 200-ml. portions of water. The solvent was removed (nitrogen atmosphere, room temperature) from the dried (calcium sulfate) solution, and the residue was chromatographed on a basic alumina column. Petroleum ether eluted unchanged azulene, and dichloromethane removed a green band and then a red fraction. The red fraction was rechromatographed and afforded an unstable red oil (probably 4-aminoazulene in *ca.* 10% yield) which was not obtained analytically pure. A dichloromethane solution showed λ_{max} in mμ (D^{20a}) at 262 (2.15), 294 (1.55), 318 (0.80), and 510 (1.0). The infrared spectrum showed a sharp peak in the N–H region at 3.0 μ. A sample of the red oil was dissolved in 5 ml. of dichloromethane and to the solution was added 3 ml. of freshly distilled acetic anhydride. The mixture was warmed on a steam bath for 15 min. and then allowed to stand overnight. Careful chromatography on alumina (the unreacted acetic anhydride reacted exothermically) with 1:1 dichloromethane–chloroform as the eluent separated a blue band which was collected, concentrated, and rechromatographed. Removal of the solvent left a blue solid which was recrystallized from *n*-hexane–dichloromethane and afforded blue needles, m.p. 170–171°. A dichloromethane solution showed λ_{max} in mμ (D^{20a}) at 266 (0.5), 294 (2.19), 305 (1.87), 374 (0.27), and 560 (1.0). The infrared spectrum showed N–H (3.0) and carbonyl (5.9 μ) absorption.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 78.11; H, 6.05.

Methyl 1-Azuloate. A. From 1-Cyanoazulene.—A solution of 158.5 mg. (1 mmole) of 1-cyanoazulene in 15 ml. of methanol and 15 ml. of 50% aqueous potassium hydroxide was heated under reflux for 24 hr., and the alcohol then was removed by distillation. The aqueous residue was diluted with 150 ml. of water, extracted with 150 ml. of dichloromethane, and then acidified with hydrochloric acid. The red precipitate which formed was extracted into ether, and the concentrate (25 ml.) of the combined extracts was treated with a large excess of an ethereal solution of diazomethane. The solvent was removed, and the residue was chromatographed on a column of neutral alumina. Elution with 1:1 petroleum ether–dichloromethane removed a lavender band which yielded 179 mg. (96%) of methyl 1-azuloate as lavender needles, m.p. 56–57°, which were identical with an authentic sample.[21]

B. From Azulene.—Small pieces of sodium (1 g.) were added to a stirred solution of 512 mg. (4 mmoles) of azulene in 100 ml. of pure, dry tetrahydrofuran, and the mixture was stirred for 24 hr. under anhydrous conditions. The maroon suspension was poured onto 500 g. of powdered Dry Ice, the mixture was allowed to come to room temperature, and the unchanged sodium was removed. The solution was acidified with hydrochloric acid and extracted with chloroform. The combined extracts were washed three times with water and then extracted twice with 75-ml. of 10% sodium carbonate solution. The combined extracts were acidified with hydrochloric acid and extracted with two 75-ml. portions of ether. The ethereal extracts were concentrated to a volume of 25 ml. and treated with an excess of diazomethane in ether. The solvent was removed, and the residue was chromatographed on alumina. Petroleum ether–dichloromethane eluted a lavender fraction and methanol removed a small yellow fraction. The residue from the lavender eluate was rechromatographed three times and yielded 50.8 mg. (6.8%) of methyl 1-azuloate as lavender needles which were identical with an authentic sample.[21] Treatment of the residue from the yellow fraction with chloranil in the usual manner afforded an additional 6 mg. (0.8%) of the same ester as the only azulenic product.

1-Bromo-3-acetylazulene.—N-Bromosuccinimide (229 mg., 1.29 mmoles) was added to a solution of 1-acetylazulene (219 mg., 1.29 mmoles) in 27 ml. of purified dichloromethane. An immediate color change from lavender to violet occurred and a starch–iodide test was negative. An additional 5 mg. of N-bromosuccinimide was consumed at once, but a second 5-mg. portion produced a faint test for positive halogen. The mixture was concentrated and chromatographed on a column of activated, acid-washed alumina. Elution with dichloromethane separated the major purple-brown band from small yellow-brown and purple-red zones. The latter fractions were discarded. The eluate then was changed to 1:1 petroleum ether–dichloromethane, and elution continued until the purple-brown band was completely removed (the column remained a pale pink). The residue from this fraction was chromatographed. Removal of the solvent and drying under reduced pressure in the presence of Drierite gave 302 mg. of crystalline material which yielded 270 mg. (84%) of 1-bromo-3-acetylazulene as deep green needles, m.p. 99–100° after recrystallization from *n*-hexane. An *n*-hexane solution showed λ_{max} in mμ (D^{20a}) at 268 (0.62), 291 (0.98), 297 (1.19), 303 (1.11), 309 (1.43), 376 (0.28), and 393 (0.3). The maximum in the visible region was at 570 mμ with shoulders at 524, 597, 618, and 683 mμ. The infrared spectrum was recorded.

Anal. Calcd. for $C_{12}H_9BrO$: C, 57.85; H, 3.64. Found: C, 57.82; H, 3.75.

α-Acetamido-β-(1-azulyl)propionic Acid.—To a stirred suspension of 0.6 g. of sodium hydride (in mineral oil) in 20 ml. of anhydrous, redistilled N,N-dimethylformamide was added carefully 1.3 g. (7.73 mmoles) of dry ethyl acetamidocyanoacetate.[22] After the evolution of hydrogen had ceased, a nitrogen atmos-

(21) A. G. Anderson, Jr., and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4979 (1953).

(22) J. D. Carbon and S. Brehm, *J. Org. Chem.*, **26**, 3376 (1961).

phere was introduced, 900 mg. (2.75 mmoles) of 1-azulylmethyltrimethylammonium iodide[4b] was added, and the solution was heated at 100–110° for 3.5 hr. The solvent was removed under reduced pressure and the residue was chromatographed on an alumina column. The blue fraction eluted by 3:1 dichloromethane–petroleum ether gave 836 mg. of a blue oil presumed to be ethyl α-acetamido-α-cyano-β-(1-azulyl)propionate.

A solution of 340 mg. (1:1 mmoles) of the blue oil in 20 ml. of a 10% solution of potassium hydroxide in 50% ethanol was heated under reflux for 2 hr. Water (50 ml.) was added and the whole was extracted with 100 ml. of ether. The separated aqueous layer was acidified with 6 *N* hydrochloric acid and then extracted with ether. The residue from the dried (sodium sulfate) ethereal solution was chromatographed on a column of silica gel. Removal of the solvent from the blue fraction eluted by ether and recrystallization of the blue solid from water gave 171 mg. (64%) of α-acetamido-β-(1-azulyl)propionic acid as blue crystals, m.p. 126–128°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 69.99; H, 5.85; N, 5.44. Found: C, 69.66; H, 6.12; N, 5.20.

Proton Nuclear Magnetic Resonance Spectra of 1-Acyl Pyrazoles

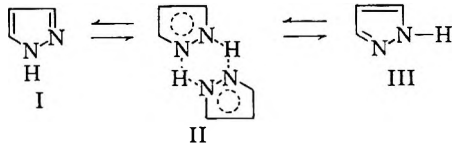
J. K. WILLIAMS

Contribution No. 923 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

Received December 10, 1963

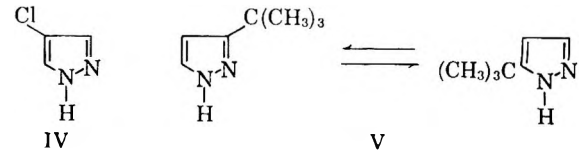
The n.m.r. spectra of the annular protons of 1-acyl pyrazoles are useful in determining the structures of isomers formed by acylation of unsymmetrically substituted pyrazoles. The spin–spin coupling constants of the annular protons fall into narrow ranges that are characteristic of the position of the protons on the pyrazole ring. The relative chemical shifts of these protons are also dependent upon their location on the ring. A 1-acyl pyrazole with an unambiguous structure has been prepared to aid in these correlations.

When the 1-position of a pyrazole is unsubstituted, the 3- and 5-positions are equivalent in the sense that tautomers of unsymmetrically substituted pyrazoles cannot be separated. It has been suggested that pyrazoles exist in solution largely as hydrogen-bonded dimers[1,2] (II), and that the equivalency of the 3- and 5-positions results from delocalization of electrons in the dimer.[3] No available evidence precludes the existence of monomeric species (I and III) in dilute solution, but in any event, if present, they would be in rapid equilibrium with each other *via* the dimeric, hydrogen-bonded species.



I II III

Evidence for the equivalency of the 3- and 5-positions of pyrazoles unsubstituted in the 1-position can be found by examining their proton n.m.r. spectra.[4] For 4-chloropyrazole (IV) only two resonances in the ratio of 1:2 are observed: a single low-field resonance at τ −3.27 corresponding to the N–H, and a single unsplit resonance at τ 2.32 corresponding to the protons on the 3- and 5-positions. If unassociated forms such as I and III were present, they would not be detectable by n.m.r. if the frequency at which they are interconverted, *via* II, is higher than that used in making the observation.[5] Because of the equivalency of the 3- and 5-protons, no spin–spin splitting is observed. Similarly, for 3(5)-*t*-butylpyrazole (V), a single, sharp resonance is observed for the protons of the *t*-butyl group at τ 8.63, and a single resonance at τ −2.96 for



IV V

the N–H. The two annular protons split each other into doublets appearing at τ 2.49 and 3.91 with a coupling constant, J, of 2.0 c.p.s. This coupling constant must be an average of the coupling constants J_{34} and J_{45} weighted by the population of each tautomer in the equilibrium mixture. Comparison of the spectrum of IV with that of V suggests that the higher field doublet at τ 3.91 is the 4-proton, since it is missing in the spectrum of IV.

The most complicated spectrum is produced by pyrazole itself. The N–H appears as a single resonance at τ −3.60. The 4-proton appears as a triplet at τ 3.60, split by the equivalent 3- and 5-protons, while the 3- and 5-protons appear as a single doublet at τ 2.26. The coupling constant for this A_2B system is 2.1 c.p.s.

When pyrazole is acetylated on the 1-nitrogen the 3- and 5-positions become nonequivalent. As a result the three annular protons of 1-acetylpyrazole (VI) appear as three separate quadruplets at τ 1.78, 2.36, and 3.60. Analysis of the splitting in these quadruplets shows that all three protons are coupled to each other and that the coupling constants have values of 0.6, 1.5, and 2.9 c.p.s. Examination of the spectrum of 1-acetyl-4-chloropyrazole (VII) reveals that the 3- and 5-protons are split by 0.7 c.p.s. into doublets that appear at τ 1.81 and 2.44. Clearly the coupling constant across the ring between the 3- and 5-protons (J_{35}) must be 0.6–0.7 c.p.s. The remaining two coupling constants of 1.5 and 2.9 c.p.s. observed in the spectrum of VI must be J_{34} and J_{45}. The problem remains of deciding which corresponds to J_{34} and which to J_{45}.

When the unsymmetrically substituted *t*-butylpyrazole (V) is acetylated, two isomeric 1-acetyl compounds, VIII and IX, could be formed. Actually, acetylation of V leads to a single product having a pair of doublets in its spectrum at τ 1.88 and 3.71 with a coupling con-

(1) W. Huckel, J. Datow, and E. Simersbach, *Z. physik. Chem.* (Leipzig), **186A**, 129 (1940).

(2) H. Hayes and L. Hunter, *J. Chem. Soc.*, 1 (1941).

(3) L. Hunter, *ibid.*, 806 (1945).

(4) All spectra were measured with a Varian A60 n.m.r. spectrometer at room temperature on 0.5 *M* solutions in carbon tetrachloride containing 0.05 *M* tetramethylsilane as an internal standard.

(5) 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.

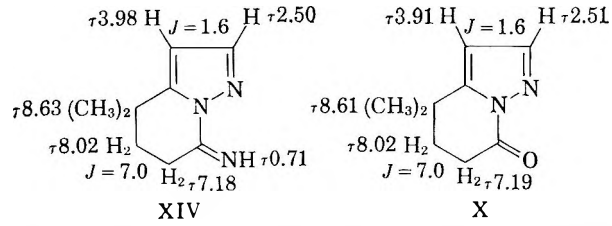
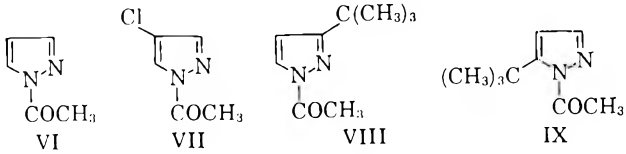
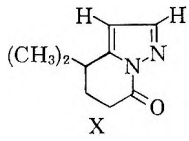


Fig. 1.—Spin-spin coupling constants (J, c.p.s.) are indicated between atoms, and chemical shifts[4] in τ (p.p.m.) are indicated adjacent to the corresponding protons.

stant of 2.9 c.p.s. On steric grounds, one would guess that the entering acetyl group would prefer the nitrogen furthest from the *t*-butyl group and that the product would be the 3-*t*-butyl isomer, VIII. On this basis J_{45} would be 2.9 c.p.s. To confirm this conclusion a 1-acyl pyrazole with an unambiguous structure (X) was prepared.



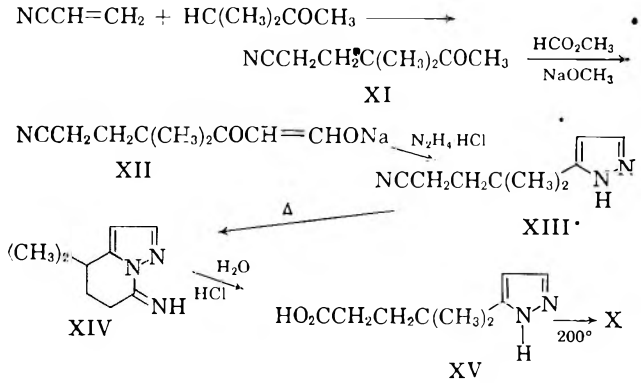
Because of its lactam ring, the identity of the protons on the pyrazole ring of 4,4-dimethyl-4,5,6,7-tetrahydro-7-ketopyrazole[2,3-*a*]pyridine (X) are fixed on the 3- and 4-positions. Consequently, the coupling constant between them must represent J_{34}. The spectrum of X showed a pair of doublets at τ 2.51 and 3.91 cor-



responding to the 3- and 4-protons with a coupling constant, J_{34}, of 1.6 c.p.s. Thus, the conclusions based on VIII are confirmed, and the coupling constants for the 1-acyl pyrazole system are J_{35} = 0.6–0.7 c.p.s., J_{34} = 1.6 c.p.s., and J_{45} = 2.9 c.p.s. In addition, the relative shifts for these protons place the 5-proton at lowest field, the 3-proton at higher field, and the 4-proton at highest field. That the resonance for the 4-proton is at highest field is consistent with the fact that the 4-position has the highest electron density and is the point at which electrophilic substitution takes place.[6]

The synthesis of X began with the known[7] cyanoethylation product of methyl isopropyl ketone, 3,3-dimethyl-5-cyano-2-pentanone (XI). This ketone was formylated, and the sodium salt of the formyl compound (XII) was converted without isolation to the pyrazole derivative (XIII) by reaction with hydrazine hydrochloride. Upon distillation, XIII partly cyclized to the imino compound XIV. Hydrolysis of XIV gave the acid (XV) which cyclized smoothly to X when it was heated.

As a result of the monumental work of Auwers,[8] much is known of the products obtained by acylating unsymmetrically substituted pyrazoles. Nevertheless, the use of n.m.r. offers a rapid, unambigous method for



determining the structures of such acylation products. The utility of the data and generalizations discussed in this paper will be illustrated in a forthcoming publication describing the acylation of a number of unsymmetrically substituted pyrazoles and the identification of the isomer mixtures obtained.

Experimental

1-Acetylpyrazole (VI),[9] 4-chloropyrazole (IV),[10] 1-acetyl-4-chloropyrazole (VII),[10] and 3(5)-*t*-butylpyrazole (V)[11] were prepared by methods described in the literature.

1-Acetyl-3-*t*-butylpyrazole (VIII).—To a mixture of 37.2 g. of 3(5)-*t*-butylpyrazole,[11] 27.0 g. of pyridine, and 500 ml. of ether was added a mixture of 27 g. of acetyl chloride and 50 ml. of ether. The addition required 10 min., and after it was complete the mixture was stirred for 2 hr. Water (100 ml.) was added, and stirring was continued for 1 hr. The ether layer was separated, washed with two 250-ml. portions of water and then with 250 ml. of saturated sodium chloride solution, and dried over magnesium sulfate. Distillation gave 39.0 g. (79%) of 1-acetyl-3-*t*-butylpyrazole, b.p. 87–88° (16 mm.), n^{25}D 1.4756. The infrared spectrum showed λ_{max}^{liq} 2.87, 313, 317, and 5.73 μ. The n.m.r. of the pure liquid showed no detectable amount of the 5-*t*-butyl isomer. The sensitivity of the n.m.r. analysis would probably have allowed detection of 5% of the 5-isomer in the 3-isomer.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.1; H, 8.49; N, 16.9. Found: C, 64.9; H, 8.50; N, 17.1.

3,3-Dimethyl-5-cyano-2-pentanone (XI).—This material was prepared in 45% yield by the method described in the literature.[7] The infrared spectrum showed λ_{max}^{liq} 4.44 and 5.83 μ. The n.m.r. spectrum[4] showed an A_2B_2 pattern centered at τ 7.92, a single CH_3 at τ 7.88, and another resonance for six protons ($2CH_3$) at τ 8.82.

4-Methyl-4-(5-pyrazolyl)pentanenitrile (XIII) and 4,4-Dimethyl-4,5,6,7-tetrahydro-7-iminopyrazolo[2,3-*a*]pyridine (XIV).—To a slurry of 84 g. of sodium methoxide in 640 ml. of ether was added a mixture of 208 g. of 3,3-dimethyl-5-cyano-2-pentanone and 108 g. of methyl formate over 20 min. The reaction mixture boiled spontaneously after one-third of the ketone ester mixture had been added. After the addition was complete, the reaction flask was cooled in ice and an additional 30 g. of methyl formate was added. The mixture was stirred at room temperature for 16 hr., reduced in volume by 200 ml. by distillation, and then cooled in ice. A solution of 77.5 g. of hydrazine hydrate and 130 ml. of concentrated hydrochloric acid in 500 ml. of water was added. A mildly exothermic reaction took place. The mixture was stirred at room temperature for 3 hr. The ether layer was separated, washed with two 150-ml. portions of saturated sodium chloride solution, and dried over magnesium sulfate. The ether was removed on a steam bath to leave a pale amber oil. The infrared spectrum of this crude product had λ_{max}^{liq} 4.45 μ (–CN) and a weak band at 5.83 μ (C=O of XI), but no band at 6.01 μ. Distillation of this oil gave 196 g. (81%) of a mixture of 4-methyl-4-(5-pyrazolyl)pentanenitrile (XIII) and 4,4-dimethyl-

(6) E. Buchner and M. Fritsch, *Ann.*, **273**, 265 (1893).
(7) A. Campbell, C. Carter, and S. Slater, *J. Chem. Soc.*, 174 (1948).
(8) See for example, K. V. Auwers and E. Cauer, *J. prakt. Chem.*, [2]**126**, 177 (1930).
(9) L. Knorr, *Ber.*, **28**, 716 (1895).
(10) R. Huttel, O. Schafer, and G. Welzel, *Ann.*, **598**, 186 (1956).
(11) P. Dayton, *Compt. rend.*, **236**, 2515 (1953).

4,5,6,7-tetrahydro-7-iminopyrazolo[2,3-*a*]pyridine (XIV), b.p. 123–126° (0.06 mm.). When the viscous distillate was allowed to stand at room temperature, massive crystals of XIV separated.

A sample of this solid was pressed on a clay plate to free it from oil and was crystallized twice from petroleum ether (b.p. 30–60°) and once from hexane to give 4,4-dimethyl-4,5,6,7-tetrahydro-7-iminopyrazolo[2,3-*a*]pyridine (XIV), m.p. 69–71°. The infrared spectrum showed λ_{max}^{KBr} 3.08, 3.22, 3.40, 6.01, and 6.45 μ, but no bands at 4.45 or 5.83 μ.

The n.m.r. spectrum of XIV is summarized in Fig. 1.

Anal. Calcd. for $C_9H_{13}N_3$: C, 66.3; H, 8.04; N, 25.8. Found: C, 66.7; H, 8.10; N, 25.7.

4-[3(5)-Pyrazolyl]-4-methylpentanoic Acid (XV).—A mixture of 169.5 g. of the crude distillate containing XIII and XIV, 92 ml. of concentrated hydrochloric acid, and 250 ml. of water was heated at 90–95° with stirring for 3 hr. The mixture was cooled with stirring, and the solid that crystallized was collected and washed with cold water to give 122.6 g. (62%) of 4-[3(5)-pyrazolyl]-4-methylpentanoic acid (XV), m.p. 157.7–159.0°. The infrared spectrum had λ_{max}^{Nujol} 2.98, 3.17, 5.92, 7.18, and 7.30 μ. In another experiment, a sample that had been recrystallized from water had m.p. 155–157° and was analyzed.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.75; N, 15.4. Found: C, 59.6; H, 6.00; N, 15.1.

4,4-Dimethyl-4,5,6,7-tetrahydro-7-ketopyrazolo[2,3-*a*]pyridine (X).—An erlenmeyer flask containing 1.0 g. of XV was heated in an oil bath maintained at 200° for 0.25 hr. During the heating period the solid melted, and water distilled out of the melt. The solid obtained when the contents of the flask had cooled was crystallized from hexane to give 0.7 g. (80%) of 4,4-dimethyl-4,5,6,7-tetrahydro-7-ketopyrazolo[2,3-*a*]pyridine (X), m.p. 196.5–198.0°. A sample with the same melting point obtained by recrystallization from heptane was analyzed. The infrared spectrum had λ_{max}^{KBr} 5.72, 6.39, 7.20, and 7.33 μ.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.9; H, 7.38; N, 17.1. Found: C, 66.0; H, 7.33; N, 16.8.

A Synthesis of Cyclopropyl Acetates[1,2]

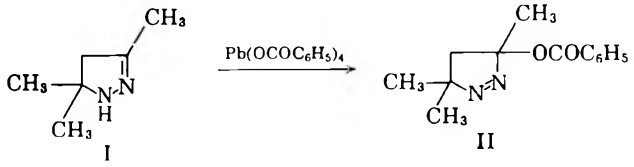
JEREMIAH P. FREEMAN

Gorgas Laboratory, Rohm and Haas Company, Redstone Arsenal Research Division, Huntsville, Alabama

Received July 15, 1963

A variety of cyclopropyl acetates may be prepared by pyrolysis of 3-acetoxy-1-pyrazolines which are obtained by the action of lead tetraacetate on 2-pyrazolines. The scope and limitations of the method and the use of n.m.r. spectra for assignment of stereochemistry is discussed.

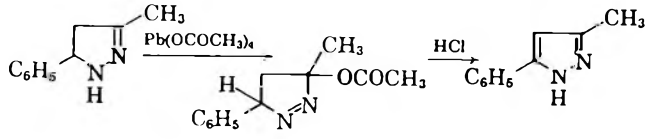
Recent interest in small ring chemistry and in particular that expressed in cyclopropanols[3] prompted an examination of the synthesis and decomposition of 3-acetoxy-1-pyrazolines. The cyclopropyl acetates expected from this decomposition can be cleaved to the desired alcohols.[3] It had been observed in connection with another investigation that 3,5,5-trimethyl-2-pyrazoline (I) could be converted to 3-benzoyloxy-3,5,5-trimethyl-1-pyrazoline (II) by the action of lead



I II

tetrabenzoate.[4] This reaction was an extension of Iffland's hydrazone oxidation reaction[5] to the pyrazoline series.

1-Pyrazolines.—This reaction, now employing lead tetraacetate, is a general one for pyrazolines even for those bearing a hydrogen atom at position 5. It might have been expected that these compounds would be oxidized to pyrazoles based upon the report that 5-ethylpyrazoline is converted to 5-ethylpyrazole by this reagent.[6] Under the mild conditions employed in the present work the pyrazolines were not aromatized nor were the 1-pyrazolines isomerized to 2-pyrazolines during the lead tetraacetate reaction. However, it was possible to isomerize and aromatize 3-acetoxy-3-methyl-5-phenyl-1-pyrazoline (III) to 3-methyl-5-phenylpyrazole by heating it in dilute ethanolic hydrochloric acid. This isomerization also occurred upon standing or upon warming below the decomposition

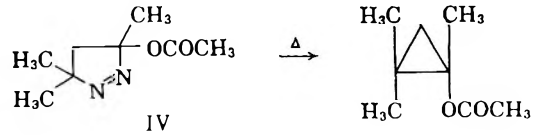


III

point. For best results, the thermal decomposition of the crude pyrazolines was conducted immediately after their preparation.

In some cases the intermediate 1-pyrazolines were isolated and characterized. However, those bearing α-phenyl substituents appeared to be particularly prone to decomposition and little effort was made to purify them. The 1-pyrazolines were characterized by a band at 1565 cm.$^{-1}$ in their infrared spectra which may be attributed to the *cis*-azo function and by low intensity absorption at 330 mμ in the ultraviolet. Other 1-pyrazolines are characterized by similar spectral properties.[7]

Cyclopropyl Acetates.—Preliminary efforts to decompose pyrazoline IV with ultraviolet light[7] indicated that this method was effective but slow. However, by simply heating the compound under reflux, nitrogen



IV

(1) This research was carried out under Army Ordnance Contract DA-01-021 ORD-11878.

(2) A preliminary report of this work has been published: J. P. Freeman, *J. Org. Chem.*, **28**, 885 (1963).

(3) C. H. DePuy, L. R. Mahoney, and K. L. Eilers, *ibid.*, **26**, 3616 (1961); C. H. DePuy, R. A. Klein, and G. M. Dappen, *ibid.*, **27**, 3742 (1962).

(4) J. P. Freeman, *Tetrahedron Letters*, No. **21**, 749 (1961).

(5) D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Am. Chem. Soc.*, **83**, 747 (1961).

(6) R. Kuhn and K. Henkel, *Ann.*, **549**, 279 (1941). An azoacetate may have been involved in this aromatization, since an intermediate impure product was further treated with acid dichromate to obtain the pyrazole.

(7) K. L. Rinehart, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **84**, 3736 (1962).

TABLE I

PROPERTIES OF CYCLOPROPYL ACETATES

Compound	B.p., °C. (mm.)	$n^{20}D$	Yield, %[a]	Anal., % C Calcd.	C Found	H Calcd.	H Found
1,2,2-Trimethyl (V)	46 (20)	1.4141	62,[d] 36[e]	67.57	67.34	9.92	10.28
cis-2-Phenyl[b] (VII)	64 (0.8)	1.5160	10[d]	74.97	74.22	6.86	7.12
trans-2-Phenyl[b] (VIII)	64 (0.8)	1.5179		74.97	75.05	6.86	7.07
1-Phenyl-2,2-dimethyl (IX)	70–72 (0.5)	1.4990	42[d]	76.44	76.04	7.90	7.87
cis-2-Phenyl-1-methyl[b] (X)	70 (0.35)	1.5081	61[d]	75.76	76.06	7.42	7.57
trans-2-Phenyl-1-methyl[b] (XI)	70 (0.35)	1.5060		75.76	75.35	7.42	7.60
cis-1,2-Diphenyl (XII)[c]	53–53.5 (m.p.)		30[d]	80.92	80.66	6.39	6.34
1,2-Diethyl-2-methyl (XIII)[f]	42 (5)	1.4256	64[c]	70.55	70.37	10.66	10.76
1-Phenyl (XIV)	68–70 (0.4)	1.5232	20[d]	74.97	75.21	6.87	6.99
trans-2-Methyl-1-phenyl (XV)[b]	110 (1.2)	1.5071	60[d]	75.76	75.64	7.42	7.70
cis-2-Methyl-1-phenyl (XVI)[b]	110 (1.2)	1.5100		75.76	75.42	7.42	7.45
1-Cyclopropyl-2-phenyl (XVII)[f]	96–98 (0.8)	1.5180	62[d]	77.75	77.95	7.46	7.89

[a] Over-all yield based on starting 2-pyrazoline. [b] The boiling point and yields recorded are for the mixture of isomers which were separated by gas chromatography on a Carbowax M-Chromosorb column operating at 180°. The *cis* isomers were eluted first. *cis* and *trans* refer to the relation of phenyl and acetate groups except for XII. [c] Prepared by method A, Experimental section. [d] Prepared by method B, Experimental section. [e] The *trans*-1,2-diphenyl isomer was a high boiling oil which could not be entirely freed of *cis* isomer. Its yield is not included in this table but may be found in the Experimental section. [f] Mixture of *cis* and *trans* isomers.

was evolved rapidly and 1,2,2-trimethylcyclopropyl acetate was produced in 60% yield. The properties of the cyclopropyl acetates prepared in this manner are summarized in Table I. The reaction proceeds best when there is no hydrogen at positions 3 or 5 of the pyrazolines and fails altogether with mono- or dialkylated pyrazolines. For example, it has not yet been possible to convert either the 5-methyl- or 3,5-dimethyl-3-acetoxy-1-pyrazolines to their respective cyclopropyl acetates by either light or heat. Monoaryl pyrazolines yielded cyclopropanes but in lower yield. It is tempting to relate the decomposition of the pyrazolines to the stability of the presumed intermediate biradical. When the intermediate radical is primary or secondary, and thus formed more difficultly, isomerization becomes competitive and no nitrogen evolution occurs. While small amounts of the corresponding pyrazoles were obtained from these compounds, these do not appear to be the major products; this side reaction is under investigation. It is interesting that cyclopropane formation is favored over pyrazole formation with 3-acetoxy-1-pyrazolines in view of the predominance of the latter with 3-sulfonyl-[8a] and 3-nitro-1-pyrazolines.[8b]

Other methods of obtaining cyclopropyl esters include the addition of diazo compounds[9] or iodomethylzinc iodide[2] to enol esters, the reaction of Grignard reagents with epichlorohydrins in the presence of iron salts,[2,10] and the oxidation of methyl cyclopropyl ketones with peroxytrifluoroacetic acid.[2,11] Since pyrazolines are among the most accessible and versatile starting materials required for these various cyclopropane syntheses, the presently described method provides a simple route to a variety of cyclopropyl acetates.

Since stereochemistry of the decomposition of 1-pyrazolines is unknown, it is not possible to determine whether the pyrazoline–lead tetraacetate reaction is stereospecific. However, one or the other of the two reactions is highly stereoselective, since in those cases where isomers were possible a *trans* arrangement of the bulkier groups at C-1 and C-2 predominated. If it may be assumed that the decomposition of 1-pyrazolines is predominantly stereospecific,[7,12] then it appears that the acetoxylation reaction occurs predominantly by approach of the acetate group (whether by an ionic or radical mechanism) to the least hindered side of the pyrazoline ring thus becoming oriented *trans* to the bulkier group at position 5. Such selectivity seems quite reasonable. 3-Phenyl-5-methylpyrazoline yielded a nearly equimolar mixture of *cis*- and *trans*-2-methyl-1-phenylcyclopropyl acetates showing that there was little difference between orientation of the methyl group with the phenyl or acetate groups. In the case of 3-methyl-5-phenylpyrazoline, *trans*-2-phenyl-1-methylcyclopropyl acetate predominated by a ratio of at least 6:1.

N.m.r. Spectra.—At the beginning of this investigation n.m.r. spectra were run routinely in order to follow the course of the pyrolysis of pyrazoline to cyclopropane. This was done in the case of compounds V and XIII by observing the appearance of the typical high-field cyclopropane ring hydrogen resonance. It soon became apparent that phenyl substitution greatly affected this high-field resonance to the extent that its absence cannot be taken as evidence that the cyclopropane ring is not present. In the case of compound IX, for example, the ring protons are found near τ 8.9 compared with τ 9.5 in the aliphatic cyclopropane V. This effect of phenyl groups on the cyclopropane proton resonance has recently been commented upon.[13] It would be of interest to know whether this effect is due to paramagnetic shielding or to a change in hybridization within the cyclopropane ring.

However, n.m.r. analysis was quite helpful in an unanticipated way in the assignment of configuration to geometric isomers of this series. It has been shown by Curtin and co-workers[14] that the *cis–trans* isomers of 1,2-diphenylcyclopropane may be distinguished by the

(8) (a) W. E. Parham, H. G. Braxton, Jr., and D. R. Theissen, *J. Org. Chem.*, **27**, 2632 (1962); (b) W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.*, **73**, 4664 (1951).

(9) I. A. D'Yakonov, *J. Gen. Chem. USSR*, **20**, 2385 (1950).

(10) C. W. Stahl and D. L. Cottle, *J. Am. Chem. Soc.*, **65**, 1782 (1943).

(11) W. D. Emmons and G. B. Lucas, *ibid.*, **77**, 1187 (1955).

(12) C. G. Overberger and J. P. Anselme, *ibid.*, **84**, 869 (1962). Controversy on this point still rages, but it appears that thermal decompositions, although not so specific as photochemical decompositions, largely maintain the stereochemistry of the pyrazoline.

(13) J. D. Graham and M. T. Rogers, *ibid.*, **84**, 2249 (1962).

(14) D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *ibid.*, **83**, 4838 (1961); D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind.* (London), 1205 (1958).

TABLE II

PROTON N.M.R. SPECTRA OF CYCLOPROPYL ACETATES

Compound	Group chemical shift, τ[a] 1-CH_3	2-CH_3	CH_3CO_2-
1,2,2-Trimethyl (V)	8.52	8.95, 8.88	8.08
1-Methyl (VI)[b]	8.53	...	8.12
cis-2-Phenyl (VII)	...	...	8.30
trans-2-Phenyl (VIII)	...	...	8.12
1-Phenyl-2,2-dimethyl (IX)	...	9.20, 8.70	8.10
cis-2-Phenyl-1-methyl (X)	8.35	...	8.35
trans-2-Phenyl-1-methyl (XI)	8.80	...	8.03
cis-1,2-Diphenyl (XII)	...	...	8.13
1,2-Diethyl-2-methyl (XIII)[c]	...	8.98, 8.95	8.12
1-Phenyl (XIV)	...	...	8.12
trans-2-Methyl-1-phenyl (XV)	...	9.18	8.13
cis-2-Methyl-1-phenyl (XVI)	...	8.74	8.02

[a] Spectra were measured on Varian Associates V-4300B 40-Mc. and A-60 spectrometers on dilute (5–10%) solutions in carbon tetrachloride, tetramethylsilane internal standard. We are indebted to Mrs. Carolyn Haney for measurement of the spectra. [b] We are indebted to Dr. C. H. DePuy for the spectrum of this material. [c] Mixture of *cis*–*trans* isomers.

different chemical shifts of the benzylic hydrogens; there is increased shielding of these protons in the *trans* isomer by the adjacent benzene ring. It appears that the benzene ring may shield other functional groups *cis* to it in cyclopropanes.[15] As model compounds we have used 1-methylcyclopropyl acetate,[2] 1,2,2-trimethylcyclopropyl acetate, *trans*-2-phenylcyclopropyl acetate,[2] and *cis*- and *trans*-1-phenyl-2-methylcyclopropane.[16] From the data summarized in Table II the following τ values may be assigned to the various "unperturbed" methyl groups: 1-methyl, τ 8.5; 2-methyl, 8.9; acetate methyl, 8.1. The effect of a *cis*-phenyl group on the 2-methyl resonance may be gaged from *cis*-1-phenyl-2-methylcyclopropane in which the methyl group appears at much higher field (τ 9.2)[16] than in the model compounds. In compound IX one of the methyl groups appears at τ 9.2 and is thus the one *cis* to the phenyl group.[18] One of the two isomers (XV) of 2-methyl-1-phenylcyclopropyl acetate also has a signal at τ 9.2, and it is assigned the structure with the phenyl and methyl groups *cis*.

In the case of the isomers of 2-phenyl-1-methylcyclopropyl acetate (X and XI), the methyl resonance of XI appears at τ 8.80, higher than expected upon the basis of models V and VI. On this basis, XI is assigned the structure in which the methyl group is *cis* to the adjacent phenyl group. In the minor product the 1-methyl group and the acetate methyl group have the same chemical shifts. Thus the 1-methyl group is in the normal region, but the acetate methyl group has shifted to higher field. That this shift is related to its *cis* orientation to the phenyl group is shown by the spectra of *cis*- and *trans*-2-phenylcyclopropyl acetates in which the acetate methyl group appears in the normal region in the *trans* isomer but at the higher field position in the *cis* isomer. This diamagnetic shielding of the acetate methyl group is a rather striking example of long range shielding.

Because of the complexity of the ring hydrogen signals no attempts have been made to correlate their chemical shifts and coupling constants with the configuration of the ring.

Experimental

Reagents.—The lead tetraacetate was obtained from Arapahoe Chemical Company, Boulder, Colorado. Apparently some batches of this material contain substantial amounts of acetic anhydride. This material is detrimental since it reacts with the pyrazolines to form N-acetyl derivatives which reduce the yields of cyclopropanes and complicates their purification. This side reaction could be substantially reduced or completely eliminated by recrystallizing the lead tetraacetate from acetic acid immediately preceding its use.

The pyrazolines were prepared by standard literature methods as indicated. 3-Phenyl-5,5-dimethylpyrazoline was prepared from β,β-dimethylacrylophenone[19] and 90% hydrazine in ethanol solution. The pyrazoline was not purified, but rather the crude product was oxidized directly.

3,5,5-Trimethylpyrazoline,[20] 3,5-dimethylpyrazoline,[21] 3,5-diphenylpyrazoline,[22] 3-methyl-5-phenylpyrazoline,[22] 3-phenyl-5-methylpyrazoline,[21] 5-phenylpyrazoline,[22] and 3-cyclopropyl-5-phenylpyrazoline[23] were prepared from the corresponding α,β-unsaturated carbonyl compounds and hydrazine. 3-Phenylpyrazoline[22] was prepared from β-dimethylaminopropiophenone and hydrazine. 3,5-Diethyl-5-methylpyrazoline was prepared by the cyclization of methyl ethyl ketazine with formic acid.[24]

Synthesis of Azoacetates. Preparation of 3-Acetoxy-3,5,5-trimethyl-1-pyrazoline.—A solution of 11.2 g. (0.1 mole) of 3,5,5-trimethylpyrazoline in 25 ml. of methylene chloride was added over a 15-min. period at 10–15° to a solution of 50 g. (0.11 mole) of lead tetraacetate in 200 ml. of methylene chloride. The mixture was stirred at 20–25° for 30 min. Water (200 ml.) was added and the solution was filtered. The organic layer was separated and washed with water and 10% sodium bicarbonate solution until it was free of acid. The organic extracts were dried over magnesium sulfate, concentrated *in vacuo*, and distilled to yield a pale yellow oil, b.p. 72–76° (3 mm.), $n^{20}D$ 1.4422, yield 10.6 g. (62%).

Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C 56.40; H, 8.38; N 16.76.

Infrared spectrum: ν_{CO} 1750 cm.$^{-1}$, $\nu_{N=N}$ 1570 cm.$^{-1}$; ultraviolet spectrum: λ_{max} 330, ϵ_{max} 196 (ethanol).

3-Acetoxy-3,5-diethyl-5-methyl-1-pyrazoline.—The same procedure was followed using 13.4 g. (0.11 mole) of 3,5-diethyl-5-methylpyrazoline. Distillation yielded a yellow oil, b.p. 74° (1 mm.), $n^{20}D$ 1.4514, yield 11.5 g. (53%).

Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.57; H, 9.15; N, 14.14. Found: C, 60.39; H, 9.06; N, 14.47.

(15) While this manuscript was being prepared, a report appeared in which the stereochemistry of several cyclopropanes was assigned on the basis that the group *cis* to the phenyl group was shifted to higher fields while that *trans* to the phenyl group was shifted to lower fields: G. L. Closs, R. A. Moss, and J. J. Coyle, *J. Am. Chem. Soc.*, **84**, 4986 (1962). These results are in complete accord with the results reported here.

(16) An authentic sample of *trans*-1-phenyl-2-methylcyclopropane was prepared by the Simmons-Smith reaction[17] on *trans*-propenylbenzene. Surprisingly, this same isomer was obtained by sodium reduction of the reported *cis*-1-phenyl-2-methyl-3,3-dichlorocyclopropane.[13] It could be shown that this latter compound was actually the *trans* isomer and sodium reduction of its authentic *cis* isomer yielded *cis*-1-phenyl-2-methylcyclopropane. The methyl proton signal of the *cis* isomer was found at τ 9.20 and that of the *trans* isomer at τ 8.87. Details of these preparations may be found in the Experimental section. In line with this reassignment of the Graham and Rogers dichlorocyclopropane[13] as the *trans* isomer, it was found that the vicinal proton n.m.r. coupling constant of authentic *cis* isomer (J = 11.5 c.p.s.) was larger than that reported by Graham and Rogers for their product (J = 8.28 c.p.s.). Vicinal proton coupling constants of *cis* cyclopropanes are consistently larger than those of the *trans* isomers.[13] The rather large values for the coupling constants in these two dichlorocyclopropanes may reflect the dependence of coupling constants upon substituents. [For a recent discussion of this phenomenon, see K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963).]

(17) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).

(18) All the methyl groups *trans* to phenyl groups appear at lower field than those in the model compounds. This shift to lower field is apparently due to deshielding by the phenyl groups.[15]

(19) L. I. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, **71**, 2671 (1949).

(20) S. Curtius and B. Wirsing, *J. prakt. Chem.*, [2]**50**, 548 (1894).

(21) K. von Auwers and P. Heimke, *Ann.*, **458**, 186 (1927).

(22) S. G. Beech, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 4686 (1952).

(23) L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.*, **73**, 3840 (1951).

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

Infrared spectrum: ν_{CO} 1750 cm.$^{-1}$, $\nu_{N=N}$ 1565 cm.$^{-1}$; ultraviolet spectrum: λ_{max} 330, ϵ_{max} 180 (ethanol).

3-Acetoxy-3,5-dimethyl-1-pyrazoline.—By the same procedure using 4.9 g. (0.05 mole) of 3,5-dimethylpyrazoline, a bright yellow oil, b.p. 72–76° (0.3 mm.), $n^{20}D$ 1.4545, was obtained.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 55.05; H, 8.17; N, 17.97.

Infrared spectrum: ν_{CO} 1750 cm.$^{-1}$; $\nu_{N=N}$ 1568 cm.$^{-1}$; ultraviolet spectrum: λ_{max} 330, ϵ_{max} 186 (ethanol).

Synthesis of Cyclopropyl Acetates. A. From Azoacetates. 1,2,2-Trimethylcyclopropyl Acetate.—3,5,5-Trimethyl-3-acetoxy-1-pyrazoline (5.0 g., 0.03 mole) was heated under reflux (*ca.* 200°) until nitrogen evolution ceased (1 hr.). The residue was distilled to yield 2.5 g. (63%) of 1,2,2-trimethylcyclopropyl acetate (Table I).

B. From 2-Pyrazolines. 2-Phenyl-1-methylcyclopropyl Acetate.—A solution of 8.0 g. (0.05 mole) of crude 3-methyl-5-phenylpyrazoline in 25 ml. of methylene chloride was added to 25 g. (0.056 mole) of lead tetraacetate in 200 ml. of methylene chloride at 10–15° with good stirring. After the addition the mixture was allowed to warm to room temperature and stirred there for an hour. The mixture was diluted with water, the organic layer separated, and the aqueous layer extracted with two 50-ml. portions of methylene chloride. The combined organic extracts were washed with water and 5% sodium bicarbonate solution until the aqueous layer was free of acid. The organic extracts were dried over magnesium sulfate and concentrated. The residue was heated under reflux until gas evolution ceased. The crude product (8.9 g.) was distilled through a Holzman column to yield 5.8 g. (61%) of 2-phenyl-1-methylcyclopropyl acetate, b.p. 70° (0.35 mm.).

Vapor chromatography of the material on a Carbowax 20 M on Chromosorb column at 180° using an Aerograph Model 90 gas chromatograph resolved it into two components. The smaller component eluted first proved to be 1-methyl-*cis*-2-phenylcyclopropyl acetate; the predominant product was the *trans* isomer; ratio of isomers, 1:6 (Table I).

1,2-Diphenylcyclopropyl Acetate.—The crude pyrazoline prepared from 20.8 g. (0.1 mole) of benzalacetophenone and 40 ml. of 90% hydrazine was diluted with 50 ml. of methylene chloride and added at 10–15° to 49 g. (0.11 mole) of lead tetraacetate in 300 ml. of methylene chloride. The work-up procedure was the same as described for 2-phenyl-1-methylcyclopropyl acetate. The residual oil (20 g.) was induced to partially crystallize by addition of hexane. By further crystallizations of the oil a total of 7.5 g. (30%) of *cis*-1,2-diphenylcyclopropyl acetate, m.p. 52–53° (hexane) was obtained. The residual oil was distilled at 125° (0.4 mm.) to yield 8.8 g. (35%) of a viscous oil whose n.m.r. spectrum indicated that it was mainly the *trans* isomer, but which still contained substantial amounts of the *cis* isomer.

***trans*-1-Phenyl-2-methylcyclopropane.**—To a solution of iodomethylzinc iodide[17] prepared from 13.4 g. (0.05 mole) of methylene iodide, 0.05 g. of iodine, and the zinc–copper couple (4 g. of zinc) in 50 ml. of anhydrous ether was added 11.8 g. (0.1 mole) of *trans*-propenylbenzene[25] in 25 ml. of anhydrous ether. After stirring under reflux overnight, the mixture was worked up and the organic product distilled through a spinning-band column to yield 3.0 g. (53%) of *trans*-1-phenyl-2-methylcyclopropane, b.p. 76° (19 mm.), $n^{20}D$ 1.5215. From a mixture of *cis*- and *trans*-propenylbenzene, Simmons and Smith[17] obtained a mixture of phenylmethylcyclopropanes, b.p. 78–79° (20 mm.), $n^{25}D$ 1.5204. Since reduction of the reported[13] 1-phenyl-2-methyl-3,3-dichlorocyclopropane yielded *trans*-1-phenyl-2-methylcyclopropane, it must have the *trans* configuration.

***cis*-1-Phenyl-2-methyl-3,3-dichlorocyclopropane.**—A mixture of 18.2 g. (0.1 mole) of sodium trichloroacetate, 65 g. (0.5 mole) of *cis*-propenylbenzene,[26] and 75 ml. of ethylene glycol dimethyl ether was heated under reflux overnight. The dichlorocyclopropane was isolated by distillation, b.p. 60–62° (0.5 mm.), $n^{20}D$ 1.5405, yield 12.1 g. (61%).

Anal. Calcd. for $C_{10}H_{10}Cl_2$: C, 59.73; H, 5.01. Found: C, 59.65; H, 5.22.

***cis*-1-Phenyl-2-methylcyclopropane.**—A solution of 10 g. (0.05 mole) of *cis*-1-phenyl-2-methyl-3,3-dichlorocyclopropane in 200 ml. of ether was reduced with 23 g. (1 g.-atom) of sodium and 150 ml. of methanol containing 5 ml. of water. Distillation of the ether extracts yielded 2.4 g. (36%) of *cis*-1-phenyl-2-methylcyclopropane, b.p. 78–80° (20 mm.), $n^{20}D$ 1.5201.

Acknowledgment.—We are indebted to Dr. C. H. DePuy of Iowa State University for helpful correspondence concerning the spectra of cyclopropyl acetates.

(25) *trans*-Propenylbenzene of high purity may be obtained from Columbia Organic Chemicals Company. Their product was purified by gas chromatography on a Dow 710 silicone-on-Chromosorb column at 125°. The properties of the purified material agreed in detail with those reported: R. Y. Mixer, R. F. Heck, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **75**, 4094 (1953).

(26) W. R. R. Park and G. F. Wright, *J. Org. Chem.*, **19**, 1435 (1954).

Factors Influencing the Separation of 4-Hydroxyproline Diastereomers by Ion-Exchange Chromatography

HARUHIKO AOYAGI, MOTONORI OHNO, NOBUO IZUMIYA, AND BERNHARD WITKOP

Laboratory of Biochemistry, Faculty of Science, Kyushu University, Fukuoka, Japan, and the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, United States Department of Health, Education, and Welfare, Bethesda, Maryland

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On a preparative scale 4-hydroxy-DL-proline and allo-4-hydroxyproline were separated on ion-exchange resin. By working in alcoholic buffer systems, optimal conditions for accurate and rapid separation were elaborated. The method was applied to the preparation of pure diastereomers from mixtures obtained by two different synthetic pathways. The ratios of crystalline hydroxyproline to allohydroxyproline were 1:2 in the *intra*molecular cyclization of 2-amino-4-hydroxy-5-bromopentanoic acid, and 7:5 in the *inter*molecular reaction of 2,5-dichloro-γ-valerolactone with ammonia.

In the previous study[1] we reported on the preparation, separation, and quantitative determination of the diastereomers of hydroxyproline. The subject of this paper is the manipulation of the variables in the ion-exchange technique and an improved method for the rapid and quantitative separation of hydroxyproline diastereomers.

Reviewing the literature on the separation of the diastereomers of hydroxyamino acids, one notices that DL-threonine and DL-allothreonine[2] have been separated on Dowex 50 by elution with 1.5 *N* hydrochloric acid, the diastereomers of hydroxylysine by a buffer system of pH 5.0,[3] the diastereomers of β-hydroxy-DL-aspartic acid on Dowex 1 with dilute

(1) N. Izumiya and B. Witkop, *J. Am. Chem. Soc.*, **85**, 1835 (1963).

(2)(a) A. T. Shulgin, O. G. Lien, Jr., E. M. Gal, and D. M. Greenberg, *ibid.*, **74**, 2427 (1952); (b) throughout this paper the use of the name hydroxyproline refers to 4-hydroxy-DL-proline and its diastereomer.

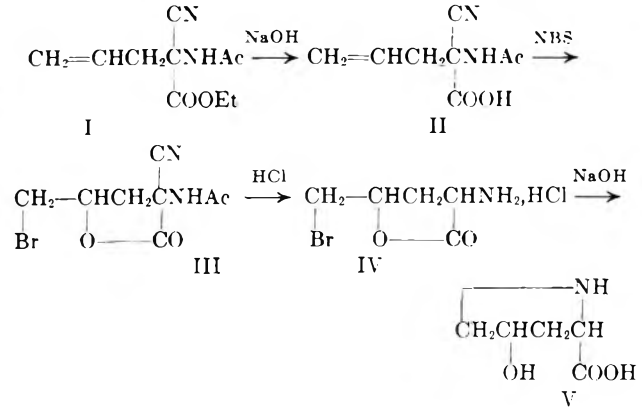
(3) P. G. Hamilton and R. A. Anderson, *J. Biol. Chem.*, **213**, 249 (1955).

formic acid,[4] the diastereomers of γ-hydroxyornithine on Dowex 50,[5] and D-leucyl-L-tyrosine and L-leucyl-L-tyrosine on Dowex 50 and a cellulose column.[6]

In a similar manner, the diastereomers of hydroxylysine, isoleucine, and hydroxyproline have been separated in aqueous buffer systems.[7] In the separation of the diastereomers of isoleucine and threonine, addition of ethanol was reported to be very effective for the separation of the diastereomers.[8] In addition, the same authors[8] have separated the diastereomers of hydroxyproline on a column of Amberlite CG-120 by elution with ethanolic aqueous ammonium acetate buffer,[9] a procedure which has been utilized to advantage for the preparation of 4-H^3-hydroxy- and 4-H^3-allohydroxy-L-proline.[10] These observations have been extended to a study of various solvents as they influence the separation of the diastereomers of threonine, isoleucine, and phenylserine.[11]

In this investigation we have studied the effects of organic solvents, buffer systems, and different resins in order to find optimal conditions for the separation of a representative example of a pair of diastereomeric hydroxyamino acids, such as hydroxyproline and allohydroxyproline, and found that a solvent system containing 40% methanol at pH 4.0 affords rapid and quantitative separation.

On a preparative scale the improved method has been applied to an easy separation of 4-hydroxy- and allo-4-hydroxy-DL-proline obtained by two different synthetic routes. One synthesis utilized ethyl allylacetaminocyanoacetate (I) rather than allylglycine[1] as an intermediate. By bromolactonization (III) of



the acid II, hydrolysis (IV), and ring closure (V) a 2:1 ratio of allohydroxyproline to hydroxyproline was obtained, indicative of the preponderant formation of the *cis*-disubstituted lactone as noted previously.[1]

The second synthetic route, VI–IX, is a modification of the method of Gaudry and Godin.[12] From the dichlorolactone VIII, hydroxyproline and allohydroxy-

(4) M. L. Kornkuth and H. J. Sallach, *Arch. Biochem. Biophys.*, **91**, 39 (1960).

(5) B. Witkop and T. Beiler, *J. Am. Chem. Soc.*, **78**, 2882 (1956).

(6) S. Yanari, M. Volini, and M. A. Mitz, *Biochim. Biophys. Acta*, **45**, 595 (1960); S. Blackburn and P. Tetley, *ibid.*, **20**, 423 (1956).

(7) K. A. Piez, *J. Biol. Chem.*, **207**, 77 (1954).

(8) K. Michi, S. M. Birnbaum, and M. Winitz, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1959, p. 19C.

(9) S. M. Birnbaum, personal communication.

(10) A. V. Robertson, E. Katz, and B. Witkop, *J. Org. Chem.*, **27**, 2676 (1962).

(11) H. Aoyagi, H. Okai, M. Bessho, and N. Izumiya, *J. Chem. Soc. Japan*, in preparation.

(12) R. Gaudry and C. Godin, *J. Am. Chem. Soc.*, **76**, 139 (1954).

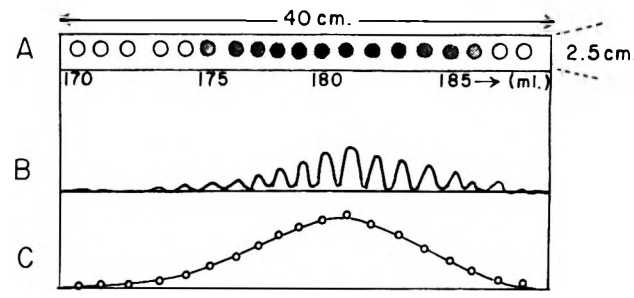


Fig. 1.—Separation and assay of mixtures of hydroxy-L- and allohydroxy-D-proline on Dowex 50W-X8: A, spotting of aliquots on filter paper strips by the isatin method; B, evaluation of color intensities with the aid of a densitometer; and C, integration of areas.

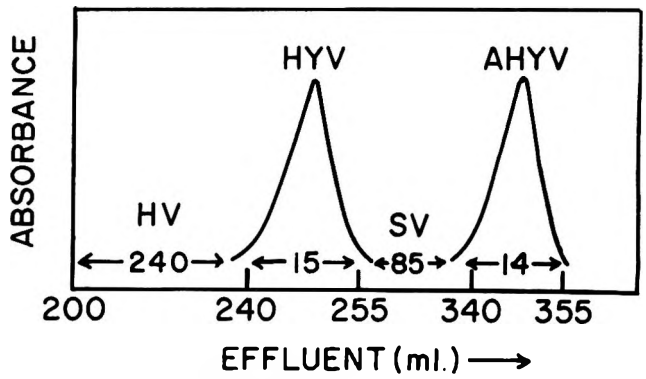
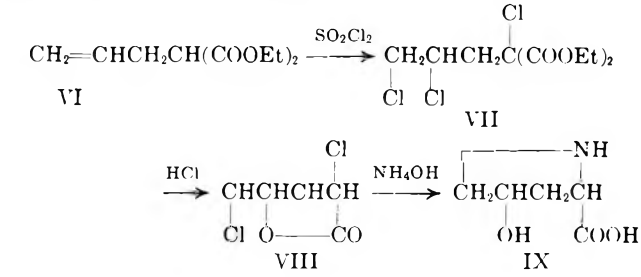


Fig. 2.—Elution pattern of mixtures of hydroxyproline and allohydroxyproline expressed in the four stages of HV (holdup volume), HYV (hydroxyprolone volume), SV (separation volume), and AHYV (allohydroxyproline volume).

proline were obtained in a ratio of 7:5 in an over-all yield of 60% of crystalline products.



Experimental

Separation Studies on Ion-Exchange Resins. A. Isatin Assay. Preparation of Column and Buffer Systems.—A column (1.8 × 110 cm.) was filled with Dowex 50W-X8 (200–400 mesh), NH_4^+ form, and washed with a solvent system prepared by the addition of acetic acid to 0.4 *M* ammonium hydroxide (2.5 l.) until the solution reached the desired pH. To the solution was then added the appropriate alcohol (1 or 2 l.). The solution was made up to 5 l. with water, and adjusted again to the desired pH by the addition of ammonium hydroxide or acetic acid. The final buffer solution was 0.2 *M* ammonium acetate containing 20 to 40% of alcohol at a chosen pH.

Chromatography of Model Mixtures.—Samples of 6.56 mg. (0.05 mmole) of hydroxy-L-proline and of allohydroxy-D-proline were dissolved in 1 ml. of water (total amino acid, 0.1 mmole), the solution applied to a column and eluted with the appropriate solvent system at room temperature (20–25°) and a flow rate of 4.5–5.5 ml./hr. One-milliliter fractions were collected, and 0.01 ml. from each tube was spotted on a strip of filter paper. The strip was put in an oven (100°) for 5 min., immersed in a trough with 0.2% isatin acetone solution for a moment, and again heated in an oven (100°) for 5 min. (Fig. 1A). The amounts of color

developed were determined by an Atago AG-4 densitometer (slit 1 × 18 mm., 440 mμ) (Fig. 1B), and the integrated areas were plotted on a graph (Fig. 1C). The terms of HV (holdup volume), HYV (hydroxyproline volume), SV (separation volume), and AHYV (allohydroxyproline volume) (Fig. 2) are used to describe the elution pattern. In all experiments we ascertained that HYV contained *hydroxyproline* and *allohydroxyproline*. The pH of the 20% alcoholic buffer system was 6.0 (see Table I). The conditions were as described above. Among many alcohols tested, methanol and *t*-butyl alcohol most effectively separated the diastereomers. Cross-linked Dowex 50W-X2 and X8 gave about the same results, but X12 gave poorer separation (see Table II and III). Therefore, resin X8 was used exclusively in all our subsequent experiments.

TABLE I

INFLUENCE OF VARIOUS ALCOHOLS ON THE SEPARATION OF HYDROXYPROLINE AND ALLOHYDROXYPROLINE

Alcohol, 20%	HV[a]	HYV[a]	SV[a]	AHYV[a]
No alcohol	149	13	28	16
MeOH	175	13	55	14
EtOH	141	19	31	20
n-PrOH	175	21	41	21
i-PrOH	152	28	38	21
t-BuOH	171	26	50	25

[a] In milliliters.

TABLE II

EFFECT OF CROSS LINKAGE OF THE RESIN ON THE SEPARATION[a]

Dowex 50W (200–400 mesh)	HV[b]	HYV[b]	SV[b]	AHYV[b]
X2	200	28	44	27
X8	171	26	50	25
X12	92	18	20	17

[a] pH 6.0, 20% *t*-BuOH. [b] In milliliters.

TABLE III

ROLE OF CATION IN THE SEPARATION[a]

Cationic partner of the resin	Buffer system	HV[b]	HYV[b]	SV[b]	AHYV[b]
NH_4^+	0.2 *M* $AcONH_4$	171	26	50	25
Na^+		158	20	45	23
$NHEt_3^+$		112	11	14	11
Pyridinium$^+$	0.2 *M* pyridine–acetic acid	130	23	35	24

[a] pH 6.0, 20% *t*-BuOH. [b] In milliliters.

The effect of pH in buffer systems containing *n*-propyl alcohol or methyl alcohol is shown in Table IV. As noted in Table VI, 0.2 *M* pyridine–acetic acid buffer (pH 4.0) containing 40% methanol under somewhat different conditions effected better separation than the ammonium acetate buffer system. At lower pH, and especially in the presence of methanol, a better separation was achieved.

TABLE IV

EFFECT OF pH IN BUFFER SYSTEM pH 6

pH	HV	HYV	SV	AHYV
		20% *n*-PrOH		
7	154	28	33	15
6	175	21	41	21
4	196	25	67	21
		20% MeOH		
7	160	12	50	14
6	175	13	55	14
4	225	15	78	16

Concentration of Alcohol.—Among many conditions tested by us in a series of experiments, the solvent of pH 4.0 and 40% methanol gave best results (see Table V). The separation of the two pairs of diastereomers, DL-threonine and DL-allothreonine, L-isoleucine and D-alloisoleucine, was tried and achieved under conditions similar to those described above. The use of ammonium acetate buffer (0.1, 0.2, and 0.3 *M*) with 20% *t*-butyl alcohol at pH 6.0 gave good separations. Variations in temperature (5, 25, and 45°) had little effect on the separation pattern.

TABLE V

EFFECT OF CONCENTRATION OF ALCOHOL

Alcohol, %	HV[a]	HYV[a]	SV[a]	AHYV[a]
20[b]	171	26	50	25
40[b]	184	19	56	19
20[c]	225	15	78	16
40[c]	240	15	85	14

[a] In milliliters. [b] *t*-BuOH at pH 6.0. [c] MeOH at pH 4.0.

B. Ninhydrin Assay.—Ten micromoles (1.31 mg.) each of hydroxy-L-proline and allohydroxy-D-proline was dissolved in 0.5 ml. of water. The resin, Dowex 50W-X8 (200–400 mesh), was in the NH_4^+ or pyridinium$^+$ form. The two buffer systems were 0.2 *M* ammonium acetate with 40% methanol at pH 4.0 and pyridinium acetate solvent—0.2 *M* pyridinium acetate with 40% methanol at pH 4.0. The flow rate was 4 ml./hr.; the temperature was 20–25°.

The sample solution (20 μmoles of the equimolar mixture) was passed through the column and eluted with the appropriate buffer. The effluent was collected in 1-ml. fractions; each fraction was analyzed by ninhydrin colorimetry[13] (440 mμ, in the case of pyridinium acetate buffer) or by densitometry as described above for the ammonium acetate buffer system. The results are shown in Table VI. The areas of the HYV and AHYV peaks were integrated to give the exact ratios of the two diastereomers. The results of experiment no. 2 were unaffected by a higher flow rate, such as 6 ml./hr. One such run will, therefore, be completed within less than 8 hr. when a column of 0.9 × 30 cm. is used.

Separation of Hydroxy-DL-proline and Allohydroxy-DL-proline Obtained from Ethyl Allylacetaminocyanoacetate.—To a suspension of ethyl allylacetaminocyanoacetate[14] (10.5 g., 0.05 mole) in water (50 ml.) was added 1.0 *N* sodium hydroxide (50 ml.) with stirring at room temperature. When stirring was continued for 2 hr. the suspension gradually became a solution. After addition of 1.0 *N* hydrochloric acid (50 ml.) the solution was evaporated *in vacuo*. The residue was extracted with hot acetone (total volume 150 ml.) and the acetone solution was evaporated *in vacuo* to a sirup (8.8 g.). The sirupy allylacetaminocyanoacetic acid in acetonitrile (100 ml.) and water (50 ml.) was treated with a solution of N-bromosuccinimide (NBS, 9.1 g.) in acetonitrile (100 ml.) and water (50 ml.) at room temperature. After standing for 1 hr. the solution was evaporated *in vacuo*. The residue, 2-acetamino-2′-cyano-4-hydroxy-5-bromopentanoic acid lactone, was dissolved in 6.0 *N* hydrochloric acid (100 ml.). The solution was refluxed for 5 hr. and evaporated *in vacuo* to dryness to the hydrochloride of 2-amino-4-hydroxy-5-bromopentanoic acid lactone. This salt was dissolved in water (100 ml.) and adjusted with 2.0 *N* sodium hydroxide at 50–55° to a final pH of 9.5–9.6.[1] Total volume of 2.0 *N* sodium hydroxide used was 135 ml. The solution was passed through a column (3 × 30 cm.) of Dowex 50W-X8 (100–200 mesh, H^+ form), washed with water, and eluted with 2 *N* NH_4OH. The ammonia-containing solution was evaporated *in vacuo*. The residue was dissolved in 20 ml. of water (solution A).

Half of solution A (10 ml.) was put on a column (1.8 × 110 cm.) of Dowex 50W-X8 (200–400 mesh, NH_4^+ form), previously washed with 0.2 *M* ammonium acetate containing 40% methanol, pH 4.0, and eluted with the same solvent at room temperature and a flow rate of 6 ml./hr. Each fraction (3 ml.) was tested on a paper strip by the isatin reaction. The results were HV, 174; HYV, 93; SV, 24; and AHYV, 138 ml. The other half of solution A was chromatographed and gave a similar ratio: 177, 96, 21, and 132 ml.

The two HYV fractions (93 + 96 ml.) were pooled and evaporated *in vacuo* to dryness. Most of the ammonium acetate was removed by sublimation *in vacuo* for about 2 hr. at 100°. The residue, dissolved in a small volume of hot water, on the addition of ethanol gave 1.31 g. of crystalline hydroxy-DL-proline. On recrystallization from water–ethanol 1.07 g. was obtained (16%

(13) H. Rosen, *Arch. Biochem. Biophys.*, **67**, 10 (1957).
(14) N. F. Albertson, *J. Am. Chem. Soc.*, **68**, 450 (1946).

TABLE VI

Expt. no.	Size of column, cm.	Buffer system	HV	HYV	SV	AHYV	Ratio of hypro-allohypro
1	0.9 × 50	Pyridinium acetate	33	9	18	11	49.8:50.2
2	0.9 × 30		20	9	7	10	49.7:50.3
3	0.9 × 20		14	9	2	9	49.9:50.1
4	0.9 × 50	Ammonium acetate	41	10	14	10	46:54

yield from ethyl allylacetaminocyanoacetate), m.p. 245–246° dec., lit. m.p. 247°.[12]

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.89; H, 6.83; N, 10.65.

The two AHYV fractions (138 + 132 ml.), processed as above, yielded 2.37 g. Further recrystallization with water–ethanol gave 2.11 g. (32%) of allohydroxy-DL-proline, m.p. 239–240° dec., lit.[12] m.p. 238°.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.70; H, 6.79; N, 10.52.

Separation of Hydroxy-DL-proline and Allohydroxy-DL-proline Obtained from Dichlorovalerolactone.—2,5-Dichloro-4-valerolactone was prepared by the action of sulfuryl chloride on diethyl allylmalonate. The dichlorolactone (13.5 g., 0.08 mole) dissolved in concentrated ammonium hydroxide (200 ml.) was left for 5 days at room temperature. This procedure was found more convenient than the ammonolysis at 100° in a pressure vessel.[12] The solution was evaporated *in vacuo*. The residue on paper chromatography (*n*-BuOH–AcOH–pyridine–H_2O = 4:1:1:2, v./v.) showed two ninhydrin-positive spots, one belonging to hydroxyproline (R_f 0.23, yellow), and another (R_f 0.16, purple) belonging to an unknown material, *not* proline amide, which disappeared after refluxing for 3 hr. in 100 ml. of 6.0 *N* hydrochloric acid. After evaporation to dryness the residue was dissolved in water (100 ml.), and the solution was passed through a column (3 × 30 cm.) of Dowex 50W-X8 (100–200 mesh, H^+ form), washed with water, and eluted with 2 *N* ammonium hydroxide.

TABLE VII

Expt. no.	HV[a]	HYV[a]	SV[a]	AHYV[a]
1	177	78	15	81
2	180	81	18	81
3	177	81	15	84

[a] In milliliters.

The ammonia solution was evaporated *in vacuo*, and the residue was made up to a volume of 30 ml. with water.

Each 10 ml. of the above solution was chromatographed as described above. The results obtained are shown in Table VII. The three HYV fractions were pooled and processed as described to yield 4.05 g. of hydroxyproline. Further recrystallization with water–ethanol gave 3.76 g. (35%) of pure hydroxy-DL-proline, m.p. 244–245° dec. By the same synthetic route and separation *via* the copper salts the yield of hydroxy-DL-proline was only 27%.[12]

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.77; H, 6.85; N, 10.61.

Similarly, the three portions yielded 2.85 g. of allohydroxyproline. Further recrystallization from water–ethanol gave 2.63 g. (25%), m.p. 238–239° dec. A yield of 27% of allohydroxyproline has been reported *via* the copper salts.[12]

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.81; H, 6.88; N, 10.73.

A Novel Method for the Preparation of Acid Anhydrides by Means of *trans*-Dibenzoylethylene and Tertiary Phosphines

ISAO KUWAJIMA AND TERUAKI MUKAIYAMA

Tokyo Institute of Technology, Laboratory of Organic Chemistry, Ookayama, Meguro-Ku, Tokyo, Japan

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Reactions of *trans*-dibenzoylethylene with tertiary phosphines in the presence of carboxylic acids have been studied. When two equivalents of carboxylic acid were treated with *trans*-dibenzoylethylene and tertiary phosphine, the corresponding acid anhydrides were obtained in good yields, along with dibenzoylethane and phosphine oxide. Similar reactions were further extended to the phosphoric monoesters, and *sym*-pyrophosphates were obtained in good yields. The mechanism of the reaction is discussed.

It has recently been reported that the various carboxylic acids, phosphoric acids, and sulfonic acid were converted into the corresponding acid anhydrides in the course of oxidation–reduction reactions between diphenylmercury and tri-*n*-butylphosphine.[1]

$$(C_6H_5)_2Hg + 2RCO_2H + (n\text{-}C_4H_9)_3P \longrightarrow Hg + 2C_6H_6 + (RCO)_2O - (n\text{-}C_4H_9)_3P{=}O$$

In the present study, it was found that *trans*-dibenzoylethylene can be employed as a hydrogen acceptor in place of the diphenylmercury mentioned in the above experiments. When tri-*n*-butylphosphine was added to an anhydrous benzene solution of *trans*-dibenzoylethylene at room temperature, it assumed a red color with evolution of heat. After standing for 10 min., it was added to an anhydrous benzene solution of two equivalents of propionic acid and the mixture was refluxed for 2 hr.; propionic anhydride was obtained in 78% yield along with dibenzoylethane (77%) and tri-*n*-butylphosphine oxide (84%). Similar reaction was observed in the cases of the other carboxylic acids (see Table I).

$$C_6H_5COCH{=}CHCOC_6H_5 + (n\text{-}C_4H_9)_3P + 2RCO_2H \longrightarrow C_6H_5COCH_2CH_2COC_6H_5 + (n\text{-}C_4H_9)_3P{=}O + (RCO)_2O$$

Triphenylphosphine was likewise successfully used as an oxygen acceptor and propionic anhydride was obtained in 70% yield under the same condition.

The most probable pathway of this reaction may be sketched in the following manner. Initially, tri-*n*-butylphosphine reacts with *trans*-dibenzoylethylene to form an adduct (I),[2] which in turn is transformed into "phosphonium carboxylate" (II) in the presence of car-

(1) T. Mukaiyama, I. Kuwajima, and Z. Suzuki, *J. Org. Chem.*, **28**, 2024 (1963).

(2) Horner, *et al.*, reported that *trans*- and *cis*-dibenzoylethylene react with triethylphosphine to form an adduct similar to I in 95% and 65% yields, respectively: L. Horner and K. Klupfel, *Ann.*, **591**, 69 (1955).

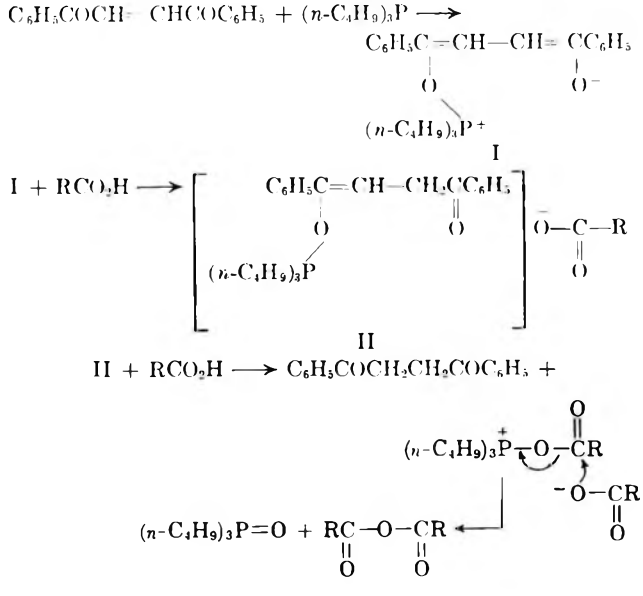
TABLE I

THE REACTIONS OF TRI-*n*-BUTYLPHOSPHINE WITH *trans*-DIBENZOYLETHYLENE IN THE PRESENCE OF CARBOXYLIC ACIDS

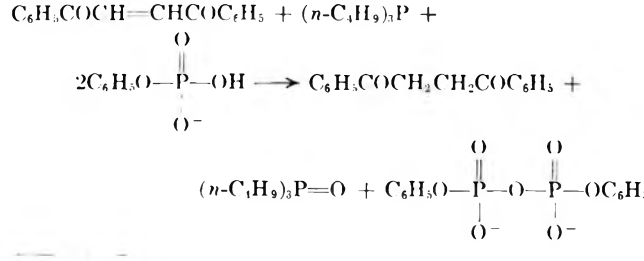
Carboxylic acid	Yield, % Anhydride (m.p. or b.p., °C.)	Dibenzoylethane	$(n\text{-}C_4H_9)_3P{=}O$
Propionic	78 (66–68° at 18 mm.)	77	84
n-Butyric	77 (85–86° at 18 mm.)	76	79
Isobutyric	81 (74–76° at 18 mm.)	77	83
Benzoic	52[a]	49	
Phthalic	63 (130–131°, m.p.)	45	58
Succinic	82 (117–119°, m.p.)	89	87

[a] Since benzoic anhydride could not be separated from tri-*n*-butylphosphine oxide by fractional distillation, the yield was determined from the weight of the corresponding anilide derived from the anhydride. [b] The reactions were carried out in anhydrous benzene for 2 hr. at reflux.

boxylic acid. The "phosphonium carboxylate" (II) thus formed may react with the other carboxylic acid to yield the corresponding acid anhydride, dibenzoylethane, and tri-*n*-butylphosphine oxide.[3,4]



Further extension of this reaction to phosphoric monoesters was examined. When phenyl dihydrogen phosphate was used in place of carboxylic acid, a reaction could not be observed and the starting materials were recovered almost quantitatively. This may be due to poor nucleophilicity of the phosphate anion and the reaction is stopped in the step of phosphonium



(3) S. Tripett, *J. Chem. Soc.*, 2337 (1962).
(4) L. J. Borowitz and R. Virkhaus, *J. Am. Chem. Soc.*, **85**, 2185 (1963).

TABLE II

THE REACTIONS OF TRI-*n*-BUTYLPHOSPHINE WITH *trans*-DIBENZOYLETHYLENE IN THE PRESENCE OF PHOSPHORIC MONOESTERS[a]

$RO\text{-}\overset{\overset{O}{\|}}{P}(OH)_2$	Yield, % Pyrophosphate (R_f value)	Dibenzoylethane	$(n\text{-}C_4H_9)_3P{=}O$
R = C_6H_5	82 (0.80)	75	
R = *p*-$CH_3C_6H_5$	84 (0.82)	80	

[a] The reactions were carried out in anhydrous benzene. When acetonitrile was used as solvent, a reaction was not observed and the starting materials were recovered.

phosphate. Based on these results, tertiary ammonium phenyl hydrogen phosphate was used in the above experiment in order to increase its nucleophilicity. While the triethylammonium salt gave *sym*-diphenyl pyrophosphate, the pyridinium salt did not.

Experimental

Materials.—*trans*-Dibenzoylethylene (m.p. 109–110°) was prepared by the method of Lutz.[5]

Reaction of Propionic Acid with *trans*-Dibenzoylethylene and Tri-*n*-butylphosphine.—Tri-*n*-butylphosphine (3.00 g., 0.015 mole) was added dropwise to *trans*-dibenzoylethylene (3.54 g., 0.015 mole) in 20 ml. of anhydrous benzene. It turned red with evolution of heat. After 10-min. standing, it was mixed with propionic acid (2.22 g., 0.03 mole) and refluxed for 2 hr. Then the reaction mixture was concentrated and the separated dibenzoylethane, 2.74 g. (77%), m.p. 142–144°, was filtered off. Its filtrate was distilled *in vacuo*, giving propionic anhydride, 1.52 g. (78%), b.p. 66–68° (18 mm.), and tri-*n*-butylphosphine oxide, 2.74 g. (84%), b.p. 133–135° (0.8 mm.).

By a similar procedure, the other carboxylic anhydrides were obtained.

Reaction of Benzoic Acid with *trans*-Dibenzoylethylene and Tri-*n*-butylphosphine.—Benzoic acid (2.44 g., 0.02 mole) reacted with tri-*n*-butylphosphine (2.00 g., 0.01 mole) and *trans*-dibenzoylethylene (2.36 g., 0.01 mole) under the same condition as described above. Then the reaction mixture was concentrated and dibenzoylethane, 1.17 g. (49%), m.p. 140–143°, was filtered off. The filtrate was dissolved in 30 ml. of ether and it was treated with cold aqueous sodium bicarbonate solution. From the ether layer, benzanilide, 1.03 g. (52%), m.p. and m.m.p. 159–161°, was obtained by treatment with aniline (0.93 g., 0.01 mole). From the aqueous layer, benzoic acid, 0.89 g. (36%), m.p. and m.m.p. 118–120°, was isolated by the acidification with dilute hydrochloric acid.

Reaction of Triethylammonium Phenyl Hydrogen Phosphate with *trans*-Dibenzoylethylene and Tri-*n*-butylphosphine.—Tri-*n*-butylphosphine (1.00 g., 0.005 mole) and *trans*-dibenzoylethylene (1.18 g., 0.005 mole) were treated as described above. The resulting solution was added to 20 ml. of an anhydrous benzene solution of phenyl dihydrogen phosphate (1.74 g., 0.01 mole) and triethylamine (0.51 g., 0.01 mole). It was refluxed for 2 hr. Then the reaction mixture was concentrated and dibenzoylethane, 0.90 g., (75%), m.p. 142–144°, was filtered off. A solution of barium chloride ($BaCl_2 \cdot 2H_2O$, 2.30 g.) in 10 ml. of water and pyridine (3 ml.) was added to the cold reaction mixture and allowed to stand in a refrigerator for about 30 min. The white precipitate was washed twice with acetone, dried, and then washed with 30 ml. of water thoroughly. The undissolved precipitate was filtered and dried *in vacuo* over phosphorus pentoxide at room temperature; 2.00 g. (80%) of barium diphenyl pyrophosphate was obtained, R_f 0.80 (1-propanol–concentrated ammonia–water, 6:3:1).

By the same procedure barium di-*p*-tolyl pyrophosphate was obtained.

(5) R. E. Lutz, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 248.

Condensations of 2-Dimethylaminomethylbenzyllithium and Related Amino Organolithium Reagents with Aldehydes and Ketones. Cyclizations to Isochromans[1]

RANN L. VAULX, FRANK N. JONES, AND CHARLES R. HAUSER

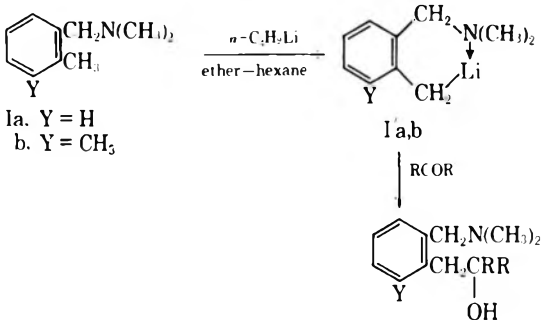
Department of Chemistry, Duke University, Durham, North Carolina

Received December 10, 1963

2-Dimethylaminomethylbenzyllithium and some related amino organolithium reagents were prepared by metalation of the appropriate 2-methyl- or 2-benzylbenzyldimethylamines with *n*-butyllithium, and condensed with benzaldehyde and certain ketones to form corresponding amino alcohols. Several of these products were dehydrated to form amino olefins and cyclized through their methiodides to give isochromans. One of the amino alcohols was converted to a cyclic quaternary bromide. One of the amino organolithium compounds was condensed with benzonitrile to form an amino ketone. The adduct of 2-dimethylaminomethylphenyllithium and cyclohexene oxide was cyclized through its methiodide to afford 1,2,3,4,4a,10b-hexahydro-6H-dibenzo[*b,d*]pyran.

2-Dimethylaminomethylbenzyllithium (I'a) and the related amino organolithium reagent I'b have recently[2] been prepared by metalation of 2-methyl- and 2,3-dimethylbenzyldimethylamine (Ia and b) with *n*-butyllithium. The site of metalation was determined by deuteration.[2] We have now condensed these amino organolithium reagents with benzaldehyde and appropriate ketones to form amino alcohols IIa–e (see Scheme A).

SCHEME A

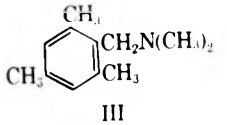


Ia, Y = H
b, Y = CH_3

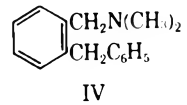
I'a,b

IIa, Y = H; R = H; R' = C_6H_5
b, Y = H; R, R' = C_6H_5
c, Y = H; R, R' = CH_3
d, Y = CH_3; R, R' = C_6H_5
e, Y, R, R' = CH_3

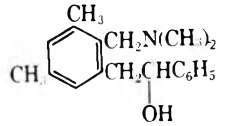
Similarly 2,4,6-trimethylbenzyldimethylamine (III) and 2-benzylbenzyldimethylamine (IV) were metalated and condensed with benzaldehyde and benzophenone to give amino alcohols V and VI, respectively.



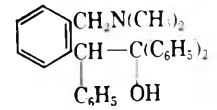
III



IV



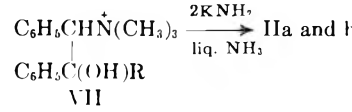
V



VI

In Table I are summarized the yields of these amino alcohols, in Table II physical data and analyses, and in Table III data for derivatives. Although amino alcohols IIc and IIe contained small amounts of impurities, they afforded pure derivatives.

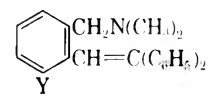
Amino alcohols IIa and b were identified by comparison with samples prepared recently by the *ortho*-substitution rearrangement of appropriate quaternary ion alcohols VII (eq. 1).[3]



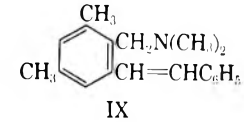
VII (1)

The structures of amino alcohols IId, V, and VI were supported by analyses and infrared spectra, which showed bands in the regions 4000–3000 and 854–837 cm.$^{-1}$ for the hydroxyl[4] and dimethylaminomethyl[5] groups, respectively. Bands designating the appropriate aromatic substitution were present (see Table II).

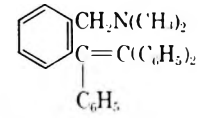
The structures of amino alcohols IIb, IId, V, and VI were further supported by dehydration with 20% sulfuric acid to form amino olefins VIIIa, VIIIb, IX, and X, respectively (Table IV). The formation of these products shows that the amino alcohols were not the possible ring substitution derivatives, for example, XI, which could not undergo such a dehydration.



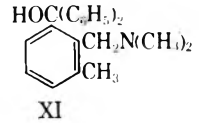
VIIIa, Y = H
b, Y = CH_3



IX



X



XI

Next, the methiodides of certain of the amino alcohols were cyclized thermally to form isochromans and presumably trimethylamine hydroiodide.[6] Thus methiodides XIIa and b afforded isochromans XIIIa and b, respectively (eq. 2).

Similarly, amino alcohol V was cyclized through its methiodide to form isochroman XIV. Methiodide

(1) Supported by Army Research Office, Durham, N. C.

(2) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

(3) W. H. Puterbaugh and Charles R. Hauser, *J. Am. Chem. Soc.*, **86**, 1105 (1964); see also *ibid.*, in press.

(4) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958; p. 96.

(5) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

(6) For a related thermal cyclization to form phthalans, see R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **29**, 505 (1964).

TABLE I

CONDENSATION OF AMINES WITH ALDEHYDES AND KETONES BY MEANS OF *n*-BUTYLLITHIUM IN ETHER–HEXANE

Amine	Mole of amine	Aldehyde or ketone	Condensation product	Yield,[a] %
Ia	0.08	Benzaldehyde	2-[α-(Dimethylamino)-*o*-tolyl]-1-phenylethanol (IIa)[b]	77
Ia	0.08	Benzophenone	2-[α-(Dimethylamino)-*o*-tolyl]-1,1-diphenylethanol (IIb)[b]	80
Ia	0.15	Acetone	2-[α-(Dimethylamino)-*o*-tolyl]-1,1-dimethylethanol (IIc)[c]	46[d]
Ib	0.05	Benzophenone	2-[2-Dimethylaminomethyl-6-methylphenyl]-1,1-diphenylethanol (IId)	80
Ib	0.086	Acetone	2-[2-Dimethylaminomethyl-6-methylphenyl]-1,1-dimethylethanol (IIe)[e]	61[d]
III	0.10	Benzaldehyde	2-[2-(Dimethylaminomethyl)-3,5-dimethylphenyl]-1-phenylethanol (V)	81
IV	0.06	Benzophenone	2-[α-(Dimethylamino)-*o*-tolyl]-1,1,2-triphenylethanol (VI)	88

[a] The yield is based on the starting amine. The melting point of the product on which the yield is based is slightly lower than those given in Table II. [b] Amino alcohols IIa and b were identified by the mixture melting point method and by comparison of infrared spectra with samples prepared previously.[3] [c] 2-(Dimethylaminomethyl)phenyl-*t*-butyl alcohol. [d] Crude yield, see Experimental. [e] 2-(Dimethylaminomethyl)-6-methylphenyl-*t*-butyl alcohol.

TABLE II

PHYSICAL DATA AND ANALYSES OF AMINO ALCOHOLS

Amino alcohol	Recrystn. solvent	M.p., °C.	Infrared data, cm.$^{-1}$	Elemental analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IId	95% ethanol	163–164	3356, 855, 775, 760, 709, 700	83.44	7.88	4.05	83.50	7.77	4.27
V	Hexane	120–121	3356, 845, 763, 700	80.52	8.89	4.94	80.49	8.72	5.01
VI	Ethanol–acetone	190–191	3448, 842, 752, 704	85.46	7.17	3.44	85.24	7.35	3.31

TABLE III

DATA FOR DERIVATIVES OF AMINO ALCOHOLS

Amino alcohol	Derivative	Recrystn. solvent	M.p., °C.	Empirical formula	Elemental analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	Methiodide (XIIa)	Acetonitrile–ether	142.5–143.5	$C_{18}H_{24}INO$	54.41	6.09	3.53	54.44	6.18	3.62
IIb	Methiodide (XIIb)	Ethanol–ether	174–175	$C_{24}H_{28}INO$	60.89	5.96	2.96	60.87	6.18	2.92
IIc	Methiodide	Acetonitrile	176.5–177.5	$C_{14}H_{23}INO$	48.28	6.66	4.03	48.31	6.61	4.25
IIc	Picrate	95% ethanol	170–171	$C_{19}H_{24}N_4O_8$	52.29	5.54	12.84	52.20	5.58	12.99
IId	Methiodide	Acetonitrile	195.5–197.5	$C_{28}H_{30}INO$	61.62	6.20	2.87	61.82	6.05	3.12
IIe	Picrate	95% ethanol	177–177.5	$C_{20}H_{26}N_4O_8$	53.33	5.82	12.44	53.02	5.51	12.58
IIe	Methiodide	Acetonitrile	191–192	$C_{15}H_{26}INO$	49.59	7.21	3.86	49.74	7.10	3.87

TABLE IV

DEHYDRATION OF AMINO ALCOHOLS WITH REFLUXING 20% SULFURIC ACID

Amino alcohol	Reflux time, hr.	Dehydration product	M.p., °C.	Yield,[a] %	Elemental analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIb	18	*o*-(2,2-Diphenylvinyl)-N,N-dimethylbenzylamine (VIIIa)[b]	69–70	78	88.13	7.40	4.47	88.29	7.25	4.54
IId	16	*o*-(2,2-Diphenylvinyl)-N,N,3-trimethylbenzylamine (VIIIb)[b]	68–69	91	88.03	7.70	4.28	88.31	7.66	4.30
V	12	N,N,2,4-Tetramethyl-6-styrylbenzylamine (IX)[c]	70–71.5	54	85.98	8.74	5.28	85.93	8.62	5.27
VI	7	*o*-(1,2,2-Triphenylvinyl)-N,N-dimethylbenzylamine (X)[d]	136–137	97	89.42	6.99	3.60	89.23	7.01	3.56

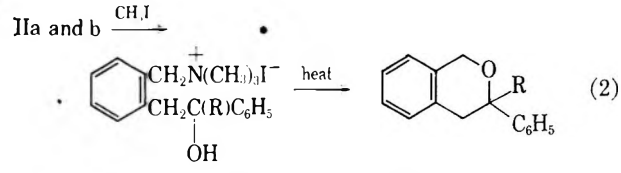
[a] The yield is based on the starting amino alcohol. The melting point of the product on which the yield is based is slightly lower than that given. [b] Recrystallized from hexane. [c] Recrystallized from 95% ethanol. [d] Recrystallized from absolute ethanol.

TABLE V

ISOCHROMANS FROM METHIODIDES OF AMINO ALCOHOLS

Methiodide	Mole of methiodide	Reaction time, hr.	Isochroman	M.p. or b.p., °C.	Yield,[a] %	Infrared data, cm.$^{-1}$	Elemental analysis, % Calcd. C	Calcd. H	Found C	Found H
XIIa	0.012	0.5	3-Phenyl (XIIIa)[b]	76–77.5	68	1093, 767, 744, 698	85.68	6.71	85.47	6.67
XIIb	0.04	1.0	3,3-Diphenyl (XIIIb)[b]	120–121	61	1068, 758, 746, 697	88.08	6.34	87.92	6.50
V[c]	0.05	2.0	6,8-Dimethyl-3-phenyl (XIV)[d]	84.5–86	62	1087, 854, 765, 704	85.67	7.61	85.55	7.49
XV	0.026	6	XVI[e]	101–104 (0.4 mm.)	80	1105, 1030, 957, 742	82.93	8.57	83.06	8.61

[a] The melting points on which these yields are based were slightly lower than the reported values. Yields are based on the methiodides. [b] Recrystallized from absolute ethanol. [c] This methiodide was prepared from amino alcohol V but was not characterized. [d] Recrystallized from 95% ethanol. [e] This compound, which solidified on standing, was indicated to be pure by v.p.c.

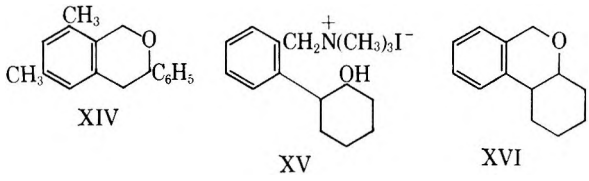


(2)

XIIa, R = H
b, R = C_6H_5

XIIIa, R = H
b, R = C_6H_5

XV[7] was cyclized to give the isochroman-type product XVI, which appears to be the first example and parent compound of the ring system 1,2,3,4,4a,10b-hexahydro-6H-dibenzo[*b*,*d*]pyran.

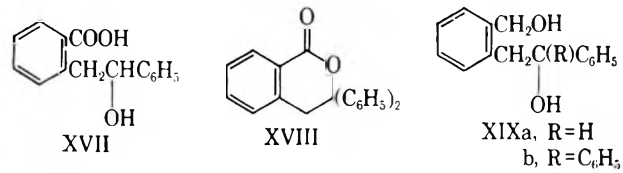


These results are summarized in Table V. The structures of XIIIa and b, XIV, and XVI were supported by analyses and infrared spectra which showed strong peaks in the 1140–1070-cm.$^{-1}$ region indicating a cyclic ether.[8] In the spectrum of XVI, bands appearing at 1030 and 957 cm.$^{-1}$ were attributed to the cyclohexane ring.[9] In the spectra of all four compounds, appropriate aromatic substitution bands were observed (see Table V).

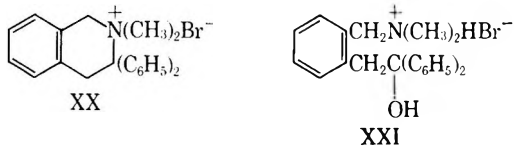
Further evidence supporting structures XIIIa and b, XIV, and XVI was obtained from their n.m.r. spectra. The spectra of XIIIa and XIV were quite similar, both showing a singlet for the C-1 hydrogens at -291 ± 1 and -287 ± 1 c.p.s., respectively, a doublet for the C-4 hydrogens centered at -171 ± 1 and -169 ± 1 c.p.s., respectively, and a triplet for the C-3 hydrogen centered at -275 ± 1 and -272 ± 1 c.p.s., respectively. The spectrum of XIV showed two additional singlets at -123 ± 1 and -133 ± 1 c.p.s. for the two methyl groups. The spectrum of isochroman XIIIb showed singlets for the C-1 and C-4 hydrogens at -276 ± 1 and -204 ± 1 c.p.s., respectively. In each of these three spectra, the coupling constant was 7 c.p.s. and aromatic peaks appeared between -400 and -440 c.p.s.

The n.m.r. spectrum of compound XVI was considerably more complex than that obtained for XIIIa and b and XIV. The chemical shift for the isolated $-CH_2-$ was -311 ± 1 cps. The area ratios (obtained by the method of weights) were as follows: C_6H_4/CH_2 = 2.2 (calculated 2.0), cyclohexane/C_6H_4 = 2.5 (calculated 2.5), and cyclohexane/CH_2 = 5.6 (calculated 5.0).

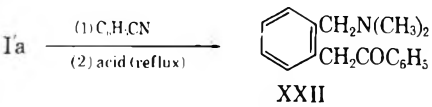
The structures of isochromans XIIIa and b were confirmed by independent synthesis from acid alcohol XVII and lactone XVIII, respectively.[10] These compounds were reduced with lithium aluminum hydride to form diols XIXa and b, which were cyclized with acid to give isochromans XIIIa and b, respectively.



Next, amino alcohol IIb was cyclized by hot 48% hydrobromic acid to form apparently the six-membered ring quaternary ammonium bromide XX.[11] Cold ethanolic hydrobromic acid merely converted IIb to its hydrobromide XXI.



Finally, lithioamine I'a was condensed with benzonitrile to form amino ketone XXII (eq. 3). The structure of this product was supported by analysis and infrared spectrum (see Experimental).



(3)

Discussion

Most of the reactions described above were realized in good to excellent yields (see Tables I, IV, and V, and Experimental). The conversions of the amino alcohols to their methiodides were almost quantitative. The metalations and condensations, which are readily accomplished, furnish convenient methods for the synthesis of amino alcohols, amino ketones, and presumably other types of compounds. Moreover, the amino alcohols are useful intermediates for the synthesis of amino olefins, isochromans, and cyclic quaternary ions. The present method for the amino alcohols (see Scheme A) is probably preferable to that involving the *ortho*-substitution rearrangement (eq. 1).[3] The method for isochromans involving thermal cyclization of quaternary ion alcohols, which should be quite general, appears superior to that through diols such as XIXa and b, at least for isochromans XIIIa and b. Diol XIXa has previously been prepared by another method and reportedly cyclized to form isochroman XIIIa.[12] However, the melting point given for the latter compound was considerably higher than that observed by us (see Experimental). Apparently the other isochromans presented here have not been described previously, though a number of others have been prepared by other methods.[13]

(7) This compound has recently been prepared by condensation of 2-dimethylaminomethylphenyllithium with cyclohexene oxide followed by methylation [F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963)].

(8) See ref. 4, p. 115.

(9) See ref. 4, p. 31.

(10) The method of preparation of these compounds involved N- and C-metalation of N-methyl-*o*-toluamide with excess *n*-butyllithium and condensation of the resulting dilithio intermediate with benzaldehyde and benzophenone, respectively. The details will be published soon along with a general study of this dilithio reagent.

(11) For a related cyclization to form a five-membered ring quaternary bromide see ref. 7.

(12) S. Siegel and S. Coburn, *J. Am. Chem. Soc.*, **73**, 5494 (1951).

(13) See especially P. Maitte, *Compt. rend.*, **239**, 1508 (1954); E. Schmitz and A. Rieche, *Ber.*, **89**, 2807 (1956); and A. Jacot-Guillarmond, *Helv. Chim. Acta*, **40**, 1639 (1957).

Experimental[14]

Metalations of Amines and Condensations with Aldehydes and Ketones to Form Amino Alcohols (Tables I, II, and III).—To 0.05–0.15 mole of the appropriate amine in a 250-ml. erlenmeyer flask was added a 10% excess of approximately 1.5 *M* *n*-butyllithium in hexane,[15] analyzed as described previously.[16] The flask was filled completely with anhydrous ether, tightly stoppered, and stirred magnetically at room temperature for 6 hr. The resulting metalation mixture was added slowly to a boiling solution of the appropriate aldehyde or ketone (10% excess over the *n*-butyllithium) in 200–300 ml. of anhydrous ether contained in a 1-l. erlenmeyer flask. The reaction mixture was stoppered and allowed to stand at room temperature for 4–8 hr., then hydrolyzed by cautious addition of 200–250 ml. of water. The resulting amino alcohols were isolated as described below.

Amino alcohols IId, V, and VI precipitated on hydrolysis of the reaction mixture. They were removed by filtration, and the organic layer of the filtrate was concentrated to afford second and third crops.

Amino alcohols IIa, IIb, IIc, and IIe remained in solution on hydrolysis of the reaction mixture. The layers were separated. The organic phase was extracted with three 100-ml. portions of 1 *M* hydrochloric acid. The combined acid extracts were cooled and made basic with excess of 6 *M* sodium hydroxide. The basic mixture was extracted with three 100-ml. portions of ether, and the extracts were combined. The ethereal solution was dried over anhydrous magnesium sulfate, and the solvent was removed to leave a light yellow oil. IIb crystallized on standing; IIa was crystallized by addition of one and one-half volumes of hexane. IIc and IIe were distilled *in vacuo* to give fractions boiling at 97–98° at 0.9 mm. and 87–89° at 0.18 mm., respectively. These products were shown by v.p.c. to contain 10 and 3% impurities, respectively. The impurity in the latter product was indicated to be starting amine Ib. These products were converted to pure derivatives (see Table III).

The solid amino alcohols were recrystallized from appropriate solvents and derivatives were prepared. Methiodides were made by refluxing the amino alcohol with excess methyl iodide in acetonitrile and adding anhydrous ether to the cooled reaction mixture. Picrates were obtained by addition of saturated ethanolic picric acid to ethanolic solutions of the amino alcohols.

Dehydration of Amino Alcohols to Form Amino Olefins (Table IV).—The amino alcohol (5.0–6.0 g.) was refluxed for several hours with 100 ml. of 20% sulfuric acid. The reaction mixture was cooled and made strongly basic with 6 *M* sodium hydroxide to liberate the amino olefin. Product X, which precipitated, was removed by filtration and recrystallized. Products VIIIa, VIIIb, and IX were taken up in ether and the solution was dried over anhydrous magnesium sulfate. Removal of the solvent afforded oils which were crystallized and recrystallized from appropriate solvents (see Table IV).

Cyclization of Methiodides of Amino Alcohols to Form Isochromans (Table V).—The appropriate methiodide was placed in a round-bottom flask fitted with a two-necked adaptor for gas inlet and condenser. The system was evacuated to 1 mm. and refilled with dry nitrogen three times. After flushing the system for 30 min. with a slow stream of nitrogen (which was continued during the reaction), the flask was immersed in a Wood's metal bath which was preheated to 200–210°.[17] After an appropriate time (see Table V), the mixture was allowed to cool, then boiled with several portions of anhydrous ether to remove the isochroman from the solid residue, presumably trimethylammonium iodide. The combined ethereal extracts were dried over anhydrous magnesium sulfate. The solvent was removed on the steam bath and then *in vacuo* (1 mm.). The residual oils from methiodides XIIa and b and V' crystallized. The oil from methiodide XV[7] was distilled *in vacuo* (see Table V).

Independent Synthesis of Isochroman XIIIa. Consideration of Earlier Method.—A solution of 2.5 g. (0.011 mole) of 2-(*o*-carboxyphenyl)-1-phenylethanol (XVII)[10] in 250 ml. of anhydrous ether was refluxed overnight with 1.9 g. (0.05 mole) of lithium aluminum hydride.[18] The reaction mixture was worked up[18] to give 2.38 g. (95%) of 2-(*o*-hydroxymethylphenyl)-1-phenylethanol (XIXa), m.p. 85–89°, and 88.5–90° after recrystallization from hexane–ethanol.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.74; H, 7.02.

A solution of 0.8 g. (0.0035 mole) of diol XIXa in 15 ml. of glacial acetic acid containing 0.5 ml. of phosphoric acid was warmed on the steam bath for 20 min., and ice then was added. The resulting thick oil was collected, crystallized, and recrystallized from absolute ethanol to give 0.1 g. (14%) of isochroman XIIIa, m.p. 76–77°, undepressed on admixture with a sample of XIIIa prepared by eq. 2. Also the infrared spectra of the two samples were identical.

An attempt to cyclize diol XIXa with concentrated sulfuric acid in acetic acid, as described in the next section for the cyclization of diol XIXb, afforded an oil which could not be crystallized even when seeded with crystals of isochroman XIIIa.

The earlier method[12] for isochroman XIIIa involved reduction of 3-phenylisocoumarin with lithium aluminum hydride followed by cyclization with concentrated sulfuric acid in glacial acetic acid. In contrast to our results (see above), the intermediate diol XIXa was obtained as a high boiling liquid and isochroman XIIIa was reported to melt at 114–115°. Moreover, the XIIIa was reported to be easily oxidized by air, whereas our XIIIa was not.

Independent Synthesis of Isochroman XIIIb.—A solution of 5.6 g. (0.018 mole) of 3,3-diphenyl-3,4-dihydroisocoumarin (XVIII)[10] in 250 ml. of anhydrous ether was refluxed for 15 hr. with 0.38 g. (0.01 mole) of lithium aluminum hydride.[18] One gram of the resulting crude diol XIXb (m.p. 118–129°) was dissolved in 25 ml. of glacial acetic acid and 1 ml. of concentrated sulfuric acid was added dropwise. After stirring at room temperature for 5 min., the solution was treated with ice. The resulting solid was collected and recrystallized twice from absolute ethanol to give 0.6 g. (57% based on XVIII) of isochroman XIIIb, m.p. 120.5–122°, undepressed on admixture with a sample of XIIIb prepared by eq. 2. Also, the infrared spectra of the two samples were identical.

Cyclization of Amino Alcohol IIb to Quaternary Bromide XX.—A solution of 5.0 g. (0.015 mole) of IIb in 50 ml. of 48% hydrobromic acid was refluxed for 1.5 hr. The reaction mixture was allowed to cool to room temperature and some ether was added. The resulting solid was collected, washed with water, and dried to afford 5.05 g. (85%) of presumably 2,2-dimethyl-3,3-diphenyl-1,2,3,4-tetrahydroisoquinolinium bromide (XX). After two recrystallizations from absolute ethanol, the product melted at 216–217.5° when placed on a block preheated to 190°.

Anal. Calcd. for $C_{23}H_{24}BrN$: C, 70.05; H, 6.13; N, 3.55. Found: C, 70.07; H, 6.18; N, 3.21.

When a sample of amino alcohol IIb was stirred in 95% ethanol containing some 48% hydrobromic acid (room temperature) and anhydrous ether was added with cooling, the hydrobromide salt XXI was obtained. After two recrystallizations from aqueous ethanol, a sample melted at 132.5–133° dec. when placed in a block preheated to 220°.

Anal. Calcd. for $C_{23}H_{26}BrNO$: C, 66.66; H, 6.42; N, 3.43. Found: C, 66.78; H, 6.20; N, 3.16.

Condensation of Amino Organolithium Reagent I'a with Benzonitrile to Form Amino Ketone XXII.—Amine Ia (11.9 g., 0.08 mole) was metalated for 6 hr. using a 10% excess of 1.5 *M* *n*-butyllithium as described above. To the stirred solution of I'a in a three-necked flask (which had been flushed with dry nitrogen) was added dropwise 10.3 g. (0.10 mole) of freshly distilled benzonitrile in 100 ml. of anhydrous ether. After refluxing 6 hr., the red mixture was cooled in ice and 30 ml. of water was added carefully followed by 6 ml. of glacial acetic acid. The layers were separated, the aqueous layer was washed twice with ether, and the washings were added to the original organic layer. The ethereal solution was dried over anhydrous magnesium sulfate, and the solvent was removed. The oily residue was stirred and refluxed in 250 ml. of 4 *M* hydrochloric acid for 8 hr. and allowed to stand overnight. The mixture was washed with ether, then cooled, and made basic with sodium hydroxide pellets. The liberated oil was taken up in ether, and the solution was dried over anhydrous magnesium sulfate. The solvent was removed, and the oily residue was distilled to afford 13.7 g. (68%)

(14) Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded using Perkin-Elmer Infracords, Models 137 and 237. Nuclear magnetic resonance spectra were obtained on a Varian A-60 NMR spectrometer.

(15) Foote Mineral Company, New Johnsonville, Tenn.

(16) C. W. Kamienski and D. L. Esmay, *J. Org. Chem.*, **25**, 115 (1960).

(17) For methiodide XIIa, the temperature was 180–190°.

(18) See R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947).

of 2-(dimethylaminomethyl)benzyl phenyl ketone (XXII), b.p. 143–146° (0.3 mm.).[19]

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.39; H, 7.64; N, 5.74.

The picrate, recrystallized twice from 95% ethanol, melted at 176–177.5°.

(19) On standing several weeks, this light yellow oil became a red viscous material which resisted attempts at crystallization.

Anal. Calcd. for $C_{23}H_{22}N_4O_8$: C, 57.26; H, 4.60; N, 11.61. Found: C, 57.44; H, 4.67; N, 11.42.

The infrared spectrum of XXII showed a strong peak at 1690 cm.$^{-1}$ for the carbonyl group,[20] at 845 cm.$^{-1}$ for the dimethylaminomethyl group,[5] and at 753, 740, and 690 cm.$^{-1}$ for four and five adjacent aromatic hydrogens.[21]

(20) See ref. 4, p. 132.

(21) See ref. 4, pp. 76–78.

Cyclization of Certain o-Chlorophenyl-β-dicarbonyl Compounds through Dicarbanion–Benzyne Intermediates[1]

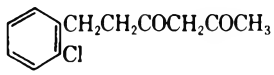
THOMAS M. HARRIS AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

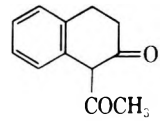
Received November 19, 1963

Bunnett's principle of ring closure involving the intramolecular reaction of an anion with the benzyne moiety was adapted to certain cyclizations in which the terminal methyl group of an *o*-chlorophenyl β-diketone or β-ketoaldehyde was condensed with the aromatic ring through a dicarbanion–benzyne intermediate. The cyclizations, which were effected by means of excess potassium amide in liquid ammonia, afforded five- and six-membered rings. One of these reactions was useful for the synthesis of 3-acetyl-2-tetralone (IX).

Bunnett,[2] Huisgen,[3] and co-workers have effected a number of cyclizations that involve the intramolecular condensation of an anion and the benzyne moiety. Bunnett has formulated this general principle[2a,b] of cyclization and has applied it to the synthesis of homocyclic,[2c] and heterocyclic[2b,d] products. One of these interesting cyclizations was observed with *o*-chlorophenyl β-diketone I, the methylene group of which was condensed intramolecularly with the aromatic ring to give II.[2c] This reaction was effected by excess potassium amide in liquid ammonia.



I

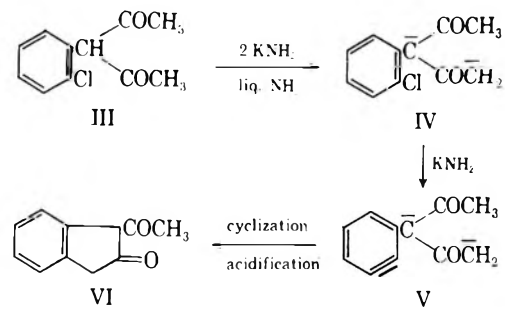


II

In the present investigation Bunnett's principle of ring closure was adapted to certain cyclizations in which a terminal methyl group of a β-diketone or β-ketoaldehyde was condensed intramolecularly with the aromatic ring through the intermediate formation of a dicarbanion and the benzyne moiety. The analogous intermolecular phenylation at the terminal methyl group of acetylacetone had been effected previously through the intermediate formation of benzyne and of the dicarbanion of the β-diketone.[4]

First, the *o*-chlorophenyl β-diketone III was cyclized to form the five-membered ring β-diketone VI in almost quantitative yield (Scheme A).

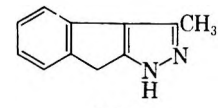
This reaction was effected by the gradual addition of excess[5] potassium amide in liquid ammonia to III in this medium, IV and V presumably being intermediates.



III IV V VI

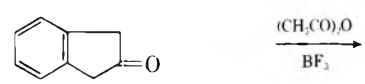
The intermediate formation of dicarbanion IV was indicated by a transient green color similar to that observed with the dicarbanion of 3-phenyl-2,4-pentanedione.[6] Indirect evidence, that the twofold ionization to form IV preceded dehydrohalogenation, was the lack of appreciable amination, which might have been expected if a benzyne were produced first.

Structure VI for the product was supported by analysis, by agreement of its melting point with the reported value,[7] by a positive enol test, and by cyclization with hydrazine to form pyrazole VII.



VII

Structure VI was confirmed by independent synthesis involving acetylation of β-indanone by means of boron trifluoride (eq. 1).



(1)

Similarly, *o*-chlorobenzyl β-diketone VIII was cyclized to form the six-membered ring β-diketone IX in 65% yield.

That the cyclization product was a carbocyclic derivative, not a heterocyclic derivative such as the

(1) Supported by the National Science Foundation.

(2) (a) B. F. Hrutford and J. F. Bunnett, *J. Am. Chem. Soc.*, **80**, 2021 (1958); (b) J. F. Bunnett and B. F. Hrutford, *ibid.*, **83**, 1691 (1961); (c) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962); (d) J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *ibid.*, **28**, 1 (1963).

(3) R. Huisgen and H. König, *Angew. Chem.*, **69**, 268 (1957); R. Huisgen and H. König, *Ber.*, **92**, 203, 429 (1959); R. Huisgen, H. König, and A. R. Lepley, *ibid.*, **93**, 1493 (1960).

(4) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(5) At least three molecular equivalents of this reagent should be required to effect the reaction since the dicarbanion of product VI would probably be formed.

(6) W. I. O'Sullivan and C. R. Hauser, *J. Org. Chem.*, **26**, 1110 (1960).

(7) M. Konieczny, *Bull. acad. polon. sci., Ser. sci., chim., geol., geograph.*, **8**, 229 (1959).

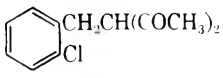
TABLE I

ULTRAVIOLET SPECTRA[a]

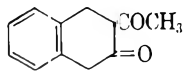
XV[b] λ (ε × 10⁻³), mμ	IX λ (ε × 10⁻³), mμ	2-Naphthol λ (ε × 10⁻³), mμ	1,1′-Binaphthol[b] λ (ε × 10⁻³), mμ
	228 (3.90) min		
261 (3.77) min	251 (6.50) max	248 (2.00) min	253 (3.02) min
267 (4.59) max	258 (6.19) sh	264 (3.86) max	268 (4.08) max
273 (3.95) min	268 (4.84) min	268 (3.52) min	270 (4.06) min
278 (4.59) max		275 (4.73) max	278 (4.73 max
286 (2.72) min		281 (2.74) min	284 (3.98) min
288 (2.77) max	291 (8.11) max	286 (3.30) max	288 (4.17) max
298 (0.77) min		295 (0.55) min	305 (1.55) min
320 (2.03) sh		318 (1.76) max	324 (2.81) sh
		323 (1.73) min	
332 (2.49) max	340 (0.11) min	335 (2.08) max	335 (3.65) max
	385 (0.25) max		

[a] max = maximum, min = minimum, and sh = shoulder. [b] The extinction coefficients given for these dimers are one-half the observed values. They were used to allow comparison with IX and 2-naphthol.

possible O-derivative X, was shown by permanganate oxidation to form phthalic acid in good yield. Structure IX was supported by analysis, by a positive enol

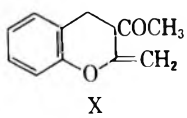


VIII

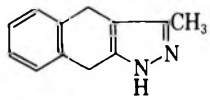


IX

test, by conversion to a copper chelate, and by formation of pyrazole XI and β-tetralone[8] with hydrazine and alkali, respectively.

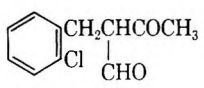


X

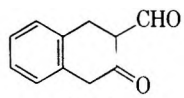


XI

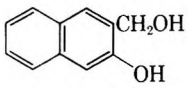
Likewise, the *o*-chlorophenyl-β-ketoaldehyde XII was cyclized to form presumably the six-membered ring β-ketoaldehyde XIII, but this compound was not isolated. Evidently, XIII underwent aromatization to give carbinolnaphthol XIV followed by oxidative dimerization to afford XV, which was obtained in 29% yield.



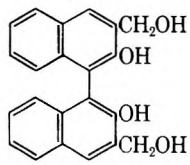
XII



XIII



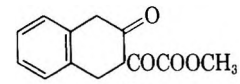
XIV



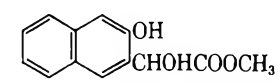
XV

Although the product isolated gave a positive enol test, the compound failed to form a copper chelate or a pyrazole. This suggested that it was a naphthol, such as XIV, rather than β-ketoaldehyde XIII. Moreover, the ultraviolet spectrum of the product was greatly different from that of IX, the keto analog of XIII, but resembled that of β-naphthol (Table I). However, the elemental analysis indicated slightly less hydrogen than is required for structure XIV and a molecular weight determination suggested that the compound was dimer XV. The ultraviolet spectrum correlated well with that of 1,1′-bi-2-naphthol (Table I). Such a dimerization would not be surprising, since ferric ion was employed in the preparation of the potassium amide used in the reaction and such metal ions are known to catalyze (in air) the oxidative dimerization of phenols and naphthols.[9]

A precedent for the aromatization of XIII to form XIV is the observation that, although acylation of β-tetralone with methyl oxalate by sodium methoxide presumably affords oxalyl derivative XVI, the product isolated was the carbinolnaphthol XVII.[10]



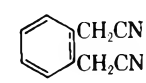
XVI



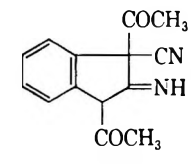
XVII

Discussion

The present method of cyclization is useful for the synthesis of 3-acetyl-2-tetralone (IX) and perhaps of dimer XV, both of which are new compounds. The method is satisfactory for the synthesis of 1-acetyl-2-indanone (VI) but the method of choice is probably that represented by eq. 1 even though the yield was only 35%. Both of these methods appear to be superior to one reported recently[7] involving reaction of dinitrile XVIII with ethyl acetate. The product, described as iminonitrile XIX, was hydrolyzed to give VI and β-indanone in unstated yields.



XVIII



XIX

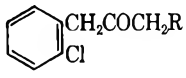
The result in Scheme A is of interest in connection with those obtained by Bunnett and co-workers on *o*-chlorophenyl ketones XXa and XXb under similar conditions.[2b,c] Thus, whereas diketone III was converted to VI, no such carbocyclic product was isolated

(8) A ketone acid resulting from cleavage at the carbonyl group of the ring may have been produced, but no attempt was made to isolate it.

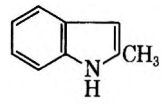
(9) See L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 764.

(10) M. D. Soffer, R. A. Stewart, and G. I. Smith, *J. Am. Chem. Soc.*, **74**, 1556 (1952).

from the reactions of XXa and XXb. Apparently XXa was converted to its dicarbanion but not to a benzyne, and XXb was converted to a benzyne but not to a dicarbanion.[11] This resulted in recovery of XXa, and conversion of XXb to the heterocyclic product XXI.



XXa, R = C_6H_5
b, R = H



XXI

The cyclization of diketone VIII through its dicarbanion–benzyne to form IX is similar to that of diketone I to form II observed by Bunnett and Skorcz.[2c] Interestingly, the latter reaction also may involve the formation of a dicarbanion–benzyne intermediate. If so, this appears to be the first example of the less nucleophilic 3-position of such a dicarbanion reacting in preference to the more nucleophilic terminal position.[4] This would, of course, then be attributed to the greater ease of formation of a six-membered ring as compared with an eight-membered ring.

It should be mentioned that 4-(*o*-chlorophenyl)-2-butanone, which was formylated to form ketoaldehyde XII, was prepared by cleavage of diketone VIII,[12] rather than by the acetoacetic ester method employed previously.[2c] Formylation of the ketone in ethanol afforded a good yield of ketoaldehyde XII. Studies by Roch of similar systems indicated that formylation would be expected to occur at the methylene group rather than at the methyl group under these conditions.[13] The stability of the reaction product and the green color of the derived copper chelate confirmed that formylation had, in fact, occurred at the methylene position.[14]

Experimental[15]

3-(*o*-Chlorophenyl)-2,4-pentanedione (III).—Diketone III was prepared by the boron trifluoride method essentially as described for 3-phenyl-2,4-pentanedione.[16] From the reaction of a mixture of 122 g. (0.72 mole) of *o*-chlorophenylacetone,[2b] 110 g. (1.08 moles) of acetic anhydride, and 28 g. (0.15 mole) of *p*-toluenesulfonic acid was isolated 75 g. (43%) of the green copper chelate of 3-(*o*-chlorophenyl)-2,4-pentanedione (III), m.p. 258–264°, and m.p. 271–272° after recrystallization from benzene.

Anal. Calcd. for $C_{22}H_{20}O_4Cl_2Cu$: C, 54.72; H, 4.18. Found: C, 54.76; H, 4.18.

The chelate was decomposed with dilute hydrochloric acid to give 61.4 g. (40%) of 3-(*o*-chlorophenyl)-2,4-pentanedione (III), m.p. 44–49°, and m.p. 51–53° after recrystallization from cyclohexane–pentane.

Anal. Calcd. for $C_{11}H_{10}O_2Cl$: C, 62.76; H, 5.26; Cl, 16.83. Found: C, 62.65; H, 5.18; Cl, 17.01.

Cyclization of III to 1-Acetyl-2-indanone (VI).—In a 500-ml. inverse addition flask[17] was prepared a solution of 0.262 mole of potassium amide[4] from 10.2 g. of potassium in 400 ml. of commercial, anhydrous liquid ammonia. This solution was added over 10 min. to a solution of 10.52 g. (0.05 mole) of diketone III in 125 ml. of liquid ammonia and 125 ml. of anhydrous ether. During the course of the addition the reaction mixture changed from light amber through a transient green and finally to a yellow suspension. After 1 hr., ammonium chloride was added to neutralize the excess base. Ether was added and the ammonia was evaporated. Immediately dilute hydrochloric acid was added and the ether layer separated. Evaporation of the ether left 8.55 g. (98%) of 1-acetyl-2-indanone (VI) as a tan solid, m.p. 121.5–122.5°. Sublimation and recrystallization from ethanol gave m.p. 122.5–123.5°, lit.[7] m.p. 122°.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.88; H, 5.84.

Diketone VI gave a blue enol test with ethanolic ferric chloride. Treatment of VI with hydrazine in refluxing ethanol gave pyrazole VII in 20% yield, m.p. 204–205° after two recrystallizations from ether–cyclohexane.

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.62; H, 5.80; N, 16.41.

Diketone VI was independently synthesized from 26.4 g. (0.2 mole) of β-indanone[18] and 40.8 g. (0.4 mole) of acetic anhydride by means of the boron trifluoride–ethyl acetate complex prepared from 52.8 g. (0.6 mole) of the ester.[19] Sublimation afforded 12.0 g. (35%) of 1-acetyl-2-indanone (VI), m.p. 112–117°, and m.p. 122.5–123.5° after recrystallization from ethanol. A mixture melting point with diketone VI prepared from III was undepressed.

3-(*o*-Chlorobenzyl)-2,4-pentanedione (VIII).—A mixture of 100 g. (1.0 mole) of acetylacetone, 80.5 g. (0.05 mole) of *o*-chlorobenzyl chloride, 69 g. (0.05 mole) of potassium carbonate, and 250 ml. of absolute ethanol was refluxed gently on the steam bath for 1.5 hr. After the reaction mixture had cooled, sufficient water was added to dissolve the salts present, and the mixture was extracted with ether. The ethereal solution was distilled until a vapor temperature of 60° (0.5 mm.) was reached, and the residue was treated with aqueous cupric acetate to form 62.5 g. (53%) of the green copper chelate of 3-(*o*-chlorobenzyl)-2,4-pentanedione (VIII), m.p. 209–210°. The chelate was treated with dilute hydrochloric acid, and the diketone extracted into ether. Distillation afforded a good recovery of diketone VIII, b.p. 121–123° (0.7 mm.).

Anal. Calcd. for $C_{12}H_{13}O_2Cl$: C, 64.14; H, 5.83; Cl, 15.79. Found: C, 64.27; H, 5.86; Cl, 15.57.

Diketone VIII underwent crystallization under varying conditions to give a wide range of melting points from below room temperature to 69°. Different crops showed slight differences in the infrared spectrum, but all gave violet enol tests with ethanolic ferric chloride.

Treatment with cupric acetate gave a good yield of the green copper chelate, m.p. 223–225° after recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{24}O_4Cl_2Cu$: C, 56.24; H, 4.73; Cl, 13.88; Cu, 12.44. Found: C, 56.23; H, 5.23; Cl, 14.15; Cu, 12.30.

Treatment of diketone VIII with refluxing ethanolic hydrazine afforded in good yield 4-(*o*-chlorobenzyl)-3,5-dimethylpyrazole, m.p. 126–127° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{13}N_2Cl$: C, 65.30; H, 5.93; Cl, 16.07; N, 12.70. Found: C, 65.19; H, 5.81; Cl, 15.95; N, 12.72.

Cyclization of VIII to 3-Acetyl-2-tetralone (IX).—To a solution of 12.3 g. (0.056 mole) of diketone VIII in 250 ml. of ammonia was gradually added a solution of 0.33 mole of potassium amide (prepared from 13.0 g. of potassium) in 500 ml. of liquid ammonia. After 45 min., ammonium chloride was added to the green suspension which had formed in order to neutralize the excess base. The ammonia was evaporated and the residue was taken up in dilute hydrochloric acid and ether. The ethereal layer was separated and evaporated. The remaining oil was treated with ethanol to afford 6.7 g. (65%) of 3-acetyl-2-tetralone (IX), m.p. 45–49°, and m.p. 48–49° after recrystallization from ethanol.

(11) For evidence that the related phenylacetone affords the methylene monocarbanion but not appreciable dicarbanion under similar conditions, see T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 1154 (1959).

(12) It was found convenient not to isolate VIII. Thus, 4-(*o*-chlorophenyl)-2-butanone was isolated in 78% yield on refluxing a mixture of *o*-chlorobenzyl chloride, acetylacetone, and potassium carbonate in ethanol for 16 hr. The generality of this method is being investigated.

(13) L. M. Roch, *Ann. chim.* (Paris), **6**, 105 (1961).

(14) See T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3273 (1963).

(15) Melting points were taken on a capillary melting point apparatus and are uncorrected. Ultraviolet spectra were determined in 95% ethanol solution with a Cary 14 spectrophotometer. Elemental analyses and the molecular weight were by Galbraith Laboratories, Knoxville, Tenn.

(16) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 133 (1954).

(17) See C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(18) J. E. Horan and R. W. Schiessler, *Org. Syn.*, **41**, 53 (1961).

(19) See ref. 16, pp. 131–132.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.53; H, 6.21.

Diketone IX gave a red-violet enol test with ferric chloride. Oxidation of IX with alkaline potassium permanganate gave phthalic acid in 76% yield.

Treatment of diketone IX with refluxing ethanolic hydrazine gave a good yield of pyrazole XI, m.p. 173.5–174° after recrystallization from benzene–hexane.

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.30; H, 6.67; N, 15.22.

A sample of diketone IX was refluxed with aqueous sodium hydroxide under a nitrogen atmosphere to give β-tetralone, which was isolated as its semicarbazone, m.p. 191–192° after three recrystallizations from ethanol, lit.[20] m.p. 193–194°. The odor of acetic acid could be detected in the acidified hydrolysate. When the hydrolysis was not conducted in a nitrogen atmosphere, the blue-black color, characteristic of the base-catalyzed air oxidation of β-tetralone,[21] was detected.

2-(*o*-Chlorobenzyl)-1,3-butanedione (XII).—To a cooled solution of 1.0 mole of sodium ethoxide (prepared from 23 g. of sodium) in 500 ml. of absolute ethanol was added a mixture of 172 g. (0.94 mole) of 4-(*o*-chlorophenyl)-2-butanone[12] and 80.0 g. (1.08 moles) of ethyl formate.[13] The solution was stirred at room temperature for 16 hr. Ethanol was removed under reduced pressure. To the residue was added ice–water, followed by 100 ml. of hydrochloric acid, and finally 500 ml. of ether. Crystals of XII (74 g., m.p. 120–122°) formed in the mixture, and were removed by filtration. The ethereal layer of the filtrate was separated and evaporated to a small volume to give an additional 42 g. of XII, m.p. 107–117°. The total yield of 2-(*o*-chlorobenzyl)-1,3-butanedione (XII) was 116 g. (58%). Recrystallization from methanol afforded crystals, m.p. 122–123°.

Anal. Calcd. for $C_{11}H_{11}ClO_2$: C, 62.76; H, 5.26; Cl, 16.83. Found: C, 62.69; H, 5.08; Cl, 17.04.

The green copper chelate of XII, m.p. 202–203° after recrystallization from benzene, was prepared by treatment with aqueous cupric acetate.

Anal. Calcd. for $C_{22}H_{20}Cl_2O_4Cu$: C, 54.72; H, 4.18; Cl, 14.69; Cu, 13.16. Found: C, 55.06; H, 4.10; Cl, 15.00; Cu, 13.46.

Formation of Binaphthol XV from XII.—To a solution of 13.2 g. (0.063 mole) of β-ketoaldehyde XII in 125 ml. of liquid ammonia and 125 ml. of anhydrous ether was added 0.264 mole of potassium amide (prepared from 10.3 g. of potassium) in 300 ml. of liquid ammonia. After 1 hr., ammonium chloride was added to the dark green solution to neutralize excess base and the ammonia was evaporated. The residue was extracted with dilute hydrochloric acid and ether. The ethereal solution was separated and evaporated. The residual solid was washed with benzene to leave 3.1 g. (29%) presumably of 2,2′,α,α′-tetrahydroxy-3,3′-dimethyl-1,1′-binaphthyl (XV), m.p. 216°, and m.p. 231–232° after chromatography on silica gel and recrystallization from ethyl acetate.

Anal. Calcd. for $C_{22}H_{18}O$: C, 75.84; H, 5.79; mol. wt., 346. Found: C, 76.03, 75.94; H, 5.07, 5.08; mol. wt., 356.[22]

This compound gave an enol test with ethanolic ferric chloride, but neither a copper chelate nor a pyrazole could be prepared.

(20) N. M. Przhiyalgovskaya, L. N. Lavrisheva, and V. N. Belov, *J. Gen. Chem. USSR*, **27**, 1349 (1957).

(21) J. W. Cornforth, R. H. Cornforth, and R. Robinson, *J. Chem. Soc.*, 689 (1942).

(22) The molecular weight was determined at 37° in acetone solution employing a Mechrolab osmometer.

Benzylation and Dehydrogenation of 3-Phenylindan-1-one through Its α,β-Dicarbanion. Synthesis of 3-Phenylindenone[1]

BERNARD W. ROCKETT AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

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3-Phenylindan-1-one (I) underwent a twofold acid–base reaction with two molecular equivalents of sodium amide in liquid ammonia to form α,β-disodio salt II, which underwent alkylation with benzyl chloride to give β-benzyl derivative III. The monosodio salt of I was benzylated to afford the α-benzyl derivative V. III was reduced to give 1-benzyl-1-phenylindane. Dehydrogenation of I through its disodio salt II was effected with 2,3-dibromo-2,3-dimethylbutane to form 3-phenylindenone. Similar dehydrogenations of 2,3-diphenylindanone and 2,3,3-triphenylpropionitrile were effected through their dicarbanions to yield 2,3-diphenylindenone and 2,3,3-triphenylacrylonitrile, respectively. Possible mechanisms for this new method of dehydrogenation are mentioned.

Since 3-phenylindan-1-one (I) has not only α-hydrogens but also a β-hydrogen activated by two aryl groups, it might be expected to undergo a twofold acid–base reaction with sodium amide in liquid ammonia to form α,β-disodio salt II. This was realized as demonstrated not only by production of a deep red color like that of the diphenylmethide ion[2] but also by alkylation with a molecular equivalent of benzyl chloride to form β-benzyl derivative III in 73% yield (Scheme A).

Similar to the benzylation of sodium diphenylmethide in liquid ammonia,[2] that of disodio salt II was rapid as indicated by immediate discharge of the red color by the equivalent of halide.

That the conversion of I to II as represented in Scheme A was essentially complete was indicated not only by the high yield of III but also by the lack of formation of an isolable amount of stilbene, some of which would probably have been produced had there been an appreciable amount of amide ion present in the equilibrium.[3]

Although disodio salt II was generally prepared by addition of I to the reagent, the inverse addition procedure was also employed to show the intermediate formation of monosodio salt IV. Thus, when sodium amide in liquid ammonia was added slowly to I in ether the yellow-brown color of IV persisted until slightly more than a molecular equivalent had been added; then the red color of II became evident and deepened until addition of the second equivalent of the base was complete.

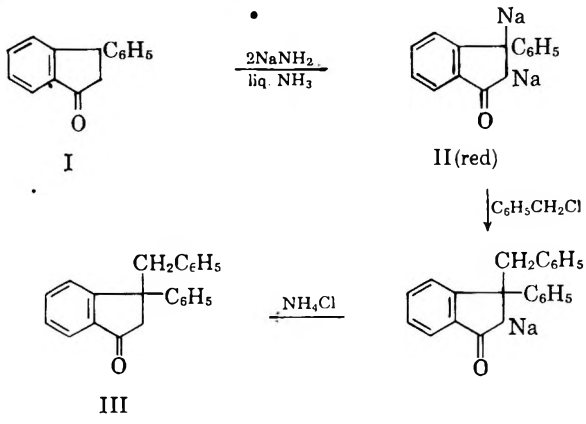
The product from the benzylation of II was shown *not* to be the possible α-benzyl derivative V, which was prepared from monosodio salt IV and benzyl chloride in diglyme (β,β′-dimethoxydiethyl ether) at 100°. Incidentally, IV failed to afford an isolable amount of

(1) Supported by the National Science Foundation Grant No. G 14527.

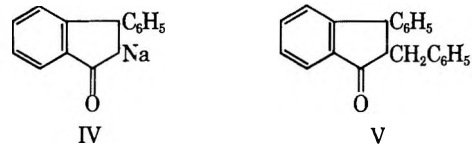
(2) C. R. Hauser and P. J. Hamrick, *J. Am. Chem. Soc.*, **79**, 3142 (1957).

(3) The stilbene would have arisen through self-alkylation of the benzyl chloride; see C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *ibid.*, **78**, 1653 (1956).

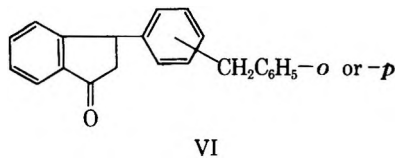
SCHEME A



V with benzyl chloride in liquid ammonia during an hour. This is not surprising since benzylation of potassioacetophenone has been observed to be very slow in this medium (−33°).[4]

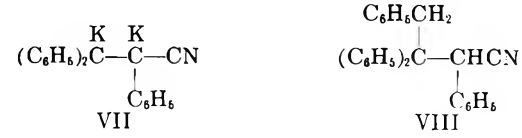


The assignment of structure III to the product obtained from benzylation of II was supported by its nuclear magnetic resonance spectrum[5] which showed, beside the aromatic multiplet resonance, a singlet at τ 6.58 and an unperturbed AB quartet at τ 7.16 (J = 18 c.p.s.). The integrated peak area ratio for the singlet to the quartet is 1:1. The rather large spin–spin coupling constant for the AB system indicates that this coupling is of the *geminal* rather than the *vicinal* type. The band at τ 6.58 was assigned to the β-benzyl protons of III and the quartet at higher frequency to the α-methylene protons.[6] In agreement with structure III the resonance frequency of one of these latter protons was increased by the shielding effect of the β-phenyl substituent.[7] This spectrum is incompatible with V or the *o*- or *p*-benzyl derivatives VI, which appear to be the only other possible structures for the benzylation product of II.



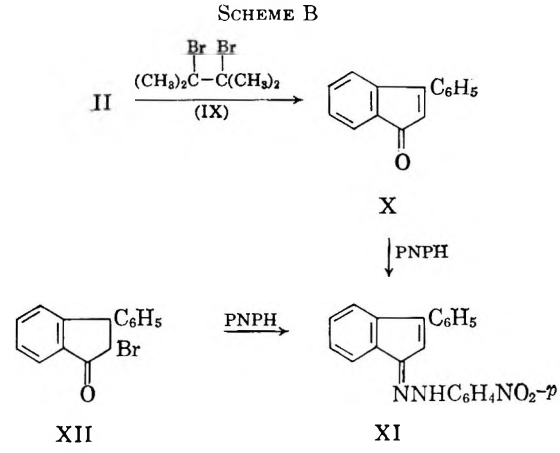
As anticipated, Clemmensen reduction of β-benzyl derivative III afforded a hydrocarbon, which was presumably 1-benzyl-1-phenylindane (66%).

The formation of α,β-disodio salt II and its benzylation at the β-position to give III (Scheme A) is similar to the previously observed formation of α,β-dipotassio salt VII and its benzylation to afford VIII.[8]



Next, 3-phenylindan-1-one (I) was dehydrogenated through its disodio salt II to form 3-phenylindenone (X) in 40–50% yield. This was accomplished with 2,3-dibromo-2,3-dimethylbutane (IX), which was presumably converted to 2,3-dimethylbutene.[9] The infrared spectrum of the crude product X showed bands at 1713 and 1621 cm.$^{-1}$ which may be ascribed to the cyclopentadienone[10] and the conjugated olefinic groups,[11] respectively. Because of its susceptibility to oxidation, X was isolated as its *p*-nitrophenylhydrazone XI. The over-all yield of XI from I was 37–46%. The structure of XI was established by an independent synthesis from α-bromo ketone XII[12] and *p*-nitrophenylhydrazine (PNPH) as described previously[13] (Scheme B).

SCHEME B



That the product obtained in the reaction of disodio salt II with dibromide IX was not the possible α-bromo ketone XII (see Scheme B) was shown by negative Lassaigne and Beilstein tests for halogen and by comparison of the infrared spectra of the two compounds.

Although the conversion of α-bromo ketone XII to *p*-nitrophenylhydrazone XI involved dehydrobromination, attempts to effect dehydrobromination of XII to form X by means of aqueous sodium acetate and of aqueous or alcoholic potassium hydroxide were unsatisfactory; apparently X was unstable towards the latter reagent.

The present method of synthesis of unsaturated ketone X appears to be superior to an earlier method involving cyclization and dehydration of β-hydroxy ester XIII, which has been reported to afford X in extremely poor yield.[14] No analysis was given.[14] Several attempts by us to prepare X from XIII were unsatisfactory apparently because the conditions that appeared to be required for cyclization converted X to truxones XIV (see Experimental).

(4) C. R. Hauser and T. A. Mashburn, *J. Org. Chem.*, **26**, 1795 (1961).

(5) We are indebted to Dr. Walter L. Meyer, Dept. of Chemistry, Indiana University, Bloomington, Ind., for this spectrum.

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 57.

(7) See ref. 6, p. 125.

(8) C. R. Hauser, T. M. Harris, and T. G. Ledford, *J. Am. Chem. Soc.*, **81**, 4099 (1959).

(9) K. Ziegler and B. Schnell, *Ann.*, **437**, 227 (1924).

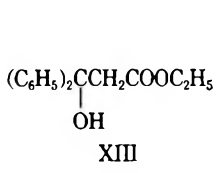
(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 148.

(11) L. J. Bellamy, *ibid.*, p. 35.

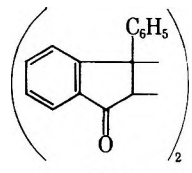
(12) R. Weiss and S. Luft, *Monatsh.*, **48**, 337 (1927).

(13) K. von Auwers and R. Hugel, *J. prakt. Chem.*, **143**, 157 (1935).

(14) R. de Fazi, *Gazz.*, **49**, 253 (1919).



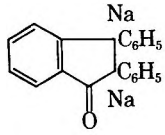
XIII



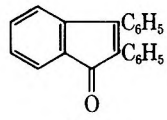
XIV

However, the recent method of Blomquist and Moriconi[15] involving dehydrogenation of I with selenium dioxide furnishes another satisfactory method. As in our case, these workers isolated X as a derivative (semicarbazone).

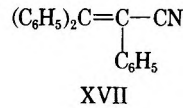
To show that the present method is quite general, 2,3-diphenylindanone and 2,3,3-triphenylpropionitrile were dehydrogenated similarly through their dialkali salts XV and VII to form XVI and XVII, respectively. Although the yields were good (70%), other satisfactory methods are available for XVI[16] and XVII.[17]



XV



XVI



XVII

In Table I are summarized the yields of X, XVI, and XVII that were obtained from α,β-dicarbanions on varying the metallic cation and mode of addition. The best of these yields were essentially duplicated in other runs. In dehydrogenation of I, two molecular equivalents of dibromide IX affected a better yield than one equivalent, though slightly more than one may have been equally satisfactory. In the two other dehydrogenations, only one equivalent of IX was used. Table I shows that the metallic cation and the mode of addition influence considerably the yields of products.

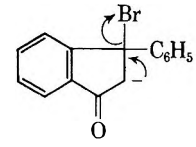
TABLE I

DEHYDROGENATIONS THROUGH α,β-DICARBANIONS BY DIBROMIDE IX[a]

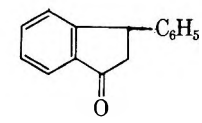
α,β-Dicarbanion	Metallic cation	Mode of addition	Unsaturated product	Yield, %
II	Na	Inverse	X	40–50
II	Na	Direct	X	0
II[b]	K	Inverse	X	*ca.* 10
XV	Na	Direct	XVI	70
XV	Na	Inverse	XVI	35
XV[b]	K	Direct	XVI	17
VII	K	Direct	XVII	70
VII[c]	Na	Direct	XVII	40
VII[c]	Na	Inverse	XVII	Trace

[a] Only the experiment that afforded the highest yield of each unsaturated product is described in Experimental. [b] Dipotassio salt. [c] Disodio salt.

Two mechanisms appear possible for the conversion of α,β-dicarbanions to the unsaturated products. One would involve displacement on the bromine of IX by the dicarbanion to form, for example, XVIII, which undergoes elimination to give X. The other would involve the intermediate formation of an ion radical, for example, XIX by displacement of one electron on the bromine of IX by the dicarbanion. Recent papers have described displacement on the halogen of certain halides by diphenylmethide ion,[18] and the formation, in equilibrium, of ion radicals when 1,2-dicarbanions are present with the corresponding unsaturated compounds.[19]



XVIII



XIX

Experimental[20]

3-Phenylindan-1-one (I).—This compound was prepared from 3,3-diphenylpropionic acid[21] by cyclization of its acid chloride with aluminum chloride.[22]

Conversion of I to α,β-Disodio Salt II.—To a stirred suspension of 0.05 mole of sodium amide in 200 ml. of commercial, anhydrous liquid ammonia[23] was added, during 5 min., 5.2 g. (0.025 mole) of 3-phenylindan-1-one (I) in 30 ml. of dry ether. After stirring for 45 min., the resulting dark red solution was assumed to contain 0.025 mole of α,β-disodio salt II.

Benzylation of II to Form β-Benzyl Derivative III.—To the stirred solution of 0.025 mole of α,β-disodio salt II (see above) was added, during 5 min., 3.2 g. (0.025 mole) of benzyl chloride in 30 ml. of dry ether. The red color of II was discharged immediately. After 30 min., 1.35 g. (0.025 mole) of ammonium chloride was added, and the ammonia evaporated as 200 ml. of ether was added. The resulting ethereal suspension was shaken with water, and the layers were separated. The ethereal layer was dried over anhydrous magnesium sulfate, and the solvent removed. The residue was recrystallized from 95% ethanol to give 5.4 g. (73%) of 3-benzyl-3-phenylindanone (III) as colorless cubes, m.p. 115–116°. Its infrared spectrum (as Nujol mull) showed principal bands at 700, 707, 754, 760, 771, 1240, and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.45; H, 6.15.

Reduction of 0.45 g. of III by refluxing it with 3.5 g. of amalgamated zinc and 10 ml. of aqueous–ethanolic concentrated hydrochloric acid for 9 hr. (further portions of the acid being added)[24] afforded 0.28 g. (66%) of 1-benzyl-1-phenylindane, m.p. 88–88.5° (recrystallized from 95% ethanol). Its infrared spectrum showed principal bands at 702, 748, 760, 775, 1082, 1447, 1455, 1497, and 3050 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}$: C, 92.92; H, 7.09. Found: C, 93.05; H, 7.17.

Benzylation of Monosodio Salt IV to Form α-Benzyl Derivative V.—To a stirred suspension of 0.03 mole of sodium amide in 150 ml. of liquid ammonia was added 6.24 g. (0.03 mole) of 3-phenylindan-1-one (I) in 25 ml. of dry ether. The resulting yellow-brown solution of monosodio salt IV was stirred for 15 min. The ammonia was evaporated as 150 ml. of dry diglyme was added, followed by 3.81 g. (0.03 mole) of benzyl chloride in 30 ml. of dry ether. After heating on the steam bath for 1.5 hr. and cooling, the reaction mixture was shaken with water. Ether was added, and the layers were separated. The organic layer was dried, and the ether was removed. The black, oily residue was chromatographed on alumina to give 1.52 g. (17%) of 2-benzyl-3-

(15) A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).
(16) C. F. Koelsch, *J. Am. Chem. Soc.*, **56**, 1337 (1934).
(17) S. Wawzonek and E. M. Smolin, *Org. Syn.*, **31**, 52 (1951).
(18) C. R. Hauser, W. G. Kofron, W. R. Dunnavant, and W. F. Owens, *J. Org. Chem.*, **26**, 2627 (1961).
(19) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **84**, 4155 (1962).
(20) Analyses were by Galbraith Laboratories, Knoxville, Tenn. Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord by the potassium bromide pellet method except where noted. The n.m.r. spectrum was obtained from dilute solution in carbon tetrachloride with tetramethylsilane as internal standard using a Varian A-60 spectrometer.
(21) K. von Auwers and E. Auffenberg, *Ber.*, **52**, 92 (1919).
(22) P. Pfeiffer and H. L. de Waal, *Ann.*, **520**, 185 (1935).
(23) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).
(24) E. Clemmensen, *Ber.*, **47**, 681 (1914).

phenylindanone (V), m.p. 82–83° (recrystallized from 95% ethanol). Its infrared spectrum showed principal bands at 698, 710, 740, 760 1222, 1492, 1605, 1702, 2915, and 3030 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.68; H, 6.17.

Dehydrogenation of I through Disodio Salt II to Form X.—To a stirred solution of 24.4 g. (0.1 mole) of 2,3-dibromo-2,3-dimethylbutane (IX)[25] in dry ether was added, during 30 min., a solution of 0.05 mole of disodio salt II in 200 ml. of liquid ammonia. The red color of II was discharged immediately, but the reaction mixture soon darkened. The resulting brown mixture was stirred for 30 min., and the ammonia was replaced by ether. The resulting yellow-green suspension was filtered, and the solvent was removed from the filtrate. The residue was placed immediately on an alumina column. The column was eluted immediately[26] with hexane to remove the excess dibromide IX, and then with 20% benzene–hexane to remove 3-phenylindenone (X), which was obtained as a yellow-orange oil on evaporation of the solvent, yielding 4.1–5.2 g. (40–50%). Its infrared spectrum (liquid film) showed principal bands at 693, 752, 765, 1621, and 1713 cm.$^{-1}$. Compound X produced an emerald green color with concentrated sulfuric acid.[14] Compound X (0.67 g.) was treated with 0.6 g. of *p*-nitrophenylhydrazine in ethanol–hydrochloric acid[27] at 40° for 45 min. to afford *p*-nitrophenylhydrazone XI in 90–92% yield. After recrystallization from acetonitrile, XI melted at 266–267°, lit.[13] m.p. 266–267°. Compound XI produced a blue color with aqueous sodium hydroxide.[13]

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 74.01; H, 4.56; N, 12.28.

Independent synthesis of XI was effected from 2-bromo ketone XII[12] and the *p*-nitrophenylhydrazine reagent.[27,13] The product had m.p. 266–267°, undepressed on admixture with a sample of XI prepared from X as described above. Infrared spectra of the two samples were identical.

Attempted Preparation of X from 3-Hydroxy Ester XIII.—A 0.3-g. sample of ethyl 3-hydroxy-3,3-diphenylpropionate (XIII)[28] was dissolved in 3 ml. of concentrated sulfuric acid to produce the emerald-green color indicative of the formation of 3-phenylindenone (X, see above) but, on standing 24 hr. at room temperature as described by de Fazi,[14] the color changed to brown. There was isolated only a white powder, m.p. 205–235° (recrystallized from 95% ethanol), which was presumably a mixture of α- and γ-diphenyltruxones, m.p. 253 and 224°, respectively.[29] Similar results were obtained with ester XIII and with the corresponding acid employing 96% sulfuric acid for 30 min. or 3 hr. and 90% sulfuric acid for 12 hr. When the ester was treated with 80% or 60% sulfuric acid for 12 hr., and with polyphosphoric acid for 3 or 12 hr., the emerald-green color failed to appear, and the only product isolated was 3-phenylcinnamic acid. When the acid corresponding to XIII was treated similarly, it was largely recovered.

Dehydrogenation of 2,3-Diphenylindanone to Form XVI.—2,3-Diphenylindanone was prepared in 60% yield from 2,3,3-triphenylpropionic acid[30] through its acid chloride, which was cyclized with aluminum chloride.[16,22] The product melted at 99–100°, lit.[16] m.p. 100–101°.

A dry, ethereal solution of 1.42 g. (0.005 mole) of 2,3-diphenylindanone was added dropwise to a stirred suspension of 0.01 mole of sodium amide in 150 ml. of liquid ammonia; the mixture was stirred for 30 min. To the resulting deep red solution containing XV was added, with stirring, a dry, ethereal solution of 1.22 g. (0.005 mole) of dibromide IX. After 60 min., the ammonia was replaced by ether, and the mixture was filtered. The solvent was removed from the filtrate, and the residue recrystallized from hexane to give 0.99 g. (70%) of 2,3-diphenylindenone (XVI) as red needles, m.p. 152–153°, lit.[31] m.p. 150–151°.

Dehydrogenation of 2,3,3-Triphenylpropionitrile to Form XVII.—2,3,3-Triphenylpropionitrile[5] (3.55 g., 0.0125 mole) was converted to its dipotassio salt VII,[32] which was treated with a molecular equivalent of dibromide IX essentially as described above for disodio salt XV. During the addition of IX, the red color of VII changed to intense purple, which faded to brown when the addition was complete. There was obtained 2.45 g. (70%) of 2,3,3-triphenylacrylonitrile (XVII), m.p. 165–166°, lit.[32] m.p. 165°.

(25) This compound was prepared by bromination of 2,3-dimethylbutane, as described by A. V. Grosse and V. N. Ipatieff [*J. Org. Chem.*, **8**, 438 (1943)], and purified by chromatography on alumina.

(26) When the product was allowed to remain on the column overnight, the yellow-orange band became dark green and the yield of X was reduced considerably.

(27) Concentrated hydrochloric acid was added to a suspension of *p*-nitrophenylhydrazine (0.6 g.) in 95% ethanol until solution was achieved; then 5 drops more of the acid were added.

(28) W. R. Dunnavant, and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

(29) R. de Fazi, *Gazz.*, **57**, 551 (1927).

(30) W. R. Dunnavant and C. R. Hauser, *Org. Syn.*, **40**, 38 (1960).

(31) G. Heyl and V. Meyer, *Ber.*, **28**, 2776 (1895).

(32) W. G. Kofron, W. R. Dunnavant, and C. R. Hauser, *J. Org. Chem.*, **27**, 2737 (1962).

The Reaction of Chloramine with Alkyl Sulfides[1]

JOSEPH A. COGLIANO AND GEORGE L. BRAUDE

The Research Division, W. R. Grace and Company, Washington Research Center, Clarksville, Maryland

Received December 18, 1963

Organic sulfides react with chloramine to give a series of compounds having the probable general formula, $(R_2\overset{+}{S}\overset{-}{N}HNH)_2$, bis(iminodialkylsulfilimine) and its salts. It is postulated that a sulfiliminium salt is initially formed from sulfide and chloramine and then aminated by another mole of chloramine as is shown. The

$$R_2S + NH_2Cl \longrightarrow (R_2\overset{+}{S}-\overset{-}{N}H_2)\overset{-}{Cl} \xrightarrow{NH_2Cl} (R_2\overset{+}{S}-\overset{-}{N}HNH)_2HCl$$

labile hydrogen chloride can be removed completely by sublimation in the presence of sodium methylate to give the free base, $(R_2\overset{+}{S}\overset{-}{N}HNH)_2$. In solution and especially in the solid phase, this dimer is postulated as consisting of two betaine-type monomeric units held together in a six-membered ring by electrostatic attraction or by resonance stabilization. The monomer is capable of existence in the vapor phase.

Organic sulfides have, for many years, been known to react with aromatic N-chlorosulfonamides such as chloramine B and T to form sulfilimines.[2,3]

$$R_2S + p\text{-}CH_3C_6H_4SO_2NClNa \longrightarrow p\text{-}CH_3C_6H_4SO_2NSR_2 + NaCl$$

In a recent series of papers, Appel[4] described the preparation of similar compounds from chloramine, NH_2Cl, and O-aminosulfonic acid, NH_2OSO_3H.

$$R_2S + NH_2X \longrightarrow [R_2\overset{+}{S}NH_2]\overset{-}{X}$$

Previous to the publication of these studies, we treated sulfides with chloramine in the expectation of

(1) Presented before the Organic Division at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) A. S. Ash, F. Challenger, and D. Greenwood, *J. Chem. Soc.*, 1877 (1951).

(3) F. G. Mann and W. J. Pope, *ibid.*, 1052 (1922).

(4) R. Appel, *et al.*, *Ann.*, **618**, 53 (1958); *Angew. Chem.*, **71**, 701 (1959); *Chem. Ber.*, **95**, 849 (1962).

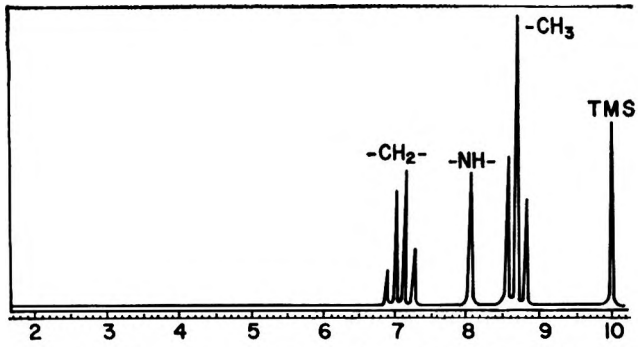


Fig. 1.—N.m.r. spectrum of bis(iminodiethylsulfilimine); solvent, carbon tetrachloride; filter band width, 4 c.p.s.; R_f field, 0.02 mg.; sweep time, 500 sec.; sweep width, 500 c.p.s.; sweep offset, 0.0 c.p.s.; and spectrum amperes, 1.0.

obtaining sulfilimines in analogy to the bimolecular displacement reaction of chloramine with tertiary amines.[5,6]

$$R_3N + NH_2Cl \longrightarrow [R_3\overset{+}{N}NH_2]\overset{-}{Cl}$$

Instead of the expected 1:1 addition product, $[R_2\overset{+}{S}NH_2]\overset{-}{Cl}$, two moles of chloramine reacted with one mole of sulfide to form a hydrochloride of bis(iminodialkylsulfilimine).[7]

$$2R_2S + 4NH_2Cl \longrightarrow [(R_2\overset{+}{S}N\overset{-}{H}NH)_2]HCl + 3HCl$$

Discussion

The preparation of the ethyl sulfide adduct was studied in detail to ascertain the properties of this general class of compounds. The reactions and proposed structures are summarized in Chart I. Similar compounds were obtained with dimethyl and di-*n*-butyl sulfides, indicating the generality of this reaction.

Addition of a mole of hydrochloric acid to bis(iminodiethylsulfilimine) hydrochloride (I) yielded iminodiethylsulfilimine hydrochloride (III). Both compounds could be converted to the free base, bis(iminodiethylsulfilimine) (II). Disproportionation occurs during vacuum sublimation of I to give II and III. In presence of sodium methoxide, only II is obtained (III is inert under these conditions unless a base is present to react with the hydrogen chloride allowing II to sublime).

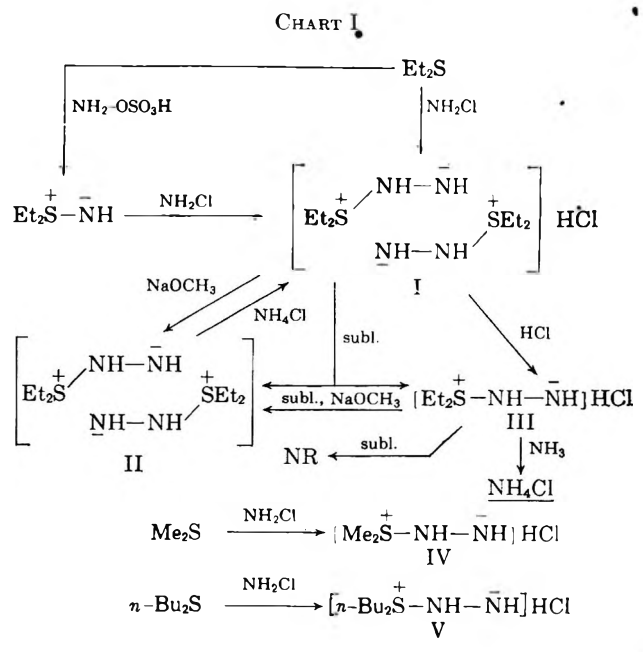
The exact number of hydrogens could not be ascertained by elemental analysis. The area of the peaks of the proton magnetic resonance spectrum of II was measured and corresponded to 3:1:2 for CH_3, NH, and CH_2, respectively (see Fig. 1). This indicates a 1:1 ratio of nitrogen-bonded protons to ethyl groups (and therefore to nitrogen).

The position of the proton absorption was similar to that of the nitrogen-bonded proton of morpholine indicating a cyclic structure. This was substantiated by the infrared spectrum, in which the positions of the bands and their relative sharpness was typical for cyclic structures (see Fig. 2). In addition, no bands indicative of a primary amino group were detected.

Ebullioscopic molecular weight determinations of II in benzene gave 158, a value intermediate between the monomer (mol. wt. 120.2) and dimer (mol. wt. 240.4). Mass spectrometry was indicative of a monomer since

(5) G. M. Omietanski and H. H. Sisler, *J. Am. Chem. Soc.*, **78**, 1211 (1956).
(6) G. L. Braude and J. A. Cogliano, *J. Chem. Soc.*, 4172 (1961).
(7) Proposed nomenclature.

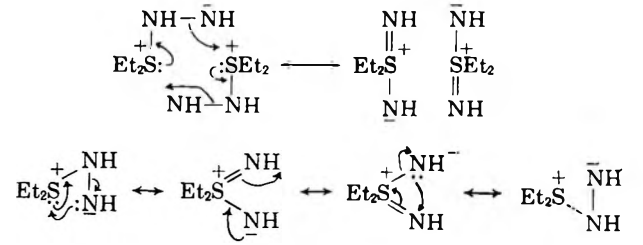
CHART I



the last significant peak appeared at m/e of 120. The rate of effusion of the compound corresponded to a molecular weight of approximately 100.

The proposed structure for this group of compounds as shown in Chart I is in agreement with these data. The dimers thus can be visualized as two betaine-type monomeric units held together either by electrostatic attraction or by resonance stabilization. In solution and especially in the vapor phase, this dimeric structure is largely destroyed.

Several alternate resonance structures can be visualized for the monomeric and the dimeric compounds.



Reaction Mechanism.—To understand the route of formation of these compounds and their structure, diethylsulfilimine was prepared from ethyl sulfide and O-aminosulfonic acid as described by Appel.[4] Its further reaction with chloramine to give I established diethylsulfilimine as a probable intermediate.[8]

The initial reaction is probably the formation of a sulfilimine salt from the sulfide and chloramine, which then is aminated by another mole of chloramine to give the iminosulfilimine salt (as shown below). Since

$$R_2S \xrightarrow{NH_2Cl} [R_2\overset{+}{S}-NH_2]\overset{-}{Cl} \xrightarrow{NH_2Cl} [R_2\overset{+}{S}-NHN\overset{-}{H}]HCl$$

the hydrogen chloride is labile in all these compounds, it is not known whether the sulfilimine or sulfiliminium chloride is the reactive species. The free sulfilimine,

(8) Appel treated alkyl sulfides with chloramine in the presence of ether and obtained sulfilimines. We have shown that under these conditions the dialkylsulfilimine hydrochloride precipitates in the course of the reaction, because it is insoluble in nonpolar solvents. This material thus cannot undergo the further reaction with chloramine to the iminosulfilimine compounds which we have obtained in such solvents as alcohols.

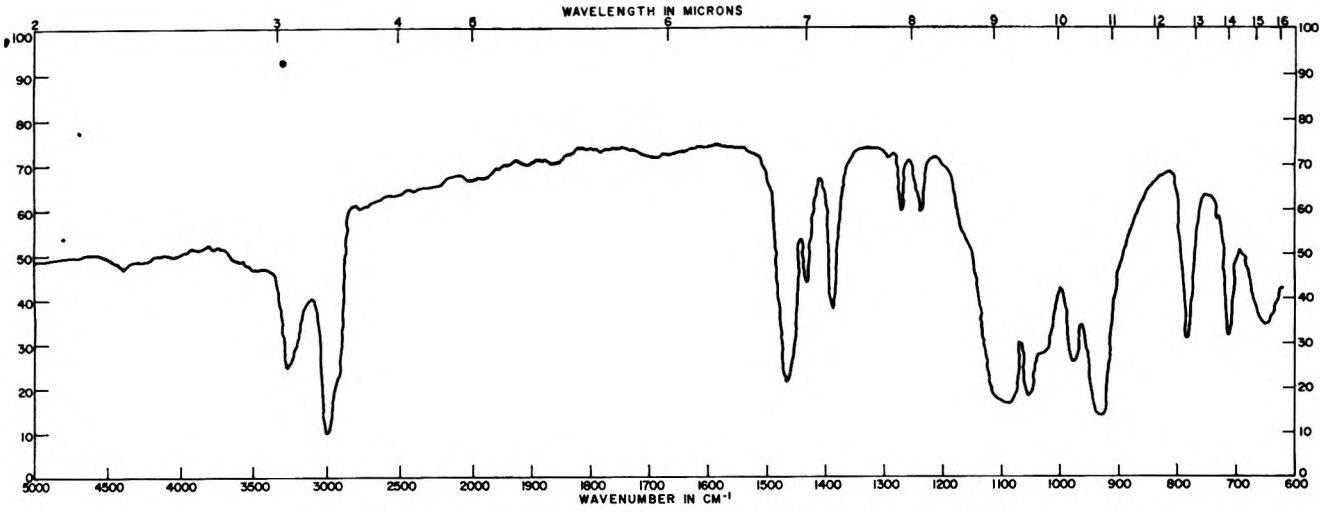
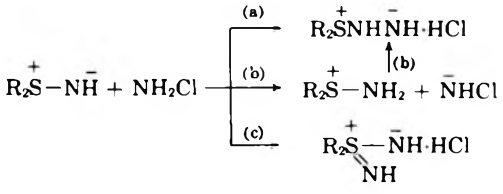


Fig. 2.—Infrared spectrum of bis(iminodiethylsulfilimine) in Nujol mull.

being a strong base, may abstract a proton from chloramine to give the chloramide ion which then reacts with the sulfiliminium salt (mechanism b). An alternate route may involve the displacement on nitrogen as in mechanism a or on sulfur, as in c.



Experimental

Bis(iminodiethylsulfilimine) Hydrochloride (I). A. From Chloramine and Diethyl Sulfide.—A stream of chloramine in excess ammonia, prepared by the method of Sisler[9] and filtered free of ammonium chloride, was introduced into 2 l. of 2-propanol containing 90 g. (1.0 mole) of diethyl sulfide at the rate of 0.01 mole/min. An external water bath was used to maintain the solution near room temperature. Three moles of chloramine was added over a 5-hr. period. Absorption was quantitative as evidenced by the absence of chloramine in the vented gas from the reaction vessel. The reaction mixture was filtered, and the filtrate was evaporated under vacuum to give 147 g. of a brownish oil. The oil was diluted with 75 g. of acetone and crystallized by cooling to 8–10° for 1 week. The precipitate obtained was filtered, washed with 2-propanol, and dried, yielding 32 g. (23% yield) of colorless crystals, m.p. 91–93°. Recrystallization from 2-propanol–acetone raised the melting point to 94.2–95.8° (decompn. 186°).

Anal. Calcd. for $C_8H_{25}ClN_4S_2$: C, 34.70; H, 9.10; Cl, 12.81; N, 20.23; S, 23.16. Found: C, 34.73; H, 9.57; Cl, 12.97; N, 20.19; S, 23.55.

This compound was found to contain one acidic and one basic group per molecule by titration, did not react with benzaldehyde, and displayed no oxidizing (KI) or reducing (KIO_3) properties in aqueous solution. The pure crystals were soluble in water (hygroscopic) and hot 2-propanol or methanol, and insoluble in carbon tetrachloride, acetone, ether, hexane, and benzene.

The product was prepared also more conveniently without removal of ammonium chloride from the chloramine-containing gas stream. In a concentric submerged spray nozzle, chlorine gas was introduced into the reaction solution through the central opening at the rate of 3 g. of chlorine per minute. Gaseous anhydrous ammonia was simultaneously added through the outer nozzle at the rate of 7 g. per minute. The solution contained 90 g. (1.0 mole) of diethyl sulfide in 2 l. of 2-propanol. The gas introduction was continued until a total of 385 g. (5.4 moles) of chlorine was added. The reaction mixture was filtered and washed with 2-propanol. The combined filtrates were concentrated under vacuum to a sirupy slurry weighing 144 g. Crystals deposited on cooling were filtered, yielding 38.8 g. of bis(iminodiethylsulfilimine) hydrochloride, m.p. 91.5–96°. A second crop of 5.5 g. was obtained on further evaporation of the filtrate and addition of acetone. The over-all yield was 44.3 g. (32%). Mixture melting point of the recrystallized material with a known sample of I proved the compounds to be identical.

B. From Diethylsulfilimine.—Following the method described by Appel,[4] a solution of 12.7 g. (0.141 mole) of ethyl sulfide in 100 ml. of methanol was added to 100 ml. of methanol containing 3.3 g. (0.143 g.-atom) of sodium. Fifty milliliters of methanol containing 9.1 g. (0.08 mole) of O-aminosulfonic acid then was introduced slowly over a 15-min. period. Slight heating was noticed during the addition. The mixture was heated to reflux, cooled, and filtered. The filtrate was evaporated under vacuum to give 7.3 g. of a brownish oil.

To check its composition, a portion of this oil (2.0 g.) was treated in 10 ml. of water with 10 ml. of a picric acid solution saturated at 50°. Orange-yellow needles were precipitated, m.p. 113.5–114.5°. The melting points for the picric acid salt of diethylsulfilimine are reported to be 111 and 115°.[4]

A 5.3-g. sample of the crude diethylsulfilimine as prepared above was dissolved in 2-propanol and treated with 0.3 mole of gaseous chloramine in excess ammonia. The resulting slurry was filtered to remove the ammonium chloride, and the filtrate was evaporated under vacuum. Excess acetone was added, precipitating 2 g. of white crystals, m.p. 89–93°. Recrystallization from 2-propanol–acetone raised the melting point to 92.5–95°. The ionic chloride content of this sample was 12.5% (calcd. for $C_8H_{25}ClN_4S_2$, 12.8%).

Bis(iminodiethylsulfilimine) (II). A. By Reaction of I with Sodium Methoxide.—A 73-ml. portion (0.05 mole) of a 0.68 *N* solution of sodium methoxide in 2-propanol was treated with 13.7 g. (0.05) of I dissolved in 2-propanol. The sodium chloride was filtered and the solvent was evaporated at room temperature under vacuum. The residue was recrystallized from acetone to give hygroscopic crystals melting at 43–49° which could easily be sublimed at 80° under vacuum.

In an attempt to duplicate this experiment on a larger scale, 420 ml. (0.25 mole) of 0.6 *N* sodium methoxide in methanol was added to a methanolic solution containing 68.6 g. (0.25 mole) of I. Upon evaporation under vacuum, 92 g. of oil was obtained. The oil was transferred to a distillation flask and heated under 10-mm. pressure. Rapid decomposition occurred causing disruption of the apparatus.

B. By Sublimation of I.—A 4-g. sample of bis(iminodiethylsulfilimine) hydrochloride (I) was placed in a sublimation apparatus and heated to 80° at 0.1 mm. A low melting (47.5–49°) solid slowly sublimed (*ca.* 1.5 g.).

Anal. Calcd. for $C_4H_{12}N_2S$: C, 39.96; H, 10.06; N, 23.30; S, 26.67. Found: C, 39.76; H, 9.68; N, 23.13; S, 26.87.

The sublimation residue crystallized after standing for 1 week. On recrystallization from hot 2-propanol, a white solid, m.p. 76.5–77.5, was obtained; it was believed to be iminodiethyl-

(9) H. H. Sisler, F. T. Neth, R. S. Drago, and D. Yaney, *J. Am. Chem. Soc.*, **76**, 3906 (1954).

sulfilimine hydrochloride (III). A known sample of III had a melting point of 75–77°.

Potentiometric titration of II with perchloric acid in glacial acetic acid gave an equivalent weight of 118.9 (calcd. 120.2). Only one of the nitrogens in the monomeric unit is thus basic. A molecular weight determination, run with 0.45 g. of II in 10.21 g. of benzene, gave a freezing depression of 1.43° (calcd. mol. wt. 158).

Reaction of II. A. With Hydrochloric Acid: Formation of Iminodiethylsulfilimine Hydrochloride (III).—To 1.79 g. (0.0075 mole) of the chloride-free sublimate in 10 ml. of 2-propanol was added 7 ml. (0.0067 mole) of a 0.96 *N* 2-propanol solution of hydrochloric acid. Ether (20 ml.) precipitated crystals which were filtered and recrystallized from 2-propanol–ether to give a white crystalline solid, m.p. 75–77°. A test for ionic chloride gave 22.3% (calcd. for $C_4H_{13}ClN_2S$: 22.6%).

B. With Ammonium Chloride: Formation of Bis(iminodiethylsulfilimine) Hydrochloride (I).—A sample of the chloride-free solid was dissolved in excess 2-propanol. Ammonium chloride was added and the mixture was heated repeatedly on the steam bath followed by partial vacuum stripping. After cooling, seeding with a known sample of I produced crystals having a melting point of 90–91°. This compound required 92.5% of theoretical equivalent of base in aqueous titration.

Iminodiethylsulfilimine Hydrochloride (III).—A solution of 2.74 g. (0.01 mole) of I in a few milliliters of 2-propanol was treated with 10 ml. (0.0096 mole) of 0.96 *N* hydrochloric acid in 2-propanol. Ether was added to precipitate the product, which was recrystallized from 2-propanol–ether to give colorless crystals of III, m.p. 75–77°. Analysis gave 22.4% ionic chloride (theoretical: 22.6%).

Addition of ammonia into a 2-propanol solution of III precipitated ammonium chloride. No solid could be obtained from the filtrate. It is believed that an equilibrium is present between the free base and the monochloride, and possibly the dichloride, in the presence of ammonia. This mixture then depresses the melting point of II, making the isolation of the solid difficult. The free base (II) is probably present in the largest concentration, since ammonia appears to be a strong enough base to precipitate ammonium chloride from I.

Compound III did not sublime on heating to 85° under 0.1-mm. pressure except when solid sodium methylate was mixed with the crystals beforehand. Under these conditions, II was obtained.

Iminodimethylsulfilimine Hydrochloride (IV).—Gaseous chloramine (1.65 moles) in excess ammonia was treated with 2 l. of 2-propanol containing 31 g. (0.5 mole) of dimethyl sulfide, as described above for diethyl sulfide. The reaction was maintained at room temperature for 45 min. and filtered to remove ammonium chloride. The filtrate then was evaporated to dryness, yielding a viscous residue which slowly crystallized. The melting point was 111–113° (decompn. 172°).

Anal. Calcd. for $C_2H_9ClN_2S$: C, 18.67; H, 7.05; N, 21.78; S, 24.93. Found: C, 18.39; H, 6.53; N, 21.71; S, 25.20.

Iminodi-*n*-butylsulfilimine Hydrochloride (V).—Filtered chloramine (2.9 moles) was bubbled through 146 g. (1 mole) of *n*-butyl sulfide in 1 l. of 2-propanol, as described above. The reaction mixture was filtered, and the filtrate was evaporated under vacuum at room temperature to give a semisolid material. A 20-g. sample (about 0.05 mole) of this material was dissolved in 100 ml. of cold 2-propanol, heated to 45°, and filtered. The clear filtrate was then combined with 40 ml. (0.04 mole) of a 2-propanol solution of hydrochloric acid. Upon cooling, 4.5 g. of flat white plates were obtained. These plates were recrystallized from warm 2-propanol, m.p. 131–132°.

Anal. Calcd. for $C_8H_{21}ClN_2S$: C, 45.15; H, 9.95; Cl, 16.66; N, 13.17; S, 15.07. Found: C, 44.49; H, 9.98; Cl, 16.59; N, 12.71; S, 15.20.

Reaction of Dioctyl Sulfide with Chloramine.—An 81-g. sample (0.32 mole) of dioctyl sulfide dissolved in 244 g. of 2-propanol was treated with 2.25 moles of filtered chloramine at room temperature. The ammonium chloride was filtered from the reaction mixture at room temperature and the filtrate was evaporated under vacuum to give a waxy solid. Attempts to isolate a crystalline product so far have been unsuccessful.

Acknowledgment.—The authors are indebted to J. N. Lomonte, J. L. McClanahan, and G. L. Kearns of W. R. Grace and Company for infrared, nuclear magnetic resonance, and mass spectrographic studies and to H. H. Sisler and G. A. Russell for their valuable comments.

Competing Reactions in the Ozonation of Anthracene

PHILIP S. BAILEY, PER KOLSAKER, BISWAJIT SINHA, JOSEPH B. ASHTON, FRANK DOBINSON, AND JOHN E. BATTERBEE

Department of Chemistry, The University of Texas, Austin, Texas 78712

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Evidence is presented that in protolytic solvents anthraquinone is derived from ozonation of anthracene by two different routes. The first requires three mole-equivalents of ozone and the evolution of three mole-equivalents of molecular oxygen. The second involves the 1,4-addition of a single ozone molecule. In non-protolytic solvents, anthraquinone is produced only by the first route. The second route leads to phthalic acid. Phthalic acid is also produced, in both solvent types, *via* a minor competing bond attack on an outer ring. The solvent effect observed is of a different type than originally suggested. A strong ozone concentration effect also exists.

Anthracene (I) was first ozonized in 1907, in chloroform solution, but no identifiable products were obtained.[1] Roitt and Waters[2] obtained anthraquinone (XI) from ozonation of anthracene in acetic anhydride, but they neither reported the yield nor proved that ozone rather than oxygen was the oxidizing agent. Certain aspects of the ozonation of anthracene were discussed in two preliminary communications from this laboratory.[3–5] The first one[3] showed that ozone was the reactant and proposed that the production of anthraquinone involves the 1,4-addition of one mole-equivalent of ozone to the reactive 9- and 10-positions of anthracene. The second communication[4] reported the evolution of molecular oxygen during the ozonation of anthracene and suggested that three mole-equivalents of ozone are required per mole of anthraquinone produced.[6] The second paper[4,5b] also reported a solvent effect which was thought to control the ratio of atom attack (leading to anthraquinone) to bond attack (leading to phthalic acid) of ozone on anthracene.

(1) E. Molinari, *Ber.*, **40**, 4160 (1907).
(2) I. M. Roitt and W. A. Waters, *J. Chem. Soc.*, 3060 (1949).
(3) P. S. Bailey and J. B. Ashton, *J. Org. Chem.*, **22**, 98 (1957).
(4) F. Dobinson and P. S. Bailey, *Chem. Ind.* (London), 632 (1961).
(5) See also: (a) P. S. Bailey, S. S. Bath, and J. B. Ashton, *Advan. Chem. Ser.*, **21**, 143 (1959); (b) P. S. Bailey, paper presented before the Petroleum Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962; preprints, Petroleum Division, American Chemical Society, Vol. 7, No. 4, C-151.
(6) P. G. Copeland, R. E. Dean, and D. McNeil [*J. Chem. Soc.*, 3858 (1961)] also report molecular oxygen to be a product of the ozonation of anthracene.

TABLE I

OZONATION OF ANTHRACENE WITH OZONE–NITROGEN

Experiment	Solvent (mixed, v./v.)	Temp., °C.	Anthracene used, mmoles	Anthracene reacted, mmoles	O_3 reacted, mmoles	Ozonation time, min.	O_2 evolved, mmoles	Anthraquinone, mmoles	Anthraquinone,[a] %	O_3–AQ ratio (actual)	O_3–AQ ratio[b] (corrected)	Acidic products[a]	Work-up procedure[c]
1	CCl_4	−18	3.00	1.60	3.0	40	1.8	0.55	34	3.3			B
2	CCl_4	−18	3.00	2.52	6.0	50	3.8	0.60	24	6.3	4.5		B
3	CH_2Cl_2–CH_3OH (9:1)	−30	3.00	1.54	3.0	40		0.57	37				B
4	CH_2Cl_2–CH_3OH (9:1)	30	10.00	4.37	10.0	100	5.7	1.63	37	3.5			B
5	CH_2Cl_2	−30	3.00	1.68	3.0	90		0.67	40				B
6	CH_2Cl_2	−30	3.00	1.71	3.0	40	2.1	0.67	39	3.1			B
7	CH_2Cl_2	−30	3.00	2.88	6.0	50	3.6	0.80	28	4.5	3.2		B
8	CH_2Cl_2	0	5.00	2.75	5.7	50	3.7	1.12	41	3.3			B
9	CH_2Cl_2	−30	10.00	3.00	5.0	60	2.7	0.80	27	3.4	2.3		B[d]
10	CH_2Cl_2	−30	10.00	3.14	5.0	100	2.7	1.13	36	2.4		0.22 g. of crude acids; 15% XXXIV, 2% XXXIII	C
11	CH_2Cl_2	−30	10.00	5.49	10.0	100		2.15	39				C
12	CH_2Cl_2	−30	10.00	5.03	10.0	80	6.2	1.88	37	3.3	3.1	0.7 g. of crude acids; 28% XXXIV, 4% XXXIII	C
13	CH_2Cl_2	−30	10.00	8.87	20.0	115	11.7	3.17	36	3.7	3.3	1.01 g. of crude acids; 17% XXXIV, 1% XXXIII	C
14	CH_2Cl_2	−30	10.00	10.00	30.0	175	21.0	3.48	35	6.0	5.3	1.14 g. of crude acids; 38% XXXIV	C
15	gl. HOAc	16	3.00	1.65	3.0	40		0.86	52				B
16	gl. HOAc	15	10.00	5.70	10.0	100	6.8	2.84	50	2.4	2.1[e]		B
17	AcOH–HOH (9:1)	14	3.00	1.60	3.0	40		1.16	73				B
18	AcOH–HOH (9:1)	14	3.00	3.00	7.5	60	4.0	1.90	63	2.1	1.8		A
19	AcOH–HOH (9:1)	14	10.00	5.02	10.0	105	6.3	3.37	67	1.9	1.7[f]	0.321 g. of crude acids; 9% XXXIV, 7% XXXIII	C
20	AcOH–HOH (9:1)	14	10.00	10.00	25.0	150	14.6	6.44	64	2.3	2.0	0.619 g. of crude acids; 18% XXXIV, 1% XXXIII	C

[a] Per cent yields calculated on basis of anthracene reacting. [b] Corrected to moles of oxygen/mole of anthraquinone at highest anthraquinone yield in same solvent (*i.e.*, expt. 1, 5, 17). [c] See Experimental section. [d] This experiment was carried out twice with nearly identical results. [e] Based on maximum anthraquinone yields obtained by oxidative work-up: expt. 37, Table II. [f] In other similar experiments this value ranged from 1.3–1.7.

TABLE II

OZONATION OF ANTHRACENE WITH OZONE–OXYGEN

Experiment	Solvent (mixed, v./v.)	Temp., °C.	Anthracene used, mmoles	Anthracene reacted, mmoles	O_3 reacted, mole-equiv.	O_3 reacted concn., %[a]	Anthraquinone yield, %[b]	Phthalic acid yield, %	Work-up procedure[c]
21	CCl_4	−18	5.00	2.34	1.0	4	20		B
22	CCl_4	−20	10.00	10.00	3.1–3.7	3–5	11–19[d]	67 crude 38–63 pure[d,j]	A
23	CH_2Cl_2	−30	5.00	2.70	1.0	4	25		B
24	CH_2Cl_2	−30	5.00	2.72	1.0	4	25		B[e]
25	CH_2Cl_2	−30	5.00	2.53	1.0	2	36		B
26	CH_2Cl_2	−78	10.00	10.00	3.7	4	24		A
27	CH_2Cl_2	−30	10.00	10.00	3.5–3.7	4	23–25[d]	72 crude 50–65 pure[d,j]	A
28	CH_2Cl_2	0	10.00	10.00	3.7	4	26–27[d]		A
29	CH_2Cl_2–CH_3OH (9:1)	−30	10.00	10.00	3.5	4	31–32[d]	54–56 crude[d] 42 pure	A
30	CH_2Cl_2–CH_3OH (5:5)	−30	10.00	10.00	3.5	4	32	55 crude 40 pure	A
31	CH_3Cl_3–CH_3OH (5:5)	−30	10.00	10.00	2.8	3–5	40		D
32	CH_2Cl_2–HOAc (9:1)	0	10.00	10.00	3.5	4	32–35[d]	66 crude 46 pure	A
33	CCl_4–HOAc (5:5)	13	10.00	10.00	3+	3–5	41 crude 36 pure	45 crude 19 pure	E
34	CH_2Cl_2–BF_3[f]	−30	6.00	6.00	3+	3–5	64 crude		A
35	*t*-BuOH–HOH (5:5)	15	5.00	1.93	1.2	4	50		B
36	*t*-BuOH–HOH (3:7)	15	10.00	10.00	3.6	3–5	66 crude		F
37	gl. HOAc	14	10.0	10.0	2.6	4	55–58[d]		A
38	gl. HOAc–NaOAc[g]	14	10.0	10.0	2.6	4	53–55[d]		A
39	HOAc–HOH (9:1)	14	10.0	10.0	2.0	4	72		A
40	HOAc–HOH (9:1)	14	10.0	10.0	2.6	4	65–68[d]	22 crude 18 pure	A
41	HOAc–HOH + NaOAc[g]	14	10.0	10.0	2.6	4	65		A
42	HOAc–Ac_2O (9:1)	14	10.0	10.0	2.6	4	55–58[d]		A
43	HOAc–HOF[h] (3:7)	11	10.0	10.0	3+	3–5	64[i]		E
44	HOAc–CH_3OH (5:5)	10	10.0	10.0	3.3	3–5	62		D

[a] Approximate % O_3 by weight in ozone–oxygen stream. [b] Yield based on anthracene reacting. [c] See Experimental section. [d] Results of several experiments. [e] Same as procedure B, except solution was not refluxed before chromatography. [f] Slightly more than one mole of BF_3 etherate per mole of anthracene. [g] Contained 5 g. of sodium acetate in glacial acetic acid or acetic acid–water, 9:1 (v./v.). [h] The formic acid was a 90% solution in water. [i] A 49% yield of anthraquinone precipitated during the ozonation. The rest was obtained during work-up. [j] The higher yields of phthalic acid were obtained by continuous extraction with ether.

The present paper reports the completed study of the ozonation of anthracene (I) in several different solvents (Tables I and II) and presents evidence that aspects of both mechanisms proposed in the preliminary papers[3–5] are involved in the ozonation. Evidence is also presented that the solvent effect is of a different type than originally supposed.

In 90% solutions of acetic acid in water, ozone absorption by anthracene (I) was very nearly quantitative up to 1.5–1.6 mole-equivalents, after which it occurred fairly readily through 2.5–2.6 mole-equivalents. A 30–45% yield of anthraquinone (XI) precipitated during the ozonation. From the peroxidic filtrate could be obtained either additional anthraquinone, *via* an alkaline or thermal work-up, or anthrahydroquinone (IX ⇄ X) by sodium iodide reduction (which does not affect anthraquinone). The anthrahydroquinone (IX) was isolated and identified in the form of its diacetate (XIII).

After the absorption of one or two mole-equivalents of ozone and an alkaline or thermal work-up procedure, the anthraquinone (XI) yield was 67–73%, based on the amount of anthracene reacting (expt. 17, 19, 39). The yield tended to be slightly lower after an oxidative (expt. 19) rather than a thermal and chromatographic (expt. 17) work-up, probably owing to losses from extra manipulations. Neither anthracene nor anthraquinone is affected by alkaline hydrogen peroxide. The other products were from carbon–carbon bond cleavages. From a one-mole-equivalent run (expt. 19) a mixture of 9% phthalic acid (XXXIV) and 7% 2,3-naphthalenedicarboxylic acid (XXXIII) was obtained. The English workers[6] also isolated XXXIII in 6% yield. In order to isolate a single ozonolysis (bond cleavage) product in good yield it was necessary to use 2.5–2.6 mole-equivalents of ozone and the oxidative work-up procedure. Under these conditions the anthraquinone (XI) yield was 63–68% (expt. 18, 20, 40), and an 18–22% yield of phthalic acid (XXXIV) was obtained (expt. 20, 40).

The results were the same whether ozone–oxygen or ozone–nitrogen[7] mixtures were used. Ozone was also shown to be the ozidizing agent, without the aid of molecular oxygen, by passing the usual volume of ozone–oxygen mixture, but with only catalytic amounts of ozone, through the reaction mixture and showing that the ozone–anthracene stoichiometry was similar to that in experiments using normal ozone concentrations.

Using ozone–nitrogen mixtures and our technique described earlier,[8] it was found that approximately

(7) G. A. Cook, A. D. Kiffer, C. V. Klumpp, A. H. Malik, and L. A. Spence, *Advan. Chem. Ser.*, **21**, 44 (1959).

(8) P. S. Bailey and A. M. Reader, *Chem. Ind.* (London), 1063 (1961).

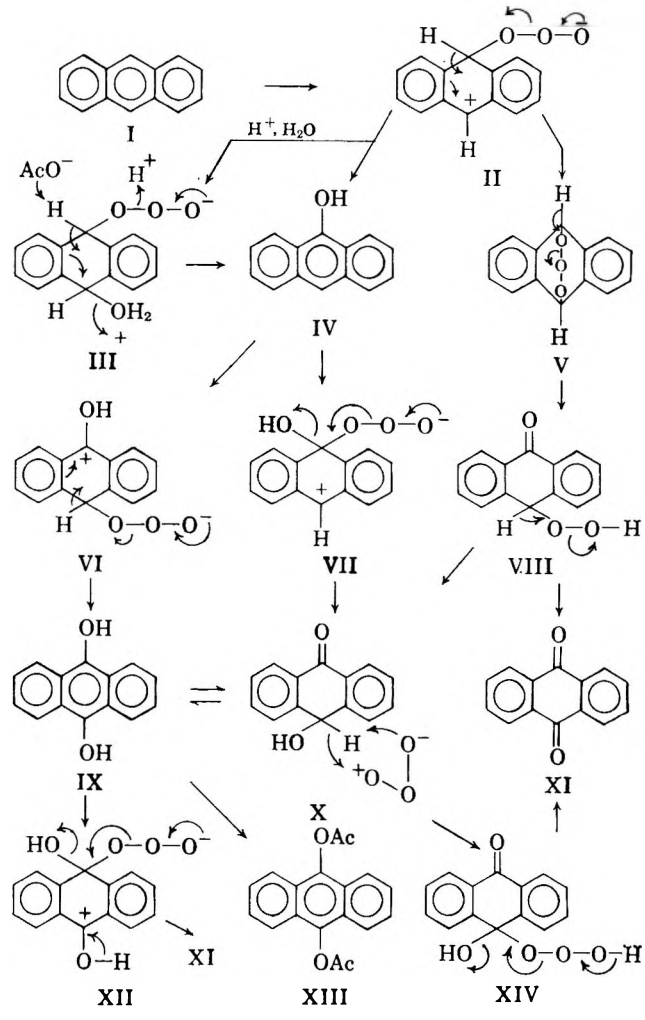
1.3–1.7 moles of molecular oxygen were evolved per mole of anthraquinone (expt. 19) obtained from the one mole-equivalent of ozone runs by the nonoxidative work-up procedure (expt. 17). However, the ratio of molecular oxygen evolved per mole of anthraquinone precipitating during the ozonation was approximately 3.

In nonprotolytic solvents, such as methylene chloride or carbon tetrachloride, ozone absorption was very nearly quantitative up to 2.5–2.8 mole-equivalents of ozone, after which considerable ozone passed into the iodide trap. The best yield of anthraquinone (XI) that resulted from nonprotolytic solvents was 39–41% (expt. 5, 6, 8, 11). This was obtained in methylene chloride solvent, using only one mole-equivalent of ozone from an ozone–nitrogen[8] rather than an ozone–oxygen mixture, chromatographically separating anthraquinone and unreacted anthracene, and calculating the anthraquinone yield on the basis of the anthracene actually used in the reaction. From carbon tetrachloride under the same conditions only a 34% anthraquinone yield was obtained (expt. 1). The anthraquinone could be obtained with or without thermal decomposition and with or without acidic or basic conditions or a chromatographic column, showing that it was directly formed. The molecular oxygen evolved to the anthraquinone obtained ratio was approximately 3[8] (expt. 1, 6, 8, 12). By an oxidative work-up procedure it was shown that the major bond-cleavage product from 0.5 and 1 mole-equivalent of ozone experiments was phthalic acid (XXXIV), along with a small amount of 2,3-naphthalenedicarboxylic acid (XXXIII, expt. 10, 12). Another, unidentified, acid was also found by thin layer chromatography. As more ozone was employed the phthalic acid to naphthalenedicarboxylic acid ratio increased (expt. 13). None of the latter was found when three mole-equivalents of ozone were employed (expt. 14). In these experiments acid yields were low owing, partly, to losses in attempts to isolate all acidic products, and also, probably, to incomplete oxidation of phthalic acid intermediates.

When the reaction was allowed to proceed until 3.0–3.6 mole-equivalents of ozone had been absorbed, in order to ensure completion of bond cleavages in two rings, phthalic acid (XXXIV) was obtained in as high as 67–72% crude and 65% pure yields (expt. 22, 27). It was because of this that it was thought that in nonprotolytic solvents the major ozone attack was at the bonds of lowest bond-localization energy,[9] whereas in protolytic solvents it occurred at the atoms of lowest atom-localization energy.[4,5b,9] For reasons to be discussed, however, it is now apparent that this sort of solvent effect is minor if it exists at all. Also there is no appreciable temperature effect, as shown by comparison of expt. 26–28.

There is a definite ozone-concentration effect with nonprotolytic solvents, but not with protolytic solvents. Whereas, using one mole-equivalent of ozone from ozone–nitrogen mixtures, the anthraquinone yield averaged 40% with methylene chloride solvent (expt. 5, 6, 8), the yield, using one mole-equivalent of ozone from ozone–oxygen and the same solvent and work-up procedure, was only 25% (expt. 23, 24). When two mole-equivalents of ozone were employed from ozone–nitrogen, the anthraquinone yield was only 28% (expt. 7). Similar results were obtained with carbon tetrachloride solvent (expt. 1, 2, 21, 22). It is difficult to estimate the average ozone concentration when ozone–nitrogen mixtures are employed. However, it must be much lower than the roughly 4% used with ozone–oxygen, since expt. 23 and 24 required only about ten minutes and expt. 6 required forty minutes. The same silica gel column was used for the two mole-equivalent of ozone run in expt. 7, but the reaction time was only fifty minutes; thus the ozone concentration in the ozone–nitrogen stream must have been considerably higher than in expt. 6. That these results were actually due to an ozone-concentration effect was proven in two ways. First, when only a 2% ozone–oxygen stream was employed, the anthraquinone yield increased to 36% (expt. 25). When the reaction was carried out in a saturated solution of ozone in methylene chloride at a low temperature, the anthraquinone yield decreased to 18%. Second, the length of the silica gel column for the ozone–nitrogen mixtures was doubled and tripled in expt. 13 and 14 in comparison to 12. Although the reaction time did not double and triple, it at least increased, and the anthraquinone yield was 37–35% in all three experiments. No higher than a 40–41% yield of anthraquinone was ever obtained, even when the ozone-concentration was further decreased (*cf.* expt. 5, 6). No ozone concentration effect was observed with 90% acetic acid solvent (expt. 17, 39).

SCHEME I



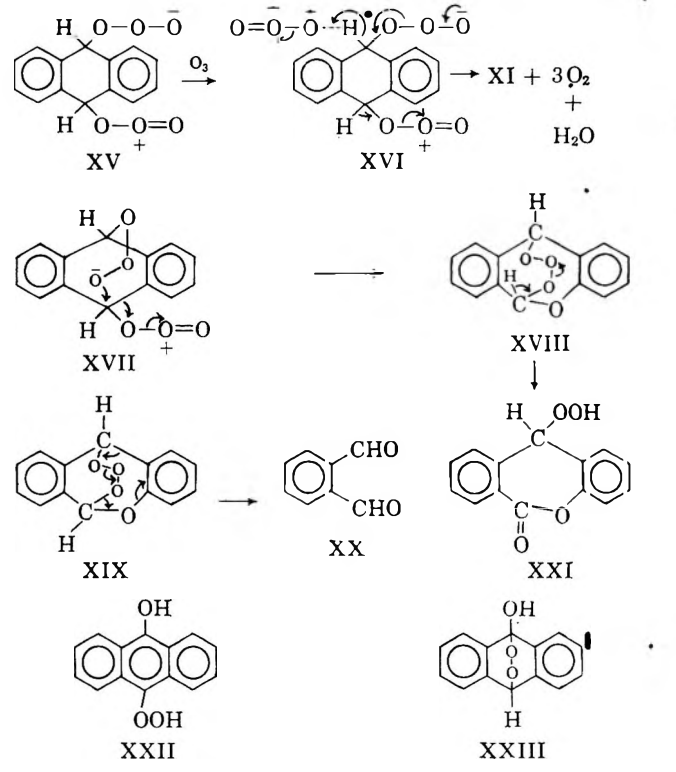
(9) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

It is obvious that the reactions in 90% acetic acid are less complicated than those in nonprotolytic solvents, but that there are, nevertheless, at least two paths to anthraquinone (XI) and also to phthalic acid (XXXIV). It is significant and must be more than coincidental that, using ozone–nitrogen mixtures,[8] three moles of molecular oxygen are evolved per mole of anthraquinone produced, both for the highest yields of anthraquinone obtained using one mole-equivalent of ozone in nonprotolytic solvents and for the anthraquinone which precipitated during the ozonations in 90% acetic acid. It is reasonable to assume, therefore, that the anthracene reacting by this route requires three mole-equivalents of ozone.

Since the center ring is the location of the atoms of lowest atom-localization energy of anthracene, it is reasonable that all reactions of ozone at this ring involve an initial electrophilic attack[9] to give II. There are several possible routes from II to anthraquinone (XI) involving two more mole-equivalents of ozone and the release of three mole-equivalents of molecular oxygen. We believe that the route (or routes) involving IV and IX as intermediates better explains the solvent and ozone-concentration effects. The comparatively clean-cut reactions in 90% acetic acid are due, we believe, to the availability of protons and nucleophilic water molecules, which control the course of the reactions from II to IV as shown in III. Intermediate IV could then undergo an electrophilic ozone attack to give VI, which could react exactly as described for II to give IX. An electrophilic ozone attack on IX should readily give anthraquinone (XI) *via* XII, or the solvent-stabilized form thereof. Alternatively, IV might react with ozone to give VII, which could go on to anthraquinone (XI) *via* intermediate steps such as illustrated by X and XIV; or IV might tautomerize to anthrone, which reacts with two mole-equivalents of ozone to give anthraquinone and two mole-equivalents of molecular oxygen.[10] (See Scheme I.)

In nonprotolytic solvents it is likely that most of the anthraquinone arises by essentially the same route, except that no aid comes from the solvent (*i.e.*, I → II → IV → VI → IX → XII → XI). It is here that we believe the ozone-concentration effect comes into play. The reactions are slower without the aid of protons, but, nevertheless, occur smoothly when the ozone concentration is low. At higher ozone concentrations, however, ozone attacks intermediates II, VI (or VII), and XII nucleophilically, as illustrated in XV, and stops to some degree the reaction course to anthraquinone (XI). This is the mechanism suggested in our second preliminary communication.[4,5b] Intermediate XV could go on over to anthraquinone (XI), but this would require the aid of a third ozone molecule to remove hydride ion as shown in XVI. This should be a slow reaction and, thus, probably occurs to only a minor extent. It is more likely that XV would undergo a rearrangement, as shown in XVII → XVIII, involving cleavage of the central ring and loss of oxygen, and leading eventually to phthalic acid (XXXIV). This 1,2-shift to positive oxygen is analogous to similar shifts in Baeyer–Villiger reactions, which involve the nucleophilic attack of peracids.[11] Possible fates of the rearrangement product are shown by XVIII → XXI and XIX → XX; further rearrangements could occur with XXI, leading directly to products easily convertible to XXXIV during work-up. Such nucleophilic ozone attacks and rearrangements could also occur with intermediates VI (or VII) and XII. In all of these reactions oxygen is a product, which would explain the fact that, as the anthraquinone yield decreased with nonprotolytic solvents, the ratio of molecular oxygen evolved to anthraquinone produced increased (expt. 2, 7, 12, 13, 14), and, at least in the case of carbon tetrachloride solvent, the increase was greater than can be accounted for by assuming that bond attack of ozone, leading to phthalic acid, had occurred with anthraquinone. Further, anthraquinone was shown to be resistant to ozone attack in all solvents. It also does not seem possible that outer ring attack could be occurring with a precursor to anthraquinone, such as IV or IX, since the central ring of these substances should be more reactive toward ozone in reactions leading to anthraquinone than should the central ring of anthracene itself.

SCHEME II



The anthraquinone which does not precipitate during ozonation of anthracene in 90% acetic acid, but is obtained by alkaline or thermal decomposition of a peroxidic intermediate, must have arisen from a reaction involving only one mole-equivalent of ozone and no release of molecular oxygen. Based on an average 1.5 molar ratio of molecular oxygen to total anthraquinone obtained (expt. 19), roughly 50% of the anthraquinone should have arisen by the three mole-equivalent of ozone route and 50% by the one mole-equivalent route. This agrees reasonably well with the amounts isolated, considering the experimental error involved.[8]

The most logical mechanism for the one mole-equivalent of ozone route to anthraquinone involves the completion, II → V, of a 1,4-addition of ozone, as suggested in our first communication.[3,5a] Such an adduct has

(10) P. S. Bailey and J. E. Batterbee, studies in progress.
(11) C. H. Hassall, *Org. Reactions*, **IX**, 73 (1957).

actually been isolated from ozonation of 9,10-dimethylanthracene, and its structure was proven by n.m.r. spectroscopy.[12] The extent to which such an adduct is produced should be greater with 9,10-dimethylanthracene than with anthracene, owing to activation of the central ring by the methyl groups. Further, it should be more stable in the case of the substituted anthracene.

It is in regard to intermediate V that we believe the principal solvent effect occurs. In the presence of a protolytic solvent, we suggest that V rearranges to VIII, aided by the donation and acceptance of protons by the solvent. Alternative structures to VIII are XXII and XXIII. Intermediate VIII (or its alternatives) then remains in the reaction mixture until alkaline (or strongly acidic) work-up conditions or heat converts it to anthraquinone (XI), reduction converts it to anthrahydroquinone (IX, or its tautomer X), or it is destroyed by excess ozone. Since some phthalic acid was obtained from one mole-equivalent of ozone runs in 90% acetic acid (expt. 19) and since the ozone absorption and oxygen evolution data indicate that this could not have arisen from outer ring attack, intermediate VIII must also undergo rearrangement to some extent as shown by XXIV → XXV. Further oxidation of XXV or XXVI should lead to phthalic acid (XXXIV). Alternatively, the minor cleavage of the central ring could occur at stage V, as will be discussed for reactions in nonprotolytic solvents.

Further evidence for intermediate VIII is as follows. First, the anthrahydroquinone (IX) obtained after the reductive work-up procedure could only have come from reduction of a stable peroxidic intermediate, for had it been produced during the ozonation, it would have been converted to anthraquinone (IX → XII → XI). Second, the easy thermal or alkaline conversion of the peroxide to anthraquinone (work-up procedures A, B, or C) favors VIII, as does also the fact that, when an acetic acid–formic acid mixture was used as solvent, the amount of anthraquinone precipitating during the ozonation increased to 49% (expt. 43). The stronger acid conditions should catalyze the conversion of hydroperoxide VIII to anthraquinone (XI). Third, it is noteworthy that, when only one mole-equivalent of ozone was employed in the 90% acetic acid reactions, the yield of anthraquinone (XI) produced directly was only about 30%, whereas, when 2.0–2.6 mole-equivalents of ozone were employed, this value increased to about 45%; yet, the ratio of molecular oxygen to anthraquinone produced directly was 3 (within experimental error[8]) in both cases. The most logical explanation is that some of hydroperoxide VIII reacted with ozone to give X, followed by X → XIV → XI. This would also result in the evolution of approximately three mole-equivalents of molecular oxygen, since certain hydroperoxides have been reported to react with ozone with release of molecular oxygen, approximately according to the equation $ROOH + O_3 \rightarrow ROH + 2O_2$.[13] Apparently hydroperoxide VIII can also be attacked by ozone at an outer ring, as the 67–73% yields of anthraquinone obtained from the one–two mole-equivalent of ozone reactions in 90% acetic acid (expt. 17, 19, 39) decreased to 63–68% when 2.5–2.6 mole-equivalents of ozone were allowed to react (expt. 18, 20, 40) and to 38% when ten mole-equivalents of ozone were passed through the reaction mixture (glacial acetic acid). In the last instance the phthalic acid (XXXIV) yield increased to 43% (crude). Since anthraquinone (XI) does not react appreciably with ozone under these conditions and since, in the last case, most of the anthraquinone was produced directly, a precursor to XI (presumably VIII or its alternatives) must have been destroyed. In line with this reasoning are the increased ratios of molecular oxygen to total anthraquinone in expt. 18 and 20.

It can be seen from expt. 1, 5, 6, 11, and 12, in which one mole-equivalent of ozone was employed in nonprotolytic solvents, that, after three moles of ozone were used to produce one mole of anthraquinone, the rest of the ozone which reacted was enough to react with only one or two bonds of the remainder of the reacting anthracene. The same conclusion, as will be discussed in greater detail later, can be drawn from expt. 9 and 10 in which only 0.5 mole-equivalent of ozone was employed. Yet the major acidic product obtained from these reactions was phthalic acid (XXXIV), and 2,3-naphthalenedicarboxylic acid (XXXIII) was only a minor product (expt. 10, 12). The inescapable conclusion seems to be that phthalic acid must have arisen from initial attack on the central ring, followed by rearrangement of the product (*e.g.* V or VIII) to a substance which can be oxidized easily to phthalic acid (XXXIV). Since we were unable to get any evidence for intermediate VIII in nonprotolytic solvents by reduction as we did in the acetic acid experiments, we believe that the rearrangement occurs at stage V. It is not surprising that when protons are not available intermediate V undergoes a 1,2-shift to positive oxygen, as indicated by XXVII → XXVIII. Intermediate XXVIII could then undergo the shifts shown to yield XXV ⇄ XXVI, which possibly could be converted to phthalic acid (XXXIV) during the oxidative work-up procedure. Perhaps the unidentified acid found in expt. 12–14 was an incomplete oxidation product of XXVI. Another possible fate of XXVIII is shown in XXIX, whereby phthalaldehydic acid (XXX) is produced directly, along with benzyne. However, no XXX was found after a nonoxidative work-up procedure. (See Scheme III.)

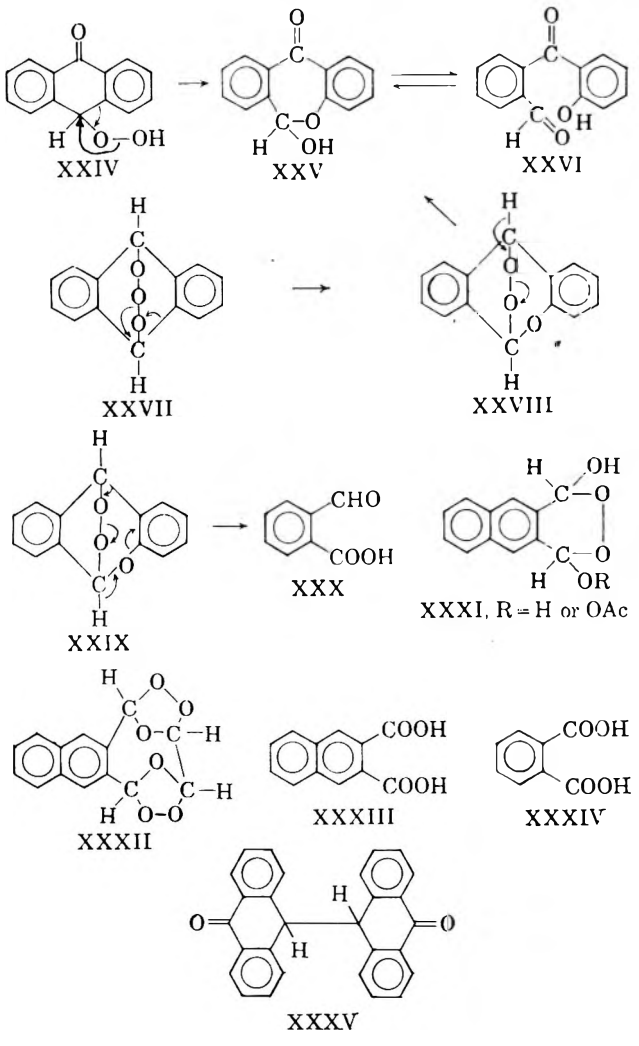
1,4-Transannular ozone additions could also be completed at stages VI, VII, or XII. All of these could go over easily to either anthraquinone (XI) or phthalic acid (XXXIV). However, at stages VII and XII it appears more likely that the indicated reactions would occur before the transannular ozone adduct could form.

Two other observations are worthy of note. First, in expt. 9 where 0.5 mole-equivalent of ozone was employed in methylene chloride solvent, the yield of anthraquinone (XI) was considerably lower than in the corresponding one mole-equivalent of ozone reactions (expt. 5, 6, 8, 11, 12). A careful examination of the data shows that not enough ozone reacted to convert 40% of the reacting anthracene to anthraquinone (XI) by the three mole-equivalent of ozone route and yet bring about conversion of the rest of the reacting anthracene to the precursors of acids XXXIV and XXXIII. Thus, the low yield of anthraquinone (XI) must have been due to the presence of compounds such as IV

(12) R. E. Erickson, P. S. Bailey, and J. C. Davis, Jr., *Tetrahedron*, **18**, 388 (1962).

(13) D. Barnard, G. P. McSweeney, and J. F. Smith, *Tetrahedron Letters* No. **14**, 1 (1960).

SCHEME III



and IX in the reaction mixture (*i.e.*, incomplete conversion to XI by the three-mole ozone route). These acidic substances would be expected to remain on the chromatographic column. If one corrects the ratio of molecular oxygen to anthraquinone in expt. 9 (basing it on the 40% anthraquinone yield of expt. 5), the value becomes 2.3, which is in line with the above reasoning. This explanation was verified by expt. 10 where an oxidative work-up procedure was used. Here the anthraquinone (XI) yield increased to 36%, undoubtedly owing to conversion of IV and/or IX to XI during the oxidative work-up. The molecular oxygen to anthraquinone ratio was only 2.4, since only one mole-equivalent of oxygen would be evolved in going to IV and two would be evolved in going to IX during the ozonation.

Second, in one experiment using glacial acetic acid solvent and work-up procedure B, with the exception that the glacial acetic acid mixture was heated during the evaporation of the solvent, the anthraquinone yield fell to 34%, and an 8% yield of bianthrone (XXXV) was isolated along with a small amount of an unknown compound, which might be the methyl acetal of XXV. This furnishes additional evidence for the proposed mechanisms. Presumably, during the heating in glacial acetic acid, an intermediate such as VIII dimerized to bianthrone (XXXV). This is not unreasonable since bianthrone was obtained when a glacial acetic acid solution of 10-bromoanthrone was refluxed.[14] During the heating of the acidic reaction mixture, reactions such as XXIV → XXV must have been promoted, also lowering anthraquinone (XI) yield. No bianthrone (XXXV) was obtained, and the anthraquinone yield was closer to normal (expt. 37) when the reaction was repeated without heating the glacial acetic acid reaction mixture (expt. 16).

It is evident from the foregoing discussion that there is a powerful solvent effect in the ozonation of anthracene, but that it involves largely the fates of intermediates from atom attack rather than the competition between atom and bond attack of ozone. As already stated, this effect appears to be principally the result of the degree of protolytic character of the solvent, as is evidenced by the fact that the per cent yield of anthraquinone (XI) increases as the solvent varies from carbon tetrachloride to methylene chloride to glacial acetic acid to aqueous acetic acid (Tables I and II); this is also roughly the order of decreasing molecular oxygen to anthraquinone ratios (Table I). A mixture of glacial acetic acid and methanol gave, with ozone oxygen, results similar to those from aqueous acetic acid (*cf.* expt. 40, 44). The patent literature reports a 72% anthraquinone yield from aqueous *t*-butyl alcohol solvent.[15] We were not able to duplicate this (expt. 35, 36), but this may be due to solubility difficulties; the patent used an anthracene–phenanthrene mixture.

The greater yield of anthraquinone (XI) from methylene chloride than from carbon tetrachloride reaction mixtures may be due to either or both the greater protolytic character of methylene chloride or the fact that methylene chloride reacts slightly with ozone to produce small amounts of hydrogen chloride.[16] Another factor may be that the greater polarity of methylene chloride simply increases the ease of ionic reactions. The English authors[6] obtained approximately the same yield of anthraquinone in chloroform solution that we did in methylene chloride, using ozone–oxygen.

Also in line with the proposed theory is the good yield of anthraquinone (XI) obtained using as the ozonation solvent a solution of the Lewis acid boron trifluoride in methylene chloride (expt. 34).

It is difficult to say whether or not there is any solvent effect of the type involving competition between atom and bond attack of ozone on anthracene, as it is difficult to ascertain how much phthalic acid (XXXIV) came from initial bond attack and how much came from center ring attack followed by rearrangements. The seemingly clean-cut reaction in aqueous acetic acid to give nearly 75% anthraquinone (XI) would appear to indicate that 25% initial bond attack occurs. Further, the 2.5–2.6 mole-equivalents of ozone required to complete the reaction fits in well with the 40–45% anthraquinone yield requiring three mole-equivalents of ozone, the 30–35% anthraquinone yield requiring one mole-equivalent of ozone, and 25% bond attack requiring four mole-equivalents of ozone (the fact that more ozone is required with nonprotolytic solvents is probably due to the fact that more intermediates such as XXVI are produced and react further with ozone).

(14) W. Tadrost and A. B. Sakla, *J. Chem. Soc.*, 3210 (1957).

(15) M. G. Sturrock, E. L. Cline, and K. R. Robinson, U. S. Patent 2,898,350 (Aug. 4, 1959).

(16) G. Slomp, Jr., *J. Org. Chem.*, **22**, 1277 (1957).

By analogy to the ozonation of the 9,10-dihaloanthracenes, where the acid products from bond attack are different from those from rearrangement of atom-attack products, it is possible that a solvent effect involving atom *vs.* bond attack is occurring in the present case also to a small extent.[17] However, this type of solvent effect appears to be dependent on the nucleophilicity of the solvent, and methylene chloride–methanol was as good as or better than aqueous acetic acid for quinone formation.[17] This is not true in the case of anthracene. The yields of anthraquinone were not significantly different from mixtures of methylene chloride, chloroform, or carbon tetrachloride and methanol or glacial acetic acid than from methylene chloride or carbon tetrachloride alone (*cf.* expt. 3, 5, 16, 27, 29–33). Further, the anthraquinone yield was not increased by the addition of sodium acetate to either glacial or aqueous acetic acid (expt. 38, 41). Thus, it appears that the solvent effect involving the competition between bond and atom ozone attack is relatively unimportant. Since neither we nor the English authors have isolated greater than 8% yields of 2,3-naphthalenedicarboxylic acid (XXXIII) from ozonations of anthracene with one–two mole-equivalents of ozone in either protolytic or nonprotolytic solvents, or when only 0.5 mole-equivalent of ozone was employed (expt. 10), this may be close to the extent to which initial bond attack occurs in either type of solvent.

Whatever the extent of the initial bond attack, it apparently involves first the outer ring and then the central ring of anthracene, predominantly, since the only acidic product isolated after complete ozonolysis and a strong oxidative work-up was phthalic acid (XXXIV), expt. 22, 27, 40). This must mean that ozone attack at the outer ring involves a diozonide (*e.g.*, XXXII, as also found with naphthalene[18]) with nonprotolytic solvents, and either XXXI or a mixture of XXXI and XXXII[19] from 90% acetic acid. Upon oxidative work-up, XXXI and XXXII would be converted to 2,3-naphthalenedicarboxylic acid (XXXIII). Further ozonolysis should occur at the original central ring, due to the activating influences of the groups attached, to give, after oxidative work-up, phthalic acid (XXXIV). In contrast, the major bond-attack reactions are at the outer rings of the 9,10-dihaloanthracenes, owing to deactivation by the halogens.[17]

Badger[20] has suggested that the production of anthraquinone during ozonation of anthracene in acetic acid is due to reaction between ozone and acetic acid to give peracetic acid and the attack of the latter on anthracene. At that time he did not know that anthraquinone is also produced in other solvents. Such an explanation is highly unlikely, also, because ozone absorption in acetic acid solutions of anthracene is rapid, whereas we and others[21] have shown that ozone does not react with acetic acid appreciably under ordinary conditions.

(17) P. Kolsaker, P. S. Bailey, F. Dobinson, and B. Kumar, *J. Org. Chem.*, in press.

(18) P. S. Bailey, S. S. Bath, F. Dobinson, F. J. Garcia-Sharp, and C. D. Johnson, *ibid.*, **29**, 697 (1964).

(19) Compare with the phenanthrene peroxidic ozonolysis product from acetic acid [P. S. Bailey and S. B. Mainthia, *ibid.*, **23**, 1089 (1958)].

(20) G. M. Badger's statement in the discussion section of A. Albert, G. M. Badger, and C. W Shoppee, "Current Trends in Heterocyclic Chemistry," Academic Press, Inc., New York, N. Y., 1958, pp. 5–6.

(21) (a) F. L. Greenwood, *J. Org. Chem.*, **10**, 414 (1945); (b) H. Paillard and E. Briner, *Helv. Chim. Acta*, **25**, 1528 (1942).

Thus it appears that, regardless of solvent, Moriconi[22] was correct in placing anthracene in the group of polycyclic aromatic hydrocarbons which are attacked by ozone predominantly at the atoms of lowest atom-localization energy rather than at the bonds of lowest bond-localization energy. Whether or not his theoretical correlations with oxidation–reduction potentials are meaningful, or merely fortuitous, however, remains to be seen.

Experimental

The ozonation set-up and equipment are described in earlier publications.[8,23] In several cases the ozonation and cooling vessels were placed over a magnetic stirrer, so that the ozonation mixture containing undissolved anthracene and/or products could be stirred. Solvents were pure and anhydrous, unless otherwise stated. The anthracene was usually Matheson's blue-violet fluorescence grade and was dried before use. Where lesser grades were used, the anthracene was purified by chromatography over alumina, m.p. 213° (uncor.).

Ozonation of Anthracene (I).—Several different work-up procedures were used as described below. The results are shown in Tables I and II.

Work-Up Procedure A.—In these experiments a mixture of 3–10 mmoles of finely powdered anthracene in 70–100 ml. of solvent was heated until as much anthracene as possible dissolved, after which the mixture was cooled to the desired reaction temperature. In most cases an ozone–oxygen stream containing approximately 4% by weight ozone was passed through the reaction mixture, which was stirred magnetically, until the desired amount of ozone had reacted. Ozone absorption was near quantitative until 1.5–1.6 (acetic acid solvents) or 2.5–2.8 mole-equivalents (nonprotolytic solvents) had reacted. Reaction appeared to be complete when 2.5–2.6 (acetic acid solvents) and about 3.5–3.6 mole equivalents (nonprotolytic solvents) of ozone had been absorbed. In acetic acid solutions, anthraquinone precipitated during the ozonation. In nonprotolytic solvents, a white "ozonide" began to precipitate after the absorption of about two mole-equivalents of ozone. After the ozonation, the reaction mixture was swept with nitrogen and the solvent was evaporated under reduced pressure on a rotar. To the yellowish sticky residue was added 10 ml. of ethanol and, slowly, a mixture of 10 ml. of 30% hydrogen peroxide and 60 ml. of 2–3% sodium hydroxide (per 10 mmoles of anthracene). The mixture was heated, with stirring, at 65–70° for 2 hr., after which it was cooled and extracted three to six times with 50–100-ml. portions of methylene chloride and once with ether (50 ml.). The combined extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give anthraquinone (XI), crude m.p. 275–278°, recrystallized (ethanol) m.p. 282–283°. Identification was by comparison of infrared spectra and mixture melting point method.

To the alkaline mother liquor plus aqueous washings was added hydrogen peroxide (10 ml. of 30% per 10 mmoles of anthracene), and the resulting mixture was heated over a steam bath for 3 hr., cooled, acidified with hydrochloric acid, saturated with sodium chloride, and either continuously extracted or extracted eight times with 70-ml. portions of ether. The ethereal extract was dried over anhydrous magnesium sulfate and evaporated to a tan sticky solid. The crude solid was triturated for 30 min. with refluxing chloroform (20 ml. for 10-mmole runs), after which the mixture was cooled and filtered, giving crude phthalic acid (XXXIV), m.p. (from complete ozonation runs) 190–195°, recrystallized (ethyl acetate) m.p. 202–203°. Identifications were by the mixture melting point method or comparison of infrared spectra.

Work-Up Procedure B.—In most cases an ozone–nitrogen stream was used (desorbed from a 20-cm. silica gel column[7,8]), and molecular oxygen yields were determined by techniques described previously.[8]

The formula used for the final calculation was mmoles of O_2 = [wt. O_2 graph × % O_2 in standard × cc. of gas per min. × min. run × 273° × mm. pressure/wt. total graph × 100 × temp.

(22) F. J. Moriconi and L. B. Taranko, *J. Org. Chem.*, **28**, 1831 (1963); and preceding papers in the series.

(23) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956).

(°K.) × 760 mm. × 22.4 ml. per mmole] − mmoles of O_3 reacting in a potassium iodide trap.

Ozone absorption by the reaction mixture was usually quantitative, since the ozone concentrations were low. After ozonation, the solvent (unless it was carbon tetrachloride) was removed under reduced pressure (rotar) at room temperature or below. the residue was taken up in 100 ml. of carbon tetrachloride, and the resulting mixture was refluxed until it was no longer peroxidic (approximately 1 hr.). The carbon tetrachloride solution was cooled and poured onto an alumina column. Elution with petroleum ether (b.p. 35–60°, *ca.* 200–300 ml. per mmole run) gave anthracene upon evaporation (m.p. 210–212°), and elution with methylene chloride (*ca.* 150–200 ml. per mmole run) gave anthraquinone (m.p. 282–283°). Identifications were by the mixture melting point method or comparison of infrared spectra.

Work-up procedure C was a combination of A and B. After the oxidative work-up and methylene chloride extraction, the methylene chloride extract was evaporated and the residue was dissolved in carbon tetrachloride and separated on the alumina column to give anthracene and anthraquinone.

The acid yields were determined by a combination of actual isolation and thin layer chromatography; identifications were by thin layer chromatography (t.l.c.) and comparison of infrared spectra. For thin layer chromatography, 8 × 8 in. glass plates sprayed with silica gel G were used. The best developing solvent was methanol. Even with it, however, 2,3-naphthalenedicarboxylic acid (XXXIII) moved more as an elliptical smear than as a spot; thus, quantitative t.l.c. estimates were made only with phthalic acid (XXXIV). The spray reagent was bromocresol green[24] which gave yellow spots on a blue background with both acids (XXXIII and XXXIV). Quantitative estimates were made by comparisons of the chromatographs of 10 mg. of the unknown mixture and 10 mg. of the pure known compound. The spot areas were measured with a Desaga labeling template. R_f values were not reproducible from plate to plate because of variations in layer thickness; thus, all comparisons with known compounds were made on the same plate. The techniques are illustrated by the following example: expt. 19, Table I.

The ether extract containing the acid fraction from ozonation of 10 mmoles of anthracene with 10 mmoles of ozone in 100 ml. of 90% acetic acid gave 0.3210 g. of a brown gummy solid upon evaporation. The solid was triturated for 10 min. with 40 ml. of refluxing chloroform after which the resulting mixture was allowed to stand overnight, and then filtered to give 0.1365 g. of a tannish solid (precipitate A.). On further standing 0.0200 g. of B was obtained from the chloroform mother liquor. Precipitate B was shown both by infrared spectrum and t.l.c. comparisons to be entirely 2,3-naphthalenedicarboxylic acid (XXXIII) with infrared bands at 5.95, 8.20, 8.79, 9.70, 12.90, 13.22, and 15.10 μ. Both infrared and t.l.c. comparisons with precipitate A showed the presence of both XXXIII and phthalic acid (XXXIV, characteristic infrared bands at 6.00, 9.36, 12.47, 12.59, 14.9 μ). The material was triturated with 15 ml. of hot ethyl acetate, and the resulting mixture was allowed to stand overnight. The precipitate (C) weighed 0.0298 g. and was shown by infrared spectra and t.l.c. comparisons to be entirely the naphthalenedicarboxylic acid (XXXIII). Concentration of the ethyl acetate mother liquor gave precipitate D (0.0134 g.) which was shown by t.l.c. comparison with an equal amount (10 mg.) of phthalic acid (XXXIV) to be a 50:50 mixture of XXXIII and XXXIV; this was verified by infrared spectra comparisons which showed the presence of both acids. The ethyl acetate filtrate was evaporated to dryness, and the residue (0.0891 g.) was crystallized from water, giving 0.0150 g. of precipitate E, which was shown by its infrared spectrum to be 2,3-naphthalenedicarboxylic acid (XXXIII). Evaporation of the water mother liquor and trituration of the residue with chloroform gave 0.0701 g. of precipitate F, which was shown by its infrared spectrum to be phthalic acid. Thus, the total yield of phthalic acid (XXXIV) was 0.0768 g. (0.46 mmole or 9% yield based on anthracene reacting) and the infrared spectrum was identical with that of known sample; crude m.p. 212–225° dec., recrystallization (aqueous ethanol) m.p. 242–243° dec.[25]

The original chloroform mother liquor was shown by infrared spectra and t.l.c. comparisons to contain no more phthalic acid (XXXIV) or 2,3-naphthalenedicarboxylic acid (XXXIII). There was, however, at least one other acid present, which could not be obtained pure enough for identification. This was also true with the methylene chloride reaction mixtures (expt. 10, 12–14), although the acids in the two solvent types did not appear to be the same.

Work-up procedure D was the same as A except that the oxidizing solution consisted of 2 ml. of 30% hydrogen peroxide and 10 ml. of 90% formic acid (for 10 mmoles of anthracene), and the anthraquinone (XI) was filtered from the cooled oxidation mixture.

Work-Up Procedure E.—Anthraquinone (XI) was filtered from the reaction mixture, after which 10 ml. of 30% hydrogen peroxide and 5 ml. of 90% formic acid (per 10 mmoles of I) were added to the filtrate, and the resulting solution was refluxed from 2–8 hr. Anthraquinone was again filtered off, and the filtrate was evaporated to dryness. The residue was treated with 10% sodium hydroxide solution, and anthraquinone was filtered off. The crude anthraquinone melted at 264–286°; it was recrystallized from acetic acid, m.p. 285–286°, and identified by mixture melting point. Phthalic acid (XXXIV) was obtained from the alkaline filtrate as in procedure A.

With **work-up procedure F,** the anthraquinone (XI) was filtered directly from the *t*-butyl alcohol–water ozonation mixture.

Reductive Work-Up to Give Anthrahydroquinone (IX ⇄ X). Ratio of Molecular Oxygen Released to Anthraquinone (XI) Produced Directly. A. Anthrahydroquinone Diacetate (XIII).—The ozonation was carried out as usual with 5 mmoles of anthracene and 10 mmoles of ozone (from an ozone–oxygen stream) in 70 ml. of 90% acetic acid. The reaction mixture was cooled in an ice bath and reduced with sodium iodide. The liberated iodine was reduced with standard sodium thiosulfate; 0.0052 g.-atom of active oxygen was indicated. The precipitate in the reaction mixture was filtered off, dissolved in carbon tetrachloride, and chromatographed as in procedure B, yielding 0.47 g. (2.26 mmoles, 45% yield) of anthraquinone (XI). Based on the molecular oxygen yield in expt. 20 (Table I), the ratio of molecular oxygen to anthraquinone directly produced was 3.2. The filtrate was diluted with 800 ml. of cold water, whereupon 0.21 g. (20% yield) of crude anthrahydroquinone (IX ⇄ X) precipitated. The material gave a transient deep red color with sodium hydroxide solution. A solution of the material and 2 g. of anhydrous sodium acetate in 10 ml. of acetic anhydride was heated at 100° in a nitrogen atmosphere for 2 hr. The solution then was cooled and poured into ice–water, whereupon a pale yellow solid precipitated. The material was washed and dried (0.2 g., m.p. 270–271°) and shown to be anthrahydroquinone diacetate (XIII) by a mixture melting point and comparison of infrared spectra with an authentic sample, prepared by reduction of anthraquinone with zinc dust in acetic anhydride–sodium acetate solution.[26] Similar iodide reductions of nonprotolytic solvent ozonation mixtures gave no XIII. Anthraquinone (XI) treated with acetic anhydride–sodium acetate in the absence of zinc dust was recovered unchanged in 98% yield.

B. Ozonation with Ozone–Nitrogen.—Five millimoles (0.89 g.) of anthracene in 70 ml. of 90% acetic acid solution was ozonized with 5 mmoles of ozone from ozone–nitrogen[7,8] by the procedure described earlier. From the curve obtained with the oxygen analyzer it was determined that 2.6 mmoles of oxygen were evolved. The reductive work-up of the preceding experiment showed 0.0022 g.-atom of active oxygen and gave 0.42 g. (2.4 mmoles) of anthracene and 0.164 g. (0.79 mmoles, 30% yield based on anthracene reacting) of anthraquinone (XI). The ratio of molecular oxygen to anthraquinone was thus 3.3. The filtrate containing anthrahydroquinone (IX ⇄ X) was diluted with water and oxidized with hydrogen peroxide, giving 0.145 g. (0.7 mmole) of anthraquinone. The total anthraquinone yield (m.p. 282–283°) was low (57%), apparently owing to losses in converting anthrahydroquinone to anthraquinone.

C. Anthraquinone (XI) Precipitating Directly.—A solution of 5 mmoles of anthracene in 100 ml. of 90% acetic acid was ozonized with 2.4 mmoles of ozone from an ozone–oxygen mixture,

(24) Prepared according to J. G. Kirchner, J. M. Miller, and G. J. Keller, *Anal. Chem.*, **23**, 423 (1951).

(25) M. Freund and K. Fleischer, *Ann.*, **399**, 213 (1913).

(26) C. Liebermann, *Ber.*, **21**, 1172 (1888).

and the precipitated anthraquinone was filtered off; yield 0.41 g. (39%), m.p. 282–284°.

D. Alkaline Decomposition of Peroxidic Intermediate (VIII).—In another experiment the entire acetic acid ozonation reaction mixture was poured into 1500 ml. of water and the mixture of solids was removed by filtration and washed with dilute potassium hydroxide solution. A 71% yield of crude anthraquinone was obtained; it was recrystallized from acetic acid, m.p. 283–284°.

Miscellaneous Ozonations of Anthracene. A. With Catalytic Quantities of Ozone in Acetic Acid.—The usual volume of oxygen–ozone (but containing only 0.2% ozone) was passed through 10 mmoles of anthracene (I) in acetic acid solution. A total of 2 mmoles of ozone reacted and an 86% recovery of anthracene was made.

B. Anthraquinone Produced Directly in Nonprotolytic Solvents.—A solution of anthracene in methylene chloride was ozonized with 2.5 mole-equivalents of ozone in an oxygen mixture. The precipitated "ozonides" were filtered off and the filtrate was evaporated under reduced pressure at room temperature (rotar). The residue (0.82 g. from 0.89 g. of anthracene) was shown by infrared spectra comparison to consist of approximately 40% anthraquinone (XI, carbonyl peak at 5.98 μ). Some unidentified carboxylic acids were also present, none of which were XXXIV, XXXIII, or phthalaldehydic acid (XXX).

C. Ozonation with Large Excess of Ozone in Methylene Chloride.—Methylene chloride (300 ml.) was saturated with ozone at −78°. While the solution was kept saturated by the passage of more ozone–oxygen, a solution of 3 mmoles of anthracene in 60 ml. of methylene chloride was added dropwise to the ozonation mixture. The reaction mixture was worked up by procedure B. The anthraquinone yield was 18%.

D. Overozonation in Acetic Acid Solution.—More than ten mole-equivalents of ozone was passed through an acetic acid–anthracene ozonolysis mixture. After the reaction of 2.6 mole-equivalents of ozone, ozone absorption was very slow. The reaction mixture was worked up by procedure E, giving 38% crude or 35% pure (m.p. 285–286°) anthraquinone (XI), and 43% crude or 39% pure (m.p. 206–208°) phthalic acid (XXXIV). Most of the anthraquinone (30% yield) precipitated during the ozonation.

E. Test for Hydrogen in Exit Gases.—The ozonolysis was carried out as usual with ozone–oxygen in 90% acetic acid solution. The exit gases, after passing through the iodide trap, were led through a drying tower and into a sample gas collector. A sample taken after about 0.6 mole-equivalent of ozone had reacted was shown by its mass spectrum to contain no molecular hydrogen. This shows that the 1.5–2.0-mole ratio of molecular oxygen to anthraquinone was not due to loss of oxygen and hydrogen from XV.

F. Dianthrone (XXXV) from Ozonation of I in Glacial Acetic Acid.—The ozonation was carried out as usual with 10 mmoles of ozone in ozone–nitrogen and 10 mmoles of anthracene (I) in glacial acetic acid. Work-up was by procedure B, except that heat (steam bath) was used to evaporate the ozonation mixture under reduced pressure. From the petroleum ether eluate a 4-mmole recovery of anthracene was obtained. From the methylene chloride eluate pure anthraquinone (XI) was first obtained, after which a mixture shown by infrared spectra comparisons to be approximately 80% dianthrone[27] (XXXV, distinctive bands at 6.02, 7.41, 8.50, 12.70, 13.60, and 14.40 μ) and 20% anthraquinone (XI, distinctive bands at 5.98, 7.79, and 12.40 μ) was obtained. This amounted to a 34% yield of anthraquinone and an 8% yield of dianthrone (XXXV) based on the anthracene reacting. In addition, a small amount of an unknown compound was obtained. Infrared bands at 6.01 and 6.30 μ suggest that a diaryl ketone structure was present. No other characteristic bands for functional groups were present.

Attempted ozonations of anthraquinone (XI) were carried out in methylene chloride at −30° and in 90% acetic acid at 14°, using two mole-equivalents of ozone. Titrations of the iodide trap showed that 86 and 98% of the ozone passed through the reaction mixture unchanged in methylene chloride and acetic acid solvents, respectively. The respective anthraquinone recoveries were 95 and 98%; m.p 282–283°. Identification was by the mixture melting point method

Attempted Oxidation of Anthracene (I) and Anthraquinone (XI) with Alkaline Hydrogen Peroxide.—A mixture of 1 g. of each (I and XI separately) in 20 ml. of 30% hydrogen peroxide and 60 ml. of 2–3% sodium hydroxide solution was heated with stirring over a steam bath for 2 hr., after which the mixture was filtered, and the filtrate was extracted with methylene chloride. The recovery of each (I or XI) was 97–99%; anthracene (I) m.p. 212–213°, anthraquinone (XI) m.p. 282–283°. Identifications were by the mixture melting point method.

Attempted Ozonation of Glacial Acetic Acid.—An ozone–nitrogen stream containing 4.44 mmoles of ozone was passed through glacial acetic acid at 16°. The exit gases passed through the iodide trap and into the oxygen analyzer.[8] Titration of the iodide trap with thiosulfate showed that 4.5 mmoles of ozone had passed through it, and the oxygen analyzer indicated that 4.0 mmoles of oxygen was produced, which is within experimental error.[8] An iodide test on the acetic acid showed only a trace of peroxide.

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(27) E. Barnett and M. Matthews, *J. Chem. Soc.*, 380 (1928).

Ozonation of 9,10-Dihaloanthracenes

PER KOLSAKER, PHILIP S. BAILEY, FRANK DOBINSON, AND BALDEV KUMAR

Department of Chemistry, The University of Texas, Austin, Texas 78712

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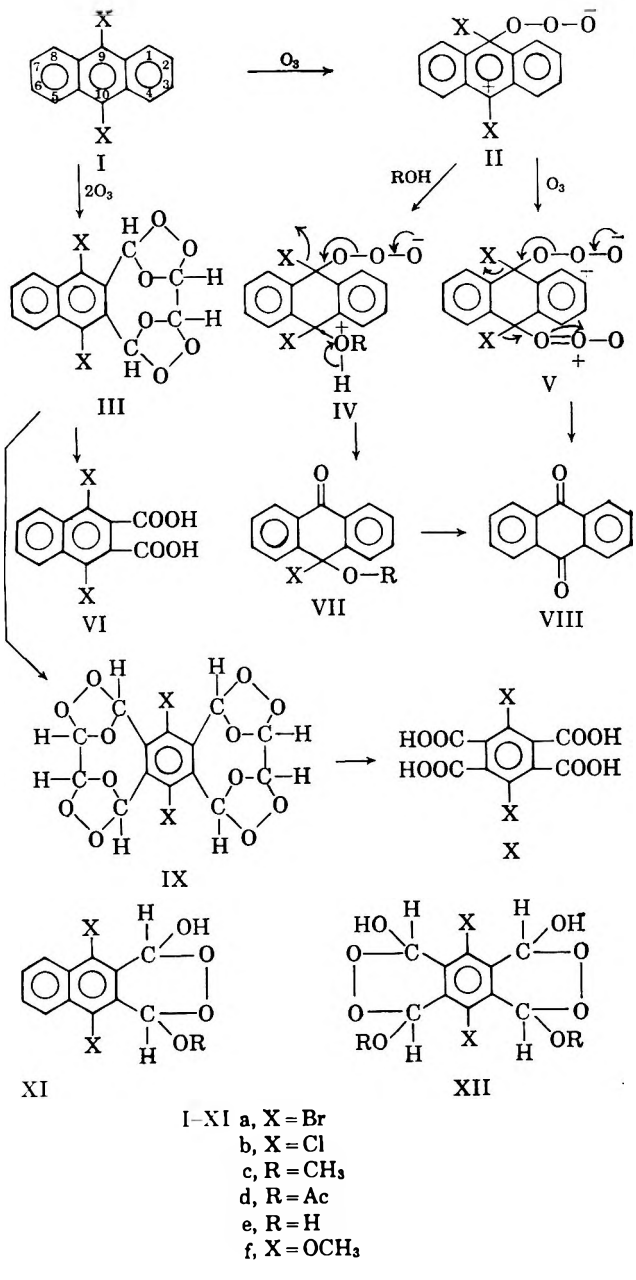
Ozonation of 9,10-dibromoanthracene gave anthraquinone, 1,4-dibromo-2,3-naphthalenedicarboxylic acid, and 3,6-dibromo-1,2,4,5-benzenetetracarboxylic acid (dibromopyromellitic acid). Approximately 2 moles of molecular oxygen was evolved per mole of anthraquinone produced when 2 mole equiv. or less of ozone was used. Bromine was also a product and reacted with ozone when more than 2 mole equiv. was employed. There is a definite, though not so great as originally reported, solvent effect involving the competition between atom and bond attack of ozone. Similar results were obtained with 9,10-dichloroanthracene, except that there was little, if any, solvent effect. Mechanisms are discussed.

A preliminary communication[1] reported the ozonation of 9,10-dibromoanthracene (Ia) to give dibromopyromellitic acid (Xa) as the major product and anthraquinone (VIII) as the minor product from methylene chloride solvent and to give the reverse when the solvent was 90% methylene chloride and 10% methanol. It was considered that this solvent effect of nonprotonic *vs.* protonic solvents determined whether initial bond attack[2] or atom attack[2] of ozone on the polycyclic system predominated. Unfortunately, the

(1) F. Dobinson and P. S. Bailey, *Tetrahedron Letters*, **No. 13**, 14 (1960).

(2) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

SCHEME I



I–XI a, X = Br
b, X = Cl
c, R = CH_3
d, R = Ac
e, R = H
f, X = OCH_3

investigator in the early stages of the work[1] assumed that, because anthraquinone (VIII) came out pure from the methylene chloride reactions at the appropriate point in the work-up procedure, it also came out pure at this point from the methylene chloride–methanol reaction mixtures. Repetition of the early work has proven this to be untrue, and, although there is a definite solvent effect, it is not nearly so great as originally reported.[1] The present paper reports the experimental details of the ozonation of 9,10-dibromo- and 9,10-dichloroanthracenes (I) in several solvents and suggests possible mechanisms for the reactions involved.

In methylene chloride solvent 9,10-dibromoanthracene (Ia) absorbed 2 mole equiv. of ozone nearly quantitatively, after which the rate of absorption decreased and approximately an additional 2 mole equiv. of ozone slowly reacted. The yield of anthraquinone (VIII) was 15–20% regardless of whether ozone–oxygen or ozone–nitrogen[3,4] was used, whether 2 or 4 mole equiv. of ozone reacted, and whether an oxidative or a nonoxidative work-up procedure was used (expt. 1–4, Table I). Thus, anthraquinone (VIII) was produced by ozonation rather than by hydrogen peroxide oxidation. Further, it was found that Ia was partially converted to VIII and Ib by hydrogen peroxide in hydrochloric acid solution, but not by alkaline or neutral hydrogen peroxide. In the 2 mole equiv. of ozone reaction the acid product isolated (from initial bond attack) was 1,4-dibromo-2,3-naphthalenedicarboxylic acid (VIa) in 48% crude or 18% pure yield (expt. 1, Table I). It was not possible to identify the impurities in the crude acid product. From the 4 mole equiv. of ozone reaction the acid product isolated was dibromopyromellitic acid (Xa) in 76% crude or 66% pure yield (expt. 2, Table I). Small amounts of unidentified acids were present in crude Xa.

In the methylene chloride–methanol reactions (expt. 5–8) the ozone absorption was similar, except that it continued well past 4 mole equiv. (expt. 8). This is perhaps due to some ozone attack on methanol. The anthraquinone (VIII) yields from the 2 mole equiv. or less of ozone reactions (expt. 5–7) were considerably higher than those from methylene chloride solvent and did not vary whether ozone–oxygen or ozone–nitrogen[3,4] was used, or whether an oxidative or a nonoxidative work-up procedure was employed (expt. 6 and 7). In contrast to the results in methylene chloride solution, the anthraquinone yields from the methylene chloride–methanol reaction mixtures decreased somewhat as more ozone reacted (expt. 5–8), showing that a precursor to anthraquinone was being destroyed. Anthraquinone itself does not react appreciably under these conditions.[5] No ozone concentration effect, such as was found with anthracene,[5] was observed with the ozonation of Ia in either methylene chloride or methylene chloride–methanol solution. From an exhaustive ozonation of Ia in methylene chloride–methanol solution, the acid product (from initial bond cleavage) was dibromopyromellitic acid (Xa) in 73% crude or 51% pure yield (expt. 8). In glacial and aqueous acetic acid solutions the anthraquinone (VIII) yields were similar (expt. 9, 10) to those from the methylene chloride–methanol reaction mixtures (expt. 5).

It was obvious in all solvents that molecular bromine was a product. In one experiment, with methylene chloride–methanol solvent, approximately 1 mole of bromine per mole of anthraquinone (VIII) produced was found by titration with standard phenol solution.

With ozonations using 2 mole equiv. or less of ozone (expt. 1, 5, 9) approximately 2 moles of molecular oxygen were evolved per mole of anthraquinone (VIII) produced. The molecular oxygen to anthraquinone ratios were 2.6–3.4 in expt. 6 and 10. We believe this is due to the lesser solubility of the starting material (Ia) in the solvents employed and the resulting greater ability of bromine to compete with Ia for the ozone. In expt. 2, where 4 mole equiv. of ozone were employed, the ratio of molecular oxygen to anthraquinone was 6.4–8.5. The large increase is undoubtedly due to the reaction between ozone and molecular bromine which is

(3) G. A. Cook, A. D. Kiffer, C. V. Klumpp, A. H. Malik, and L. A. Spence, *Adran. Chem. Ser.*, **21**, 44 (1959).
(4) P. S. Bailey and A. M. Reader, *Chem. Ind.* (London), 1063 (1961).
(5) P. S. Bailey, P. Kolsaker, B. Sinha, J. B. Ashton, F. Dobinson, and J. E. Batterbee, *J. Org. Chem.*, **29**, 1400 (1964).

TABLE I

OZONATIONS OF 9,10-DIHALOANTHRACENES (I)

Experiment	Compound	Solvent[a]	Temp., °C.	Starting I, mmoles	Reacting I, mmoles	Reacting O_3, mole equiv.[b,c]	O_2 yield, mmoles	Anthraquinone (VIII) yield, mmoles[d]	% yield of VIII[d,f]	O_2-anthraquinone ratio	Acid products,[e,f] %	Work-up procedure[g]
1	Ia	CH_2Cl_2	−30	6.0	6.0	2.0	2.3	0.9–1.2	15–20	1.9–2.6	VIa 48 C 18 P	A
2	Ia	CH_2Cl_2	−30	4.0	4.0	4.1	5.1	0.6–0.8	15–20	6.4–8.5	Xa 76 C 66 P	A
3	Ia	CH_2Cl_2	0	6.0	6.0	3.8[b]	...		15–18	...		A
4	Ia	CH_2Cl_2	−30	3.0	3.0	4.0[b]	...		15	...	...	F
5	Ia	CH_2Cl_2–CH_3OH (9:1)	−30	3.0	2.3	1.2	1.2	0.6–0.7	26–30	1.7–2.0	...	D
6	Ia	CH_2Cl_2–CH_3OH (9:1)	−30	3.0	3.0	2.0	2.1	0.7–0.8	23–27	2.6–3.0	...	D
7	Ia	CH_2Cl_2–CH_3OH (9:1)	−30	3.0	3.0	1.9[b]	...		23–28	...		A
8	Ia	CH_2Cl_2–CH_3OH (9:1)	−30	6.0	6.0	4.7[b]	...		19–22	...	Xa 73 C 51 P	B
9	Ia	gl. HOAc	15	2.5	1.9	1.2	1.2	0.5	26	2.4	...	D
10	Ia	HOAc–HOH (9:1)	20	2.5	1.8	1.2	1.7	0.5	28	3.4	...	D
11	Ib	CH_2Cl_2	−30	4.0	4.0	3.9	3.7	1.1–1.3	28–32	2.8–3.4	Xb 67 C 59 P	C
12	Ib	CH_2Cl_2	0	10.0	10.0	3.4[b]	...		27	...		A
13	Ib	CH_2Cl_2–CH_3OH (9:1)	−30	3.0	2.7	1.5			33–36		...	E
14	Ib	CH_2Cl_2–CH_3OH (9:1)	−30	6.0	6.0	3.6[b]	...		25–27	...	Xb 68 C 51 P	B
15	Ib	HOAc–HOH (9:1)	15	3.4	2.2	0.9	1.4	0.8	36	1.7	...	D

[a] Where mixed solvents are used, the numbers refer to parts by volume of each component in the mixture. [b] All ozonations, except those of expt. 3, 4, 7, 8, 12, and 14, were with ozone–nitrogen mixtures.[3,4] [c] The ozone reacting is listed in moles per mole of starting dihaloanthracene (I). [d] The yields listed are of pure anthraquinone. [e] C stands for crude and P stands for pure. [f] Per cent yields are calculated on bases of reacting I. [g] See Experimental section.

reported to occur according to the following equation,[6] accounting for 4 moles of oxygen per mole of bromine produced, assuming that all of the bromine reacts: $Br_2 + 4O_3 \rightarrow 2BrO_2 + 4O_2$. The rest of the excess oxygen probably comes from decomposition of the bromine oxide according to the following equation[6]: $2BrO_2 \rightarrow Br_2 + 2O_2$.

It seems obvious, therefore, that at least the major reaction producing anthraquinone (VIII) requires 2 moles of ozone and releases 2 moles of molecular oxygen and 1 mole of bromine per mole of anthraquinone produced. We suggest that the initial ozone attack on the central ring of Ia is electrophilic, to give IIa, as was suggested in the case of anthracene.[5] Owing to deactivation of the 9-position of the anthracene ring by the bromo groups of Ia, this reaction does not occur to so great an extent with Ia as it did with anthracene.[5] In methylene chloride (a nonnucleophilic solvent) solution, at least, we believe that, next, IIa is attacked nucleophilically by a second ozone molecule to give Va, which loses a molecule of bromine and two molecules of oxygen to give anthraquinone (VIII). Since halogen rather than hydrogen groups are present in Ia, it is unlikely that reactions similar to those suggested for the major route of anthracene to anthraquinone[5] would occur in the present case. The accepted structure of the ozone molecule suggests that it should be able to attack organic molecules nucleophilically.[2]

The loss of halogen from V should be much easier than the loss of hydrogen from a similar intermediate in the ozonation of anthracene, and, thus, the reaction of V to anthraquinone (VIII) should occur in preference to the rearrangements suggested in the case of anthracene.[5] It is possible, however, that competing rearrangements of this sort account for the impurities in the crude dibromopyromellitic acid (Xa).

We suggest that, in the presence of methanol, acetic acid, or water (expt. 5–10), IIa is attacked by the nucleophilic solvent to give IVa rather than Va. Loss of hydrogen bromide and molecular oxygen would give VIIa. In one experiment the methylene chloride–methanol reaction mixture was poured into methanolic sodium methoxide solution. The anthraquinone obtained was contaminated with colorless crystals which decomposed to anthraquinone either on standing or during recrystallization; this substance may have been VIIcf. It was too unstable to purify. Hydrolysis during work-up of VIIac or VIIad to VIIae, followed by loss of hydrogen halide, would give anthraquinone (VIII). The bromine found in the reaction mixture would then be produced by the reaction of hydrogen bromide with a second mole equiv. of ozone to give bromine and oxygen. As said earlier, the decreasing yields of anthraquinone as more ozone is employed in expt. 5–8 must be due to the partial destruction of an intermediate to anthraquinone (VIII). This intermediate is perhaps VIIac, which would undergo ring attack by ozone much more easily than would anthraquinone.

Although the solvent effect is not great, it appears to be definite and to involve competition between initial atom and initial bond attack, since anthraquinone can come only from atom attack and the major acidic products (VIa and Xa) can come only from bond attack. If one bases the degree of solvent effect on the quinone yields obtained, it amounts to about 10% (*i.e.*, 15–20% VIII from methylene chloride, expt. 1, *vs.* 26–30% VIII from nucleophilic solvents, expt. 5, 9, 10). It is more accurate to compare these experiments than to compare expt. 1 or 2 with 6, 7, and 8, since it has been shown that quinone yields decrease in methylene chloride–methanol solvent (and probably other nucleophilic solvents) as the amount of ozone reacting increases, whereas this is not true in the case of methylene chloride solvent. One arrives at a figure of 15% for the solvent effect if it is assumed that the impurities in the acid fractions are produced by atom attack, as was true with anthracene,[5] and yields of pure Xa in the two solvent types are compared (expt. 2, 8).

Since methylene chloride–methanol is as good a solvent for quinone formation as is 90% acetic acid, which was not true in the case of anthracene,[5] we believe that the nucleophilicity of the solvent is more important than its protonic character and that the solvent effect is caused by the stabilization of intermediate IIa (and the transition state leading to it) to give IVa, thus lowering the activation energy for atom attack and allowing it to compete more favorably with bond attack.

The ozonation results with 9,10-dichloroanthracene (Ib, expt. 11–15) were similar to those with Ia, except that the yields of anthraquinone (VIII) were higher than those from Ia (*cf.* expt. 2 with expt. 11, and expt. 5 and 10 with expt. 13 and 15) and the solvent effect, if any, was smaller (*cf.* expt. 11, 13). It is assumed that, since the quinone (VIII) yield did not decrease with increasing amount of ozone during ozonation of Ia in methylene chloride, the same is true with Ib. The higher yields of anthraquinone (VIII) from Ib than from Ia are logical on the basis that the carbonium ion initially produced (IIb and the transition state leading to it) would be stabilized to a greater extent by the adjacent chloro group than would be IIa by the adjacent bromo group, thus causing ozone attack at position 9 to be greater with Ib than Ia. This factor would not be as important when solvent stabilization of II (*i.e.*, IV) can occur; thus the solvent effect is not so great.

Bond attack[2] with the dihaloanthracenes (I) differs from that with anthracene[5] in that it occurs at least predominantly, first at one outer ring and then at the other outer ring, owing to the deactivating effect of the halogen groups on the central ring. By analogy to results with naphthalene,[7] the peroxidic ozonolysis products are probably III and IX from nonprotonic solvents and XI and XII from protonic solvents. Oxidation of III and XI would give VI, and oxidation of IX and XII would give X.

Experimental

The ozonation equipment and techniques are described in earlier publications.[4,5,8] Starting materials were obtained commercially and were purified by recrystallization or by chromatography to sharp, constant melting points. Solvents were pure and anhydrous, unless otherwise stated.

Ozonation of 9,10-Dihaloanthracenes (I).—A finely divided suspension of the dihaloanthracene (I) in the solvent (25–40 ml. per mmole of I) was ozonized either with ozone–oxygen (about

(6)(a) M. Schmeisser and K. Joergen, *Angew. Chem.*, **71**, 523 (1959); (b) R. Schwarz and M. Schmeisser, *Ber.*, **70**, 1163 (1937).

(7) P. S. Bailey, S. S. Bath, F. Dobinson, F. J. Garcia-Sharp, and C. D. Johnson *J. Org. Chem.*, **29**, 697 (1964).

(8) (a) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956); (b) P. S. Bailey and S. S. Bath, *ibid.*, **79**, 3120 (1957).

4% ozone by weight) or ozone–nitrogen[3,4] mixtures. The ozone absorption was very nearly quantitative until 2 mole equiv. was absorbed, during which time the starting material slowly dissolved and reacted. With methylene chloride solvent a white precipitate formed during the ozonation. It proved best either to shake the reaction vessel intermittently or stir it magnetically[5] during the ozonation. Ozone absorption was much slower after 2 mole equiv. The iodide trap was titrated with standard thiosulfate, and the mole equivalents of ozone listed as reacting in Table I are the amounts obtained by subtracting that which reacted in the trap from the total amount employed. When ozone–nitrogen mixtures were used, the molecular oxygen yield was usually obtained, by procedures described previously.[4,5] Several different work-up procedures were employed. These are described below and the results are listed in Table I.

Procedure A. Oxidative Work-Up.—The reaction mixture was poured into 6% hydrogen peroxide solution (30–35 ml. per mmole of I) and the resulting mixture was refluxed for 1 hr., after which the organic solvent was removed by distillation, and refluxing was continued until the reaction mixture was no longer peroxidic (about 45 hr.). The resulting mixture was made alkaline with solid potassium hydroxide and the yellow precipitate which remained was extracted carefully with methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate and evaporated, giving crude anthraquinone, m.p. 278–282°; recrystallized from ethanol, m.p. 285–286°; identifications were by comparison of infrared spectra with that of an authentic sample. The aqueous alkaline solution was acidified with hydrochloric acid. The 1,4-dibromo-2,3-naphthalenedicarboxylic acid (VIa) immediately precipitated. The dihalopyromellitic acids (X) remained in solution. The solution was saturated with sodium chloride and exhaustively extracted with ether. Evaporation of the ether gave crude X. Yields of pure X were calculated on the basis of the tetramethyl esters, which were obtained by refluxing methanol solutions (50 ml.) of X for 30 min., cooling, and adding ether (50 ml.) and excess ethereal diazomethane. The crude esters from ozonations in methylene chloride were shown by comparisons of infrared spectra with those of pure samples (ester band at 5.72 μ) to be 97–98% pure; those from ozonations in methylene chloride–methanol solutions were shown to be 80–83% pure. Yields of pure esters (and thus pure X) were calculated on this basis and are given in Table I.

Crude **1,4-dibromo-2,3-naphthalenedicarboxylic acid (VIa)** had m.p. 220–235°; recrystallized from ethanol (charcoal), m.p. 246–247°.

Anal. Calcd. for $C_{12}H_6Br_2O_4$: C, 38.5; H, 1.6; Br, 42.7. Found: C, 38.6; H, 1.7; Br, 43.2.

The material gave a positive Beilstein test for halogen and a positive test for *o*-dicarboxylic acids.[9]

Crude **3,6-dibromo-1,2,4,5-benzenetetracarboxylic acid (or dibromopyromellitic acid, Xa)** melted at 365–372°. The pure acid, recrystallized from 5 *N* hydrochloric acid, melted too high to obtain an accurate melting point.

Anal. Calcd. for $C_{10}H_4Br_2O_8$: C, 29.2; H, 1.0; Br, 38.8. Found: C, 29.3; H, 1.2; Br, 38.9.

The crude **tetramethyl ester** of Xa was purified by recrystallization from methanol, m.p. 195–196°.[10]

Anal. Calcd. for $C_{14}H_{12}Br_2O_8$: C, 35.9; H, 2.6; Br, 34.1; OCH_3, 26.5. Found: C, 36.0; H, 2.6; Br, 32.8; OCH_3, 26.2.

The acid (Xa) was further identified by catalytic dehalogenation (Pd–$BaSO_4$) to give pyromellitic acid, m.p. 270–271°. Identification was by a mixture melting point with an authentic sample.[11]

Procedure B. Oxidative Work-Up.—This procedure was exactly the same as procedure A, except that after the ozonation the reaction mixture was evaporated and the residue was taken up in 50 ml. of methanol, 30 ml. of 30% hydrogen peroxide, and 70 ml. of 5% aqueous sodium hydroxide solution. The resulting mixture was stirred for 36 hr., after which time active oxygen was no longer present.

3,6-Dichloro-1,2,4,5-benzenetetracarboxylic acid (or dichloropyromellitic acid, Xb) melted too high to obtain an accurate melting point. It was recrystallized from 5 *N* hydrochloric acid.

Anal. Calcd. for $C_{10}H_2Cl_2O_8$: C, 37.2; H, 1.2; Cl, 22.0. Found: C, 36.9; H, 1.5; Cl, 21.5.

The pure **tetramethyl ester of Xb** (recrystallized from methanol) melted at 176–177°.[12]

Anal. Calcd. for $C_{14}H_{12}Cl_2O_8$: C, 44.3; H, 3.2; Cl, 18.7; OCH_3, 32.7. Found: C, 44.6; H, 3.2; Cl, 18.7; OCH_3, 32.7.

Procedure C. Oxidative Work-Up.—This procedure was exactly the same as procedure A, except that the oxidizing mixture was 100 ml. of 4% aqueous sodium hydroxide and 30 ml. of 30% hydrogen peroxide, and it was necessary to reflux the mixture for only 3 hr. to destroy all active oxygen.

Procedure D. Nonoxidative Work-Up.—After ozonation, 5–10 ml. of water was added to the reaction mixture, and the resulting mixture was stirred at room temperature (27°) until no more active oxygen was present (2–3 hr.). The reaction mixture was evaporated to dryness (rotar) and the residue was dissolved in 75–150 ml. of carbon tetrachloride and chromatographed on acid-washed alumina (Merck). Elution with 400–800 ml. of petroleum ether (b.p. 40–60°) gave unchanged dihaloanthracene (Xa, m.p. 218–221°; Xb, m.p. 209–211°). Elution with 300–600 ml. of methylene chloride gave the fraction from which pure anthraquinone (VIII) was obtained by recrystallization from ethanol.

Procedure E. Nonoxidative Work-Up.—This procedure was exactly the same as procedure D, except that after the ozonation, the reaction mixture was evaporated (rotar), the residue was taken up in carbon tetrachloride, and the carbon tetrachloride solution was refluxed until it was no longer peroxidic, and then was chromatographed.

Procedure F. Nonoxidative Work-Up.—The precipitated ozonide was filtered off and the filtrate was evaporated, giving anthraquinone (VIII) melting at 280–282°.

Determination of Bromine in Ozonation Mixture.—A solution of 3 mmoles of 9,10-dibromoanthracene (Ia) in 90 ml. of methylene chloride and 10 ml. of methanol was ozonized with 2 mole equiv. of ozone from ozone–oxygen. The solution was titrated with standard phenol solution (American Hospital Supply Corp., Evanston, Ill.); 0.26 mmole of phenol reacted, indicating 0.78 mmole of bromine. On the basis of the anthraquinone yield in expt. 6 and 7 (Table I), this represents approximately a quantitative yield of the expected bromine.

Treatment of 9,10-Dibromoanthracene (Ia) with Hydrochloric Acid and Hydrogen Peroxide.—A mixture of 0.266 g. of 9,10-dibromoanthracene (Ia), 90 ml. of methylene chloride, 10 ml. of methanol, 5 drops of concentrated hydrochloric acid, and 5 drops of 30% hydrogen peroxide was heated on the steam bath for 6 hr. Evaporation of the reaction mixture gave material, the infrared spectrum of which indicated it to be a mixture of 9,10-dibromomoanthracene (Ia), 9,10-dichloroanthracene (Ib), and anthraquinone (VIII). 9,10-Dibromoanthracene was recovered unchanged after treatment with alkaline or neutral hydrogen peroxide.

Acknowledgment.—This work was made possible by grants from the Robert A. Welch Foundation, the American Chemical Society Petroleum Research Fund, and the National Science Foundation. We are also grateful for fellowships (to P. K.) from the Norwegian Research Council for Sciences and Humanities and the University of Oslo, Norway. One of the experiments recorded in this paper was performed by Mr. Terry D. Copeland.

(9) F. Feigl, "Spot Tests in Organic Analysis," Engl. Ed., Elsevier Publishing Co., New York, N. Y., 1960, p. 256.

(10) H. Hopff, P. Doswald, and B. K. Manukian [*Helv. Chim. Acta*, **44**, 1231 (1961)] report 190–191°.

(11) E. Philippi and R. Thelan, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 551.

(12) Previously recorded melting point was 176–177° (ref. 10).

Synthesis of Fluorinated 1,2-Benzanthracenes[1]

MELVIN S. NEWMAN AND SHOSHANA BLUM[2]

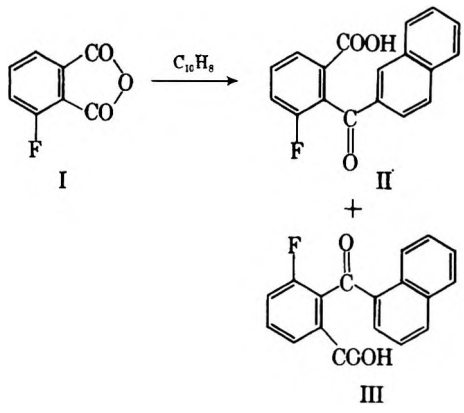
Evans Chemistry Laboratory, The Ohio State University, Columbus 10, Ohio

Received December 16, 1963

A compound previously believed to be 8-fluoro-10-methyl-1,2-benzanthracene[3] has been shown to be 5-fluoro-9-methyl-1,2-benzanthracene. The syntheses of 5-fluoro-10-methyl-1,2-benzanthracene, 5-fluoro-9,10-dimethyl-1,2-benzanthracene, and 8-fluoro-9,10-dimethyl-1,2-benzanthracene are described.

In a previous publication[3] the synthesis of 8-fluoro-10-methyl-1,2-benzanthracene was described. We now show that an error was made and that the compound believed to be 8-fluoro-10-methyl-1,2-benzanthracene was really 5-fluoro-9-methyl-1,2-benzanthracene.[4] In this paper we also describe the synthesis of 5-fluoro-10-methyl-1,2-benzanthracene, 5-fluoro-9,10-dimethyl-1,2-benzanthracene, and 8-fluoro-9,10-dimethyl-1,2-benzanthracene. This synthetic work continues the program outlined previously.[5]

The error can be traced to a mistake in identification of the ketone formed by decarboxylation of a keto acid formed by the condensation of 3-fluorophthalic anhydride (I) with naphthalene. In the previous paper,[3] it was stated that 3-fluoro-2-(1-naphthoyl)benzoic acid



(III) was the sole product whereas we have shown in the accompanying paper[6] that a mixture of II and III in the ratio 3:1 is formed. We cannot account for the differing results described in the two papers other than to say that, in the hands of two subsequent workers, the results reported in the earlier paper[3] could not be duplicated. In addition, the error in proof of structure of the supposed acid III stems from the fact that the Friedel–Crafts condensation of *o*-fluorobenzoyl chloride with naphthalene at about 90° in *o*-dichlorobenzene gives mainly 2-fluorophenyl 2-naphthyl ketone, whereas it was assumed[3] that this condensation gave 2-fluorophenyl 1-naphthyl ketone. Hence the decarboxylation product was said to be the latter ketone whereas it was the former.[6] Accordingly, the keto acid used previously[3] was mainly II and not III.

The structure of other compounds described[3] must accordingly be revised. Compound III[3] was 4-fluoro-3-(2-naphthyl)phthalide, compound IV[6] was 3-fluoro-2-(2-naphthylmethyl)benzoic acid, and compound V[3] was 5-fluoro-9-methyl-1,2-benzanthracene.[4,7]

The syntheses of 5-fluoro-10-methyl-1,2-benzanthracene (VIII) and 5-fluoro-9,10-dimethyl-1,2-benzanthracene (IX) from II and 8-fluoro-9,10-dimethyl-1,2-benzanthracene (XIII) from III were carried out as shown in Chart I. A point of interest is the high yield (96%) and stability of anthrone VI, formed from V on cyclization with anhydrous hydrogen fluoride. In our experience anthrones in the 1,2-benzanthracene series have never been obtained pure in such a yield.[8] Unfortunately, the yield of IX from treatment of VI with methyllithium was low (12%) so that the alternate route to IX (V to VII to IX) was preferable.

Previously, the pyrolysis of 1-(2-methyl-3-fluorobenzoyl)naphthalene at 400° to give 1,2-benzanthracene was reported.[3] Repetition of this work at about 365–385° afforded 5-fluoro-1,2-benzanthracene, although the product was contaminated with an isomeric compound which proved difficult to separate. Professor Bergmann supplied us with a sample of pure 5-fluoro-1,2-benzanthracene, the synthesis of which is described in the paper referred to in ref. 4 of this paper.

Experimental[9]

4-Fluoro-3-methyl-3-(2-naphthyl)phthalide (IV) and 4-Fluoro-3-methyl-3-(1-naphthyl)phthalide (X).—Treatment of a solution of 10.5 g. of II in 300 ml. of benzene with a solution of the Grignard reagent prepared from 1.8 g. of magnesium and excess

(1) This work was supported by a grant from the National Institutes of Health, Bethesda, Md.

(2) Postdoctoral Fellow, 1963.

(3) M. S. Newman and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961).

(4) After our error was discovered (by S. Blum) we received a letter from Professor E. D. Bergmann, Hebrew University, Jerusalem, stating that he had synthesized 5-fluoro-9-methyl-1,2-benzanthracene and had submitted an article to the *Bulletin de la societe chimique de France* describing its synthesis [see E. D. Bergmann and M. Bentov, *Bull. soc. chim. France*, 963 (1963)]. We then obtained a sample of this compound from Dr. Bergmann and showed that it was identical with our compound, supposedly the 8-fluoro-10-methyl derivative. We were then certain that the compound we had previously described as 8-fluoro-10-methyl-1,2-benzanthracene was actually 5-fluoro-9-methyl-1,2-benzanthracene. During this correspondence we learned that the synthesis of 8-fluoro-10-methyl-1,2-benzanthracene was being carried out by Professor Bergmann. We discontinued our efforts to prepare this compound as he very kindly consented to supply us with our needs.

(5) M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

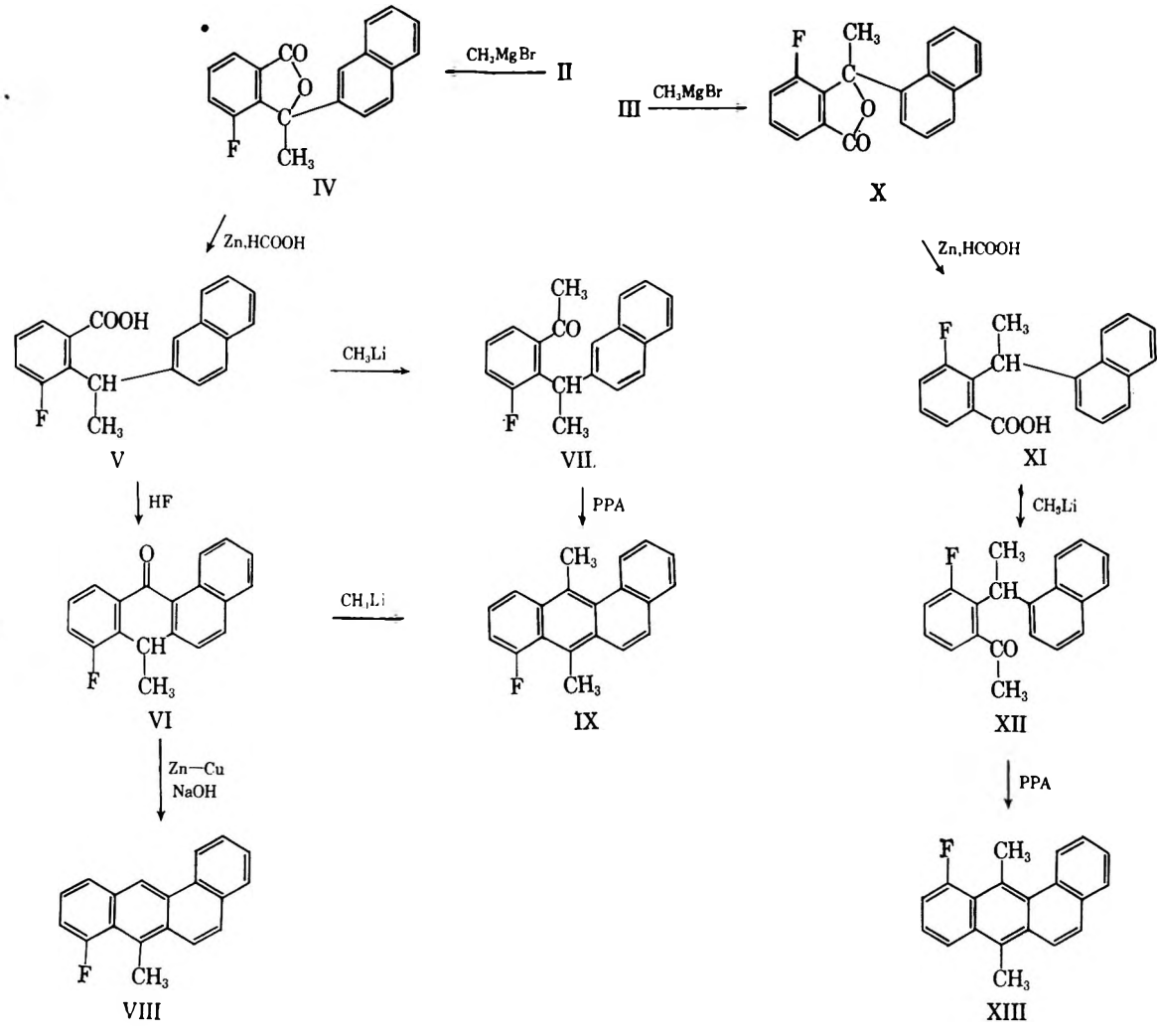
(6) M. S. Newman and S. Blum, *ibid.*, **29**, 1416 (1964).

(7) In a recent letter, Dr. James A. Miller, McArdle Memorial Laboratory for Cancer Research, University of Wisconsin, states that 5-fluoro-9-methyl-1,2-benzanthracene is rather active as a carcinogen.

(8) See, for example, M. S. Newman and S. Seshadri, *J. Org. Chem.*, **27**, 76 (1962), and ref. 3 and 10 therein; see also L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **61**, 1272 (1939), and references therein for a discussion of earlier results.

(9) All melting points are uncorrected. The term "worked up in the usual manner" means that a solution of the products in an organic solvent, usually ether–benzene, was washed with acid and/or alkali as required and saturated sodium chloride solution, and then was dried by shaking with, or filtration through, anhydrous magnesium sulfate. The solvents then were removed and the residue was purified by crystallization, distillation, or chromatography.

CHART I



methyl bromide in 80 ml. of ether essentially as described[10] afforded 7.9 g. (76%) of crude IV, m.p. 110–115°, suitable for the next step. The analytical sample of IV, obtained with little loss by crystallization from methanol, melted at 128–129°. Similarly 11.3 g. (71%) of crude X, m.p. 175–178°, was obtained from 16.0 g. of III. The analytical sample, obtained with little loss by crystallization from methanol, melted at 183–184°.

Anal. Calcd. for $C_{19}H_{13}FO_2$: C, 78.0; H, 4.4; F, 6.5. Found[11] for IV: C, 77.9; H, 4.5; F, 6.7. Found for X: C, 77.9; H, 4.6; F, 6.6.

3-Fluoro-2-(α-2-naphthylethyl)benzoic Acid (V) and 3-Fluoro-2-(α-1-naphthylethyl)benzoic Acid (XI).—A mixture of 7.0 g. of crude IV, 50 g. of zinc dust, 500 ml. of formic acid (98%), and 50 ml. of water was stirred at reflux for 20 hr.[12] After appropriate work-up there was obtained 6.7 g. (94%) of V, m.p. 157–159°, as colorless crystals. Similarly XI, m.p. 172–173° (analytical sample), was obtained in 95% yield after crystallization from toluene. The analytical sample of V, m.p. 160–161°, was obtained by crystallization from toluene–cyclohexane.

Anal. Calcd. for $C_{19}H_{15}FO_2$: C, 77.5; H, 5.1; F, 6.5. Found for V: C, 77.4; H, 5.1; F, 6.6. Found for XI: C, 77.8; H, 5.3; F, 6.8.

5-Fluoro-9,10-dihydro-9-keto-10-methyl-1,2-benzanthracene (VI).—To 7.0 g. of powdered V in a polyethylene bottle was added 200 ml. of anhydrous hydrogen fluoride. After the hydrogen fluoride had evaporated, a conventional work-up, including extraction with benzene and recrystallization from cyclohexane, afforded 6.3 g. (96%) of VI as pale yellow elongated crystals, m.p. 108.5–109.5° (infrared band at 6.05 μ, no band in the OH region).

Anal. Calcd. for $C_{19}H_{13}FO$: C, 82.6; H, 4.7; F, 6.9. Found: C, 82.4; H, 4.7; F, 7.0.

5-Fluoro-10-methyl-1,2-benzanthracene (VIII).—A mixture of 1.5 g. of VI, 3 g. of zinc dust activated with copper sulfate, 12 g. of sodium hydroxide, 15 ml. of toluene, and 150 ml. of water was held at reflux for 24 hr. A conventional work-up, including careful extraction of the zinc with boiling benzene followed by treatment of the benzene extracts with hydrochloric acid yielded a crude product which was purified by chromatography over alumina [using benzene-petroleum ether, b.p. 65–70° (Skellysolve B), in a 1:1 ratio as eluent] to yield 1.03 g. (73%) of pure VIII, m.p. 140–141°, on crystallization from benzene–ethanol.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found[b]: C, 87.8; H, 5.1; F, 7.5.

The 2,4,7-trinitrofluorenone (TNF) derivative, m.p. 212–213°, was prepared in, and recrystallized from, benzene.

Anal. Calcd. for $C_{32}H_{18}FN_3O_7$: C, 66.8; H, 3.1; F, 3.3; N, 7.3. Found[a]: C, 67.0; H, 3.3; F, 3.5; N, 7.1.

3-Fluoro-2-(α-2-naphthylethyl)acetophenone (VII) and 3-Fluoro-2-(α-1-naphthylethyl)acetophenone (XII).—A solution of methyllithium prepared from 6.5 g. of methyl iodide and 0.7 g. of lithium in 100 ml. of ether was added rapidly under nitrogen to a stirred solution of 3.6 g. of V in 50 ml. of ether. After stirring at room temperature for 30 min. a conventional work-up yielded 2.3 g. (64%) of pure VII, after crystallization from ethanol, as colorless crystals, m.p. 89–90° (infrared band at 5.9

(10) L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **58**, 2376 (1936).

(11) Analyses were by Galbraith Analytical Laboratories, Knoxville, Tenn., except a few marked [b], by A. Bernhardt, Max Planck Institute, Mulheim, Germany, and [a], by Spang Laboratory, Ann Arbor, Mich.

(12) Compare R. L. Letsinger, J. D. Jamison, and A. L. Hussey, *J. Org. Chem.*, **26**, 97 (1961); see also M. S. Newman and S. Seshadri, *ibid.*, **27**, 76 (1962), and M. S. Newman and K. Naiki, *ibid.*, **27**, 863 (1962).

μ). Similarly XII, m.p. 114–116°, was obtained in 80% yield. Recrystallization of XII from methanol afforded the analytical sample, m.p. 117–118° (infrared band at 5.92 μ). Small amounts of the acids V and XI, were received from alkaline extracts of the reaction mixtures.

Anal. Calcd. for $C_{20}H_{17}FO$: C, 82.2; H, 5.9; F, 6.5. Found for VII: C, 81.9; H, 6.0; F, 6.5. Found for XII: C, 82.2; H, 5.9; F, 6.4.

5-Fluoro-9,10-dimethyl-1,2-benzanthracene (IX) and 8-Fluoro-9,10-dimethyl-1,2-benzanthracene (XIII).—A solution of 1.5 g. of VI in 50 ml. of benzene was treated with a solution of methyllithium made from 1.0 g. of lithium and 10 g. of methyl iodide in 150 ml. of ether. After refluxing overnight the mixture was worked up to yield crude IX which purified by chromatography over alumina (as above) to yield 174 mg. (12%) of IX, m.p. 130–131°. Alternately, in the best of several runs, 2.2 g. of VII was stirred into 50 g. of polyphosphoric acid[13] (PPA) at 85°. After 40 min. the mixture was poured on ice and left until the dark color disappeared (2–3 hr.). The yellow solid was purified by chromatography over alumina and recrystallization from ethanol to yield 0.86 g. (41%) of pure IX, m.p. 130–131°, as pale yellow plates.

In a similar way (at 80° for 40 min.), 4.2, g. of XII afforded 1.95 g. (50%) of pure XIII, m.p. 61.5–62.5, as pale yellow crystals, b.p. 35–40° on recrystallization from petroleum ether.

Anal. Calcd. for $C_{21}H_{15}F$: C, 87.6; H, 5.5; F, 6.9. Found for IX: C, 87.4; H, 5.5; F, 7.1. Found for XIII: C, 87.5; H, 5.6; F, 6.8.

(13) Compare C. K. Bradsher and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 343 (1957). We thank the Victor Chemical Co., Chicago, Ill., for a generous gift of polyphosphoric acid.

The TNF derivative of IX was prepared in benzene and was recrystallized from acetic acid to yield brown crystals, m.p. 177–178°. The TNF derivative of XIII was prepared in, and recrystallized from, benzene. It formed brown elongated crystals, m.p. 175–176°.

Anal. Calcd. for $C_{33}H_{20}FN_3O_7$: C, 67.3; H, 3.4; F, 3.2; N, 7.1. Found for IX-TNF: C, 67.1; H, 3.3; F, 3.1; N, 7.4. Found for XIII-TNF: C, 67.3; H, 3.5; F, 3.2; N, 7.2.

5-Fluoro-1,2-benzanthracene.—In a typical experiment (repeated several times) 2.0 g. of 1-(2-methyl-3-fluorobenzoyl)-naphthalene, m.p. 49–50° (obtained from the sample of ketone previously reported[3] as a liquid), was heated in a bath from 365 to 385° during 3 hr. Distillation at 3 mm. afforded a crude product which was purified by chromatography over alumina. Colorless needles, m.p. 105–106°, were obtained in about 32% yield. This material, which vapor phase chromatography on a 9 ft. × 0.125 in. Carbowax 20M column showed to be a mixture of two compounds in a ratio of 88:12, gave satisfactory analysis for a fluorobenzanthracene.

Anal. Calcd. for $C_{18}H_{11}F$: C, 87.8; H, 4.5; F, 7.7. Found: C, 87.6; H, 4.7; F, 7.4.

The red TNF derivative, m.p. 223–224°, was obtained by crystallization from benzene.

Anal. Calcd. for $C_{31}H_{16}FN_3O_7$: C, 66.4; H, 2.9; F, 3.4; N, 7.5. Found: C, 66.7; H, 3.2; F, 3.6; N, 7.3.

The melting point of pure 5-fluoro-1,2-benzanthracene[4] is 150°. Our crude material (about 88% pure) could be converted into the pure substance by careful purification. However because of the difficulties involved, this route is not a good one. Our pure compound was identical with the sample supplied by Professor Bergmann as determined by comparison of the infrared spectra and X-ray powder photographs.

The Behavior of 3-Fluorophthalic Anhydride in Friedel–Crafts and Grignard Reactions[1]

MELVIN S. NEWMAN AND SHOSHANA BLUM[2]

Evans Chemistry Laboratory, The Ohio State University, Columbus 10, Ohio

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Condensation of 3-fluorophthalic anhydride (I) with naphthalene in *o*-dichlorobenzene at 95° took place only on the 2-carbonyl group to yield a mixture of 53% of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 18% of 3-fluoro-2-(1-naphthoyl)benzoic acid (III). In Grignard reactions with 1-naphthyl- and 2-naphthylmagnesium bromides, both possible keto acids were formed. In the case of 2-naphthylmagnesium bromide, condensation occurred at the 1-carbonyl in preference to the 2-carbonyl group of I in the ratio of about 1.4:1, whereas with 1-naphthylmagnesium bromide condensation at each carbonyl was about the same.

In previous studies from this laboratory, the reaction of 3-substituted phthalic anhydrides in Grignard and Friedel–Crafts condensations have been described.[3,4] In summary,[4] Grignard condensations take place preferentially on the 1-carbonyl group in both 3-methyl- and 3-chlorophthalic anhydride. In the Friedel–Crafts reaction, condensation occurs on both carbonyl groups in 3-methylphthalic anhydride, but with 3-chlorophthalic anhydride, condensation is almost entirely at the 2-carbonyl group.

In this paper we report on the reactions of 3-fluorophthalic anhydride with naphthalene and with 1- and 2-naphthylmagnesium bromides. This work was undertaken not only to obtain more information about the behavior of unsymmetrical anhydrides but also to ascertain the source of an error in a previous publication.[5] The consequences of this error is discussed in the accompanying article.[6]

The Friedel–Crafts condensation of 3-fluorophthalic anhydride (I) with naphthalene in *o*-dichlorobenzene at 95° gave a mixture of about 53% of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 18% of 3-fluoro-2-(1-naphthoyl)benzoic acid (III) as determined by fractional recrystallization of the methyl esters (compare ref. 5). In a run at 45°, II and III were produced in about 22 and 45% yields, respectively. At 125° the proportion of II increased over that in the run at 95°, but yield of acids was lower owing to tar formation. Thus in the Friedel–Crafts condensation with naphthalene, 3-fluorophthalic anhydride behaves like 3-chlorophthalic anhydride in that condensation occurs

(1) This work was supported by a grant from The National Institutes of Health, Bethesda, Md.

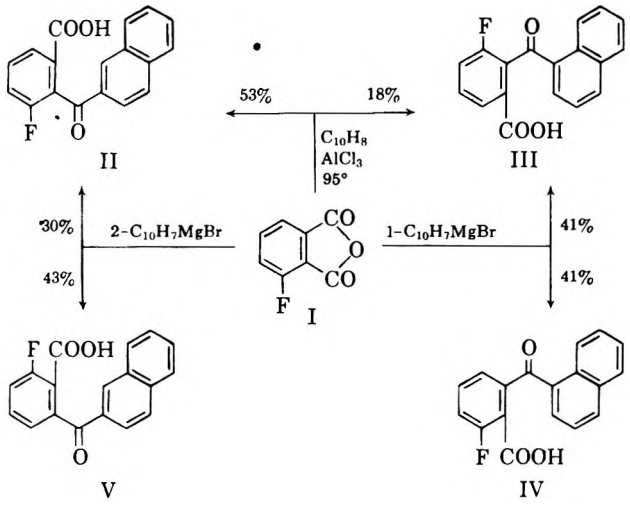
(2) Postdoctoral Fellow, 1963.

(3)(a) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941); (b) M. S. Newman and C. W. Muth, *ibid.*, **72**, 5191 (1950).

(4) M. S. Newman and P. G. Scheurer, *ibid.*, **78**, 5004 (1956).

(5) M. S. Newman and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961).

(6) M. S. Newman and S. Blum, *ibid.*, **29**, 1414 (1964).



exclusively at the internal 2-carbonyl. This result does not agree with that reported previously.[5] We believe the previous report to be in error.

When a solution in ether–benzene (2:1) of the Grignard reagent from 1-bromonaphthalene was added to a solution of 3-fluorophthalic anhydride in benzene, about 84% of a mixture of crude keto acids III and IV was obtained. After several unsuccessful attempts at separation of the mixture were made (see Experimental section) an excellent analysis was made by n.m.r. The τ values of the methyl groups in the methyl esters of III and IV (made with diazomethane) were sufficiently different that n.m.r. analysis could be used to show that about equal amounts of III and IV had been formed.[7]

When 2-naphthylmagnesium bromide reacted with I under similar conditions, the acids II and V were formed in about 30 and 43% yields, respectively. The greater preference of the 2-naphthyl Grignard reagent to react at the 1-carbonyl group of I is what would be expected since a similar result was obtained with phenylmagnesium bromide with both 3-methyl- and 3-chlorophthalic anhydrides.[3,4] However, the proportion reacting at the 1-carbonyl as compared to the 2-carbonyl is not so great as in the previous cases.[3,4] The most surprising fact, however, is that 1-naphthylmagnesium bromide reacts about equally well at each carbonyl in I. We have no explanation to offer for this fact.

The structures of the keto acids II–V were proved by decarboxylation to fluorophenyl naphthyl ketones. Authentic samples were made by condensation of Grignard reagents with nitriles. Identities were established by mixture melting point determination and by infrared spectral comparisons.

Experimental[8]

3-Fluorophthalic Anhydride (I).—A slight modification of the directions for oxidation of 2,3-dimethylfluorobenzene[5] made it possible to obtain the stated yield more consistently. To a stirred mixture of 93 g. of 3-fluoro-1,2-dimethylbenzene,[9] 25 g. of potassium hydroxide, and 500 ml. of water at reflux was added 100 ml. of a boiling solution made from 600 g. of potassium permanganate in 2.5 l. of water. Heat was applied until oxidation commenced (a short induction time, 15–30 min., followed by precipitation of manganese dioxide), whereupon heating was discontinued and the addition of the remaining permanganate solution was made at such a rate as to hold the reaction under control (about 2–3 hr.). Heat was then applied (about 30 min.) until all of the water-insoluble layer had disappeared. The excess permanganate was destroyed with sodium bisulfite and the manganese dioxide was filtered and washed with boiling water. The filtrate and washings were worked up as described[5] to yield 108 g. of 3-fluorophthalic acid, m.p. 162–165°.

Distillation afforded the anhydride[5] I.

Friedel–Crafts Reactions. 3-Fluoro-2-(2-naphthoyl)benzoic Acid (II) and 3-Fluoro-2-(1-naphthoyl)benzoic Acid (III).—Powdered anhydrous aluminum chloride (74 g.) was added (*ca.* 2 hr.) in portions to a stirred solution of 41.5 g. of I and 38.5 g. of naphthalene in 500 ml. of *o*-dichlorobenzene so that the temperature remained at 95–98°. After 2 hr. more of stirring at this temperature the cooled mixture was poured on ice and worked up to yield 67 g. (91%) of light tan acid,[10] m.p. 135–141°. Separation of this mixture was effected by the following procedure. A solution of 90 g. of the above acid was refluxed in 1 l. of methanol containing much hydrogen chloride for 16 hr. The esters produced were isolated by conventional procedure and recrystallized from methanol. The more insoluble methyl ester of III (III_{me}) was obtained in 18% yield in several crops as slightly tan crystals, m.p. 121–123°. The analytical sample,[11] m.p. 124.5–125.5°, was obtained by recrystallization from ethanol. On standing and by further concentration of certain portions of the mother liquors from the above crystallization there was obtained a total of 49.5 g. (53%) of methyl 3-fluoro-2-(2-naphthoyl)benzoate (II_{me}), m.p. 91–94°. The analytical sample, m.p. 95–96°, was obtained with little loss on crystallization from cyclohexane.

Anal. Calcd. for $C_{19}H_{13}FO_3$: C, 74.0; H, 4.2; F, 6.2. Found[12] for II_{me}: C, 74.2; H, 4.2; F, 6.4. Found for III_{me}: C, 73.8; H, 4.1; F, 6.4.

On hydrolysis with alcoholic alkali, the above esters yielded II, m.p. 200.0–201.5° after recrystallization from xylene, and III, m.p. 187–188° on recrystallization from toluene, in high yields.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.7; F, 6.5. Found for II: C, 73.6; H, 3.8; F, 6.7. Found for III: C, 73.5; H, 3.8; F, 6.6.

Grignard Reactions.—The Grignard reagent prepared from 21 g. of 1-bromonaphthalene in 100 ml. of ether and 50 ml. of benzene was added during 10 min. to a stirred boiling solution of 16.6 g. of I in 150 ml. of benzene. After refluxing for 6 hr. the mixture was cooled and worked up as usual to yield 24.8 g. (84%) of acids, m.p. 114–120°. A suspension of 19 g. of this acid in ether was treated with diazomethane to yield a mixture of methyl 3-fluoro-2-(1-naphthoyl)benzoate (III_{me}) and methyl 2-fluoro-6-(1-naphthoyl)benzoate (IV_{me}). Analysis of this mixture by n.m.r. showed that the yields of III and IV were about 41% each (average of three runs).[13]

Pure samples of III_{me} and IV_{me} were obtained as follows. In a typical experiment a solution of 5.0 g. of the mixed methyl esters of III and IV, made by treatment with diazomethane, in a

(7) In a private communication during the course of our work, Dr. E. D. Bergmann and Dr. M. Bentov informed us that 2-fluoro-6-(1-naphthoyl)-benzoic acid is formed in 63% yield when the condensation is carried out in tetrahydrofuran [see *Bull. soc. chim. France*, 963 (1963)]. This strong solvent effect is noteworthy.

(8) All melting points are uncorrected. The term "worked up in the usual manner" means that a solution of the products in an organic solvent, usually ether–benzene, was washed with acid and/or alkali as required and saturated sodium chloride solution, and then was dried by shaking with, or filtration through, anhydrous magnesium sulfate. The solvents were then removed and the residue was purified by crystallization, distillation, or chromatography.

(9) This was obtained from the Pierce Chemical Company, Rockford, Ill.

(10) In ref. 5 a melting point of 176–178° was reported for acid obtained by essentially the same procedure. However, we have never been able to repeat this result, as invariably in many runs acid, m.p. 135–141°, was obtained by Dr. S. Blum and Dr. D. Alsop.

(11) In ref. 5, this ester was reported to melt at 95–96°. However, we are certain that the ester referred to therein was methyl 3-fluoro-2-(2-naphthoyl)benzoate (II_{me}), as an authentic sample of this ester melts at 95–96°.

(12) All analyses by Galbraith Microanalytical Laboratory, Knoxville, Tenn.

(13) The use of n.m.r. to determine the amounts of normal methyl esters of these acids was prompted by the publication by P. T. Lansbury and J. F. Bieron [*J. Org. Chem.*, **28**, 3564 (1963)] for which M. S. N. was a referee. We thank Mr. B. Bossenbroek for carrying out the spectral determinations. The value for the methyl group in III_{me} was 6.46 and in IV_{me} was 6.50.

TABLE I

PREPARATION OF KETONES AND DNPH DERIVATIVES

Keto acid	Ketone[a]	Yield,[b] %	M.p.,[c] C.	Anal.,[a] % C	H	F	DNPH, m.p. dec., °C.	Color	Anal.,[e] % C	H	F	N
II	*o*-FC_6H_4-2-$C_{10}H_7$-	26	81.0–82.0	81.3	4.6	7.5	300–302	Orange	64.1	3.5	4.7	12.8
III	*o*-FC_6H_4-1-$C_{10}H_7$-	25	58.5–60.0	81.8	4.6	7.6	283–285	Orange	64.1	3.7	4.6	12.9
IV	1-$C_{10}H_7$-*m*-FC_6H_4-	50	60.2–61.0	81.8	4.2	7.6	220–222	Yellow[f]	64.0	3.8	4.4	13.0
							258–260	Orange[f]	64.4	3.8	4.5	12.8
V	2-$C_{10}H_7$-*m*-FC_6H_4-	81	122.5–123.0	81.6	4.7	7.5	248–250	Deep yellow[g]	64.4	3.5	4.7	13.0
							283–285	Orange[g]	64.5	3.7	4.6	12.8

[a] The group used as nitrile in the synthesis is listed first and the group used as Grignard reagent, second. [b] Yield of pure ketone in Grignard reaction. [c] M.p. of pure ketone. [d] Calcd. for $C_{17}H_{11}FO$: C, 81.6; H, 4.4; F, 7.6. [e] Calcd. for $C_{23}H_{15}FN_4O_4$: C, 64.2; H, 3.5; F, 4.4; N, 13.0. [f] The mixture of DNPH derivatives was recrystallized from xylene and washed on the funnel with diglyme (dimethyl ether of diethylene glycol); the yellow form dissolved while the orange form remained. [g] Separated by recrystallization from acetic acid; the orange isomer was the more insoluble.

solution of 5.0 g. of 30% oleum and 49 g. of 98% sulfuric acid was held at 20–25° for 4 hr. The mixture was poured onto ice and separated into acid and neutral fractions by treatment with sodium carbonate.[14] There was obtained 2.6 g. (52%) of pure III_{me}, identical with that described under the Friedel–Crafts reaction. On recrystallization of the acid fraction, 1.2 g. (25%) of pure 2-fluoro-6-(1-naphthoyl)benzoic acid (IV), m.p. 144–145°, was obtained. The pure methyl ester of IV, IV_{me}, m.p. 94–95°, was prepared with diazomethane and was recrystallized from methanol.[15]

In an analogous reaction 2-naphthylmagnesium bromide was added to 3-fluorophthalic anhydride to yield a mixture, m.p. 135–157°, of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 2-fluoro-6-(2-naphthoyl)benzoic acid (V) in 71–75% yield (two runs). This mixture was converted into the mixture of methyl esters by treatment with diazomethane and was analyzed by the n.m.r. method described above[13]; II_{me} had a τ value of 6.35 and V_{me}, a τ value of 6.41. The ratio of II_{me} to V_{me} was about 3:2. The average yields of II and IV are thus calculated to be about 43 and 30%, respectively.

Separation of esters II_{me} and V_{me} by the sulfuric acid method[14] was not very successful. However, pure V, m.p. 160–161°, was obtained from the acidic portion by several recrystallizations from toluene. The methyl ester V_{me}, m.p. 103–104°, was obtained by treatment with diazomethane.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.7; F, 6.5. Found for IV: C, 73.5; H, 3.8; F, 6.3. Found for V: C, 73.8; H, 3.9; F, 6.8.

Anal. Calcd. for $C_{19}H_{13}FO_3$: C, 74.0; H, 4.2; F, 6.2. Found for IV_{me}: C, 74.2; H, 4.4; F, 6.0. Found for V_{me}: C, 74.3; H, 4.2; F, 6.5.

Proof of Structure of Keto Acids.—The structure of each acid, II–V, was established by decarboxylation to a fluorophenyl naphthyl ketone by boiling with copper powder in quinoline (yields 76–82%), followed by comparison with an authentic sample prepared by reaction of a Grignard reagent with a nitrile. The ketones were converted into the 2,4-dinitrophenylhydrazones (DNPH); identity of the ketones was established by mixture melting point determinations of the ketones and the DNPH derivatives and by comparison of the infrared spectra of the ketones and the DNPH derivatives. The work is summarized in Table I.

In previous work[5] *o*-fluorophenyl 1-naphthyl ketone was reported as an oil, b.p. 212–213° at 6 mm., which gave a DNPH derivative, m.p. 282–283°, and *m*-fluorophenyl 1-naphthyl ketone was reported as a solid, m.p. 122–123°, which formed a DNPH derivative, m.p. 262–264°. Actually *o*-fluorophenyl 1-naphthyl ketone is a solid, m.p. 58.5–60.0°, which forms a DNPH derivative, m.p. 283–285°, and *m*-fluorophenyl 1-naphthyl ketone melts at 60–61° and forms two DNPH derivatives, m.p. 220–222° and 258–260°. Since the *m*-fluorophenyl 1-naphthyl ketone reported before[5] was formed by a Friedel–Crafts condensation of *m*-fluorobenzoyl chloride with naphthalene in *o*-dichlorobenzene, it must have been[16] *m*-fluorophenyl 2-naphthyl ketone, since we have shown that 3-fluorophthalic anhydride condenses mainly at the 2-position of naphthalene. The melting point of 122–123° reported[5] for *m*-fluorophenyl 1-naphthyl ketone is in agreement with the melting point of 122–123° found in this paper for *m*-fluorophenyl 2-naphthyl ketone.

All ketones in Table I were recrystallized from methanol.

(14) Compare M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1537 (1941).

(15) In the Bergmann and Bentov reference cited previously in ref. 7, this methyl ester is stated to melt at 115°. Our ester, IV_{me}, m.p. 94°, is a polymorphic form as we obtained the same melting point when we prepared this ester from a pure sample of IV supplied by Professor Bergmann. Both the acid IV and the methyl ester IV_{me} had infrared spectra identical with those prepared from the acid sent to us.

(16) The sample labeled *m*-fluorophenyl 1-naphthyl ketone, m.p. 122–123°, in our sample box when re-examined proved to be identical with our sample of *m*-fluorophenyl 2-naphthyl ketone, m.p. 122–123°, prepared from 2-naphthonitrile.

The Synthesis and the Exhaustive Methylation of the *cis* and *trans* Isomers of 1,2,3,4,4a,5,6,10b-Octahydrophenanthridine and 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinoline[1]

TADASHI MASAMUNE, MASAJI OHNO, MASATO KOSHI, SHIGEHIRO OHUCHI, AND TSUKASA IWADARE

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

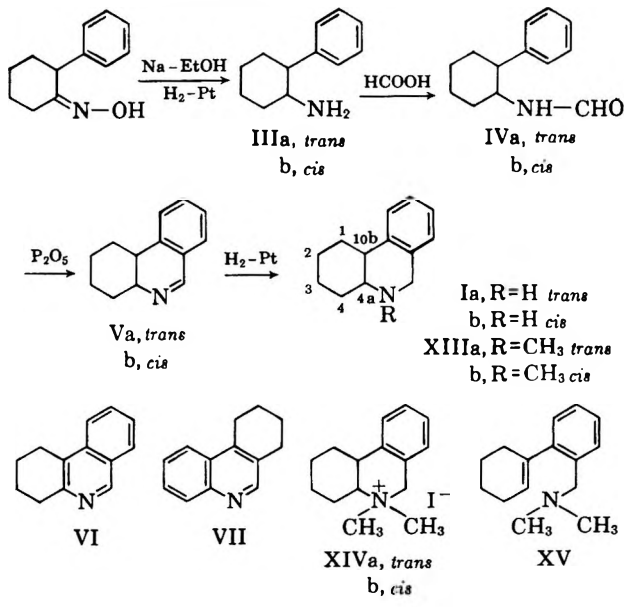
Received October 1, 1963

Preparation of *trans*- and *cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines (Ia and Ib) and *trans*- and *cis*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (IIa and IIb) is described. The configuration of those compounds was established on the basis of the stereospecific synthesis. The exhaustive methylation of Ia and Ib resulted in formation of *o*-dimethylaminomethylphenylcyclohexene (XV), involving the splitting of hydrogen on carbon substituted with a phenyl group. The same reaction of IIa and IIb afforded an analogous result, producing 1-(3-dimethylaminopropyl)-3,4-dihydronaphthalene (XVI).

In the course of an investigation of the exhaustive methylation of hydrogenated tricyclic bases,[2,3] it became desirable to prepare *trans*- and *cis*-1,2,3,4,4a,5,6,-10b-octahydrophenanthridines (Ia and Ib) and 1,2,3,4,-4a,5,6,10b-octahydrobenzo[*f*]quinolines[4] (IIa and IIb). The present paper describes the synthesis and exhaustive methylation of those bases.

The synthesis of octahydrophenanthridines (Ia and Ib) employed the Bischler–Napieralski reaction,[5] and 2-phenylcyclohexanone, prepared by the method of Newman and Farbman,[6,7] was selected as a starting substance. Reduction of the oxime with sodium and ethanol gave 1-amino-2-phenylcyclohexane (IIIa), m.p. 60–61°, quantitatively. Treatment of IIIa with formic acid at 150–160° for several hours rendered the N-formyl derivative (IVa), m.p. 97–98°, in a yield of 75%. On the other hand, catalytic hydrogenation of the oxime in the presence of Adams' platinum in acetic acid resulted in the formation of a semisolid mixture of IIIa and the stereoisomer IIIb, the ratio being found to be 1 to 2 by gas chromatography. As it was difficult to isolate IIIb from the mixture at this stage, the mixture was subjected to formylation without further purification, and 1-formylamino-2-phenylcyclohexane (IVb), m.p. 112–113°, stereoisomeric with IVa, was isolated in low yield. A pure sample of IIIb was obtained by hydrolysis of IVb and showed m.p. about 20°. It is clear on the basis of the well-known stereochemistry of similar reductions[8,9] that IIIa has the *trans* configuration and IIIb, the *cis* configuration.

Treatment of the *trans*-formylamino derivative (IVa) with phosphorus pentoxide in refluxing tetralin led to formation of *trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (Va), m.p. 52–53°, in only 15% yield, and IIIa and 1,2,3,4-tetrahydrophenanthridine (VI), an oil, were isolated as by-products. The latter base VI was obtained in good yield by dehydrogenation of Va and could be well differentiated from 7,8,9,10-tetrahydrophenanthridine[10] (VII) by its characteristic ultraviolet spectrum (Fig. 1). Cyclodehydration of the *cis*-formylamino derivative (IVb) similarly produced *cis*-hexahydrophenanthridine (Vb), m.p. 52.5–54°, in almost the same yield as in the case of the *trans* isomer. The base Vb appeared to be more unstable than the corresponding *trans* isomer; prolonged treatment of the reaction mixture sometimes gave VI as a main product. Hydrogenation of the *trans*- and *cis*-hexahydro derivatives (Va and Vb) proceeded smoothly to yield *trans*-octahydrophenanthridine (Ia), m.p. 89.5–90.5°, and the corresponding *cis* isomer (Ib), an oil, respectively.



Recently, Nelson, *et al.*,[11] reported the elegant synthesis of N-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinoline (VIIIb), the configuration of which was tentatively assigned to be a *cis* modification. On the other hand, Bamberger and Müller[12] had obtained 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIa). The present investigation started with the re-examination of Bamberger's experiment; reduction of benzo[*f*]-quinoline (IX) with sodium and amyl alcohol gave IIa,

(1) Part XIII of "The Condensed Polynuclear Perhydro Compounds Containing Nitrogen"; part XII, ref. 3.

(2) T. Masamune, *Bull. Chem. Soc. Japan*, **30**, 49 (1957).

(3) T. Masamune, M. Takasugi, H. Suginome, and M. Yokoyama, *J. Org. Chem.*, **29**, 681 (1964).

(4) The synthesis and exhaustive methylation of IIa and IIb were reported as a communication: T. Masamune and M. Koshi, *Bull. Chem. Soc. Japan*, **32**, 1006 (1959).

(5) W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. VI, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p. 74.

(6) M. S. Newman and M. D. Farbman, *J. Am. Chem. Soc.*, **66**, 1550 (1944).

(7) J. W. Cook, C. K. Hewett, and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936).

(8) D. H. R. Barton, *ibid.*, 1027 (1953); F. E. King, T. Henshall, and R. L St. D. Whitehead, *ibid.*, 1373 (1948); F. E. King, J. A. Barltrop, and R. J. Willey, *ibid.*, 277 (1945).

(9) J. McKenna and A. Tulley, *ibid.*, 945 (1962); for a recent review of conformational analysis, see D. H. R. Barton and G. A. Morrison, "Progress in The Chemistry of Organic Natural Products," Vol. 19, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1961, p. 165.

(10) B. L. Hollingsworth and V. Petrow, *J. Chem. Soc.*, 1537 (1948).

(11) N. A. Nelson, J. E. Ladburg, and R. S. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(12) E. Bamberger and R. Müller, *Ber.*, **24**, 2648 (1891).

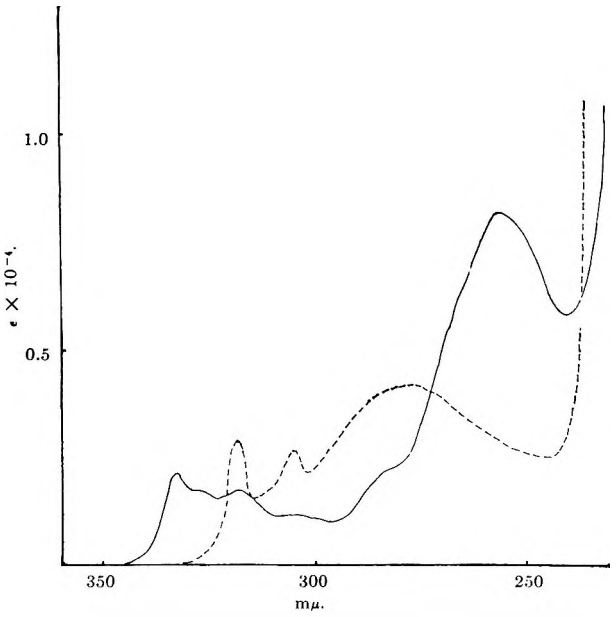


Fig. 1.—Ultraviolet absorption spectra of tetrahydrophenanthridines: solvent, ethanol; ———, 1,2,3,4-tetrahydrophenanthridine; and – – – –, 7,8,9,10-tetrahydrophenanthridine.

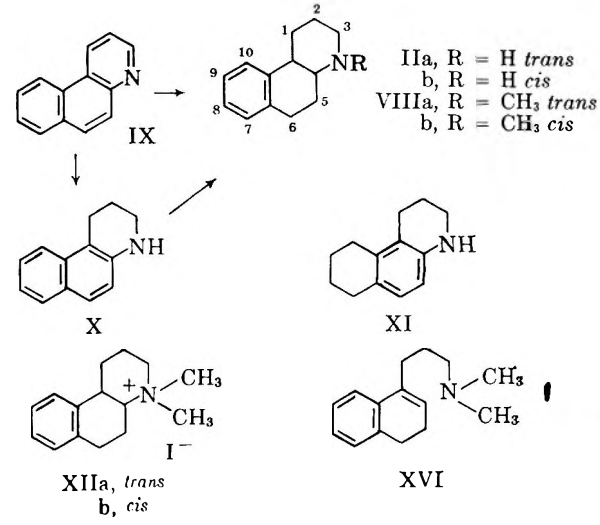
m.p. 88–90°, in 3% yield along with the 1,2,3,4-tetrahydro derivative[13] (X) and the 1,2,3,4,7,8,9,10-octahydro derivative[12] (XI). Methylation of IIa with methyl iodide gave the corresponding methiodide (XIIa), m.p. 238–240°, whereas the methiodide (XIIb) obtained from VIIIb has been reported to melt at 295°. The discrepancy of the melting points strongly suggested that XIIa and XIIb are stereoisomers. Catalytic hydrogenation of IX over Raney nickel at 150° has now afforded a new 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIb) as an oil. It was isolated in 5% yield as the carbonate from the ether solution of the oily reaction product. The main product was XI and no isomer (IIa) could be isolated. In an attempt to produce IIb in better yield the 1,2,3,4-tetrahydro derivative was hydrogenated in the presence of platinum in acetic acid, but the main product was XI, and IIb was obtained only in 3% yield along with IIa (4.5%). Formation of stereoisomers IIa and IIb would occur not only because the solvent was acidic but also because a long hydrogenation was required for the consumption of 2 moles of hydrogen.[14] Hydrogenation of the hydrochloride of X in ethanol[15] over platinum gave only IIb (4%) besides XI. Methylation of IIb gave rise to the methiodide (XIIb), m.p. 294–295°. While direct comparison was not attained, there is no doubt from comparison of the melting points that XIIb is the same compound as Nelson's methiodide.[11] It is apparent on the basis of the reduction conditions[9] and Nelson's assignment[11] that IIa is a *trans* isomer and IIb a *cis* isomer, although no rigid proof can be given for the configuration of IIa and IIb.

(13) Bamberger's tetrahydrobenzo[*f*]quinoline is a molecular compound of IX and X [(a) T. Masamune and M. Koshi, *Bull. Chem. Soc. Japan*, **30**, 307 (1957); (b) E. Bamberger and R. Müller, *Ber.*, **24**, 2641 (1891)].

(14) Hydrogenation of quinoline, 1,2,3,4,4a,9,9a,10-octahydroacridines and *trans*-5,6,6a,7,8,9,10,10a-octahydrophenanthridine over platinum in acetic acid gives the corresponding perhydro compounds with *trans*-fused rings. [W. Hückel and F. Stepf, *Ann.*, **453**, 163 (1927); T. Masamune and S. Wakamatsu, *J. Chem. Soc. Japan*, **77**, 1145 (1956); T. Masamune and Y. Kubota, *ibid.*, **77**, 1467 (1956); also see G. R. Clemo, J. G. Cook, and R. Paper, *J. Chem. Soc.*, 1183 (1938)].

(15) *Cf.* N. J. Leonard, L. A. Miller, and P. D. Thomas, *J. Am. Chem. Soc.*, **78**, 3463 (1956).

Methylation of Ia and Ib with formalin and formic acid gave the N-methyl-*trans* and -*cis* derivatives (XIIIa and XIIIb), respectively. Addition of methyl iodide to an acetone solution of XIIIa or XIIIb gave N-methyl-*trans*-octahydrophenanthridine methiodide (XIVa), m.p. 265–267°, or the corresponding *cis*-methiodide (XIVb), m.p. 242–244°. The Hofmann degradation of XIVa produced a single oily base (XV),



$C_{15}H_{21}N$, in 65% yield, which was found to be identical with the degradation product of XIVb. The ultraviolet spectrum of XV resembled closely that of *o*-methylphenylcyclohexene. Taking into consideration that XV was produced from each of the stereoisomers XIVa and XIVb, it might be reasonably concluded that XV is *o*-dimethylaminomethylphenylcyclohexene. In a similar way the exhaustive methylation of XIIa gave the same oily base (XVI), $C_{15}H_{21}N$, as that of XIIb. The base (XVI) showed a similar ultraviolet spectrum to 1,2-dihydronaphthalene[16] and XVI was, therefore, formulated as 1-(3-dimethylaminopropyl)-3,4-dihydronaphthalene (XVI). The structure for the degradation product of *cis*-methiodide (XIIb) has been confirmed to be XVI by Nelson, *et al.*[11]

From a study of molecular models it is clear that the *trans* compounds in both series must have a quasi-axial hydrogen at position 10b. In the *cis* series the 10b hydrogen may be either quasi-axial or quasi-equatorial. The two principle conformations of the *cis* compounds should be readily interchangeable, at least under conditions of the Hofmann elimination. In each *cis* series it is possible to arrive at a conformation in which the 10b hydrogen is ideally situated for an E2 elimination reaction. For each *trans* compound this is not true, and it was expected that elimination of methanol from the methohydroxide (substitution reaction) would take place.[3] In the present experiment the 10b hydrogen has been eliminated preferentially by the influence of the phenyl group.[17] It would appear that the *trans* compounds undergo a two-step elimination.[18a,b]

(16) E. Boyland and J. B. Solomon, *Biochem. J.*, **69**, 518 (1955).

(17) H. Wieland, W. Koschara, E. Dane, J. Renz, W. Schwarze, and W. Linde, *Ann.*, **540**, 103 (1939); C. Schöpf, E. Schmidt, and W. Braun, *Ber.*, **64**, 683 (1931); J. Weinstock, R. G. Pearson, and F. G. Bordwell, *J. Am. Chem. Soc.*, **78**, 3468 (1956); S. J. Cristol, J. Q. Welber, and M. C. Brindell, *ibid.*, **78**, 598 (1956).

(18) (a) A. C. Cope and E. R. Trumbull, "Organic Reactions," Vol. XI, A. C. Cope, Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 317; (b) we are indebted to a referee for these suggestions.

Experimental

Ultraviolet and infrared spectra were measured in ethanol and in Nujol, respectively, unless otherwise stated.

trans-1-Amino-2-phenylcyclohexane (IIIa).—The starting material, 2-phenylcyclohexanone, was prepared according to the method of Newman and Farbman[6] and was converted quantitatively into the oxime, m.p. 174–175°. To the oxime (52 g.) dissolved in warm absolute ethanol (500 ml.) was added sodium (63 g.) little by little, and the solution was further refluxed for 1 hr. After cooling, the mixture was acidified with concentrated hydrochloric acid, when sodium chloride precipitated. After separation of the salt and the solvent, the residue was treated with water and ether. The aqueous solution was made alkaline to yield a crude base which was extracted with ether. The base was then submitted to distillation and a fraction of b.p. 133–136° (12 mm.) was collected and solidified on cooling. On recrystallization from petroleum ether, *trans*-1-amino-2-phenylcyclohexane (39 g.), m.p. 60–61°, was obtained (lit.[19] m.p. 60°).

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.10; H, 9.88.

The hydrochloride was prepared by addition of dry hydrogen chloride to the ether solution of the base and melted at 249–251° on recrystallization from acetone (lit.[16] m.p. 253°). The picrate was prepared in ether and recrystallized from a mixture of ether and acetone to give m.p. 181–182°.

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: N, 13.86. Found: N, 13.70.

trans-1-Formylamino-2-phenylcyclohexane (IVa).—A mixture of *trans* base (IIIa, 17 g.) and formic acid (9.0 g.) was heated at 150–160° (bath temperature) for 4 hr. To the cooled mixture was added ether and water, and the ether solution was washed with 1 *N* hydrochloric acid. The aqueous and hydrochloric acid solutions were combined and made basic to give the crude starting base (IIIa, 2.0 g.). The ether solution yielded the solid N-formyl derivative on removal of ether. Recrystallization from a mixture of petroleum ether (b.p. 30–60°, 200 ml.) and a small volume of ethanol followed by quick washing with a small volume of ether yielded *trans*-1-formylamino-2-phenylcyclohexane (IVa, 13 g.), m.p. 88–90°. Upon concentration of the combined filtrates followed by distillation, a further quantity (1.0 g.) of IVa, b.p. 200–205° (16 mm.) and m.p. 87–90°, was obtained. The samples of m.p. 90° could be used for the subsequent cyclodehydration without further purification, but an analytical sample had m.p. 97–99° after recrystallization from petroleum ether or aqueous ethanol, ν_{max} 1655 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 77.02; H, 8.13.

cis-1-Amino-2-phenylcyclohexane (IIIb) and the N-Formyl Derivative (IVb).—2-Phenylcyclohexanone oxime (10.0 g.) was hydrogenated over Adams' platinum (0.6 g.) at room temperature in acetic acid (500 ml.), and 2750 ml. of hydrogen was consumed after 24 hr., the calculated value for 3 moles of hydrogen being 2600 ml. After removal of the catalyst and acetic acid, the reaction mixture was shaken with ether and water. The aqueous solution was made basic and treated with ether. An oily base obtained from the ether solution was a mixture of *trans*- and *cis*-1-amino-2-phenylcyclohexanes (IIIa and IIIb), and the ratio of IIIa to IIIb was found to be 1 to 2 by gas chromatographic examination.[20] The mixture was formylated without further purification; the mixture (10 g.) of IIIa and IIIb was heated with formic acid (4 ml.) at 140–160° for 8 hr. The reaction mixture was worked up similarly as in the case of IIIa and an oily formyl compound (10.0 g.) was obtained. When allowed to stand in a refrigerator overnight, it solidified partially and the solid was collected by filtration. An oily substance included in the solid was removed by treatment with warm petroleum ether (about 150 ml.) and the crude *cis*-N-formyl derivative (IVb, 2.7 g.), m.p. 100–106°, was obtained. Recrystallization from benzene gave pure *cis*-1-formylamino-2-phenylcyclohexane (IVb, 1.85 g.), m.p. 112–113°, ν_{max} 1650 cm.$^{-1}$. On admixture of IVb with IVa, the melting point was depressed to 67–74°. The sample of m.p. 106° mentioned above showed practically the same infrared spectrum as the pure compound.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.80; H, 8.15.

The *cis*-N-formyl compound (IVb, 0.5 g.) of m.p. 113° was hydrolyzed with 6 *N* hydrochloric acid (1 ml.) in refluxing ethanol (3 ml.) for 5 hr. The reaction mixture was worked up as usual and pure *cis*-1-amino-2-phenylcyclohexane (IIIb, 0.38 g.), m.p. *ca.* 20° and b.p. 140–142° (15 mm.), was obtained.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.01; H, 9.65.

The picrate melted at 182–184° after preparation in ether and recrystallization from acetone. The mixture melting point with the corresponding *trans* isomer was depressed to 160–169°.

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: N, 13.86. Found: N, 13.59.

trans-1,2,3,4,4a,10b-Hexahydrophenanthridine (Va).—In a three-necked flask fitted with a reflux condenser and a stirrer, *trans*-1-formylamino-2-phenylcyclohexane (IVa, 23 g.) was dissolved in boiling tetralin (230 ml., distilled over phosphorus pentoxide). To the solution was added phosphorus pentoxide (35 g.) in small quantities for 35 min. under vigorous stirring, and the solution was continuously refluxed for 1 hr. After cooling, it was treated with ether (300 ml.) and 2 *N* hydrochloric acid (300 ml.). An oily substance which separated by alkalinization of the acidic solution was distilled to yield a fraction (6.6 g.) of b.p. 157–172° (22 mm.), which solidified on cooling. In order to prepare *trans*-octahydrophenanthridine (Ia), it is convenient to hydrogenate this crude base without further purification. Recrystallization from petroleum ether gave *trans*-hexahydrophenanthridine (Va, 3.5 g.), m.p. 52–53°, λ_{max} 254 mμ (ϵ 15,500) and ν_{max} 1620 and 1571 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}N$: C 84.28; H, 8.16. Found: C, 84.31; H, 8.03.

The picrate melted at 190–192° on recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38. Found: C, 55.31; H, 4.01.

The hydrochloride melted at 220–222° on recrystallization from acetone.

Anal. Calcd. for $C_{13}H_{16}ClN$: C, 70.41; H, 7.28. Found: C, 70.20; H, 7.50.

The mother liquors obtained on recrystallization of the crude hexahydrophenanthridine were combined and evaporated to dryness. The residue was acetylated with refluxing acetic anhydride. The reaction mixture was worked up as usual and gave *trans*-1-acetylamino-2-phenylcyclohexane (2.2 g.), m.p. 128–130° on recrystallization from aqueous ethanol, which was identified by the mixture melting point method with an authentic specimen[19] of m.p. 128–130°.

Cyclodehydration of IVa under more drastic conditions gave 1,2,3,4-tetrahydrophenanthridine (VI). In such a case it was found convenient to purify the reaction product through the picrate; IVa (10 g.) was refluxed with phosphorus pentoxide (15 g.) for 8 hr. An oily base obtained from the reaction product was converted into the picrates in ethanol, when two kinds of crystals, needles and plates, appeared. The former (3.5 g.) had m.p. 190–192° and the latter (0.28 g.) had m.p. 192–193°. It was shown, by regeneration of those picrates into the corresponding free bases followed by comparison of their infrared spectra with those of authentic specimens, that the former was the picrate of Va and the latter of VI.

1,2,3,4-Tetrahydrophenanthridine (VI).—A solution of *trans*-hexahydrophenanthridine (Va, 0.5 g.) in tetralin (10 ml.) was refluxed with 30% palladized charcoal[21] (0.25 g.) for 4 hr. The reaction mixture was treated with ether and 6 *N* hydrochloric acid, and the acidic solution was made basic to yield an oily base which was extracted with ether. The oily base (0.4 g.) obtained on removal of ether was converted into the picrate, which had m.p. 192–193° on recrystallization from ethanol or by washing with ethanol. The picrate was regenerated into the free base, 1,2,3,4-tetrahydrophenanthridine (VI, 0.3 g.).

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.20; H, 7.15. Found: C, 85.01; H, 7.30.

The hydrochloride melted at 282–284° on recrystallization from acetone.

Anal. Calcd. for $C_{13}H_{14}ClN$: C, 71.06; H, 6.42. Found: C, 70.78; H, 6.29.

trans-1,2,3,4,4a,5,6,10b-Octahydrophenanthridine (Ia).—*trans*-Hexahydrophenanthridine (Va, 0.5 g.) was hydrogenated over Adams' platinum (0.2 g.) at room temperature in acetic acid and took up 100 ml. of hydrogen (1 mole) after 30 min. Hydrogenation did not proceed beyond this stage. The reaction

(19) J. van Braun, H. Gruber, and G. Kirschbaum *Ber.*, **55**, 3664 (1922).

(20) The gas chromatography was conducted at 200° using polyethylene glycol (Shimazu 6000).

(21) A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **23**, 781 (1940).

product was worked up as usual and gave a solid base. Recrystallization from petroleum ether or aqueous methanol gave rise to *trans*-octahydrophenanthridine (Ia, 0.39 g.), m.p. 89.5–90.5°, λ_{max} 273 mμ (ε 370) and 266 mμ (ε 380), and ν_{max} 1502, 1485, and 1442 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.20; H, 9.10.

The picrate melted at 178–179° on recrystallization from acetone–ether.

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 54.55; H, 4.59.

The hydrochloride had m.p. 280–282° on recrystallization from a mixture of acetone and a small amount of ethanol.

Anal. Calcd. for $C_{13}H_{18}ClN$: C, 69.77; H, 8.29. Found: C, 69.78; H, 8.11.

The crude hexahydrophenanthridine (6.6 g.) of b.p. 157–172° (22 mm.) obtained in preparation of Va was hydrogenated over Adams' platinum (0.3 g.) under similar conditions and 600 ml. of hydrogen (0.7 mole) was consumed. Recrystallization of hydrogenated bases gave Ia (3.7 g.), m.p. 88–90°.

***cis*-1,2,3,4,4a,10b-Hexahydrophenanthridine (Vb).**—To *cis*-1-formylamino-2-phenylcyclohexane (IVb, 5.0 g.), m.p. 113°, dissolved in boiling tetralin (150 ml.) was added phosphorus pentoxide (10 g.) during 10 min. under stirring, and the whole solution was refluxed for 50 min. The product was worked up as above, and crude *cis* base (Vb, 1.5 g.), b.p. 148–152° (17 mm.), was obtained. It gradually crystallized and, on recrystallization from petroleum ether, *cis*-hexahydrophenanthridine (Vb, 0.7 g.), m.p. 52.5–54°, was obtained, λ_{max} 258 mμ (ε 10,500) and ν_{max} 1622 and 1571 cm.$^{-1}$. Concentration of the mother liquor gave a further quantity (0.45 g.) of Vb, m.p. 51.5–54°.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16. Found: C, 84.10; H, 8.35.

It was difficult to prepare the picrate in pure state. The hydrochloride melted at 210–212° on recrystallization from acetone.

Anal. Calcd. for $C_{13}H_{16}ClN$: C, 70.41; H, 7.28. Found: C, 70.15; H, 7.41.

Prolonged treatment of IVb with phosphorus pentoxide in boiling tetralin rendered only VI as an isolated product; IVb (2.0 g.) gave an oily base (0.2 g.) by treatment with phosphorus pentoxide (3.0 g.) for 4 hr., and the oil was converted into picrate (0.15 g.) which melted at 190–192° on recrystallization from methanol and was identified as the picrate of VI. Since the picrate of Vb could not be obtained in crystalline form in methanol, the yield of Vb was not determined. However, the oily mixture was found to contain at least 50% of VI, judging from the intensity of its ultraviolet spectrum.

***cis*-1,2,3,4,4a,5,6,10b-Octahydrophenanthridine (Ib).**—*cis*-Hexahydrophenanthridine (Vb, 2.0 g.) of m.p. 52.5–54° was hydrogenated in the presence of platinum oxide (0.5 g.) at room temperature in acetic acid (100 ml.) and took up 440 ml. of hydrogen, the calculated value for 1 mole of hydrogen being 425 ml. The usual treatment of the product yielded *cis*-octahydrophenanthridine (IIb, 1.95 g.), b.p. 141–5° (17 mm.), which was shown to be a single compound by gas chromatography,[20] λ_{max} 273 mμ (ε 400) and 266 mμ (ε 420) and ν_{max} 1490, 1465, and 1451 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.20; H, 9.30.

The picrate melted at 165–166° after preparation in ether and recrystallization from methanol.

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 54.68; H, 4.99.

The hydrochloride melted at 225–227° on recrystallization from acetone–methanol.

Anal. Calcd. for $C_{13}H_{18}ClN$: C, 69.77; H, 8.29. Found: C, 69.60; H, 8.40.

Methylation of *trans*- and *cis*-1,2,3,4,4a,5,6,10b-Octahydrophenanthridines (Ia and Ib).—A mixture of *trans*-octahydrophenanthridine (Ia, 2.0 g.), formic acid (1.0 ml.), and 33% formalin (2 ml.) was gently refluxed for 6 hr. with a small free flame, and the cooled mixture then was treated with ether (30 ml.) and water (50 ml.). The ether solution was washed with 2 *N* aqueous acetic acid. The aqueous solution and the acidic washings were combined, made basic, and treated with ether. An oily base (1.6 g.) obtained from the ether solution was refluxed with acetic anhydride (5 ml.) for 30 min. The reaction mixture afforded an oily base after decomposition of the excess of acetic anhydride with hot water (30 ml.) followed by alkalinization of the aqueous layer. It was again extracted with ether and distilled under reduced pressure to yield N-methyl-*trans*-octahydrophenanthridine (XIIIa, 1.3 g.), b.p. 161–163° (15 mm.).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.30; H, 9.68.

The picrate melted at 167–168° on preparation in ether and recrystallization from a small amount of ethanol or acetone.

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 56.02; H, 5.01.

Into an acetone solution of the N-methyl derivative (XIIIa, 0.5 g.) was added an excess of methyl iodide under cooling, and the precipitate thus formed was washed with acetone and ether. On recrystallization from acetone–ethanol, N-methyl-*trans*-octahydrophenanthridine methiodide (XIVa, 0.55 g.), m.p. 265–267°, was obtained.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.30; H, 6.58.

In a similar way, *cis*-octahydrophenanthridine was methylated to the N-methyl derivative (XIIIb), b.p. 165–170° (15 mm.).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.23; H, 9.85.

The picrate could not be obtained in a crystalline form. The methiodide (XIVb) had m.p. 242–244° on recrystallization from acetone–ethanol.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.30; H, 6.70.

The Exhaustive Methylation of N-Methyl-*trans*- and -*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine Methiodides (XIVa and XIVb).—A solution of *trans*-methiodide (XIVa, 0.50 g.) in a mixture of water (5 ml.) and methanol (5 ml.) was shaken for 1 hr. with silver oxide freshly prepared from silver nitrate (0.30 g.). After removal of silver oxide and silver iodide by filtration, the solution was evaporated to dryness. The resulting sirupy methohydroxide was heated to 170° (bath temperature) under reduced pressure and the decomposition was completed practically at 145°. The product extracted with ether was purified by distillation, and *o*-dimethylaminomethylphenylcyclohexene (XV, 0.20 g.), b.p. 140–160° (bath temperature, 15 mm.), was obtained.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.50; H, 9.80.

The picrate melted at 170–172° after preparation in ethanol and recrystallization from the same solvent.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.42; H, 5.52.

Similar treatment of N-methyl-*cis*-octahydrophenanthridine methiodide (XIVb, 0.18 g.) gave an oily base (0.06 g.). The base (XV), b.p. 140–160° (bath temperature, 15 mm.), and its picrate, m.p. 170–172° (from ethanol), showed the same infrared spectra as the corresponding specimens obtained from the *trans* isomer.

Catalytic Hydrogenation of Benzo[*f*]quinoline (IX) over Raney Nickel.—A starting substance, benzo[*f*]quinoline (IX), was prepared according to the method of Clem and Hamilton,[22] and had m.p. 92–93°, lit.[22] m.p. 93°; λ_{max} 346 mμ (ε 3000), 330 (2600), 316 (1400), 267 (15,000), and 234 (21,000).

Benzo[*f*]quinoline (IX, 20 g.) was hydrogenated over Raney nickel (2.0 g.) at 100° under high pressure (70 atm.) for 1 hr. and absorbed 2 moles of hydrogen. The cooled reaction mixture was extracted with ethanol and then distilled under reduced pressure after removal of ethanol. 1,2,3,4-Tetrahydrobenzo[*f*]-quinoline (X, 20 g.), b.p. 200–202° (14 mm.), was obtained, with λ_{max} 360 mμ (ε 2200), 300 (6600), 288 (7500), and 277 (5300). The infrared spectrum was identical with that of the authentic specimen.[13a]

When IX (20 g.) was similarly treated at 150°, about 4 moles of hydrogen were consumed after 1 hr. The ethanol solution of the product was acidified with acetic acid and then ethanol was distilled. The residue was diluted with water, and the aqueous solution was washed with ether and then made basic. The oily substance which separated was extracted with ether, and into the ether solution was passed carbon dioxide, when the carbonate precipitated. It was collected by filtration, washed with ether, and had m.p. 88–90°.

Anal. Calcd. for $C_{13}H_{17}N \cdot 0.5H_2CO_3$: C, 74.28; H, 8.31. Found: C, 74.08; H, 8.19.

(22) W. J. Clem and C. S. Hamilton, *J. Am. Chem. Soc.*, **62**, 2349 (1940); and H. Hepneo, *Monatsh.*, **27**, 1044 (1906).

Regeneration of the carbonate yielded *cis*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIb, 1.0 g.), b.p. 160–165° (5 mm.). As analysis of the free base was difficult because of rapid absorption of atmospheric carbon dioxide, IIb was converted into the hydrochloride, which melted at 258–259° on recrystallization from aqueous acetone.

Anal. Calcd. for $C_{13}H_{18}ClN \cdot H_2O$: H_2O, 8.78. Found: H_2O, 8.23. Calcd. for $C_{13}H_{18}ClN$: C, 64.65; H, 8.28. Found: C, 64.46; H, 8.09.

The benzoyl derivative was prepared by shaking the ether solution of IIb with benzoyl chloride and 1 *N* aqueous sodium hydroxide, and melted at 96–97° on recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.65; H, 7.10.

The picrate had m.p. 197–198.5° (from ethanol).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 54.55; H, 4.85.

On the other hand, the ethereal filtrate and washings obtained on isolation of the carbonate of IIb were combined, washed with alkaline solution, and dried. On removal of the solvent and recrystallization of the residue from petroleum ether, 1,2,3,4,7,8,9,-10-octahydrobenzo[*f*]quinoline (XI, 15 g.), m.p. 64–66°, was obtained.

Reduction of Benzo[*f*]quinoline (IX) with Sodium and Amyl Alcohol.—The reduction was conducted in essentially the same way as described by Bamberger and Müller.[12] To small pieces of sodium (30 g.) was added rapidly benzo[*f*]quinoline (10 g.) dissolved in hot amyl alcohol (200 ml.) under stirring, when vigorous boiling took place and, after about 10 min., ceased. The solution was continuously refluxed until all the sodium disappeared. To the cooled reaction mixture was added water (500 ml.), and the aqueous layer was acidified with hydrochloric acid. After the amyl alcohol was distilled by steam distillation, the acidic solution was made basic and then treated with ether. Into the ether solution was passed carbon dioxide to give the precipitate of carbonate. The precipitate, after washing with ether, was reconverted into a solid free base, from which *trans*-1,2,3,4,-4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIa, 0.3 g.), m.p. 88–90°, was obtained after recrystallization from petroleum ether (lit.[12] m.p. 91°).

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.25; H, 9.12.

The hydrochloride melted at 251–253°, lit.[12] m.p. 252°, and the picrate melted at 189–190° (from ethanol).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 55.06; H, 5.04.

The benzoyl derivative, prepared like the corresponding *cis* isomer, melted at 100–102° on recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.69; H, 7.16.

The ethereal filtrate and washings obtained on separation of the carbonate were combined, washed with alkali, and dried. On removal of the solvent, a semisolid mixture of base was obtained. The solid was collected by filtration and recrystallized from petroleum ether to give 1,2,3,4,7,8,9,10-octahydrobenzo[*f*]-quinoline (XI, 3.0 g.), m.p. 64–66°, lit.[12] m.p. 60.5°, λ_{max} 300 mμ (ε 2000) and 251 mμ (ε 8500).

Anal. Calcd. for $C_{13}H_{17}N$: C, 82.37; H, 9.15. Found: C, 82.62; H, 8.97.

The hydrochloride melted at 220–222°, lit.[12] m.p. 219°; the picrate melted at 150–152° (from ethanol).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 55.03; H, 4.95.

The benzoyl derivative melted at 144–146° (from ethanol).

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.60; H, 7.25.

The oily filtrate (4.0 g.) obtained on isolation of XI was found to consist mainly of X on the basis of the ultraviolet and infrared spectra, but it was not further examined.

Catalytic Hydrogenation of Tetrahydrobenzo[*f*]quinoline (X) over Platinum. A.—Tetrahydrobenzo[*f*]quinoline (4.0 g.) was hydrogenated over platinum oxide (0.4 g.) at room temperature in acetic acid (30 ml.). During the hydrogenation, three 0.1-g. portions of the catalyst were added, and after 15 hr. 2 moles of hydrogen was absorbed. The reaction mixture was worked up as usual and gave a mixture of bases, which was dissolved in ether. Carbon dioxide was passed into the ether solution for 3 hr. and the precipitate thus formed was separated from the ether solution. The carbonate was again regenerated to a semisolid mixture (0.5 g.) of bases, which was allowed to stand in air for 7 to 10 days. A part of the mixture was again converted to the carbonate, which was collected after treatment with ether. The carbonate was reconverted into the *cis*-octahydro derivative (IIb, 0.12 g.), b.p. 160–165° (5 mm.). On the other hand, the ether solution afforded *trans* isomer (IIa, 0.18 g.), m.p. 88–90°, on removal of the solvent followed by recrystallization of the residue from petroleum ether. Identification was carried out by comparison of their infrared spectra with those of pure samples mentioned above. The ether solution free from the carbonates of IIa and IIb yielded a solid base, which was recrystallized from petroleum ether to give the 1,2,3,4,7,8,9,10-octahydro derivative (XI, 3.0 g.), m.p. 61–63°.

B.—The hydrochloride[13a] (7.0 g.) of X was hydrogenated in presence of Adams' platinum (0.5 g.) at room temperature in ethanol. During the hydrogenation more platinum oxide (0.1 g.) was added and 2 moles of hydrogen were consumed after 10 hr. The reaction product was worked up as mentioned above, and *cis*-octahydrobenzo[*f*]quinoline (IIb, 0.27 g.) and the 1,2,3,4,7,8,-9,10-octahydro derivative (XI, 5.0 g.) were obtained. No *trans* isomer (IIa) could be isolated.

Methylation of *trans*- and *cis*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines (IIa and IIb).—*trans*-Octahydrobenzo[*f*]-quinoline (3.5 g.) was gently refluxed with methyl iodide (3.0 g.) in methanol (20 ml.) for 2 hr. After removal of the excess of methyl iodide and methanol, the residue was shaken with ether and 6 *N* aqueous potassium hydroxide (20 ml.), when the crude methiodide (2.0 g.), insoluble in the two layers, separated and was collected by filtration. By passing carbon dioxide into the ether solution, the carbonate of IIa was obtained. The ether solution free from the carbonate gave a crude N-methyloctahydro derivative (1.5 g.), which was again used in formation of the methiodide without further purification; it was treated with methyl iodide under similar conditions and the crude methiodide (1.8 g.) was formed. Recrystallization of the combined methiodides from acetone afforded N-methyl-*trans*-octahydrobenzo[*f*]-quinoline methiodide (XIIa, 2.5 g.), m.p. 238–240°.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.24; H, 6.44.

An analytical sample of N-methyl-*trans*-octahydrobenzo[*f*]-quinoline (VIIIa), b.p. 145–150° (4 mm.), was obtained by purification through the picrate.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.57; H, 9.51. Found: C, 83.45; H, 9.62.

The picrate melted at 210–212° after crystallization from ethanol.

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.67; H, 4.98.

cis-Octahydrobenzo[*f*]quinoline (IIb, 3.5 g.) was methylated under the same conditions to give the *cis*-methiodide (XIIb, 3.0 g.), m.p. 294–295° (from acetone).

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.26; H, 6.26.

The N-methyl derivative (VIIIb) had b.p. 145–151° (4 mm.).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.57; H, 9.51. Found: C, 83.39; H, 9.48.

The picrate melted at 165–167° (from ethanol).

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 56.09; H, 5.31.

The Exhaustive Methylation of N-Methyl-*trans*- and -*cis*-1,2,3,-4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Methiodides (XIIa and XIIb).—A solution of the *trans*-methiodide (XIIa, 2.5 g.) in 50% aqueous ethanol (50 ml.) was treated with silver oxide in the dark for 12 hr. After removal of the inorganic compounds by filtration, the reaction product was evaporated to dryness below 70° under reduced pressure. The sirupy residue was heated to 170° under reduced pressure (4 mm.) and decomposition took place at about 140°. The product was extracted with ether, and the ether solution was subjected to distillation after drying. 1-(3-Dimethylaminopropyl)-3,4-dihydronaphthalene (XVI, 0.5 g.), b.p. 150–155° (4 mm.), was obtained, λ_{max} 261 mμ (ε 8900). Ultraviolet spectrum[16] of 1,2-dihydronaphthalene showed λ_{max} 262 mμ (ε 10,230).

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.45; H, 9.78.

The base (XVI) was converted into the picrate, m.p. 87–88° (from acetone).

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.98; H, 5.43.

The Hofmann degradation of the *cis*-methiodide (XIIb, 3.0 g.) was conducted in practically the same way, and the base (XVI, 0.8 g.) was obtained. The ultraviolet and infrared spectra of the product were completely identical with those of the base from the *trans* isomer.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.79; H, 9.68.

The picrate melted at 87–88° (from acetone).

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.40; H, 5.26.

Acknowledgment.—The authors are greatly indebted to Professor T. Irie for his continuous encouragement during this work, and to Miss A. Maeda for microanalyses.

Degradation of α-Methyl-3,4-dihydroxyphenylalanine (α-MethylDOPA)

H. L. SLATES, D. TAUB, C. H. KUO, AND N. L. WENDLER

Merck Sharp and Dohme Research Laboratories, Merck and Company, Inc., Rahway, New Jersey

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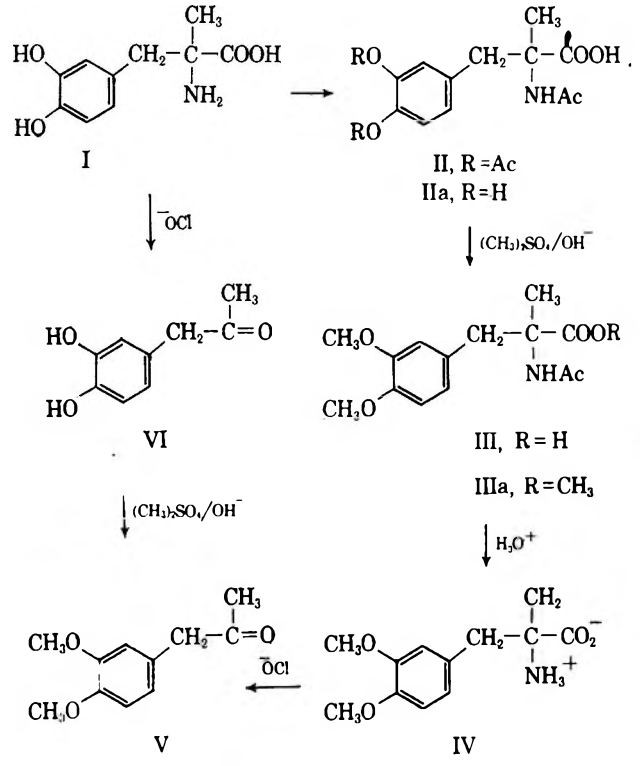
α-MethylDOPA has been degraded in high yield by several pathways to derivatives of 3,4-dihydroxyphenylacetone. These degradations comprise recycle routes for the utilization of D-(+)-α-methylDOPA in the synthesis of L-(−)-α-methylDOPA.

The importance of α-methylDOPA as an antihypertensive agent is well recognized.[1] The synthesis of this substance from 3,4-dimethoxyphenylacetone *via* the Strecker hydantoin sequence[2] requires an optical resolution whereby the biologically inactive D-(+) isomer is made available in equal amount with the active component, L-(−)-α-methylDOPA.[3]

It became of interest to examine possible modes for utilization of the biologically inactive D-(+) isomer for resynthesis of its optical antipode. In view of the character of substitution at the optically active α-position and the consequent inaccessibility of the latter to normal racemization procedures, attention was directed to degradation of the α-methylDOPA system to a precursor, namely, 3,4-dimethoxyphenylacetone. As a result of this investigation, two methods were developed for effecting this degradation in 85–90% conversion and a third method was found effective to the extent of 70–75%.

The great instability to alkali of the catechol system present in α-methylDOPA had long represented a formidable deterrent to procedural undertakings designed to inactivate this portion of the molecule, and, thereby, provide latitude for chemical manipulation of the amino acid segment. It subsequently was discovered that, by scrupulous exclusion of air and by working with solutions previously purged with nitrogen, α-methylDOPA could be handled in alkaline solution without decomposition. A further observation was made as well, namely, that the N-acetyl group of acetylated α-methylDOPA is exceedingly resistant to alkaline saponification and is stable, for example, to 10% sodium hydroxide solution at 150°. Pursuant to these observations, the O,O′,N-triacetate of α-methylDOPA (II),[3] obtained quantitatively from α-methylDOPA, was methylated with dimethyl sulfate and potassium hydroxide, in a typical Schotten–Baumann manner, to give 95% of the N-acetyl dimethyl ether (III), m.p. 187–188°, together with 5% of the corresponding methyl ester (IIIa), m.p. 126–127°. The total methylation product (III + IIIa) was hydrolyzed essentially quantitatively with hydrochloric acid to α-methylDOPA dimethyl ether (IV).[2] Thus, α-methylDOPA could be converted to its dimethyl ether in nearly quantitative over-all conversion. Methylation of α-methylDOPA unprotected by the N-acetyl group resulted in N-methylation products. The N-acetyl derivative of α-methylDOPA, on the other hand, was easily prepared by hydrolysis of the corresponding triacetate and it, in turn, gave results similar to its precursor in the methylation reaction. The transformation of α-methylDOPA dimethyl ether to 3,4-dimethoxyphenylacetone (V) was effected oxidatively with sodium hypochlorite[4] in 90% yield. Thus, the total

CHART I



(1) See, for example: L. Gillespie, Jr., *Ann. N. Y. Acad. Sci.*, **88**, 1011 (1960); H. Smirk, *Brit. Med. J.*, 146 (1963), and references therein.

(2) G. Stein, H. A. Bronner, and K. Pfister, III, *J. Am. Chem. Soc.*, **77**, 700 (1955).

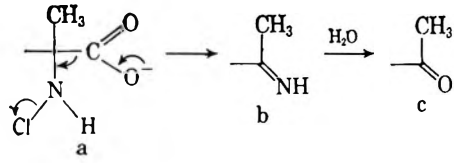
(3) E. W. Tristram, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *J. Org. Chem.*, in press.

(4) For the employment of hypochlorite in the degradation of natural amino acids, see: (a) K. Langheld, *Ber.*, **42**, 392 (1909); (b) H. P. Dakin *Biochem. J.*, **10**, 319 (1916); **11**, 79 (1917); (c) D. D. van Slyke, D. A Mcfayden, and D. Hamilton, *J. Biol. Chem.*, **141**, 627 (1941); (d) I. D. Spenser, J. C. Crowhall, and D. G. Smyth, *Chem. Ind.* (London), 796 (1956).

sequence (Chart I) from α-methylDOPA to 3,4-dimethoxyphenylacetone, consisting of the four steps, acetylation, methylation, hydrolysis, and hypochlorite oxidation, can be effected with a potential over-all yield of 90%.

The direct hypochlorite oxidation of α-methylDOPA itself proceeds in the desired manner to give 3,4-dihydroxyphenylacetone in *ca.* 50% yield. The latter substance is highly water soluble and sensitive as well to manipulation, although it can be methylated to V in reasonable yield. To a large and competitive extent, however, the direct hypochlorite oxidation of α-methylDOPA involves nuclear attack as evidenced by accompanying resinification. The use of *t*-butyl hypochlorite was found to be superior to sodium hypochlorite in this instance and suggests, thereby, that the breakdown reaction to ketone is faster than nuclear involvement. The hypochlorite degradation of the 3-monomethyl ether of α-methylDOPA to 3-methoxy-4-hydroxyphenylacetone also can be accomplished in at least 60–70% yield.

The oxidative degradation IV → V would appear clearly to be initiated by N-chlorination (compare a → b → c) inasmuch as the N-acetate derivative III is unchanged under the conditions of hypochlorite oxidation, whereas the latter (III) is oxidized smoothly by lead tetraacetate (see later text), a reagent known to attack carboxyl functions.[5]



Acetylation of α-methylDOPA (I) or its dimethyl ether (IV) with acetic anhydride in pyridine produces directly the corresponding azlactones VII and VIIa (Chart II) in the absence of a hydrolytic work-up. The former (VII) was obtained as a viscous distillable liquid, whereas VIIa was isolated as a crystalline compound, m.p. 90–91°. Ultraviolet irradiation of the azlactone VIIa in dioxane solution slowly but smoothly converted this substance *via* VIII (or its eneamine tautomer) to 3,4-dimethoxyphenylacetone (V) with liberation of carbon monoxide. The latter was characterized by displacement from dioxane solution and identification by its infrared spectrum. The course of the irradiation could be followed readily by the decrease in optical rotation with time. The irradiation was arbitrarily interrupted after 3 days at a point corresponding to 85% conversion and a commensurate amount of 3,4-dimethoxyphenylacetone was isolated. Irradiation of the corresponding diacetoxy azlactone VII took an indeterminate course. Work-up of the irradiation product, however, did yield a small amount of α-methylDOPA triacetate (II) identical by melting point and infrared spectrum with authentic II but exhibiting a 14% lower optical rotation. This finding suggests that II derived from the irradiation of VII had suffered racemization to a commensurate extent

(5) W. von E. Doering, M. Farber, and A. Sayigh, *J. Am. Chem. Soc.*, **74**, 4370 (1952); C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958); E. J. Corey and J. Casanova, Jr., *J. Am. Chem. Soc.*, **85**, 165 (1963).

CHART II

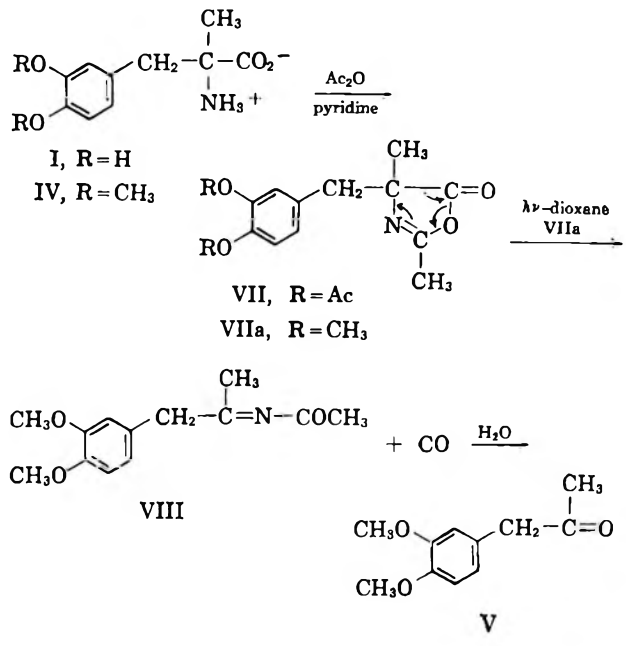
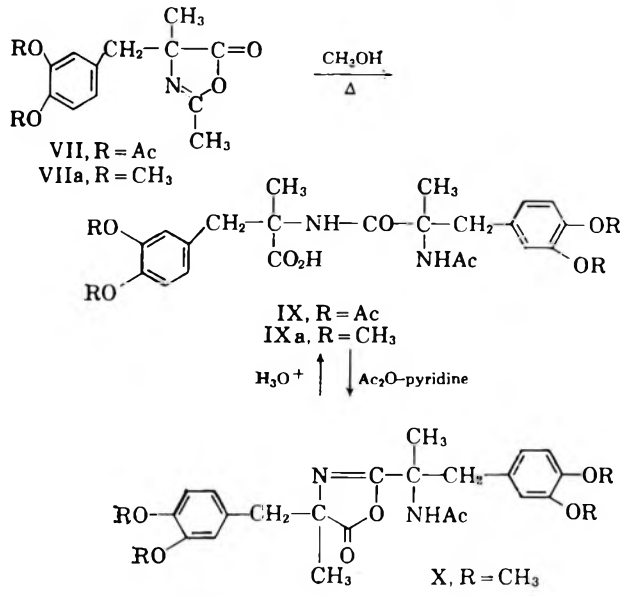


CHART III



and in a manner quite possibly parallel with the light-induced isomerization of estrone to lumiestrone.[6]

Treatment of the azlactone VIIa with anhydrous methyl alcohol, in the anticipation of preparing the corresponding methyl ester of III, produced an unexpected result (Chart III). The dipeptide acid IXa was formed in consequence to this treatment. The latter was subsequently treated with acetic anhydride in pyridine to give the dipeptide azlactone X. The dipeptide acid IXa also was formed from VIIa in hot ethyl alcohol but was recovered when *t*-butyl alcohol was employed. Treatment of VIIa with 2 equiv. of sodium methoxide in methyl alcohol afforded the methyl ester of IV (m.p. 128–129°) but only in 15–20% yield. One might wish to speculate as to the pathway whereby VIIa, under ostensibly anhydrous conditions, is converted to the dipeptide in alcohol solution. If, as an alternative to methanolysis of the lactone ring to

(6) A. Butenandt, A. Wolff, and P. Karlson, *Ber.*, **74**, 1308 (1941).

CHART IV

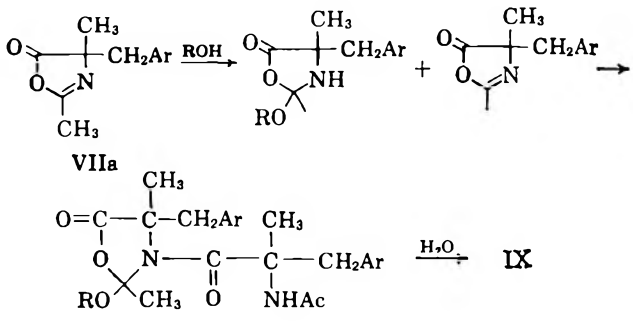


CHART V

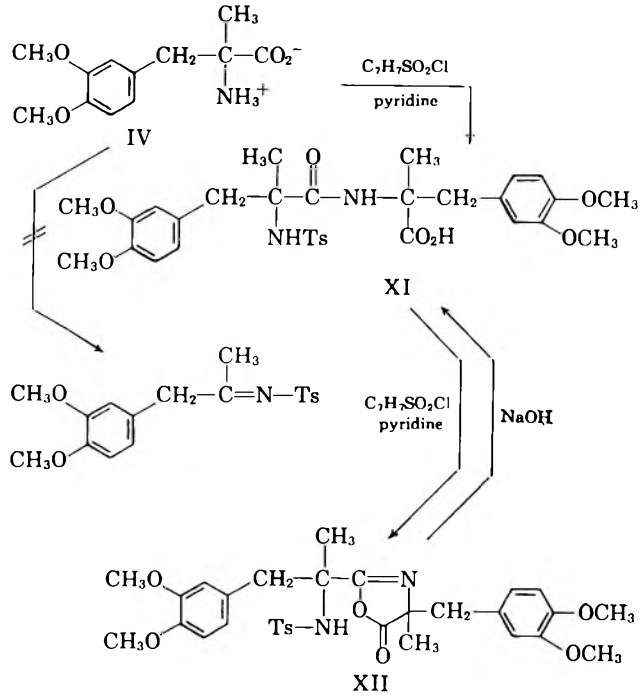
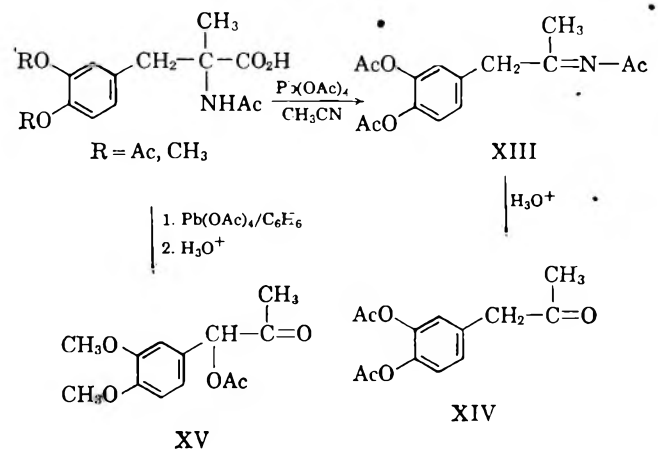


CHART VI



give ester, addition of this reagent were to occur at the azomethine linkage, a donor center would then be created which could function as a coupler with a second azlactone molecule (Chart IV).

Attempts to effect conversion of α-methylDOPA dimethyl ether to 3,4-dimethoxyphenylacetone by means of the mixed-anhydride degradation with *p*-toluenesulfonyl chloride[7] were not successful. Instead of the anticipated reaction, the dipeptide azlactone (XII) was formed (Chart V). The latter was, in turn, readily hydrolyzed to the dipeptide acid (XI). This result parallels in kind the experience observed on methyl alcohol treatment of the azlactone (VIIa). In this instance, it may be surmised that in the tosylation reaction untosylated amino acid reacts with tosylated material to provide the coupled system XI. This suggests that the primary locus of tosylation is the carboxyl group rather than the amine function.

The final degradation conversion of α-methylDOPA to its ketone precursor was effected by means of lead tetraacetate oxidation of α-methylDOPA triacetate in acetonitrile solution (Chart VI). The intermediate ketimine acetate (XIII) (or its enamine tautomer) was hydrolyzed with dilute acid to provide the ketone XIV in 70–75% over-all yield. This method is advantageous in being simple and straightforward[8] and providing a rapid means of executing the desired degradation. If the lead tetraacetate oxidation is effected in benzene solution, there results, in addition to oxidative decarboxylation, acetoxylation at the position α to the aromatic nucleus. The latter consequence was ascertained in the case of III by hydrolysis of the oxidation product to the corresponding ketol acetate XV which exhibited a strong positive tetrazolium test and possessed bands in the infrared at 5.72 and 5.78 μ characteristic of this functional type.[9] The structure of XV was secured by alkaline hydrolysis which led to a mixture of ketols that was cleaved by periodic acid to veratraldehyde and veratric acid.

Experimental

L-(−)-**N-Acetyl-α-methyl-3,4-diacetoxyphenylalanine (II).**[3]—Acetic anhydride, 400 ml. was added portionwise to a stirred slurry of 100 g. of L-(−)-α-methyl-3,4-dihydroxyphenylalanine[10] [L-(−)-α-methylDOPA contained 12.1% water by Karl Fischer titration] in 400 ml. of pyridine. A clear yellow solution was obtained after 0.5 hr., and the reaction mixture was maintained at room temperature for 16 hr. The reaction mixture was concentrated *in vacuo* and flushed three times with toluene, cooled in an ice bath, and acidified with 2.5 *N* hydrochloric acid. The semisolid product was extracted with hot ethyl acetate and the ethyl acetate extract washed with saturated salt solution, dried over magnesium sulfate, and concentrated *in vacuo*. Addition of ether afforded a 134-g. first crop of L-(−)-α-methylDOPA triacetate (II). The latter gave a negative methanolic ferric chloride test and melted at 178–180°. A sample recrystallized from hot acetone melted at 178–180°; $\lambda_{max}^{CH_3OH}$ 268 mμ (ε 372) and 263 (415); $\lambda_{max}^{CHCl_3}$ 2.96, 3–4.2, 5.69, 5.85, 5.99, 6.15, and 6.6 μ; $[\alpha]^{acetone}D$ −45.6°.

Anal. Calcd. for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.20; H, 6.17; N, 4.06.

A second crop of 1–2 g. was obtained from the above ether filtrate.

L-(−)-**N-Acetyl-α-methyl-3,4-dimethoxyphenylalanine (III).**—A stream of nitrogen was bubbled through 200 ml. of 4 *N* potassium hydroxide solution for 20 min. and the alkaline solution was cooled to 5–10° prior to the addition of 50.0 g. (0.148 mole) of L-(−)-α-methylDOPA triacetate (nitrogen flow maintained

(7) Compare A. F. Beecham, *J. Am. Chem. Soc.*, **79**, 3257 (1957); E. Wünsch, *Proc. Symp. Methods Peptide Syn.*, 1958; *Collection Czech. Chem. Commun.*, **24**, 60 (1959). See also J. C. Sheehan and J. W. Frankenfeld, *J. Org. Chem.*, **27**, 628 (1962).

(8) Lead tetraacetate has been reported not to react with N-acetyl- and N-benzoyl-α-amino acids [review by R. Criegee, *Angew. Chem.*, **53**, 321 (1940)]. However, cleavage of N-acyl-α-amino acids by this reagent has been described [O. Süss, *Ann.*, **564**, 137 (1949)].

(9) See, for example, R. N. Jones and G. Roberts, *Chem. Ind.* (London), 1269 (1957), and references listed therein.

(10) For reasons of convenience and availability, the L-(−) isomer was employed. Obviously the optical antipode could have been utilized with the same essential consequences.

throughout). The cooling bath was removed and 50 ml. of dimethyl sulfate (0.56 mole) and 100 ml. of 4 *N* potassium hydroxide were then added with occasional use of a cooling bath to maintain the temperature at about 25°. An essentially negative methanolic ferric chloride reaction was obtained after stirring for 30 min. An additional 25 ml. of dimethyl sulfate (0.28 mole) followed by 50 ml. of 4 *N* potassium hydroxide were added and stirring was continued for an additional 30 min.[11] The strongly basic reaction mixture was then extracted with ether.

The ethereal solution was washed to neutrality with water and salt solution, dried over magnesium sulfate, and concentrated *in vacuo* to give 2.5 g. of crystalline O,O-dimethyl-N-acetyl-L-(−)-α-methylDOPA methyl ester (IIIa),[12] m.p. 127–129° after recrystallization from acetone–ether; $\lambda_{max}^{CH_3CN}$ 233 mμ (ε 8850) and 280 (2970); $[\alpha]^{acetone}D$ −45.5°.

Anal. Calcd. for $C_{15}H_{21}O_5N$: C, 61.01; H, 7.17; N, 4.74. Found: C, 61.12; H, 6.83; N, 5.14.

The aqueous solution was chilled and acidified with concentrated hydrochloric acid to yield a heavy precipitate of III. The latter was aged and filtered. This product (m.p. 182–185°) was dissolved in hot ethyl acetate,[13] washed with salt solution, dried over magnesium sulfate, and concentrated under reduced pressure to give 35.10 g. of L-(−)-α-methylDOPA dimethyl ether N-acetate as fine needles, m.p. 186–187°; $\lambda_{max}^{CH_3CN}$ 232 mμ (ε 8960) and 288 (2980); $[\alpha]^{acetone}D$ −21.0°.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 60.10; H, 6.77; N, 4.74.

The aqueous filtrate was saturated with salt and extracted with ethyl acetate; the organic phase was washed with salt solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford an additional 4.97 g. of III, m.p. 181–184° (total 96.5%). The combined product, namely, III and its methyl ester, correspond to a 100% yield of utilizable methylation product.

L-(−)-α-Methyl-3,4-dimethoxyphenylalanine Hydrochloride.—The dimethoxy-α-methylDOPA N-acetate (160 g.) in 1800 ml. of 6 *N* hydrochloric acid was magnetically stirred and refluxed for 2 hr. The light brown reaction mixture was concentrated *in vacuo* to dryness and flushed three times with *t*-butyl alcohol, two two times with toluene, and twice with ether to afford 161 g. (97%) of the hydrochloride IV, m.p. 235–238°, with phase change from granular to star-like needles at 192°. Crystallization from aqueous acetone gave the analytical sample, melting point unchanged; $\lambda_{max}^{CH_3OH}$ 231 mμ (ε 8160) and 278 (2680); λ_{max}^{Nujol} 2.86, 2.99, 3.3–3.5, 5.74, 6.17, 6.25, and 6.59 μ.

Anal. Calcd. for $C_{12}H_{18}NO_4Cl \cdot H_2O$: C, 49.08; H, 6.86; N, 4.77; Cl, 12.07; H_2O, 6.1 (Karl Fischer test). Found: C, 48.93; H, 6.75; N, 4.81; Cl, 12.10; H_2O, 5.7 (Karl Fischer test).

α-Methyl-3,4-dimethoxyphenylalanine (IV).—L(−)-α-Methyl-3,4-dimethoxyphenylalanine hydrochloride (518 mg., 1.78 mmoles) in 15 ml. of water was magnetically stirred and 2.00 g. of the basic resin Dowex 1-X8[14] added. A net change of 1.35 pH units from 2.3 to 3.65 was realized within 1 hr. The resin was filtered and washed thoroughly with water. The combined aqueous filtrate was azeotroped to dryness with toluene to afford 450 mg. of crystalline free amino acid monohydrate in quantitative yield exhibiting a negative Beilstein test and a single spot by paper chromatogram (*n*-butyl alcohol–acetic acid–water system, 4:1:1), m.p. 246–249°, with phase change from granular to needles at 215–240°; λ_{max}^{Nujol} 2.7, 2.85, 6.1 (sh), and 6.3 μ; Karl Fischer test, 13.2% (calculated for monohydrate, 14.4%).

The L-(−)-α-methylDOPA dimethyl ether monohydrate was recrystallized from aqueous isopropyl alcohol to afford a first crop of 350.7 mg. of the corresponding anhydrous amino acid; plates, m.p. 250–254°, with phase change at 223–245° from plates to needles; $\lambda_{max}^{CH_3OH}$ 233 mμ (ε 9450) and 280 (3200); λ_{max}^{Nujol} 3.8–4.2, 6.08, 6.33, and 6.61 μ.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.23; H, 7.16; N, 5.86. Found: C, 59.92; H, 7.28; N, 5.91.

Dipeptide Azlactone (XII) Derived from α-Methyl-3,4-dimethoxyphenylalanine (IV).—*p*-Toluenesulfonyl chloride (29.96 g., 0.157 mole) was added in portions to a stirred suspension of 9.38 g. (0.039 mole) of L-(−)-α-methylDOPA dimethyl ether (IV) in 80 cc. of dry pyridine at 0° and the reaction mixture was stored at 0° for 16 hr. Pyridine salts were removed by filtration and the filtrate was acidified with 6 *N* hydrochloric acid to give a gummy residue which was extracted into ethyl acetate. The organic phase was washed with water, 5% sodium bicarbonate, and salt solution, dried over magnesium sulfate, and concentrated *in vacuo* to 12.3 g. of yellow foam. The latter crystallized on trituration with ether. The crystalline compound was filtered to afford 6.7 g. of crude dimeric lactone (XII), m.p. 156–168°. The latter was recrystallized from acetone–ether to provide 3.35 g. of product, m.p. 179–184°. Another recrystallization from the same solvent combination furnished the analytical sample, m.p. 184–185°; $\lambda_{max}^{CH_3OH}$ 278 mμ (ε 5600) and 230 (28,300); $\lambda_{max}^{CHCl_3}$ 5.50, 5.95, 6.20, 6.56, and 7.42 μ; n.m.r., in accord with the structure.

Anal. Calcd. for $C_{31}H_{36}O_8N_2S$: C, 62.39; H, 6.08; N, 4.70; S, 5.37; neut. equiv., 596. Found: C, 62.67; H, 5.86; N, 5.16; S, 5.15; neut. equiv., 550.

Hydrolysis of the above azlactone was effected with 1 *N* sodium hydroxide by dissolving hot and precipitating the free acid with hydrochloric acid. The crude dipeptide acid (XI) was obtained in amorphous form from acetone (m.p. 91–95°); $\lambda_{max}^{CH_3OH}$ 279 mμ (ε 5480) and 230 (26,200); $\lambda_{max}^{CHCl_3}$ 2.9, 3.0–4.2, 5.75, 5.94, 6.2, and 6.55 μ.

Anal. Calcd. for $C_{31}H_{38}N_2O_9S$: N, 4.56; S, 5.22. Found: N, 4.94; S, 5.06.

3,4-Dimethoxyphenylacetone (V) from IV.—To a stirred solution (20–25°) of 956 mg. (4.00 mmoles) of α-methyl-3,4-dimethoxyphenylalanine (IV) in 25 ml. of water was added 10 ml. of benzene. Sodium hypochlorite solution (14 ml., 0.3 *N* active chlorine)[15] was added dropwise over 20 min. The reaction was followed by spotting aliquots on starch–iodide paper. After each addition of hypochlorite, a negative test was obtained in about 30 sec. At the reaction's completion, a positive test was obtained 5 min. after addition of the last drop of hypochlorite. The layers were separated and the basic aqueous layer was extracted twice with 50% benzene–ether; the combined organic phase was dried over magnesium sulfate and concentrated to dryness *in vacuo*. The neutral residue (725 mg., 92%) consisted of 3,4-dimethoxyphenylacetone; infrared spectrum was identical with standard; v.p.c. showed it to be 97% pure.

Semicarbazone.—The semicarbazone crystallized from ether–chloroform and had m.p. 171–174°; mixture melting point was undepressed with an authentic sample of m.p. 175–176°.

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.34; H, 6.82; N, 16.73. Found: C, 57.21; H, 6.67; N, 16.51.

3,4-Dihydroxyphenylacetone (VI). A. Sodium Hypochlorite.—To a stirred solution of 844 mg. (4.00 mmoles) of α-methyl-3,4-dihydroxyphenylalanine (I) in 20 ml. of 0.5 *M* borax buffer (pH 8.5)[16] was added 10 ml. of benzene. Nitrogen was bubbled through the solution and 12.0 ml. of 0.34 *N* sodium hypochlorite solution added dropwise. The red solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The latter extract was dried and concentrated to dryness. The residue was triturated with chloroform, the latter suspension filtered, and the filtrate concentrated to dryness *in vacuo* to give 3,4-dihydroxyphenylacetone, 235 mg. (~36%), with additional mate-

(11) The completion of this reaction is marked by a negative ferric chloride test which at this point was essentially secured. The additional quantities of dimethyl sulfate and potassium hydroxide solution added thereafter were, in the pertinent case, precautionary rather than essential.

(12) A separate experiment revealed that the methyl ester is hydrolyzable with 6 *N* hydrochloric acid to afford the same L-(−)-α-methylDOPA dimethyl ether hydrochloride monohydrate as the product of the subsequent step. Thus, the step involving removal of the ester is neither essential nor, in fact, to be recommended.

(13) The precipitated material which may be directly filtered from the acidified aqueous solution is chemically pure in all respects and utilizable as such for the subsequent acid hydrolysis. This step, therefore, is not necessary in a large run.

(14) Basic resin (200–400 mesh), Dowex 1-X8 (Technical Service and Development, Dow Chemical Co., Midland, Mich.), in the chloride form was converted to the corresponding quaternary hydroxide by eluting with five volumes of 5% sodium hydroxide on a chromatographic column followed by washing to near-neutrality with water. Three volumes each of ethyl alcohol and ether were passed through the column to provide the resin in a dry form which was further dried to constant weight in a vacuum desiccator. The base equivalence of the dry resin was determined by slurrying a weighed sample in excess standard hydrochloric acid followed by filtration and back titration of the filtrate with standard sodium hydroxide.

(15) Commercial "5%" sodium hypochlorite was used. A 5.00-ml. aliquot was added to 2 g. of potassium iodide in 30 ml. of 0.5 *N* hydrochloric acid and the iodine formed titrated vs. 0.1 *N* sodium thiosulfate; 30.50 ml. of 0.1 *N* sodium thiosulfate was required.

(16) Borax buffer: 3.1 g. of boric acid in 50 ml. of water, 8.5 ml. of 1 *N* sodium hydroxide, and enough water to bring the total to 100 ml.

rial still in the aqueous mother liquors; $\lambda_{max}^{CHCl_3}$ 2.75, 2.90 (O–H), and 5.88 μ (C=O). Acetylation of a probe (pyridine–acetic anhydride, 25°, 18 hr.) gave 3,4-diacetoxyphenylacetone. The latter was identified as the diacetate by comparison with an authentic sample (see diacetoxyphenylacetone section).

B. *t*-Butyl Hypochlorite.—To a stirred suspension of 844 mg. (4.00 mmoles) of α-methyl-3,4-dihydroxyphenylalanine in 10 ml. of water (under nitrogen) was added 340 mg. (4.00 mmoles) of sodium bicarbonate. *t*-Butyl hypochlorite (0.50 g., 4.5 mmoles) in 10 ml. of *t*-butyl alcohol was added dropwise over 30 min. The deep red reaction mixture was acidified with 5 ml. of 2 *N* hydrochloric acid and extracted thoroughly with ethyl acetate. Further work-up as in A led to 335 mg. (50%) of 3,4-dihydroxyphenyl acetone; infrared spectrum was identical with that of an authentic sample.

3,4-Diacetoxyphenylacetone (XIV) from II.—To a stirred solution of 16.85 g. (50 mmoles) of N-acetyl-α-methyl-3,4-diacetoxyphenylalanine (II) in 125 ml. of acetonitrile was added 4.00 ml. (50 mmoles) of pyridine followed by 22.15 g. (50 mmoles) of lead tetraacetate. The mixture was warmed cautiously to reflux temperature at which point lead acetate precipitated rapidly from solution. The mixture was refluxed gently for 30 min., cooled, filtered, and the filtrate concentrated to dryness. The residue, consisting mainly of the intermediate decarboxylated imine triacetate (XIII), was hydrolyzed by heating on the steam bath (90–95°) with 15 ml. of acetic acid and 10 ml. of water for 50 min. The mixture was cooled, water was added, and it was extracted with chloroform. The chloroform extract was washed with dilute potassium bicarbonate solution and salt solution, dried over magnesium sulfate, and concentrated to dryness to give 3,4-diacetoxyphenylacetone (XIV), 9.4 g. (75%); b.p. 145–150° (0.05 mm.); $\lambda_{max}^{CHCl_3}$ 5.80 and 5.84 μ; v.p.c. showed a single peak.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.05; H, 5.75.

The diacetoxy ketone was converted in good yield by the appropriate processes to the corresponding dimethoxy ketone V and to the dihydroxy hydantoin and α-methylDOPA.

Similar lead tetraacetate treatment of the N-acetyldimethoxyamino acid IIIa in acetonitrile–pyridine led to the dimethoxy ketone V.

α-Acetoxy-3,4-dimethoxyphenylacetone (XV) from IIIa.—To a stirred suspension of 2.81 g. (10 mmoles) of N-acetyl-α-methyl-3,4-dimethoxyphenylalanine (IIIa) in 70 ml. of benzene and 0.80 ml. (10 mmoles) of pyridine was added 4.41 g. (10 mmoles) of lead tetraacetate.

The mixture was refluxed 30 min. and cooled; the precipitated lead acetate was removed by filtration; the filtrate was concentrated to dryness to give an orange oil, 2.32 g. A 1-g. portion of the latter in 20 ml. of 50% aqueous acetic acid was warmed on the steam bath for 1 hr., cooled, and extracted with chloroform. The latter extract was washed with dilute aqueous potassium bicarbonate and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness to give a yellow oil. By paper chromatography (benzene–cyclohexane (2:1)–formamide), this material contained only a minor amount of 3,4-dimethoxyphenylacetone (V). It consisted mainly of the slightly more mobile substance XV which gave a strong positive tetrazolium test characteristic of α-ketol systems (V gave a negative test); $\lambda_{max}^{CHCl_3}$ 5.72 and 5.78 μ.

Veratraldehyde and Veratric Acid from XV.—A 250-mg. sample of the above dimethoxyphenyl ketol acetate XV was treated with 110 mg. of sodium hydroxide in 5 ml. of methyl alcohol and 2 ml. of water for 30 min., following which, periodic acid dihydrate (700 mg.) in 4 ml. of water was added. After 18 hr. at 25° the methyl alcohol was removed *in vacuo*, water was added, and the mixture was extracted with chloroform. The latter extract was washed with 5% potassium bicarbonate solution, acidification of which led to a precipitate (60 mg.) of veratric acid. Crystallization from aqueous acetone led to 50 mg., m.p. 176–179°, mixture melting point undepressed with an authentic sample of m.p. 180°. The neutral residue (120 mg.) from the original chloroform extract had an infrared spectrum similar to that of veratraldehyde and, on treatment with 2,4-dinitrophenylhydrazine in aqueous methanolic sulfuric acid, the corresponding red 2,4-dinitrophenylhydrazone (m.p. 250–255°, plates from ethyl acetate) was produced. This substance gave an undepressed mixture melting point with authentic veratraldehyde 2,4-dinitrophenylhydrazone of m.p. 254–256°.

L-(−)-2,4-Dimethyl-4-(3,4-dimethoxybenzyl)-2-oxazolin-5-one (VIIa).—L-(−)-N-Acetyl-α-methyl-3,4-dimethoxyphenylalanine (IV), 4.0 g., was dissolved in 30 ml. of pyridine and 20 ml. of acetic anhydride and the reaction mixture was allowed to stand at room temperature overnight. The solvents were removed *in vacuo* and the residue was crystallized from ether–hexane to give 3.5 g. of L-(−)-2,4-dimethyl-4-(3,4-dimethoxbenzyl)-2-oxazolin-5-one (VIIa), m.p. 91–92°, $[\alpha]_D^{acetone}$ −84.2°.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.82; H, 6.21; N, 5.45.

Irradiation of L-(−)-2,4-Dimethyl-4-(3,4-dimethoxybenzyl)-2-oxazolin-5-one (VIIa) to Give 3,4-Dimethoxyphenylacetone (V).—A solution of 1.1 g. of L-(−)-2,4-dimethyl-4-(3,4-dimethoxybenzyl)-2-oxazolin-5-one (VIIa) in 40 ml. of dioxane in a quartz flask was irradiated for 90 hr. with a high pressure mercury arc ultraviolet lamp[17] equipped with a heat filter. At this point, the solution had lost 85% of its optical activity. The reaction mixture was concentrated *in vacuo* and the residue dissolved in 60 ml. of ether. The ether solution was extracted thoroughly with saturated potassium bicarbonate solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford 0.65 g. of esssentially pure 3,4-dimethoxyphenylacetone characterized spectroscopically and by comparison with authentic material.

In a similar experiment, the irradiation was carried out in a quartz flask equipped with a reflux condenser and connected to a nitrometer. After 90 hr., the reaction mixture was refluxed briefly and the gas phase product was collected. The presence of carbon monoxide in the gas phase was shown by strong bands at 4.2 and 4.7 μ in its infrared spectrum.

L(−)-2,4-Dimethyl-4-(3,4-diacetoxybenzyl)-2-oxazolin-5-one (VII).—L-(−)-α-Methyl-3,4-dihydroxyphenylalanine, 10 g., was dissolved in 70 ml. of pyridine and 50 ml. of acetic anhydride and the reaction mixture was held at room temperature overnight. The solvents were removed *in vacuo* and the residue was distilled at 160–170° (0.05 mm.) in a short-path still. There was obtained, as a viscous colorless oil, 9.0 g. of the azlactone, $[\alpha]_D^{acetone}$ −66.8°.

Anal. Calcd. for $C_{16}H_{17}O_6N$: C, 60.19; H, 5.36; N, 4.39. Found: C, 59.81; H, 5.22; N, 3.87.

Irradiation of L-(−)-2,4-Dimethyl-4-(3,4-diacetoxybenzyl)-2-oxazolin-5-one (VII).—A solution of 600 mg. of the azlactone (VII) in 20 ml. of dry dioxane in a quartz flask was irradiated with a high pressure mercury arc ultraviolet lamp[17] equipped with a heat filter (transmission cut-off at 220 mμ). The reaction mixture was sampled periodically for measurement of optical rotation. After 6 days, the optical rotation value of the reaction mixture had diminished 24%. The solvent was removed *in vacuo* and the residue was warmed on the steam bath for 1 hr. with aqueous acetone containing a few drops of acetic acid. The hydrolysis mixture was concentrated *in vacuo* to a small volume and allowed to stand at room temperature overnight. There was isolated *ca.* 100 mg. of crystalline material which, after recrystallization from acetone–hexane, afforded 30 mg. of α-methyl-3,4-dihydroxyphenylalanine triacetate, $[\alpha]_D^{acetone}$ −39.1°, m.p. 176–179°. The infrared spectrum in chloroform was identical with an authentic specimen. This material exhibits a change of optical rotation attributable to 14% racemization.

Dipeptide Acid IX.—To a solution of 500 mg. of the azlactone (VII) in 10 ml. of methyl alcohol was added a trace of *p*-toluenesulfonic acid.

The mixture was held at room temperature for 18 hr. and then concentrated *in vacuo*. The residual gel was crystallized from aqueous methanol to give 400 mg. of the dipeptide acid IX with m.p. 219–221°. Recrystallization from the same solvents afforded an analytical sample, m.p. 228–230°, $[\alpha]_D^{acetone}$ −11.5°.

Anal. Calcd. for $C_{30}H_{34}N_2O_{12}$: C, 58.62; H, 5.58; N, 4.56; neut. equiv., 614. Found: C, 58.72; H, 6.00; N, 4.58; neut. equiv., 581.

The infrared and n.m.r. spectra were in accord with the proposed structure.

Dipeptide Acid IXa. A.—A solution of 500 mg. of the azlactone (VIIa) in 20 ml. of methyl alcohol was refluxed for 18 hr. and then concentrated *in vacuo*.

The residue was treated with 25 ml. of boiling acetone and

(17) Hanovia mercury arc lamp, Utility Model Type 30600.

an insoluble crystalline product, 70 mg., m.p. 255–259°, was isolated by filtration and identified as α-methylDOPA dimethyl ether (IV). From the filtrate there was obtained, after concentration on the steam bath, 230 mg. of the dipeptide acid IXa, m.p. 213–222°. Recrystallization from acetone gave an analytical sample with m.p. 220–221°, $[\alpha]^{pyridine}D$ −37.9.

Anal. Calcd. for $C_{26}H_{34}N_2O_8$: C, 62.13; H, 6.83; N, 5.58; neut. equiv., 502. Found: C, 61.59; H, 6.53; N, 5.88; neut. equiv., 486.

The infrared and n.m.r. spectra were in agreement with the assigned structure.

The filtrate from the isolation of the dipeptide acid IXa was shown by thin-layer chromatography to contain, in addition to IXa, a small amount of the methyl ester of the N-acetyl dimethyl ether IIIa.

Substitution of ethyl for methyl alcohol in the above reaction gave analogous results. However, no reaction was observed with *t*-butyl alcohol.

B.—To a solution of 263 mg. of the dimethoxy azlactone VIIa in 30 ml. of dry pyridine was added 239 mg. of α-methylDOPA dimethyl ether. The amino acid gradually dissolved as the suspension was refluxed gently for 18 hr. The reaction mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. Crystallization of the residue from acetone afforded 150 mg. of the dipeptide acid IXa, m.p. 219–2221°, identical with that described in A preceding.

Dipeptide Azlactone X.—A solution of 100 mg. of dipeptide acid IXa in 2 ml. of pyridine was treated with 2 ml. of acetic anhydride and allowed to stand at room temperature for 18 hr. The reagents were evaporated *in vacuo* and flushed by toluene distillation. The residue was dissolved in ether, filtered, and crystallized from the same solvent to provide 50–60 mg. of X, m.p. 105–108°; $\lambda_{max}^{CHCl_3}$ 2.94 (N–H), 5.46 (azlactone), 5.98 and 6.58 (amide), and 6.2 and 6.25 (aromatic).

Anal. Calcd. for $C_{26}H_{32}N_2O_7$: C, 64.46; H, 6.61; N, 5.78. Found: C, 64.42; H, 6.57; N, 5.83.

The Synthesis of 3,3′-Bipyrrolidines in Both Configurational Series[1a]

PHILIP L. SOUTHWICK, JULIUS A. VIDA, AND DAVID P. MAYER[1b]

Department of Chemistry, Carnegie Institute of Technology, Pittsburgh 13, Pennsylvania

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New compounds in the 3,3′-bipyrrolidine series have been obtained from the aldol condensation product of 1-cyclohexyl-2,3-dioxopyrrolidine, the enol of 1,1′-dicyclohexyl-3-hydroxy-2,4′,5′-trioxo-3,3′-bipyrrolidine (I). Sodium borohydride reduction of I yielded a mixture of diastereoisomeric 1,1′-dicyclohexyl-3,4′-dihydroxy-2,5′-dioxo-3,3′-bipyrrolidines (II) from which one of the four possible racemic forms was separated. Lithium aluminum hydride reduction of compounds of structure II yielded 1,1′-dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidines (III); two of the four possible racemic forms were separately characterized. The dehydration product of I, 1,1′-dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidylidene (IV), yielded the enol of 1,1′-dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidine (V) when hydrogenated. Sodium borohydride reduction of V produced a mixture of the four possible racemic forms of 1,1′-dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidine (VI), all of which were separated. These four compounds were converted to 1,1′-dicyclohexyl-3,3′-bipyrrolidines (VIII); as expected, two of the forms yielded the symmetric (*meso*) structure (VIIIa) and two yielded the racemic form of the dissymmetric structure (VIIIb). Lithium aluminum hydride reduction of the four racemic forms of VI yielded corresponding forms of 1,1′-dicyclohexyl-4-hydroxy-3,3′-bipyrrolidine (IX). Compounds of types III and IX yielded bismethiodides. Stereoisomer IIIb displayed antiinflammatory and hypotensive effects, but also toxicity.

It was pointed out previously[2] that the very facile aldol condensation of those 2,3-pyrrolidinediones which are unsubstituted in the 4-position provides ready synthetic access to compounds in the little-known[3] 3,3′-bipyrrolidine series. The present investigation was undertaken with the objective of developing procedures for preparing other types of 3,3′-bipyrrolidine derivatives from the initial condensation products (I), and thereby permitting examination of the potential physiological activity of compounds in the series. As had been anticipated, the formation of mixtures of stereoisomers constituted the principal difficulty in the synthetic operations which were conducted. The assignment of configurations to the stereoisomers obtained was another desirable objective which presented difficulties but was accomplished in part.

The work to be described here is concerned with a series of compounds having the cyclohexyl substituent on both nitrogen atoms. The pyridine-catalyzed self-condensation of 1-cyclohexyl-2,3-dioxopyrrolidine, which approaches completion within a few minutes at room temperature, was described previously,[2] and it had been observed that product I was enolized. Since the enol I would contain only one asymmetric carbon atom, only one racemic form should exist, and the product did, in fact, behave as a single substance rather than a mixture. Reduction of I with sodium borohydride (see Chart I) reduced the enolic function to yield the 1,1′-dicyclohexyl-3,4′-dihydroxy-2,5′-dioxo-3,3′-bipyrrolidine structure (II) in the form of a mixture of solid diastereoisomers. One racemic form (IIa, m.p. 229.5–231°) crystallized in *ca.* 18% yield after this mixture had been dissolved in an acetone–ethanol solvent mixture. Efforts to induce the separation of other isomers were not successful.

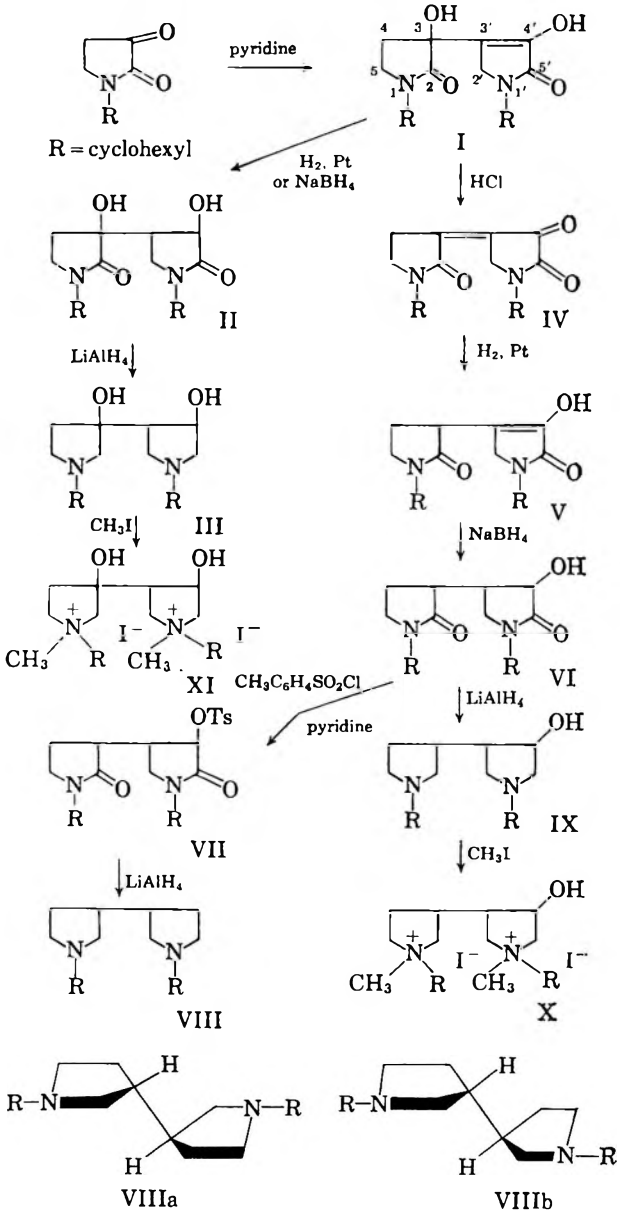
Lithium aluminum hydride reduction of IIa yielded one of the racemic forms of 1,1′-dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidine (IIIa, m.p. 123.5–125°). On the other hand, reduction by the same procedure of the total unseparated mixture of diastereoisomers of structure II yielded a mixture of diastereoisomers of structure III from which a second, higher melting form (IIIb, m.p. 185–186°) was separated by fractional crystallization. Thus two of the four possible racemic forms of III were separately characterized, whereas only one of the four forms of II was so characterized.

(1) (a) This investigation was supported by a research grant (RG-4371) from the National Institutes of Health, Public Health Service. Parts of the work are described in theses submitted by J. A. Vida (1960) and D. P. Mayer (1958) in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology; (b) Allied Chemical Corp. Fellow, 1957–1958.

(2) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(3) A few other compounds in the 3,3′-bipyrrolidine series have been described by S. Gabriel [*Ber.*, **47**, 3033 (1914)], E. B. Knott [*J. Chem. Soc.*, 1196 (1947)], and E. Buchta and K. Greiner [*Chem. Ber.*, **94**, 1331 (1961)]. No work on the stereochemistry of these compounds has been reported to this time.

CHART I



Preliminary tests for physiological activity[4a] which were conducted on compounds IIIa and IIIb indicated that compound IIIb, as well as the unseparated mixture of stereoisomers of structure III, had a rather prolonged hypotensive effect[4b] and some antiinflammatory action.[4c] Unfortunately, toxicity was also evident. On the other hand, the stereoisomer IIIa was devoid of hypotensive or antiinflammatory effects. It seems apparent that biological activity will be strongly influenced by configuration in the 3,3′-bipyrrolidine series. Unfortunately, although some progress has been made in elucidating the configurations of other members of the 3,3′-bipyrrolidine series (*vide infra*), similar efforts applied to compound IIIb have been unsuccessful.

As described previously,[2] the condensation product I is dehydrated in high yield by heating with hydrochloride acid to yield 1,1′-dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidylidene (IV). Catalytic hydrogenation of IV over a platinum catalyst (Adams' platinum oxide) saturated only the olefinic bond to yield the enol form (V) of 1,1′-dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidine. The compound appeared to be highly enolized; its infrared spectrum completely lacked the carbonyl band near 5.67 μ which is characteristic of the ketonic carbonyl at position 3 of 2,3-pyrrolidinediones,[2,5] but had a broad hydrogen-bonded hydroxyl absorption at 3.20–3.32 μ, was soluble in aqueous sodium hydroxide, and gave an intense purple color with ferric chloride. There were no indications of the presence of diastereoisomers such as might have been expected if the substance had existed in the keto form and contained two asymmetric carbons. The compounds represents another example of the enolic character of 2,3-pyrrolidinediones which carry one substituent in the 4-position.[2,5]

Sodium borohydride reduction of compound V reduced the enolic function to yield 1,1′-dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidine (VI) in the form of an amorphous solid representing a mixture of diastereoisomers. Since the structure VI contains asymmetric carbons at positions 3, 3′, and 4′, four racemic forms are possible. By a combination of fractional crystallization and chromatography on alumina four crystalline isomers were separated from the mixture. The yields of the separated forms were as follows: VIa (m.p. 240°), 25%; VIb (m.p. 166°), 20%; VIc (m.p. 156°), 1.9%; and VId (m.p. 140°), 8%.

By removing the hydroxyl and carbonyl groups from structure VI the 1,1′-dicyclohexyl-3,3′-bipyrrolidine structure VIII would be obtained. Stereoisomerism in VIII would be limited to that arising from the like asymmetric centers at positions 3 and 3′; only a symmetric (*meso*) form (see formula VIIIa) and a dissymmetric (racemic) form (see formula VIIIb) could result from carrying out such an operation on any of the four forms of VI. In the staggered conformation shown in Chart I, structure VIIIa possesses a center of symmetry. It could also assume an eclipsed conformation with a plane of symmetry. Neither element of symmetry is present in structure VIIIb. Thus, the 3,3′-bipyrrolidines can be subdivided into a symmetric (abbreviated *sym*) and a dissymmetric (abbreviated *dissym*) series according to whether the system of two rings has the configuration present in structure VIIIa or in VIIIb; the parent compounds of the two series could be called *sym*-3,3′-bipyrrolidine and *dissym*-3,3′-bipyrrolidine. Such terminology, which describes the symmetry of the ring systems only, and not necessarily that of the molecule as a whole, will be used in the remainder of the paper to designate ring system con-

(4) (a) The authors are indebted to the Lilly Research Laboratories and to the Endocrine Evaluation Branch of the Cancer Chemotherapy National Service Center, National Institutes of Health (CCNSC), for biological testing. (b) A small (8% maximum) hypotensive effect of 6-hr. duration was observed in the hypertensive (Goldblatt) rat at an oral dose of 20 mg./kg. (Lilly, results obtained under the direction of Dr. Francis Henderson). The compound was highly toxic to rats at 100 mg./kg. (c) A preliminary bioassay (CCNSC) indicated that at a subcutaneous dose of 24 mg., the mixed isomers produced an apparent reduction in the granuloma induced by a cotton pellet in the immature adrenalectomized rat averaging about 25%. This effect was slightly less than that produced by 1.2 mg. of cortisol. The material showed no antiinflammatory activity at a dose of 1.2 mg. and no thymolytic activity at doses up to 24 mg., or glucocorticoid activity (promotion of liver glycogen deposition in mature adrenalectomized rats) at doses up to 15 mg.

(5) For other observations on enolization of 2,3-pyrrolidinediones, see (a) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 98, 1554, 1560 (1957); (b) W. R. Vaughan and J. S. Covey, *J. Am. Chem. Soc.*, **80**, 2197 (1958); (c) P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, **27**, 98 (1962); (d) P. L. Southwick and J. A. Vida, *ibid.*, **27**, 3075 (1962).

figurations in individual compounds when such configurations have been determined.[6]

The steps required in the conversion of the four racemic forms of structure VI into the two forms of VIII involved forming the *p*-toluenesulfonates (VII) and reducing these compounds with lithium aluminum hydride. The *p*-toluenesulfonates were not fully characterized, but were directly reduced in the crude form. The two compounds of structure VIII which were produced were form A, m.p. 90–92°, obtained from compounds VIa and VIb, and forms B, m.p. 37–39°, obtained from compounds VIc and VId. The assignments of configuration to forms A and B of structure VIII were based on resolution experiments which demonstrated that form B was resolvable and therefore must represent the dissymmetric configuration depicted by formula VIIIb in the reaction chart. No indications that form A could be resolved were observed; it was concluded that A was the symmetric form represented by formula VIIIa.

Unfortunately, none of the acid resolving agents thus far tested yielded salts of the compounds of structure VIII which could be recrystallized or fractionally crystallized efficiently. The salts prepared from (+)-10-camphorsulfonic acid were unsatisfactory in this respect, as were the salts from (+)-dibenzoyltartaric acid. The salts obtained with (+)-tartaric acid itself were not easily crystallized either, but that from form A did melt over a rather narrow range (182–184°) and show a rotation unchanged by recrystallization, whereas the salts from form B melted over a considerable range and changed in both melting point and rotation upon repeated recrystallization. Form A displayed no detectable rotation when liberated from its tartrate, but form B was obtained with specific rotations in chloroform or ethanol, $[\alpha]^{25}D$, varying from $-30°$ to $+12°$ when liberated from different fractions of its tartrate. Whether the material with a specific rotation of $-30°$ represents a sample which is almost completely resolved remains to be seen; the difficulty of recrystallizing either the tartrate or the free base rendered the optical purity of the resolved product uncertain.

The configurations at the 4′-carbon in the stereoisomers of structure VI have not been determined. Results of an investigation of sodium borohydride reductions of enols of a related group of 4-substituted 2,3-pyrrolidinediones suggest that probably the more abundant product should be that in which the hydroxyl group at the 4′-position is *trans* to the bond at 3′ which joins the two rings. However, no clear evidence to support such a conclusion in the case of these 3,3′-bipyrrolidine derivatives has yet been obtained.

The four stereoisomers (racemic forms) of structure VI were also reduced directly with lithium aluminum hydride to yield the 1,1′-dicyclohexyl-4′-hydroxy-3,3′-bipyrrolidines (IX). These reductions evidently proceeded without affecting adjacent asymmetric centers; each form of VI yielded a different isomer of IX with no apparent interchange of configurations. Chart II summarizes relationships of stereoisomeric 3,3′-bipyrrolidines of the types VI, IX, and VIII.[7a]

CHART II

Symmetric Series		Dissymmetric Series	
VIIIa		VIIIb	
m.p. 90–92°		m.p. 37–39°	
VIa	VIb	VIc	VId
m.p. 239.5–240°	m.p. 164–166°	m.p. 155–156°	m.p. 139–140°
↓	↓	↓	↓
IXa	IXb	IXc	IXd
m.p. 139.5–141°	m.p. 165–166°	m.p. 114–116°	m.p. 103–104°

When compounds IIIb and IXb were treated with excess methyl iodide, bismethiodides of the expected composition (corresponding to structures XI and X) were formed in both instances. Possibly because of the opportunity for additional stereoisomerism resulting from the formation of two unlike asymmetric nitrogens in the quaternization, the methiodides were difficult to crystallize and only a low yield of compound X was obtained after recrystallization. A crystalline form of the methiodide XI, m.p. 253–253.5°, was examined for physiological effects, but failed to show activity comparable to that of the parent bipyrrolidine (IIIb).[7b]

Experimental[8,9]

The 1,1-Dicyclohexyl-3,4′-dihydroxy-2,5′-dioxo-3,3′-bipyrrolidines (II).—To 6 g. (0.158 mole) of sodium borohydride was added 200 ml. of 95% ethanol. Over a period of 30 min., 27 g. (0.074 mole) of 1,1′-dicyclohexyl-3-hydroxy-2,4′,5′-trioxo-3,3′-bipyrrolidine (I)[2] was added in portions. The reaction mixture was kept in an ice bath during the addition and swirled frequently. After the reaction mixture had been allowed to stand overnight at room temperature, 20% hydrochloric acid was added dropwise to the reaction mixture to destroy the excess hyride. The solvent was evaporated under reduced pressure to leave a gummy residue, which was treated with 200 ml. of water. The aqueous mixture was extracted twice with chloroform. The chloroform extracts were combined, dried over sodium sulfate, and evaporated under reduced pressure to yield a yellow, glassy residue, which was treated with a 2:1 mixture of petroleum ether (b.p. 30–60°) and ether and cooled to $-15°$ for an hour with frequent stirring. The glassy residue was converted into a white solid, which was removed by filtration. The dried product, m.p. 178–200°, weighed 26.71 g. (98.6% yield). Recrystallization from a 10:1 mixture of acetone and 95% ethanol with cooling only to room

(6) Although dissymmetric has become the accepted term to describe a configuration which cannot be superimposed upon its mirror image, this terminology may not have been used previously as part of the name of a compound. There are terms already in use in the names of compounds which could be applied to the designation of the configurations of these bipyrrolidine systems, but only by the modification of generally accepted meanings. Thus the terms *meso* and racemic could be applied to the symmetric and dissymmetric systems, respectively, provided that it be understood that the absence of optical activity would not be implied in all compounds carrying these designations for the ring system configurations. The application of the terms *erythro* and *threo*, as suggested by a referee, to the symmetric and dissymmetric 3,3′-bipyrrolidine systems (regarded as analogous to 1,1,2,2-tetrasubstituted ethanes) would be suitable if it were understood that the terms would in this instance not necessarily carry the usual implication of two *unlike* asymmetric centers.

(7) (a) The higher-melting isomers IXa and IXb failed to show biological activity in the rat comparable to that of compound IIIb when administered orally; there was merely a slight hypertensive effect and a slight anti-inflammatory activity at toxic dose levels (Lilly). The lower-melting isomers IXc and IXd were not tested separately because only very small amounts were available, but a mixture of all of the isomers of structure IX (obtained by lithium aluminum hydride reduction of the unseparated mixed isomers of structure VI) was also inactive in the same tests. The mixture produced a strong (maximum 43%) decrease in blood pressure of 1- to 2-hr. duration when administered intravenously to the anesthetized dog at 1 mg./kg., but the result is regarded as of questionable significance because the responses in the rat and the dog were not consistent. (b) The only biological activity found was a hypotensive effect of short duration in the dog. There was no effect on respiration in the dog and no antibacterial action was discovered.

(8) Microanalyses were by Geller Microanalytical Laboratories, Charleston, W. Va., and Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

(9) Infrared data were obtained with a Perkin-Elmer Model 21 spectrophotometer. Figures quoted are wave lengths of bands in μ. The letters after each number signify the following: i, intense; m, medium; w, weak; b, broad; si or sm, intense or medium band with shoulder (weak, 0–30% absorption; medium, 30–60% absorption; intense, >60% absorption).

temperature yielded 5.1 g. (18%) of white needles, m.p. 229.5–231°. When the mother liquor from the recrystallization was cooled to −15°, a white microcrystalline solid was deposited, yielding 7.30 g. (27%), m.p. 205–225°. Further recrystallization did not greatly effect this melting range.

The crystalline compound melting at 229.5–231° is the isomer designated IIa. The following spectral data were obtained for this substance (infrared spectrum, chloroform): 3.08 bm, 3.44 i, 3.49 si, 6.02 bi, 6.72 m, 6.91 i, 7.80 i, 7.97 i, 8.88 m, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_4$: C, 65.90; H, 8.85; N, 7.69. Found: C, 66.26; H, 8.93; N, 7.54.

The large broad-melting fraction (m.p. 205–225°) described above had an infrared spectrum very similar to that of IIa, as did a product melting over the range *ca.* 213–220° and having the same composition as IIa, which was obtained by hydrogenation of I over a platinum catalyst (Adams' platinum oxide) in methanol. A similar hydrogenation product described previously[2] was reported to melt at 204–206°. It seems evident that all of these products have the structure II, but it is questionable whether any but the high-melting form IIa represents a single racemic form.

The 1,1′-Dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidines (III). The Low-Melting Form IIIa.—To 2.0 g. (0.053 mole) of lithium aluminum hydride suspended in 250 ml. of dry ether was added portionwise 3.54 g. (9.7 mmoles) of the isomer IIa of 1,1′-dicyclohexyl-3,4′-dihydroxy-2,5′-dioxo-3,3′-bipyrrolidine (m.p. 229–231°) over a period of 30 min. The reaction mixture was stirred and refluxed for an additional 5 hr., and refluxing was continued overnight. A solution of 1.48 g. of sodium potassium tartrate[10] dissolved in 6.5 ml. of water was added dropwise with stirring to the reaction mixture to destroy the excess hydride. The solid was removed from the ether solution by filtration and extracted twice with chloroform. The ether and chloroform solutions were combined, dried over sodium sulfate, and evaporated under reduced pressure to yield a clear, glassy residue. The residue was then treated with 20 ml. of a 1:1 mixture of ether and petroleum ether (b.p. 30–60°) and cooled to −15°. In a few hours the glassy residue assumed the form of a white solid, which was filtered and washed with 10 ml. of ether. The yield was 2.80 g. (85.6%), m.p. 122–123.5°. Recrystallization from a 4:3 mixture of ether and acetone gave 1.4 g. of product in the form of very fine white crystals, m.p. 123.5–125°; infrared spectrum (chloroform): 2.96–3.08 sw, 3.44 i, 3.50 i, 6.90 m, 7.28 m, 7.44 w, 8.80–9.0 bw, and 11.22 w μ.

Anal. Calcd. for $C_{20}H_{36}N_2O_2$: C, 71.38; H, 10.78; N, 8.33. Found: C, 71.17; H, 10.86; N, 8.48.

A mixture of IIIa and IIIb melted over a broad range (121.5–150°) beginning slightly below the melting point of IIIa.

The High-Melting Form IIIb.—Mixed isomers of II (7.85 g., 0.022 mole, m.p. 207–217°), obtained by sodium borohydride reduction of I, were reduced with lithium aluminum hydride (3 g. 0.07 mole) in dry ether (200 ml.) as described above for the preparation of IIIa. The crude product, obtained after the same type of work-up procedure, was a clear, light yellow glass. After it was stirred with a 3:1 mixture of petroleum ether (b.p. 30–60°) and ether at −15° for several hours, a white powder was collected by filtration. The melting point was 109–135°; yield was 6.10 g. (84.2%). Recrystallization from a 4:1 mixture of acetone and 95% ethanol cooled only to room temperature yielded 0.8 g. (29%) of white platelets, m.p. 178–181°. Repeated crystallization from the same solvent mixture raised the melting point to 185–186°; infrared spectrum (chloroform): 2.88 w, 3.42 i, 3.50 i, 6.89 m, 7.28 m, 7.43 m, 8.70–9.00 bm, and 11.22 m μ.

Anal. Calcd. for $C_{20}H_{36}N_2O_2$: C, 71.38; H, 10.78; N, 8.35. Found: C, 71.60; H, 10.53; N, 8.45.

The lithium aluminum hydride reduction of the mixed isomers of II, m.p. 213–220°, prepared by the catalytic reduction of I with platinum oxide, gave a mixture of diastereoisomers of III, m.p. 100–120°. Recrystallization of the product failed to yield any sharp-melting crystalline fractions.

The Dimethiodide (XI) of the High-Melting 1,1′-Dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidine (IIIb).—To 1.9 g. (5.64 mmoles) of compound IIIb (m.p. 178–181°) dissolved in 40 ml. of dioxane, 5 ml. of methyl iodide was added. The reaction mixture was allowed to stand overnight at room temperature. The solid which had formed was removed by filtration and washed with a small amount of acetone to yield 3.2 g. (92%) of very fine white crystals, m.p. 250–253°. Recrystallization of the product from 95% ethanol yielded 1.8 g. of product, m.p. 253–253.5°.

Anal. Calcd. for $C_{22}H_{42}I_2N_2O_2$: C, 42.59; H, 6.84; N, 4.52. Found: C, 42.15; H, 7.03; N, 4.07.

The attempted preparation of a dimethiodide from a mixture of diastereoisomers of 1,1′-dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidine yielded no solid material.

1,1′-Dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidine (V, Enol Form). — 1,1′-Dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidylinene (IV)[2] (30 g., 0.088 mole) was suspended in 300 ml. of glacial acetic acid and hydrogenated over 200 mg. of platinum oxide. The initial hydrogen pressure was 65 p.s.i.g.; the reaction period was 15 hr. At the end of this time all of the starting material had dissolved. The catalyst was removed by filtration and the light-colored solution was poured into 1.8 l. of distilled water. The mixture was allowed to stand for 24 hr. at room temperature and then filtered to collect the solid product, which was washed repeatedly with water and dried at 50°. The weight of the dried, white product was 24.1 g. (80.3% yield); the melting point was 220–222°. Repeated recrystallization from a 1:1 mixture of acetone and 95% ethanol raised the melting point to 223–226°. The compound gave a deep purple color with ferric chloride in ethanol; infrared spectrum (chloroform): 3.20–3.32 sm, 3.46, 3.50 i, 6.00 bi, 7.00 bi, 8.00 bi, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.04. Found: C, 69.63; H, 8.56; N, 7.90.

The 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidines (VI). Preparation of the Mixed Isomers.—1,1′-Dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidine (V, 122 g., 0.35 mole) was added over a period of 30 min. to a precooled solution of 36.2 g. (0.96 mole) of sodium borohydride in 1.8 l. of 95% ethanol. The addition was completed at a temperature of 0–5° and the mixture was stirred vigorously with cooling in an ice bath for an additional 3 hr. The dark solution was allowed to stand overnight at room temperature. The color of the solution faded upon acidification with 20% hydrochloric acid to pH 3. The solvent was evaporated under reduced pressure leaving a solid residue, which was treated with 1.0 l. of distilled water. The solution was extracted repeatedly with chloroform and the combined chloroform extract was dried over sodium sulfate, filtered, and evaporated at reduced pressure to yield a light yellow glass. The yield was 105 g. (86%).

The High-Melting 1,1-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*sym*-3,3′-bipyrrolidine (VIa).—The mixture of stereoisomers of VI described above was dissolved in 600 ml. of 95% ethanol with heating. The hot solution was treated with Norit A, filtered, and stored at 0° for 30 hr. The crystalline precipitate was collected by filtration, washed with cold ethanol, and dried. Recrystallization from 95% ethanol yielded 31 g. (25.3%) of platelets, m.p. 231–233°; m.p. 239–240° after further recrystallization; infrared spectrum below 8 μ (methylene chloride)[11]: 3.01 bm, 3.40 i, 3.48 i, 5.88 si, 6.01 si, 6.64 w, 6.70 m, 6.92 bm, 7.27 w, 7.48 w, and 7.72 m μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 69.21; H, 8.90 N, 8.10.

The Low-Melting 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*sym*-3,3′-bipyrrolidine (VIb).—The ethanol mother liquor from the separation of VIa was evaporated under reduced pressure to

(10) *Cf.* W. G. Brown, *Org. Reactions*, **6**, 469 (1951). The use of this decomposition method avoids the emulsion formation encountered with other procedures.

(11) The close similarity of the spectra of the four different isomers in methylene chloride solution supports the assumption that all of the compounds have the same structure and differ only in configuration. The following full listing of conspicuous bands for spectra taken in potassium bromide pellets is given to supplement the melting point data as a means of distinguishing between the isomers. The bands are not compared as to relative intensity, but those in parentheses are conspicuous in the spectrum of the isomer in question but much weaker or absent in two or more of the other forms.

VIa: 3.08, 3.40, 3.49, 5.94, (6.11), (6.63), 6.69, 6.88, 7.24, (7.64), 7.81, 7.94, 8.00, 8.08, 8.25, 8.34, 8.45, 8.66 (8.83), 9.09, (9.24), 9.49, 10.05, 10.18, 10.45, 11.22, 12.36, 13.37, (13.78), 14.69 μ.

VIb: 2.96, 3.41, 3.48, 5.96, 6.70, 6.87, 7.00, 7.79, 7.98, 8.30, 8.39, 8.68, 8.89, (9.52), 9.70, 9.98, 10.12, 10.24, (10.53), 11.23, 11.59, 11.92, 12.48, 12.58, (13.24) μ.

VIc: 2.90, 3.06, 3.39, 3.49, 5.94, (6.07), 6.70, 6.88, 6.99, 7.28, (7.70), 7.80, 7.94, 8.44, 8.70, 8.87, 9.03, 9.18, 9.49, 9.71, 10.16, 11.23, 11.66, 11.92, 12.30, 12.65, (13.38), 13.78, 14.76 μ.

VId: 3.03, 3.41, 3.48, 6.00, 6.68, 6.87, 7.02, 7.26, 7.58, 7.79, 7.95, 8.31, 8.70, 8.93, 9.18, 9.50, (9.67), 10.15, 11.21, 11.65, 11.94, 12.23, 12.37, (12.63), (13.36), 13.66, 14.78 μ.

give a light tan glass, which was dissolved in 80 ml. of a 3:1 petroleum ether–ether mixture. The solution was cooled at 0° for 20 hr. The crystalline precipitate was collected by filtration and washed repeatedly with boiling ether (200 ml. total) to yield 24 g. (19.6%) of cubes, m.p. 164–166°. An analytical sample of this same melting point was obtained by recrystallization from a 1:4 ethanol–water mixture; infrared spectrum below 8 μ (methylene chloride): 3.01 bm, 3.40 i, 3.48 i, 5.90 si, 6.01 si, 6.70 m, 6.92 bm, 7.27 w, 7.40 w, 7.48 bw, and 7.80 bm μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 68.73; H, 9.36; N, 8.33.

A mixture of VIa and VIb melted at 135–144°, a mixture of VIb and VIc at 130–135°.

In order to assure the complete removal of VIb from the remaining mixture of stereoisomers, the mother liquor was combined with the ether washings described above and the combined solution (volume 290 ml.) was seeded with VIb and stored at 0° for 20 hr. A white solid (10 g., m.p. 92–164°) was filtered out. Fractionation of this material yielded only an insignificant additional amount of VIb in pure form.

The High-Melting 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*dissym*-3,3′-bipyrrolidine (VIc).—After separation of VIb and the mixed solids described above, the mother liquor was evaporated under reduced pressure, and 280 ml. of a 4:1 ether–petroleum ether mixture was added with heating to dissolve the residue. The solution was cooled at 0° for 20 hr. The white crystals which separated were collected by filtration. The yield was 10 g. (8.15%) of material melting at 84–92°.

This mixture was fractionated by means of chromatography, using a column containing 100 g. of adsorption alumina (Fisher Scientific Co., 80–200 mesh). The material was placed on the column using 100 ml. of carbon tetrachloride. The column was washed successively with 500 ml. of petroleum ether and 500 ml. of carbon tetrachloride, then eluted with 1.5 l. of benzene, followed by 4.0 l. of ether and 4.5 l. of chloroform. The residue from evaporation of the ether eluate was crystallized from a 1:1 mixture of benzene and *n*-hexane to yield 2.2 g. (1.88%) of white crystals, m.p. 155–156°; infrared spectrum below 8 μ (methylene chloride): 2.99 bm, 3.40 i, 3.48 i, 5.96 si, 6.20 w, 6.70 m, 6.88 bm, 7.27 w, 7.40 w, 7.48 w, and 7.74 bm μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 69.13; H, 8.94; N, 7.85.

The Low-Melting 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*dissym*-3,3′-bipyrrolidine (VId).—After separation of the fraction containing VIc, the mother liquor was evaporated. The residue was a light-colored oil. The oil was treated with 200 ml. of a 1:3 mixture of petroleum ether and ether. The mixture was kept at room temperature for 24 hr. and filtered to yield 12 g. (9.8%) of material melting at 90–150°. This mixture was fractionated by means of chromatography on a column containing 200 g. of alumina (Fisher Scientific Co., 80–200 mesh). The material was placed on the column using 50 ml. of carbon tetrachloride. The column was washed with 500 ml. of petroleum ether, 500 ml. of high-boiling (65–110°) petroleum ether, and 2 l. of carbon tetrachloride, then eluted first with 2 l. of ether, next with 3 l. of chloroform. The residue from evaporation of both eluates was crystallized from benzene–*n*-hexane mixtures (1:1) to give white crystals, m.p. 139–140°. The yield from the ether eluate was 5 g., that from the chloroform eluate 5.1 g. The total was thus 10.1 g. (8.25%); infrared spectrum below 8 μ (methylene chloride): 3.00 bm, 3.40 i, 3.48 i, 5.95 si, 6.70 m, 6.88 bm, 7.27 w, 7.40 w, 7.48 bw, 7.76 bm μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 68.91; H, 9.21; N, 8.31.

A mixture of VIc and VId melted at 99–112°.

After separation of the fraction which yielded VId, the mother liquor was evaporated under reduced pressure and treated with 300 ml. of petroleum ether (b.p. 30–60°). The mixture was kept at room temperature for 4 days. The mixture was filtered to remove 12 g. of material melting at 84–130°. The attempted fractionation of this mixture by means of chromatography yielded only mixtures of stereoisomers with wide melting ranges.

The 1,1′-Dicyclohexyl-4′-hydroxy-3,3′-bipyrrolidines (IX).—Over a period of 30 min. the diastereoisomeric 1,1′-dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidines (VI) were added with vigorous stirring to suspensions of lithium aluminum hydride in dry ether, using 0.45–0.54 g. of lithium aluminum hydride and 24–30 ml. of ether per gram of the bipyrrolidine to be reduced. The reaction mixtures were refluxed with stirring for 5 hr. Refluxing was then continued for 16–20 hr. without stirring. Excess lithium aluminum hydride was destroyed by dropwise addition with stirring of 25% solutions of potassium sodium tartrate in water, using *ca.* 4 g. of solution per gram of lithium aluminum hydride originally present. After an additional hour of stirring the solutions were filtered and the filter cake was washed with chloroform on the filter, then twice broken up, and extracted with boiling chloroform. The combined filtrate and washings were dried over sodium sulfate and concentrated under reduced pressure. Solid products were obtained in all cases.

Crystallization was carried out by using acetone or acetone–ethanol and treating the hot solutions with Norit, filtering, and cooling the hot filtrates to 0° for 24 hr. Results with the individual compounds are given below.

The Low-Melting 1,1′-Dicyclohexyl-4-hydroxy-*sym*-3,3′-bipyrrolidine (IXa).—The reduction of compound VIa, m.p. 234–236° (7.16 g., 0.021 mole), yielded 6.7 g. (100%) of crude IXa, m.p. 135–137°. Following recrystallization from a 3:7 mixture of 95% ethanol and acetone, 4.0 g. (59.5%) of white needles were obtained, m.p. 139.5–141°.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 75.04, 74.65; H, 11.42, 11.00; N, 8.63, 8.60.

The High-Melting 1,1′-Dicyclohexyl-4-hydroxy-*sym*-3,3′-bipyrrolidine (IXb).—The reduction of compound VIb, m.p. 164–166° (23 g., 0.066 mole), yielded 13.15 g. (62.5%) of compound IXb as white crystals, m.p. 165–166°, following recrystallization from 400 ml. of a 1:1 mixture of 95% ethanol and acetone.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 74.83; H, 11.34; N, 8.63.

A mixture of IXa and IXb softened at 135° and melted at 138.5–144°.

The High-Melting 1,1′-Dicyclohexyl-4-hydroxy-*dissym*-3,3′-bipyrrolidine (IXc).—The reduction of compound VIc, m.p. 155–156° (2.1 g., 0.0060 mole), yielded 1.5 g. (77.5%) of compound IXc as white crystals, m.p. 110–112°, following recrystallization from 40 ml. of acetone. Recrystallization from 25 ml. of acetone yielded 1.25 g. (64.6%) of a product, m.p. 114–116°; melting point unchanged by further recrystallization.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 74.66; H, 11.12; N, 8.80.

The Low-Melting 1,1′-Dicyclohexyl-4-hydroxy-*dissym*-3,3′-bipyrrolidine (IXd).—The reduction of compound VId, m.p. 139–140° (10 g., 0.0287 mole), yielded 6.25 g. (67.3%) of compound IXd, m.p. 101–102°, following crystallization from 240 ml. of acetone. Recrystallization from acetone yielded 5.0 g. (53.7%) of a product, m.p. 103–104°; melting point unchanged by further recrystallization; m.m.p. 101–112° with IXc.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 74.69; H, 11.34; N, 8.55.

The infrared spectra of the four isomers did not differ significantly. The following data were obtained from compound IXb (infrared spectrum, Nujol mull): 3.24 bm, 3.42 i, 3.49 i, 3.62 sm, 6.85 bi, 7.27 m, 7.44 m, 7.52 sw, 7.70 w, 7.98 w, 8.06 w, 8.24 w, 8.42 w, 8.68 bm, 8.94 m, 9.22 bw, 9.36 bm, 9.58 w, 9.80 w, 10.20 w, 10.86 w, 11.33 mb, 11.90 bw, and 12.65 bw μ.

The 1,1′-Dicyclohexyl-3,3′-bipyrrolidines (VIII).—To solutions of each of the isomeric 1,1′-dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidines (VI) in pyridine (10 ml. of pyridine per gram of bipyrrolidine) were added solutions of *p*-toluenesulfonyl chloride in dry pyridine (4 to 4.5 g. of *p*-toluenesulfonyl chloride and 10 ml. of pyridine per gram of bipyrrolidine). The reaction mixtures were allowed to stand for an extended period of time, then were poured onto cracked ice (50 to 100 g. of ice per gram of bipyrrolidine). The resulting mixtures were usually allowed to stand for 1 to 2 hr. (24 hr. at 0° in the case of the isomer VIc) and then filtered to collect the precipitated tosylates. The crude products were washed with water and dried in a desiccator or purified by further crystallization.

Solutions of the tosylates in tetrahydrofuran (8 to 30 ml. of tetrahydrofuran per gram of tosylate) were added with vigorous stirring to refluxing suspensions of lithium aluminum hydride in tetrahydrofuran, using at least 4 g. (a large excess) of lithium aluminum hydride and 40–65 ml. of tetrahydrofuran per gram of the tosylate to be reduced. Refluxing and stirring were continued for 20 to 24 hr. and the reaction mixtures were then allowed to stand at room temperature for 24 to 48 hr.

Excess lithium aluminum hydride was destroyed by dropwise addition with stirring of 25% solutions of potassium sodium tartrate in water, using *ca.* 4 g. of solution per gram of lithium aluminum hydride originally present. After an initial hour of

stirring, ethyl acetate was added (50 to 150 ml. per gram of tosylate reduced), and the mixture was heated to the reflux temperature. The hot solutions were filtered and the filter cake was washed with ethyl acetate on the filter, then twice broken up, and extracted with boiling ethyl acetate. The combined filtrate and washings were dried over sodium sulfate and concentrated under reduced pressure. From the first and second isomers (VIa and VIb) a solid product was obtained at this point, but the third and fourth isomers (VIc and VId) yielded oils.

These crude products were crystallized by dissolving them in hot acetone (6–7 ml. per gram of tosylate reduced), treating the hot solutions with Norit A, filtering, and cooling the filtrates to −15° for 36 hr. The crystalline products which separated were collected by filtration, washed with cold acetone (*ca.* 1 ml. per gram of tosylate reduced), and dried in a desiccator.

1,1′-Dicyclohexyl-*sym*-3,3′-bipyrrolidine (VIIIa). From Compound VIa.—The tosylate from 20 g. (0.0575 mole) of VIa (m.p. 231–233°), obtained after a reaction period of 12 hr. at room temperature, was crystallized from a mixture of 200 ml. of ethanol and 100 ml. of water with decolorization of the solution by charcoal. The crystalline precipitate was collected after the solution had been kept at 0° overnight. The yield was 20 g. (68.4%) of white crystals, m.p. 138–140°. Reduction of this product yielded 10 g. (83%) of 1,1′-dicyclohexyl-*sym*-3,3′-bipyrrolidine (VIIIa) as white cubes, m.p. 90–92°. A mixture of VIIIa and VIIIb (*vide infra*) melted over the range 35–89°.[12] The following spectral data were obtained for VIIIa (infrared spectrum, Nujol mull): 3.42 i, 3.49 i, 3.62 m, 6.85 i, 7.27 i, 7.42 m, 7.58 w, 7.66 w, 7.96 w, 8.04 w, 8.28 w, 8.70 m, 8.79 m, 8.84 sm, 10.90 w, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{36}N_2$: C, 78.88; H, 11.92; N, 9.20. Found: C, 78.91; H, 11.78; N, 9.18.

From Compound VIb.—From 2.0 g. (0.0058 mole) of compound VIb (m.p. 164–166°) there was obtained after a reaction period of about 12 hr. at room temperature 1.4 g. (48.6%) of the crude tosylate, m.p. 80–84°, which was reduced to yield 0.3 g. (35%) of VIIIa, m.p. 88–90°. The infrared spectrum was the same as that of the sample obtained from VIa, and there was no melting point depression.

1,1′-Dicyclohexyl-*dissym*-3,3′-bipyrrolidine (VIIIb). From Compound VIc.—From 4.0 g. (0.0116 mole) of VIc (m.p. 155–156°) there was obtained after a reaction period of 24 hr. at 0° (solution cooled at 0° before mixing) and 48 hr. at room temperature, 2.6 g. (45%) of the tosylate, m.p. 66–70°, which was reduced to yield 0.44 g. (29%) of compound VIIIb, m.p. 36–38°; infrared spectrum (Nujol mull): 3.42 i, 3.49 i, 3.62 m, 6.85 i, 7.27 i, 7.42 m, 7.58 w, 7.66 w, 7.96 w, 8.04 w, 8.28 w, 8.70 m, 8.78 m, 8.84 m, 10.90 w, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{36}N_2$: C, 78.88; H, 11.92; N, 9.20. Found: C, 79.02; H, 11.91; N, 9.09.

From Compound VId.—From 10.0 g. (0.0288 mole) of VId (m.p. 138–140°), 6 g. (45.7%) of crude tosylate (m.p. 162–164°) was obtained using a 24-hr. reaction period at room temperature. It was reduced to yield 1.0 g. (27.6%) of compound VIIIb, m.p. 37–39°. The infrared spectrum was identical with that of the sample of VIIIb from compound VIc, and there was no melting point depression.

Resolution Experiments with 1,1′-Dicyclohexyl-3,3′-bipyrrolidines (VIII). The Bisbitartrate of 1,1′-Dicyclohexyl-*sym*-3,3′-bipyrrolidine (VIIIa).—1,1′-Dicyclohexyl-*sym*-3,3′-bipyrrolidine, m.p. 90–92° (1.0 g., 0.00328 mole), and 1.0 g. (0.00663 mole) of (+)-tartaric acid were dissolved in 20 ml. of boiling absolute methanol. The solution was cooled to 30°, 10 ml. of absolute ether was added, and the mixture was kept at room temperature for 1 hr., then at 0° for 2 hr. The crystals which separated were filtered out and washed with ether. The yield was 1.95 g. (97.5%) of white crystals, m.p. 182–184°. The salt was recrystallized from 20 ml. of absolute methanol with cooling to 0°. The recovery was 0.860 g. (43%) of material melting at 183–184°, $[\alpha]^{25}D$ +12.80° (*c* 2.5%, 50% ethanol). The analysis indicated that the salt was a bisbitartrate, formed from 2 moles of tartaric acid and from 1 mole of the bipyrrolidine.

Anal. Calcd. for $C_{28}H_{48}N_2O_{12}$: C, 55.25; H, 8.00; N, 4.64. Found: C, 55.82; H, 8.11; N, 4.74.

Repeated crystallization did not change the melting point or specific rotation. Material recovered from the mother liquors of recrystallizations was also identical in melting point, rotation, and composition. When any of the fractions of the tartrate were dissolved in water and treated with concentrated ammonium hydroxide, the liberated base was devoid of optical activity.

Partial Resolution of 1,1′-Dicyclohexyl-*dissym*-3,3′-bipyrrolidine (VIIIb).—1,1′-Dicyclohexyl-*dissym*-3,3′-bipyrroldine, m.p. 37–39° (0.500 g., 0.00164 mole), and 0.500 g. (0.003315 mole) of (+)-tartaric acid were dissolved in a mixture of 20 ml. of isopropyl alcohol (carefully dried) and 15 ml. of absolute ethanol with heating. The solution was allowed to cool to room temperature and to stand for 14 hr. The separated crystals were filtered out and dissolved in 30 ml. of boiling ethyl acetate. The solution was allowed to stand at room temperature for 24 hr. and filtered to collect the product. The yield was 0.400 g. (40%) of white crystals, m.p. 138–140°.

The salt was dissolved in 10 ml. of water and the solution was decolorized with Norit A and filtered. Concentrated ammonium hydroxide was then added. An oil separated. After addition of 60 ml. of a saturated potassium carbonate solution, the mixture was extracted several times with ethyl acetate. The combined ethyl acetate solutions were dried over sodium sulfate, filtered, and evaporated under reduced pressure to leave an oily residue. The residue was dissolved in 5 ml. of boiling acetone, and the solution was cooled at −15° for 24 hr. The separated crystals were filtered out and washed with cold acetone. The yield was 0.056 g. of white crystals m.p. 37–39°, $[\alpha]^{25}D$ −30° (*c* 1%, chloroform).

The mother liquor remaining after separation of the first 400-mg. fraction was evaporated under reduced pressure to leave an oily residue. This was dissolved in 10 ml. of water and the solution was decolorized with Norit A, filtered, and treated with concentrated ammonium hydroxide. After addition of 50 ml. of saturated potassium carbonate solution, the mixture was extracted several times with ethyl actate. The combined ethyl acetate solutions were dried over sodium sulfate, filtered, and evaporated under reduced pressure to leave an oily residue. The residue was dissolved in 5 ml. of boiling acetone and the solution was cooled at −15° for 24 hr. The separated crystals were collected by filtration and washed with cold acetone. The yield was 0.053 g. of white crystals, m.p. 37–39°, $[\alpha]^{25}D$ +12° (*c* 1%, chloroform).

Analysis of the salts obtained in other similar experiments showed that they were bisbitartrates. Thus a salt prepared in a methanol–ether mixture and crystallized from ethyl acetate showed the m.p. 120–121°, $\alpha]^{25}D$ +5.6° (*c* 2.5%, 50% ethanol).

Anal. Calcd. for $C_{28}H_{48}N_2O_{12}$: C, 55.70; H, 8.00; N, 4.64. Found: C, 55.42; H, 7.95; N, 4.56.

After separation of the fraction described above, the residue obtained from the mother liquors was crystallized from *n*-butyl alcohol. White crystals, m.p. 140–144°, $[\alpha]^{25}n$ +18.8° (*c* 2.5%, 50% ethanol), separated.

Anal. Calcd. for $C_{28}H_{48}N_2O_{12}$: C, 55.70; H, 8.00; N, 4.64. Found: C, 55.37; H, 7.76; N, 4.82.

The 1,1′-Dicyclohexyl-4′-hydroxy-3,3′-bipyrrolidine Dimethiodide (X). From Compound IXb.—The compound IXb (1.1 g., 3.13 mmoles) was dissolved in 20 ml. of dioxane. To the solution was added *ca.* 3 ml. of methyl iodide and the mixture was allowed to stand overnight at room temperature. The light yellow solid which separated was removed by filtration and washed with a small amount of acetone to remove the yellow color. The very fine white crystals weighed 1.7 g. (85% yield) and melted at 257–259°. Recrystallization from a 2:1 mixture of acetone and 95% ethanol yielded 0.5 g. of small white platelets melting at 267–268.5°.

Anal. Calcd. for $C_{22}H_{42}I_2N_2O$: C, 43.72; H, 7.02; N, 4.64. Found: C, 42.90; H, 7.02; N, 4.44.

Recrystallization of the product from 95% ethanol with cooling only to room temperature raised the melting point to 278–280°.

Anal. Found: C, 43.25; H, 6.91; N, 5.45, 4.27.

(12) The lack of a pronounced melting point depression might conceivably indicate that the samples of m.p. 37–39° are actually eutectic mixtures containing the symmetric isomer VIIIa as well as the dissymmetric form VIIIb demonstrated by the resolution experiments. However, it seems very unlikely that much of the form melting at 92° could have been present, since it did not become evident during the fractionations involved in the resolution procedures. The fact that partial resolution did not change the melting point of VIIIb would seem to indicate that the enantiomorphs of VIIIb form solid solutions, and the same may be true of mixture of VIIIa with VIIIb.

The Synthesis of 2-Pyridones from Cyclic Cyano Ketones. A New Aromatization Procedure for Dihydro-2-pyridones[1]

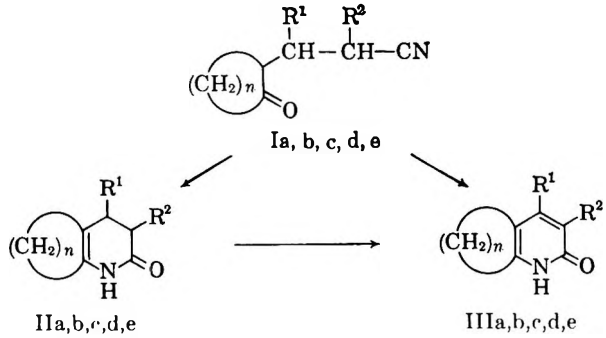
A. I. MEYERS AND G. GARCIA-MUNOZ[2]

Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122

Received June 28, 1963

Treatment of 2-(2-cyanoalkyl)cyclohexanones with 96% sulfuric acid for several hours at room temperature results in the formation of the corresponding cycloalkano[*e*]-2-pyridones by means of a consecutive cyclization–aromatization. Similar treatment of 3,4-dihydro-2-pyridones obtained by another route also leads to the 2-pyridones. The cyclization reaction is considered to be a further extension of the Ritter reaction, whereas the aromatization process appears to be novel.

During the course of a study directed toward the use of certain polyfunctional nitriles[3] in azasteroid synthesis, it was necessary to determine the behavior of various cyanoalkyl cyclohexanones and cyclopentanones (I) in sulfuric acid. It was found that cold 5–30% solutions of simple nitriles (cyanoethylcyclopentane and cyanoethylcyclohexane) and chloronitriles (4-chlorobutyronitrile and 2-chlorocyanoethylcyclohexane and -cyclopentane) in sulfuric acid could be recovered unchanged by dilution with water after 1–2 hr. with very little loss of material (10%). However, when 2-(2-cyanoethyl)cyclohexanone (Ib) was added to cold sulfuric acid and allowed to stand at 0–3° for 2 hr., there was no keto nitrile in the diluted solution. Instead, two crystalline products were recovered, one from the acid solution, the other from the neutralized solution. The product obtained from the extraction of the dilute acid solution showed infrared absorption at 3.15, 3.25 and 6.05 μ, all typical of the amide grouping but no bands attributable to a keto group. The ultraviolet spectrum exhibited only a single maximum at 254 mμ (ϵ 5020). This data excluded the possibility of the product being the corresponding keto amide IV which would have arisen from partial hydrolysis of the nitrile group. The n.m.r. spectrum[4] in deuteriochloroform exhibited a *single* proton signal at 575 c.p.s., which vanished when the sample was treated with deuterated water. The lack of further deuterium exchange led to the assigned structure, IIb, 3,4,5,6,7,8-hexahydro-2-quinoline. A search of the literature revealed that this product was prepared[5] from the same keto nitrile using methanolic potassium hydroxide in *t*-butyl alcohol. Comparison of the products obtained from both routes confirmed their identity.



a, R^1 = H, R^2 = H, n = 3
b, R^1 = H, R^2 = H, n = 4
c, R^1 = H, R^2 = H, n = 5
d, R^1 = CH_3, R^2 = H, n = 4
e, R^1 = H, R^2 = CH_3, n = 4

The second product isolated from the sulfuric acid treatment of the keto nitrile Ib formed a picrate in the usual manner and exhibited spectral properties rather different from the previous compound, IIb. The infrared spectrum revealed two strong carbonyl bands at 6.05 and 6.20 μ, as well as N–H absorption at 3.1 and 3.2 μ. The ultraviolet spectrum, λ_{max}^{EtOH} 318 mμ (ϵ 6500), strongly suggested an aromatic system and the n.m.r. spectrum confirmed this. The n.m.r. spectrum indicated methylene protons (multiplet, centered at 112 c.p.s.), allylic protons (multiplet, centered at 165 c.p.s.), and vinyl protons (3-position, doublet at 392 c.p.s., $J_{H_3H_4}$ = 9.8 c.p.s.; 4-position, doublet at 441 c.p.s., $J_{H_4H_3}$ = 9.8 c.p.s.). The integrated ratio was 4:4:1:1. The N–H proton, which occurs at 805 c.p.s., was confirmed by exchange with heavy water. These data were all consistent with the structure of 5,6,7,8-tetrahydro-2-quinolone (IIIb). When a comparison of this product with that previously reported by Thesing and Muller[6] was made, both products proved to be identical.

The use of keto nitriles Id and Ie under these conditions led directly to the 4-methyl (IIId) and the 3-methyl (IIIe) derivatives of the tetrahydroquinolone. The structure of these products also was supported by their infrared and ultraviolet spectra which possessed the expected features and strongly resembled the parent compound, IIIb. The n.m.r. spectrum of IIIb, IIId, and IIIe are virtually identical except for the vinyl proton region. When the 4-position is substituted by methyl (IIId), the 441-c.p.s. doublet in IIIb disappears and the remaining 3-vinyl proton appears as a singlet at 377 c.p.s. Thus the low-field proton doublet in IIIb is due to the 4-H substituent. When the 3-position is substituted by methyl (IIIe), the 392-c.p.s. doublet vanishes and the signal at 424 c.p.s. is due to the lone proton at the 4-position. These values are all in close agreement with a variety of 1-methylpyridones studied by Elvidge and Jackman with regard to their aromaticity.[7] The NH proton for IIId and IIIe appears as a

(1) This investigation is supported by a grant [RG-6248(C5)] from the National Institutes of Health.

(2) Research Associate, on leave from the Institute of Chemistry, Alonso Barba, Madrid, Spain.

(3) A. I. Meyers, J. Schneller, and N. K. Ralhan, *J. Org. Chem.*, **28**, 2944 (1963); A. I. Meyers and N. K. Ralhan, *ibid.*, **28**, 2950 (1963).

(4) All spectra were taken on the Varian A-60 instrument using tetramethylsilane as the internal standard.

(5) A. D. Campbell and I. D. R. Stevens, *J. Chem. Soc.*, 959 (1956).

(6) J. Thesing and A. Muller, *Ber.*, **90**, 711 (1957). We thank Dr. Thesing for supplying us with a sample of his quinolone.

(7) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 860 (1961). Comparison of the products reported here with those of the present study allows a rough estimate of the aromaticity to be made by the same method. The values of τ_{obs} in the present study for positions 3, 4, 5, and 6 are very close ($\Delta\tau_{obs}$ = 0.5 p.p.m.) to those reported by these authors. The models used for the calculation of degree of aromaticity as well as the method are given in ref. 7.

broad peak at 765 and 770 c.p.s., respectively, both disappearing rapidly upon the addition of deuterated water. A report[8] claims that the 4-methyl derivative (IIId) melts at 217–218°. The product obtained in the current report melts at 240–241°. In view of the data (infrared, ultraviolet, and n.m.r.) obtained here, there can be little doubt concerning the structure of these products.

That the hexahydro-2-quinolone (IIb) was indeed an intermediate in this reaction was demonstrated by treating it for 3 hr. in 96% sulfuric acid at room temperature and obtaining a 77% yield of the corresponding tetrahydro-2-quinolone (IIIb). There was present throughout the experiment a slow, constant evolution of sulfur dioxide indicating that the aromatization step involved reduction of sulfur from the +6 to the +4 state. An attempt to isolate the intermediates II when treating the keto nitriles with sulfuric acid always led to mixtures of the reduced (II) and oxidized (III) forms of the cyclic products. It was found advantageous to allow the keto nitriles to remain in the sulfuric acid for at least 3 hr. to ensure completion of the successive cyclization–aromatization process. The only exception found in this study was due to 2-(2-cyanoethyl)-cyclopentanone (Ia), which did not cyclize in the sulfuric acid, but was only hydrolyzed to the keto amide V. The latter product, however, was converted to the dihydro-2-pyridone (IIa) by neat heating at 170–180°, and this was readily aromatized to the 2-pyridone (IIIa) in sulfuric acid. In the case of 2-(2-cyanoethyl)cycloheptanone (Ic), it was necessary to allow the sulfuric acid-catalyzed condensation to proceed overnight to ensure complete reaction to the 2-pyridone (IIIc). Shorter reaction times always resulted in a mixture containing the dihydro-2-pyridone (IIc). In order to study the aromatization reaction in the absence of the cyclization process, the dihydro-2-pyridones (II) were prepared according to the method of Campbell and Stevens.[5] When the dihydro compounds (II) were treated with 96% sulfuric acid, they gave products (III) identical with those obtained directly from the series of keto nitriles I.

The initial formation of the hexahydro-2-quinolone (IIb) and dihydro-2-pyridones (II) may be represented as still a further extension of the Ritter reaction to the synthesis of N-heterocycles,[9,10] in which a nitrile can condense with an electrophilic site in sulfuric acid (Chart I). The Ritter reaction using the carbonyl group to generate the carbonium ion has already been described[11a] for simple nitriles and cyclic ketones to give analogous products (VI) as well as more complex materials.

With regard to the aromatization reaction, this process was examined further and found to proceed equally well in the absence of air (nitrogen) with the liberation of sulfur dioxide. When a quickly prepared solution (10^{-5} *M*) of the hexahydro-2-quinolone (IIb) in 96% sulfuric acid was inserted in a recording spectrophotometer, its spectrum changed rapidly (in less than 10 min.) from a single peak at 252 mμ to two peaks at 282 (sulfur dioxide) and 294 mμ (ε 8600) which was unchanged after 1 week. The rate of aromatization was slowed down considerably by the addition of either water or acetic acid to the sulfuric acid solution.[12] Because of the overlapping of the sulfur dioxide maximum upon the product maximum, as well as loss of sulfur dioxide from the cells, quantitative measurements were not feasible. Based upon the preceding observations, a mechanism for this process may be brought forward which involves initially a tautomeric shift of the hexahydro-2-quinolone (IIb) to the immonium form (VII) (Chart II). This is based on studies which have shown that amides protonate an oxygen rather than nitrogen in concentrated sulfuric acid.[11b] The transfer of two electrons from VII to sulfur trioxide or its solvate (disulfuric acid, $H_2S_2O_7$) is tentatively considered to be the rate-determining step. This is based upon the fact that the concentration of the acceptor is

(8) A. Dornow and E. Neuse, *Arch. Pharm.*, **287**, 361 (1954).

(9) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045, 4048 (1948).

(10) See ref. 3 and earlier references cited therein.

(11) (a) A. Y. Khorlin, O. S. Chizhov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **29**, 3411 (1959); (b) G. Fraenkel and C. Franconi, *J. Am. Chem. Soc.*, **82**, 4478 (1960).

(12) NOTE ADDED IN PROOF.—After the submission of this manuscript, two more references came to our attention regarding sulfuric acid-catalyzed cyclization of cyano ketones: O. Y. Magidson, *Zh. Obshch. Khim.*, **33**, 2173 (1963), and A. Vigier and J. Dreux, *Bull. soc. chim. France*, (**10**), 2293 (1963). Neither of these articles described the aromatization of the resulting dihydropyridones. The former paper reported the preparation of the 5,6-diphenyl derivative (X) which was also reported by us not to aromatize. The latter reference describes the transformation of a series of acyclic cyano ketones (A) to 3,4-dihydropyridones (B–F) using 90–92% sulfuric acid. Although it would be expected that B, E, and F should undergo aromatization to the α-pyridones under these conditions, our results indicate that the rate of aromatization in 90% sulfuric acid is about one-fortieth that in 97% acid. The reaction time reported by the French group for all the products was listed as 10 hr. We have observed that the oxidation is less than 20% complete after this period of time. Another fact that would account for the absence of the aromatized product in their report is the lack of ether solubility of the α-pyridones. These workers isolated their product by ether extraction, whereas we have found that only the dihydropyridones are ether soluble. This is presumably due to the zwitterionic character of the α-pyridones. See diagram below.

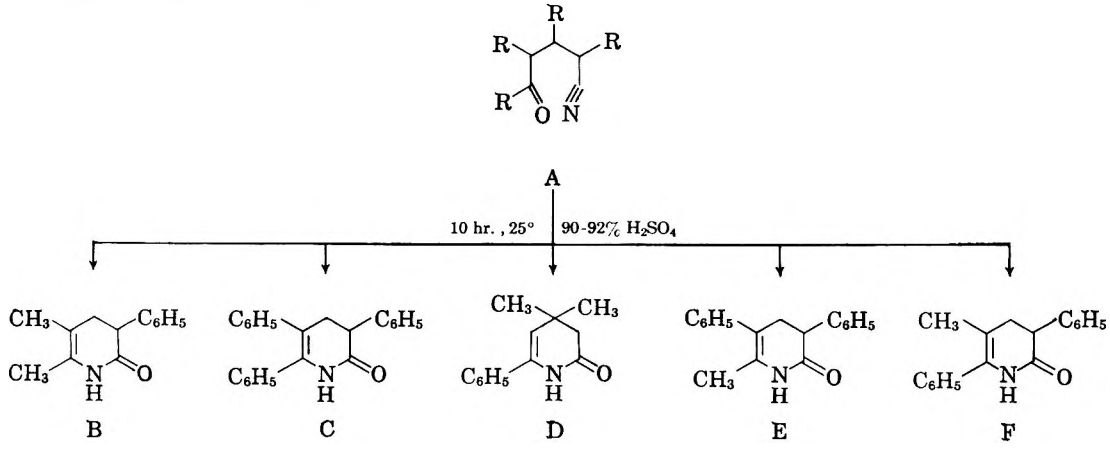


CHART I

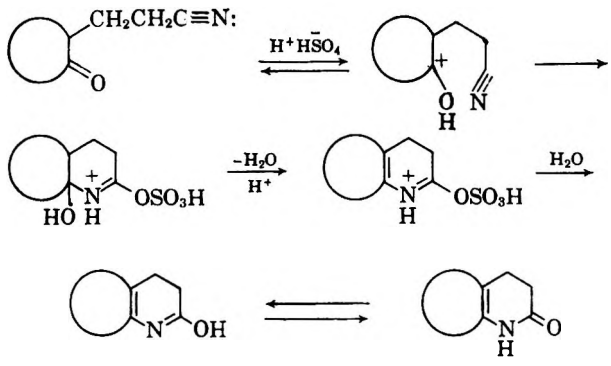
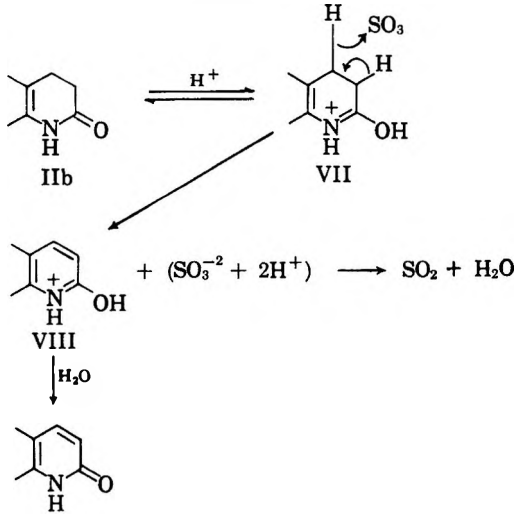
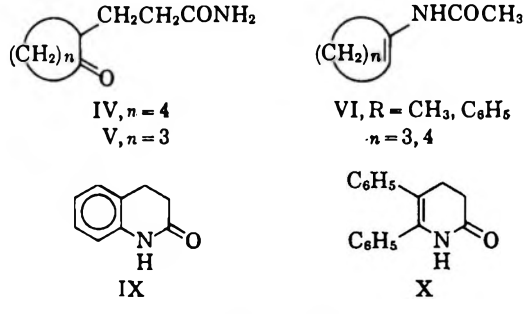


CHART II



dependent upon the sulfuric acid concentration.[13] That is, the concentration of sulfur trioxide will be greatly reduced by the addition of a strong base such as water or acetic acid, thus lowering the rate of oxidation. A rapid removal of a proton by the solvent then gives rise to the aromatized product, VIII, which is isolated upon dilution with water.



When the dihydrocarbostyril (IX) and 5,6-disphenyl-3,4-dihydro-2-pyridone (X) were treated with sulfuric acid in the usual manner, no aromatization occurred. The major difference between the latter two compounds on all the others studied is the delocalization of the olefinic bond in the 5,6-position. Thus it appears that the decreased bond order in IX and X serve to deactivate the 4-position which is the one currently considered as being oxidized. It may appear questionable to describe the attack of the very electrophilic sulfur trioxide upon the σ bond at the 4-position when there is also available in the molecule a π bond at the 5,6-position. However, the driving force toward aromatization by VII could make the electrons at the 4-position very labile toward the highly electron-attracting sulfur atom.[14] All the keto nitriles employed in this study were prepared from the appropriate cyclo alkanone and α,β-unsaturated nitrile *via* the enamine intermediate.[15] Further studies to extend this reaction, both the cyclization and the aromatization, to more complex ring systems are currently in progress.

Experimental[16,17]

5,6,7,8-Tetrahydro-2-quinolone (IIIb). A. From 2-(2-Cyanoethyl)cyclohexanone (Ib).—To 100 ml. of cold 96% sulfuric acid was added dropwise over a 2-hr. period 15.1 g. (0.1 mole) of the keto nitrile Ib. After the addition was complete, the reddish reaction mixture was allowed to warm to room temperature and stirring was maintained for an additional 3 hr. The mixture was poured over chipped ice; the resulting aqueous solution was extracted with chloroform[18] and then neutralized with ammonia. A white solid precipitated which was removed by extraction with chloroform. After drying with magnesium sulfate and removing the solvent, recrystallization of the residue from water yielded 8.1 g. (54%) of the product, m.p. 205–206°. A second recrystallization from ethyl acetate did not change the melting point. The infrared spectrum exhibited absorption at 3.1 and 3.3 (NH, NH assoc.) and 6.05 and 6.15 μ (C=O, C=N). The ultraviolet maximum appeared at 318 mμ (ethyl alcohol) (ϵ 6500).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.48; H, 7.38; N, 9.39. Found: C, 72.55; H, 7.43; N, 9.52.

The **picrate** (from water) had m.p. 145–146°.

Anal. Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.61; H, 3.70; N, 14.81. Found: C, 47.70; H, 3.93; N, 14.49.

B. From 3,4,5,6,7,8-Hexahydro-2-quinolone (IIb).—To 4 ml. of cold sulfuric acid was added 0.6 g. (0.0039 mole) of the hexahydro-2-quinolone[6] (IIb); the mixture was stirred at room temperature for 3 hr. and made alkaline with ammonia after being poured over chipped ice and the solid removed as above. The product, obtained in 77% yield, was identical with that obtained from part A.

3-Methyl-5,6,7,8-tetrahydro-2-quinolone (IIIe). A. From 2-Methyl-3-(2-oxocyclohexyl)propionitrile (Ie).—Ten grams (0.06 mole) of the cyano ketone was added slowly to 96% sulfuric acid at 0°. The solution, after completion of addition, was allowed to stir at room temperature for 3 hr. and then poured over chipped ice. Extraction of the aqueous acid solution with chloroform yielded 4.7 g. of the aromatized product, which after recrystallization from water melted at 210–211°. Neutralization of acidic solution with ammonia and extraction with chloroform yielded an additional 0.6 g. of the same material (m.p. 210–211°) isolated above. The total yield, 5.3 g. (54%) of IIId, possessed infrared absorption at 3.0 (NH) and 6.1 and 6.2 μ (C=O, C=N).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.39; H, 7.77; N, 8.34.

The **picrate** (from ethyl alcohol) had m.p. 179–180°.

Anal. Calcd. for $C_{16}H_{16}N_4O_8$: C, 48.97; H, 4.08; N, 14.28. Found: C, 48.99; H, 4.25; N, 14.05.

B. From 3-Methyl-3,4,5,6,7,8-hexahydro-2-quinolone (IIe).—One gram of the hexahydro-2-quinolone was added to cold 96% sulfuric acid and then stirred at room temperature for 3

(13) R. J. Gillespie and E. A. Robinson, "The Sulfuric Acid Solvent System" in "Advances in Inorganic Chemistry and Radiochemistry," Vol. I, H. J. Emeleus and A. G. Sharpe, Ed., Academic Press, New York, N. Y., 1959.

(14) F. A. Cotton and G. Wilkenson, "Advanced Inorganic Chemistry," Interscience–Wiley, Inc., New York, N. Y., 1962, p. 422.

(15) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovic, and J. Terrell, *J. Am. Chem. Soc.*, **85**, 217 (1963).

(16) All boiling points and melting points are uncorrected, and all infrared spectra were taken in carbon tetrachloride or chloroform.

(17) Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(18) This step was performed in order to remove any polymeric substances and unaromatized material (IIb), which under these conditions were present in only trace amounts. The quantity of IIb that could be isolated *via* this procedure varies with the time of the reaction. The maximum amount was obtained when the keto nitrile was kept at 0–5° in 96% sulfuric acid for 2 hr. and then poured over chipped ice.

hr. The mixture was poured on ice and the aqueous solution extracted with chloroform. Drying and removal of the solvent left a glassy residue. The acidic aqueous solution was neutralized with ammonia and extracted with chloroform. The removal of the solvent left a small amount of solid material. When the residues from both extractions were combined, dissolved in ethyl alcohol, and treated with picric acid, they yielded 0.7 g. of a picrate. This picrate when mixed with that obtained from A did not depress the melting point. The yield of free base was 30%.

3-Methyl-3,4,5,6,7,8-hexahydro-2-quinolone (IIe).—IIe was prepared by treating 2-methyl-3-(2-oxocyclohexyl)propionitrile (Ie) with methanolic potassium hydroxide in *t*-butyl alcohol by a previously described procedure.[5] Yield of material was 40%, m.p. 115–116° (from 1:1 alcohol–water) or sublimation at 90–100° (0.5 mm.). The infrared spectrum exhibited bands at 3.1 and 3.2 (NH, NH assoc.) and 6.0 μ (C=O).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.72; H, 9.09; N, 8.48. Found: C, 72.99; H, 9.05; N, 8.63.

2-Methyl-3-(2-oxocyclohexyl)propionitrile (Ie).—A solution of 30.2 g. (0.2 mole) of the pyrrolidine enamine[11] of cyclohexanone in 200 ml. of dry dimethylformamide was refluxed for 36 hr. with 24.1 g. (0.36 mole) of α-methacrylonitrile. After the addition of 10 ml. of water, the mixture was refluxed for 1 hr. and then poured into 1 l. of water. The aqueous solution was extracted several times with ether and the combined extracts were washed with 5% hydrochloric acid and then with 5% sodium bicarbonate. The ethereal solution, after drying overnight with magnesium sulfate, was concentrated, and the residue was distilled at 114–115° (0.5 mm.), n^{29}D 1.4625. The product weighed 22 g. (66%) and the infrared spectrum exhibited bands at 4.4 (C≡N) and 5.8 μ (C=O).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.72; H, 9.09; N, 8.48. Found: C, 72.93; H, 9.10; N, 8.44.

The **semicarbazone** (from ethyl alcohol) had m.p. 164–165°.

Anal. Calcd. for $C_{11}H_{18}N_4O$: C, 59.45; H, 8.10; N, 25.22. Found: C, 59.58; H, 8.35; N, 24.96.

4-Methyl-5,6,7,8-tetrahydro-2-quinolone (IIId). **A. From 3-methyl-3-(2-oxocyclohexyl)propionitrile** (Id).—The cyano ketone was added in the usual manner to 96% sulfuric acid and, after isolation procedure similar to that of IIIe, gave the 4-methyl derivative in 40% yield, m.p. 240–241° (lit.[7] m.p. 217–218°). The infrared spectrum exhibited the expected quinolone absorption with bands at 3.1 (NH) and 6.05 and 6.20 μ (doublet, C=O, C=N). The n.m.r. spectrum is in good agreement[7] with the other quinolone structures reported herein.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.38; H, 8.07; N, 8.58.

B. **From 4-methyl-3,4,5,6,7,8-hexahydro-2-quinolone** (IId).—A solution of 0.2 g. of the hexahydro derivative in 2.0 ml. of 96% sulfuric acid was stirred for 3 hr. at room temperature. Quenching of the solution in ice–water and neutralization with ammonium hydroxide gave a solid (0.1 g., 50%), which, upon admixing with the product obtained from A above, gave no depression in melting point.

4-Methyl-3,4,5,6,7,8-hexahydro-2-quinolone (IId).—IId was prepared by treating the keto nitrile Id with methanolic potassium hydroxide in *t*-butyl alcohol according to Campbell and Stevens[5] and had m.p. 124–125° (from water). The infrared spectrum exhibited bands at 3.1 and 3.2 (NH, NH assoc.) and 6.0 μ (C=O).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.72; H, 9.09; N, 8.48. Found: C, 72.92; H, 8.94; N, 8.70.

3-Methyl-3-(2-oxocyclohexyl)propionitrile (Id).—Id was prepared *via* the cyclohexanone enamine and crotonitrile using the procedure described for Ie. The yield was rather low (20%). Id had b.p. 145–147° (0.5 mm.), n^{26}D 1.4710. The infrared spectrum exhibited bands at 4.4 (C≡N) and 5.85 μ (C=O).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.72; H, 9.09; N, 8.48. Found: C, 72.78; H, 9.08; N, 8.24.

The **semicarbazone** (from ethyl alcohol) had m.p. 179–180°.

Anal. Calcd. for $C_{11}H_{18}N_4O$: C, 59.45; H, 8.10; N, 25.22. Found: C, 59.41; H, 8.23; N, 25.08.

Cyclopentano[*e*]-2-pyridone (IIIa). **A. From 2-(2-Cyanoethyl)cyclopentanone** (Ia).—To 100 ml. of cold concentrated sulfuric acid was added slowly 13.7 g. (0.1 mole) of the keto nitrile Ia over a 2-hr. period. After stirring in the cold for 3 hr., the mixture was diluted in ice–water. The acid solution was extracted with chloroform and then neutralized with ammonia. The clear solution was extracted repeatedly with chloroform; the combined extracts were dried; the solvent was removed. Recrystallization (ethyl acetate–hexane) of the solid residue (m.p. 82–83°) gave a product which was identified as the corresponding amide (V).[19] The infrared exhibited bands at 5.83 (C=O) and 6.02 μ (C=O, amide). The amide V was heated at 170–180° for 1 hr. and then sublimed *in vacuo* [80–100°(0.2 mm.)] to give pure **cyclopentano[*e*]-3,4-dihydro-2-pyridone** (IIa), m.p. 114–115°. The infrared spectrum of IIa exhibited bands at 3.1 and 3.2 (NH, NH assoc.) and 6.0 μ (C=O). The ultraviolet maximum (ethyl alcohol) appeared at 246 mμ (ϵ 5029).

Anal. Calcd. for $C_8H_{11}NO$: C, 70.07; H, 8.02; N, 10.21. Found: C, 69.55; H, 8.00; N, 10.45.

When the dihydro derivative (IIa) was dissolved in cold 96% sulfuric acid (0.5 g. in 4 ml.) and the solution stirred at room temperature for 3 hr., then poured over ice, neutralized with ammonia, and extracted with chloroform, there was obtained 0.35 g. (71%) of the 2-pyridone (IIIa), m.p. 181–182° (lit.[20] m.p. 180–181°). The **picrate** (ethyl alcohol) melted at 160–161° (lit.[8] m.p. 160°).

Cycloheptano[*e*]-2-pyridone (IIIc). **A. From 2-(2-cyanoethyl)cycloheptanone** (Ic).—A solution of 5.45 g. (0.033 mole) of the keto nitrile[11] in 20 ml. of 96% sulfuric acid was, after mixing in the cold, stirred at room temperature for 3 hr. After dilution with ice–water the mixture was extracted several times with chloroform; the combined extracts were dried (magnesium sulfate) and concentrated. The residue, after recrystallization from aqueous ethyl alcohol (1:1), had m.p. 114–115°; infrared spectrum, 2.89 and 3.05 (NH, NH assoc.) and 6.00 μ (C=O). This product (45%) was identical with the one prepared (15%) by treating the keto nitrile with methanolic potassium hydroxide in *t*-butyl alcohol and, therefore, identified as the 3,4-dihydro-2-pyridone derivative (IIc).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.72; H, 9.09; N, 8.48. Found: C, 72.56; H, 9.12; N, 8.50.

Neutralization of the acidic aqueous solution after chloroform extraction (above) led to a second precipitated product, which after extraction with chloroform, drying, solvent removal, and sublimation *in vacuo* [140–160° (0.5 mm.)], melted at 199–200°. The yield was 0.2 g. The infrared spectrum exhibited bands at 3.0 (NH) and 6.08 and 6.25 μ (C=O, C=N).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.67; H, 7.78; N, 8.72.

B. **From the 3,4-Dihydro-2-pyridone** (IIc).—One gram of the dihydro-2-pyridone (IIc) in 4 ml. of 96% sulfuric acid was stirred overnight at room temperature. The mixture was poured onto chipped ice and extracted with chloroform. The acid solution was then made alkaline with ammonium hydroxide and the precipitated solid was removed by filtration. Sublimation at 140–160° (0.5 mm.) yielded 0.56 g. (57%) of the 2-pyridone (IIIc).

Acknowledgment.—We wish to thank Mr. Gordon Boudreaux, U. S. Department of Agriculture, Southern Regional Research Laboratory, for the n.m.r. spectra.

(19) N. P. Shusherina, R. Y. Levina, and M. Y. Jure [*Vestnik Moskov. Univ., Ser., Mat., Mekh., Astron., Fiz., Khim.*, **12**, No. 6, 173 (1957); *Chem. Abstr.*, **53**, 2175*d* (1959)] give m.p. 77–78°.

(20) N. P. Shusherina, R. Y. Levina, and N. D. Dmitrieva, *Vestnik. Moskov. Univ., Ser., Mat., Mekh., Astron., Fiz., Khim.*, **13**, No. 5, 191 (1958); *Chem. Abstr.*, **53**, 12,287*g* (1959).

The Synthesis of β-Diketones Containing Chlorodifluoromethyl and Perfluoroethyl Groups and Certain Related Reactions[1]

RICHARD A. MOORE[2] AND ROBERT LEVINE

Department of Chemistry, University of Pittsburgh, Pittsburgh 13, Pennsylvania

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A series of β-diketones of the type $RCOCH_2COR'$, where R = CF_2Cl and C_2F_5, and R′ = alkyl, aryl, and heterocyclic, has been prepared in high yields by the sodium methoxide-effected acylations of the appropriate ketones with methyl chlorodifluoroacetate and methyl pentafluoropropionate. While $CF_2ClCOCH_3$ (I) and $C_2F_5COCH_3$ (VII) may be acylated under basic conditions with the very reactive esters methyl chlorodifluoroacetate and methyl oxalate, respectively, they undergo aldol condensation when treated with sodium methoxide in the presence or absence of methyl benzoate. The reaction of equivalents of I and sodium methoxide for 24 hr. at room temperature gives a mixture of the aldol dimer (II), 1,5-dichloro-4-hydroxy-4-methyl-1,1,5,5-tetrafluoropentan-2-one, and the cyclized aldol trimer (IV), 2,4-dihydroxy-2,4,6-tris(chlorodifluoromethyl)-6-methyltetrahydropyran. Under similar conditions, VII gives a mixture of the aldol product, 1,1,1,2,2,6,6,7,7,7-decafluoro-5-hydroxy-5-methyl-3-heptanone (VIII), its dehydrated derivative, 1,1,1,2,2,6,6,7,7,7-decafluoro-5-methyl-4-hepten-3-one (IX), and 3-hydroxy-3-methyl-4,4,5,5,5-pentafluoropentanoic acid (X), and none of the cyclized aldol trimer (XIII), 2,4-dihydroxy-2,4,6-tris(pentafluoroethyl)-6-methyltetrahydropyran. However, III was obtained by refluxing VII for 72 hr. over barium hydroxide in a Soxhlet apparatus. When a mixture of VII, methyl benzoate, and sodium methoxide in ether was refluxed for 2 days, VII undergoes an unusual type of Claisen condensation to give pentafluoropropionylacetone (XV).

A number of β-diketones containing the trifluoromethyl[3-8] and the perfluoro-*n*-propyl[6,8] groups have been prepared by the sodium methoxide-effected acylations of the appropriate ketones with esters of trifluoroacetic and perfluoro-*n*-butyric acid. Since high yields of products (in some cases up to 90%) were obtained, the perfluorinated esters must be very reactive acylating agents. This is not too surprising since it was shown earlier[9,10] in this laboratory that, when esters of varying structure are subjected to reaction with ketone anions, those esters which have highly electrophilic carbonyl carbon atoms are very active in Claisen condensations. Thus, a highly electronegative perfluoroalkyl group would be expected to make an α-carbonyl carbon atom electron-poor and, therefore, electrophilic, and active in Claisen condensations.

To our knowledge, the synthesis of only one β-diketone containing the perfluoroethyl group, *i.e.*, $C_2F_5COCH_2COCH_3$ (prepared in 84.5% yield by the reaction of acetone with ethyl perfluoropropionate), has been reported[8] and, apparently, the preparation of β-diketones containing the CF_2Cl group are not in the literature. Therefore, a study was made of the synthesis of β-diketones containing the CF_2Cl and the C_2F_5 groups.

Two routes which may be envisioned as leading to the desired β-diketones are indicated.

route 1 $RCO_2CH_3 + CH_3COR' \xrightarrow{NaOCH_3}$

route 2 $R'CO_2CH_3 + CH_3COR \xrightarrow{NaOCH_3}$

$RCOCH_2COR' + CH_3OH$

R = CF_2Cl and C_2F_5
R′ = alkyl, aryl, and heterocyclic

Using route 1 a number of β-diketones containing halogenated alkyl, as well as alkyl, aryl, alicyclic, and heterocyclic, groups were prepared in 55–89% yields (Table I). The synthesis of β-diketones by route 2 involves the acylation of methyl perhaloalkyl ketones with nonhalogenated esters. Apparently the only reported base-catalyzed Claisen condensation involving the acylation of an alkyl perhaloalkyl ketone is the synthesis of hexafluoroacetylacetone by the reaction of 1,1,1-trifluoroacetone with ethyl trifluoroacetate using sodium ethoxide[3] or sodium metal[11] as condensing agent.

Since there are apparently no reported examples of the condensation of alkyl perhaloalkyl ketones with nonfluorinated esters under basic conditions, it was of interest to study the feasibility of using this method (route 2) to prepare β-diketones such as $RCOCH_2COC_6H_5$ (R = CF_2Cl and C_2F_5) which have been prepared in high yield, 89%, by route 1.

First, 1 equiv. of methyl benzoate (in anhydrous ether) was added to 1 equiv. of sodium methoxide (suspended in anhydrous ether) over a 10-min. period followed by the addition of 1 equiv. of CH_3COCF_2Cl (I) over a 5-min. period. The reaction mixture was stirred for 24 hr. at room temperature and processed. None of the desired β-diketone, $C_6H_5COCH_2COCF_2Cl$, was obtained. Instead, the ester was recovered essentially completely, and a 51% yield of 2,4-dihydroxy-2,4,6-tris-(chlorodifluoromethyl)-6-methyltetrahydropyran (IV), the solid, cyclized aldol trimer of I, was obtained. An attempt was made to minimize the formation of IV by adding an excess (1.5 equiv.) of the ester to 1 equiv. of sodium methoxide followed by the addition, over a 5-hr. period, of a dilute ether solution of 1 equiv. of the ketone. After the reaction mixture was allowed to stand at room temperature for 12 hr., it was processed. Again, the ester was almost completely recovered and the only product obtained was IV (43.5%).

To prove that the solid IV can arise from the ketone alone, a sample of I was treated with (a) sodium methoxide and (b) barium hydroxide. From both of these reactions there was obtained a mixture of products

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(2) This paper is based on part of a thesis presented by R. A. M. to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) A. L. Henne, M. S. Newman, L. L. Quill and R. A. Staniforth, *J. Am. Chem. Soc.*, **69**, 1819 (1947).

(4) J. C. Reid and M. Calvin, *ibid.*, **72**, 2948 (1950).

(5) R. Levine and J. K. Sneed, *ibid.*, **73**, 4478 (1951).

(6) L. B. Barkley and R. Levine, *ibid.*, **73**, 4625 (1951).

(7) L. B. Barkley and R. Levine, *ibid.*, **75**, 2059 (1953).

(8) J. D. Park, H. A. Brown, and J. R. Larcher, *ibid.*, **75**, 2753 (1953).

(9) J. K. Sneed and R. Levine, *ibid.*, **72**, 5219 (1950).

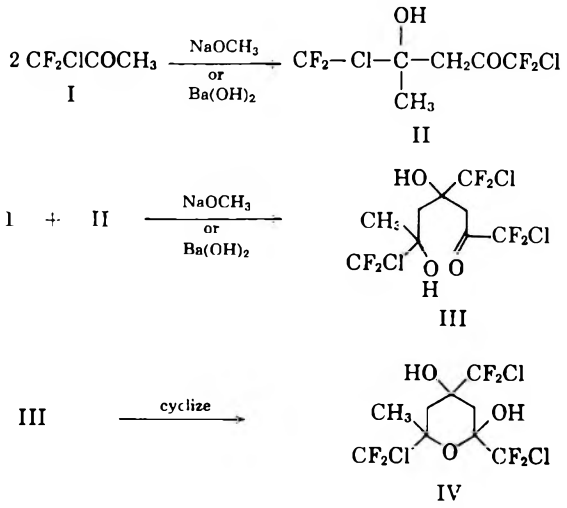
(10) R. Levine and J. K. Sneed, *ibid.*, **73**, 5614 (1951).

(11) R. N. Haszeldine, W. K. R. Musgrave, F. Smith, and L. M. Turton, *J. Chem. Soc.*, 609 (1951).

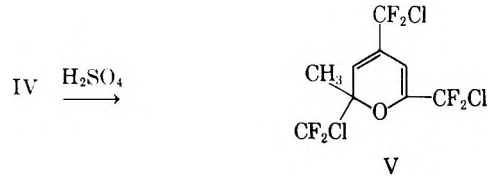
which consisted of the solid tetrahydropyran IV and the liquid aldol dimer (II), 1,5-dichloro-4-hydroxy-4-methyl-1,1,5,5-tetrafluoropentan-2-one.

The solids isolated from the last four reactions were shown to be identical by superimposition of their infrared spectra. The compound does not give an enol test with alcoholic ferric chloride solution and is not oxidized by neutral potassium permanganate at room temperature. On the basis of the above evidence and its elemental analysis, it appears that the compound has structure IV and is structurally analogous to 2,4-dihydroxy-2,4,6-tris(trifluoromethyl)-6-methyltetrahydropyran, which was obtained by Henne and Hinkamp[12] and Simmons and Wiley[13] when 1,1,1-trifluoroacetone was treated with sodium and potassium carbonate, respectively.

It was also found that IV can be obtained in 97% yield by the reaction of I with sodium, employing the procedure used earlier[12] in the analogous reaction with 1,1,1-trifluoroacetone. The tetrahydropyran IV described above may be envisioned as arising according to the following scheme.



Further proof of the structure of IV was obtained by dehydrating it with concentrated sulfuric acid to form 2,4,6-tris(chlorodifluoromethyl)-2-methyl-2H-pyran (V) in 57.5% yield. The structure of V was elucidated



by (a) carbon and hydrogen analysis, (b) its infrared spectrum, and (c) its proton and fluorine magnetic resonance spectra. The infrared spectrum of V showed that it is structurally similar to 2,4,6-tris(trifluoromethyl)-2-methyl-2H-pyran (VI).[12,14] In addition, treatment of a chloroform solution of V with aluminum chloride produces a deep red color while VI gives a magenta color[12] when similarly treated.

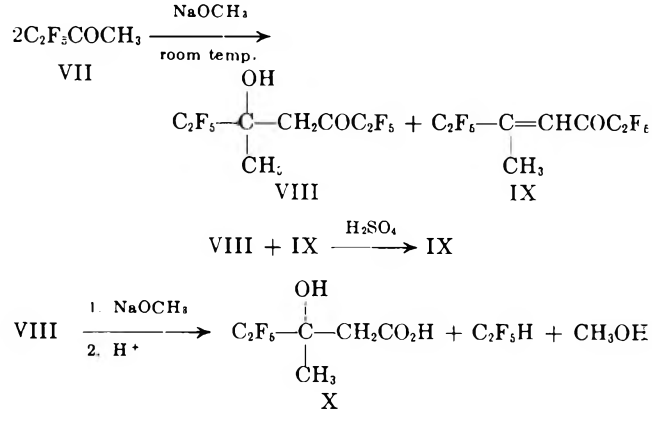
(12) A. L. Henne and P. E. Hinkamp, *J. Am. Chem. Soc.*, **76**, 5147 (1954).

(13) H. E. Simmons and D. W. Wiley, *ibid.*, **82**, 2288 (1960).

(14) A sample of this compound was generously supplied by Professor A. L. Henne.

Since Henne, *et al.*,[3] were able to prepare hexafluoroacetylacetone in 72% yield and obtained none of VI by the sodium ethoxide-effected reaction of 1,1,1-trifluoroacetone with ethyl trifluoroacetate in refluxing ether for 50 hr., it was felt that the interaction of methyl benzoate, I, and sodium methoxide under comparable conditions might give the desired β-diketone, $C_6H_5COCH_2COCF_2Cl$. However, refluxing equivalents of the reactants for 47 hr. gave none of the diketone. Again, the only condensation product isolated was IV (39.0%). To show that a very active acylating ester, such as a fluorinated one, appears to be necessary to compete with the ketone for the anion of the ketone, a reaction was effected between equivalents of I, $CF_2ClCO_2CH_3$, and sodium methoxide at room temperature. There was obtained a 28% yield of what is probably $CF_2ClCOCH_2COCF_2Cl$. This liquid is extremely hygroscopic and changes to a white solid, presumably the dihydrate,[15] when exposed to air.

In general, attempts to effect the acylation of $CH_3COC_2F_5$ (VII) with methyl benzoate in the presence of sodium methoxide led to ketone self-condensation products. However, in contrast with the results obtained with I, VII does not form a cyclic trimer readily. Thus, the interaction of equivalents of VII and sodium methoxide at room temperature for 24 hr. gave what is probably a mixture of the ketone dimer, 1,1,1,2,-2,6,6,7,7,7-decafluoro-5-hydroxy-5-methyl-3-heptanone (VIII), and its dehydrated derivative, 1,1,1,2,2,6,6-7,7,7-decafluoro-5-methyl-4-hepten-3-one (IX), and 22.5% of 3-hydroxy-3-methyl-4,4,5,5,5-pentafluoropentanoic acid (X). The mixture of VIII and IX was converted to IX by distilling it from concentrated sulfuric acid. The hydroxy acid X appears to arise by a haloform-type cleavage of the initially formed aldol product (VIII). The origin of X is analogous to the formation of 3-hydroxy-3-methyl-4,4,4-trifluoro-



butanoic acid which McBee, *et al.*,[16] isolated from the reaction of 1,1,1-trifluoroacetone with aqueous sodium or potassium hydroxide.

The structure of X was established by (a) elemental analysis, (b) its infrared spectrum, (d) its proton and fluorine magnetic resonance spectra, and (d) its mass spectrum. The mass spectrum, at low ionizing potential, showed two bands at mass numbers 204 and 160, the latter being more intense. These mass numbers correspond to the masses of 3-methyl-4,4,5,5,5-penta-

(15) B. G. Schultz and E. M. Larson [*J. Am. Chem. Soc.*, **71**, 3250 (1949)] have reported that $CF_3COCH_2COCF_3$ readily forms a dihydrate.

(16) E. T. McBee, D. H. Campbell, R. J. Kennedy, and C. W. Roberts, *ibid.*, **78**, 4597 (1956).

fluoropenten-2-oic acid (XI) and 2-methyl-3,3,4,4,4-pentafluoro-1-butene (XII) which are the dehydrated and the dehydrated decarboxylated derivatives of X, respectively

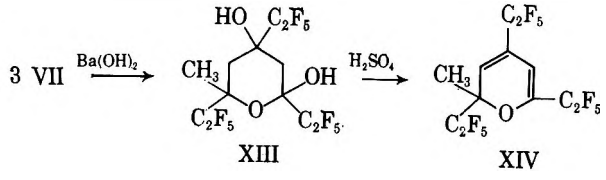
$$X \xrightarrow{-H_2O} C_2F_5C(CH_3)=CHCO_2H$$

XI, mol. wt. 204

$$XI \xrightarrow{-CO_2} C_2F_5C(CH_3)=CH_2$$

XII, mol. wt. 160

Although none of the cyclic trimer of VII was isolated in the previous reaction, refluxing a sample of VII over barium hydroxide in a Soxhlet apparatus for 72 hr. gave a 28% yield of the trimer, 2,4-dihydroxy-2,4,6-tris(pentafluoroethyl)-6-methyltetrahydropyran (XIII) which was dehydrated by concentrated sulfuric acid to 2,4,6-tris(pentafluoroethyl)-2-methyl-2H-pyran, (XIV) in 84% yield.



XIII XIV

Since attempts at room temperature (*vide supra*) to acylate I with methyl benzoate failed, it seemed superfluous to attempt the condensation of VII with methyl benzoate under these conditions. However, a condensation was effected at room temperature between VII and methyl oxalate (an ester known to be very reactive in Claisen acylations),[17] using sodium methoxide as the condensing agent, to give a 32% yield of methyl pentafluoropropionylpyruvate, $C_2F_5COCH_2COCO_2CH_3$. It seems, therefore, that as in the acylations of CH_3COCF_2Cl with $CF_2ClCO_2CH_3$ (*vide supra*), and of CF_3COCH_3 with $CF_3CO_2C_2H_5$,[3,11] a Claisen acylation of VII can be effected if a very active acylating agent is used in the reaction.

To determine whether there is any difference in reactivity towards methyl benzoate between I and VII due to the size of the perhaloalkyl group, a condensation was attempted by refluxing equivalents of VII, methyl benzoate, and sodium methoxide in ether for 2 days. Most of the ester (84%) was recovered and although none of the expected β-diketone, $C_6H_5COCH_2COC_2F_5$ was obtained, a small amount (20%) of another β-diketone, pentafluoropropionylacetone, $C_2F_5COCH_2COCH_3$ (XV), was isolated. The identity of XV was established by carbon–hydrogen analysis and by showing that its boiling point, refractive index, infrared spectrum, and the melting point of its copper chelate are identical with the corresponding properties of an authentic sample.[8]

The formation of XV in this reaction, which involves an unusual type of Claisen condensation, was completely expected, and the mechanism for its formation is not known with certainty. However, a possible route by which its formation may be rationalized follows. The anion (XVI) of the ketone undergoes an aldol condensation with unchanged ketone (VII) to give the anion (XVII) of the aldol product, which may be decomposed at the temperature of refluxing ether to give XV, sodium fluoride, and tetrafluoroethylene. It should be pointed out that the presence of tetrafluoroethylene was not established. It is also possible that XVII decomposes to XV and sodium pentafluoroethide. The loss of perhaloalkyl groups under basic conditions is known. As has been mentioned above, the aldol dimer VIII of the ketone VII is cleaved to the β-hydroxy acid X by reaction with sodium methoxide at room temperature. Bergman[18] has reported that ethyl perfluoropropionate is cleaved in refluxing ethanolic sodium ethoxide to give a mixture of pentafluoroethane and diethyl carbonate. It is also of interest to note that Greene and Zook[19] have observed that methyl trityl ketone (XVI) reacts with sodium triphenylmethide at 210° to give 1,1,1-triphenylacetylacetone, $(C_6H_5)_3COCH_2COCH_3$. This β-diketone appears to arise from a route analogous to that described above for the formation of XV with the difference that the stable triphenylmethyl anion is eliminated from the initially formed aldol dimer of XVI.

$$C_2F_5COCH_3 + Na^+OCH_3^- \rightleftharpoons C_2F_5COCH_2^-Na^+ + CH_3OH$$

VII XVI

$$VII + XVI \rightleftharpoons C_2F_5COCH_2C(O^-Na^+)(CH_3)(C_2F_5)$$

XVII

$$XVII \longrightarrow NaF + CF_2=CF_2 + C_2F_5COCH_2COCH_3$$

XV

Experimental

Halogenated Intermediates. A. Methyl Perfluoropropionate.—A mixture of perfluoropropionic acid (164 g., 1.0 mole), absolute methanol (48 g., 1.5 moles), and 50 ml. of concentrated sulfuric acid was refluxed for 19 hr., and the crude product was distilled from the reaction mixture. The ester was washed with a saturated sodium carbonate solution, a saturated calcium chloride solution, and finally with water. It was distilled from phosphorus pentoxide to give 160 g. (90%) of methyl perfluoropropionate, b.p. 59.5–61° (732 mm.).[20]

B. Methyl Chlorodifluoroacetate.—This ester was prepared by the procedure described above except that a 2.5-hr. reflux period was used. From a mixture of chlorodifluoroacetic acid (261 g., 2.0 moles, supplied through the courtesy of General Chemical Division of Allied Chemical Corporation), absolute methanol (96 g., 3.0 moles), and 100 ml. of concentrated sulfuric acid, there was obtained 261 g. (90%) of methyl chlorodifluoroacetate, b.p. 78.0–78.5° (738 mm.), $n^{25}D$ 1.3474.[21]

C. Methyl Pentafluoroethyl Ketone.—This ketone was prepared by the method of Dishart and Levine.[22] Thus, from the interaction of methylmagnesium iodide (1.8 moles) and pentafluoropropionic acid (98.5 g., 0.6 mole) in *n*-butyl ether at 35°, there was obtained 39.4 g. (40.0%) of methyl pentafluoroethyl ketone, b.p. 38–41° (737 mm.).[22]

D. Methyl Chlorodifluoromethyl Ketone.—This ketone was prepared using the procedure described above for the synthesis of methyl pentafluoroethyl ketone except that ethyl ether was the solvent. From the interaction of methylmagnesium iodide (3.0 moles) and chlorodifluoroacetic acid (130.5 g., 1.0 mole) in 1200 ml. of refluxing ethyl ether, there was obtained 50.0 g.

(17) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 65 (1954).

(18) E. Bergman, *J. Org. Chem.*, **23**, 476 (1958).

(19) J. L. Greene and H. D. Zook, *J. Am. Chem. Soc.*, **80**, 3629 (1958).

(20) D. R. Husted and A. H. Albrecht, *ibid.*, **75**, 1605 (1935).

(21) N. N. Yarovenko, S. P. Motornyi, and L. I. Kirenskaya, *Zh. Obsch. Khim.*, **27**, 2796 (1957); *Chem. Abstr.*, **52**, 8042b (1958).

(22) K. T. Dishart and R. Levine, *ibid.*, **78**, 2268 (1956).

(39.0%) of methyl chlorodifluoromethyl ketone, b.p. 54–55° (730 mm.), $n^{25}D$ 1.3417.[23]

Acylation of Ketones with Methyl Chlorodifluoroacetate and Methyl Perfluoropropionate. A. Procedure I.—This method is patterned after that used by Barkley and Levine[6] for similar reactions with methyl trifluoroacetate and methyl perfluoro-*n*-butyrate. To commercial 95% sodium methoxide[24] (6.0 g., 0.105 mole) suspended in 100 ml. of anhydrous ether, methyl chlorodifluoroacetate (14.4 g., 0.10 mole) of methyl perfluoropropionate (17.8 g., 0.10 mole) dissolved in 15 ml. of anhydrous ether was added in 10 min. To the rapidly stirred mixture (which had usually changed to a pasty consistency about half-way through the addition of the ester), the appropriate ketone (0.10 mole in 15 ml. of anhydrous ether) was added in 5 min. On the addition of the first few drops of the ketone, the gel-like, ester–methoxide–ether mixture changed to a liquid. Stirring was continued for 2 hr. after the addition of the ketone, and then the reaction mixture was allowed to stand at room temperature for the reaction time indicated in Table I. Then, glacial acetic acid (6.8 ml., 7.3 g., 0.12 mole, in 30 ml. of water) was added, followed by copper(II) acetate (14.7 g., 0.07 mole, in 133 ml. of warm water). The ether was distilled and the chelate which precipitated was filtered and washed with cold water and cold petroleum ether (b.p. 30–60°). The chelate was placed in a separatory funnel and was decomposed by shaking with a mixture of ether and 15% sulfuric acid. The ether was separated from the acidic, aqueous layer which was then extracted with several portions of ether. The combined ether extracts were dried over Drierite, the solvent was removed, and the residue was distilled to give the β-diketones which are listed in Table I.

B. Procedure II.—This method is a modification of procedure I. After the reaction times (Table I), 3.0 ml. of concentrated sulfuric acid in 30 ml. of water was added with stirring. The aqueous and ether phases were separated and the aqueous layer was extracted with several portions of ether. The combined ether extracts were treated as described in procedure I.

Attempted Benzoylation of Methyl Chlorodifluoromethyl Ketone (I). A. Interaction of Equivalents of Sodium Methoxide, Methyl Benzoate, and I at 25°.—Reaction of 95% sodium methoxide (6.0 g., 0.105 mole), methyl benzoate (13.6 g., 0.100 mole), and I (12.8 g., 0.100 mole) for 24 hr. according to procedure II gave 13.0 g. (96%) of recovered methyl benzoate, b.p. 84–85° (15–16 mm.), and 6.5 g. (50.8%) of 2,4-dihydroxy-2,4,6-tris-(chlorodifluoromethyl)-6-methyltetrahydropyran (IV), b.p. 83–98° (0.3 mm.), m.p. 91.2–92.2° from *n*-pentane. The infrared spectrum of IV is identical with that of an authentic sample (*vide infra*).

B. Interaction of Equivalents of Sodium Methoxide and I and Excess Methyl Benzoate with the Slow Addition of I at 25°.—Methyl benzoate (14.3 g., 0.105 mole, in 10 ml. of ether) was added in 10 min. to a slurry of 95% sodium methoxide (4.2 g., 0.074 mole, in 20 ml. of ether). Then, I (8.96 g., 0.07 mole, in 35 ml. of ether) was added over a 5-hr. period. The reaction mixture was allowed to stand for 12 hr. more at room temperature and processed by procedure II to give 13.1 g. (92%) of recovered methyl benzoate, b.p. 99–103° (31 mm.), and 3.9 g. (43.5%) of IV, b.p. 86–92° (0.3 mm.).

C. Interaction of Equivalents of Sodium Methoxide, Methyl Benzoate, and I in Refluxing Ether.—Methyl benzoate (13.6 g., 0.10 mole, in 15 ml. of ether) was added in 15 min. to 95% sodium methoxide (6.0 g., 0.105 mole, suspended in 100 ml. of ether). The mixture was heated to refluxing and I (12.8 g., 0.100 mole, in 20 ml. of ether) was added over a 30-min. period. The reaction mixture was refluxed for 47 hr. and processed by procedure II to give 12.6 g. (93%) of recovered methyl benzoate, b.p. 82–97° (13–25 mm.), and 5.0 g. (39.0%) of IV, b.p. 87–110° (0.2–1.0 mm.).

Acylation of Methyl Chlorodifluoromethyl Ketone (I) with Methyl Chlorodifluoroacetate.—Methyl chlorodifluoroacetate 21.7 g., 0.150 mole, in 30 ml. of ether) was added in 15 min. to 95% sodium methoxide (6.0 g., 0.105 mole, suspended in 75 ml. of ether). To the resulting, pasty mass, I (12.8 g., 0.100 mole, in 90 ml. of ether) was added over a period of 4 hr. The reaction mixture was stirred for 1 hr. at room temperature, was allowed to stand for 1 hr. more at room temperature and then was processed according to procedure I to give, after washing with ice–water and cold petroleum ether (b.p. 30–60°), 6.7 g. (33.5%) of the crude copper chelate, m.p. 105–120°, of what is presumably the β-diketone, $CF_2ClCOCH_2COCF_2Cl$. The chelate, which is slightly soluble in both water and petroleum ether, was recrystallized from 95% ethanol and melted at 117.2–120.2°. Decomposition of the chelate and processing according to procedure I gave on distillation 6.8 g. (28.2%) of the crude β-diketone, b.p. 118–128° (735 mm.), which is very hygroscopic and changes to a white solid, presumably the dihydrate,[15] m.p. 127–128° (in a sealed tube) without recrystallization. The crude β-diketone was distilled from phosphorus pentoxide using the method employed with hexafluoroacetylacetone,[15] but decomposition resulted and no isolable products were obtained.

Self-Condensation of Methyl Chlorodifluoromethyl Ketone (I). A. By Sodium Methoxide.—Ketone I (12.8 g., 0.10 mole in 15 ml. of ether) was added in 15 min. to 95% sodium methoxide (6.0 g., 0.105 mole suspended in 100 ml. of ether). The reaction mixture was stirred for 1 hr. at room temperature, allowed to stand for 24 hr., and processed according to procedure II to give 1.3 g. (10%) of II, 1,5-dichloro-4-hydroxy-4-methyl-1,1,5,5-tetrafluoropentan-2-one, b.p. 52–55° at 4 mm. and 75–77° at 12–13 mm. (*vide infra*), and 5.2 g. (40.5%) of crude 2,4-dihydroxy-2,4,6-tris(chlorodifluoromethyl)-6-methyltetrahydropyran (IV), b.p. 97–120° (1.25 mm.), m.p. 91.2–92.2° from *n*-pentane. The solid gave neither an enol test with alcoholic ferric chloride solution nor did it react with neutral potassium permanganate at room temperature. Its infrared spectrum, which was identical by superimposition with the spectra of the samples of IV obtained in attempted benzoylation expt. A–C, showed bands characteristic of OH (3500 $cm.^{-1}$),[25a] aliphatic C–H (2920 and 2980 $cm.^{-1}$),[25b] and aliphatic C–F (1400–1000 $cm.^{-1}$).[25c]

Anal. Calcd. for $C_9H_9Cl_3F_6O_3$: C, 28.04; H, 2.35; Cl, 27.59; F, 29.57. Found: C, 27.92; H, 2.23; Cl, 28.04; F, 30.03.

B. By Barium Hydroxide.—Using the employed method by Conant and Tuttle[26] for the self-condensation of acetone, a sample of I (25.7 g., 0.20 mole) was refluxed over barium hydroxide in a Soxhlet assembly using an oil bath as the heat source. After 6 hr. the bath temperature was 130° and heating was stopped. The liquid products were decanted and the apparatus was rinsed with *n*-pentane. The rinsings were added to the products and the combined organic material was distilled to give 9.8 g. (38%) of recovered I, b.p. 56–58° (735 mm.), and 7.0 g. (27.2%) of II, 1,5-dichloro-4-hydroxy-4-methyl-1,1,5,5-tetrafluoropentan-2-one, b.p. 75–77° (12–13 mm.) and 79.5° (24 mm.), $n^{25}D$ 1.4026.

Anal. Calcd. for $C_6H_6Cl_2F_4O_2$: C, 28.04; H, 2.35. Found: C, 27.70; H, 2.29.

The infrared spectrum of II showed bands characteristic of OH (3500 $cm.^{-1}$),[25a] aliphatic C–H (2900 and 3000 $cm.^{-1}$),[25b] aliphatic C–F (1400–1000 $cm.^{-1}$),[25c] and C=O adjacent to a perhaloalkyl group (1760 $cm.^{-1}$).[27]

In addition there was obtained 5.1 g. (20%) of IV, m.p. 86–91°.

C. By Sodium.—This reaction was effected by a modification of the procedure used by Henne and Hinkamp[12] for the cyclic trimerization of 1,1,1-trifluoroacetone. Ketone I (12.8 g., 0.10 mole) was added over 15 min. to sodium (2.3 g., 0.10 g.-atom, covered with 100 ml. of anhydrous ether) and the mixture was stirred intermittently for 24 hr. Then, 100 ml. of 20% hydrochloric acid was added cautiously to the vigorously stirred, thick, pasty reaction mixture which was kept at 0° with an ice bath. The phases were separated and the water phase was extracted with several portions of ether. The combined organic phases were dried over Drierite, the solvent was removed, and the residue was distilled to give 12.4 g. (97%) of IV, b.p. 97–101° (0.5 mm.), m.p. 89.6–92° (crude) and 91.2–92.2° from *n*-pentane. The infrared spectrum of this sample of IV is identical with the spectra of the samples of IV which are described above.

Dehydration of IV to 2,4,6-Tris(chlorodifluoromethyl)-2-methyl-2H-pyran (V).—Heating a sample of IV (5.0 g., 0.013 mole) at 150° for 12 hr. with 25 g. or concentrated sulfuric acid followed by distillation gave 2.6 g. (57.5%) of 2,4,6-tris(chloro-

(23) K. T. Dishart and R. Levine, unpublished observations.

(24) The sodium methoxide was purchased from Olin Mathieson Corp., Niagara Falls, N. Y.

(25) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 96; (b) p. 13; (c) p. 329.

(26) J. B. Conant and N. Tuttle, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 199.

(27) C. E. Griffin, *Spectrochimica Acta*, **16**, 1464 (1960).

TABLE I

SYNTHESIS OF β-DIKETONES, $RCOCH_2COR'$, CONTAINING CF_2Cl AND C_2F_5 GROUPS BY ACYLATING KETONES, CH_3COR', WITH HALOGENATED ESTERS, RCO_2CH_3

R	R′	Reaction hr.	Procedure	Yield, %	B.p. °C.	B.p. mm.	$n^{25}D$	Copper salt, m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CF_2Cl	C_6H_5	20	I	89	130–131	12		268–269.5[a]	$C_{10}H_7ClF_2O_2$	51.63	51.80	3.03	2.81
					32.4–33.4 (m.p.)[a]								
	CH_3	19	I	76	141	736	1.4347	148.2–148.8[a]	$C_5H_5ClF_2O_2$	35.21	35.02	2.96	2.71
	C_2H_5	20	I	73	158.5	735	1.4376	125.6–126.6[a]	$C_6H_7ClF_2O_2$	39.04	38.68	3.82	3.83
	n-C_3H_7	23	II	64	82	28	1.4406	76.4–77.8[a]	$C_7H_9ClF_2O_2$	42.33	42.39	4.57	5.00
	i-C_3H_7	41	II	69	72	22	1.4394	42–43[a]			41.96		4.49
	i-C_4H_9	17	II	82	91	32	1.4419	103–104[a]	$C_8H_{11}ClF_2O_2$	45.19	45.13	5.22	4.96
	t-C_4H_9	18	II	59	80	26	1.4411	103.2–104.8[a]			44.98		5.14
	n-C_5H_{11}	31	II	81	114.5	29	1.4455	[b]	$C_9H_{13}ClF_2O_2$	47.69	47.77	5.78	5.92
	n-C_6H_{13}	31	II	84	129.5	29	1.4468	[b]	$C_{11}H_{15}ClF_2O_2$	49.90	50.37	6.28	6.44
	2-C_4H_3S[c]	19	I	49	120.5	5	1.5995	253–256[a]	$C_8H_5ClF_2O_2S$	40.26	40.49	2.11	1.92
	2-C_4H_3O[c]	19	I	49	133	36	1.5665	237–239[a]	$C_8H_5ClF_2O_3$	43.17	43.35	2.26	2.17
	C_5H_8O[d]	17	II	70	102.5	32	1.4721	157–158[a]	$C_7H_7ClF_2O_2$	42.76	42.50	3.59	3.79
	$C_6H_{10}O$[d]	17	II	62	121	31	1.4781	154.6–155.8[a]	$C_8H_9ClF_2O_2$	45.62	45.92	4.31	4.33
	$C_{10}H_{10}$[d]	19	II	59	73.8–74.4 (m.p.)[e]			222.5–226[a]	$C_{12}H_9ClF_2O_2$	55.72	55.40	3.51	3.49
C_2F_5	C_6H_5	16	I	89	128.5	28	1.5033	260–261.5[a]	$C_{11}H_7F_5O_2$	49.63	49.43	2.65	2.73
	CH_3[f]	16	I	78	116	734	1.3706	111.4–112[e]					
	C_2H_5	18	II	82	133	737	1.3760	53.2–54.2[a]	$C_7H_7F_5O_2$	38.54	38.25	3.24	3.18
	n-C_3H_7	16	II	63	65.5	30	1.3848	[b]	$C_8H_9F_5O_2$	41.39	41.43	3.91	4.09
	i-C_3H_7	19	II	68	140	735	1.3834	63–65[a]			41.67		3.68
	i-C_4H_9	18	II	60	74.5	30	1.3902	67.6–68.4[a]	$C_9H_{11}F_5O_2$	43.91	43.62	4.50	4.53
	t-C_4H_9	19	II	65	65	30	1.3884	104.8–105.6[a]			44.10		4.63
	n-C_5H_{11}	22	II	67	186.5	725	1.3978	[b]	$C_{10}H_{13}F_5O_2$	46.16	46.08	5.03	4.80
	n-C_6H_{13}	18	II	74	89	10	1.4025	[b]	$C_{11}H_{15}F_5O_2$	48.17	48.43	5.51	5.58
	2-C_4H_3S[c]	19	II	68	92	2.8	1.5238	249–252[a]	$C_9H_5F_5O_2S$	39.71	38.85[h]	1.85	1.50
	2-C_4H_3O[c]	19	II	74	95.5	16	1.4939	199–201[a]	$C_9H_5F_5O_3$	42.20	43.09[g]	1.97	2.14
	C_5H_8O[d]	16	I	82	82	30	1.4070	103–105[a]	$C_8H_7F_5O_2$	41.75	41.64	3.07	3.19
	$C_6H_{10}O$[d]	18	II	55	104.5	42	1.4235	130.8–132[a]	$C_9H_9F_5O_2$	44.27	44.44	3.72	3.61
	$C_{10}C_{10}O$[d]	19	II	62	44.6–45.2 (m.p.)[a]			243.5–246[a]	$C_{13}H_9F_5O_2$	53.43	53.44	3.10	3.36

[a] Recrystallized from methanol–water. [b] Copper salt is a liquid at room temperature. [c] 2-C_4H_3S and 2-C_4H_3O are the 2-thienyl and the 2-furyl radical, respectively. [d] C_5H_8O, $C_6H_{10}O$, and $C_{10}H_{10}O$ are cyclopentanone, cyclohexanone, and 1-tetralone, respectively. [e] Recrystallized from methanol. [f] This compound was prepared by Park, *et al.* (see ref. 8). [g] The poor analysis is probably due to the fact that this compound is light sensitive.

difluoromethyl)-2-methyl-2H-pyran (V), b.p. 51.5° (2 mm.), $n^{25}D$ 1.4205.

Anal. Calcd. for $C_9H_5Cl_3F_6O$: C, 30.92; H, 1.44. Found: C, 31.18; H, 1.14.

A sample of V, when treated with anhydrous aluminum chloride, gives a deep red color.[12,14] The infrared spectrum of V shows bands characteristic of olefinic C–H bonds (3145 cm.$^{-1}$),[28] methyl groups (3010, 2940, and 1449 cm.$^{-1}$),[28,29] and C–F linkages (1400–1000 cm.$^{-1}$).[25c] In addition, two bands, which are probably characteristic of the two differently substituted double bonds of V, were observed at 1684 and 1629 cm.$^{-1}$. The latter band is probably due to the allyl ether carbon–carbon double bond since it is the more intense and appears, due to conjugation, at a lower frequency than the triply substituted ethylene frequency.[30] The band at 1684 cm.$^{-1}$ is probably due to the other carbon–carbon double bond. An infrared spectrum of 2,4,6-tris(trifluoromethyl)-2-methyl-2H-pyran (VI)[12,14] showed that V and VI are the same type of compound.

The proton magnetic resonance spectrum[31] of V, taken at 40 Mc. in carbon tetrachloride, with tetramethylsilane as the internal standard, has bands at $\tau \simeq 4.12$ and $\simeq 8.30$ p.p.m. in the intensity of 2:3. The first band is probably due to the olefinic protons[32a] and the second is presumably due to the methyl protons.[32b] The F^{19} resonance spectrum,[31] at the same frequency and in the same solvent, with fluorotrichloromethane as internal standard, has bands at about $\phi \simeq 58$ and 61 p.p.m., and a doublet centered at 69, with intensity ratios of 1:1:1, which could arise from the two vinylic chlorodifluoromethyl groups and the chlorodifluoromethyl group on the asymmetric carbon atom,[33] respectively.

Self-Condensation of Methyl Perfluoroethyl Ketone (VII). A. By Sodium Methoxide.—Treatment of VII (16.2 g., 0.10 mole) with 95% sodium methoxide (6.0 g., 0.105 mole) in the manner described previously (expt. A) in the analogous reaction with I, gave 7.3 g. of liquid, b.p. 70–80° (82 mm.), which is probably a mixture of 1,1,1,2,2,6,6,7,7,7-decafluoro-5-hydroxy-5-methyl-3-heptanone (VIII) and 1,1,1,2,2,6,6,7,7,7-decafluoro-5-methyl-4-hepten-3-one (IX). This mixture was not subjected to elemental analysis. However, its infrared spectrum in carbon tetrachloride showed bands characteristic of hydroxyl groups (3500 cm.$^{-1}$),[25a] olefinic carbon–hydrogen bonds (3030 cm.$^{-1}$),[34a] aliphatic carbon hydrogen bonds (2950 cm.$^{-1}$),[25b] a carbonyl group α to a perfluoroalkyl group (1750 cm.$^{-1}$),[27] a conjugated carbonyl group (1700 cm.$^{-1}$),[34b] a carbon–carbon double bond (1580 cm.$^{-1}$),[34a] and carbon–fluorine bonds (1400–1000 cm.$^{-1}$).[25c]

In addition, 2.5 g. (22.5%) of X, 3-hydroxy-3-methyl-4,4,5,5,5-pentafluoropentanoic acid, m.p. 68.2–69.0° (from *n*-pentane), was isolated.

Anal. Calcd. for $C_6H_7F_5O_3$: C, 32.44; H, 3.18; F, 42.77. Found: C, 32.75; H, 3.49; F, 43.17.

The infrared spectrum of X in carbon tetrachloride has bands characteristic of a saturated carboxylic acid (3400, 3300–2800 cm.$^{-1}$)[35] and carbon–fluorine bonds.[25c] The mass spectrum[36] of X, at low ionizing potential, has two bands at mass numbers 204 and 160 (the latter more intense), corresponding to the mass of 3-methyl-4,4,5,5,5-pentafluoropenten-2-oic acid (XI, mol. wt. 204) and 2-methyl-3,3,4,4,4-pentafluoro-1-butene (XII, mol. wt. 160).

The proton magnetic resonance spectrum[31] of X taken at 60 Mc. in carbon tetrachloride with tetramethylsilane as the internal standard has bands at $\tau \simeq 2.50$ p.p.m. and 8.50 p.p.m. and a quartet centered at $\tau \simeq 7.25$ p.p.m. These data are characteristic of the protons of the hydroxyl groups (both carboxylic and alcoholic),[37] the methyl group,[32b] and a methylene group on an asymmetric carbon atom[32b] with an intensity of 2:3:2, respectively, indicative of two hydroxyl groups, three methyl protons, and two methylene protons. The F^{19} resonance spectrum[31] of X obtained at 40 Mc. from a water solution, with chlorotrifluoromethane as the external standard, has bands at $\phi \simeq 78$ and 124 p.p.m., which are characteristic of a perfluoroethyl group.[38]

Distillation of 4.4 g. of the liquid mixture of VIII and IX described above, from 15 ml. of concentrated sulfuric acid, gave 2.1 g. of material, b.p. 101–102° (737 mm.), $n^{25}D$ 1.3170. Although an elemental analysis was not obtained on this compound, it is undoubtedly IX as evidenced by comparing its physical constants with those of the structurally closely related, unsaturated ketone, 1,1,1,5,5,5-hexafluoro-4-methyl-5-penten-2-one (b.p. 76°, $n^{20}D$ 1.3260)[16] and by its infrared spectrum in carbon tetrachloride solution which has bands characteristic of olefinic carbon–hydrogen bonds (3030 cm.$^{-1}$),[34a] a conjugated carbonyl group (1725 and 1640 cm.$^{-1}$),[34b] and carbon–fluoride bonds (1400–1000 cm.$^{-1}$).[25c]

B. By Barium Hydroxide.—Treatment of VII (32.4 g., 0.20 mole) with barium hydroxide, as described above (experiment 5b) in the analogous reaction with I except that the reflux period was 72 hours, gave on distillation 12.3 g. (38%) of recovered VII b.p. 40–41°, and 9.0 g. (28%) of 2,4-dihydroxy-2,4,6-tris(pentafluoroethyl)-6-methyltetrahydropyran (XIII, b.p. 84.5° at 24 mm., $n^{25}D$ 1.3372). The infrared spectrum of XIII has bands characteristic of hydroxyl groups (3550 cm.$^{-1}$),[25a] aliphatic carbon–hydrogen bonds (2990 cm.$^{-1}$),[25b] and carbon–fluorine bonds (1400–1000 cm.$^{-1}$).[25c]

Anal. Calcd. for $C_{12}H_9F_{15}O_3$: C, 29.64; H, 1.87. Found: C, 29.41; H, 1.72.

Treatment of XIII (5.0 g., 0.01 mole) with 20 ml. of concentrated sulfuric acid for 12 hr. at 150–160° gave 3.8 g. (84%) of 2,4,6-tris(pentafluoroethyl)-2-methyl-2H-pyran [XIV, b.p. 61° (25 mm.), $n^{25}D$ 1.3275]. Although this compound was not subjected to elemental analysis, from its boiling point and infrared spectrum in carbon tetrachloride solution, which has bands at the same frequencies as exhibited by 2,4,6-tris(chlorodifluoromethyl)2-methyl-2H-pyran (V) and 2,4,6-tris(trifluoromethyl)-2-methyl-2H-pyran (VI) in the 3100–1500-cm.$^{-1}$ region, there is little doubt about the identity of XIV.

Acylation of Methyl Pentafluoroethyl Ketone (VII) with Methyl Oxalate.—Methyl oxalate (11.8 g., 0.100 mole, in 75 ml. of anhydrous ether) was added over 25 min. to 95% sodium methoxide (6.0 g., 0.105 mole, suspended in 40 ml. of ether). Then, VII (16.2 g., 0.10 mole in 30 ml. of ether) was added over 6 hr. to the rapidly stirred reaction mixture. The mixture was allowed to stand at room temperature for 24 hr. and processed according to procedure II to give 8.0 g. (32%) of methyl pentafluoropropionylpyruvate, b.p. 62.5° (9 mm.), $n^{25}D$ 1.3991.

Anal. Calcd. for $C_7H_5F_5O_4$: C, 33.88; H, 2.03. Found: C, 34.18; H, 2.1

The infrared spectrum of the product in carbon tetrachloride solution has absorption bands characteristic of olefinic carbon–hydrogen bonds (3050 cm.$^{-1}$)[34a]; carbonyl groups adjacent to perfluoroalkyl groups (1750 cm.$^{-1}$),[27] α to an ester function as in methyl pyruvate (1750 cm.$^{-1}$),[39] and in β-diketones (1650 and 1580 cm.$^{-1}$)[40]; and carbon–fluorine bands (1400–1000 cm.$^{-1}$).[25c] This compound gave a positive enol test with alcoholic ferric chloride solution and formed a green copper chelate, m.p. 232–235° dec. (from aqueous methanol).

Attempted Benzoylation of Methyl Perfluoroethyl Ketone (VII).—Methyl benzoate (13.6 g., 0.10 mole, in 15 ml. of ether) was added in 10 min. to 95% sodium methoxide (6.0 g., 0.105 mole, suspended in 100 ml. of ether). The mixture was heated to refluxing and VII (16.2 g., 0.100 mole, in 15 ml. of ether) was added in 10 min. Refluxing was continued for an additional 48 hr. and the reaction was processed according to procedure II to give (a) recovered methyl benzoate (11.4 g., 84%, b.p. 95–103° at 28 mm.), (b) 2.0 g. (20%) of pentafluoropropionylacetone [XV, b.p. 116.5° at 737 mm., $n^{25}D$ 1.3693, blue-grey copper chelate, m.p. 111–112° from aqueous methanol,[8] infrared spectrum superimposable on that of an authentic sample (Table I)], and (c) 2.0 g. of material (b.p. 133–170° at 24 mm. and m.p. 109–110° from *n*-pentane).

Anal. Calcd. for $C_6H_5F_5O_2$: C, 35.31; H, 2.47. Found: C, 35.61; H, 2.37.

To date, attempts to elucidate the structure of the solid, m.p. 109–110°, by chemical and physical methods, have failed.

(28) G. D. Meakins, *J. Chem. Soc.*, 4170 (1953).

(29) See ref. 25, p. 13.

(30) See ref. 25, p. 36, 40.

(31) We are indebted to Mr. J. J. Burke of Mellon Institute for the n.m.r. spectra and their interpretation. The spectra were obtained on a Varian Associates Model A-60 Proton Magnetic Resonance Spectrometer.

(32) (a) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 61; (b) p. 53.

(33) See ref. 32, p. 101.

(34) (a) See ref. 25, p. 34; (b) ref. 25, p. 133.

(35) See ref. 25, p. 162.

(36) We are indebted to Mr. A. G. Sharkey and Miss J. Schultz of the Bureau of Mines Experiment Station, Bruceton, Pa., for running and interpreting this spectrum on a Consolidated Mass Spectrometer, Model 21-103.

(37) See ref. 32, p. 66.

(38) See ref. 32, p. 76.

(39) See ref. 25, p. 141, 184.

(40) See ref. 25, p. 142.

Bicyclobutyl Derivatives. I. Synthesis of Conjugated Diolefins and Diolefin Diketones

J. D. PARK AND WILLIAM C. FRANK[1]

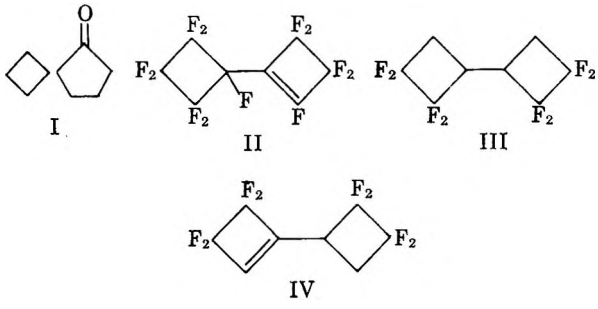
Department of Chemistry, University of Colorado, Boulder, Colorado

Received December 13, 1963

2,2′-Dichloro-2,2′,3,3,3′3′-hexafluorobicyclobutyl- and 1-(2′,3′,3′-trifluoro-1-cyclobutenyl)-2,3,3-trifluoro-2-chlorocyclobutane were synthesized by cycloaddition reactions and their elimination and replacement reactions were studied. 2,2′3,3′,3′-Hexafluorobicyclobutenyl, 2,2′-dialkoxy-3,3,3′,3′-tetrafluorobicyclobutenyl, and 2,2′-dialkoxy-3,3′-diketobicyclobutenyl were also synthesized. Several substituted 1-vinyl-1-cyclobutenes were prepared as intermediates in the preparation of the "dibox"[2] compounds.

Work done in the past on the synthesis and reactions of bicyclobutyl derivatives has been meager and quite limited.

Vogel[3] obtained a pinacol of cyclobutanone. This rearranged in acid to a spirooctanone (I). Miller[4] treated perfluorocyclobutene with fluorine at −78° to synthesize a cyclobutylcyclobutene (II). 2,2,2′,2′,3,3,-3′,3′-Octafluorobicyclobutyl (III) was prepared by Du Pont workers[5] in low yield (10–15%) by successive cycloadditions of tetrafluoroethylene with butadiene. 1-(2′,2′,3′,3′-Tetrafluorocyclobutyl)-2,2,3,3-tetrafluorocyclobutene (IV) was prepared also by the above workers[5] by the cycloaddition of vinylacetylene with tetrafluoroethylene.



I II III IV

The relative inaccessibility of these "dibox" compounds and their intermediates has probably prevented active interest in their chemistry. This paper reports the results of a study leading to routes to several reactive "dibox" compounds.

Discussion

The thermal cycloaddition of butadiene with trifluorochloroethylene has been reported and 1:1 adduct characterized.[6] In repeating this work it was found that, in addition to the 1:1 cycloadduct V, a considerable amount (5–10%) of a 1:2 (diene–CF_2=$CFCl$) adduct VI was also formed. By using 2 moles of trifluorochloroethylene per mole of butadiene, the proportion of 1:2 adduct (VI) was increased, but only to 15–20%, the main products being the 1:1 adduct (V) and the cyclic dimer of trifluorochloroethylene.

(1) This paper represents part of a Ph.D. thesis submitted to the Graduate School, University of Colorado.

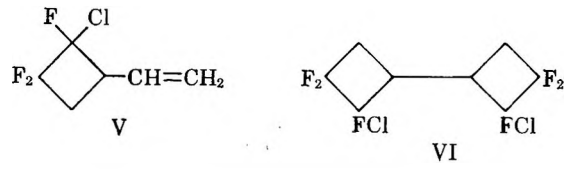
(2) "Dibox" is a trivial name used to designate bicyclobutyl and its derivatives.

(3) E. Vogel, *Chem. Ber.*, **85**, 25 (1952).

(4) W. T. Miller, U. S. Patent 2,716,141 (1951); *Chem. Abstr.*, **50**, P7852*a* (1950).

(5) D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *J. Am. Chem. Soc.*, **71**, 490 (1949).

(6) J. D. Park, H. V. Holler, and J. R. Lacher, *J. Org. Chem.*, **25**, 990 (1960).



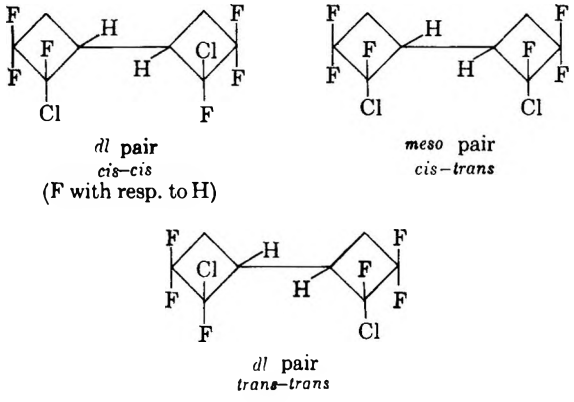
V VI

Addition of a second mole of trifluorochloroethylene to the pure 1:1 adduct V proceeded with low conversion (10–15%) to VI and offered no advantage over direct combination of trifluorochloroethylene to butadiene.

VI was especially difficult to purify. Vapor phase chromatography on a strongly polar absorbent showed the presence of three stereoisomers.

The structure predicted on the basis of the most stable diradical intermediate is the symmetrical head-to-head adduct.

Compound VI would have two *dl* pairs and one *meso* form in agreement with the three v.p.c. peaks found.

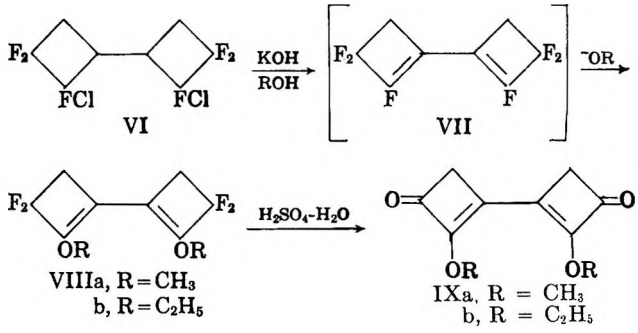


dl pair *cis–cis* (F with resp. to H)

meso pair *cis–trans*

dl pair *trans–trans*

The formal structure proof for this compound (VI) is based on microanalyses, infrared, ultraviolet, and n.m.r. spectra of the derivatives prepared as follows.



VI VII

VIIIa, R = CH_3
b, R = C_2H_5

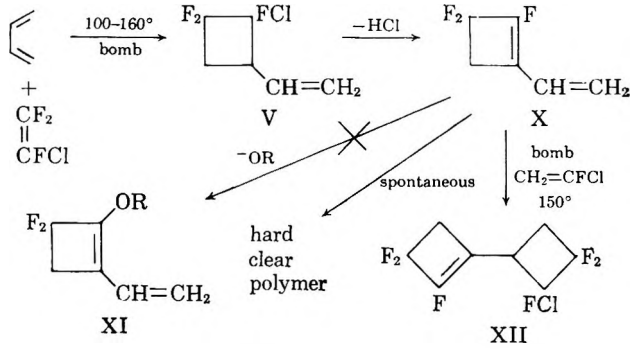
IXa, R = CH_3
b, R = C_2H_5

Refluxing VI with potassium hydroxide in methanol resulted in the elimination of 2 moles of hydrochloric acid followed rapidly by the replacement of both vinylic

fluorines to give a conjugated diene diether (VIIIa where R = CH_3). Potassium hydroxide in ethanol gave similarly VIIIb (R = C_2H_5). Numerous unsuccessful attempts were made to perform the elimination reaction to yield VII without the accompanying replacement reaction. Two moles of potassium hydroxide in methanol were treated with VI slightly below room temperature in hopes of eliminating hydrochloric acid twice. Instead of obtaining VII, *ca.* 0.5 mole each of diether VIIIa and the starting material (VI) was recovered. The relative proportions of the stereoisomers of VI in the latter were compared with that of the fresh starting material VI and found to be virtually identical. Thus, there was no stereospecificity in this elimination reaction. This does not imply a carbanion mechanism for the elimination; but it does, however, cast much doubt for a concerted mechanism since the latter would be expected to exhibit some degree of stereospecificity.

The diene diethers (VIII) were hydrolyzed to corresponding diketones (IX) very easily with sulfuric acid containing water. This was affected by simply dissolving the diethers in sulfuric acid and slowly dropping in water. The yellow diketones (IX) were quickly precipitated on pouring the acid solutions into cold water. Similar hydrolyses have been reported with fluorinated phenyl- and cyclohexenylcyclobutene ethers.[7,8]

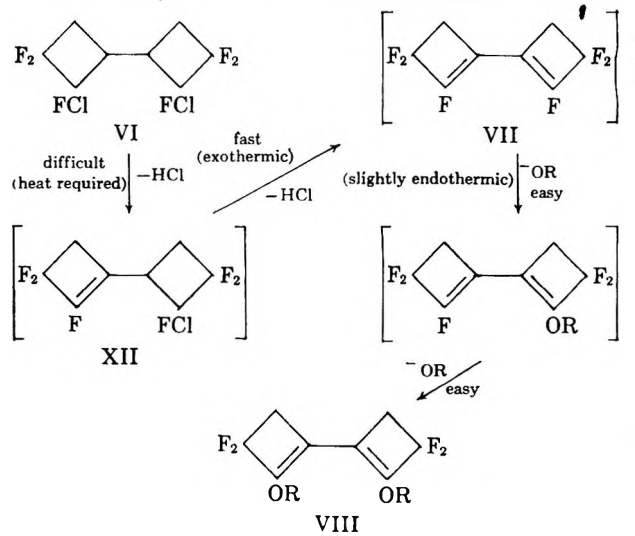
Since conjugated diolefins undergo cycloaddition reactions much more easily than monoolefins, owing to greater stabilization of the free-radical intermediates, the best cycloaddition route to "dibox" compounds would be the addition to one molecule of trifluorochloroethylene, then an elimination reaction to regenerate the diene system, followed by a second cycloaddition of trifluorochloroethylene.



The dehydrochlorination V to X with potassium hydroxide in alcohol was expected to be accompanied by replacement of vinylic fluorine. To avoid this, a suspension of potassium hydroxide in mineral oil was tried first to affect the elimination. This method gave 1-vinyl-2,3,3-trifluoro-1-cyclobutene (X) but in low yield and conversion. Triethylamine in ether with V gave the same product but with even lower conversion. Potassium hydroxide in ethanol was then tried. Vapor phase chromatography showed a high conversion and the infrared spectrum showed that the product was not the expected vinyl ether XI but was X, identical with that prepared by the two previous methods. In fact, replacement of the vinylic fluorine of X with ethoxide was found to be very difficult even on refluxing overnight. X was found to be a very reactive monomer. A freshly distilled sample polymerized spontaneously overnight to a hard, clear, glassy solid.

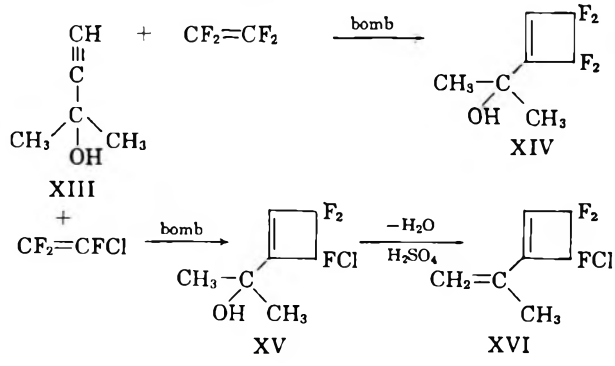
The cycloaddition of trifluorochloroethylene with the vinylcyclobutene (X) proceeded rather easily to give the unsaturated "dibox" compound XII in good yield, which was readily purified by distillation.

The reaction of XII with potassium hydroxide in alcohols was very exothermic yielding VIII identical with that prepared from the saturated "dibox" compound VI by refluxing with alcoholic potassium hydroxide. However, by adding 2 moles of base per mole of XII and holding the temperature below 25°, elimination occurred without replacement of the vinylic fluorine to yield 2,2′,3,3,3′,3′-hexafluorobicyclobutenyl (VII) which had been sought earlier from VI but without success. The inability to isolate VII as an intermediate on treating VI with an alkoxide can thus be explained by the instability of the intermediates in the conditions required for the first elimination step.



The *ability* to isolate VII from XII can be rationalized by the relative ease of the elimination reaction compared with that of the replacement reaction. The conversion of XII to VII proceeded best using triethylamine in anhydrous ether; however, high concentration of triethylamine caused the formation of a black tarry material.

The cycloadditions of tetrafluoroethylene and of trifluorochloroethylene with 3-methyl-1-butyn-3-ol (XIII) were successfully performed to obtain intermediates for other "dibox" compounds. The products were the expected cyclobutenylisopropyl alcohols (XIV and XV). These can be dehydrated with sulfuric acid to the corresponding conjugated dienes, *e.g.*, XVI.

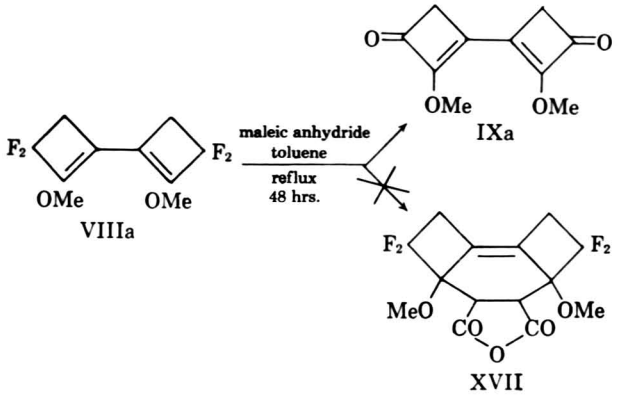


(7) E. F. Silversmith and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 4083 (1958).

(8) C. M. Sharts and J. D. Roberts, *ibid.*, **83**, 871 (1961).

Cycloaddition reactions were also attempted with 2,-3-dichlorobutadiene and with 1,3-cyclooctadiene using trifluorochloroethylene as coreactant. In the case of 2,3-dichloro-1,3-butadiene, heating at 130° for 7 hr. caused formation of a rubber-like polymer. No codimerization was observed with 1,3-cyclooctadiene and trifluorochloroethylene at 160° for 15 hr. Apparently the cyclooctane structure causes steric inhibition for the interaction between the two double bonds of the diene in addition to making approach by the fluoro olefin difficult. Thiophene also failed to react with CF_2=CFCl, but here the failure to react is probably due to inhibition of radical formation by the sulfur atom.

Diels–Alder reactions were attempted using tetracyanoethylene as dienophile and compounds VIIIa, X, and XVI as dienes. In each case, there was no colored π-complex observed and no adducts were isolated. X polymerized on refluxing with maleic anhydride in toluene, and VIIIa was converted to diketone IXa.



Experimental

Cycloaddition of Butadiene with Trifluorochloroethylene (1 Mole).[4]—A 2-l. steel bomb containing 5 ml. of limonene as inhibitor was cooled in a Dry Ice–acetone bath for several hours and then charged with 350 g. (2.9 moles) of trifluorochloroethylene and 150 g. (2.78 moles) of butadiene. This was heated under autogenous pressure in a shaker at 105° for 24 hr., 125° for 24 hr., 150° for 15 hr., and 175° for 24 hr. On cooling, bleeding off excess gases, and opening, 412 g. of liquid product was obtained, plus a considerable amount of solid material. On distillation, 350 g. (75%) of the 1-vinyl-2,3,3-trifluoro-2-chlorocyclobutane (V)[4] was obtained, boiling at 108.5–109.0° (630 mm.). The distillation residue was placed in a refrigerator at −20° for 2 weeks, at which time 15 g. of colorless crystalline material was filtered off *in the cold* (−15°). The crystals melted at 49–60° and were identified as 2,2′-dichloro-2,2′-3,3,3′,3′-hexafluorobicyclobutyl (VI). The product was dissolved in hot ethanol (50 ml.) and decolorized twice with charcoal; water was added to the boiling solution. The clear solution on cooling yielded colorless needles, m.p. range 57–67°.

Cycloaddition of Butadiene with Trifluorochloroethylene (2 Moles).—A 0.5-l. stainless steel bomb containing 2 ml. of "Terpene B" inhibitor was chilled in a Dry Ice–acetone bath and then charged with 270 g. (2.28 mmoles) of trifluorochloroethylene and 60 g. (1.1 moles) of butadiene. The bomb was then heated under autogenous pressure at 100° for 4 hr., 140° for 28 hr., and 170° for 28 hr. On cooling the bomb, bleeding off gases, and opening, 330 g. of crude liquid product was obtained. Distillation yielded 162.5 g. of 1,2,3,3,4,4-hexafluoro-1,2-dichlorocyclobutane, b.p. 54–55° (630 mm.); 36.0 of 1-vinyl-2-chloro-2,3,3-trifluorocyclobutane (V), b.p. 107–109° (630 mm.); and about 75 g. of distillation residue. The residue was diluted with 20 ml. of ethanol, cooled to −20° for 2 days, and filtered *in the cold* (−15°). About 60 g. of 2,2′-dichloro-2,2′,3,3,3′,3′-hexafluorobicyclobutyl (VI) was thus obtained (17–20% yield). This was recrystallized from ethanol–water mixture, m.p. 65–67°. An analytical sample was prepared by two recrystallizations from ethanol–water solution.

Anal. Calcd. for $C_8H_6Cl_2F_6$: C, 33.5; H, 2.09; Cl, 24.7; F, 39.7. Found: C, 33.09; H, 2.06; Cl, 22.88; F, 38.38.

Vapor phase chromatography of compound VI on a highly polar absorbent (Fluorocarbon FS on Firebrick R) gave three peaks in the ratios 1.0:1.3:1.0. These peaks correspond to the three types of stereoisomers, the *cis–cis* isomers (F with respect to adjacent H), the *trans–cis* isomer, and the *trans–trans* isomers. The compound gave distinctive infrared peaks at 2930 and 1420 cm.$^{-1}$. Nuclear magnetic resonance showed a very complex splitting pattern.

Cycloaddition of 1-Vinyl-2-chloro-2,3,3-trifluorocyclobutane (V) with Trifluorochloroethylene.—A 0.5-l. stainless steel bomb containing 175 g. (1.02 moles) of V and 1 ml. of "Terpene B" was cooled and charged with 135 g. (1.16 moles) of trifluorochloroethylene. It was then heated at 160° for 25 hr. On cooling the bomb, bleeding off the gases, and opening, 267 g. of liquid product was obtained. The product was not worked up in the usual manner (see previous experimental procedure), but rather was analyzed by vapor phase chromatography, which showed 16 parts of trifluorochloroethylene dimer (50% of orig. CF_2=CFCl), thirty-six parts of V (86% recovery), seven parts of VI (10% yield), and five parts of an unidentified higher boiling product.

2,2′-Dimethoxy-3,3,3′,3′-tetrafluorobicyclobutenyl (VIIIa).—About 2.78 g. (0.0097 moles) of 2,2′-dichloro-2,2′,3,3,3′,3′-hexafluorobicyclobutyl (VI) was dissolved in 20 ml. of methanol and to this solution was added a solution of 3.0 g. (0.053 moles) of potassium hydroxide in 15 ml. of methanol. This was then heated over a steam bath to slow reflux for 15 min. The yellow-orange fluid was filtered hot and the crystals formed in the funnel were washed through with hot methanol. The methanolic solution was concentrated *in vacuo* and allowed to cool and crystallize. A 1.10-g. sample of pale yellow needles of VIIIa (m.p. 98–99°) was obtained. A second crop gave 0.2 g. more of VIIIa, making a yield of 56%. VIIIa was further purified by treatment with activated charcoal and recrystallization from an alcohol–water solution to give colorless needles, m.p. 101°; ultraviolet spectrum: λ_{max} 2700 Å. (ϵ 18,000); infrared spectrum: bands at 1440, 1620, and 2990 cm.$^{-1}$; n.m.r. spectrum showed a —CH_2— split by an adjacent —CF_2—.

Anal. Calcd. for $C_{10}H_{10}F_4O_2$: C, 50.4; H, 4.20; F, 31.9. Found: C, 50.20; H, 4.44; F, 31.62.

1,2′-Dimethoxy-3,3′-diketobicyclobutenyl (IXa).—Approximately 2.0 g. (0.0075 mole) of the diene diether (VIIIa) as prepared above was added with stirring to 10 ml. of concentrated sulfuric acid. When the solid had dissolved, 5 ml. of cold water was slowly added dropwise with stirring, care being taken to avoid severe overheating. The resulting brownish solution was poured into 100 ml. of cold water. A yellow solid immediately precipitated. After the addition, the yellow solid was filtered off and washed with water. Typical yields of IXa were 1.2–1.5 g. (85–100% yield). The diketone was conveniently recrystallized from hot toluene or hot aqueous ethanol (the former was a better solvent). Yellow needles were thus obtained, m.p. 203°; ultraviolet spectrum: λ_{max} 3650 Å. (ϵ 13,000); infrared spectrum: bands at 1277, 1580, and 1730 cm.$^{-1}$; the n.m.r. spectrum showed two single peaks for —OCH_3 and for —CH_2—CO—.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.9; H, 5.16. Found: C, 61.91; H, 5.40.

2,2′-Diethoxy-3,3,3′,3′-tetrafluorobicyclobutenyl (VIIIb).—A 2.78-g. sample (0.0097 mole) of VI was dissolved in 25 ml. of absolute ethanol and to this was added a solution of 3.0 g. (0.053 mole) of potassium hydroxide in 20 ml. of ethanol. It was heated to reflux for 10 min. The orange fluid was filtered to remove the salts. The filtrate was concentrated to half its original volume by heating under vacuum. The concentrated solution was poured into cold water (100 ml.) and then extracted with one 25-ml. portion of chloroform followed by extraction with a 10-ml. portion of the same solvent. The chloroform extracts were dried over anhydrous potassium carbonate and then evaporated *in vacuo*. A red liquid (about 1.2 g., 50% yield) was thus obtained. This crystallized readily upon refrigeration and melted readily on warming. The material was heated in alcohol with activated charcoal, allowed to recrystallize at −20°, and filtered off *in the cold*. After two such recrystallizations, white crystals were obtained melting at 32.3°. The crude liquid product is of sufficient purity for subsequent steps; infrared spectrum: bands at 1440, 1620, and 2960 cm.$^{-1}$. No microanalysis was submitted since the product darkened rapidly on standing.

2,2′-Diethoxy-3,3′-diketobicyclobutenyl (IXb).—The diethoxy diketone (IXb) was prepared by the same procedure as the corresponding dimethoxy compound (IXa) from XI. Recrystallization from hot alcohol–water yielded bright yellow needles, m.p. 118–119°; typical yields were 80%; ultraviolet spectrum: λ_{max} 3650 Å. (ϵ 12,670); infrared spectrum: peaks at 1260, 1580, and 1730 cm.$^{-1}$; the n.m.r. spectrum showed an unsplit methylene for —CH_2—CO and the expected series of peaks for —O—CH_2—CH_3.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.3. Found: C, 65.23; H, 6.64.

1-Vinyl-2,3,3-trifluoro-1-cyclobutene (X).—About 34.0 g. (0.20 mole) of 1-vinyl-2,2,3-trifluoro-2-chlorocyclobutane (V) was dissolved in 50 ml. of absolute methanol. A solution of 13.0 g. of potassium hydroxide (0.23 mole) in 50 ml. of methanol was added dropwise with stirring and cooling. The temperature was maintained at 10–20° throughout the addition. After the addition, the temperature was allowed to rise to 25–30° for 0.5 hr. and then the mixture was heated to reflux for 10 min. It was then poured into 500 ml. of cold water in a separatory funnel. After shaking, the product which separated to the bottom was removed. After drying over anhydrous calcium chloride, 20–25 g. (80–90% yield) of crude straw-colored liquid (XV) was obtained. (Additional portions were obtained by extracting the aqueous phase with chloroform.) Fractional distillation under reduced pressure yielded 1-vinyl-2,3,3-trifluoro-1-cyclobutene (X), b.p. 44.0° (174 mm.), $n^{25}D$ 1.3971. Freshly distilled samples were found to polymerize very readily to a hard, clear and colorless solid. It can be stored for short periods of time (1–2 days) at −20° in the presence of inhibitors (*e.g.*, hydroquinone or *t*-butylcatechol); infrared spectrum: bands at 1370, 1460, and 1720 cm.$^{-1}$.

Anal. Calcd. for $C_6H_5F_3$: C, 53.5; H, 3.73; F, 42.5. Found: C, 53.2; H, 4.06; F, 42.1.

1-(2,3,3-Trifluoro-1-cyclobutyl)-2,3,3-trifluoro-2-chlorocyclobutene (XII).—About 186 g. (1.37 moles) of 1-vinyl-2,3,3-trifluoro-1-cyclobutene (X, freshly prepared by the previous method, dried over magnesium sulfate, but not distilled) was placed in a 0.5-l. stainless steel bomb along with 1 g. of hydroquinone and about 2 ml. of "Terpene B" inhibitor. The bomb was sealed, checked for leaks, chilled in Dry Ice, and evacuated; then 190 g. (1.63 moles) of trifluorochloroethylene was bled in. It was then heated in a heater-shaker at 150° for 5.5 hr. On cooling and opening the bomb, 316 g. of an orange liquid was obtained. Vapor phase chromatography showed the absence of starting diolefin, the presence of a small amount of trifluorochloroethylene and its dimer, and a high proportion of the desired product (XII). Distillation at atmospheric pressure gave 255 g. (75%) of a colorless liquid boiling at 160° (630 mm.); $n^{25}D$ 1.4676, $n^{25}D$ 1.3910; infrared spectrum: bands at 1440, 1650 (w), and 1720 cm.$^{-1}$.

Anal. Calcd. for $C_8H_5ClF_6$: C, 38.3; H, 2.00; F, 45.5. Found: C, 38.52; H, 1.83; F, 45.70.

2,2′-Dimethoxy-3,3,3′,3′-tetrafluorobicyclobutyl (VIIIa). Method B.—About 3.16 g. (0.0126 mole) of XII was dissolved in 10 ml. of methanol and to this was added dropwise 20 ml. of a 10% solution of potassium hydroxide in methanol. The reaction was quite exothermic and salts precipitated immediately. After the initial reaction, the mixture was warmed slightly for 5 min. and then poured into 100 ml. of cold water. The white solid was filtered off, washed with water, and air-dried, yielding 2.80 g. of VIIIa, m.p. 101–102°. The infrared spectrum was identical with that of VIIIa prepared from VI. Hydrolysis with sulfuric acid–water yielded a diketone identical with XIVa described earlier.

2,2′-Diethoxyl-3,3,3′,3′-tetrafluorobicyclobutyl (VIIIb). Method B.—To a solution of 3.16 g. of XII (0.0126 mole) in 10 ml. of ethanol was added dropwise 20 ml. of a 10% solution of potassium hydroxide in ethanol. The reaction was vigorous. After the initial reaction, the mixture was warmed slightly for 5 min. The solution was filtered and the filtrate was concentrated to half its original volume. The concentrated solution was poured into water and extracted with two 15-ml. portions of dichloromethane. The extracts were dried over magnesium sulfate, and the solvent then was stripped *in vacuo* to yield 2.70 g. of straw-colored liquid (80% yield). The infrared spectrum was identical with that of VIIIb prepared directly from VI.

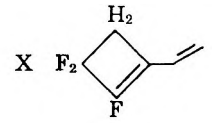
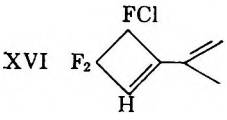
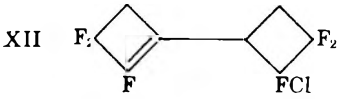
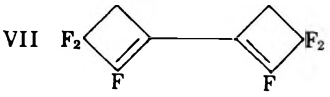
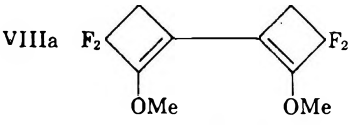
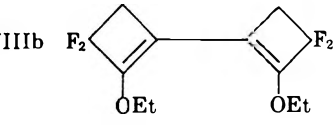
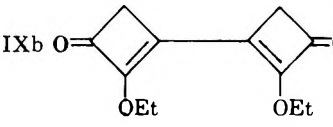
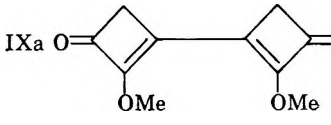
2,2′,3,3,3′,3′-Hexafluorobicyclobutenyl (VII). A.—About 25 g. (0.10 mole) of XII was dissolved in 100 ml. of absolute ethanol, and the solution was cooled in an ice–water bath. A 56-ml. quantity of a 10 g./100 ml. solution of potassium hydroxide in absolute ethanol was added slowly with stirring and cooling. Precipitation occurred immediately. After the addition, the solution was allowed to warm to 25°, and then poured into a separatory funnel with 500 ml. of water. On separation of the organic layer, much of the material solidified, requiring use of a heat lamp to remove it. This yielded 7.8 g. of VII. The product melted at 50–55°. The filtrate was also found to be very rich in product, along with some of the diether VIIIb.

B.—About 25 g. (0.10 mole) of XII was dissolved in 70 ml. of absolute ether, and 12 g. (0.12 mole) of triethylamine in 10 ml. of absolute ether was added at once. The mixture was left in a stoppered flask for 2 days after which time it was poured into 300 ml. of lukewarm water, care being taken to keep the ether from boiling over. It was then left for 1 day at which time the product crystallized. The product was filtered off and washed with water. A 17-g. sample (80%) of XII, m.p. 57°, was obtained. An analytical sample was prepared by sublimation; ultraviolet spectrum: λ_{max} 2375 Å. (ϵ 8330); infrared spectrum: bands at 1340 and 1655 cm.$^{-1}$; n.m.r. spectrum: CH_2 split by cross-ring vinylic F, and resplit by adjacent —CH_2—.

Anal. Calcd. for $C_8H_4F_6$: C, 44.9; H, 1.87; F, 53.3. Found: C, 44.51; H, 1.89; F, 53.02.

2-(3,3,4,4-Tetrafluoro-1-cyclobutenyl)isopropyl Alcohol (XIV).—A 0.5-l. stainless steel bomb containing 42 g. (0.50 mole) of 3-methyl-1-butyn-3-ol (XIII) and 1 ml. of "Terpene B" inhibitor was cooled in Dry Ice–acetone and charged with 65 g. (0.65 mole) of tetrafluoroethylene. It was then heated for 24 hr. at 140°. At the end of the heating period, it was cooled and the excess gaseous material was bled off. On opening the bomb, 75 g. of liquid was obtained. This was extracted with three 15-ml. portions of water to remove the unchanged methylbutynol. On distillation at 100-mm. pressure, the material decomposed

TABLE I

		Infrared, cm.$^{-1}$	Ultraviolet, λ_{max} Å. (ϵ)
X		1370, 1460, *1720*	
XVI		1588, *1635*	
XII		1440 (1650), *1720*	
VII		1340, *1655*	2375 (8330)
VIIIa		1440, *1620*, 2990	2700 (18,000)
VIIIb		1440, *1620*, 2960	
IXb		1260, *1580*, 1730	3650 (12,670)
IXa		1277, *1580*, 1730	3650 (13,000)

considerably, but 20 g. of product (XIX) boiling at 101° (100 mm.) was obtained (19.9% yield); infrared spectrum: bands at 1610, 1650, 2960, and 3350 cm.$^{-1}$; n.m.r. spectrum showed a single peak for a hydroxyl H, a single peak for 2(—CH_3), and a series of peaks corresponding to a vinylic hydrogen split by a cross-ring —CH_2— and resplit by an adjacent —CH_2—.

Anal. Calcd. for $C_7H_8F_4O$: C, 45.6; H, 4.35; F, 41.3. Found: C, 45.85; H, 4.38; F, 40.95.

2-(3,3,4-Trifluoro-4-chloro-1-cyclobutenyl)isopropyl Alcohol (XV).—A 2-l. steel bomb containing 600 g. (7.15 moles) of 3-methyl-1-butyn-3-ol (XIII) and 5 ml. of "Terpene B" inhibitor was chilled in a Dry Ice bath and then evacuated. A 610-g. sample (5.25 moles) of trifluorochloroethylene was bled in, and the bomb was heated at 160° for 24 hr. On cooling, bleeding off gases, and opening, 1110 g. of brown liquid was obtained. This was steam distilled to yield 676.3 g. (after drying over magnesium sulfate) of steam volatile material. Vapor phase chromatography showed this to be 70% pure adduct XV. The yield was thus 45%. The product had the following properties: b.p. 97–98° (38 mm.); d^{25}_{25} 1.468; n^{26}D 1.4198; infrared spectrum: bands at 1610, 2960, and 3350 cm.$^{-1}$; n.m.r. spectrum showed single peaks for a hydroxyl H and a methyl H, and a series of peaks corresponding to a vinylic hydrogen split once by a cross-ring —CFCl— and split again by an adjacent —CF_2—.

Anal. Calcd. for $C_7H_9ClF_3O$: C, 42.0; H, 4.00; Cl, 17.7; F, 28.5. Found: C, 41.83; H, 3.77; Cl, 18.99; F, 28.93.

1-Isopropenyl-3,4,4-trifluoro-3-chloro-1-cyclobutene (XVI).—About 50 g. (0.25 mole) of the above 2-(3,3,4-trifluoro-4-chloro-1-cyclobutenyl)isopropyl alcohol was added dropwise with stirring into 130 ml. of concentrated sulfuric acid previously cooled to 5° in an ice bath. The temperature was maintained at 5–15° throughout the addition. Afterwards the temperature was allowed to rise to 20° for 2.5 hr., at which time it was poured into 500 g. of ice with stirring. A black tar resulted which was extracted several times with dichloromethane (a process which proved very messy and tedious). The extracts were dried over anhydrous magnesium sulfate and then stripped to a volume of about 75 ml. The product was distilled at 38-mm. pressure. A 12-g. sample of XXI (27% yield) was obtained, boiling at 61–65° (38 mm.), n^{25}D 1.4304; infrared spectrum: bands at 1588 and 1635 cm.$^{-1}$. Sharts and Roberts[8] reported this compound earlier and listed properties as follows: infrared bands at 1588 and 1635 cm.$^{-1}$, b.p. 60–65° (32–37 mm.), n^{25}D 1.4288–1.4295.

Attempted Diels–Alder Reactions of 2,2′-Dimethoxy-3,3,3′,3′-tetrafluorobicyclobutenyl (VIIIa). A. With Maleic Anhydride.—A 2.38-g. sample (0.01 mole) of the above "dibox" compound (VIIIa) and 1.5 g. (0.015 mole) of maleic anhydride were refluxed with 50 ml. of toluene for 55 hr. At the end of the reflux period, a small amount of black solid was filtered off. The filtrate, on cooling, yielded 0.45 g. of bright yellow needles. Infrared spectra (see Table I) showed this to be identical with 2,2′-diethoxy-3,3′-diketobicyclobutenyl (IXa) prepared by sulfuric acid hydrolysis of the same starting material.

B. With Tetracyanoethylene.—A 2.38-g. sample (0.01 mole) of XIIIa and 1.30 g. of tetracyanoethylene (0.01 mole) were dissolved separately in 10 ml. portions of tetrahydrofuran and the two solutions were then mixed. No colored π-complex was observed. A day later the solvent was stripped *in vacuo*. The residual solid was found to be a mixture of the two starting materials. There was no indication of any reaction having occurred.

Acknowledgment.—The authors wish to express their appreciation to the Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, and the U. S. Army Quartermaster Research and Engineering Command, Natick, Massachusetts, under Scientific Project Officer, Dr. Malcolm C. Henry, for their partial support of this work.

The Synthesis and Properties of 1,1-Dimethylindolium Perchlorate, an N-Quaternized Indole

R. L. HINMAN AND J. LANG

The Union Carbide Research Institute, Union Carbide Corporation, Tarrytown, New York

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1,1-Dimethylindolium perchlorate (IVb), the first example of an N-quaternized indole, has been prepared *via* the sequence: isatin, 3-hydroxyindoline (I), 1,1-dimethyl-3-hydroxyindolmium chloride (II), 3-chloro-1,1-dimethylindolinium chloride (III), and dehydrochlorination of the last compound to the indolium salt. The ultraviolet spectrum of IVb bears a striking resemblance to those of indene and styrene. The indolium salts are powerful methylating agents, attacking even chloride ion at room temperature. Dehydrochlorination of III can also be effected by chloride ion. Both reactions are favored by nonpolar media.

In the course of our investigations of the protonation of indoles[1a,b] and pyrroles,[1c,d] it became desirable to know the general characteristics of the ultraviolet spectra of N-protonated indoles. Although N-protonated salts have been isolated,[1a,b] the principal conjugate acid of an indole in solution in strong acids is the 3-protonated isomer.[1b] A model for the N-protonated species was prepared, therefore, in the form of 1,1-dimethylindolium perchlorate (IVb), the first example of an N-quaternized salt of an indole. This report describes the synthesis of the indolium salt and some of its rather remarkable properties as a methylating agent.[2]

Since indoles undergo alkylation—like protonation—on carbon,[3] the double bond of the indolium salt was formed after quaternization of the ring nitrogen. This was accomplished *via* the reaction sequence shown in the accompanying chart. 3-Hydroxyindoline had been prepared previously[4] by reduction of isatin with lithium aluminum hydride. Since the yields were consistently low (12–14% as compared to a reported[4] yield of 21%), other methods of synthesis of this key compound were examined. Indoxyl is an obvious choice as a precursor, but attempts to reduce it selectively have been largely unsuccessful.[4] Our attempts to reduce indoxyl O-acetate with lithium aluminum hydride, sodium borohydride, sodium dithionite, or by catalytic hydrogenation at 3 atm. over

(1) (a) R. L. Hinman and J. Lang, *Tetrahedron Letters*, **21**, 12 (1960); (b) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1963); (c) E. B. Whipple, Y. Chiang, and R. L. Hinman, *ibid.*, **85**, 26 (1963); (d) Y. Chiang and E. B. Whipple, *ibid.*, **85**, 2763 (1963).

(2) Two examples of pyrrolium salts have been reported [(a) R. Lukeš and J. Trojánek, *Collection Czech. Chem. Commun.*, **18**, 454 (1953); and (b) O. Achmatowicz, S. Achmatowicz, and W. J. Rodwald, *Roczniki Chem.*, **35**, 497 (1961)], but demethylation was observed only incidentally and under relatively severe conditions.

(3) See, for example, W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 32.

(4) E. Giovannini and T. Lorenz, *Helv. Chim. Acta*, **40**, 1553 (1957).

platinum oxide in methanol, under neutral, acidic, or basic conditions, were all unsuccessful.[5]

Conversion of the quaternary indolinol (II) to the chloride (III) was readily effected with thionyl chloride, but dehydrochlorination of III was more difficult to achieve because of the facile demethylation of the indolium salt. When an excess of base such as ammonia or triethylamine was used, a sizeable portion of the product was converted to 1-methylindole, as shown by changes in the ultraviolet spectra (Table I). Although demethylation could be suppressed by keeping the per cent conversion low, separation of starting material from product and from by-product ammonium salts proved exceedingly difficult. When it was discovered that *even chloride ion caused demethylation*, these methods were abandoned.

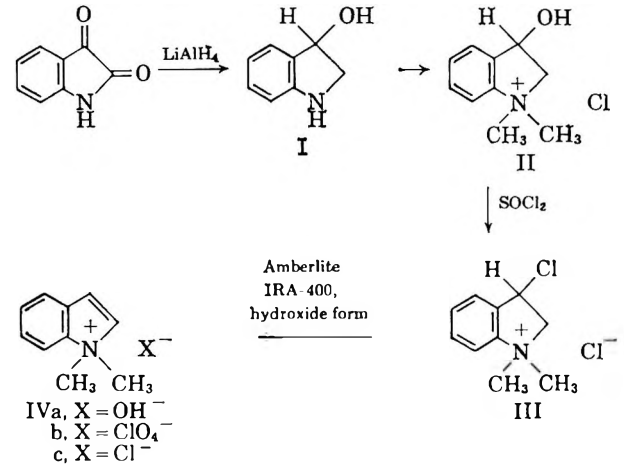


TABLE I

ULTRAVIOLET SPECTRA OF 1,1-DIMETHYLINDOLIUM PERCHLORATE AND RELATED COMPOUNDS IN 95% ETHANOL[a]

3-Chloro-1,1-dimethylindolinium chloride (III)	216 sh (6840)	249 sh (170) 254 (230) 260 (260) 267 sh (170)	
1,1-Dimethylindolium perchlorate (IVb)	215 (15600)	250 (8700)	278 (350) 282 (350) 288 (230)
Indene[b]	220 sh (9340)	249 (9340)	280 (480) 285 sh (240) 290 sh (140)
$C_6H_5CH{=}CH_2$[c]		248 (14600)	273 (770) 282 (760) 291 (530)
$C_6H_5CH{=}CHCH_3$[c]		251 (17300)	284 (960) 293 (620)
$C_6H_5CH{=}\overset{+}{C}HN(CH_3)_3\ Br^-$[d]		247 (15300)	

[a] Wave lengths are given in mμ; values of ε are in parentheses. [b] T. W. Campbell, S. Linden, S. Godshalk, and W. G. Young, *J. Am. Chem. Soc.*, 69, 880 (1947). [c] C. G. Overberger and D. Tanner, *ibid.*, 77, 369 (1955). [d] W. E. Truce and J. A. Simms, *J. Org. Chem.*, 22, 762 (1957).

It was finally found that dehydrochlorination could be carried out efficiently by merely passing the chloro derivative (III) down a strongly basic ion-exchange column in the hydroxide form. The indolium hydroxide (IVa) was recognized by its characteristic ultraviolet spectrum (Table I), from which the virtual absence of 1-methylindole was also apparent. Titration of the resulting solution of indolium hydroxide with perchloric acid gave the desired salt in the form of its perchlorate. The relatively low nucleophilicity of this anion permitted isolation of the product (IVb) in high yield.

The anticipated structure of IVb was supported by elemental analysis, an ultraviolet spectrum which resembled those of indene and styrene (Table I), and the n.m.r. spectrum, which showed a complex pattern in the vinyl region of total area equal to that of a single sharp peak at τ 6.38, assigned to the six N-methyl protons.[6] Confirmation of the structure was obtained by demethylation with sodium hydroxide, from which the picrate of 1-methylindole was isolated in 54% yield, based on the indolium perchlorate.

The ultraviolet spectrum of 1,1-dimethylindolium perchlorate shows a striking resemblance (Table I) to that of styrene, and, especially in the intensity of the 250-mμ band, to that of indene, in which the cyclic *cis* configuration has the usual effect on intensity of absorption. In addition to the position and intensity of the principal bands, the similarity of the fine structure in the 280-mμ region is especially noteworthy. The spectrum of the β-styryltrimethylammonium cation also resembles that of styrene (Table I). On the other hand, no similarity can be found between the ultraviolet spectrum of 1,1,2-trimethylpyrrolium iodide, λ_{max}^{EtOH} 213 mμ (ϵ_{max} 13,700),[2b] and that of cyclopentadiene, λ_{max}^{EtOH} 235 mμ (ϵ_{max} 4000).[7,8]

The remarkably facile demethylation of indolium salts in the presence of even weak nucleophiles such as chloride ion, which undoubtedly has the formation of the aromatic ring system as its driving force, is illustrated by the experiments under controlled conditions summarized in Table II. Stronger nucleophiles such as amines, acetate ion, and hydroxide ion were, of course, more effective than chloride, but as shown in the table the demethylation process was in all cases highly solvent-dependent. The effect of medium on the rate of demethylation suggests that this reaction should be considered as a simple bimolecular displacement reaction in which charge is cancelled. As is typical of this class of reaction,[9] an increase in rate accompanies a decrease in the polarity of the medium. It should be noted, however, that the system is unique as a case in which an amine is a particularly good leaving group.

That even weaker nucleophiles than chloride might effect demethylation was suggested by the slow demethylation of the indolium perchlorate in tetrahydrofuran,

(5) Reduction of indoxyl derivatives has been achieved *via* the N-acetyl derivatives [J. R. Johnson and J. H. Andreen, *J. Am. Chem. Soc.*, 72, 2862 (1950)], but, under the conditions of deacetylation the hydroxyindoline was converted to an indole, making the method useless for our work.

(6) The infrared spectrum had four peaks of weak intensity in the 1620–1710-cm.$^{-1}$ region; it is not known which of these arises from the double-bond stretching vibration.

(7) J. D. Idol, C. W. Roberts, and E. T. McBee, *J. Org. Chem.*, 20, 1743 (1955).

(8) The similarity of the ultraviolet spectra of benzene and of anilinium salts is well known, although the relationship does not appear to hold as well when the anilinium salt bears groups in the *para* position capable of significant resonance interaction with the ring [L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, 69, 2714 (1947)].

(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 345 ff.

TABLE II

EFFECT OF SOLVENT AND ATTACKING NUCLEOPHILE ON RATES OF DEMETHYLATION AND DEHYDROCHLORINATION OF IVb AND III[a]

Source of added nucleophile[c]	Solvent[d]	Product[e]		Rate
		1,1-Dimethylindolium Perchlorate (IVa)[b]		
	A			No reaction after 25 hr.
	AT	M	Very slow	Very slight reaction after 25 hr.
LiCl	A			No reaction after 25 hr.
LiCl	AT	M	Slow	About one-third complete after 25 hr.
NaOH	A	M	Medium	Almost complete after 25 hr.
NaOH	AT	M	Fast	Complete in 1 hr.
		3-Chloro-1,1-dimethylindolinium Chloride (III)[f]		
	A			No reaction after 25 hr.
	AT	I + M	Very slow	Slight reaction after 6 hr.
LiCl	A			No reaction after 25 hr.
LiCl	AT	I + M	Very slow	Slight reaction after 25 hr.
NaOH	A	I	Very fast	Almost complete within 30 min.
		M	Medium	Complete after 25 hr.
NaOH	AT	I	Very fast	Complete in less than 35 min.
		M	Fast	Complete in more than 35 min., but less than 1.5 hr.

[a] All reactions carried out at 23° in quartz cuvettes and followed by changes in the ultraviolet spectra by means of a Beckman DK-2 recording spectrophotometer. [b] Concentration 6.7×10^{-3} *M*. [c] In all cases the concentration of the added salt was ten times that of the quaternary salt. [d] A = methanol, AT = a 1:2 mixture of methanol and tetrahydrofuran (v./v.). [e] M = 1-methylindole, I = indolium cation. These products were easily recognized by their ultraviolet spectra which differ greatly from each other and from that of the indolinium salt (III). [f] Concentration 6.9×10^{-3} *M*.

which is reminiscent of the methylation of ethers by oxonium salts.[10] However, acetamide, cyclohexanone, and butyrolactone, which are alkylated by oxonium cations,[10b] did not react with IVb under the conditions of Table II, and sufficient material was not available for comparison under the conditions (neat reactants) usually used with the oxonium compounds.

The available data do not permit exact comparison of the ease of demethylation of indolium and pyrrolium salts. 1,1-Dimethylpyrrolium hydroxide appeared to undergo demethylation easily in aqueous solution at room temperature,[2a] indicating a higher order of reactivity than that of the indolium hydroxide. On the other hand, 1,1,2-trimethylpyrrolium acetate, chloride, and iodide have been isolated,[2b] the last salt under conditions (evaporation of an acetone solution) which would favor demethylation of the indolium structure prepared in our work. Although an unusual substituent effect may be responsible for the increased stability of the second pyrrolium salt, the unusual method of synthesis and the failure of the ultraviolet correlation noted above leave some doubt as to the identity of the salt.

Attention is also called to the data in Table II on the dehydrochlorination of 3-chloro-1,1-dimethylindolinium chloride (III), from which two significant points emerge: dehydrochlorination can be effected by chloride ion, and elimination is much faster than demethylation.[11] Since the effect of the medium was much more pronounced in the demethylation step, media could be selected so that build-up of the indolium salt could be observed in the ultraviolet, followed by slower conversion of the latter to 1-methylindole (Table II). Moreover, the markedly different rates and different responses to medium made it possible to select a solvent system (methanol–water, 4:1) such that demethylation of the indolium salt did not occur to an appreciable extent during dehydrochlorination on a preparative scale. No conditions were found under which isolation of the indolium chloride (IVc) could be carried out without the occurrence of extensive demethylation.

In none of the work on dehydrochlorination was any evidence found to indicate the intrusion of ring opening by elimination. Such a reaction is probably precluded by the acidity of the hydrogens β to the halogen, which would be high compared to those of more common aralkyl halide systems which undergo base-catalyzed elimination reactions. The same reasoning leads to the prediction that the C_β–H bond would be more completely broken than the C–Cl bond in the transition state,[12] which would, in turn, favor displacement on hydrogen in the chloride-ion-catalyzed elimination rather than attack on carbon in the "merged elimination–substitution" type of mechanism proposed for other cyclic systems.[13]

The cyclic systems described in this report offer particular advantages for kinetic studies of displacement reactions with an amine as the leaving group, since these processes take place at convenient rates at or near room temperature, and can be followed with ease by spectrophotometric methods. The indolium system can probably be extended also to studies of the mechanism of elimination with the amine as leaving group since that process may be encountered with alkyl groups larger than methyl on the quaternized nitrogen. The close relationship of the indole system to vinylamines generally[14] suggests that these proc-

(10) (a) H. Meerwein, U. Eisenmenger, and H. Matthiae, *J. prakt. Chem.*, **866**, 150 (1950); (b) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Chem. Ber.*, **89**, 2060 (1956).

(11) Elimination must precede demethylation since 1,1-dimethylindolinium chloride itself is stable under all conditions studied.

(12) See the chapter by D. J. Cram, "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 345, 346.

(13) D. N. Kevill, P. H. Hess, P. W. Foster, and N. H. Cromwell, *J. Am. Chem. Soc.*, **84**, 983 (1962); N. H. Cromwell, D. N. Kevill, and G. A. Coppens, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 8M.

(14) R. L. Hinman and E. R. Shull, *J. Org. Chem.*, **26**, 2339 (1961).

esses will be encountered very widely when the appropriate N-quaternized vinylamines are available.

A number of other methods of synthesis of indolium salts were tried without success. Attempted dehydration of 1,1-dimethyl-3-hydroxyindolinium chloride (II) with 9 *M* hydrochloric acid caused no appreciable change in the ultraviolet spectrum after 48 hr., including 12 hr. of heating on the steam bath, and II was also unreactive towards boron fluoride etherate in glacial acetic acid. The positive charge probably hindered either protonation of the hydroxyl or formation of a carbonium ion at the 3-position, which would also account for the report that 3-hydroxyindoline (I), when pure, resists attack by concentrated hydrochloric and sulfuric acids.[4,15]

Hydrogen bromide in acetic acid reacted with compound II, but produced unidentifiable materials. With sodium acetate in acetic anhydride, 1-methylindole was obtained. Dehydration to the indolium salt apparently took place but was followed immediately by demethylation by the highly nucleophilic acetate ion. Thermal dehydration of II, either solid or in solution, yielded only 1-methylindole.

Attempted dehydrogenation of 1,1-dimethylindolinium chloride (V) with either chloranil or 10% palladium on carbon in refluxing xylene, yielded mixtures in which only starting material and indolic substances could be recognized.

Several attempts were also made to prepare the 3-chloro intermediate (III) by direct chlorination of 1,1-dimethylindolinium chloride (V), but the latter compound was completely resistant to *t*-butyl hypochlorite in chloroform, acetic acid, or neat *t*-butyl hypochlorite under irradiation with ultraviolet light for periods up to 2.5 hr., and to chlorine in a 1:1 mixture of carbon tetrachloride and acetic acid during 1 hr. of irradiation by ultraviolet light at 25°. The positively charged nitrogen probably inhibits attack by chlorine molecule or atom and *t*-butoxy radical, all of which are electron-seeking species.[16]

Experimental[17]

3-Hydroxyindoline.—The procedure was similar to that reported previously[4] but the yields were only 12–14% as compared to the reported value of 21%. Indole and indigo were the major products. In one experiment, decreasing the isatin–lithium aluminum hydride mole ratio from 0.6 to 0.24 was accompanied by a marked decrease in the yield. The highest melting point obtained was 92–93°, lit.[4] m.p. 96°. The infrared spectrum had a strong band at 3220–3225 cm.$^{-1}$ and other prominent bands at 2970, 2890, 1610, 1490, 1475, 1478, 1325, 1317, 1255, 1204, 1062, 933, 923, 813, 787, and 741 cm.$^{-1}$. The ultraviolet spectrum in 95% ethanol showed λ_{max} 241 and 295 mμ, (ϵ_{max} 7200 and 2100, respectively).

1,1-Dimethyl-3-hydroxyindolinium Iodide.—To a chilled, stirred solution of 1.93 g. (0.014 mole) of 3-hydroxyindoline in 110 ml. of acetone was added 20.5 g. (0.14 mole) of methyl iodide, followed by 4.01 g. (0.029 mole) of potassium carbonate. After the mixture had come to room temperature, it was stirred for 2 hr. and filtered. The solid was mixed with about 100 ml. of 95% ethanol and heated on the steam bath for 15 min. The mixture was filtered, and the filtrate was evaporated *in vacuo*, yielding 4.16 g. of a white solid. The acetone filtrate was evaporated almost to dryness under reduced pressure, leaving a brown paste which was recrystallized from 95% ethanol, from which three crops were obtained, totalling 1.49 g. of fine ivory-colored crystals. The combined crops, which contained inorganic salts, were used in the subsequent step without further purification.

1,1-Dimethyl-3-hydroxyindolinium Chloride (II).—A solution of 1.66 g. of the impure methiodide, obtained as described above, in 60 ml. of a 4:1 (v./v.) mixture of ethanol and water was passed down a column of Amberlite resin IRA-400 in the chloride form and eluted with 80% ethanol until the eluent no longer gave a positive silver nitrate test. The eluent was evaporated under reduced pressure, and the residue was triturated with absolute ethanol and filtered. After concentration of the filtrate, ether was added until a precipitate appeared. The mixture was heated to effect solution and then chilled, producing 0.52 g. of ivory crystals, which, after washing with a cold ethanol–ether mixture, melted at 190–191° dec. A second crop (33 mg.) was obtained by concentration of the filtrate and addition of ether. The total yield was 48%. Two recrystallizations from an ethanol–ether mixture afforded an analytical sample, m.p. 201.5° dec. The infrared spectrum (potassium bromide) had a strong band at 3220 cm.$^{-1}$ and other prominent bands at 1473, 1075, 984, and 770 cm.$^{-1}$. The ultraviolet spectrum (95% ethanol) showed λ_{max} 246 sh, 252, 258, and 266 mμ (ϵ_{max} 150, 210, 250, and 200, respectively). In water, an additional band at λ_{max} 206 mμ (ϵ_{max} 8300) was observed.

Anal. Calcd. for $C_{10}H_{14}ClNO$: C, 60.05; H, 7.07; Cl, 17.76; N, 7.02. Found: C, 60.04; H, 7.05; Cl, 17.81; N, 7.14.

3-Chloro-1,1-dimethylindolinium Chloride (III).—To a stirred mixture of 1.31 g. (0.0065 mole) of 1,1-dimethyl-3-hydroxyindolinium chloride in 15 ml. of chloroform in an ice bath was added 7.14 g. (0.060 mole) of thionyl chloride. The mixture was allowed to warm to room temperature and, after all the solid had dissolved (about 10 min.), it was heated to 65°. When the reaction appeared from the ultraviolet spectrum to be complete (about 45 min.), the yellow solution was concentrated under a stream of nitrogen. Ether was added to the residual yellow oil and the white solid which formed was filtered and washed with ether. Recrystallization from an ethanol–ether mixture afforded 1.22 g. (85%) of white crystals, m.p. 165–167° dec.; two additional crops were collected to give a total yield of 1.26 g. (88%). Three recrystallizations from a methanol–ether mixture, afforded an analytical sample, m.p. 168° dec. The infrared spectrum showed major bands at 3010, 2930, 1480, 1475, 1460, 1450, 1270, 1140, 982, 943, 882, 876, 856, 773, and 699 cm.$^{-1}$. The ultraviolet spectrum is given in Table I. In water an additional shoulder at 209 mμ (ϵ 7400) was observed.

Anal. Calcd. for $C_{10}H_{13}Cl_2N$: C, 55.06; H, 6.01; Cl, 32.51; N, 6.42. Found: C, 55.06; H, 5.67; Cl, 32.53; N, 6.54.

1,1-Dimethylindolium Perchlorate (IVb).—A solution of 0.31 g. (0.0014 mole) of 3-chloro-1,1-dimethylindolinium chloride in 20 ml. of an 80% methanol–water mixture was passed down a column of Amberlite resin IRA-400 in the hydroxide form, and eluted with the same solvent. Six fractions of an average volume of 12 ml. were collected, of which the first four contained a substance with an ultraviolet spectrum resembling that of indene. The fractions containing this material, which was assumed to be **1,1-dimethylindolium hydroxide**, were combined, and 0.1 *M* perchloric acid was added until the solution was neutral to pHydrion paper. The neutralized solution was concentrated to a slurry under reduced pressure and the slurry was taken up in absolute ethanol. Concentration of this solution yielded 0.26 g. (75%) of a white solid, m.p. 185–186° dec. Further concentration of the filtrate yielded a second crop to give a total yield of 83%. An analytical sample, m.p. 185–186° dec., was obtained by two recrystallizations from a methanol–ether mixture.

Anal. Calcd. for $C_{10}H_{12}ClNO_4$: C, 48.89; H, 4.93; Cl, 14.43; N, 5.70. Found: C, 48.57; H, 5.03; Cl, 14.31; N, 6.00.

The infrared spectrum (potassium bromide) had the following major peaks (in cm.$^{-1}$): 3070 (s), 1470 (s), 1427 (m), 1406 (m), 1050–1120 (vs, ClO_4^-), 950 (s), 872 (s), 784 (s), 763 (vs), 767 (vs), and 738 (s). In the double-bond region were the following bands of weak intensity: 1708, 1656, 1638, and 1620 cm.$^{-1}$. An n.m.r. spectrum in perdeuterio dimethyl sulfoxide had a multiplet at τ 1.6–1.9, a multiplet at τ 2.2–2.5, and a sharp singlet at τ 6.38, with relative areas of 1:2:3, respectively. The ultraviolet spectrum is given in Table I.

(15) A solution of 0.01 mmole of 1,1-dimethyl-3-hydroxyindolinium chloride in 10 ml. of 1 *M* aqueous sodium hydroxide was stable for 3 days at room temperature. Pure 3-hydroxyindoline (I) has also been shown to be stable under similar conditions.

(16) C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6113 (1960).

(17) Melting points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics, and n.m.r. spectra were obtained with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard.

1-Methylindole from 1,1-Dimethylindolium Perchlorate.—To 2 ml. of methanol was added 108 mg. (0.44 mmole) of the perchlorate followed by 8 ml. of water and 10 ml. of 1 *M* aqueous sodium hydroxide. The solution was heated for a total of 17.5 hr. at 53–75° over a period of 2 days, until ultraviolet spectra showed no remaining indolium salt. At the end of this time the solution was cloudy and the odor of 1-methylindole was very strong. The mixture was extracted with ether and the ether extract dried over sodium sulfate and concentrated *in vacuo* to a volume of about 2 ml. To the residue was added a few milliliters of ethanol followed by about 5 ml. of a warm ethanolic solution containing 109 mg. of picric acid. The long red needles of picrate which formed after cooling were collected in two crops, giving a total yield of 85 mg. (54%). Two recrystallizations from ethanol did not change the melting point. A mixture melting point with an authentic sample of the picrate of 1-methylindole, m.p. 143–145° dec., lit.[18] m.p. 144–145° dec., was not depressed.

Anal. Calcd. for $C_9H_9N \cdot C_6H_3N_3O_7$: C, 50.00; H, 3.36; N, 15.55. Found: C, 50.05; H, 3.23; N, 15.52.

(18) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).

New Thyroxine Analogs. Halogen Derivatives of 3-Carbethoxy-5-hydroxy-2-methylbenzofuran

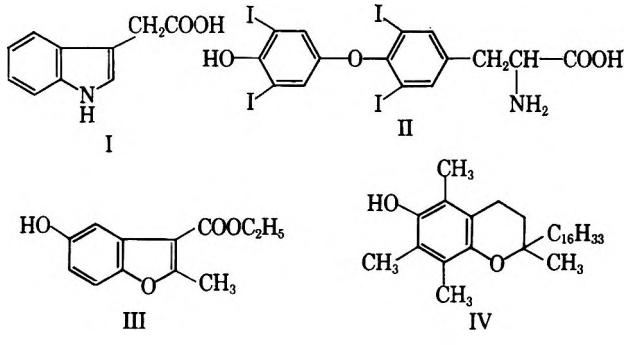
C. A. GIZA AND R. L. HINMAN

The Union Carbide Research Institute, Union Carbide Corporation, Tarrytown, New York

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In an effort to combine the structural features of the plant growth hormone, indole-3-acetic acid, and the mammalian hormone, thyroxine, a number of mono and dihalo derivatives of the title compound (III) have been synthesized. Chlorination and bromination were achieved by use of the elemental halogens, whereas only a combination of iodine and morpholine, of a wide variety of reagents examined, was suitable for iodination. Bromination and iodination of III yielded the 6-monosubstituted derivatives, but chlorination afforded primarily the 4-monochloro derivative. Mercuration also occurred at the 4-position, affording a route to the 4-iodo derivative. Deiodination was readily effected by zinc and acetic acid without ring cleavage, but chlorine was not removed by this procedure. Iodine at the 4-position was especially labile toward base, and by the use of potassium cyanide in dimethyl sulfoxide a remarkably selective removal of a 4-iodo group was achieved while a 6-iodo was untouched. The 4,6-dihalo derivatives of III formed methanol- and water-insoluble salts with alkyl and alicyclic amines, as did many simple di-*o*-halophenols. Since mono-*o*-halophenols did not form such salts, the reaction is of value for identification and separation purposes. The 4- and 6-monoiodo derivatives of III showed thyromimetic activity.

Recent demonstrations in this laboratory of living systems in which the plant growth hormone indole-3-acetic acid ("auxin," I) and the mammalian hormone thyroxine (II) show similar types of behavior[1] suggested that interesting physiological activity might be found in a synthetic hormone having the structural features of both I and II. The 4,6-diiodo derivative IX of the title compound (III) approaches this hybrid form, the 2,3-double bond taking the place of the second benzene ring of II. This hydroxybenzofuran is also related to α-tocopherol (IV), one of the E vitamins. The known antioxidant character of IV[2] and the suggestion that antioxidant activity and hormonal behavior may be related in a general way[3,4] were additional reasons for choosing this system. Finally, these hydroxybenzofurans appeared to be readily accessible by condensation of *p*-benzoquinones with β-keto esters and β-diketones.[5–8]



There were few examples of the 2,3-disubstituted 5-hydroxybenzofurans in the literature prior to the recent work of Grinev, Terentyev, *et al.*,[5–7] and Bernatek, *et al.*[5,6,8] These authors have not discussed halogenation of this system, although the former group did describe the synthesis of two 6,7-dichloro derivatives by condensation of 2,3-dichlorobenzoquinone with the appropriate β-keto ester.[9] The earlier representatives of the series include 2-methyl-3-carbethoxy-, 2,3-dimethyl-, 2,3-diphenyl-, and 2,3-benzo-5-hydroxybenzofuran (2-hydroxydibenzofuran). Reactions of the last compound with bromine have been reported.[10] A compound, $C_{12}H_9Cl_3O_4$, obtained from the condensation of chloroanil with the sodium derivative of ethyl acetoacetate, is said[5b] to be the 4,6,7-trichloro derivative of III.

A description of the chlorination, bromination, and iodination of 3-carbethoxy-5-hydroxy-2-methylbenzo-

(1) S. M. Siegel, F. Porto, and P. Frost, *Arch. Biochem. Biophys.*, **82**, 330 (1959); S. M. Siegel and P. Frost, *Proc. Natl. Acad. Sci. U. S.*, **45**, 1379 (1959).

(2) See, for example, "Handbook of Food and Agriculture," F. C. Blanck, Ed., Reinhold Publishing Co., New York, N. Y., 1955, pp. 243, 253, 286, 592; also "Autoxidation and Antioxidants," Vol. I, W. O. Lundberg, Ed., Interscience Publishers, Inc., New York, N. Y. 1962, pp. 1069–1084.

(3) S. M. Siegel, F. Porto, and P. Frost, *Physiol. Plantarum*, **12**, 727 (1959).

(4) S. M. Siegel and F. Porto, "Plant Growth Regulation," R. Klein, Ed., Iowa State University Press, Ames, Iowa, 1961, pp. 341–353.

(5) (a) H. von Pechmann, *Chem. Ber.*, **21**, 3005 (1888); (b) M. Ikuta, *J. prakt. Chem.*, [2]**45**, 65 (1892); (c) A. N. Grinev, P. B. Khvar, and A. P. Terentyev, *J. Gen. Chem. USSR*, **27**, 1172 (1957), and earlier papers; (d) E. Bernatek and T. Ledaal, *Acta Chem. Scand.*, **12**, 2053 (1958); (e) V. J. Grinsteins and V. A. Slavinskaya, *Latvijas Valsts. Univ. Kim. Fak. Zinatniskie Raksti*, **22**, 119 (1958); *Chem. Abstr.*, **53**, 7090d (1959).

(6) (a) E. Bernatek, *Acta Chem. Scand.*, **10**, 273 (1956); (b) A. N. Grinev, P. B. Khvar, and A. P. Terentyev, *J. Gen. Chem. USSR*, **27**, 897 (1957).

(7) A. N. Grinev, L. A. Bukhtenko, and A. P. Terentyev, *ibid.*, **29**, 927 (1959).

(8) E. Bernatek, *Acta Chem. Scand.*, **7**, 677 (1953).

(9) A. N. Grinev, N. K. Venevtseva, and A. P. Terentyev, *J. Gen. Chem. USSR*, **28**, 1900 (1958).

(10) H. Gilman and P. R. Van Ess, *J. Am. Chem. Soc.*, **61**, 1365 (1939).

TABLE I

N.M.R. SPECTRA OF 3-CARBETHOXY-5-HYDROXY-2-METHYLBENZOFURAN AND HALOGEN DERIVATIVES[a]

Compound	Aromatic region	5-OH	5-OCH_3	2-CH_3	3-$COOCH_2CH_3$ $-CH_2-$ quartet centered at	3-$COOCH_2CH_3$ $-CH_3-$ triplet centered at
III[b]	Complex multiplet of not less than 9 peaks, between 2.42–3.27	3.73		7.27	5.57 (6.5)	8.57 (7)
III[c,d]	Complex multiplet of not less than 7 peaks, between 2.66–3.35		6.20	7.32	5.65 (7)	8.58 (7)
V[b,d]	First doublet, 2.82 (9) Second doublet, 3.19 (9)		6.14	7.42	5.64 (7)	8.60 (7)
VI[b,d]	Singlet, 2.64		6.08	7.30	5.64 (7)	8.57 (7.5)
VIII[b]	First doublet, 2.67 (8.5) Second doublet, 3.03 (8.5)	4.34		7.42	5.54 (6.5)	8.56 (7)
VII[b]	Singlet, 2.62	4.03		7.38	5.60 (7)	8.60 (7)

[a] Chemical shift in τ-units with tetramethylsilane as internal reference, J in c.p.s. given in parentheses [b] $CDCl_3$. [c] CCl_4. [d] Methyl ether of designated compound.

furan (III) forms the principal part of this report.[11]

Reaction of compound III with 1 equiv. of chlorine in chloroform solution proceeded rapidly at −5°. Two monochlorinated derivatives of III were isolated in a combined yield of 92–100% (crude). The less soluble isomer (VI), obtained in about 8% yield, melted at 182–182.5°, whereas the principal isomer melted at 90–92°. Evidence for designating the chlorine substituents as *ortho* to the 5-hydroxyl was provided by the fact that both V and VI were readily chlorinated further to the same 4,6-dichlorohydroxybenzofuran (VII) that was obtained in 35% yield by condensation of 2,6-dichlorobenzoquinone with ethyl acetoacetate.[12]

Identification of the low-melting isomer as V, the 4-chloro derivative of III, was based on the proton magnetic resonance spectrum (Table I) of its methyl ether, which showed a pair of doublets centered at τ 2.82 and 3.19, each with a 9 c.p.s. splitting, indicating the presence of two protons situated *ortho* to each other on the aromatic ring.[13] Since the n.m.r. spectrum of the methyl ether of the high-melting isomer had a single sharp line in the aromatic region, it was identified as the 6-chloro derivative of III. This isomer was also obtained in low yield by reaction of chlorobenzoquinone and ethyl acetoacetate (Scheme I).

Compound III reacted with 2 equiv. of chlorine in chloroform solution at 0–5° to give high yields of the 4,6-dichloro derivative. At this temperature, an excess of chlorine did not have an adverse effect on the reaction, but, at 20° or higher, excess chlorine was absorbed exothermically, and an intensely orange oil was formed. Similar behavior was noted when excess chlorine reacted with the preformed 4,6-dichloro derivative. The nature of this and related products will be discussed elsewhere.

A number of other methods of chlorination were tried (see Experimental) but were of little preparative value.

Bromination was also carried out in chloroform, but in contrast to chlorination which effected substitution mainly at the 4-position, reaction of III with 1 equiv. of bromine gave high yields of the 6-bromo derivative (XII). From the reaction of a second equivalent of bromine a dibromo derivative was isolated in 50–77% yield. The mono and dibromo compounds are designated as 6- (XII), and 4,6- (XIII), respectively, owing to the close similarity of physical and spectral properties with the chloro and iodo analogs (Table II).

The 6-bromo compound (XII) was also the major product of the reaction of III with anhydrous cupric bromide and lithium bromide in hot dimethylformamide solution[14]; when applied to chlorination this method gave a mixture of the 4- and 6-chloro isomers. No satisfactory synthesis of the 4-bromo isomer was found.

Other methods were necessary to effect iodination of III, and a wide variety of procedures was examined (see Experimental) before it was found that iodine and morpholine[15] could be used effectively. Even substitution of other amines for morpholine gave unsatisfactory results. The reaction of III in methanol with elemental iodine and morpholine at 30–35° gave a monoiodo derivative of III in 53% yield, m.p. 194–194.5°. This product resembled the high-melting monochloro compound (VI) in the gross features of its ultraviolet spectrum, the positions of the peaks in the hydroxyl and carbonyl regions of the infrared (Table II), its solubilities in common organic solvents, and its ease of sublimation (~100° at 0.5 mm.). The methyl ether of this monoiodo compound showed a single sharp band in the aromatic region of its n.m.r. spectrum, and was therefore assumed to be the 6-iodo compound (X).

Proof of this assumption comes from the following chemical transformation, summarized in Scheme I. Compound X was treated with 1 equiv. of chlorine in chloroform solution at 5°; the resulting product analyzed for a monoiodo, monochloro derivative of III. From treatment of this dihalo compound with zinc dust

(11) Fluorination with perchloryl fluoride [D. Taub, *Chem. Ind.* (London), 558 (1962)] in chloroform solution at 20 and 50° and in pyridine at 20° was attempted, but starting material was recovered quantitatively.

(12) The low-melting isomer, as well as the two monoiodo derivatives of III, were examined in the near infrared (Table II), where the hydroxyl absorption showed the splitting typical of *o*-halophenols [A. W. Baker, *J. Am. Chem. Soc.*, **80**, 3598 (1958)].

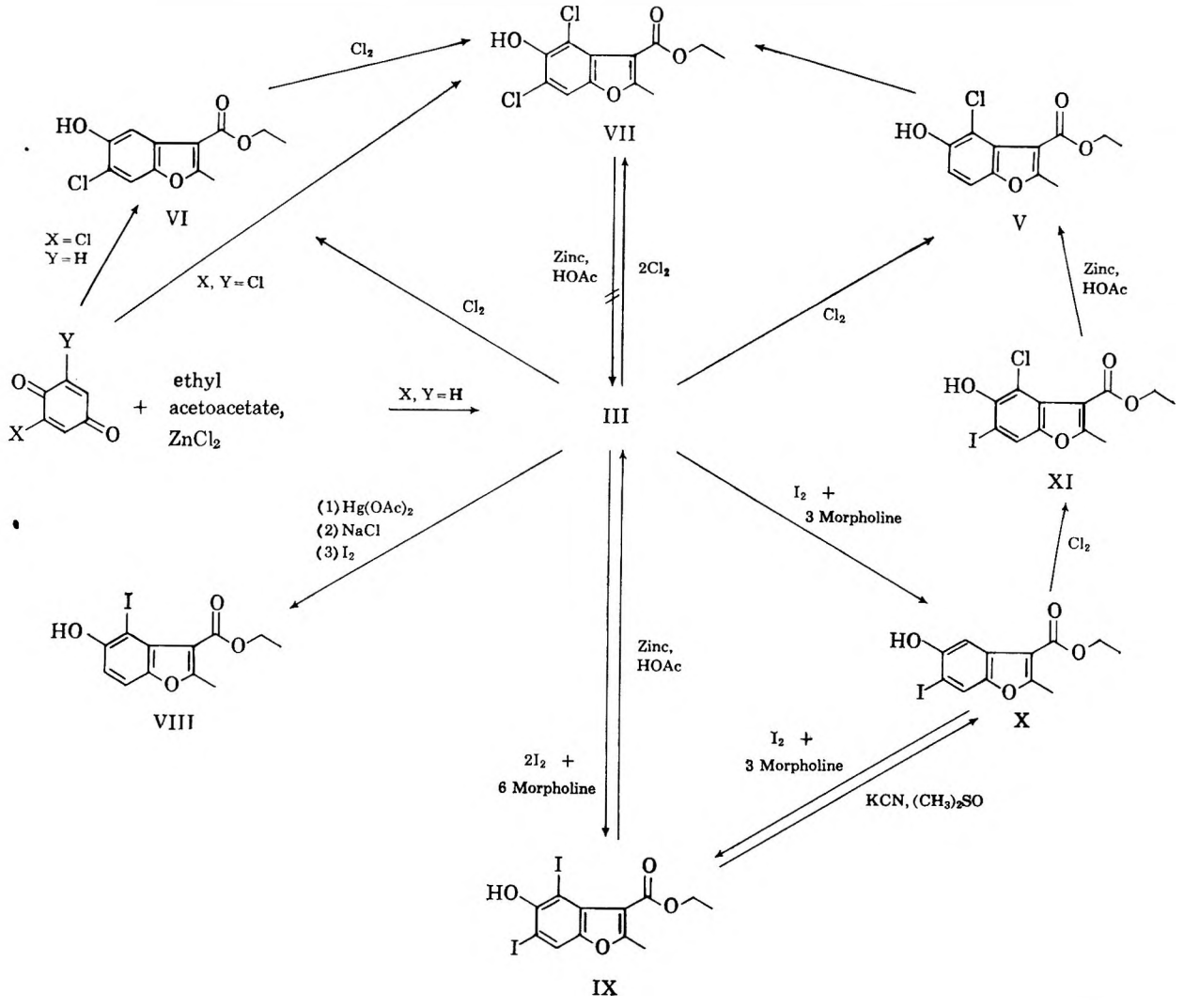
(13) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 193. These authors quote a 5–8.5-c.p.s. range for *ortho*-proton splitting in benzene rings.

(14) E. M. Kosower, W. J. Cole, G. S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

(15) P. Chabrier, J. Seyden-Penne, and A. Fouace, *Compt. rend.*, **245**, 174 (1957); *Chem. Abstr.*, **53**, 21,726c (1959). These authors specify a 1:1:3 molar ratio of phenol, iodine, and morpholine, respectively (" . . . le rapport molecularire morpholine/iode = 3 . . . "). The abstract incorrectly states " . . . and to the solution added 1 mole morpholine and 3 moles iodine."

SCHEME I

INTERRELATIONSHIPS AMONG THE HALOGEN DERIVATIVES OF 3-CARBETHOXY-5-HYDROXY-2-METHYLBENZOFURAN



in acetic acid, the only product isolated (>70% yield) was a monochloro derivative of III identical in every respect with the low-melting monochloro compound V. That only iodine was removed by the zinc dust treatment was established by quantitative recovery of the dichloro compound VII after treatment under similar conditions.[16]

A second monoiodo derivative of III was obtained *via* a mercuration sequence, from which a product presumed to be the 4-chloromercuri derivative was isolated. From treatment of the latter with a chloroform solution of elemental iodine a monoiodo derivative (VIII), m.p. 117–118°, was obtained in 44% yield. The infrared and n.m.r. spectra were all quite different from the high-melting iodo compound X, but were very similar to the spectra of the 4-chloro compound V.[12] The ultraviolet spectrum showed some resemblance to that of the 4-chloro derivative (V), but lacked the maximum in the 240-mμ region (Fig. 1). That VIII was the 4-iodo derivative of III was confirmed by its proton magnetic spectrum, which showed a pair of doublets centered at τ 2.67 and 3.03, with an 8.5 c.p.s. splitting of the aromatic hydrogens.[13]

A diiodo derivative (IX) was obtained in 53% yield by treatment of III with iodine and morpholine in 1:2:6 molar proportions. By analogy with the structure of the product formed by dichlorination of III, the diiodo derivative would be expected to have the halogens in the 4- and 6-positions. The physical properties and ultraviolet (see Fig. 2) and infrared spectra resemble those of the 4,6-dichloro compound (VII), 4,6-dibromo compound (XIII), and the 4-chloro-6-iodo derivative (XI). The diiodo compound formed a methanol- and water-insoluble morpholinium salt; all but one of the polyhalo phenols tested which had their *ortho* positions substituted by halogen also gave such salts, while those phenols with only one *ortho* halogen did not. This point is discussed in detail at the end of this paper.

An attempt was made to prepare an authentic sample of IX by reaction of 2,6-diiodobenzoquinone with ethyl acetoacetate, but only decomposition occurred in contrast to the success of the reaction with the chloroquinones. The failure may have been due to the sensitivity of the iodoquinone or of the product to the zinc

(16) A number of attempts were made to prove the structure of the 6-iodo and 6-bromo derivatives of III by the metallation–carbonation sequence, and comparison of the product with the known compound, 3-carbethoxy-5-methoxy-2-methylbenzofuran-6-carboxylic acid. We were unable to effect reaction using either metallic lithium or *n*-butyllithium in ether, tetrahydrofuran, or diglyme, at several temperatures with either the halophenols or their methyl ethers, although this procedure has been used successfully in the dibenzofuran series [H. Gilman, J. Swislowsky, and G. E. Brown, *J. Am. Chem. Soc.*, **62**, 348 (1940)].

TABLE II

PHYSICAL AND SPECTRAL DATA ON 3-CARBETHOXY-5-HYDROXY-2-METHYLBENZOFURAN AND HALOGEN DERIVATIVES

Derivative of III	Designation	M.p., °C.	Infrared (KBr) OH	Infrared (KBr) C=O	Ultraviolet (95% ethanol)[a]			
	III	143.5–144	3.00	5.99	[b]	225	255	296
						11,350	8,025	4,730
6-Chloro-	VI	182–182.5	3.05	5.97	209	228	257	301
					39,000	12,850	8,870	6,660
5-Bromo-	XII	192.5–193	3.04	5.96	208	227	258	301
					40,000	13,800	9,150	7,220
6-Iodo-	X	194–194.5	3.04[c]	5.97	210	232	260	305
					41,000	16,500	10,800	8,600
4-Chloro-	V	90–92	2.93[c]	5.85	211	238	256	298
					30,000	9,530	9,600	4,010
4-Iodo-	VIII	115–117.5	2.99[c]	5.86	215	244 (sh)	263	302
								(309 sh)
					31,200	8,450	11,500	4,570
								(4,050)
4,6-Dichloro-	VII	135–136	2.95	5.86	212		262	300
					35,000		10,180	5,170
4,6-Dibromo-	XIII	118–119	2.95	5.86	217		265	301
								(309 sh)
					34,200		11,170	5,660
								(5,450)
4,6-Diiodo-	IX	121.5–122.5	2.91	5.87	218	230	273	304
								(312 sh)
					21,000	24,170	16,000	6,720
								(6,930)
4-Chloro-6-Iodo-	XI	121.5–122.5	2.98	5.92	215		265	302
								(309 sh)
					38,850		13,100	6,720
								(6,250)

[a] Upper value is λ_{max} (mμ), lower is ϵ_{max}. [b] Minimum about 220 mμ, then only intense end absorption unlike halo derivatives. [c] Each of these compounds showed two peaks in the hydroxyl region of the near infrared (Beckman DK-2). The 4-iodo (0.02 *M* in CS_2) and 6-iodo (saturated solution in CS_2) derivatives had peaks at 3472 and 3571 cm.$^{-1}$, and at 3497 and 3546 cm.$^{-1}$, respectively, giving values of $\Delta\bar{\nu}$ of 99 and 68 cm.$^{-1}$, compared to a reported[12] value of 93 cm.$^{-1}$ for 0.07 *M* *o*-iodophenol in CCl_4. For the 4-chloro derivative (0.02 *M* in CS_2) peaks were at 3524 and 3571 cm.$^{-1}$, with $\Delta\bar{\nu}$ = 51 cm.$^{-1}$, compared to 57 cm.$^{-1}$ found for *o*-chlorophenol and 58 cm.$^{-1}$ reported.[12] In the halo derivatives of III the peak at shorter frequency was about twice as intense as the other.

chloride, although facile deiodination of the diiodo derivative (IX) was effected by zinc and acetic acid from which the parent phenol (III) was isolated in 65% yield.

A difference in chemical reactivity of the two iodines in IX is shown by the remarkable preferential deiodination of IX to the 6-iodo derivative (X) when warmed with potassium cyanide in dimethyl sulfoxide solution. This reaction does not occur with dimethyl sulfoxide alone, nor have we been able to bring it about with simple *o*-diiodophenols such as 2,4,6-triiodophenol, 2,6-diiodo-4-nitrophenol, or 3,5-diiodotyrosine.

Methyl ethers of III and most of its halo derivatives were obtained easily by the use of dimethyl sulfate in basic solution. Exceptions were the 4-iodo derivative (VIII) and the 4,6-diiodo derivative (IX), from which ethers could not be obtained, probably due to the instability of these iodophenols under the basic reaction conditions. The instability of the 4-iodo derivatives to base is probably related to the facile deiodination by cyanide, mentioned above.

Halogenation of the methyl ether of III was also carried out. In contrast to the behavior of the parent phenol (III), the methyl ether gave the 6-chloro isomer in high yield when treated with 1 equiv. of chlorine in chloroform at 0°. Sodium hypobromite in acetic acid gave the 6-bromo ether in good yield, whereas hypochlorite gave a mixture of products which could not be identified.

The results of the halogenations of III indicate a seeming anomaly in that chlorination gives predominantly the 4-halo derivative, while bromination and iodination give only the 6-halo derivatives. One generally anticipates greater similarity in chlorination and bromination than in bromination and iodination, reflecting a difference in reactivity of the elements. Moreover, in our work the reaction conditions used in chlorination and bromination were very similar and different from those used in iodination.

This difference can be rationalized if it is assumed that electrophilic substitution of the 5-hydroxybenzofuran system is analogous to that of β-naphthol, and would occur at the 4-position but for steric crowding of that position by the 3-carbethoxy group, which tends to shift substitution to the 6-position as the bulk of the attacking species is increased. Crowding of the 4-position is clearly shown in models and this interpretation is supported by the observations that bromination of 2-hydroxydibenzofuran takes place at the 1-position[10] and, as noted above, chlorination of the methyl ether of III gave only the 6-chloro derivative.[17] Furthermore, crowding by the 3-carbethoxy group would be buttressed by the 2-methyl group, an interpretation advanced to explain results in a closely analogous system, the nitration of gramine. Both 4- and 6-nitro derivatives were obtained from gramine itself, but

(17) Although β-naphthol is usually substituted at the 1-position, Friedel-Crafts reactions give 1- or 6-derivatives according to the conditions, and the 2-naphthyl ethers give only 6-acyl derivatives [E. H. Rodd and J. van Alphen, "Chemistry of Carbon Compounds," Vol. III, Elsevier, Amsterdam, 1956, p. 1309].

TABLE III

RATES OF PRECIPITATE FORMATION BY PHENOLS AND AMINES IN METHANOL

Phenol (with morpholine)[a]	Rate of formation of ppt. at 25°[b]	Amine (with 2,4,6-triiodophenol)[a]	Rate of formation of ppt. at 25°[b]
2,4,6-Cl_3–	R	Morpholine	R
2,4,6-Br_3–	R	Piperidine	R
2,4,6-I_3–	R	Piperazine	R
2,6-Cl_2–4–OH	R	Pyrrolidine	VS
2,6-Cl_2–4–NO_2–	S	Di-*n*-butylamine	R
2,6-Br_2–4–NO_2	R	Diethylamine	S
2,6-I_2–4–NO_2–	R	Dicyclohexylamine	X
2,6-Br_2–	S	Diethanolamine	X
4,6-Cl_2 III	S	N-Methylmorpholine	S
4,6-Br_2 III	R	N-Methylpiperazine	R
4,6-I_2 III	R	2-Methylpiperidine	R
2,4-Cl_2–	X	2-Methylpiperazine	S
2,4-Cl_2-1-Naphthol	X	2,6-Dimethylmorpholine	S
2,4-Br_2-1-Naphthol	X	2,6-Dimethylpiperidine	R
1,3,6-Br_3-2-Naphthol	X	Triethylamine	X
2,4-I_2-6-COOH–	X	N,N′-Dimethylcyclohexylamine	X[c]
3,5-I_2-L-tyrosine	X	*n*-Butylamine	S
2-I–	X	Ethylenediamine	X
2,4,6-(*t*-Bu)$_3$–	X	N-Methylaniline	X
2,6-(*t*-Bu)$_2$–	X	N,N-Dimethylaniline	X
3,5-(*t*-Bu)$_2$–	X	Pyridine	X
2,6-(MeO)$_2$–	X	Dimethylformamide	X
2,6-Me_2–	X	Di-*n*-butylformamide	X
2,3,6-Me_3–	X	Pyrrole	VS
4-NO_2–	X		

[a] About 2 g. of the phenol and 5 g. of the amine were dissolved in 10–20 ml. of methanol. [b] R = <1 min.; S = 30–120 min.; VS = ~15 hr.; X = no precipitate. [c] With chloranil hydroquinone.

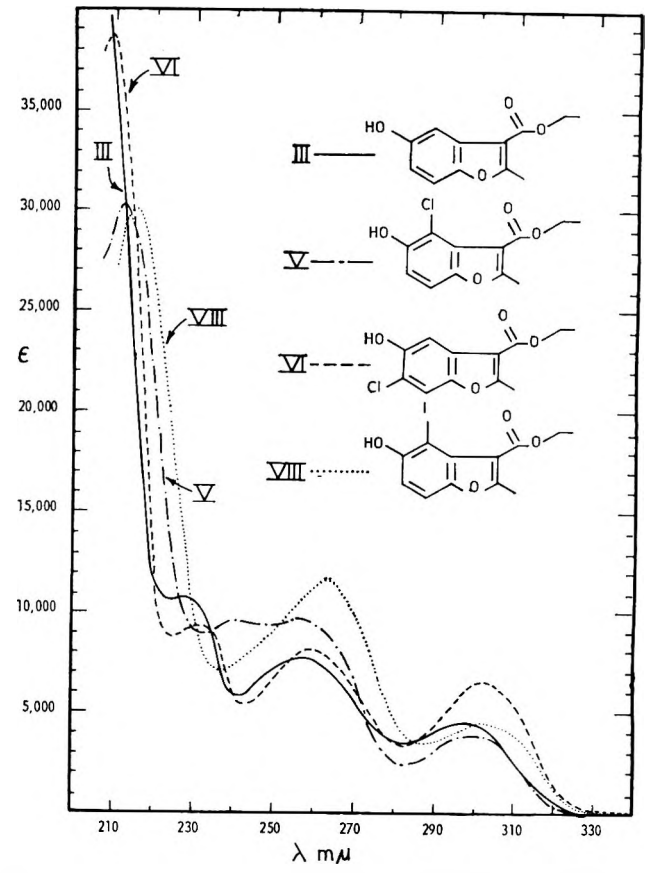


Fig. 1.—Ultraviolet absorption spectra of 3-carbethoxy-2-methyl-5-hydroxybenzofuran and monohalogen derivatives.

only the 6-nitro isomer was obtained from 2-methyl- and 1,2-dimethylgramine.[18]

Steric hindrance may also account for our observation that compound III gives a positive ferric chloride test under anhydrous conditions in a chloroform–pyridine mixture.[19] but, as reported previously,[5c] no coloration is observed in aqueous solution. It is known that this test with enolizable compounds is strongly dependent on steric factors in the enol,[20] and the solvation and hence the bulk of the ferric chloride would certainly differ in the two media.[21] Particularly pertinent are the reports that 5-hydroxy-2-methylbenzofuran readily gives a positive test with aqueous ferric chloride,[5c] but 7-hydroxy-1-naphthoic acid does not.[22]

That the effect of steric crowding on the balance between 4- and 6-substitution is a subtle one is shown by the fact that only the 4-nitro isomer was isolated (68% yield) from nitration of the methyl ether of III,[23] mercuration took place at the 4-position, and preliminary results on the sulfonation of III indicate that the 4-sulfonic acid is the chief product.[24]

Once substitution at the 4-position has been achieved, a marked effect of the halogen on the ester carbonyl absorption is observed in the infrared spectra (Table II). The position of the ester carbonyl in III is close to those of esters of anthranilic and salicylic acids (5.92–5.99 μ)[25] all of which have an ester carbonyl conjugated with an aromatic ring and an atom with unshared electron pairs. In all of the derivatives of III which bear at least one halogen at the 4-position, a shift of the ester carbonyl to shorter wave lengths is observed. This is the direction expected from decreased resonance interaction of the ester carbonyl with the remainder of the conjugated system, and is attributed to steric inhibition. The ultraviolet spectra of the isomeric monohalo derivatives also show differences (Fig. 1 and Table II) ascribable to these steric interactions. As would be expected on this basis, the monoiodo (Fig. 1) and diiodo (Fig. 2) derivatives show distinct differences from the derivatives bearing smaller halogens.

Morpholinium Salts.—In the course of studying iodination in the presence of morpholine, it was found that the diiodo derivative (IX) formed a stable mor-

(18) G. Berti and A. Da Settimo, *Gazz. chim. ital.*, **90**, 525 (1960).

(19) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 113.

(20) W. Hückel, "Theoretical Principles of Organic Chemistry," Elsevier, New York, N. Y., 1955, p. 312.

(21) Although the 5-hydroxyl group of III is acidic enough to form a sodium salt, in other ways it is not typically phenolic. In addition to its failure to give a positive ferric chloride test under aqueous conditions, no reaction was observed when III was treated with diazotized sulfanilic acid, nor when refluxed in toluene containing methyl iodide and aluminum chloride. Several attempts to replace the 5-hydroxyl group under Bücherer conditions were unsuccessful.

(22) M. Stumpf, *Ann.*, **188**, 6 (1877).

(23) A. N. Grinev and A. P. Terentyev, *J. Gen. Chem. USSR*, **28**, 80 (1958).

(24) Cases are known in which phenols react with electrophilic reagents such that one *ortho* position is favored more than the other (or even exclusively). With *m*-hydroxybenzaldehyde and *m*-nitrophenol chlorination and nitration occur at the 2-position, while bromination goes 6, closely paralleling our results. In 2-nitro-1,4-dimethoxybenzene nitration occurs at 3. An explanation of this behavior based on electronic factors has been advanced by P. B. D. De la Mare and J. H. Ridd, "Aromatic Substitution," Academic Press, New York, N. Y., 1959, p. 132.

(25) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 179.

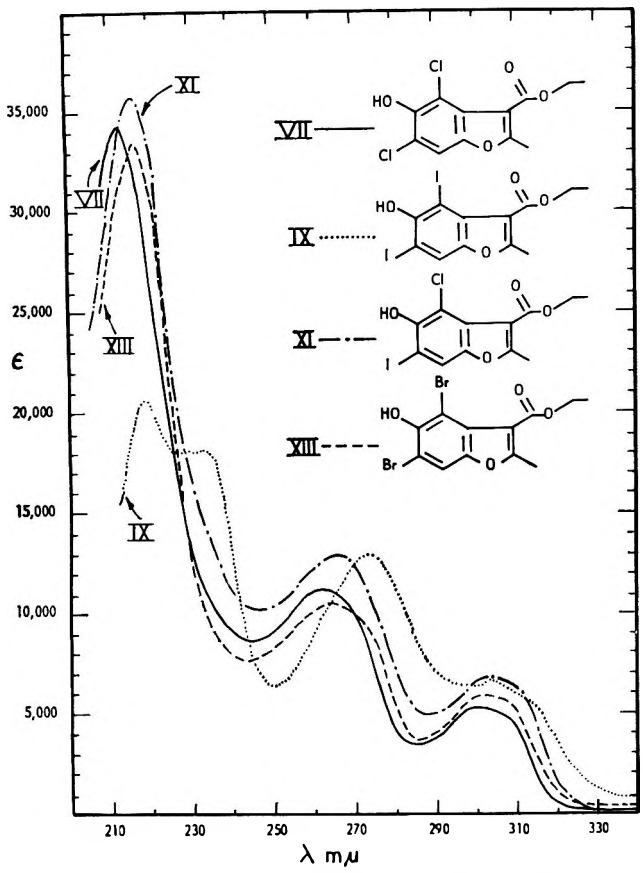


Fig. 2.—Ultraviolet absorption spectra of dihalo derivatives of 3-carbethoxy-2-methyl-5-hydroxybenzofuran.

pholinium salt insoluble in methanol. The dichloro- and dibromophenols (VII and XIII) also formed insoluble salts, but none of the monohalo derivatives gave precipitates under these conditions.

Several simpler phenols were tested for this property (Table III). Of ten di-*o*-halo phenols tested, only two failed to form insoluble salts, *viz.*, 1,3,6-tribromo-2-naphthol and 3,5-diiodotyrosine, the latter itself being virtually insoluble in methanol. If only one *ortho* halogen was present, even if a nonhalogen substituent occupied the other *ortho* position, and even if a second halogen was *para* to the hydroxyl, no salt precipitated. It is also apparent from Table III that while the amine must be secondary and quite basic, formation of a precipitate is highly dependent on subtle structural variations. Thus, morpholine, N-methylmorpholine, piperazine, and 1,4-diazabicyclooctane formed salts with 2,4,6-triiodophenol and chloranil hydroquinone, but N-phenylmorpholine, the anilines, the cyclohexylamines, diethylamine, propylamine, and pyrrolidine did not. The reaction is sensitive to small amounts of dihalo compound.

The property of certain bases to form insoluble salts with di-*o*-halo phenols but not with mono-*o*-halo phenols or similar phenols having other nonhalogen substituents can serve as a means of separation of such mixtures. One complication is the tendency of the moist salts to turn dark on standing in air; the dry salts are stable in this respect. The morpholinium salts of VII, IX, and XIII differ from the picrates of morpholine, piperidine, and piperazine in that they are much less soluble in methanol and other solvents. Furthermore, the melting points of the former group are generally higher than those of the picrates, and the $>N^+-H$ salt bands in their infrared spectra are consistently more intense and spread over a broader range than are those of the picrates.

Physiological Properties.—The parent phenol (III) and several of its derivatives possess phytohormonal properties.[26] The monoiodo derivatives VIII and X possess substantial thyroactivity,[27] even though these molecules do not have the di-*o*-iodophenyl ether link generally assumed necessary.[28]

Experimental

All melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer double beam recording spectrophotometer, Model 21; ultraviolet spectra on a Beckman DK-1 recording spectrophotometer, with the 1-cm. quartz cells thermostatted at 25 ± 0.5°; proton magnetic resonance spectra on Varian Associates 60-Mc. n.m.r. instruments, Models A-60 and HR-60. Analyses were performed at the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

3-Carbethoxy-5-hydroxy-2-methylbenzofuran (III).—This was prepared according to Grinev, *et al.*,[5c] but because of the great difficulty we (and others[5d]) have encountered, a detailed description of an improved procedure is given. About 140 g. (~1 mole) of commercial anhydrous zinc chloride was placed in a three-necked 1-l. round-bottomed flask, and kept molten under vacuum for 15 min. to remove moisture. Nitrogen was bled into the flask, which was fitted with a thermometer and continuous extraction apparatus. After 160 ml. of anhydrous ethanol (distilled from sodium ethoxide–diethyl phthalate) had been added, the contents were refluxed until the zinc chloride dissolved. The mixture was cooled to 25° and 260 ml. (~2 moles) of vacuum-redistilled ethyl acetoacetate was added, followed by 200 ml. of anhydrous ether from a newly opened container. The extractor thimble was charged with 103 g. (0.95 mole) of dry, steam-distilled *p*-benzoquinone, and a calcium chloride drying tube was affixed to the condenser. Nitrogen was flushed through the system for about 5 min. The reaction mixture was kept at an internal temperature of 78–82°, and quinone was extracted very slowly into the flask over a period of 66 hr.; heating was continued for one additional hour. On cooling to 25°, the reaction mixture solidified; the contents of the flask were transferred to a Büchner funnel and washed with 250 ml. of cold benzene. Of a wide variety of solvents tried, only glacial acetic acid was effective for crystallization of the crude product. This treatment followed by recrystallization from toluene gave product melting above 140° in about 70% yield. The highest melting point obtained from any run was 143.5–144°, and material of m.p. 143°, with correct analysis for $C_{12}H_{12}O_4$, was obtained routinely by the above procedure (lit.[5c] m.p. 137°, lit.[5d] 138°). The product from acetic acid crystallization was apparently a hemisolvate, since it still smelled of acetic acid after weeks of drying at room temperature, but further drying *in vacuo* over sodium hydroxide was accompanied by a loss in weight equal to 0.5 mole of acetic acid per mole of III.

Compound III did not give any observable color reaction with 1, 3, or 5% aqueous ferric chloride solution, but a stable blue-green color formed rapidly when a saturated solution of anhydrous ferric chloride in chloroform containing a few drops of pyridine was added. When a concentrated dioxane solution of III was treated with 30% aqueous sodium hydroxide solution, the sodium salt of III precipitated promptly. The moist salt turned brown in air, but the dry salt was stable. A deep purple color formed when III was warmed in concentrated sulfuric acid, a change said to be typical of compounds containing the benzofuran nucleus.[5b]

The methyl ether of III was prepared by adding to a dioxane solution of III an excess of dimethyl sulfate and 10% sodium hydroxide with vigorous shaking. To ensure complete reaction more dimethyl sulfate and base were added, followed by shaking.

(26) C. A. Giza and S. M. Siegel, *Physiol. Plantarum*, **16**, 52 (1963).

(27) S. M. Siegel, C. A. Giza, G. Davis, and R. L. Hinman, *Proc. Natl. Acad. Sci. U. S.*, **49**, 107 (1963).

(28) C. D. Turner, "General Endocrinology," W. B. Saunders Co., Philadelphia, Pa., 1960, pp. 113–120.

After a third such addition, the methyl ether was isolated by pouring the reaction mixture onto crushed ice and filtering. The brown waxy solid was ultimately purified by molecular distillation of the melt, and then by recrystallization from a benzene–hexane mixture. It had m.p. 45–46°, lit.[5b] m.p. 47°, with correct analysis for $C_{13}H_{14}O_4$.

3-Carbethoxy-6-chloro-5-hydroxy-2-methylbenzofuran (VI). Method A.—Chlorobenzoquinone (7.1 g., 0.05 mole), from oxidation of chlorohydroquinone with aqueous potassium bromate was extracted continuously (see preparation of III) in 5.5 hr. into a solution of 7 g. of zinc chloride, 7 g. of anhydrous ethanol, and 10 g. (0.075 mole) of redistilled ethyl acetoacetate kept at 100°. The reaction mixture was cooled, and diluted with carbon tetrachloride, and the precipitated solid was filtered. Sublimation, followed by recrystallization from carbon tetrachloride, gave 2.2 g. (17%) of an off-white powder, m.p. 170–172°. This compound was identified as the 6-chloro derivative of III by comparison with an authentic sample (see following).

Method B.—In a three-necked, 500-ml. round-bottomed flask with stirrer, vented addition funnel, and thermometer, a suspension of 20.0 g. (0.091 mole) of III in 175 ml. of chloroform was prepared, and to it was added, in 1.5–2 hr. at −5 to 0°, 57.5 ml. (0.091 mole) of a chlorine solution made by diluting 28 g. of the trapped gas in chloroform until the total volume was 250 ml. The chlorine–chloroform solution in the dropping funnel was kept cold by surrounding the funnel with powdered carbon dioxide wrapped in a towel. After addition was complete, the solution was warmed to 10°, and the white solid (0.55 g., 2.3%) was isolated by filtration. Additional material was obtained from the filtrate, as described below. Recrystallization from 60 g. of carbon tetrachloride gave an analytical sample, m.p. 182–182.5°.

Anal. Calcd. for $C_{12}H_{11}ClO_4$: C, 56.59; H, 4.35; Cl, 13.92. Found: C, 56.61; H, 4.47; Cl, 13.38.

The **methyl ether** of VI was prepared by the method used for the ether of III. From 0.5 g. of VI was obtained, after recrystallization from methanol, 0.35 g. of ether. The analytical sample, recrystallized from *n*-hexane, melted at 125.5–126°. This same compound was obtained in nearly quantitative yield (crude) by chlorination of the methyl ether of III, using the procedure described above for VI itself (method B).

Anal. Calcd. for $C_{13}H_{13}ClO_4$: C, 58.11; H, 4.88; Cl, 13.20. Found: C, 58.25; H, 4.92; Cl, 13.00.

3-Carbethoxy-4-chloro-5-hydroxy-2-methylbenzofuran (V).—The filtrate from the reaction in method B above was evaporated to dryness. The residue weighed 23.4 g. [97.5%; total yield of isolated crude material (both isomers) was 23.95 g., or 100%]. On recrystallization from 125 g. of carbon tetrachloride, a precipitate of 16.6 g. was obtained and, on evaporation of the filtrate, a residue of 5.2 g. The filter cake was found (by infrared) to be a mixture of the 4- and 6-chloro compounds V and VI; the residue consisted essentially of the 4-isomer. By repeated recrystallization of the mixture an additional yield of 1.2 g. of the 6-chloro compound was obtained (total yield pure, 1.7 g., 7%). The total yield of the 4-chloro derivative (V) was 6.45 g., m.p. 82–85°. The analytical sample of V, m.p. 90–92°, was prepared by recrystallization from a methanol–water mixture.

Anal. Calcd. for $C_{12}H_{11}ClO_4$: C, 56.59; H, 4.35; Cl, 13.92. Found: C, 56.76; H, 4.40; Cl, 14.31.

The **methyl ether** was prepared as described under III, and purified by triturating the crude solid with hot hexane. On cooling to −5°, the hexane deposited large colorless cubes. The analytical sample, from hexane, melted at 47.5–48°.

Anal. Calcd. for $C_{13}H_{13}ClO_4$: C, 58.10; H, 4.88; Cl, 13.20. Found: C, 58.32; H, 4.87; Cl, 12.99.

3-Carbethoxy-4,6-dichloro-5-hydroxy-2-methylbenzofuran (VII). Method A.—The same general procedure was used as in the preparation of III, employing 14.5 g. (0.01 mole) of zinc chloride, 30 ml. of absolute ethanol, 20 ml. (0.15 mole) of redistilled ethyl acetoacetate, and 11.75 g. (0.065 mole) of 2,6-dichlorobenzoquinone. The quinone was extracted into the solution over a period of 13 hr. The dark red-brown solution was cooled to −5° and filtered. After washing with cold ethanol, 1.7 g. (9%) of an off-white microcrystalline solid was obtained, m.p. 130–133°. The filtrate was diluted with ether, washed with water, and dried; the solvents were removed by evaporation *in vacuo*. The oily black residue was distilled molecularly, and 7.8 g. of a yellowish solid was recovered. Recrystallization from carbon tetrachloride gave 5.1 g. (26%) of off-white solid, m.p. 131–133°. Total yield of solids melting over 130° was 6.8 g. (35%). The compound was identical with the dichloro compound obtained on chlorination of III (see method B following).

Method B.—Apparatus and procedure are the same as for VI, method B. Compound III (7.25 g. 0.033 mole) was suspended in 65 g. of chloroform and cooled to 10°. To this was added a chloroform solution containing not more than 4.9 g. (0.069 mole, 2.1 equiv.) of chlorine, at 10–14° within 30 min. After stirring for 0.5 hr. longer at 10°, the volume was reduced to one-half and the solid was filtered and washed with hexane, yielding 3.45 g., m.p. 134–135°. By repeated concentration of the filtrate a total yield of 8.4 g. (88%) of material melting over 131° was obtained. The analytical sample, m.p. 135–136°, was recrystallized from ethanol–water.

Anal. Calcd. for $C_{12}H_{10}Cl_2O_4$: C, 49.85; H, 3.48; Cl, 24.52. Found: C, 50.66; H, 3.53; Cl, 24.48.

Other methods of chlorination were tried, but were found to be of little preparative value. Compound III reacted readily with 2 equiv. of cupric chloride and lithium chloride in dimethylformamide solution,[14] forming a mixture of the 4- and 6-monochloro derivatives as chief products, with little unchanged III remaining. Although it was not possible to separate the isomers, their presence was established by means of their infrared spectra. Treating a cold acetic acid solution of III with dilute aqueous sodium hypochlorite did not give any of the three known chloro derivatives, but instead gave a bright yellow compound, melting about 104–106°, of as yet unproved structure. When III was refluxed in chloroform with sulfuryl chloride for several hours, III was recovered unchanged with only a trace of halogenated product. Reaction of III with N-chlorosuccinimide or chloramine T gave colored mixtures whose components were not separated or identified.

The **methyl ether** of VII was prepared as described under III; the reaction of 2.9 g. of VII with excess dimethyl sulfate gave 2.6 g. (86%) of crude product, m.p. 93–98°. After molecular distillation, 2.35 g. of a colorless solid was obtained with m.p. 96–98°. Recrystallized from methanol, the analytical sample melted at 99–100°.

Anal. Calcd. for $C_{13}H_{12}Cl_2O_4$: C, 51.51; H, 3.99. Found: C, 51.66; H, 3.94.

Compound VII (0.50 g.) was heated with excess zinc dust in glacial acetic acid at 100–110° for 16 hr., and was recovered (0.47 g.) unchanged (contrast with behavior of IX and XI, below).

3-Carbethoxy-5-hydroxy-6-iodo-2-methylbenzofuran (X).—To a solution of 18.5 g. (0.084 mole) of III in 65 ml. of anhydrous methanol in a glass-stoppered erlenmeyer flask was added 33.2 g. (0.14 mole, 1.6 equiv.) of elemental iodine, followed by 21.3 g. (0.25 mole, 2.9 equiv.) of morpholine. A purple solid separated immediately and the mixture was shaken under a cold water tap to dissipate the heat generated. The reaction mixture was then shaken mechanically for 90 hr. at 30–35°, filtered, and washed with cold (5°) methanol. The yellowish solid remaining was then continuously extracted with ether for 4 hr. The ether extract gave 8.0 g. of a white solid, m.p. 190–191.5°. When the original reaction filtrate was evaporated to dryness and then continuously extracted with ether, it gave 7.5 g. of solid, m.p. 190–191°. Total yield of material melting above 189° was 15.5 g. (53.5%). The combined solids were subjected to sublimation (from a 100–110° oil bath at 0.5 mm.), then recrystallized from ethyl acetate. The analytical sample, recrystallized from chloroform–hexane, was a microcrystalline white solid, m.p. 194–194.5°.

Anal. Calcd. for $C_{12}H_{11}IO_4$: C, 41.64; H, 3.20; I, 36.66. Found: C, 41.43; H, 3.44; I, 36.87.

The formation of the 6-iodo derivative from III is apparently slow, and complicated by a side reaction in which iodine is consumed without iodination of the phenolic substance. *The side* reaction is markedly favored by a rise in temperature. When III was treated with iodine and morpholine in anhydrous methanol for only 4.5 hr. at 70–75°, all the iodine disappeared, yet III was recovered quantitatively. However, when the same amounts of materials were allowed to react at 30–35° for 90 hr., a 53% yield of the 6-iodo compound X was obtained.

Attempts to use ethylamine, ethylenediamine, or diethanolamine in place of morpholine were largely unsuccessful. In the last case a high yield of the 6-iodo compound was obtained on a 1-g. scale but the yields were poor on a larger scale.

Other attempts to effect direct iodination of III were made, but these were by and large unsuccessful or of less preparative value. Formation of iodinated derivatives of III by the action of ele-

mental iodine in chloroform or carbon tetrachloride at 20° and 75° was not observed; even adding metallic iron or ferric chloride catalyst, or prolonged reaction gave only traces of iodinated products, which were isolated as tars. Most of the starting material was recovered. The reaction of III with iodine monochloride in acetic acid at 50–60° gave a complex mixture from which approximately equal amounts (3–4% yield) of the 4- and 6-monoiodo derivatives, and the 4,6-diiodo compound, were separated along with much starting material. Reaction of iodine monochloride with III in chloroform solution did not appear to proceed until triethylamine was added, whereupon the color of the reagent disappeared rapidly and the 6-iodo compound was obtained pure in 20–30% yield. Reaction of III with sodium hypoiodite gave some 6-iodo product, but its purification was difficult. Also found of little utility were the reagents N-iodosuccinimide, iodine with mercuric oxide or dilute nitric acid, or sodium persulfate, all in mixed aqueous–organic solvents.

The **methyl ether** of X (same procedure as under III), recrystallized from acetone, was a white solid, m.p. 136.5–137.5°.

Anal. Calcd. for $C_{13}H_{13}IO_4$: C, 43.36; H, 3.64; I, 35.24. Found: C, 43.43; H, 3.73; I, 35.46.

3-Carbethoxy-4-chloro-5-hydroxy-6-iodo-2-methylbenzofuran (XI).—Following the chlorination procedure under VI, method B, 6.4 g. of partially purified (m.p. 187–188°) X was treated with 1 equiv. of chlorine–chloroform solution in 25–30 min. at 1–2°. The solution was allowed to stand 10 min., then nitrogen was passed through to remove acid fumes. On evaporation to dryness *in vacuo*, there remained 7.0 g. (100%) of an off-white solid, from which 6.6 g. of clustered needles, m.p. 121–122.5°, was obtained by recrystallization from 60 g. of carbon tetrachloride. The analytical sample, recrystallized from an acetone–water mixture, was a white solid, m.p. 121.5–122.5°.

Anal. Calcd. for $C_{12}H_{10}ClIO_4$: C, 37.87; H, 2.65. Found: C, 38.37; H, 2.67.

Deiodination of XI.—A solution of XI (0.42 g.) in glacial acetic acid was heated at 100–105° with excess zinc dust for 4 hr. It was filtered while hot onto 100 ml. of crushed ice. Filtration gave 0.18 g. (71%) of product, m.p. 81.5°, identified as V by comparison with an authentic specimen.

3-Carbethoxy-5-hydroxy-4-iodo-2-methylbenzofuran (VIII).—The clear solution obtained by warming 16 g. (0.073 mole) of III in glacial acetic acid was treated with 16 g. (0.074 mole) of yellow mercuric oxide, in 2-g. portions at 68–72°. The yellow oxide dissolved rapidly with loss of color, and a white solid began precipitating. After 3.25 hr. at 65–70°, the suspension was cooled and filtered. The dried solid (18.4 g.) was continuously extracted with acetone for 4 hr., leaving 15.8 g. of a gray powder, presumably the acetoxymercuri derivative of III, m.p. 262–263° dec. This solid, when refluxed with 6.5 g. of sodium chloride, 50 ml. of water, and 15 ml. of 95% ethanol (added to prevent foaming), was converted to a tan powder (14.9 g., 45% over-all yield from III), decomposing at 240–250°.

Fourteen grams (0.031 mole) of the latter solid was suspended in 50 ml. of chloroform, and treated with 7.8 g. (0.031 mole) of elemental iodine dissolved in 250 ml. of chloroform (iodine in aqueous potassium iodide could also be used), over a period of 1 hr. The first 50 ml. of iodine–chloroform solution was decolorized almost instantaneously, and a more pronounced brown color appeared in the suspension. Near the end of the reaction, the iodine color in 2 ml. of added solution was discharged in about 2 min. (In contrast, III did not decolorize iodine–chloroform solutions at all, even during several hours under these conditions.) A pale red amorphous solid was already forming toward the end of the addition. After standing overnight, the solid obtained by filtration weighed 10.4 g. (93%, assuming it was mercuric iodochloride). After evaporating the filtrate to dryness *in vacuo*, 10.7 g. of a red oily solid remained. Fractional crystallization from a carbon tetrachloride–hexane mixture gave 4.0 g. (37%) of an off-white solid, m.p. 114–118°. The analytical sample obtained by recrystallization from cyclohexane was a white solid, m.p. 115–117.5°.

Anal. Calcd. for $C_{12}H_{10}IO_4$: C, 41.64; H, 3.20; I, 36.66. Found: C, 41.45; H, 3.63; I, 36.56.

3-Carbethoxy-4,6-diiodo-5-hydroxy-2-methylbenzofuran (IX).—To 13.2 g. (0.06 mole) of III in 125 ml. of anhydrous methanol was added in one portion 30.4 g. (0.12 g.-atom, 2 equiv.) of elemental iodine. This suspension and a solution of 31.1 g. (0.36 mole, 6 equiv.) of morpholine in 20 g. of methanol were chilled in a refrigerator for 0.75 hr., then mixed. The heat of reaction was dissipated by swirling the flask under a cold water tap for several minutes, after which the reaction mixture was stirred magnetically for 92 hr. at 6°. Filtration, followed by two successive concentrations *in vacuo* and filtrations, yielded three crops of solid, weighing 24.5, 6.0, and 27.0 g., respectively. The first crop was recrystallized from about 600 ml. of ethyl acetate (the solution became dark in color as the temperature was raised) and gave 18 g. of a tan solid, which was identified as the morpholinium salt of the diiodo derivative (IX). By treatment of the salt with 10% sulfuric acid in the presence of ether, 15 g. (53%) of the diiodo compound (IX) was obtained. The analytical sample of the diiodo compound, recrystallized from methanol, was a pale yellow powder, m.p. 121.5–122.5°.

Anal. Calcd. for $C_{12}H_{10}I_2O_4$: C, 30.53; H, 2.14; I, 53.77. Found: C, 30.79; H, 2.19; I, 54.06.

The second crop was almost pure morpholine hydriodide, m.p. 207–211°, identical after recrystallization from a methanol–ether mixture with an authentic sample (m.p. 215–216°). The third crop, after continuous extraction with ether for 4 hr., weighed 24 g., m.p. 205–211°. After recrystallization from a methanol–ether mixture there remained 18.9 g. (m.p. 214–215°) of a white, water-soluble powder. The methanol–ether and ethyl acetate mother liquors (from the first crop) were combined and reduced to dryness. By sublimation and recrystallization 3.4 g. of the 6-iodo derivative (X) was obtained. The isolated iodinated derivatives accounted for 68% of the starting material.

Attempts to prepare a methyl ether of IX under the usual conditions with dimethyl sulfate and sodium hydroxide gave a tarry product. Sodium hydroxide solution alone had a similar effect on IX.

The isolated **morpholinium salt of the diiodo derivative (IX)** discussed above was found to be identical with a compound obtained by mixing a methanol solution of the purified diiodo compound with an excess of morpholine. The analytical sample was recrystallized from methanol. Though analytically pure it melted over a wide range (160–180°), the exact range depending on the rate of heating.

Anal. Calcd. for $C_{16}H_{19}I_2NO_5$: C, 34.37; H, 3.42; I, 45.39. Found: C, 34.69; H, 3.63; I, 45.76.

The morpholinium salt was more stable in ethanolic solution than the parent phenol. While solutions of IX in 95% ethanol quickly began turning yellow on standing under fluorescent laboratory lighting, the morpholinium salt of IX only acquired a very pale pink color and, after three months, the former solution was deep orange, the latter pale yellow. Under these conditions ethanolic solutions of III, V, VI, VII, X, XII, and XIII remained colorless, but that of XI turned yellow

Deiodination of IX (Complete).—After dissolving 0.5 g. of IX in 20 ml. of glacial acetic acid, an excess of zinc dust was added and the mixture was heated. A pale purple color formed and persisted for some 5 min., then disappeared. The reaction mixture was kept at 100–110° for 6 hr., left to cool overnight, then reheated, and filtered. The filtrate was poured onto 100 ml. of crushed ice. The white solid isolated by filtration and drying weighed 0.15 g. (65%), and melted at 142.5–143.5°. It was identical in melting point, mixture melting point, and infrared spectrum with an authentic sample of III. This complete deiodination is a marked contrast to the complete stability of the dichloro phenol (VII) under similar conditions.

Compound IX was tested for its stability under the conditions of the quinone–active methylene compound condensation. A quarter of a gram of IX was added to a solution of 0.25 g. of anhydrous zinc chloride in 2.5 g. of anhydrous ethanol. As no color change was noted within 10 min. at room temperature, the mixture was heated gently. As the temperature neared 65°, a dark red-brown violet color appeared suddenly. Heating was continued at 75–80° for 1.5 hr., and then the solution was poured onto 50 ml. of crushed ice. Ether extracts of the resulting dark-colored solution yielded only a small amount of an unidentified dark brown oil.

Deiodination of IX (Partial).—One-quarter gram (0.53 mmole) of IX was dissolved in acetone, and to this was added a solution of potassium cyanide (0.25 g. 3.85 mmoles) which had been dissolved in 1.0 g. of water and then diluted with 5.0 g. of acetone. A yellow color formed immediately, but did not intensify even on warming to 50° for several minutes. The solvent was removed *in vacuo* and replaced with dimethyl sulfoxide; a deep yellow color formed immediately. The reaction mixture was kept at 45–50° for 4–5 hr., then poured onto 50 ml. of crushed ice and diluted to 100 ml. The crude solid which precipitated was identified as the 6-iodo derivative (X) by melting point, mix-

ture melting point, and infrared spectrum. The recrystallized solid weighed 0.10 g. (55%), m.p. 191.5–192.5°.

6-Bromo-3-carbethoxy-5-hydroxy-2-methylbenzofuran (XII).—The reaction apparatus used was that in method B for VI, except that nitrogen was bubbled through the reaction solution, and the exiting vapors were passed through a water-rinsed gas trap. Temperature was kept at 10–15° throughout the reaction. A solution of 22.0 g. (0.10 mole) of III in chloroform was treated with a solution of 16 g. (0.10 mole) of bromine in 100 ml. of chloroform over a period of 70–80 min. The bromine color of the first 75 ml. of this reagent solution was discharged rapidly, but the last 25 ml. were discharged more slowly. The mixture was stirred an additional 20 min., poured into 500 ml. of saturated sodium bicarbonate solution, and, after stirring 10 min. longer, was filtered. The filter crop was triturated with two 100-ml. portions of 5% aqueous sodium thiosulfate solution and with three 100-ml. portions of water. After drying, the solid weighed 24.5 g. (82%). It was dissolved in 600 g. of hot acetone, treated with charcoal, then filtered hot. When cooled, filtered, and air-dried for 4 hr., the microcrystalline white solid, m.p. 191–192°, was recovered from the acetone mother liquor. The total yield of XII melting over 191° was 24.1 g. (81%). The analytical sample was recrystallized from an ethanol–acetone mixture, m.p. 192.5–193°.

Anal. Calcd. for $C_{12}H_{11}BrO_4$: C, 48.18; H, 3.71; Br, 26.72. Found: C, 48.21; H, 3.89; Br, 26.85.

The **methyl ether** of XII was prepared as described under III. Treatment of 3.1 g. of XII gave 3.4 g. of the crude methyl ether; recrystallization from a benzene–pentane mixture (9 g., 20 g.) gave 1.6 g., m.p. 122.5–123.5°. Further recrystallization from carbon tetrachloride gave a granular white solid, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{13}H_{13}BrO_4$: C, 49.86; H, 4.18; Br, 25.52. Found: C, 49.94; H, 4.25; Br, 25.78.

It is interesting that bromination proceeds smoothly in chloroform without added base or catalyst. In ether, or a 3:7 mixture of ether–chloroform, brominated derivatives of III were obtained only in trace quantities, III being recovered nearly quantitatively.

3-Carbethoxy-4,6-dibromo-5-hydroxy-2-methylbenzofuran (XIII).—The same procedure was used as for XII, except that 2 equiv. of bromine were used, and the temperature was kept at 22–26°. When 5.5 g. of III was allowed to react with bromine in this way for 3 hr., a crude product weighing 7.28 g. (77%) was obtained, m.p. 116–118°. Attempted recrystallization from ethanol was accompanied by formation of an orange-brown color. The recovered solid, 6.2 g., m.p. 115–118°, was somewhat orange in color. Further purification was by molecular distillation from a 120–125° oil bath at 0.5 mm. The analytical sample, from carbon tetrachloride, was a white solid, m.p. 118–119°.

Anal. Calcd. for $C_{12}H_{10}Br_2O_4$: C, 38.13; H, 2.66; Br, 42.28. Found: C, 38.07; H, 2.82; Br, 42.10.

The **methyl ether** of XIII was prepared as indicated under III, and recrystallized first from carbon tetrachloride, then from acetone–water (charcoal). The analytical sample was recrystallized from acetone–water (0.48 g. of methyl ether, 4.0 g. of acetone, 1.8 g. of water) to give long white needles (0.38 g.), m.p. 87.5–88.5°.

Anal. Calcd. for $C_{13}H_{12}Br_2O_4$: C, 39.83; H, 3.09; Br, 40.76. Found: C, 40.36; H, 3.44; Br, 40.35.

Acknowledgment.—The authors wish to thank Miss Yvonne Chiang and Dr. Earl Whipple for taking and advising on the interpretation of the n.m.r. spectra.

Degradation and Synthesis of Desosamine

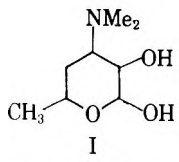
HOWARD NEWMAN[1]

The Chemical Research and Development Laboratories, Agricultural Division, American Cyanamid Company, Princeton, New Jersey

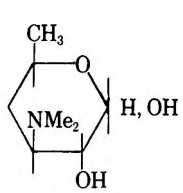
Received December 11, 1963

The degradation of desosamine (I) to 2-ethoxy-3,4-epoxy-6-methyl-tetrahydropyran (IVa) and the reconversion of the latter to desosamine are described. A synthesis of racemic IVa is also presented.

Desosamine (I), the amino sugar component of a considerable number of the macrolide antibiotics,[2,3] has recently evoked considerable interest. Foster, *et al.*, showed it to be a D-hexose.[4] Foster, *et al.*,[5] and Newman[6] presented chemical evidence which established a *trans* relationship between the C-2 hydroxyl and C-3 dimethylamino substituents, while n.m.r. studies by Hofheinz and Grisebach[7] and Woo, *et al.*,[8] established its configuration as D-*gluco* (Ia). Two non-



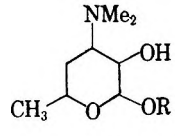
I



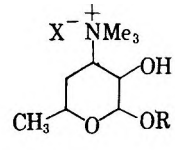
Ia

stereospecific syntheses of I have been described,[6,9] as has its formation from 3-amino-3-deoxy-D-glucose by replacement of the C-4 and C-6 hydroxy substituents with hydrogen from suitably constituted intermediates.[10] In this paper we described, in detail, the degradation of desosamine hydrochloride (I + HCl) to 2-ethoxy-3,4-epoxy-6-methyltetrahydropyran (IVa), the synthesis of racemic IVa, and the reconversion of optically active IVa to desosamine hydrochloride (I + HCl).

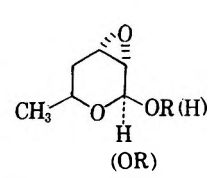
Ethyl desosaminide (IIa) was degraded to the epoxide IVa by pyrolysis of its quaternary hydroxide derivative IIIb which was, in turn, prepared from the corresponding methiodide IIIa. The stereochemical im-



IIa, R = ethyl
b, R = methyl



IIIa, X = I⁻
b, X = OH⁻



IVa, R = ethyl
b, R = methyl

plication of this degradation has already been discussed.[6]

(1) Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

(2) A. B. Foster and D. Horton, *Advan. Carbohydrate Chem.*, **14**, 213 (1959).

(3) H. Els, W. D. Celmer, and K. Murai, *J. Am. Chem. Soc.*, **80**, 3777 (1958).

(4) C. H. Bolton, A. B. Foster, M. Stacey, and J. M. Webber, *J. Chem. Soc.*, 4831 (1961).

(5) C. H. Bolton, A. B. Foster, M. Stacey, and J. M. Webber, *Chem. Ind.* (London), 1945 (1962).

(6) H. Newman, *ibid.*, 372 (1963).

(7) W. Hofheinz and H. Grisebach, *Tetrahedron Letters*, **No. 9**, 377 (1962).

(8) P. Woo, H. Dion, L. Durham, and H. Mosher, *ibid.*, **No. 17**, 735 (1962).

(9) F. Korte, A. Bilow, and R. Heinz, *Tetrahedron*, **18**, 657 (1962).

(10) A. C. Richardson, *Proc. Chem. Soc.*, 131 (1963).

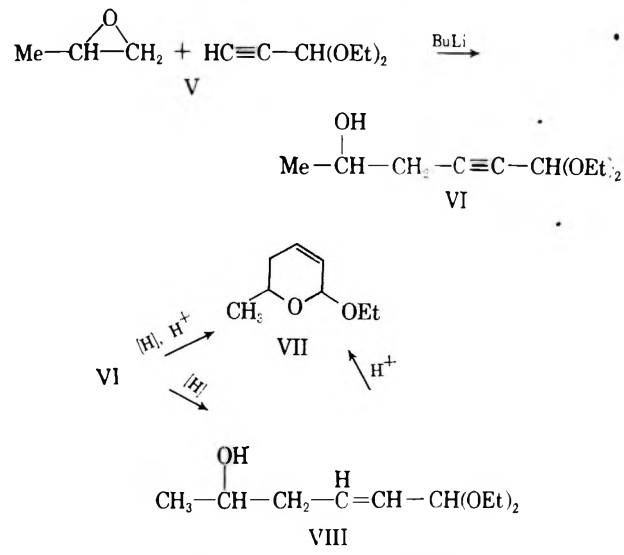
Vapor phase chromatographic analysis of the epoxide IVa indicated the presence of both the α- and β-anomers. The fact that desosamine (I) was known to be a D-hexose[4] permitted the assignment of configuration to the two anomeric components on the basis of their optical rotations and the application of Hudson's Isorotation Rule.[11] The lower retention time component exhibited the more negative rotation and was consequently assigned the β-configuration.

Methyl desosaminide (IIb) was also degraded to the corresponding epoxide IVb, and here, too, the lower retention time component exhibited the more negative rotation and was assigned the β-configuration.

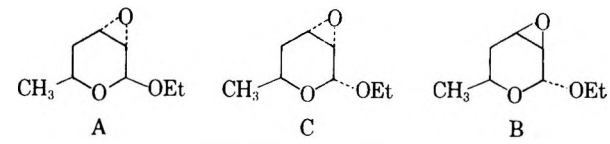
The nuclear magnetic resonance spectra of the two anomeric methyl glycosides IVb support the configurational assignment made. Thus, the C-1 proton resonance of the lower retention time component appeared at τ 5.25 ($J_{12} \cong 0$), while this signal for the higher retention time component appeared at τ 5.09 (J_{12} = 2.5 c.p.s.). This observation parallels the commonly observed phenomenon[8,12-14] that axial protons in the chair form of cyclohexane and pyranose derivatives resonate at higher field than their equatorial counterparts.[15]

The racemic modifications of the α- and β-anomers of IVa were synthesized as follows. The lithium salt of propargyl aldehyde diethylacetal[17] (V) reacted with propylene oxide to give 1,1-diethoxy-5-hydroxyhex-2-yne (VI) in 60% yield. VI could be converted directly to 2-ethoxy-6-methyl-5,6-dihydro-2H-pyran (VII) by reduction over 10% palladium on charcoal until a molar equivalent of hydrogen was consumed, followed by the addition of a small amount of concentrated hydrochloric acid and shaking for an additional short period. Omission of the acid treatment permits the isolation of the acyclic olefin, 1,1-diethoxy-5-hydroxyhex-2-ene (VIII), which can, in turn, be cyclized to VII by treatment with acid. Traces of acid must be rigorously excluded from the hydrogenation system if it is desired to prevent cyclization of the initially formed VIII. In one experiment (see Experimental), VII was the only product isolated, although no acid was added; this was presumably due to traces already present.

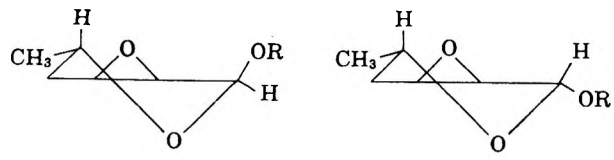
The amounts of the two isomers of VII (*cis* and *trans*)[18] present could be extrapolated from the composition of the epoxide mixture IX obtained from it by perbenzoic acid oxidation (see below), with the result that, in all preparations of VII but one, the *trans* isomer largely ($\geq$85%) predominated. In the one exception, VII was inadvertently obtained in an attempt to convert VI to VIII by hydrogenation over 10% palladium on charcoal in the absence of acid. The *cis*–*trans* isomer ratio of VII obtained in this preparation was roughly 1:2, a considerable amount of *cis* isomer having been formed.



Epoxidation of VII with perbenzoic acid was investigated first. (The same results were subsequently obtained with commercially available *m*-chloroperbenzoic acid.) The epoxide IX obtained was a three-component mixture, A, B, and C (in order of increasing retention time), separable by gas chromatography. The infrared spectra of components A and C were identical with those of the β- and α-anomers, respectively, of epoxide IVa obtained by the degradation of desosamine. A and C must, therefore, be the *cis* and *trans*[18] 2-ethoxy-3,4-epoxy-6-methyltetrahydropyran isomers, respectively, in which the epoxide ring is *trans* to the C-5 methyl substituent, while B must be the isomeric epoxide in which the oxide ring and the C-5 methyl group are *cis* oriented.[19] The *trans* (methyl, ethoxyl) configuration is assigned to B on the basis of the variation in the A:B ratio in the various preparations of IX obtained from different preparations of VII (1:30 to 1:1.5) as compared to the essential constancy of the B:C ratio in those same cases (3.5:1 to 2.5:1).[20] This is indicative of a common precursor for B and C, which must be *trans*[19] VII since the methyl and ethoxyl substituents in C are known to be *trans*.



The homogeneity of B follows from its n.m.r. spectrum in which only a single peak at τ 5.05 ($J_{12} \cong 0$) due



(11) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).

(12) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958); R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **41**, 889 (1963).

(13) J. van der Veen, *J. Org. Chem.*, **28**, 564 (1963).

(14) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

(15) It is assumed that the conformations of the α- and β-anomers of IVb are represented by i and ii, respectively. The basis for this expectation will be discussed later in the paper. (The chair conformations are taken to be more stable than the boat by analogy with the preferred chair conformation for cyclohexene oxide.[16])

(16) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).

(17) J. C. Sheehan and C. A. Robinson, *J. Am. Chem. Soc.*, **71**, 1436 (1949).

(18) *cis* and *trans* refer to the relative configuration of the methyl and ethoxyl substituents.

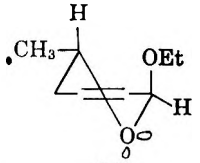
(19) The possibility that component B is a positional isomer is ruled out by the product of its reaction with dimethylamine described later.

(20) Considering the fact that the retention times of the components were such that peak separation was not complete, no significance is attached to the 3.5:1 to 2.5:1 variation. (Peak areas were approximated by multiplying the peak width at half-height by the peak height.)

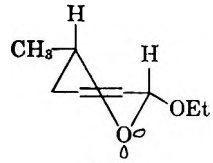
to the C-1 proton was present. If B was, in fact, a mixture, epimeric at C-1, one would expect to see the C-1 proton n.m.r. signals corresponding to both epimers by analogy with the behavior of the α- and β-anomer mixture IVb, in which two C-1 protons signals at τ 5.09 ($J_{12} \cong 2.5$ c.p.s.) and 5.25 ($J_{12} \cong 0$) were clearly visible. The essential coincidence in τ-values between the C-1 proton signal of the α-anomer of IVb and that of component B is further support for the *trans*[18] configuration assigned to the latter.

Thus, of the four possible epoxides that could be formed from the two epimers of VII, only three were obtained, two (B and C) corresponding to *trans* VII and one (A) to *cis* VII.

The results can be rationalized on the basis of conformations VIIa and VIIb for *trans* and *cis* VII, respectively, which would be expected to be very largely preferred based on a consideration of pertinent steric



VIIa

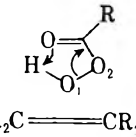


VIIb

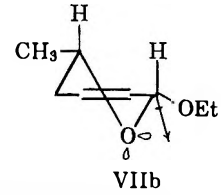
and electronic factors. Thus, for *trans* VII (conformation VIIa) the difference in A-values[14] between methyl[14] and ethoxyl[21] (0.7 kcal.) plus the "anomeric effect"[22] (preferred axial orientation for the anomeric oxygen of a pyranose, 1.1 kcal.[22]) would result in a free-energy difference of 1.8 kcal. in favor of the conformer shown, corresponding to a 95% equilibrium concentration ($\Delta F = -RT \ln K$) of VIIa. Similarly for *cis* VII (conformation VIIb) the sum (since, in the other chair conformer, both substituents become axial) of the A-values for methyl and ethoxyl (2.7 kcal.) minus 1.1 kcal. for the "anomeric effect" leads to a 1.6-kcal. difference in favor of conformer VIIb, which corresponds to an equilibrium concentration of 94% (see ref. 15). The above values are, of course, only crude estimates, since the A-values used were determined for cyclohexane, and the "anomeric effect" value is also only approximate[22]; however, they do indicate that it is not unreasonable to interpret the observed results in terms of conformations VIIa and VIIb.

On this basis then, peracid attack of *trans* and *cis* VII takes place predominantly (*ca.* 75%) and exclusively, respectively, from the side opposite the ethoxyl substituent, which is quasi-axial in *trans* VII and quasi-equatorial in *cis* VII.

If it is assumed that the transition state for olefin epoxidation with peracid is of the type proposed by Bartlett[23] (see diagram), the results can be explained as follows. The epoxidation of *trans* VII from the side opposite the quasi-axial ethoxyl substituent is favored



because of the adverse steric factor involved in a *cis* approach. A possible unfavorable electronic factor resulting from the interaction of the electron pairs on the ethoxyl oxygen with those of O-1 and/or O-2 of the peracid will be assumed to be cancelled, more or less, by a similar effect operating between the axially oriented pair of electrons on the ring oxygen[24] and the oxygen electrons of the peracid on the other side of the ring plane. In the case of *cis* VII, exclusive attack from the topside of VIIb is suggested to be the result of an adverse electronic effect which is a combination of the interaction of the oxygen electrons of the peracid with the axially oriented electron pair of the ring oxygen and the dipole–dipole interaction (see diagram) of the type proposed by Henbest[25] to explain predominant *trans* attack of peracid on 4-methoxy and 4-cyano cyclopentene.[26] (The dipole–dipole interaction would not



VIIb

(Approach of an electrophile is expected to take place from the side opposite the resultant dipole vector which in this case extends below the ring plane)

seem to apply to *trans* VII where the resultant dipole vector would be pretty much in the plane of the ring.)

That the *cis–trans* isomer distribution of olefin VII may be obtained directly from the composition of the epoxide IX follows from the fact that IX is recovered unchanged from glacial acetic acid after 72 hr. at room temperature. If epimerization of IX by the generated benzoic acid accompanied the epoxidation, one would have expected to observe the replacement of ethoxyl by acetoxyl.

It was thought that the observed preferential attack of peracid from the side opposite the ethoxyl substituent in *trans* VII might be turned to good advantage by substituting acetyl hypobromite for the peracid. Assuming the primary factor responsible for the direction of peracid attack on *trans* VII is steric in origin, the positive bromine initiating the attack[27] would then approach predominantly from the side opposite ethoxyl, and *trans* opening[28] of the resulting bromonium ion would yield an acetoxy bromide which, on base treatment, would give, as the major product, the epoxide of opposite configuration to that predominantly obtained with peracid, and one which is configurationally correct for opening to desosamine.

In actual fact, reaction of a mixture of *cis* and *trans* VII with acetyl hypobromite in carbon tetrachloride and subsequent base treatment of the resulting acetoxy

(21) D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961).

(22) J. T. Edwards, P. F. Morand, and I. Puskas, *Can. J. Chem.*, **39**, 2069 (1961), and references cited there.

(23) P. D. Bartlett, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **11**, 47 (1950).

(24) C. A. Coulson, "Valence," Oxford University Press, London, 1952, p. 209.

(25) See H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963), for a review of his work relating to the directive effects of substituents on additions to cyclic olefins.

(26) Since the question of the relative size of hydrogen *vs.* a pair of electrons is unsettled [A. R. Katritzky, *et al.*, *J. Chem. Soc.*, 2637 (1962), and references cited therein], the relative steric environment above and below the ring plane cannot be assessed. It is assumed, for purposes of discussion, that there is little, if any, difference between them.

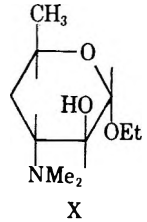
(27) See W. A. Waters, "Organic Chemistry: An Advanced Treatise," Vol. IV, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, p. 1230.

(28) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **76**, 1654 (1954).

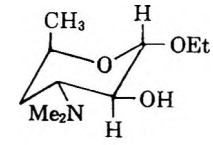
bromide mixture gave a mixture of four components, A, B, C (identical with A, B, and C obtained from peracid treatment of VII), and D (highest retention time, not previously obtained). The ratios of A to D and of B to C remained approximately 1:1, while the relative amounts of A (or D) to B (or C) varied depending on the *cis–trans* ratio of VII. These results may be explained by a nonselective attack of *cis* VII as a common precursor leading to A and D and of *trans* VII as a precursor to B and C.

The nonselectivity of the acetyl hypobromite reaction is compatible with the extreme rapidity (in contrast to the peracid reaction) with which it occurs.[29a]

Treatment of the epoxide mixture IX obtained from perbenzoic acid oxidation of VII with saturated aqueous dimethylamine gave, after recrystallization of the initially obtained oily solid from petroleum ether (b.p. 30–60°), a crystalline dimethylamino alcohol, m.p. 42.5–45.5°. Its hydrolysis product rapidly consumed a molar equivalent of periodate. [The hydrolysis product of the material obtained from the petroleum ether mother liquor (40% of the total dimethylamino alcohol) consumed 0.73 of a molar equivalent.] The n.m.r. spectrum of the compound, m.p. 42.5–45.5°, showed a single doublet centered about τ 5.43 (J_{12} = 6.1 c.p.s.) due to the proton at C-1. Comparison of its n.m.r. spectrum with that of authentic ethyl desosaminide (IIa, 3:1 mixture of α- and β-anomers from extrapolation of the composition of the epoxide mixture obtained from it) indicated that the synthetic material contained *no* α-ethyl desosaminide, the latter showing a single doublet centered about τ 5.07 (J_{12} = 3.6 c.p.s.). The signal due to the C-1 proton of the β-anomer was obscured by a complex multiplet at higher field and could not be unequivocally assigned. However, since the amount of component A (the only possible precursor of β-ethyl desosaminide) present in the starting epoxide mixture was less than 10%, and since, as will be pointed out, the epoxide corresponding to desosamine reacts with dimethylamine to give roughly a 1:1.5 mixture of 2- and 3-dimethylamino sugar glycosides, the synthetic material, m.p. 42.5–45.5°, could not contain more than 6% of β-ethyl desosaminide.[29a] The compound of m.p. 42.5–45.5° must, therefore, be a 3,4,6-trideoxy-3-dimethylamino sugar glycoside with an *altro* configuration (X). The α-configuration assigned to the ethoxyl substituent in X follows from its formation from component B of epoxide mixture IX. The relatively large value of the C-1–C-2 proton coupling



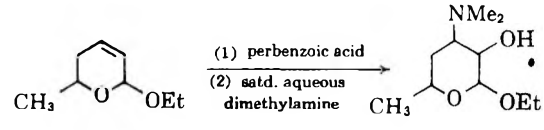
X



Xa

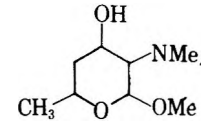
constant (6.1 c.p.s.). is compatible with conformation Xa in which the H-1–H-2 dihedral angle is approximately 180°.[8,12,13,30]

In view of the n.m.r. data which unequivocally establish the structure of the dimethylamino sugar glycoside obtained from perbenzoic acid oxidation of IX as X (possibly contaminated with not more than 6% of β-ethyldesosaminide), it is of interest that Korte and coworkers[9] were able to convert their dimethylamino sugar glycoside, obtained as indicated, which melted at 45° (presumably a purer sample than ours), to a 13%



yield of crystalline 3-dimethylamino sugar hydrochloride, which, on further purification, gave racemic desosamine hydrochloride (I + HCl, unspecified yield) identical (infrared and paper chromatography[31]) with an authentic specimen.

Ring opening of the epoxide IVa obtained by the degradation of ethyl desosaminide (IIa) gave a mixture of 2- and 3-dimethylamino-4,6-didcoxyglycosides XI and IIa in roughly a 1:1.5 ratio. This is in sharp con-



XI

trast to the essentially exclusive opening of the epoxide mixture IX obtained from the peracid oxidation of VII to the 3-dimethylaminoglycoside X. [Since the epoxide mixture IX consisted of 70–75% of component B, the other two components, A and C, being identical with the two anomeric epoxides obtained from desosamine, the consumption of 0.89 equiv. of periodate ($0.6 \times 1.00 + 0.4 \times 0.73$, see above) by the hydrolysate of the dimethylamino alcohol mixture obtained from epoxide IX indicates that component B underwent essentially exclusive attack at C-3.]

The difference in behavior of component B and the epoxide mixture IV obtained from the degradation of desosamine [conformation XII and XIII, respectively (see discussion above)] may be explained on the basis that both electronic factors (attack at the position furthest removed from C-1)[32] and stereoelectronic factors (*trans* diaxial ring opening)[33] favor attack at C-3

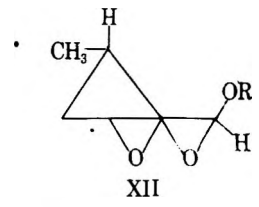
(29) (a) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955). (b) As noted by a referee, the maximum arithmetic yield possible for β-ethyl desosaminide in the *crystalline* material obtained is 17%. This, however, would require the assumption that the β-ethyl desosaminide is completely insoluble in petroleum ether (solvent of crystallization, see Experimental). It has been our experience that the petroleum ether (and other solvent) solubilities of the anomeric mixture of ethyl glycosides obtained from desosamine and the ethyl glycoside X are quite similar. It is our feeling, therefore, that, while the 17% figure is arithmetically possible, the 6% figure has the advantage of being both arithmetically possible and physically probable.

(30) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); R. U. Lemeiux, J. Stevens, and R. Fraser, *Can. J. Chem.*, **40**, 1955 (1962).

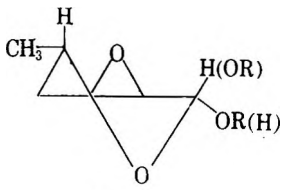
(31) We found essentially identical R_f values for X methiodide and ethyl desosaminide methiodide (0.42 and 0.43, respectively) on Whatman No. 1 paper with the upper phase of a *n*-butyl alcohol–ethanol–water mixture (4:1:5) as the developing solvent.

(32) This is in accord with previous observations on the direction of ring opening of epoxides containing polar substituents [R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959)].

(33) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).



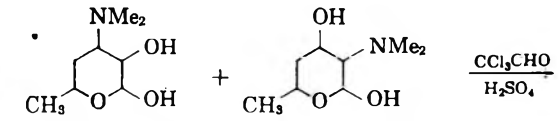
XII

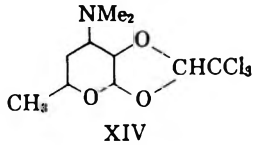


XIII

in XII, whereas, in XIII, the favorable electronic effect for attack at C-3 is counteracted by an unfavorable stereoelectronic effect (diequatorial opening). Component B is, therefore, attacked exclusively at C-3 while IV undergoes attack at both C-2 and C-3.

The mixture of 2- and 3-dimethylamino-4,6-dideoxyglycosides obtained from the epoxide mixture IVb could be separated by treating its hydrolysis product with chloral in the presence of concentrated sulfuric acid at room temperature. Only the 3-dimethylamino sugar





XIV

+ unchanged 2-dimethylamino sugar (presumably)

(desosamine) formed a trichloroethylidene derivative XIV, which was identical with that formed from authentic desosamine.

The trichloroethylidene derivative XIV was converted to methyl desosaminide in refluxing methanolic hydrogen chloride; XIV was, however, unaffected by conditions which readily hydrolyze isopropylidene and benzylidene derivatives.[34]

The hydrolysate obtained from the reaction of the 2- and 3-dimethylamino-4,6-dideoxyglycoside mixture with dilute hydrochloric acid deposited a 5% yield of desosamine hydrochloride (I + HCl) from ethanol–ether–acetone, in the cold, identical (melting point, mixture melting point, optical rotation, and infrared spectrum) with an authentic sample.

Experimental[35]

Ethyl Desosaminide (IIa). A.—The procedure of Flynn, *et al.*,[36] was followed. A solution of 7.8 g. (0.037 mole) of desosamine hydrochloride (obtained as described in ref. 4) in 125 ml. of saturated absolute ethanolic hydrogen chloride was heated under reflux for 17 hr. and evaporated. Chloroform was added to the dark yellow sirupy residue and the mixture was made basic with 10% sodium hydroxide solution to pH 12 (alkacid test paper). The aqueous phase was extracted with chloroform and the combined chloroform extracts were dried and evaporated. The red sirupy residue was distilled *in vacuo* to give 3.7 g. (42%) of ethy desosaminide, b.p. 55–63° (0.1 mm.), lit.[36] b.p. 65–67° (0.2 mm.).

B.—A solution of 21 g. (0.029 mole) of erythromycin[37] in 400 ml. of absolute ethanol was heated under reflux for 2.5 hr. with gaseous hydrogen chloride bubbling through the reaction mixture. (The reaction mixture turned black almost immediately after refluxing began.) The ethanolic hydrogen chloride was removed *in vacuo*, the black residue was dissolved in chloroform, and the chloroform solution was extracted twice with water. The aqueous solution was made basic (pH 11–12) and the resulting turbid solution was extracted with chloroform. Drying and evaporating the chloroform extracts yielded an orange liquid residue which was distilled to give 3.6 g. (61%) of ethyl desosaminide, b.p. 63–64.5° (0.1–0.3 mm.). (The ethanolysis could be conveniently run on six times this scale, ethyl desosaminide being obtained in comparable yield.)

Methyl Desosaminide (IId).—A solution of 4 g. (0.02 mole) of ethyl desosaminide in 100 ml. of saturated methanolic hydrogen chloride was heated under reflux for 2.75 hr., the methanolic hydrogen chloride was evaporated *in vacuo*, and the residue was distilled to yield 3 g. (79%) of methyl desosaminide, b.p. 76–77° (0.7–0.8 mm.), lit.[36] b.p. 61–62° (0.3 mm.).

Anal. Calcd. for $C_9H_{19}NO_3$: C, 57.11; H, 10.12; N, 7.40. Found: C, 56.84; H, 10.09; N, 7.47.

Ethyl Desosaminide Methiodide.—A solution of 3.2 g. (0.016 mole) of ethyl desosaminide prepared as in A in 10 ml. of acetone was cooled in ice–water and 5 ml. (0.08 mole) of methyl iodide was added. After cooling for an additional 3 min., the reaction mixture was permitted to warm to room temperature and kept there for 1 hr. The acetone and excess methyl iodide were evaporated and the partially solid residue was triturated with ethyl acetate to yield 5.2 g. (95%) of the colorless, solid methiodide, m.p. 153–176°.

The analytical sample was prepared by permitting a partial suspension of the methiodide in hot acetone to cool to room temperature. After keeping overnight, the methiodide was collected, washed with two small portions of acetone then ethyl acetate, and dried *in vacuo* overnight, m.p. 186–188°.

Anal. Calcd. for $C_{11}H_{24}INO_3$: C, 38.27; H, 7.00; I, 36.76; N, 4.06. Found: C, 38.31; H, 6.99; I, 37.01; N, 4.14.

Methyl Desosaminide Methiodide.—The procedure used was essentially that employed for the ethyl analog. After evaporating the excess acetone and methyl iodide, the residue was suspended in ethyl acetate. The methiodide began to crystallize within 30–45 min. After standing at room temperature overnight, 5 g. (95%) of methiodide, m.p. 142–148°, was collected.

The analytical sample was prepared by permitting a hot suspension of the methiodide in acetone–ethyl acetate to cool to room temperature and keeping overnight. The collected solid was dried *in vacuo* at 78° for 1 hr., m.p. 148–155°.

Anal. Calcd. for $C_{10}H_{22}INO_3$: C, 36.26; H, 6.69; I, 38.32; N, 4.22. Found: C, 36.95; H, 6.82; I, 38.60; N, 4.42.

2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IVa).—A solution of 5 g. (0.014 mole) of ethyl desosaminide methiodide in 100 ml. of water was stirred with silver oxide (from 26 g., 0.15 mole, of silver nitrate) for 23 hr. at room temperature. The silver oxide was removed by filtration, washed with water, and the combined aqueous filtrates were evaporated *in vacuo* below 35°. Final traces of moisture were removed by pumping (vacuum pump) for 3 hr. The light yellow, hygroscopic residual glass was pyrolyzed at 80–170° (15 mm.), the pyrolysate being collected in a Dry Ice-cooled side arm test tube receiver. The pyrolysate was dissolved in ether, washed successively with two small portions of dilute hydrochloric acid, water, and saturated sodium bicarbonate solution, dried, and evaporated to yield 1.2 g. (55%) of nearly colorless, neutral liquid residue. A temperature programmed (25–200°) vapor chromatographic analysis of the product on a 3-ft. 20% DEGS-on-Chromosorb W column (helium flow rate, *ca.* 120 cc./min.) indicated it to be a mixture of two components, A and B (appearing at 140° and 160°, respectively), in a 1:3 ratio which were separately collected (column temperature, 150°; helium flow rate, *ca.* 120 cc./min.): component A (lower retention time), $[\alpha]^{25}D$ −73° (*c* 0.52, chloroform); component B (higher retention time), $[\alpha]^{25}D$ +57° (*c* 0.79, chloroform).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found for A: C, 60.47; H, 9.15. Found for B: C, 60.45; H, 9.06.

(34) This is presumably due to the electron-withdrawing effect of the trichloromethyl group which makes oxygen protonation and the subsequent cleavage of the oxygen carbon bond more difficult.

(35) Melting points are corrected. Microanalyses are by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken either neat (liquids) or as mulls in Nujol (solids) with a Perkin-Elmer Infracord or 421 spectrophotometer. N.m.r. spectra were determined on a Varian Associates DP60 spectrometer at 56.4 Mc. in deuteriochloroform with tetramethylsilane as an internal standard. Solutions were dried over magnesium sulfate.

(36) E. H. Flynn, M. V. Sigal, P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954).

(37) Kindly supplied by Abbott Laboratories.

The infrared spectra of components A and B were identical with the first and third components, respectively, of the ternary epoxide mixture IX obtained by the synthesis described below.

2-Methoxy-3,4-epoxy-6-methyltetrahydropyran (IVb).—The procedure followed was that outlined for the ethyl analog. The epoxide IVb was obtained in 50% yield and its two components, A′ and B′ (lower retention time and higher retention time components, respectively), present in a 1:1.8 ratio, were separated on a 3-ft. 20% DEGS-on-Chromosorb W column at 150° (helium flow rate, *ca.* 150 cc./min.): component A′, $[\alpha]^{25}D$ −83° (*c* 1.15, chloroform), C-1 proton chemical shift τ 5.25 ($J_{12} \cong 0$); component B′, $[\alpha]^{25}D$ +73.3° (*c* 0.81, chloroform), C-1 proton chemical shift τ 5.09 (J_{12} = 2.5 c.p.s.).

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found for A′: C, 58.58; H, 8.75. Found for B′: C, 58.44; H, 8.61.

Reaction of 2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IVa) with Dimethylamine.—A solution of 0.46 g. (0.003 mole) of IVa in 10 ml. of saturated aqueous dimethylamine was heated at 75–80° for 18 hr. The colorless reaction mixture was diluted with water, thoroughly extracted with chloroform, and the chloroform extracts were dried and evaporated. The residue obtained was distilled to yield 0.4 g. (66%) of a colorless liquid, b.p. 85–90° (bath temperature) at 0.3 mm. The 3000–2700- and 1500–1000-cm.$^{-1}$ regions of its infrared spectrum were essentially identical with that of authentic ethyl desosaminide; the 1000–600-cm.$^{-1}$ region in the two were, however, different.

Anal. Calcd. for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.81; H, 10.18; N, 6.76.

Hydrolysis of the Product Obtained from IVa and Dimethylamine. Periodic Acid Titration of the Hydrolysate.—A solution of 0.29 g. (0.0014 mole) of the dimethylamino alcohol in 2 ml. of 2 *N* hydrochloric acid was heated on the steam bath for 20 min.[9] and evaporated to dryness at room temperature (high vacuum pump, Dry Ice-cooled rotary trap). The residue was evacuated (under high vacuum) over potassium hydroxide for 2 hr. at room temperature, triturated with anhydrous ether, and then evacuated (high vacuum) over potassium hydroxide at room temperature for 3 days to yield 0.31 g. of a colorless glass. Approximately 0.275 g. of this material was dissolved in a small amount of ethanol and ether was added until the solution became turbid. After standing overnight at −10°, a colorless solid separated accompanied by an oil. The oily substance was dissolved by the addition of a small amount of acetone, and, after an additional 4 hr. at −10°, the solid was collected and dried *in vacuo* at 100° for 5 hr., yielding 13 mg. (*ca.* 5%), m.p. 178–179° dec.; mixture melting point with an authentic specimen of desosamine hydrochloride (recrystallized from ether–ethanol–acetone, m.p. 178–179° dec.) was 175.5–178° dec.; $[\alpha]^{25}D$, authentic desosamine hydrochloride, +61.5° (*c* 1.32, ethanol); $[\alpha]^{25}D$, "synthetic" desosamine hydrochloride, +63.7° (*c* 0.66, ethanol).

The hydrolysate (17.0 mg., 8.1 × 10^{-5} mole) obtained was dissolved in 1 ml. of 0.5 *M* sodium periodate solution (pH of reaction mixture *ca.* 4) and four 50-λ aliquots were assayed by titration with 0.02 *N* arsenious oxide[38] at the intervals indicated in Table I.

TABLE I

Time	15 min.	150 min.	4 days
As_2O_3 consumed by blank (av. value), ml.	2.410		2.405
As_2O_3 consumed by sample (av. value), ml.	2.150	2.177	1.987
Moles of IO_4^-/mole of compound consumed	0.64	0.57	1.03

Since desosamine hydrochloride is reported[36] to consume 2 molar equiv. of periodate in weakly acidic solution, the first rapidly and the second slowly, the consumption of a total of 1 molar equiv. of periodate by the hydrolysate would appear to indicate that the 2-dimethylamino sugar component is unaffected under the conditions employed, perhaps owing to the formation of an unreactive 1,3-cyclic periodic acid ester.

1,2-O-Trichloroethylidene Desosaminide.—To a suspension of 1.0 g. (0.0047 mole) of desosamine hydrochloride in 10 ml. of chloral was added 2 ml. of concentrated sulfuric acid. In quick succession the desosamine hydrochloride dissolved, the solution became turbid, then cleared. After stirring for 4.5 hr., the excess chloral was removed under reduced pressure at *ca.* 35°, and the residue was partitioned between methylene chloride and 2 *N* sodium hydroxide solution. The methylene chloride extracts were washed, dried, and evaporated to yield 1.2 g. (84%) of the trichloroethylidene derivative as a pale yellow, fairly viscous liquid which slowly solidified on standing. The compound was purified by evaporative distillation, two fractions being collected. The first distilled at 50–65° (0.005 mm.), and the second at 65–75° (0.005 mm.). Both fractions solidified on the cold finger of the molecular still (it was necessary to interrupt the distillation to collect the first fraction). The first melted at 49–57° (softening at *ca.* 44°) and the second at 53–61° (softening at *ca.* 44°). (The infrared spectra of the two fractions were virtually identical.) A sample of the second fraction was submitted for analysis.

Anal. Calcd. for $C_{10}H_{16}Cl_3NO_3$: C, 39.43; H, 5.30; Cl, 34.92; N, 4.60. Found: C, 39.26; H, 5.19; Cl, 35.03; N, 4.57.

Reduction of the reaction time to 1 hr. gave the trichloroethylidene derivative in 70% yield.

Methiodide was prepared by treating a solution of the trichloroethylidene derivative in acetone with excess methyl iodide for 0.5 hr. at room temperature. The solid, m.p. 218–224° dec., obtained by evaporating the acetone and excess methyl iodide, was purified by heating in boiling acetone, cooling, and filtering. The solid obtained melted at 231–237° dec.

Anal. Calcd. for $C_{11}H_{19}Cl_3INO_3$: C, 29.58; H, 4.29; N, 3.14. Found: C, 29.78; H, 4.23; N, 2.99.

Methanolysis of 1,2-O-Trichloroethylidene Desosaminide.—A solution of 1.05 g. (0.0034 mole) of the trichloroethylidene derivative in saturated methanolic hydrogen chloride was heated under reflux for 19 hr. and the excess solvent was removed *in vacuo*. The residue was taken up in water and the aqueous solution was washed with methylene chloride, made basic (pH 12–13) with 2 *N* sodium hydroxide solution, and extracted with methylene chloride. The methylene chloride extracts were washed, dried, and evaporated to yield 0.55 g. (85%) of product identical with methyl desosaminide as indicated by comparison of its infrared spectrum and that of its methiodide with those of authentic specimens.

When the reflux time was reduced to 2.5 hr., only partial conversion to methyl desosaminide was observed (infrared analysis).

Attempted Room Temperature Hydrolysis of 1,2-Trichloroethylidene Desosaminide.—The optical rotation of a 1% solution of the trichloroethylidene derivative in 6 *N* hydrochloric acid was unchanged after 20 hr. at room temperature.

Reaction of 2-Methoxy-3,4-epoxy-6-methyltetrahydropyran (IVb) with Dimethylamine Followed by Hydrolysis.—A solution of 0.32 g. (0.002 mole) of IVb in 8 ml. of saturated aqueous dimethylamine was kept at room temperature for 26 hr. and evaporated under reduced pressure. A colorless, basic liquid residue (0.23 g., 53%) was obtained which was hydrolyzed directly with 2 ml. of 2 *N* hydrochloric acid on a steam bath for 20 min.[9] Evaporation of the aqueous solution to dryness *in vacuo* left a colorless residue which was kept under high vacuum over potassium hydroxide at room temperature for 48 hr. to yield 0.25 g. of a colorless glass. The material rapidly (within 30 min.) consumed roughly 0.5 molar equiv. of periodate, in reasonably good agreement with previous results (see above).

Reaction of the Hydrolysate with Chloral.—A suspension of 0.184 g. (8.7 × 10^{-4} mole) of the hydrolysate obtained in the previous experiment in 2 ml. of chloral was treated with 0.4 ml. of concentrated sulfuric acid. After stirring the reaction mixture for 1 hr., it was worked up as described under "1,2-O-Trichloroethylidene Desosaminide." The 0.16 g. of crude liquid product obtained was converted to its methiodide, m.p. 237–240° dec., as described for 1,2-O-trichloroethylidene desosaminide. The methiodides of both authentic and "synthetic" trichloroethylidene desosaminide were recrystallized by partially dissolving in hot acetone, cooling, and permitting most of the acetone to evaporate slowly at room temperature. The infrared spectra of the two were identical.

1,1-Diethoxy-5-hydroxyhexyne-2 (VI).—To a stirred solution of 97.9 g. (0.76 mole) of propiolaldehyde diethyl acetal[17] in 1.5 l. of anhydrous ether under nitrogen was added, rapidly, 487 ml. (0.75 mole) of a 1.6 *M* solution of *n*-butyllithium in hexane (Mineral Foote Co.). The addition of roughly the last 60 ml. of the butyllithium solution was accompanied by an abrupt color change in the reaction mixture from orange to dark brown. After stirring and heating under reflux for 1.25 hr., 87 g. (1.5 moles) of commercial grade propylene oxide was added rapidly

(38) H. Willard and L. Greathouse, *J. Am. Chem. Soc.*, **60**, 2869 (1938).

followed by an additional 100 ml. of anhydrous ether, and stirring and refluxing under nitrogen was continued for 16 hr. The cooled reaction mixture was washed with water until neutral (three washings), dried, and evaporated to yield 114 g. of a dark brown liquid which was distilled *in vacuo*. After a 1.6-g. forerun, 89 g. (61%) of 1,1-diethoxy-5-hydroxyhexyne-2 was collected, b.p. 84–86° (0.1–0.2 mm.), $n^{25}D$ −1.4493. The analytical sample had b.p. 95–96° (0.5 mm.), $n^{25}D$ −1.4531, ν_{max}^{film} 2.80 (m) and 4.97 μ (w).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.40; H, 9.94.

1,1-Diethoxy-5-hydroxyhexene-2 (VIII).—A solution of 5 g. (0.027 mole) of 1,1-diethoxy-5-hydroxyhexyne-2 in 50 ml. of hexane was hydrogenated over 0.5 g. of 10% palladium on charcoal in a Parr apparatus (initial pressure, 17 p.s.i.) until a molar equivalent of hydrogen (*ca.* 2.5 p.s.i.) was consumed (5 min., the reaction was moderately exothermic). The catalyst was removed by filtration and the hexane filtrate was evaporated to yield a 4.8-g. liquid residue which was distilled *in vacuo* to give 4.1 g. (80%) of 1,1-diethoxy-5-hydroxyhexene-2, b.p. 58–65° (0.2 mm.). The analytical sample had b.p. 60–62° (0.1 mm.), $n^{25}D$ −1.4572, ν_{max}^{film} 2.8 and 6.01 μ.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.93; H, 10.86.

The reduction was also effected using Lindlar catalyst.[39] However, both catalysts behaved erratically, the product of the reduction being, in some cases, the cyclic olefin, 2-ethoxy-6-methyl-5,6-dihydro-2H-pyran (VII). This is attributed to the fortuitous presence of traces of acid in the system. Indeed, when the reduction was conducted in the presence of a trace of quinoline (the catalyst actually used in those experiments was the Lindlar catalyst; however, it is felt that 10% palladium on charcoal would behave similarly), the acyclic olefin VIII was obtained consistently.

2-Ethoxy-6-methyl-5,6-dihydro-2H-pyran (VII). A.—A cooled solution (the reduction was moderately exothermic) of 14.2 g. (0.076 mole) of 1,1-diethoxy-5-hydroxyhexyne-2 in 80 ml. of hexane was hydrogenated over 1.4 g. of palladium on charcoal in a Parr apparatus (initial pressure, 10 p.s.i.) until a molar equivalent of hydrogen (*ca.* 7 p.s.i.) was consumed (30 min.). After shaking for an additional 15 min. (the pressure gage had dropped to zero by this time), 5 drops (Pasteur pipet) of concentrated hydrochloric acid was added and shaking was continued for 0.75 hr. The catalyst was removed by filtration, the filtrate was evaporated, and the yellow liquid residue was rapidly distilled at 25–30° (0.2 mm.), the distillate (4.2 g.) being collected in a Dry Ice-cooled receiver. This procedure was repeated with five 14.2-g. samples of 1,1-diethoxy-5-hydroxyhexyne-2, the yields of crude, colorless distillate ranging between 39 and 54%. The combined distillates were redistilled *in vacuo* (foaming), three fractions being collected: fraction 1 (0.25 g.), b.p. 25–72° (40 mm.), $n^{25}D$ −1.4321; fraction 2 (22 g.), b.p. 72–76° (40 mm.), $n^{25}D$ −1.4321; and fraction 3 (2.6 g.), b.p. 76–81° (40 mm.), $n^{25}D$ −1.4338. Fraction 1 was discarded. Fractions 2 and 3 represented a combined yield of 39%; their infrared spectra were practically identical.

The vapor phase chromatogram of fraction 2 on a 3-ft. 20% DEGS-on-Chromosorb W column at 65° (injection port temperature, 50°) with helium as the carrier gas showed a single broad peak accounting for *ca.* 85% of the total material in the chromatogram along with four other minor components. Conduction of the vapor chromatography at higher column and injection port temperatures (135 and 120°, respectively) resulted in decomposition (probably partial) of the compound.

Anal. of fraction 2. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 68.12; H, 10.22.

The major component in the vapor chromatogram of fraction 2 was collected (rechromatography indicated it to be ≥95% pure) and submitted for analysis (Found: C, 67.80; H, 10.50).

A still more acceptable analysis was obtained on a sample of VII, b.p. 71–74° (37 mm.), $n^{25}D$ −1.4348, prepared by the same procedure in another experiment (Found: C, 67.45; H, 10.06). The infrared spectra of the three analytical samples were essentially identical.

In one experiment, the cyclic olefin VII was obtained directly from the hydrogenation of VI (35.8 g., 0.19 mole) over 10% palladium on charcoal (3.5 g.), although no acid was added to effect ring closure. The crude product obtained in this experiment was separated into two fractions by distillation *in vacuo*, the first, b.p. 57–61° (17 mm.), 11.6 g., and the second, b.p. 25–30° (0.5 mm.), 3.3 g. The infrared spectra of the two were practically identical.

B.—To a solution of 2.5 g. (0.02 mole) of benzoic acid in 50 ml. of chloroform over magnesium sulfate (the solvent was kept over the drying agent for 1.5 days prior to use) was added 15 g. (0.08 mole) of 1,1-diethoxy-5-hydroxyhexene-2. After 25 hr. at room temperature, the magnesium sulfate was removed by filtration and more chloroform added; the solution was washed twice with dilute sodium hydroxide solution, dried, and evaporated. The yellow liquid residue was distilled *in vacuo* (foaming) to yield 6.25 g. (56%) of VII, b.p. 54–58° (17 mm.). The infrared spectrum of the material obtained was essentially identical with that prepared by the catalyst–hydrochloric acid cyclization method A.

2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IX). A. Peracid Oxidation of VII.—A solution of 2.1 g. (0.015 mole) of VII in 50 ml. of 0.61 *M* perbenzoic acid[40] (0.03 mole) in benzene (93% peracid) was kept at room temperature for 8 days. The essentially colorless reaction mixture was poured into methylene chloride and the excess peracid was removed by washing with 2 *N* sodium hydroxide solution (two washings). The organic phase was washed with saturated salt solution, dried, and evaporated to yield a colorless liquid residue which was distilled *in vacuo* to give 2.1 g. (90%) of IX as a colorless liquid, b.p. 77–78° (7 mm.), $n^{25}D$ −1.4390.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.63; H, 8.87.

With another preparation of perbenzoic acid (0.54 *M*, 84% peracid), VII was converted to IX in 2 days, at room temperature, in 56% yield.

Using *m*-chloroperbenzoic acid (FMC Corp.), VII was converted to IX in 2 days and 8 days at room temperature in yields (crude) of 68 and 77%, respectively. The composition of IX obtained with both peracids was the same.

The vapor chromatogram of the epoxide IX (3-ft. 20% DEGS-on-Chromosorb W column at 150°; injection port temperature, 150°; carrier gas, helium at *ca.* 150 cc./min.) indicated it to be a mixture of three components, A, B, and C (in order of increasing retention times between roughly 1–2 min.). The ratio of A to B varied between 1:30 and 1:5 in various preparations of IX using different preparations of VII obtained by either method A or B. In the case of IX obtained from fraction 2 of VII prepared by reduction of VI *without* the addition of acid (see above), the A–B ratio was inordinately low, being 1:1.5. The B–C ratio, on the other hand, varied between 3.5:1 and 2.5:1 (the B–C ratio in the case in which A–B was 1:1.5, was 2.5:1).[20]

The three components were separated and collected by vapor chromatography (column and conditions employed were essentially the same as for analysis). The infrared spectra of components A and C were identical with the β- and α-anomers, respectively, of epoxide IVa.

B. Reaction of VII with Acetyl Hypobromite Followed by Base.—To an acetyl hypobromite solution prepared by adding 0.18 ml. (0.0035 mole) of bromine to a stirred, cooled (0 to 2°) suspension of 0.66 g. (0.004 mole) of silver acetate in 10 ml. of carbon tetrachloride and stirring for an additional 10 min., was added a solution of 0.5 g. (0.0035 mole) of VII (fraction 2 of the material obtained from the palladium-on-charcoal reduction of VI *without* added acid, see above)[41] in *ca.* 2 ml. of carbon tetrachloride dropwise with stirring at 0–3° (reaction was exothermic). After the addition was complete, the reaction mixture was stirred at 0° for 15 min. and then permitted to warm to room temperature with stirring (*ca.* 15 min.). (A reaction mixture color change from yellow-orange to light yellow accompanied the addition of VII.) The silver salts were removed by filtration and the filtrate was poured into methylene chloride. The organic solution was washed with dilute sodium bisulfite solution and water, dried,

(39) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(40) L. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1336 (1962). The yield of perbenzoic acid reported could not be reproduced using the quoted ratio of peroxide to benzoic acid, but was obtained when the ratio was increased to 3:1 (see Table II, *loc. cit.*).

(41) This particular sample is singled out, since, as already noted, its epoxidation with peracid gave an exceptionally large amount of component A relative to that obtained in other preparations of VII, thus indicating it to be inordinately rich in *cis*[18] isomer. It would, therefore, be expected that the fourth possible epoxide, which would be isomeric with component A with respect to the configuration of the oxide ring, would also be formed in relatively large amount, since it too must necessarily arise from *cis* VII.

and evaporated. A colorless liquid residue (0.9 g.) was obtained which showed strong carbonyl absorption at 5.72 μ in the infrared.

The analytical sample of the acetoxy bromide prepared in a similar manner using a sample of VII from another preparation had b.p. 78° (0.2 mm.), $n^{25}D$ −1.4662.

Anal. Calcd. for $C_{10}H_{17}BrO_4$: C, 42.72; H, 6.01; Br, 28.43. Found: C, 42.70; H, 6.08; Br, 28.43.

Treatment of the 0.9 g. of crude acetoxy bromide obtained with 5 ml. of 5% methanolic potassium hydroxide at room temperature for 1.83 hr., followed by pouring the reaction mixture into methylene chloride, washing the organic solution with saturated salt, drying, and evaporating, yielded a 0.35-g. yellow liquid residue. Its infrared spectrum showed no carbonyl absorption and its vapor phase chromatogram on a 3-ft. 20% DEGS-on-Chromosorb W column at 150° (injection port temperature, 150°; helium flow rate, *ca.* 150 cc./min.) showed four peaks between roughly 1–2 min. (The amount of material in this region represented 35–40% of the total material in the chromatogram, the rest being of higher (≥3 min.) retention times. The two major peaks (≥90%), present in roughly equal amounts at retention times 0.95 and 1.6 min., corresponded to components A and C, respectively, of epoxide mixture IX obtained by method A, as indicated by comparison of their respective retention times and infrared spectra. Of the two minor components also present in roughly equal amounts, one, at retention time 1.2 min., was identical (infrared spectrum, v.p.c. retention time) with component B of IX obtained by method A, while the second, at retention time 2.0 min., component D, was not observed in any of the preparations of IX by method A.

The crude product (100 mg.) obtained from the room temperature base treatment was heated under reflux in 2 ml. of 2% methanolic potassium hydroxide, and the reaction mixture was worked up as already described. The vapor chromatogram of the product (70–75% of which consisted of the four epoxides) now showed greatly enhanced intensity in the peaks corresponding to components B and D, all four, A, B, C, and D, now being present in roughly equal amounts. The increase in intensity of the B and D component peaks was accompanied by the essential disappearance of a peak at retention time 5.2 min. present in the product from the room temperature base treatment, which presumably corresponds to the bromohydrin precursors of B and D.

Component D was collected (column and conditions used were the same as for analysis except that the column temperature was decreased to 125°) and its infrared spectrum was measured. As indicated by its infrared spectrum, component D is very largely an epoxide (ν_{max}^{neat} 2974 cm.$^{-1}$, strong). The broad absorption observed in the hydroxyl region is due, in large part, to water as indicated by the considerable reduction in the intensity of this absorption when the spectrum was measured with compensation for water. However, there is also some hydroxyl-containing material (compensated spectrum still showed absorption in this region) which is perhaps due to product resulting from ring opening of the epoxide mixture with methoxide.

Because of the paucity of material, component D was analyzed as part of a 1:1 mixture of components C and D collected as one fraction.

Anal. Calcd. for $C_8H_{14}O_3 \cdot 0.5H_2O$: C, 57.63; H, 9.03. Found: C, 56.82; H, 8.92.

Since its infrared spectrum and analytical data (Found: C, 60.35; H, 8.98. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92.) indicate no water to be associated with the previously isolated component C, it would appear reasonable to assume that the water indicated to be present in the 1:1 C–D mixture is associated with D, the analytical data being in reasonable accord with a monohydrate formulation.

Samples of VII from other preparations behaved similarly towards acetyl hypobromite followed by base, except that, in accord with expectation based on the epoxidation of these samples with peracid, components A and D constituted less than 10% of the epoxide mixture.

When fraction 1 of the material obtained from palladium-on-charcoal reduction of VI *without* added acid (see above) was treated with acetyl hypobromite in a similar manner followed by heating the resulting acetoxy bromide with excess 5% methanolic potassium hydroxide (it has been established that none of the four component epoxides is preferentially destroyed by refluxing 5% methanolic potassium hydroxide), the vapor chromatogram of the epoxide mixture obtained in 40% yield showed only *three* components in roughly equal amounts corresponding to A, B, and C. This was the experiment previously reported[6] by us; we have no explanation for this result.

Attempted Reaction of IX with Glacial Acetic Acid at Room Temperature.—A solution of 100 mg. of IX (obtained by peracid oxidation) in 0.5 ml. of glacial acetic acid was kept at room temperature for 72 hr. and poured into cold 2 *N* sodium hydroxide solution. Extraction with methylene chloride and drying and evaporating the extracts yielded a 100-mg. colorless liquid residue whose infrared spectrum and vapor phase chromatogram were identical with those of starting IX.

Reaction of 2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IX) with Dimethylamine.—A solution of 1.85 g. (0.012 mole) of epoxide IX prepared by method A in 15 ml. of saturated aqueous dimethylamine was kept at room temperature for 27 hr. and evaporated. The pale yellow liquid residue (1.7 g.) was distilled *in vacuo* to yield 1.4 g. (58%) of a colorless, basic liquid, b.p. 60–67° (0.1 mm.). The product remained liquid even after 18 hr. at room temperature; however, crystallization was induced by cooling in Dry Ice for *ca.* 5 min. The resulting oily crystalline mass was recrystallized from petroleum ether (b.p. 30–60°, the petroleum ether solution was cooled in Dry Ice for *ca.* 2 min. to induce crystallization). The solid collected melted at 42.5–45.5° after subjection to high vacuum pumping at room temperature for 2 hr.

Anal. Calcd. for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.90; H, 10.29; N, 6.89.

Evaporation of the petroleum ether mother liquor left a 0.56-g. basic liquid residue.

Hydrolysis of the Product Obtained from IX and Dimethylamine. Periodic Titration of the Hydrolysate.—A solution of 0.225 g. (0.0011 mole) of the amino alcohol in 2 ml. of 2N hydrochloric acid was heated under reflux for 30 min., evaporated to dryness, and the resulting nearly colorless sirup was subjected to high vacuum pumping over potassium hydroxide for 2 days at room temperature. The periodic acid uptake of this material was determined by titrating 50-λ aliquots of a 1-ml. solution of 22.7 mg. of the compound in 0.5 *M* sodium periodate solution (pH of reaction mixture *ca.* 2) with 0.02 *N* arsenious oxide[38] at the intervals indicated in Table II.

TABLE II

	Blank	Sample after 20 min.	Sample after 90 min.
0.02 *N* As_2O_3 consumed (av. of 3 detn.), ml.	2.330	1.807	1.761
Moles of IO_4^-/mole of compound consumed		0.98	1.07

The material isolated from the petroleum ether mother liquor was similarly hydrolyzed and the hydrolysate was assayed for 3-amino sugar content; 73% was present.

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Nucleosides. XX. 1-α-D-Ribofuranosylthymine[1]

JIŘÍ FARKAŠ, LOUIS KAPLAN, AND JACK J. FOX

The Divisions of Nucleoprotein Chemistry and Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division Graduate School of Medical Sciences, Cornell University Medical College, New York 21, New York

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"5-Methyluridine" prepared a decade ago by the Hilbert–Johnson procedure is now characterized as 1-α-D-ribofuranosylthymine (II). It is demonstrated that the Hilbert–Johnson reaction yields the known 1-β-D-ribofuranosylthymine (the true 5-methyluridine, I) as well as its α-anomer, II. A long-reported "5-methylcytidine" originating from the same procedure is most probably the α-anomer of true 5-methylcytidine, the latter prepared from I. The failure of these anomeric 1-D-ribofuranosylthymines and 5-methylcytosines to obey Hudson's Rules of isorotation shows that optical rotation cannot be used to assign configuration to anomers of pyrimidine nucleosides *in general*. The glycosyl linkage of the β-anomer (I) is cleaved by the pyrimidine phosphorylase of *Bacillus subtilis* 16; the α-anomer (II) is not cleaved by this enzyme.

5-Methyluridine (I, 1-β-D-ribofuranosylthymine) was synthesized by the Mercuri procedure[2] and shown to possess the β-configuration by its conversion to spongothymidine (1-β-D-arabinofuranosylthymine) *via* a 2,2′-anhydronucleoside intermediate.[3] Another "5-methyluridine" (II) was reported previously by Roberts and Visser[4] by use of the Hilbert–Johnson procedure.[5] Studies on both nucleosides[2] showed that II differed from I in melting point, mixture melting point, and optical rotation. Both I and II exhibited thymidine-like spectra. Both nucleosides, when treated with metaperiodate, consumed one mole of oxidant per mole rapidly without the liberation of formic acid, a behavior consistent with a furanosyl sugar moiety containing the α-*cis* glycol grouping. However, the optical rotations of the dialdehyde solution obtained from metaperiodate oxidation of I and II were different. These data suggested[2] that the Roberts–Visser "5-methyluridine" might be the α-anomer of I; But, since the rotation of II was more levorotatory than that for authentic 5-methyluridine (I) (Hudson's Rule of isorotation would require the β-anomer to be more levorotatory), the Roberts–Visser nucleoside (II) remained uncharacterized.[2,5]

On the basis of reported[6] optical rotations of several pairs of anomeric 1-(2′-deoxy-D-ribofuranosyl)pyrimidines, Fox and co-workers concluded[7,8] that assignment of configuration to pyrimidine 2′-deoxynucleosides on the basis of optical rotation *alone* was certainly unwarranted. Recent studies[9] with some of these anomeric pairs of pyrimidine 2′-deoxynucleosides with n.m.r. spectra and optical rotary dispersion measurements supported that conclusion.

If this behavior of pyrimidine 2′-deoxynucleosides is equally applicable to pyrimidine ribonucleosides, then "5-methyluridine" (II) might be the α-anomer of I. If so, it is surprising that *only* this anomer (obtained in low yield) was isolated by Roberts and Visser from their reaction, especially since Naito and Kawakami[10] recently isolated anomeric 1-D-ribopyranosylthymines in a similar Hilbert–Johnson-type condensation. Moreover, the "*trans* rule"[12,13] would require that, in the Hilbert–Johnson reaction with poly-*O*-acylglycosyl halides, the C-1,C-2 *trans* anomer should be the predominant (if not the sole) product when sugars bearing a 2-acyloxy function are employed. We therefore reinvestigated the Roberts–Visser preparation of "5-methyluridine."

Tri-*O*-acetyl-D-ribofuranosyl bromide was prepared from tetra-*O*-acetyl-β-D-ribofuranose[14] by the method of Zinner[15] and was condensed with 2,4-diethoxy-5-methylpyrimidine in anhydrous benzene at room temperature for three days. The crude condensate was subjected to acid hydrolysis. A mixture of only two nucleosides was obtained in 45% yield from which pure anomers were obtained by fractional crystallization. One of these ($[\alpha]_D$ −8°) was identical with 1-β-D-ribofuranosylthymine (I)[2] prepared by the Mercuri procedure. The other component ($[\alpha]_D$ −50°) showed properties similar to "5-methyluridine" (II)[4] and also gave elemental analyses consistent with a pentosylthymine.

The assignment of the α-configuration to the $[\alpha]_D$ −50° isomer (II) rests on the following data. II exhibits an ultraviolet absorption spectrum similar to I to show that II is an N-1-substituted pyrimidine. Both I and II consume one mole of metaperiodate per mole *rapidly* and do not liberate formic acid in this process. II is therefore a furanosyl derivative containing the α-*cis* glycol grouping. The rotation of the solution from periodate oxidation of II (−25°) differed from that resulting from I (+16°). These data exclude all 1-β-D-pentofuranosyl- and all 1-D-pentopyranosylthymines as possible structures for II. The rapid

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 03190-07 and CA 03192-07).

(2) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(3) J. J. Fox, N. Yung, and A. Bendich, *ibid.*, **79**, 2775 (1957).

(4) M. Roberts and D. W. Visser, *ibid.*, **74**, 668 (1952).

(5) See J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959), for a general review of the Hilbert-Johnson and Mercuri procedures for pyrimidine nucleoside syntheses.

(6) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959).

(7) See ref. 5, p. 340.

(8) J. J. Fox, N. C. Yung, I. Wempen, and M. Hoffer, *J. Am. Chem. Soc.*, **83**, 4066 (1961).

(9) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961).

(10) (a) T. Naito and T. Kawakami, *Chem. Pharm. Bull.* (Tokyo), **10**, 627 (1962). (b) These authors observed that the optical rotations of these anomers (as well as anomeric 1-D-xylopyranosylthymines prepared by an alternate route) did not obey Hudson's isorotation rules. However, their configurational assignments to those glycopyranosyl nucleoside anomers rests, in the final analysis, on the assignment of the β-configuration to the 1-D-xylopyranosylthymine prepared[2,11] by both the Mercuri and Hilbert-Johnson procedures. This latter assignment is derived from the "*trans* rule."[12,13] Though this assignment is probably correct, it is not to be considered as rigorously established.

(11) J. J. Fox and I. Goodman, *J. Am. Chem. Soc.*, **73**, 3256 (1951).

(12) B. R. Baker in Ciba Foundation Symposium, Chemistry and Biology of Purines, 1957, p. 120.

(13) For application of the *trans* rule[12] to the Hilbert-Johnson reaction, see ref. 5, p. 336.

(14) G. B. Brown, J. A. Davoll, and B. A. Lowy, *Biochem. Prep.*, **4**, 70 (1955). The authors are indebted to Dr. G. B. Brown for a generous supply of tetra-*O*-acetyl-D-ribofuranose.

(15) H. Zinner, *Chem. Ber.*, **83**, 153 (1950).

uptake of metaperiodate excludes the arabino- and xylofuranosylthymines. Thus, we are left with 1-α-D-ribofuranosyl- or 1-α-D-lyxofuranosylthymine as possibilities for the structure of II. The likelihood of II being the α-lyxo isomer[16] is indeed remote. Moreover, the paper electrophoretic behavior (borate buffer, pH 6) of I (+5.6 cm.) and II (+5.5 cm.) are almost identical. 1-β-D-Lyxofuranosylthymine[17] has a much higher mobility in this system (+7.8 cm.); a similar relationship is obtained when uridine is compared electrophoretically to its 1-β-D-lyxouracil isomer.[18] Finally, both I and II and *no other nucleosides* were found in the same reaction. It is concluded, therefore, that II is 1-α-D-ribofuranosylthymine.

A purified extract of *B. subtilis* 16 (a pyrimidine-requiring strain) containing pyrimidine nucleoside phosphorylase was incubated with either pure II or pure I. No detectable glycosyl cleavage (formation of thymine) of the α-anomer was observed, whereas the β-anomer under the same conditions underwent ~55% cleavage to form thymine. When pure samples of I and II were mixed (1:1) and treated similarly with this enzymatic extract, no inhibition of glycosyl cleavage of the β-nucleoside by the presence of the α-anomer was detected.

That the α-anomer is resistant to glycosyl cleavage by nucleoside phosphorylases is expected. Lampen[19] demonstrated a decade ago that the Roberts–Visser material (II) was resistant to nucleosidase preparations from *E. coli*, whereas 1-β-D-ribofuranosylthymine (I) was cleaved by extracts of *L. pentosus*, as well as *E. coli* B.[17]

General Considerations.—These findings indicate that, as far as the Hilbert–Johnson condensation procedure with ribofuranosyl halide is concerned, the "*trans* rule" is not wholly operative. The results of Naito and Kawakami[10a] with poly-*O*-acylribo- and -ylopyranosyl halides also show this limitation of the "*trans* rule" because they also obtained mixtures of anomeric nucleosides by the Hilbert–Johnson method.

Roberts and Visser[4] also prepared a "5-methylcytidine" by treatment of their condensate obtained from the Hilbert–Johnson reaction with ammonia. (This condensate was also used by them for the synthesis of II.) This "5-methylcytidine" differed in melting point from 5-methylcytidine[20] prepared by the thiation process from 1-β-D-ribofuranosylthymine (I). On the basis of the studies with anomeric 1-D-ribofuranosylthymines reported here, it is more than likely that the Roberts–Visser "5-methylcytidine"[4] is 1-α-D-ribofuranosyl-5-methylcytosine. These anomers also fail to obey Hudson's Rules of isorotation. The α-anomer gives an $[\alpha]^{23}D$ −78 ± 5°,[21] whereas 1-β-D-ribofuranosyl-5-methylcytosine has a specific rotation of +14°.[20,22] Therefore, on the basis of the rotations of pyrimidine ribonucleosides reported here and previous studies on pyrimidine 2′-deoxyribonucleosides,[6-9] it is obvious that Hudson's Rules of isorotation cannot be employed to assign anomeric configurations to pyrimidine nucleosides in general.

Experimental[23]

Synthesis of 1-D-Ribofuranosylthymine Anomers.—Tetra-*O*-acetyl-β-D-ribofuranose[14] (15 g., 0.047 mole) was dissolved in dry ether saturated with hydrogen bromide at 0°. The flask was tightly stoppered and the solution was allowed to remain for 45 min. at 0°. The solvent was removed *in vacuo* (bath temperature 40°), the sirupy residue was dissolved in 30 ml. of dry benzene, and the solvent was again removed *in vacuo*. This procedure was repeated twice. The sirupy residue was dissolved in 50 ml. of dry benzene and treated with 9.1 g. (0.050 mole) of 2,4-diethoxy-5-methylpyrimidine. The solution was kept in a flask protected from moisture at room temperature for 3 days, then it was heated at ~60° for 9 hr. After concentration of the solution to a sirup *in vacuo*, the residue (23 g.) was dissolved in 150 ml. of dry methanol and treated with 50 ml. of a methanolic solution previously saturated at 0° with hydrogen chloride. After 12 hr. at 0°, the methanol was removed, and the residue was dissolved in 100 ml. of water. The solution was neutralized by portionwise addition with vigorous stirring of silver carbonate. The silver salts were removed by filtration, and the colorless filtrate was concentrated *in vacuo* (bath temperature 40°) to a sirup (10 g.). This sirup was dissolved in 30 ml. of methanol and an aliquot was used for further investigation.

This solution (5 ml., containing 1.65 g. of crude material) was placed on a cellulose column with *n*-butyl alcohol–ethanol–water (40:11:19).[24] The first eluates contained free pyrimidines (negative periodate test).[25] Later fractions showed ultraviolet absorption at 266 mμ and a positive periodate test. These latter fractions were combined and concentrated to dryness. Upon trituration with a small amount of ethanol, the sirupy residue crystallized (1.02 g.) and the mother liquor was discarded. This crystalline material contained ~90% nucleosides by spectrophotometric determination. The total yield of mixed nucleosides was 45%. The crude crystalline material was dissolved in 5 ml. of hot ethanol and placed in the cold for 2 days. Needles rich in the α-anomer were collected. After three recrystallizations of these needles from ethanol, 180 mg. of 1-α-D-ribofuranosylthymine was obtained, m.p. 175–176°, lit.[4] m.p. 175–177°, λ_{max} 268.5 mμ, $[\alpha]^{23}D$ −50° (*c* 1.28, water).

Anal. Calcd. for $C_{10}H_{14}N_2O_6$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.51; H, 5.24; N, 10.50.

The mother liquors after several days in the cold, deposited tiny spherical-shaped clusters which were almost pure β-anomer. After two recrystallizations of this material from ethanol, pure 1-β-D-ribofuranosylthymine (169 mg.) was obtained, m.p. 183–184°, lit.[2] m.p. 183–185°. A mixture melting point with authentic material[2] showed no depression, $[\alpha]^{23}D$ −8° (*c* 2.3, water), lit.[2] $[\alpha]D$ −10°.

Metaperiodate Oxidation Studies.—These studies were carried out in a manner similar to those already described.[2] The consumption of metaperiodate and the rotation of the dialdehyde solutions of these anomers were as follows.

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(16) The synthesis of 1-α-D-lyxofuranosylthymine is underway in our laboratories for use in an enzymatic study.

(17) J. J. Fox, J. F. Codington, N. C. Yung, L. Kaplan, and J. O. Lampen, Jr., *J. Am. Chem. Soc.*, **80**, 5155 (1958).

(18) J. F. Codington, R. Fecher, and J. J. Fox, *ibid.*, **82**, 2794 (1960).

(19) J. O. Lampen, "Phosphorus Metabolism," Vol. II, W. D. McElroy and B. Glass, Ed., The John Hopkins Press, Baltimore, Md., 1952, p. 368.

(20) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.*, **81**, 178 (1959).

(21) (*c* 0.05, distilled water) The authors are indebted to Dr. D. W. Visser for a sample of this compound and to Dr. David Fukushima for the determination of its optical rotation on a 1-mg. sample. Mrs. Naishun Miller kindly performed the metaperiodate oxidation of this small sample and found that it consumed one mole of oxidant per mole within three minutes. This consumption of oxidant remained constant over a two-hour period. This data supports a furanosyl structure. A 1-mg. sample of cytidine was used as a control in the metaperiodate study. The ultraviolet absorption spectrum of the Roberts–Visser "5-methylcytidine" at pH values of 1, 7, and 13 was almost identical with that reported[20] for true 5-methylcytidine, which shows that both nucleosides are 1-substituted 5-methylcytosines.

(22) (*c* 3.2, distilled water); lit.[19] $[\alpha]D$ −3° (*c* 2.5, 1.0 *N* NaOH).

(23) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(24) L. Hough and J. K. N. Jones, "Methods in Carbohydrate Chemistry," Vol. I, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, Inc., New York, N. Y., 1962, p. 21.

(25) J. A. Cifonelli and F. Smith, *Anal. Chem.*, **26**, 1132 (1954).

	Moles of IO_4^- consumed per mole		[α]D of dialdehyde produced
	2 hr.	12 hr.	
β-Anomer (I)	0.94	0.97	+16°
α-Anomer (II)	0.99	1.01	−25°

Chromatographic Studies.—In the ionophoretic system[26] requiring borate buffer, pH 6.2, 4 hr., 800 volts, the following migrations were obtained: for the α-anomer, +5.5 cm.; β-anomer, +5.6 cm.; and for 1-β-D-lyxofuranosylthymine, +7.8 cm. The chromatographic system[27] (ethyl acetate–acetic acid–water, 9:2:1, thin layer chromatography on Merck Silica Gel G.) without benzeneboronic acid present gave, for the α-anomer, R_f 0.60, and, for 5-methyluridine, R_f 0.59. The same system containing 0.5% benzeneboronic acid gave these R_f values: for the α-anomer, 0.86, and, for the β-anomer, 0.75.

Enzymatic Studies.—*Bacillus subtilis* 16, a pyrimidine-requiring organism,[28] was used as a source of pyrimidine nucleoside phosphorylase, since preliminary studies had indicated that extracts of this mutant contained substantial amounts of this enzyme. The organism was grown in the Biogen[29] in a chemically defined liquid medium[30] supplemented with 0.5 μmole per ml. of uracil. The cells were harvested at the end of the exponential phase of growth in a Sharples centrifuge and resuspended in 0.05 *M* phosphate–0.02 *M* cysteine hydrochloride buffer (pH 7.08); extracts were prepared by their disruption in a 10 KC Raytheon sonic oscillator. Purification of the enzyme was carried out according to the procedure of Tono and Cohen[31] to give a preparation purified 14-fold. This preparation was used for the experiments listed in Tables I–III.

A calibration curve relating the amount of thymine formed to the amount of 1-β-D-ribofuranosylthymine initially present in the incubation mixture was obtained. The results are shown in tabular form (Table II).

TABLE I

CLEAVAGE OF 1-D-RIBOFURANOSYLTHYMINES BY PURIFIED PYRIMIDINE NUCLEOSIDE PHOSPHORYLASE DERIVED FROM *B. subtilis* 16[a]

Time, min.	% thymine formed from β-Anomer	% thymine formed from α-Anomer
30	36	0
60	51	0
90	53	0
180	56	0

[a] Each incubation mixture contained 80 μmoles of phosphate buffer, pH 6.95, 12 μmoles of mercaptoethanol, 0.2 ml. of purified enzyme preparation, and 6.4 μmoles of the β-anomer or 19.2 μmoles of α-anomer in a total volume of 2.0 ml. Incubation was carried out at 36.2°; aliquots were removed at various time intervals and pipetted into 2.8 ml. of 0.1 *N* NaOH. The thymine present as a result of enzymic action was measured by following the change in optical density at 300 mμ, pH 13.

TABLE II

CLEAVAGE OF 1-β-D-RIBOFURANOSYLTHYMINE BY PURIFIED PYRIMIDINE NUCLEOSIDE PHOSPHORYLASE DERIVED FROM *B. subtilis* 16[a]

[A] 1-β-D-Ribofuranosylthymine, μmole/ml.	[B] Thymine formed, μmole/ml.	% cleavage, [B]/[A] × 100
1.0	0.42	42
2.0	0.80	40
3.0	1.14	38
4.0	1.47	37

[a] Each incubation mixture contained 80 μmoles of phosphate buffer, pH 6.95, 12 μmoles of mercaptoethanol, 0.2 ml. of purified enzyme preparation, and the amount of β-anomer as indicated in a total volume of 2.0 ml. Incubation was carried out at 36.2°; at the end of 180 min., the reaction was stopped and the amount of thymine present was determined by the change in optical density at 300 mμ, pH 13.

It is evident that a constant percentage of thymine is formed from the β-anomer irrespective of its initial concentration. Furthermore, the addition of various levels of the α-anomer to the reaction mixture did not affect the per cent cleavage of the β-anomer. These results are shown in Table III.

TABLE III

EFFECT OF 1-α-D-RIBOFURANOSYLTHYMINE UPON CLEAVAGE OF 1-β-D-RIBOFURANOSYLTHYMINE BY PURIFIED PYRIMIDINE NUCLEOSIDE PHOSPHORYLASE[a]

Anomeric mixture [A] β-anomer, μmole/ml	Anomeric mixture [B] α-anomer, μmole/ml.	Thymine formed, μmole/ml.	% thymine formed, [B]/[A] × 100
4.0	0	1.43	36
3.6	0.4	1.34	37
3.0	1.0	1.12	37

[a] Incubation conditions similar to those presented in Table II.

Acknowledgment.—The authors express their appreciation to Drs. George B. Brown and C. Chester Stock for their warm and continued interest.

(26) M. P. Gordon, D. M. Intrieri, and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 5161 (1958).

(27) E. J. Bourne, E. M. Lees, and H. Weigel, *J. Chromatog.*, **11**, 253 (1963).

(28) Obtained from Dr. R. Guthrie (Children's Hospital, Buffalo, N. Y.) who isolated and characterized this mutant with respect to its pyrimidine requirements.

(29) An instrument for the continuous cultivation of microorganisms (American Sterilizer Co.).

(30) R. E. Feeney, J. A. Garibaldi, and E. M. Humphreys, *Arch. Biochem.*, **17**, 435 (1948).

(31) H. Tono and S. S. Cohen, *J. Biol. Chem.*, **237**, 1271 (1962).

Synthesis of Higher Ketoses by Aldol Reactions. II. Unsubstituted Heptuloses

ROBERT SCHAFFER

Division of Physical Chemistry, National Bureau of Standards, Washington, D. C. 20234

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Unsubstituted D-erythrose undergoes a mixed aldol reaction with 1,3-dihydroxy-2-propanone to give D-*allo*-, D-*altro*-, and D-*gluco*-heptuloses in an over-all yield of 37%.

Work in this laboratory has shown that substituted higher ketoses[1] as well as branched-chain higher aldoses[2] are obtained by aldol reactions of carbohydrates that (a) are unable to form intramolecular hemiacetal linkages because of blocked γ- or δ-hydroxyl groups, and (b) are precluded from isomerizing to ketoses by substitution of the α-hydroxyl group. Recently, however, the aldol self-addition reaction of an *unsubstituted ring-forming* sugar (D-erythrose to D-*gluco*-L-*glycero*-3-octulose) was discovered,[3] and this indicated that a mixed aldol reaction of unsubstituted tetroses

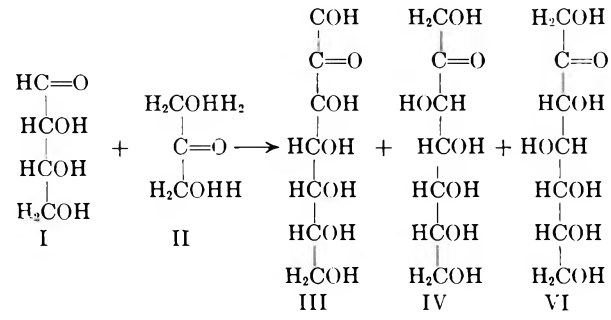
(1) R. Schaffer and H. S. Isbell, *J. Org. Chem.*, **27**, 3268 (1962).

(2) R. Schaffer, *J. Am. Chem. Soc.*, **81**, 542 (1959).

(3) R. Schaffer and A. Cohen, *J. Org. Chem.*, **28**, 1929 (1963).

with, for example, 1,3-dihydroxy-2-propanone should take place also, to give higher heptuloses. There was a suggestion of this in the literature, for in 1951 Hough and Jones[4] wrote in a review article concerning the biosynthesis of monosaccharides: "Mr. K. B. Taylor, working with us, has observed that D-erythrose and dihydroxyacetone on condensation in alkaline solution give a product which on the paper chromatogram behaves as a heptulose and shows the same colour reaction. We are now attempting the isolation of this sugar with the view of its conclusive identification." Since then, however, no details have appeared, and the authors have ceased further investigation of this subject.[5] The value of a synthesis that would make unsubstituted heptuloses readily accessible impelled a more thorough investigation of the reaction of D-erythrose (I) and 1,3-dihydroxy-2-propanone (II) at this time.

Polarimetric observation of a limewater solution of I and II showed that reaction occurred readily, and paper chromatography employing solvent mixture A (see Experimental) and an orcinol spray[6] revealed that two blue spots, characteristic of heptuloses, were form-



ing. These spots were preceded by one intensely gray spot and followed by one weakly gray-brown spot. The material responsible for the faster moving blue spot was found by chromatography to be composed of both D-*allo*-heptulose (III)[7] and D-*altro*-heptulose (IV).[8] To separate them, the mixture of the two heptuloses, eluted from a thick-paper chromatogram developed with solvent A, was rechromatographed with solvent mixture B. Compound III was then crystallized as a hydrate in 3.3% yield, and compound IV was separated, converted to its anhydride, and crystallized in 12% yield as 2,7-anhydro-β-D-*altro*-heptulopyranose hydrate (V).[8,9] From the material responsible for the slower moving blue spot, a 15.5% yield of D-*gluco*-heptulose (VI)[10] was isolated. The substance responsible for the intense gray color with the spray was the expected 4-(hydroxymethyl)-DL-*glycero*-pentulose ("dendroketose"),[1,11] the aldol self-addition product of II; the faintly colored, slowest moving ketose was D-*gluco*-L-*glycero*-3-octulose.[3] Column chromatography on cellulose of another sample of reaction mixture, using only solvent B as developer, led to the isolation of crystalline III in 3.3% yield, crystalline V in 11.7% yield, and crystalline VI in 21.7% yield. A small amount of the crystalline 3-octulose was also isolated. Thus, the preliminary observation of Hough, Jones, and Taylor that heptulose is obtained in the reaction of I and II has been verified, and the conclusive identification of three heptulose products has been made.

The proportions of mixed aldol products isolated are interesting. As in the ethylideneheptulose synthesis,[1] the heptuloses having a *threo* configuration at C-3 and C-4 (the positions where the new carbon-to-carbon bond was made) are the main products, and only one of the two potential products with an *erythro* configuration at those carbon atoms was isolated; however, in the new work it is D-*allo*-heptulose, whereas, in the older it is 4,6-*O*-ethylidene-D-*manno*-heptulose that was isolated. That D-*manno*-heptulose is absent from, or present to only a small extent in, the present study was evident from the lack of the greenish coloration that this heptulose characteristically develops with the orcinol spray; also, none could be induced to crystallize by seeding the mother liquors of the D-*gluco*-heptulose crystallizations, where the *manno* compound would have been expected from its chromatographic behavior. The predominance in both heptulose syntheses of products having the *threo* configuration shows that there is only a secondary influence exerted on the course of the reaction by the conformationally restricting acetal substituent. It is, however, significant that the absence of this substituent results in the production of D-*allo*-heptulose, an otherwise difficultly accessible ketose. Although its yield is low, the simplicity of synthesis by this method makes it now relatively easily available.

This clear evidence of aldol reactivity of unsubstituted tetroses raises the possibility that some higher ring-forming sugars may also be found that will participate in aldol reactions; although, at present, out of the many investigations of the reactions of sugars with alkali, the only recorded information that might be interpreted as evidence of this reactivity is the isolation of an incompletely characterized unbranched dodecitol, a by-product in the manufacture of hexitols by alkaline electroreduction of D-glucose.[12]

Experimental

Thick-paper chromatography was performed with Whatman seed-test paper by the descending method. Paper column chromatography was carried out using a Chro-Max Pressure Mantle, Type 3504.[13] The solvent systems employed for chromatography were: solvent A, 1-butanol–pyridine–water (6:4:3); and solvent B, 1-butanol–ethanol–water (4:1:1.2). Melting points were recorded with a Hershberg apparatus. Infrared spectra were recorded with an Infracord spectrophotometer[14] with specimens in a Nujol mull.

The Aldol Reaction.—D-Erythrose (I) was prepared from 1.57 g. of dimeric 2,4-*O*-ethylidene-D-erythrose hemialcoholate as described previously.[15] The deionized sirupy product thus obtained and 1.44 g. of 1,3-dihydroxy-2-propanone (II) were dissolved in 50 ml. of limewater (prepared at 8°), and the solution was quickly warmed to 20°. After about 22 min. of reaction at this tempera-

(4) L. Hough and J. K. N. Jones, *Nature*, **167**, 180 (1951).

(5) Private communications from Dr. L. Hough and Professor J. K. N. Jones.

(6) A. Bevenue and K. T. Williams, *Arch. Biochem. Biophys.*, **34**, 225 (1951).

(7) J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **77**, 6326 (1955). The author is indebted to Dr. N. K. Richtmyer for supplying a solvated and a dried sample of this compound.

(8) F. B. LaForge and C. S. Hudson, *J. Biol. Chem.*, **30**, 61 (1917).

(9) J. W. Pratt, N. K. Richtmyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **74**, 2200 (1952).

(10) W. C. Austin, *ibid.*, **52**, 2106 (1930).

(11) L. M. Utkin, *Dokl. Akad. Nauk SSSR*, **67**, 301 (1949).

(12) M. L. Wolfrom, W. W. Binkley, C. C. Spencer, and B. W. Lew, *J. Am. Chem. Soc.*, **73**, 3357 (1951).

(13) Product of the LKB Instruments, Inc., Bethesda, Md.

(14) Product of the Perkin-Elmer Corporation, Norwalk, Conn.

(15) R. Schaffer, *J. Am. Chem. Soc.*, **81**, 2838 (1959).

ture, the mixture was rapidly cooled to 0° and passed through a column containing 10 ml. of ice-cold Amberlite IR-120 (H^+). The effluent was concentrated at reduced pressure, transferred as a band at the origin to each of two sheets of thick chromatography paper, and developed with solvent A for 2.5 days. The ketose bands were made visible by pressing each wet chromatogram against a sheet of Whatman No. 1 paper, and then spraying the latter sheet. On elution of the slower heptulose bands from the two chromatograms, 0.325 g. of crystalline D-*gluco*-heptulose (VI)[10] was isolated. The combined material from the faster heptulose bands was rechromatographed on a single new sheet of thick paper using solvent B. The overlapping heptulose bands that resulted were located by the transfer technique, and the material corresponding to the more intense, slower band was cut away from that corresponding to the less colored, more mobile material. Crystalline D-*allo*-heptulose (III)[7] as a hydrate weighing 0.077 g. was separated from the faster moving material. From the slower portion, a sirupy product, D-*altro*-heptulose (IV), was separated. On heating a solution of the sirup in 0.2 *N* hydrochloric acid at 50° for 68 hr.,[16] there was obtained 0.251 g. of crystalline 2,7-anhydro-β-D-*altro*-heptulopyranose hydrate (V).[8,9]

Column chromatography of a similar amount of the reaction products, using solvent B as developer, led to the separation of 0.5 g. of sirup containing "dendroketose"[1,11] from the effluent fractions in the volume from 1500 to 2475 ml.; 0.076 g. of III from effluent volumes 2550 to 2820 ml.; 0.227 g. of V from volumes 2820 to 3720 ml. (compound IV was eluted but was isolated as V after dehydration); and 0.455 g. of VI from volumes 3165 to 3720 ml. and 3720 to 3975 ml. About 0.005 g. of D-*gluco*-L-*glycero*-3-octulose[3] was crystallized from the 4500- to 5400-ml. fractions. The "dendroketose" and the 3-octulose were identified by the similarities to authentic materials of their chromatographic behavior and coloration with the orcinol spray. In addition, for the 3-octulose, identity was confirmed by its melting point (164–165°), undepressed mixture melting point, and its infrared spectrum. The infrared spectrum of compound III obtained from ethanol containing a little water agrees with that of an authentic specimen of the ketose,[7] and it shows an absorption at 1650 cm.$^{-1}$ which indicates that the solvation is due to water. Analysis showed irregular amounts of water that were in a nearly equimolecular ratio with the ketose. The desolvated product (heated under vacuum) melted at 128–131°, and this melting point was unchanged when a sample was mixed with some of the dried authentic product (lit.[7] m.p. 130–132°). The hydrated product showed $[\alpha]^{25}D$ −46° in water and the reported value[7] is $[\alpha]^{20}D$ −46.6°. Compound V showed $[\alpha]^{25}D$ −133.5°, m.p. 100–102°, and, when mixed with authentic material, the melting point was 100–102°. Its infrared spectrum corresponded with that of the known substance.[17] Compound VI showed $[\alpha]^{25}D$ +67°, m.p. 170–172°, and, when mixed with authentic material, m.p. 170–173°. Its infrared spectrum was identical with that of the known sugar.[17]

Acknowledgment.—The author wishes to express his gratitude to Dr. H. S. Isbell for his interest in and support of this work.

(16) N. K. Richtmyer and J. W. Pratt, *J. Am. Chem. Soc.*, **78**, 4717 (1956).

(17) R. S. Tipson and H. S. Isbell, *J. Res. Natl. Bur. Std.*, **66A**, 31 (1962)

The Isomerization of D-*manno*-3-Heptulose by Alkali

ROBERT SCHAFFER

Physical Chemistry Division, National Bureau of Standards, Washington, D. C. 20234

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The title compound isomerizes in alkaline solution by the enolization mechanism through two pathways: (a) *via* a 2,3-enediol to yield D-*gluco*-heptulose, and (b) *via* a 3,4-enediol, an isomeric 3-ketose, and another 2,3-enediol to yield D-*altro*- and D-*allo*-heptuloses.

Throughout the long history of the Lobry de Bruyn–Alberda van Ekenstein reaction (isomerization of sugars by alkali),[1] no direct evidence has been educed for the presence of 3-keto sugars among its products, although such compounds are theoretically capable of being formed from the 2,3-enediol intermediates which are believed to be responsible for the occurrence of ketoses epimeric at C-3, *e.g.*, D-tagatose (D-*lyxo*-hexulose) *and* D-sorbose (D-*xylo*-hexulose) from the isomerization of D-galactose.[2] Perhaps the clearest implication of the participation of a 3-ketose in such a system was found by Sowden and Thompson[3] who, using D-glucose-1-C^{14}, obtained data showing that isomerization by an enolization mechanism must have proceeded through all of the secondary carbon atoms of the chain to yield L-sorbose labeled predominantly at C-6. A direct investigation of the chemical behavior of a 3-ketose in such a system was undertaken when a suitable pure study material, namely D-*manno*-3-heptulose (I), became available; this sugar had been obtained as a sirup by the selective degradation of the reducing group of a related 3-*C*-formylheptitol,[4] but β-D-*manno*-3-heptulose hydrate[5] has now been crystallized.

Discussion

In the course of several days at room temperature, a solution of compound I in dilute limewater was found to undergo a change in optical rotation from levo- to dextrorotatory. Paper chromatography revealed that, during this time, the 3-ketose was being transformed to isomeric 2-ketoses: the gray-brown spot that forms on spraying the 3-heptulose with orcinol–trichloroacetic acid[6] gradually diminished, and, simultaneously, there appeared two faster moving blue spots (2-heptuloses)[7] which gradually increased in intensity. The slower blue spot was more intense than the faster one. The location of the slower spot on the chromatogram suggested that it might be due to D-*gluco*-heptulose[8] (II), or to D-*manno*-heptulose[9] (III), or both; however, its color showed none of the greenish blue that III gives with the spray. The location of the more mobile spot suggested that it

(1) See J. C. Speck, Jr., *Advan. Carbohydrate Chem.*, **13**, 63 (1958).

(2) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **16**, 262 (1897); **19**, 5 (1900).

(3) J. C. Sowden and R. R. Thompson, *J. Am. Chem. Soc.*, **80**, 1435 (1958).

(4) R. Schaffer, *ibid.*, **81**, 2838 (1959).

(5) R. Schaffer, Abstracts, 139th Annual Meeting of the American Chemical Society, St. Louis, Mo., March, 1961, p. 4D.

(6) R. Schaffer and A. Cohen, *J. Org. Chem.*, **28**, 1929 (1963).

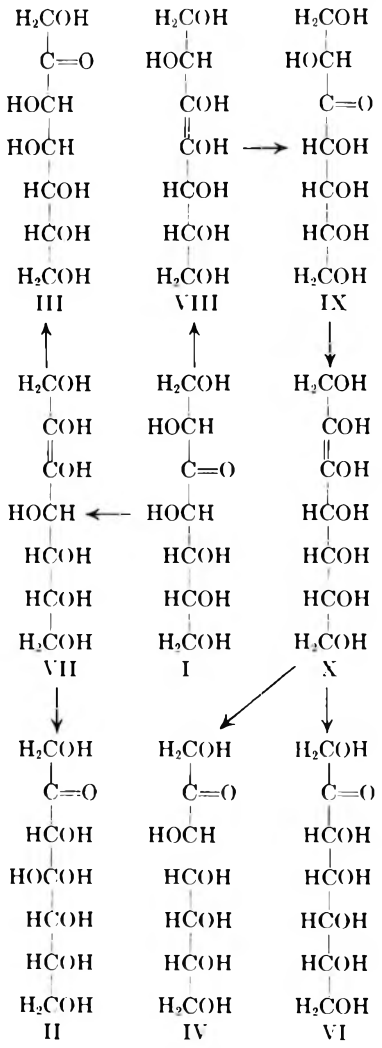
(7) A. Bevenue and K. T. Williams, *Arch. Biochem. Biophys.*, **34**, 225 (1951).

(8) W. C. Austin, *J. Am. Chem. Soc.*, **52**, 2106 (1930).

(9) (a) F. B. LaForge, *J. Biol. Chem.*, **28**, 511 (1917); (b) E. M. Montgomery and C. S. Hudson, *J. Am. Chem. Soc.*, **61**, 1654 (1939).

might correspond to D-*altro*-heptulose[10] (IV), or to D-*allo*-heptulose[11] (VI), or both. By the combined use of fractional crystallization and paper chromatography, compound II was isolated in a total yield of 40%, IV was obtained [as its crystalline 2,7-anhydride (V)] in 4% yield, and VI was crystallized as a hydrate[12] in 3% yield. Only a trace of III was detected, and it could not be crystallized from the mixture; no D-*manno*-3-heptulose was detected or recovered. Thus, the conditions of the Lobry de Bruyn–Alberda van Ekenstein reaction were found to affect the 3-heptulose profoundly. Assuming this behavior to be typical of such ketoses, it is understandable that the direct detection of 3-ketoses produced in alkaline isomerization reactions has not been realized.

The classical enolization pathway is accepted as the mechanism of alkaline interconversion of aldoses and 2-ketoses, and its occurrence is supported by the results of isotopic labeling studies.[13] The same mechanism can



account for the formation of the isomeric heptuloses that were isolated from the 3-ketose; this action, however, requires two pathways. The first of these, the route to compound II, involves enolization of I to D-*arabino*-heptitol-2-ene (VII), which is then isomerized to II. Compound III would be expected to form from this enediol intermediate, too. Because of the necessity of epimerizing the hydroxyl group at C-4 of compound I to form compounds IV and VI, the second pathway is more complex. Compound I is enolized to D-*arabino*-heptitol-3-ene (VIII), which, in turn, is isomerized to D-*altro*-3-heptulose (IX). This as-yet-unknown 3-heptulose is then transformed into the intermediate D-*ribo*-heptitol-2-ene (X), which finally is isomerized to IV and VI.

Interestingly, the composition and proportions of the ketoses isolated from the isomerization resemble those obtained by the aldol reaction of D-erythrose and 1,3-dihydroxy-2-propanone,[12] where the same heptuloses II, IV, and VI are formed, and where II constitutes the major ketose product, while its epimer III is present in a nonisolable amount. (The product compositions might have been even more alike had the aldol reaction mixture been exposed to the alkaline medium for a week, as in the isomerization, rather than for 22 minutes, the time required for the anionic addition.) The amounts of each heptulose isolated from the aldol synthesis and the isomerization reaction show that the major products in both instances have *threo* configurations at C-3 and C-4. These asymmetric centers are the newly created ones in the aldol reactions, where preference for products with *threo* configurations at the new asymmetric centers is experimentally well-established,[12] but more information regarding the isomerization of ketoses and aldoses in alkaline solution is required, in order to know whether there exists in these reactions, too, the general preference for products with this configuration.

Experimental

Crystalline β-D-*manno*-3-Heptulose Hydrate.—Hydrolysis of 2,2′:4,6-di-*O*-ethylidene-2-(D-*glycero*-1,2-dihydroxyethyl)-D-glucopyranose by acid, degradation of the liberated branched-chain octose by lead tetraacetate, rehydrolysis, and removal of aldose contaminants have been described.[5] Duolite A-4 (amine form) was used to remove the sulfuric acid employed in the first hydrolysis step.[14] Thick paper chromatography of 0.9 g. of purified, sirupy, degradation product was used with 1-butanol–ethanol–water (4:1:1.2) as developer to separate the 3-heptulose band, which was visualized by pressing the wet, developed chromatogram between sheets of Whatman No. 1 paper and spraying the latter with orcinol, or silver nitrate and alkali. The material eluted from the 3-heptulose band weighed about 0.37 g., and, from a concentrated solution of it in 95% ethanol, 0.276 g. of crystalline β-D-*manno*-3-heptulose hydrate was obtained, m.p. 84–85.5°; $[\alpha]^{27}D$ −70°, 2.6 min. → −39°, final 1 hr. (*c* 1, water). Without chromatography, from 4.3 g. of sirupy degradation product in 95% ethanol, 0.62 g. of 3-heptulose crystallized, after seeding.

Anal. Calcd. for $C_7H_{14}O_7 \cdot H_2O$: C, 36.8; H, 7.1. Found: C, 36.6; H, 7.1.

D-*manno*-3-Heptulose Phenylhydrazone.—A solution of 0.035 g. of I in 2 drops of water and 10 drops of methanol was combined with 0.030 g. of crystalline phenylhydrazine–acetic acid (prepared by addition of pentane to a concentrated solution of phenylhydrazine and acetic acid in ether) and heated for 4 hr. at 50°. The solvent was then evaporated, and the product was crystallized from absolute ethanol, m.p. 147–148° dec., $[\alpha]^{25}D$ +80 ± 5° (*c* 0.5, methanol).

Anal. Calcd. for $C_{13}H_{20}N_2O_6$: C, 52.0; H, 6.7; N, 9.3. Found: C, 52.3; H, 6.9; N, 9.2.

Crystalline phenylosazones could not be isolated.

(10) F. B. LaForge and C. S. Hudson, *J. Biol. Chem.*, **30**, 61 (1917).

(11) J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **77**, 6326 (1955). The author is indebted to Dr. Richtmyer for supplying a sample of this compound.

(12) R. Schaffer, *J. Org. Chem.*, **29**, 1471 (1964).

(13) J. C. Sowden and R. Schaffer, *J. Am. Chem. Soc.*, **74**, 499, 505 (1952).

(14) The original publication had specified cation-exchange resin.

Isomerization of D-*manno*-3-Heptulose.—A solution of 0.114 g. of β-D-*manno*-3-heptulose monohydrate in 7.5 ml. of water was mixed with 2.5 ml. of limewater (prepared at 8°). After storage in the dark for about 1 week at room temperature, the slightly yellow solution was passed through a column containing 3 ml. of Amberlite IR-120 H^+ and 5 ml. of Duolite A-4, and then concentrated. The sirup was taken up in a little methanol and 95% ethanol, and seeded with compound II, whereupon nearly pure II crystallized, 0.0375 g., $[\alpha]^{26}D$ +67°, m.p. 169–173°. Its infrared spectrum corresponded to that of authentic material.[15] The mother liquor was chromatographed on Whatman No. 3 MM paper, using the solvents and techniques previously described for separating these isomeric heptuloses.[12] Three sirupy fractions, consisting principally of II, IV, and VI, respectively, were obtained. On seeding the fractions, 0.003 g. of additional II was obtained, and 0.003 g. of VI was isolated as a hydrate. The latter was identified by its chromatographic behavior and by comparison of its infrared spectrum with that of an authentic specimen.[11] The fraction containing IV was heated for 70 hr. at 50° in 0.2 *N* hydrochloric acid,[16] and, after deionization and concentration, was obtained as crystalline V, weight 0.004 g. Compound V was identified by comparison of its infrared spectrum[15] and chromatographic behavior with those of authentic material. The orcinol-sprayed chromatogram of the reaction mixture at the conclusion of the reaction showed neither the color nor the fluorescence of the starting material.

Acknowledgment.—The interest and support of Dr. H. S. Isbell throughout this work is gratefully acknowledged. The author also thanks Mr. R. Paulson and Mr. R. J. Hall of the National Bureau of Standards for the elemental analyses.

(15) R. S. Tipson and H. S. Isbell, *J. Res. Natl. Bur. Std.*, **66A**, 31 (1962).

(16) N. K. Richtmyer and J. W. Pratt, *J. Am. Chem. Soc.*, **78**, 4717 (1956).

Sorboses. IV. Syntheses of Thio Derivatives of 2,3-*O*-Isopropylidene-α-L-sorbofuranose[1]

KANJI TOKUYAMA AND MASUMI KIYOKAWA

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

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Derivatives of 1-thio- and 6-thio-2,3-*O*-isopropylidene-α-L-sorbofuranoses were prepared *via* the corresponding benzylthio-L-sorbofuranoses, which were readily obtainable by the reactions of *O*-*p*-toluenesulfonyl-L-sorbofuranoses with sodium benzylthiolate in liquid ammonia, not in alcohol.

Although thio sugars have received renewed attention in recent years not only from the standpoint of the chemistry involved but from biochemical and metabolic interest, only one paper has been published on the preparation of thioketoses,[2] because tosyloxy groups in ketoses undergo nucleophilic displacement except when they are hindered.[2–4] The present paper reports a new method of synthesis of thio derivatives of 2,3-*O*-isopropylidene-α-L-sorbofuranose.

The treatment of 1,6-di-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (II)[5] with sodium benzylthiolate (I) in absolute methanol[6] gave colorless crystals (IV′), which had only one benzylthio group per sugar. This was also obtained from 6-*O*-*p*-toluenesulfonyl-1,4-anhydro-2,3-*O*-isopropylidene-α-L-sorbofuranose (III).[7] The acid-catalyzed acetonization of IV′ gave no acetonized compounds. Therefore, the structure of IV′ was considered to be 6-*S*-benzyl-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (IV). In order to prove the structure, the reaction of 6-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (V) with I was carried out under the same conditions employed above. However, V was not converted into IV but into 2,3-*O*-isopropylidene-α-L-sorbofuranose (VI),[8] which was considered as the reaction product of V with a trace of water in the solvent. Dehydrating all the reagents or substituting I by other thio compounds such as thiol acetate brought no improvement. The treatment of V with I in liquid ammonia solution, which was prepared from metallic sodium and α-toluenethiol in liquid ammonia, at room temperature for 2 weeks gave IV. This was identical with IV′ by comparison of its rotation, infrared spectrum, and mixture melting point. Amino sugar was not isolated in this reaction. Furthermore, the treatment of II with I in liquid ammonia gave 1,6-di-*S*-benzyl-2,3-*O*-isopropylidene-1,6-dithio-α-L-sorbofuranose (VII) in good yield. (See Chart I.)

The tosylation of IV in pyridine gave 1-*O*-*p*-toluenesulfonyl-6-*S*-benzyl-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (VIII), which was converted into 1-anilino-6-*S*-benzyl-1-deoxy-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (IX) on heating with aniline. IX was also obtainable on treating I in liquid ammonia with 1-anilino-6-*O*-*p*-toluenesulfonyl-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (X), which was derived from the tosylation of 1-anilino-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (XI).

Derivatives of 1-*S*-benzyl-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XV) were obtained in a similar manner. The treatment of 1-*O*-*p*-toluenesulfonyl-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (XII)[9] or its partially hydrolyzed product, 1-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (XIII), with I yielded, in liquid ammonia, 1-*S*-benzyl-2,3:4,6-di-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XIV) or XV, but in methanol solvent, 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (XVI)[8] or VI, respectively. (See Chart II.)

The tosylation of XV, which was also prepared by partial hydrolysis of XIV, afforded 1-*S*-benzyl-6-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XVII). This was converted into 1-*S*-benzyl-

(1) Part III: K. Tokuyama and E. Honda, *Bull. Chem. Soc. Japan*, **37**, 4 (1964).

(2) M. S. Feather and R. L. Whistler, *J. Org. Chem.*, **28**, 2567 (1963).

(3) H. Muller and T. Reichstein, *Helv. Chim. Acta*, **21**, 263 (1938).

(4) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **120**, 607 (1937).

(5) H. Ohle, *Ber.*, **71**, 562 (1938).

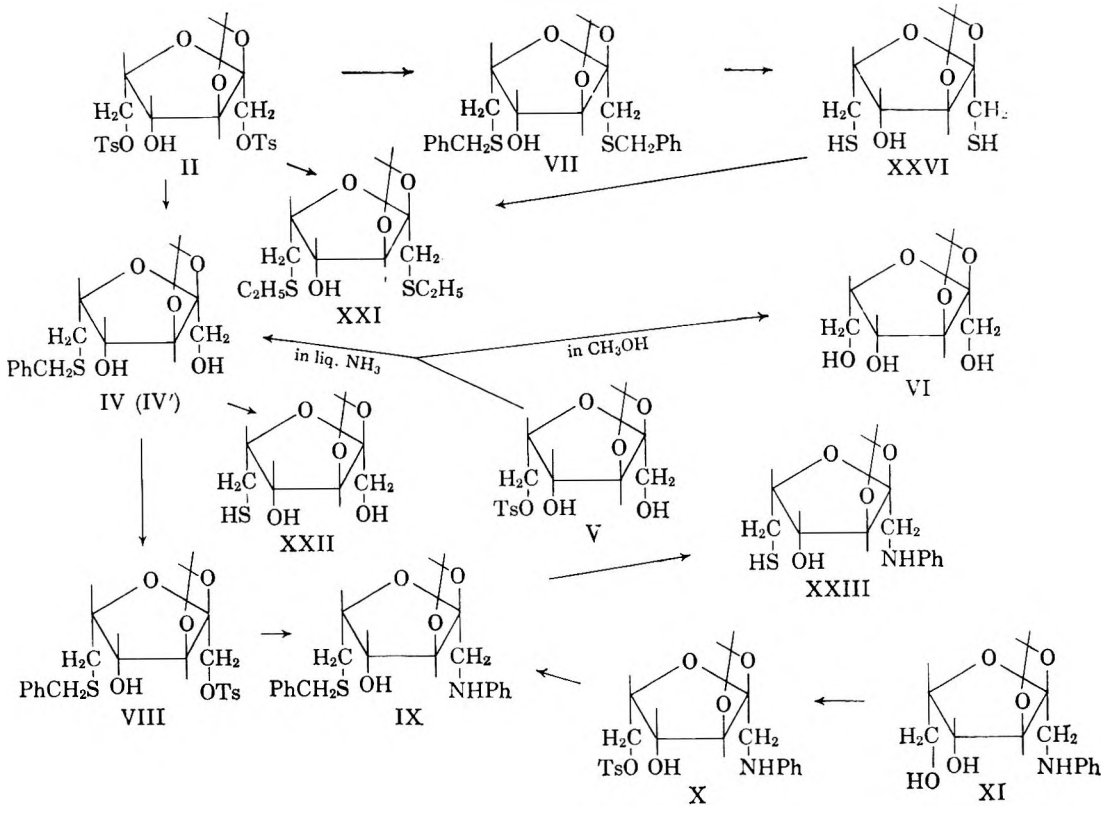
(6) N. C. Jamieson and R. K. Brown, *Can. J. Chem.*, **39**, 1765 (1961).

(7) K. Tokuyama, M. Kiyokawa, and N. Hoki, *Bull. Chem. Soc. Japan*, **36**, 1392 (1963).

(8) T. Reichstein, *Helv. Chim. Acta*, **17**, 311 (1934).

(9) W. Sullivan, *J. Am. Chem. Soc.*, **67**, 837 (1945).

CHART I



6-anilino-6-deoxy-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XVIII) on heating with aniline. XVIII was also obtained by the reaction of I in liquid ammonia with 1-*O*-*p*-toluenesulfonyl-6-anilino-6-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (XIX) which was available by the tosylation of 6-anilino-6-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (XX).[7]

The aforementioned replacement reaction of the tosyloxy group of L-sorbose by a benzylthio group showing almost no formation of amino-L-sorbose was only successful in a solvent of liquid ammonia. This reaction in liquid ammonia proceeded faster at higher temperatures in slightly lower yields.

As an example of the introduction of another thiolate, the reaction of II with sodium ethylthiolate in liquid ammonia was carried out yielding 1,6-di-*S*-ethyl-2,3-*O*-isopropylidene-1,6-dithio-α-L-sorbofuranose (XXI), which was also obtainable by ethylation of 2,3-*O*-isopropylidene-1,6-dithio-α-L-sorbofuranose (XXVI).

In recent years, Shimo and his co-workers[10,11] reported that sodium hydroxide in liquid ammonia can be used as a base like sodium amide. The treatment of II with α-toluenethiol in liquid ammonia in the presence of an equimolecular amount of sodium hydroxide yielded VII with slow dissolution of sodium hydroxide. At higher temperatures, VII was obtained even in the absence of sodium hydroxide. Instead of sodium hydroxide, use of alcoholic sodium alcoholate in liquid ammonia gave better results, indicating that these are excellent methods for the preparation of thio sugars.

The debenzylation of the above-described benzylthio-L-sorbofuranoses had been achieved by the use of sodium in liquid ammonia at low temperatures.[6] Thus, the treatment of IV, VII, IX, XV, XVIII, and XIV with sodium in liquid ammonia gave the corresponding thio-L-sorboses, 6-thio- (XXII), 1,6-dithio- (XXVI), 1-anilino-1-deoxy-6-thio- (XXIII), 1-thio- (XXIV), and 6-anilino-6-deoxy-1-thio-2,3-*O*-isopropylidene-α-L-sorbofuranose (XXV), and 2,3:4,6-di-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XXVII), respectively.

Thus the use of liquid ammonia as a solvent has proved to be a new and excellent method for the preparation of thio sugars.

Experimental

6-*S*-Benzyl-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (IV). **A.**—Sodium (4 g.) was dissolved in methanol (80 ml.) containing α-toluenethiol (5.2 g.), and to this was added 1,6-di-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (II, 10.6 g.). The mixture was refluxed under nitrogen for 2 hr. After cooling and dilution with water, the mixture was extracted with chloroform. The extract was washed with water, dried, and evaporated. Recrystallization of the residue from benzene and petroleum ether (b.p. 40–70°) gave colorless needles (4.2 g.), m.p. 99–100°, $[\alpha]^{25.5}D$ +54.6° (*c* 1.105, acetone).

Anal. Calcd. for $C_{16}H_{22}O_5S$: C, 58.90; H, 6.75; S, 9.81. Found: C, 59.10; H, 6.79; S, 9.81.

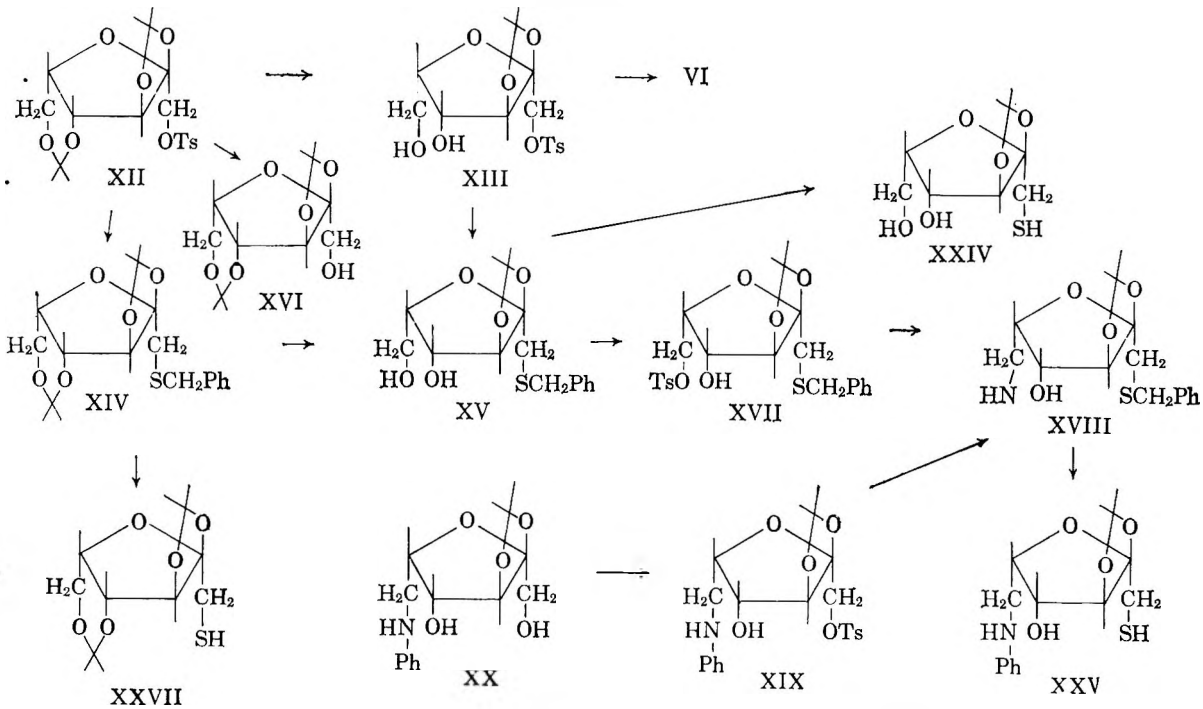
B.—To a solution of α-toluenethiol (2.2 g.) and sodium (0.4 g.) in liquid ammonia (8 ml.) was added a solution of II (1 g.) in liquid ammonia (8 ml.). (a) After standing at room temperature for 2 weeks, ammonia was allowed to evaporate and the residue was diluted with water. This was extracted with chloroform, and the extract was washed with water and dried. After removal of the solvent, the residue was recrystallized from benzene and petroleum ether to give colorless needles (0.6 g.). (b) After heating on a boiling water bath for 40 hr., IV (0.5 g.) was also obtained by the above work-up.

1-*O*-*p*-Toluenesulfonyl-6-*S*-benzyl-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (VIII).—To a solution of IV (0.5 g.) in dry pyridine (1 ml.) was added *p*-toluenesulfonyl chloride (0.34 g.). After stirring at room temperature for 5 hr., the reaction mixture was poured into a saturated potassium hydroxide solution (5 ml.)

(10) R. Asami and K. Shimo, *Sci. Rept. Research Inst., Tohoku Univ.*, **9A**, 341 (1957); *Chem. Abstr.*, **52**, 3677 (1958).

(11) K. Shimo and S. Wakamatsu, *J. Org. Chem.*, **24**, 19 (1959).

CHART II



and then extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated to dryness under reduced pressure. Recrystallization of the residue from benzene and petroleum ether gave colorless needles (0.69 g.), m.p. 137–139.5°, $[\alpha]^{23}D$ +49° (*c* 1.090, acetone).

Anal. Calcd. for $C_{23}H_{28}O_7S_2$: C, 57.50; H, 5.84; S, 13.33. Found: C, 57.56; H, 5.91; S, 13.64.

1-Anilino-6-*S*-benzyl-1-deoxy-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (IX). **A.**—A solution of VIII (1 g.) and potassium carbonate (1 g.) in aniline (10 ml.) was heated at 170–180° for 10 hr. with stirring. The reaction mixture was cooled, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure, leaving a dark brown sirup. Recrystallization of the sirup from methanol gave colorless needles (0.27 g.), m.p. 129°, $[\alpha]^{23}D$ +20.9° (*c* 1.090, chloroform).

Anal. Calcd. for $C_{22}H_{27}NO_4S$: C, 65.84; H, 6.73; N, 3.49; S, 7.98. Found: C, 65.57; H, 6.68; N, 3.42; S, 7.89.

B.—A solution of α-toluenethiol (1.1 g.) and sodium (0.2 g.) in liquid ammonia (8 ml.) was mixed with a solution of 1-anilino-6-*O*-*p*-toluenesulfonyl-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (X, 0.5 g.) in liquid ammonia (10 ml.). After heating the solution on a boiling-water bath for 42 hr., IX (0.1 g.) was isolated by the above-described procedure for IV.

1-*O*-*p*-Toluenesulfonyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (XIII).—1-*O*-*p*-Toluenesulfonyl-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (XII, 1 g.) was dissolved in 60% acetic acid (10 ml.). The solution was warmed at 70° for 30 min., diluted with water, and extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated. The residue was recrystallized from ethyl acetate and *n*-hexane to give colorless needles (0.5 g.), m.p. 120–121°, $[\alpha]^{22.5}D$ +12.6° (*c* 0.991, methanol).

Anal. Calcd. for $C_{16}H_{22}O_8S$: C, 51.34; H, 5.88; S, 8.56. Found: C, 51.70; H, 6.14; S, 8.81.

1-Anilino-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (XI).—A solution of XIII (1 g.) and potassium carbonate (1 g.) in aniline (10 ml.) was heated at 170–180° for 10 hr. with stirring. XI (0.31 g.) was obtained in a manner similar to XIV. XI had m.p. 98°, $[\alpha]^{23}D$ +35.0° (c 1.045, chloroform).

Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.02; H, 7.12; N, 4.75. Found: C, 61.29; H, 7.26; N, 4.87.

1-Anilino-6-*O*-*p*-toluenesulfonyl-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (X).—To a solution of XI (1.47 g.) in dry pyridine (5 ml.) was added *p*-toluenesulfonyl chloride (0.968 g.). After stirring at room temperature for 5 hr., X (1.82 g.) was obtained by the same work-up as that of VIII. It had m.p. 135° dec., $[\alpha]^{23}D$ +40.6° (*c* 0.903, chloroform).

Anal. Calcd. for $C_{22}H_{27}NO_7S$: C, 58.80; H, 6.01; N, 3.12. Found: C, 58.98; H, 6.17; N, 2.91.

1,6-Di-*S*-benzyl-2,3-*O*-isopropylidene-1,6-dithio-α-L-sorbofuranose (VII). **A.**—A solution of α-toluenethiol (4.4 g.) and sodium (0.8 g.) in liquid ammonia (10 ml.) was mixed with a solution of 1,6-di-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (II, 4.5 g.) in liquid ammonia (20 ml.). (a) After standing at room temperature for 2 weeks, ammonia was allowed to evaporate and the residue was washed with water, dried, and recrystallized from *n*-hexane. Colorless needles (2.53 g.) were obtained, m.p. 86°, $[\alpha]^{25.5}D$ +112.0° (*c* 1.038, chloroform).

Anal. Calcd. for $C_{23}H_{28}O_4S_2$: C, 63.89; H, 6.48; S, 14.81. Found: C, 63.77; H, 6.69; S, 14.55.

(b) After heating on a boiling-water bath for 40 hr., VII (2.7 g.) was obtained by the above-described procedure.

B.—To a mixture of α-toluenethiol (2.5 g.) and powdered sodium hydroxide (0.8 g.) was added a solution of II (3.0 g.) in liquid ammonia (10 ml.). Dissolution of sodium hydroxide was completed after 2 weeks at room temperature with occasional shaking. VII (1.5 g.) was obtained in the above-described way.

C.—A solution of α-toluenethiol (2.0 g.) and II (3.0 g.) in liquid ammonia (10 ml.) was heated on a boiling-water bath for 45 hr. VII (0.35 g.) was isolated by the above-described procedure.

D.—To a methanol solution (5 ml.) of sodium (1.0 g.) and α-toluenethiol (5.5 g.) was added a solution of II (8.5 g.) in liquid ammonia (30 ml.), and the mixture then was heated on a boiling-water bath for 30 hr. VII (4.2 g.) was obtained in the above-described manner.

1-*S*-Benzyl-2,3:4,6-di-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XIV).—A solution of α-toluenethiol (1.3 g.) and sodium (0.24 g.) in liquid ammonia (10 ml.) was mixed with a solution of 1-*O*-*p*-toluenesulfonyl-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (XII, 1 g.) in liquid ammonia (8 ml.). The solution was kept at room temperature for 2 weeks, or heated on a boiling-water bath for 40 hr. After removal of liquid ammonia, the residue was diluted with water, and then extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated under reduced pressure, to give a yellow sirup. The sirup was fractionated by chromatography with silica gel (16 g.): first fraction (benzene), 250 ml.; second fraction (benzene–ether, 9:1, v./v.), 200 ml.; and third fraction (benzene–ether, 8:2, v./v.), 250 ml. From the second and third fractions, XIV (320 mg.) was obtained as a sirup, $[\alpha]^{23}D$ −62.7° (*c* 1.056, chloroform).

Anal. Calcd. for $C_{19}H_{26}O_5S$: C, 62.30; H, 7.10; S, 8.74. Found: C, 62.50; H, 7.27; S, 8.95.

1-*S*-Benzyl-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XV). **A.**—To a solution of sodium (0.8 g.) and α-toluenethiol (4.4 g.) in liquid ammonia (10 ml.) was added a solution of XIII (4 g.) in liquid ammonia (15 ml.). The solution was kept at room temperature for 2 weeks or heated on a boiling-water bath for 40

hr. Ammonia was allowed to evaporate and the residue was diluted with water and then extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated. The residue was fractionated by chromatography with silica gel (40 g.): first fraction (benzene), 300 ml.; second fraction (benzene–ether, 9:1, v./v.), 200 ml.; third fraction (benzene–ether, 8:2, v./v.), 200 ml.; and fourth fraction (ether), 300 ml. From the fourth fraction, XV (2.0 g.) was obtained. It had m.p. 67° (recrystallized from ether and *n*-hexane), $[\alpha]^{25.5}D$ +84.5° (*c* 1.026 chloroform).

Anal. Calcd. for $C_{16}H_{22}O_5S$: C, 58.90; H, 6.75; S, 9.81. Found: C, 59.06; H, 6.77; S, 9.87.

B.—1-*S*-Benzyl-2,3:4,6-di-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XIV) (2 g.) was dissolved in 60% acetic acid (30 ml.). The solution was warmed at 70° for 30 min., diluted with water, neutralized with sodium hydroxide, and extracted with chloroform. This was washed with water, dried, and evaporated. Recrystallization of the residue gave XV (0.8 g.), m.p. 67°.

1-*S*-Benzyl-6-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XVII).—To a solution of XV (3.37 g.) in dry pyridine (20 ml.) was added *p*-toluenesulfonyl chloride (2.0 g.). After stirring at room temperature for 5 hr., the reaction mixture was poured into a saturated sodium hydroxide solution (20 ml.) and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to dryness under reduced pressure. Recrystallization of the residue from ether and *n*-hexane gave colorless needles (2.1 g.), m.p. 117°, $[\alpha]^{25.5}D$ +91.4° (*c* 1.034, chloroform).

Anal. Calcd. for $C_{23}H_{28}O_7S_2$: C, 57.50; H, 5.84; S, 13.34. Found: C, 57.36; H, 6.04; S, 13.58.

1-*O*-*p*-Toluenesulfonyl-6-anilino-6-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (XIX) was obtained from the reaction of 6-anilino-6-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (XX) (0.1 g.) with *p*-toluenesulfonyl chloride (66 mg.) in dry pyridine (1 ml.) according to the same procedure for X. The yield was 0.12 g., m.p. 98° (recrystallized from benzene and petroleum ether), $[\alpha]^{26.5}D$ +6.5° (*c* 0.642, chloroform).

Anal. Calcd. for $C_{22}H_{27}NO_7S$: C, 58.80; H, 6.01; N, 3.12; S, 7.13. Found: C, 59.08; H, 6.26; N, 3.12; S, 7.02.

1-*S*-Benzyl-6-anilino-6-deoxy-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XVIII). **A.**—A solution of α-toluenethiol (3 g.) and sodium (0.4 g.) in liquid ammonia (6 ml.) was mixed with a solution of XIX (1 g.) in liquid ammonia (8 ml.). It was kept at room temperature for 2 weeks or heated on a boiling-water bath for 40 hr. XVIII (0.5 g.) was obtained by the same procedure for IX and had m.p. 137° (recrystallized from ethyl acetate and *n*-hexane), $[\alpha]^{23}D$ +107.1° (*c* 1.070, chloroform).

Anal. Calcd. for $C_{22}H_{27}NO_4S$: C, 65.84; H, 6.73; N, 3.49; S, 7.98. Found: C, 65.74; H, 6.89; N, 3.60; S, 8.15.

B.—A solution of XVII (1 g.) and potassium carbonate (1 g.) in aniline (10 ml.) was heated at 170–180° for 10 hr. XVIII (0.6 g.) was obtained by the above-described procedure for IX.

1,6-Di-*S*-ethyl-2,3-*O*-isopropylidene-1,6-dithio-α-L-sorbofuranose (XXI). **A.**—To a solution of ethanethiol (5 g.) and sodium (0.7 g.) was added a solution of 1,6-di-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-α-L-sorbofuranose (II, 5 g.) in liquid ammonia (26 ml.). The solution was kept at room temperature for 2 weeks or heated on a boiling-water bath for 40 hr. After removal of ammonia, the residue was diluted with water and extracted with chloroform. The chloroform was washed with water and dried; the solvent was removed. Distillation of the residue gave a sirup (1.9 g.), b.p. 173° at 3 mm., which crystallized immediately, giving XXI, m.p. 48°, $[\alpha]^{26}D$ +82.5° (*c* 1.009, chloroform)

Anal. Calcd. for $C_{13}H_{24}O_4S_2$: C, 50.64; H, 7.79; S, 20.80. Found: C, 50.88; H, 7.88; S, 20.64.

B.—A solution of I (5 g.) and ethanethiol (5 g.) in liquid ammonia (10 ml.) was heated on a boiling-water bath for 40 hr.; XXI (0.9 g.) was obtained in the above-described way.

Reduction of Benzylthio-L-sorboses.[6] **General Procedure.**—With constant stirring at −40°, to a solution of benzylthio-L-sorbose in liquid ammonia were added enough small pieces of sodium metal for the blue color to persist for 20 min. After that, ammonium chloride was added to discharge the blue color. Ammonia was allowed to evaporate, and the residue was extracted with chloroform which, upon evaporation, left a colorless sirup. The sirup was purified by recrystallization or by silica gel chromatography with benzene and ether.

6-*S*-Benzyl-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (IV, 1 g.) yielded 2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (XXII, 0.42 g.), m.p. 161° (recrystallized from *n*-hexane and ethyl acetate), $[\alpha]^{22}D$ +29.9° (*c* 1.030, methanol).

Anal. Calcd. for $C_9H_{16}O_5S$: C, 45.76; H, 6.78; S, 13.56 Found: C, 46.62; H, 6.88; S, 13.46.

1-Anilino-6-*S*-benzyl-1-deoxy-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (IX, 1 g.) yielded 1-anilino-1-deoxy-2,3-*O*-isopropylidene-6-thio-α-L-sorbofuranose (XXIII, 0.46 g.), m.p., 108° (recrystallized from ethyl acetate), $[\alpha]^{24.5}D$ +51.1° (*c* 1.094 chloroform).

Anal. Calcd. for $C_{15}H_{21}NO_4S$: C, 57.87; H, 6.75; N, 4.50; S, 10.28. Found: C, 57.97; H, 6.87; N, 4.42; S, 10.19.

1-*S*-Benzyl-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XV, 2.0 g.) yielded 2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XXIV, 0.5 g.) as a sirup, $[\alpha]^{26.5}D$ −6.7° (*c* 1.362, chloroform).

Anal. Calcd. for $C_9H_{16}O_5S$: C, 45.76; H, 6.78; S, 13.56. Found: C, 46.70; H, 7.10; S, 13.45.

1-*S*-Benzyl-6-anilino-6-deoxy-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XVIII, 2 g.) yielded 6-anilino-6-deoxy-2,3-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XXV, 0.2 g.), m.p. 128° (recrystallized from ethyl acetate and *n*-hexane), $[\alpha]^{23}D$ +22.8° (*c* 1.040, chloroform).

Anal. Calcd. for $C_{15}H_{21}NO_4S$: C, 57.87; H, 6.75; N, 4.50; S, 10.28. Found: C, 57.35; H, 6.76; N, 4.82; S, 10.07.

1,6-Di-*S*-benzyl-2,3-*O*-isopropylidene-1,6-dithio-α-L-sorbofuranose (VII, 2 g.) yielded 2,3-*O*-isopropylidene-1,6-dithio-α-L-sorbofuranose (XXVI, 200 mg.), m.p. 82° (recrystallized from ethyl acetate and *n*-hexane), $[\alpha]^{28}D$ +103.9° (*c* 1.116, chloroform).

Anal. Calcd. for $C_9H_{16}O_4S_2$: C, 42.86; H, 6.35; S, 25.40. Found: C, 42.92; H, 6.60; S, 25.21.

1-*S*-Benzyl-2,3:4,6-di-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XIV, 1 g.) yielded 2,3:4,6-di-*O*-isopropylidene-1-thio-α-L-sorbofuranose (XXVII, 0.1 g.), m.p. 136° (recrystallized from *n*-hexane), $[\alpha]^{23}D$ −17.3° (*c* 0.931, chloroform).

Anal. Calcd. for $C_{12}H_{20}O_5S$: C, 52.17; H, 7.25; S, 11.59. Found: C, 52.38; H, 7.10; S, 11.69.

Acknowledgment.—The authors express their deep gratitude to Dr. K. Takeda, director of this laboratory, and Dr. K. Hamamoto, assistant direct of this laboratory, for their encouragement.

2-Amino-2-deoxy-L-xylose[1,2]

M. L. WOLFROM, D. HORTON, AND A. BÖCKMANN

Department of Chemistry, The Ohio State University, Columbus 10, Ohio

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This work describes the synthesis of the last of the eight possible 2-amino-2-deoxypentoses, the L-*xylo* isomer, by alkaline epimerization of 2-acetamido-2-deoxy-L-lyxose[3] (I) followed by acid hydrolysis.

The first reported 2-amino-2-deoxypentose, the D-*xylo* isomer, was synthesized in this laboratory[4] by definitive C-5–C-6 degradation of a 2-amino-2-deoxy-D-glucose derivative. The L-*arabino* isomer was synthesized[5] by a similar route. The D-*ribo*,[6] L-*ribo*,[7] D-*lyxo*,[6] and L-*lyxo*[3] isomers were subsequently synthesized from suitably substituted pentose derivatives by hydrazinolysis and reduction. The D-*arabino* isomer was first prepared by Kuhn and Baschang[8] by a Strecker type synthesis from 2,4-*O*-ethylidene-D-erythrose.

None of the above procedures appeared to present a satisfactory route to 2-amino-2-deoxy-L-xylose, owing to the unavailability of suitable starting materials. However, the alkaline epimerization of 2-acetamido-2-deoxy-L-lyxose offered the possibility of an interconversion which could be predicted to favor the L-*xylo* isomer at equilibrium, on the basis of greater conformational stability of its pyranose ring form. In the *1C* conformation, 2-acetamido-2-deoxy-L-xylose (II) has equatorial substituents at C-2, C-3, and C-4, but the L-*lyxo* epimer (I) has an axial acetamido group. The epimerization procedure has been found useful for preparation of a number of examples of 2-acetamido-2-deoxyaldoses from their epimers[9,10]; the inductive effect of the acetamido group markedly accelerates[10] the epimerization reaction, in comparison with that of normal aldoses, and 2-ketoses cannot be formed when the acetamido group is present.

2-Acetamido-2-deoxy-L-lyxose (I), prepared as a sirup from crystalline 2-amino-2-deoxy-α-L-lyxose hydrochloride[3] by the Roseman–Ludowieg selective *N*-acetylation procedure,[11] was epimerized in 1 *N* ammonium hydroxide solution. The reaction, followed polarimetrically and by paper chromatography, is not a true equilibrium, since degradation products are simultaneously formed. Hence, the final specific rotation is not a measure of the proportions of the epimeric sugars in solution. The conditions described in the Experimental section are the result of a series of comparative experiments, and would appear optimal for conversion into a product without occurrence of undue degradation. 2-Acetamido-2-deoxy-α-L-xylose was obtained in crystalline condition; the L-*lyxo* enantiomorph[3] (I) again resisted all attempts to bring it to crystallization.

The two epimeric acetamido sugars were separated on borate-treated paper.[12] In the system used, the L-*lyxo* derivative (I) migrated more slowly than its epimer (II). It was shown that, even after removal of a 40% yield of crystalline 2-acetamido-2-deoxy-α-L-xylose, the mother liquors still contained some of the L-*xylo* epimer (II), present with the L-*lyxo* epimer (I) in the ratio 2:3. This supports the prediction made from considerations of relative conformational stability.

The crystalline 2-acetamido-2-deoxy-L-xylose showed upward mutarotation, indicative of an α-L-anomeric configuration, and provided an X-ray powder diffraction pattern identical with that of a reference sample of the D enantiomorph.[4] The infrared absorption in the 10.5–14-μ region showed strong absorptions at 12.90, 10.90, and 10.66 μ close to the corresponding values (13.16, 11.08, and 10.70 μ) reported[13] for α-D(or L)-xylopyranose and some related derivatives.

2-Acetamido-2-deoxy-α-L-xylose gave a positive Morgan–Elson[14] reaction, as did the D-enantiomorph. The statement[4] that 2-acetamido-2-deoxy-D-xylose gives a positive Elson–Morgan reaction is incorrect.

Hydrolysis of 2-acetamido-2-deoxy-α-L-xylose with 2 *N* hydrochloric acid gave crystalline 2-amino-2-deoxy-α-L-xylose hydrochloride, identical with the known D enantiomorph[4] in all respects except for the sign of the mutarotation curve. This compound gave a positive Elson–Morgan[15] reaction.

Experimental[16]

2-Acetamido-2-deoxy-α-L-xylose.—A solution of sirupy 2-acetamido-2-deoxy-L-lyxose[3] (I, 1.00 g.) in 1 *N* ammonium hydroxide (100 ml.) was stored for 51 hr. at 20°, during which time the specific rotation changed from −12.8 to −7.1°. The solution was evaporated to dryness, traces of water were removed by

(1) Preliminary communication: M. L. Wolfrom, D. Horton, and A. Böckmann, *Chem. Ind.* (London), 41 (1963).

(2) This work was supported by a grant, No. CY-3232(C5) (Ohio State University Research Foundation Project 759E), from the National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

(3) D. Horton, M. L. Wolfrom, and A. Thompson *J. Org. Chem.*, **26**, 5069 (1961).

(4) M. L. Wolfrom and K. Anno, *J. Am. Chem. Soc.*, **75**, 1038 (1953).

(5) M. L. Wolfrom and Z. Yosizawa, *ibid.*, **81**, 3477 (1959).

(6) M. L. Wolfrom, F. Shafizadeh, R. K. Armstrong, and T. M. Shen Han, *ibid.*, **81**, 3716 (1959).

(7) M. L. Wolfrom, F. Shafizadeh, and R. K. Armstrong, *ibid.*, **80**, 4885 (1958).

(8) R. Kuhn and G. Baschang, *Ann.*, **628**, 193 (1959).

(9) C. T. Spivak and S. Roseman, *J. Am. Chem. Soc.*, **81**, 2403 (1959); R. Kuhn and G. Baschang, *Ann.*, **636**, 164 (1960); P. M. Carroll and J. W. Cornforth, *Biochim. Biophys. Acta*, **39**, 161 (1960); S. Fujii and H. Kushida, *ibid.*, **69**, 572 (1963).

(10) B. Coxon and L. Hough, *J. Chem. Soc.*, 1577 (1961).

(11) S. Roseman and J. Ludowieg, *J. Am. Chem. Soc.*, **76**, 301 (1954).

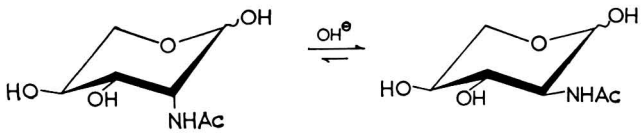
(12) C. E. Cardini and L. F. Leloir, *J. Biol. Chem.*, **225**, 317 (1957).

(13) S. A. Barker, E. J. Bourne, R. Stephens, and D. H. Whiffen, *J. Chem. Soc.*, 3468 (1954); R. S. Tipson and H. S. Isbell, *J. Res. Natl. Bur. Std.*, **64A**, 239 (1960); **65A**, 31 (1961).

(14) W. T. J. Morgan and L. A. Elson, *Biochem. J.*, **28**, 998 (1934); D. Aminoff, W. T. J. Morgan, and W. M. Watkins, *ibid.*, **51**, 379 (1952).

(15) L. A. Elson and W. T. J. Morgan, *ibid.*, **27**, 1824 (1933); R. Belcher, A. J. Nutten, and C. M. Sambrook, *Analyst*, **79**, 201 (1954).

(16) Melting points were determined on a Fisher-Johns apparatus. Optical rotations were measured in a 4-dm. tube. Microanalyses were performed by W. N. Rond. Infrared spectra were determined with a Perkin-Elmer Model 137 ("Infracord") spectrophotometer, and the pellets were pressed from a finely ground mixture of the product with dried, analytical reagent grade potassium bromide. Paper chromatography was performed by the descending technique, with detection of zones by the silver nitrate–sodium hydroxide procedure of W. E. Trevelyan, D. P. Proctor, and J. S. Harrison [*Nature*, **166**, 444 (1950)]. Borate-treated[12] Whatman No. 1 chromatography paper was stored at least 1 week in contact with the atmosphere before use. Photodensitometric determinations were made with a Photovolt Model 52-C-501A photometric densitometer. Paper-chromatographic mobilities, R_x, are relative to 2-acetamido-2-deoxyxylose.



I II

codistillation with ethanol and toluene, and the remaining sirup was dissolved in ethanol, whereupon 2-acetamido-2-deoxy-α-L-xylose crystallized (first nuclei were obtained by cellulose-column chromatography); yield 0.40 g. (40%). Recrystallization from ethanol gave pure material; yield 0.33 g.; m.p. 194–195° dec.; $[\alpha]^{19}D$ −58, initial, extrapolated, → −7.1°, 4 hr., equil. (*c* 0.5, water); λ_{max}^{KBr} 3.00 (OH), 6.10, 6.50 (NHAc), 12.90, 10.90, and 10.66 μ; X-ray powder diffraction data[17]: 8.98 vw, 6.86 vs (2), 5.09 s (3), 4.67 w, 4.27 vs (1), 3.95 m, 3.80 m, 3.51 m, 3.44 vw, 3.36 vw, 3.17 vw, 3.10 m; Morgan-Elson[14] reaction (+).

Anal. Calcd. for $C_7H_{13}NO_5$: C, 43.97; H, 6.85; N, 7.33. Found: C, 44.34; H, 7.15; N, 7.59.

The D enantiomorph has been reported[4] to have m.p. 186–189° dec., $[\alpha]D$ +56 → +9°. The X-ray powder diffraction pattern of the D enantiomorph was found to be identical with that recorded herein for the L-enantiomorph.

(17) Interplanar spacing, Å., Cu Kα radiation. Relative intensity estimated visually: s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest).

Paper chromatography of the residual mother liquors on borate-treated paper[12] with a 6:4:3 butanol–pyridine–water system, gave two principal zones, R_x value[16] 0.72 and 1.00 in the intensity ratio, determined densitometrically, of 3 to 2, together with proportions of slower moving components. The zone R_x 0.72 corresponded to starting material (I); the faster zone corresponded to the product (II). 2-Acetamido-2-deoxy-D-xylose[4] was indistinguishable from its enantiomorph on paper chromatograms. A further yield of (sirupy) 2-acetamido-2-deoxy-L-xylose (II) was obtainable by isolative paper chromatography, to raise the total yield to 62%. The two epimers were not separable on untreated Whatman No. 1 paper.

2-Amino-2-deoxy-α-L-xylose Hydrochloride.—A solution of 2-acetamido-2-deoxy-α-L-xylose (123 mg.) in 2 *N* hydrochloric acid (50 ml.) was heated for 2 hr. at 100°. The solution then was evaporated, and traces of acid were removed by codistillation with 2-propanol and ethanol. The residue was crystallized from ethanol–acetone; yield 80 mg. (68%), m.p. 164–168° dec. Recrystallization was effected, with little loss, from ethanol–acetone–ether; m.p. 165–169° dec.; $[\alpha]^{23}D$ −78, initial, extrapolated, → −46.4 ± 0.5°, 3 hr., equil. (*c* 0.5, water); λ_{max}^{KBr} 3.0–3.3 (OH, NH_3^+), 6.25, 6.61 (NH_3^+), 10.98, 11.30, and 13.25 μ; X-ray powder diffraction data[17]: 8.01 m, 6.03 s, 4.54 s (2), 4.37 s (3), 4.06 s, 3.41 s (1), 3.23 s, 3.06 w, 2.95 w, 2.78 w, 2.69 w, 2.61 m, 2.51 m, 2.37 m, 2.33 m, 2.26 m, 2.21 s; Elson–Morgan[15] reaction (+).

Anal. Calcd. for $C_5H_{12}ClNO_4$: Cl, 19.10. Found: Cl, 18.76.

For 2-amino-2-deoxy-α-D-xylose hydrochloride, Wolfrom and Anno[4] report m.p. 160–165° dec.; $[\alpha]D$ +80, initial, extrapolated → +40° (*c* 0.8, water, final).

Mercaptan–Disulfide Interchange Reactions. II. Some Equilibrium Constants[1]

GARY DALMAN, JOHN MCDERMED, AND GEORGE GORIN[2]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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Equilibrium constants have been determined for the interchange reactions between two organic disulfides and/or between a mercaptan and a disulfide for the following cases: *n*-hexyl–phenyl, *n*-hexyl–β-hydroxyethyl, *n*-hexyl–(β-diethylamino)ethyl, *n*-propyl–*sec*-butyl, and *n*-butyl–*t*-butyl. The constants differ from the statistically predicted values by a factor of two or less, except for the reactions of phenyl mercaptan with hexyl phenyl disulfide and of *t*-butyl mercaptan with *n*-butyl *t*-butyl disulfide, which have smaller constants. These data and others indicate that the interchange reactions are not sensitive to the effect of substituent groups, except ones that interfere sterically.

Mercaptans and organic disulfides can react with one another in appropriate conditions. Such reactions occur in diverse chemical systems and may have consequences of considerable importance; examples may be found in petroleum,[3] polysulfide rubber,[4] and living organisms.[5] In organic chemistry, reactions which proceed to a measurable equilibrium state are comparatively rare, and the mercaptan–disulfide interchange reactions to be described are interesting from this point of view also. The present paper will be concerned with some general aspects of the problem and with reactions taking place in an organic medium. Paper III of this series, which follows,[6] will consider reactions of water-soluble compounds in buffered aqueous medium.

(1) (a) Paper I: G. Gorin, G. Dougherty, and A. V. Tobolsky, *J. Am. Chem. Soc.*, **71**, 3551 (1949); (b) presented in part at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962.

(2) To whom inquiries concerning this paper should be sent.

(3) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., New York, N. Y., 1958, pp. 16–18.

(4) E. M. Fettes and J. S. Jorczak in "Polymer Processes," C. E. Schildknecht, Ed., Interscience Publishers, New York, N. Y., 1956, pp. 475–498.

(5) R. Cecil and J. R. McPhee, *Advan. Protein Chem.*, **14**, 296 (1959).

(6) H. A. Smith, G. Doughty, and G. Gorin, *J. Org. Chem.*, **29**, 1485 (1964).

The reaction of two symmetrical disulfides to give the unsymmetrical, or "mixed," disulfide may be represented by eq. 1a. Unsymmetrical disulfides also may

$$RSSR + R'SSR' \rightleftarrows 2RSSR' \qquad (1a)$$

result from the reaction of RSSR with a mercaptan, according to eq. 2a. The reaction may then proceed further, according to eq. 3a.

$$RSSR + R'SH \rightleftarrows RSSR' + RSH \qquad (2a)$$

$$RSSR' + R'SH \rightleftarrows R'SSR' + RSH \qquad (3a)$$

The corresponding equilibrium expressions are

$$K_1 = (RSSR')^2/(RSSR)(R'SSR') \qquad (1b)$$

$$K_2 = (RSSR')(RSH)/(RSSR)(R'SH) \qquad (2b)$$

$$K_3 = (R'SSR')(RSH)/(RSSR')(R'SH) \qquad (3b)$$

where the quantities in parentheses are the activities of the respective chemical species. The product K_2K_3 measures the equilibrium constant for reaction 4a.

$$RSSR + 2R'SH \rightleftarrows R'SSR' + 2RSH \qquad (4a)$$

$$K_4 = K_2K_3 = (R'SSR')(RSH)^2/(RSSR)(R'SH)^2 \quad (4b)$$

Finally, it should be obvious that this relation obtains.

$$K_1 = K_2/K_3 \quad (5)$$

If the distribution of R and R′ groups were determined by probability, a mixture originally containing equimolar amounts of RSSR and R′SSR′ would contain, at equilibrium, twice as much RSSR′ as either remaining symmetrical disulfide; *i.e.*, K_1 would equal 4. Similarly, a mixture originally containing 1 mole of RSSR and 2 moles of R′SH would give, at equilibrium, the following amounts: RSSR and R′SSR′, 0.25 mole each; RSSR′, 0.50 mole; RSH and R′SH, 1 mole each; *i.e.*, K_2 would equal 2, K_3 0.5, K_4 1. The aim of the present investigation was to determine the actual values of the constants for some mercaptans and disulfides and to correlate the deviations from the statistically predicted behavior with chemical constitution.

Two investigations of this problem had been conducted before the present work (excluding studies conducted in buffered aqueous medium, to be discussed in paper III[6]) by Birch, Cullum, and Dean[7] and by Haraldson, *et al.*[8] Their results will be considered in the Discussion section. It might be stated at this point that these studies were restricted to the determination of K_1 and that the results showed only small divergences from the statistical value, except in the cases involving *t*-butyl groups. In the present work, phenyl and substituted ethyl compounds were examined, to see whether more marked effects would be encountered. Values of K_1 and of K_2K_3 were determined independently, thus making possible an internal check on the validity of the data.

Experimental

Materials.—1-Hexanethiol, 1-butanethiol, 2-methyl-2-propanethiol, 2-mercaptoethanol, *n*-butyl disulfide, *n*-propyl disulfide, hexadecane (practical grade), and 1-octanol were obtained from Eastman Organic Chemicals, Rochester 3, N. Y.; benzenethiol, 1-propanethiol, benzyl ether (practical grade), and 2,2,4-trimethylpentane from Matheson Coleman and Bell, Cincinnati 12, Ohio; phenyl disulfide and *sec*-butyl disulfide from Columbia Organic Chemicals Co., Columbia, S. C.; bis(2-hydroxyethyl) disulfide from Aldrich Chemical Co., Milwaukee 10, Wis.; octadecane and tetradecane from Humphrey-Wilkenson, Inc., North Haven, Conn.; lithium aluminum hydride from Metal Hydrides, Inc., Beverly, Mass.; sodium methoxide (purified) from Fisher Scientific Co., St. Louis, Mo. 2-(Diethylamino)-ethanethiol hydrochloride was a gift from Evans Chemetics, Waterloo, N. Y. Except when otherwise designated, these substances were of the highest quality available and were used without further purification. *t*-Butyl disulfide (practical grade) from Eastman Organic Chemicals was redistilled under reduced pressure.

To prepare *n*-hexyl disulfide, iodine was added with shaking to 59.1 g. of hexanethiol in 200 ml. each of chloroform and 0.05 *M* sodium hydroxide to a slight excess. The chloroform layer was washed with 5% aqueous sodium bicarbonate and 0.1 *M* sodium thiosulfate to remove hydrogen iodide and iodine; then the solvent was removed under reduced pressure and the residue was distilled at 0.3-mm. pressure; 44.5 g. (76%) of disulfide was obtained, boiling at 108–110°. The physical properties of a center fraction collected at 109° were $n^{25}D$ 1.6756; d^{25} 0.9052; absorbance maximum in 95% ethanol at 255 mμ, molar absorbancy coefficient 410.

sec-Butyl mercaptan was prepared by placing 6.6 g. of lithium aluminum hydride and 250 ml. of dry ether in a 500-ml. three-necked flask fitted with a dropping funnel, a reflux condenser, and a mechanical stirrer, and adding 41 g. of *sec*-butyl disulfide dropwise in the course of 1 hr. The reaction mixture was refluxed 40 min., cooled in an ice bath, treated with water to decompose excess hydride, and acidified with 100 ml. of 15% sulfuric acid. After stirring for 24 hr., the mixture was extracted with ether, the ether layer was washed with water and dried, the solvent was removed under reduced pressure, and the residue was distilled. A 20-g. fraction of *sec*-butyl mercaptan, boiling at 83°, was collected for use.

(2-Diethylamino)ethanethiol was prepared by dissolving 48 g. of the hydrochloride salt in 200 ml. of air-free ethanol, adding 11 g. of sodium hydroxide in 150 ml. of ethanol, removing the precipitated sodium chloride by filtration, and distilling the filtrate under nitrogen at reduced pressure; a 15-g. fraction, boiling at 62° and 15 mm., was taken for use. Bis(2-diethylaminoethyl) disulfide was prepared by dissolving 26 g. of (2-diethylamino)-ethanethiol hydrochloride and 12 g. of sodium hydroxide in 200 ml. of methanol, passing air through the solution for 24 hr., removing the sodium chloride by filtration and the solvent by evaporation under reduced pressure, again filtering, and distilling the filtrate under reduced pressure; a 5.8-g. fraction boiling at 115–120° and 0.4 mm. was taken for use.

All the mercaptans, disulfides, and marker compounds gave a single peak on gas phase chromatography as described below.

Gas Chromatographic Procedure.—The gas chromatograph used was an Aerograph Model A-300. The SE-30 silicone columns were prepared from commercial materials or purchased ready made; the Carbowax column was purchased (Wilkens Instruments and Research Co., Walnut Creek, Calif.). Helium was the carrier gas. A thermal-conductivity detector was used. Samples were injected into the chromatograph with a 10-μl. Hamilton syringe. A 1-mv. Brown Electronik recorder (Minneapolis-Honeywell Corp., Philadelphia, Pa.) was employed. Areas under the recorder tracings were measured with an Ott compensating planimeter, Type 30 (Frederick Post Co., Chicago, Ill.), set at the scale 1 vernier unit = 4 mm.².

Disulfide Interchange Reactions.—The procedure employed for *n*-hexyl–phenyl disulfide will be described in detail. Other pairs of disulfides were handled similarly.

To calibrate the gas chromatographic analysis, known amounts of each disulfide were dissolved in ethanol, and benzyl ether was added as a "marker." Conditions were then established, by which the mixture would give well-defined and separated peaks on the recorder tracing (see Table I, p. 1482). Calibration constants were determined from the relation: $k = WA_m/W_mA$ where W and W_m are the weight of component and of marker, respectively, and A and A_m the corresponding areas.

For the equilibrium experiments, solutions were prepared in ethanol containing each of the disulfides at 0.15–0.25 *M* concentration. Sodium hydroxide, 0.01 g., was added as a catalyst (for all other disulfide pairs, the same quantity of sodium methoxide was used), and, in some cases, 0.02 g. of the *n*-alkyl mercaptan. The reaction mixture was kept in a water bath at 25 ± 0.1° and aliquot samples were taken for analysis at appropriate times. The samples were neutralized with concentrated hydrochloric acid using pH-paper indicator. They were then subjected to gas chromatography.

The tracings obtained from the reaction mixtures comprised a peak located midway between the symmetrical disulfide peaks, which could be ascribed to the mixed disulfide. It was assumed that the calibration constant for this compound would be the mean of the values for the symmetrical disulfides. In most cases, a marker compound was added after the reaction mixture had been made acidic, and the amounts of disulfides present could be calculated from the relation given above. However, the marker could be omitted, since only the relative amounts of the components need be known for calculating the equilibrium constant; the required data can be obtained by multiplying the peak areas by the calibration constants.

Hexyl–Phenyl Mercaptan–Disulfide Interchange Reactions.—To calibrate the gas chromatographic analysis, mixtures containing known amounts of *n*-hexyl mercaptan, phenyl mercaptan, and marker, decane, were prepared in ethanol solvent and subjected to analysis (see Table I, p. 1482). Some calibration experiments were also done with mixtures of mercaptans and disulfides; in this case, the column temperature was maintained at the lower value

(7) S. F. Birch, T. V. Cullum, and R. A. Dean, *J. Inst. Petrol.*, **39**, 206 (1953).

(8) L. Haraldson, C. J. Olander, S. Sunner, and E. Varde, *Acta Chem. Scand.*, **14**, 1509 (1960).

TABLE I

CONDITIONS FOR GAS CHROMATOGRAPHY

Compound	Calibrtd. k	Marker	Column temp., °C.	Column	Flow rate, ml./min.
n-Hexyl disulfide	0.98 ± 0.04	Benzyl ether	200	0.25 in. × 8 ft. Al	90
Phenyl disulfide	1.18 ± 0.07			5% SE-30	
Mixed disulfide	(1.08)[a]			60–80 Chromosorb-W	
n-Hexyl mercaptan	1.05 ± 0.02	Decane	100		
Phenyl mercaptan	1.21 ± 0.02				
n-Hexyl disulfide	1.06 ± 0.03	Octadecane	180	0.25 in. × 5.5 ft. Al	90
$(HOCH_2CH_2S)_2$	1.69 ± 0.04			5% SE-30	
Mixed disulfide	(1.38)[a]			60–80 Chromosorb-W	
n-Hexyl mercaptan	1.08 ± 0.02	Decane	80		
$HOCH_2CH_2SH$	2.54 ± 0.39				
n-Hexyl disulfide	1.26 ± 0.05	Hexadecane	180	0.25 in. × 5 ft. Al	90
$(Et_2NCH_2CH_2S)_2$	1.54 ± 0.03			5% Carbowax 20-M	
Mixed disulfide	(1.40)[a]			60–80 Chromosorb-HMDS	
n-Hexyl mercaptan	0.89 ± 0.02	Tetradecane	100		
$Et_2NCH_2CH_2SH$	1.12 ± 0.06				
n-Propyl disulfide	1.09 ± 0.02	Octanol	150	0.25 in. × 8 ft. Al	50
sec-Butyl disulfide	1.20 ± 0.02			10% SE-30	
Mixed disulfide	(1.15)[a]			60–80 Chromosorb-W	
n-Propyl mercaptan	1.03 ± 0.05	Isooctane	75		
sec-Butyl mercaptan	1.04 ± 0.05				
n-Butyl disulfide	1.12 ± 0.04	Dodecane	160	0.25 in. × 8 ft. stainless steel	50
t-Butyl disulfide	1.28 ± 0.02			10% SE-30	
Mixed disulfide	(1.20)[a]			60–80 Chromosorb-W	
n-Butyl mercaptan	1.03 ± 0.04	Toluene	80		
t-Butyl mercaptan	1.06 ± 0.03				

[a] Estimated.

specified until the mercaptans had emerged, and then the temperature was raised as quickly as possible by manual control of the heater.

Some reaction mixtures were made up with hexyl mercaptan and phenyl disulfide, others with phenyl mercaptan and hexyl disulfide, each at concentrations of 0.2–0.4 *M*. Sodium hydroxide was added in the amount of 0.01 g./10 ml. The mixture was kept at 25° and aliquot samples were taken for analysis at appropriate intervals. The catalyst was neutralized as described in the preceding section.

Other Mercaptan–Disulfide Interchange Reactions.—The procedure for all other mercaptan–disulfide systems except butyl was the same as described in the preceding section, except that sodium methoxide was used instead of sodium hydroxide.

With the *n*-butyl *t*-butyl compounds, 2 mmoles of disulfide and 2–3 mmoles of mercaptan were mixed with 0.2 mmole of sodium methoxide and 1.2 ml. of ethanol, which gave a homogeneous solution. Ampoules of 0.4-ml. capacity with a long capillary neck were made by drawing 10 × 75 mm. Pyrex test tubes in the flame. The reaction mixture was transferred into these ampoules by placing them, neck downwards, in the mixture, reducing the pressure above momentarily, and then restoring atmospheric pressure; the necks were then sealed The ampoules were placed in an aluminum heating block, the temperature of which was maintained at 60 ± 0.5° by a heater, thermoregulator, and relay.

The composition of the mixtures originally containing *n*-butyl disulfide and *t*-butyl mercaptan changed perceptibly for about 30 days; to ensure equilibrium, the mixtures were kept for another 70 days and then analyzed. After 100 days, the composition of the mixtures initially containing *t*-butyl disulfide and *n*-butyl mercaptan was still changing, and the experiments were not continued.

Oxidation of Butyl Mercaptan Mixtures.—Measured amounts of *n*-butyl and *t*-butyl mercaptan (usually, 5.0 mmoles each) were dissolved in 100 ml. of 1 *M* sodium hydroxide. Freshly prepared potassium ferricyanide solution, 20% by weight, was added with constant stirring until the yellow color of ferricyanide did not fade on standing. The oxidation was effected at room temperature. The reaction mixture was acidified with 8 ml. of concentrated hydrochloric acid and extracted with 10 ml. of ether. The organic layer was separated and dried over calcium chloride, and the ether was evaporated. The residue was taken up in methanol and analyzed by gas chromatography. No mercaptan peaks were observed.

Results

Gas chromatography effected in the conditions summarized by Table I permitted the separation of the mercaptans and disulfides mentioned therein. Four or five calibration experiments were conducted for each compound, and the average deviation from the mean value of the calibration constant indicates the degree of reproducibility obtained in the peak areas.

As has been stated, each mercaptan and disulfide used as a reagent in this investigation gave a single peak on gas chromatography. When mixtures of symmetrical disulfides or of a disulfide and a mercaptan were made up in ethanol and analyzed soon thereafter, the number of peaks corresponded to the number of components added, indicating that no interchange had taken place before or during the analysis.

As a matter of fact, little or no reaction took place in any case, even after several days, unless a catalyst were added. In the mercaptan–disulfide interchange reactions, sodium methoxide was the usual catalyst, and equilibrium was attained in 2–4 days, except with the *t*-butyl compounds. In the reaction of *n*-butyl disulfide with *t*-butyl mercaptan, 30–60 days at 60° were required to attain equilibrium, while in the case of *t*-butyl disulfide and *n*-butyl mercaptan, reaction was not complete even after 100 days.

The disulfide interchanges came to equilibrium in 2–5 days if conducted in the presence of sodium methoxide and *n*-alkyl mercaptan as catalyst (note that the experiments did not include *t*-butyl disulfide, which doubtless would take very long). In the most rapidly reacting system, hexyl–phenyl, equilibrium was attained

with sodium hydroxide alone, in about 4 days; in the presence of *n*-hexyl mercaptan, equilibrium was established in a matter of hours.

Table II summarizes the values of the constants obtained. These are indexed in accordance with equations (1–5), where RSSR represents the *n*-alkyl disulfide (propyl, butyl, or hexyl), and R′SH the "nonnormal" mercaptan (phenyl, substituted ethyl, *sec*- or *t*-butyl). Actually, the mercaptan–disulfide interchange reactions were conducted with both possible pairs of starting materials, *e.g.*, hexyl disulfide and phenyl mercaptan as well as phenyl disulfide and hexyl mercaptan, and strict adherence to the scheme represented by the equations (1–5) would lead to different constants depending on which mercaptan and disulfide was used. However, all the values reported in Table II and elsewhere in the paper refer to the equilibrium expressions written as specified above.

TABLE II
EQUILIBRIUM CONSTANTS

System	K_1	K_2[a]	K_3[a]	K_4	K_2/K_3
R = *n*-hexyl	8.5	1.02	0.14		
R′ = phenyl	8.2	1.03	0.14		
	8.0	1.16*	0.15*		
	7.7	1.15*	0.15*		
	8.1	1.09	0.15	0.16	7.3
R = *n*-hexyl	4.9	1.1	0.21		
R′ = $HOCH_2CH_2$	5.1	1.3*	0.30*		
	4.9	0.95*	0.25*		
	5.0	1.1	0.25	0.28	4.4
R = *n*-hexyl	5.08	1.31	0.25		
R′ = $Et_2NCH_2CH_2$	(5.85)	1.30	0.29		
	4.98	1.26*	0.19*		
	5.08				
	5.05	1.29	0.24	0.31	5.4
R = *n*-propyl	4.55	2.17	0.51		
R′ = *sec*-butyl	4.21	1.95	0.46		
	4.36	1.87*	0.47*		
	4.60	2.12*	0.54*		
		1.91*	0.45*		
	4.43	2.00	0.49	0.98	4.1
R = *n*-butyl		3.64	0.175		
R′ = *t*-butyl		3.20	0.154		
		3.55	0.160		
		3.18	0.150		
		3.39[b]	0.160[b]		21

[a] The unstarred values were determined in mixtures originally containing RSSR and R′SH; the starred values with R′SSR′ + RSH. [b] At 60°.

When equimolar mixtures of *n*-butyl and *t*-butyl disulfides in 1 *M* sodium hydroxide were oxidized with potassium ferricyanide, the product contained *n*-butyl disulfide, *t*-butyl disulfide, and the mixed disulfide in the ratio 1:0.88:1.7. These ratios are quite different from those obtaining at equilibrium (1:1:5).

Discussion

Although the existence of mixed disulfides was reported as early as 1886 and several were prepared subsequently,[9] it was believed by some that they were intrinsically less stable than symmetrical disulfides. In 1952–1953, McAllan, Birch, and co-workers[7,10] reported clear evidence that this is not the case for alkyl disulfides; if two disulfides, or a disulfide and a mercaptan, are mixed and allowed to come to equilibrium, the mixed disulfide is formed, often to the extent expected from probability considerations. Birch, *et al.*,[7] prepared several mixed disulfides by equilibrating two symmetrical disulfides or a disulfide and a mercaptan in ethanol solution containing a little water and sodium hydroxide. After neutralizing the base, the relative amounts of mixed and symmetrical disulfides were determined by distillation. While results of only moderate precision could be expected by this method, the presence of mixed disulfide at equilibrium was clearly demonstrated, the ratio unsymmetrical–symmetrical being 2 to 1 for methyl–ethyl, ethyl–*n*-butyl, ethyl–isobutyl; 5 to 1 for methyl–*t*-butyl; 6 to 1 for ethyl–*t*-butyl; 4 to 1 for octyl–*t*-butyl; and 3 to 1 for methyl–phenyl. Birch, *et al.*, also prepared some mixed disulfides by oxidizing mixtures of two mercaptans with hydrogen peroxide, iodine, or potassium ferricyanide; in two cases, methyl–ethyl and ethyl–*n*-butyl, the same results were obtained by oxidation and by base-catalyzed equilibration.

Haraldson, *et al.*,[8] studied the interchange reaction between pairs of disulfides and analyzed the products by gas chromatography. The values of the equilibrium constant K_1 at 25° were 5.6 for methyl–ethyl, 4.1 for ethyl–isopropyl, and 24.5 for ethyl–*t*-butyl. Essentially the same values were found at 60°, showing that the heat of reaction is very small or zero.

Since the interchange reactions are rather slow, even in the presence of catalyst, it is desirable to check the attainment of equilibrium in more than one way. Haraldson, *et al.*,[8] accomplished this by preparing the mixed disulfides, and using these compounds, as well as mixtures of two symmetrical disulfides, as the starting material in the equilibrium experiments. In all but one of the mercaptan–disulfide reactions studied in the present work, the attainment of equilibrium was checked by conducting the experiments with both the possible combinations of mercaptan and disulfide. As far as the disulfide interchange reactions are concerned, the validity of K_1 can be checked by comparison with the values of K_2/K_3 (eq. 5); the data are consistent within their limits of precision.

With the *n*-butyl–*t*-butyl compounds, only one type of equilibrium experiment was performed, starting with *n*-butyl disulfide and *t*-butyl mercaptan. This system came to equilibrium in 30–60 days at 60°, and measurements were made after 100 days. The equilibrium constant K_1 calculated from the experimentally determined values of K_2 and K_3 is quite similar to the value found experimentally for the ethyl–*t*-butyl system by Haraldson, *et al.*[8] (these workers, as well as Fava, *et al.*,[11] also noted the very slow rate of reaction for *t*-butyl compounds). The thermodynamic instability of *t*-butyl disulfide has been attributed[8] to the steric interference with the rotation of the alkyl groups.

(9) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., New York, N. Y., 1960, pp. 362, 406–411.

(10) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

(11) A. Fava, A. Iliceto, and E. Camera, *ibid.*, **79**, 833 (1957).

Oxidation of an equilibrium mixture of *n*- and *t*-butyl mercaptans did not give a product containing the disulfides in the equilibrium ratio. There is no reason to expect that they should, since the nature of the products must be determined by the relative rate of reaction. The fact that Birch, *et al.*,[7] obtained the same product by oxidation and base-catalyzed equilibration in two cases may well be a coincidence.

The propyl–*sec*-butyl system gives a value of K_1 essentially identical with that predicted on the basis of probability. This falls in line with the values found by other investigators for *n*- and isoalkyl compounds. The present work shows, furthermore, that K_2 and K_3 separately conform to the statistical values.

Substitution of diethylamino or hydroxo groups for hydrogen reduce K_1 and K_2 each by a factor of about two; *i.e.*, the substituted disulfides are slightly better oxidizing agents than the *n*-alkyl disulfides; K_1, however, conforms closely to the statistical value. Phenyl disulfide is a still better oxidizing agent, and, in addition, the mixed disulfide is relatively favored. All in all, the deviations from statistical behavior must be regarded as small, and, in view of the variety of compounds examined, it is concluded that the effect is a general one. In the absence of steric or extraneous chemical effects,[6] therefore, it may be expected that mercaptan–disulfide interchange reactions will conform closely to the distribution predicted on the basis of probability.

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Mercaptan–Disulfide Interchange Reactions.[1] III. Reaction of Cysteine with 4,4′-Dithiobis(benzenesulfonic acid)

H. A. SMITH, GAVIN DOUGHTY, AND GEORGE GORIN

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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Sodium 4,4′-dithiobisbenzenesulfonate (Na_2BSSB) has been prepared from sulfanilic acid. The ultraviolet absorption spectra have been determined for BSSB, the mixed disulfide formed from it upon reaction with cysteine (BSSR), 4-mercaptobenzenesulfonate (BSH), and its mercaptide ion (BS^-). The ionization constant of BSH is $10^{-5.7}$. The following equilibrium constants have been measured: $[(BSSR)(BSH)]/[(BSSB)(RSH)] = 1.2$ and $[(RSSR)(BSH)]/[(BSSR)(RSH)] = 1.0$ at 25°. The ionization of BSH tends to drive the reaction of cysteine with BSSB toward completion at pH values above 6.5. Some measurements of reaction rate are reported.

Cysteine and some of its derivatives are involved in many important physiological processes: for example, enzymic catalysis,[2] protein aggregation,[3] and cell division.[4] A measure of protection against ionizing radiation is afforded by cysteine and a few congeners, and it has been suggested that the radioprotective action involves the formation of mixed disulfides with protein molecules.[5] Some measurements of equilibria have been made for mercaptan–disulfide interchange reactions involving these compounds; these data will be considered briefly in the Discussion section. The experimental results are limited and in some cases uncertain. The present investigation was undertaken because further study of the problem seemed desirable.

The reaction of cysteine with 4,4′-dithiobisbenzenesulfonate can be measured with comparative ease because the 4-mercaptobenzenesulfonate formed in the reaction ionizes to give a mercaptide anion that has a characteristic absorption peak in the ultraviolet and can be determined spectrophotometrically. The ionization of 4-mercaptobenzenesulfonate and the employment of a buffered medium introduce additional considerations, however. The interchange reactions may be represented by the equations

$$BSSB + RSH \rightleftharpoons BSSR + BS^- + H^+ \quad (1)$$

$$BSSR + RSH \rightleftharpoons RSSR + BS^- + H^+ \quad (2)$$

where BSSB is the doubly charged anion, 4,4′-dithiobisbenzenesulfonate; RSH is cysteine; BSH is 4-mercaptobenzenesulfonate; BS^- is the corresponding mercaptide anion, 4-sulfidobenzenesulfonate (since the sulfonic acid groups are completely ionized in all the conditions of interest, the charges resulting from their ionizations are not indicated).

The ionization constant expression for BSH

$$K_1 = [(BS^-)(H^+)]/(BSH) \quad (3)$$

relates the equilibrium-constant expressions for eq. 1 and 2 to those given in paper II,[1] which are written for unionized compounds.

$$K_2' = [(BSSR)(BS^-)(H^+)]/[(BSSB)(RSH)] = K_2K_1 \quad (4)$$

$$K_3' = [(RSSR)(BS^-)(H^+)]/[(BSSR)(RSH)] = K_3K_1 \quad (5)$$

$$K_4 = K_2'K_3' = [(RSSR)(BS^-)^2(H^+)^2]/[(BSSB)(RSH)^2] = K_2K_3K_1^2 \quad (6)$$

Experimental

Materials.—Cysteine hydrochloride monohydrate was an "A" grade product of the California Corporation for Biochemical Research, Los Angeles 63, Calif. Cystine and oxidized glutathione were products of Schwarz Laboratories, Mt. Vernon, N. Y.

(1) See preceding paper: G. Dalman, J. McDermed, and G. Gorin, *J. Org. Chem.*, **29**, 1480 (1964).

(2) P. D. Boyer, "The Enzymes," Vol. I, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1959, p. 511.

(3) E. V. Jensen, *Science*, **130**, 1319 (1959).

(4) D. Mazia, "Sulfur in Proteins," R. Benesch, *et al.*, Ed., Academic Press, Inc., New York, N. Y., 1959, p. 357.

(5) L. Eldjarn and A. Pihl, "Mechanisms in Radiobiology," Vol. II, M. Errera and A. Forssberg, Ed., Academic Press, Inc., New York, N. Y., 1960, p. 231.

glutathione of Matheson Coleman and Bell, Cincinnati 12, Ohio. Other chemicals were of ACS reagent grade. Phosphate buffers were mixed from sodium phosphates or from sodium hydroxide and phosphoric acid to give a total phosphate concentration of 0.02 *M*; 1 g. of ethylenedinitrilotetraacetic acid (EDTA) was added per liter of solution.

Preparation of Sodium 4,4′-Dithiobisbenzenesulfonate [Na_2-BSSB].—Dissolve sulfanilic acid, 47.5 g. (0.25 mole), and 13.25 g. of anhydrous sodium carbonate (0.13 mole) in 500 ml. of water by warming. Cool to 15°. Add 18.5 g. of sodium nitrite (0.27 mole) in 50 ml. of water and pour the mixture slowly with stirring into 52.5 ml. of concentrated hydrochloric acid (0.64 mole) and 300 g. of crushed ice. After 15 min., a test for nitrous acid with starch-iodide paper should be positive.

Dissolve 65 g. of crystalline sodium sulfide nonahydrate (0.27 mole) and 8.5 g. of powdered sulfur (0.27 mole) in 75 ml. of water at 100°; add 10 g. of sodium hydroxide (0.25 mole) in 100 ml. of water. Cool below 5° and add the diazo solution over a period of 20–30 min., along with 48 g. of ice to keep the temperature below 5°. Remove the ice bath and allow the mixture to come to room temperature; the evolution of nitrogen should cease in about 2 hr. Add concentrated hydrochloric acid to pH 2, filter to remove the sulfur, and heat the filtrate to drive out hydrogen sulfide. Neutralize to pH 7 with concentrated sodium hydroxide; filter if necessary. Collect 10–15 g. (25–35% yield) of the disulfide by evaporation of the solvent at 60–80° or under reduced pressure (by further evaporation, more material can be recovered, to about 70% yield, but its purification from contaminating sodium chloride and other impurities is not worthwhile).

Crystallize the product by dissolving in the minimum amount of 80% ethanol at the boiling point, filtering hot, and cooling to 0°. The purification is repeated until the absorbancy coefficient at 254 mμ reaches the value of 48.86 l. g.$^{-1}$ cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_8Na_2O_6S_4 \cdot 2H_2O$: C, 31.44; H, 2.64; S, 27.98; H_2O, 7.86. Found: C, 31.43; H, 2.83; S, 28.25; H_2O (by drying at 110°), 7.59.

The bis(S-benzylthiuronium) salt melts at 167°.

Apparatus.—Spectra were determined at room temperature in 1-cm. silica cells using a Beckman DU spectrophotometer. Measurements of pH were done with a Beckman Model G pH meter.

Sodium 4-Mercaptobenzenesulfonate.—This substance was not isolated. It was prepared in solution by reduction of Na_2(BSSB) with (a) an excess of cysteine or (b) with zinc and hydrochloric acid.

(a) A solution of Na_2(BSSB), 3.05×10^{-5} *M*, and cysteine, 1.36×10^{-3} *M*, was adjusted to pH 9 with sodium hydroxide. The spectrum was determined against a blank containing the cysteine solution; the measurement was repeated after adjustment to pH 3.0.

(b) Na_2(BSSB), 0.668 g., was dissolved in 54 ml. of 0.5 *M* hydrochloric acid, and the zinc dust was added. After stirring for 30 min., the solution was filtered and its spectrum was determined; the spectrum was again determined after adjustment to pH 9.0 with sodium hydroxide.

Ionization Constant of Mercapto Group in 4-Mercaptobenzenesulfonate.—BSH, 2 mg., produced by either methods a or b of the preceding section, was added to 100 ml. of 0.2 *M* phosphate buffer containing 10^{-4} *M* ethylenedinitrilotetraacetic acid (EDTA). Hydrochloric acid, 1 *M*, and sodium hydroxide, 2 *M*, were added as needed to give various pH values between 4 and 9. Small aliquot portions were withdrawn and the absorbance was measured at 285 and 254 mμ. The blank contained buffer, EDTA, and the appropriate reducing agent. The concentrations of BSH and BS^- were calculated from the absorbances at the two wave lengths by solving the simultaneous equations (see Table I): $A_{285} = 1200(BSH) + 17{,}300(BS^-)$; $A_{251} = 15{,}400 \times (BSH) + 4950(BS^-)$.

TABLE I

SPECTRAL PROPERTIES OF MERCAPTANS AND DISULFIDES

Compound	λ_{max}, mμ	A_m at 254 mμ	A_m at 285 mμ
BSSB	254	22,400	4,800
BS^-	285	4,950	17,300
BSH	254	15,400	1,200
BSSR	248[a]	9,400	(2,400)[b]

[a] A_m = 10,300. [b] Assumed value, see text.

Allowance was made for dilution by the added reagents. The total concentration of BSH + BS^- could be estimated from the absorbances at pH 9 or 3, where (BSH) or (BS^-), respectively, could be set equal to 0. As a check, the sum of (BSH) and (BS^-) was calculated for each set of measurements; the sum was constant within 1% over virtually the entire pH range. Identical results were obtained with BSH produced by method a or method b. For BSH produced by method a, the blank absorbance at 254 mμ became appreciable above pH 7, and no measurements were made beyond this point at this wave length.

Procedure for Equilibrium Measurements.—The experiments were conducted in 0.02 *M* phosphate buffers of pH 5.9 to 7.6 containing EDTA. Solutions of BSSB and RSH were prepared in the appropriate buffer and mixed to give the desired compositions; all solutions were freshly prepared, that of RSH immediately before use. Absorbances were determined at 254 and 285 mμ until constant values were reached; the blank contained all reagents except BSSB. Solutions of BSSB in buffer showed no alterations in the absorbance over periods of time much longer than those required for the equilibrium measurements, but BSSB was slowly decomposed in alkaline solutions.

Procedure for Rate Measurements.—The experiments were conducted in 0.02 *M* phosphate buffers of pH 6.0, 6.5, and 7.0, containing EDTA and 0.2 *M* sodium chloride. The freshly prepared solutions were mixed and the absorbance at 285 mμ was recorded as a function of time until a constant value was reached. Corrections for the absorbances of RSH and BSSB were made in the calculations.

Results

Sodium 4,4′-dithiobisbenzenesulfonate [Na_2(BSSB)] has been prepared from sulfanilic acid by diazotization followed by coupling with sodium disulfide. Table I lists some of its spectral characteristics.

Treatment of BSSB with a large excess of cysteine at pH 9, or reduction of BSSB with zinc and acid followed by adjustment to pH 9, resulted in the disappearance of the maximum at 254 mμ and the development of a new maximum at 285 mμ; this peak can be ascribed to the BS^- ion. Lowering the pH to 3 resulted in the disappearance of the 285-mμ peak and development of a maximum at 254 mμ, which had, however, a lower intensity than that of BSSB. Titration of BS^- in the presence of buffer salts and analysis of the absorbances found at 285 and 254 mμ as a function of pH corresponded to the conversion of BS^- to BSH; Table I lists their spectral properties. The ionization constant of the mercapto group in BSH, eq. 3, was found to be $10^{-5.73}$.

Mixtures originally containing more nearly equivalent amounts of BSSB and RSH at pH 5–7 also showed the development of a 285-mμ peak. Typically, the absorbance rose quite rapidly to a maximum value and then decreased slowly. It was suspected that the slow decrease might be due to oxidation of BSH by dissolved oxygen, and it was sought to prevent this by adding some ethylenedinitrilotetraacetic acid (EDTA). In the presence of EDTA, stable values of the absorbance at 285 mμ were in fact obtained. Since BS^- is the principal absorbing species at this wave length, its concentration could be easily approximated and the amount of BSH calculated from eq. 3. It could thus be ascertained that the conversion of BSSB to (BSH + BS^-) was not complete in many conditions.

The information did not, however, suffice for calculating constants K_2' and K_3'. This can be seen from the following considerations. The experimentally determined or determinable quantities are the total amounts of mercaptan (M), of disulfide (D), and of BS residues (B) taken in any experiment, the molar ab-

TABLE II

REPRESENTATIVE EQUILIBRIUM CONCENTRATIONS

	Initial concn. × 10^5			Equilibrium concn. × 10^5						
pH	BSSB	RSH	RSSR	RSH	BSH	BS^-	RSSR	BSSR	A_{254}^{BSSR} × 10^{-4}	K_3' × 10^6
6.58	1.36	2.83	20.8	1.79	0.12	0.92	20.5	1.68	1.00	1.66
6.81	1.36	2.83	29.2	1.63	0.10	1.10	29.0	1.53	1.00	1.97
7.35	1.36	2.83	29.2	1.12	0.07	1.64	29.5	1.01	0.85	1.91
7.69	1.36	2.83	29.2	0.85	0.04	1.94	29.7	0.74	0.72	1.87
6.51	1.36	2.97	4.11	1.20	0.23	1.54	4.52	0.95	1.00	1.89
6.72	1.36	2.97	12.4	1.38	0.14	1.46	12.6	1.12	0.98	2.27
7.63	1.36	2.97	28.8	0.94	0.04	1.99	29.5	0.69	0.74	2.12
							Average[a]		0.90	1.96
							Average deviations		±0.11	±0.14

[a] Average of 22 determinations 1.88 ± 0.10 × 10^{-6}.

TABLE III

REPRESENTATIVE EQUILIBRIUM CONCENTRATIONS

	Initial concn. × 10^5			Equilibrium concn. × 10^5						
pH	BSSB	RSH	RSSR	RSH	BSH	BS^-	RSSR	BSSR	BSSB	K_2' × 10^6
6.10	3.08	3.31	1.66	0.89	0.60	1.82	2.01	1.71	1.02	2.72
6.10	3.08	4.96	1.66	1.82	0.78	2.36	2.55	1.37	0.83	1.70
6.36	3.08	3.31	1.66	0.69	0.42	2.20	2.17	1.58	0.99	2.22
6.41	3.08	3.31	3.32	0.82	0.37	2.12	3.61	1.90	0.90	2.13
6.41	3.08	4.96	3.32	1.57	0.50	2.89	4.23	1.58	0.61	1.86
6.58	3.08	3.31	4.14	0.56	0.31	2.44	4.25	2.55	0.44	2.07
6.66	3.08	4.96	6.64	1.40	0.36	3.20	7.44	1.95	0.34	2.88
								Average		2.23
								Average deviation		±0.33

sorbancy coefficients (A_m) of the several species at the wave length chosen for measurement, excepting that of the mixed disulfide (A_m^{BSSR}), and the absorbances experimentally measured. The following equations can be written

$$M = (BSH) + (BS^-) + (RSH) \quad (7)$$

$$D = (BSSB) + (BSSR) + (RSSR) \quad (8)$$

as well as an equation for the total concentration of BS residues

$$B = 2(BSSB) + (BSSR) + (BSH) + (BS^-) \quad (9)$$

(inclusion of a similar equation for RS residues results in a dependent system of equations). For the absorbances at 285 and 254 mμ one can write

$$A_{285} = 17{,}300(BS^-) + 1200(BSH) + 4800(BSSB) + A_{m,285}^{BSSR}(BSSR) \quad (10)$$

$$A_{254} = 4950(BS^-) + 15{,}400(BSH) + 22{,}400(BSSB) + A_{m,254}^{BSSR}(BSSR) \quad (11)$$

since the absorbances of RSH and RSSR are negligible (*cf.* Table I). Finally, one has eq. 3, with $K_i = 10^{-5.73}$. In these six equations there are eight unknowns, to wit, (BSH), (BS^-), (RSH), (BSSB), (BSSR), (RSSR), $A_{m,285}^{BSSR}$, and $A_{m,254}^{BSSR}$, and it follows that the system of equations cannot be solved.

The first approach to an approximate solution was made by assuming that the concentration of the mixed disulfide (BSSR) is negligible, *i.e.*, that the ratio K_2/K_3 is very small. This assumption eliminates the terms A_m^{BSSR} as well, and all other concentrations can then be calculated. However, substitution of the values obtained into eq. 6 does not give consistent values of K_4'. This is not surprising, since what is known about other mercaptan–disulfide interchange reactions leads one to expect that $K_2 \approx K_3 \approx 1$. If this is the case, however, reaction conditions can be chosen which make (BSSB) negligible, while all other species are present in substantial amounts; in general, these conditions entail a comparatively high pH, which tends to drive both reactions 1 and 2 to the right, and a large excess of RSSR, which counteracts the effect of pH in the case of eq. 2.

Table II lists a set of experiments which were designed to give minimal concentrations of BSSB at equilibrium. Attainment of equilibrium was indicated by a constant value of A_{285}. Equations 7–11 were solved on the assumptions that (BSSB) was zero and that $A_{m,285}^{BSSR}$ was 2400, one-half the value for BSSB. Since BSSR provides only a minor fraction of the total absorbance at 285 mμ (BS^- predominates above pH 6), an error in A_m^{BSSR} has little effect on the calculation. One can then estimate a value for A_m^{BSSR} at 254 mμ, which is listed in Table I, and determine other spectral characteristics. The results are consistent with the findings of Parker and Kharasch,[6] who found that in a series of unsymmetrical aromatic–aliphatic disulfides the absorption maxima of the symmetrical and unsymmetrical compounds were only a few millimicrons apart and that the absorbancy coefficients of the latter were about half those of the former. The values of K_3' calculated on this basis are quite consistent.

K_2' cannot be obtained from the experiments listed in Table II because in these cases (BSSB) was deliberately made negligible. Experiments in which substantial amounts of all participating species were present at equilibrium are reported in Table III. Since K_3' was now known, eq. 5 was available to make seven equations in six unknowns. It was decided to discard eq. 11 and calculate K_2' on the basis of the others. The values of K_2' calculated from the results are not as consistent as those of K_3', but the consistency must be considered adequate in view of the experimental and

(6) A. J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 3071 (1960).

TABLE IV

EQUILIBRIUM CONSTANTS FOR MERCAPTAN–DISULFIDE REACTIONS

Mercaptan	pH (temp., °C.)	Method	K_1	K_2	K_3	K_4	Ref.
		Disulfide = Cystine					
$HSCH_2COOH$ [a]	6 (30)	Polarimetry			1.0		*a*
		Solubility	0.8	4.1	(3.3)[b]	5.1	*c*
		Reaction velocity	7.9	1.29	(10.2)[b]	6.1	*d*
Glutathione	(25)	Solubility	2.8	1.0	(2.8)[b]	3.0	*c*
	7.4 (37)	Chromatography	12.4	0.17	(2.11)[b]	(73)[b]	*f*
$H_2NCH_2CH_2SH$	7.4 (37)	Chromatography	4.76	0.75			*e*
$MeCONHCH_2CH_2SH$	7.4 (37)	Chromatography	5.00	0.62			*e*
$Me_2NHCH_2CH_2SH$	7.4 (37)	Chromatography	2.78	55.6			*f*
$HOCH_2CH_2SH$	7.4 (37)	Chromatography	1.39	0.66			*f*
Eight other mercaptans[g]	7.4 (37)	Chromatography	2.04–2.94	0.31–0.66			*e, f*
		Disulfide = Oxidized Glutathione					
$H_2NCH_2CH_2SH$	7.4 (37)	Chromatography	5.0	0.34			*e*
$MeCOHNCH_2CH_2SH$	7.4 (37)	Chromatography	2.86	0.28			*e*
Three other mercaptans[g]	7.4 (37)	Chromatography	1.56–1.92	0.25–0.32			*e*

[a] T. Bersin and J. Steudel, *Ber.*, **71B**, 1015 (1938); [b] Calculated value. [c] I. M. Kolthoff, W. Stricks, and R. C. Kapoor, *J. Am. Chem. Soc.*, **77**, 4733 (1955); [d] H. Lamfrom and S. O. Nielsen, *Compt. rend. trav. lab. Carlsberg*, **30**, 349 (1957); [e] L. Eldjarn and A. Pihl, *J. Am. Chem. Soc.*, **79**, 4589 (1957); [f] A. Pihl and L. Eldjarn, Fourth International Congress of Biochemistry, 1958, Vienna, Vol. XIII, Colloquia, Pergamon Press, London, 1959, p. 43. [g] The following mercaptans were exchanged both with cystine and with oxidized glutathione: $Me_2NCH_2CH_2SH$, $Et_2NCH_2CH_2SH$, $C_5H_{10}NHCH_2CH_2SH$. The following mercaptans were treated with cystine: $MeNHCH_2CH_2SH$, $O(CH_2CH_2)_2NHCH_2CH_2SH$, $H_2N(C{:}NH)NHCH_2CH_2SH$, $PhCH_2NHCH_2CH_2SH$, Aletheine.

computational difficulties involved. The corresponding values of K_2 and K_3 from eq. 4 and 5 are 1.2 and 1.0, respectively.

Since two consecutive, reversible reactions are involved, the kinetics of the interchange reaction must be complicated. Only a restricted study has been made so far. Figure 1 shows some representative values obtained at pH 6.0. The initial BSSB concentration was 2.5×10^{-5} *M* and the initial cysteine concentration in one case was 5×10^{-4} *M*, in the other 1×10^{-4} *M*. In the former case, the value of A_{285} finally attained must correspond to essentially complete conversion of the BSSB to (BSH + BS^-), and the reaction takes place in about 10 min. In the latter case, the final value corresponds to 85% reaction, which accords with the point of equilibrium estimated by means of the constants given above; the time required for releasing one-half the stoichiometric amount of (BSH + BS^-) is 5.5 min. At pH 6.5 the half-time is 1.5 min., and at 7.0 <0.5 min. Clearly, the reaction is quite rapid in all cases, and the rate increases with pH; only qualitative significance should be attached to these results since the rates are too fast for accurate determination in the conditions.

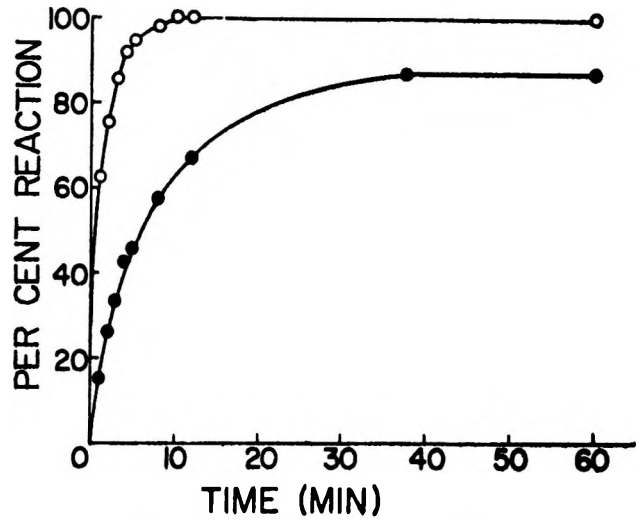


Fig. 1.—Reaction of 2.5×10^{-5} *M* BSSB with excess cysteine, at pH 6.0 and 25°: empty circles, 20:1 excess; full circles, 4:1 excess.

Discussion

Table IV summarizes the results obtained by other investigators for the equilibrium constants of mercaptan–disulfide interchange reactions that were conducted in aqueous buffered medium (for other cases, see paper II[1]). It can be seen that, unfortunately, there is not good agreement between the results of different investigators.

In the pioneering work of Bersin and Steudel on the cystine–mercaptoacetic acid system it was assumed that no appreciable amount of mixed disulfide was formed; since it is now quite certain that this cannot be the case, their value of $K_4 = 1$ must be rejected. Reasons for the other discrepancies are not so clear, however. The extensive investigation of Eldjarn and Pihl was effected with the aid of radioactively labeled compounds which were separated by paper electrophoresis and analyzed. This method probably did not give results of high accuracy, and at least one figure in the quoted values of K is of questionable significance; on the other hand, the method is more direct than those based on the measurement of a physical property. For five of the mercaptans examined by Eldjarn and Pihl, the equilibrium constants obtained in the interchange reactions with cystine and with oxidized glutathione were shown to be internally consistent; for details, the reader is referred to the original references.

Clearly, the data should be regarded with some skepticism, and confirmatory investigations are desirable. On the other hand, it is not likely that the majority of results would be grossly in error, and therefore it can be concluded that structural changes in the groups attached to sulfur have no pronounced influence on the equilibrium constants for the interchange reactions, except when steric interferences may be involved. The

results obtained in this work for cysteine–BSSB differ by a factor of about two from the values expected on the basis of probability and are in agreement with this conclusion.

Despite the fact that the constants are by no means unusual, the behavior of cysteine–BSSB is different from that of systems previously studied, and this serves to point out the important role which may be played by the buffer medium. At pH 7.0, for instance, BSH is almost completely ionized, while RSH is not. As a result, BSSB is almost completely reduced by an equivalent amount of RSH. Qualitative observations of similar import had been made by Eldjarn and Pihl, who reported that cystine was not reduced at pH 7.4 by aromatic mercaptans. It is important to realize this is not due to significant differences in the stabilities of the disulfide bonds involved, at least in the case of BSSB and RSSR, but to the fact that the acid–base reactions taking place with the buffer components provide the driving force for the reaction producing BS^-.

The case of BSH is of course an extreme one. With aliphatic mercaptans, little or no ionization will take place below pH 7, and hence there will be no effect on the interchange reaction. Above pH 7, *e.g.*, in the work of Eldjarn and Pihl that was conducted at pH 7.4, ionizations would certainly be appreciable. Their effect on the point of equilibrium is difficult to evaluate, however, since this depends on the difference between the ionization characteristics of the reactants and products, which are not known for the most part.

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Mercaptan–Disulfide Interchange Reactions. IV. Cysteine and Related Compounds with 3,5-Diimino-1,2,4-dithiazoline[1]

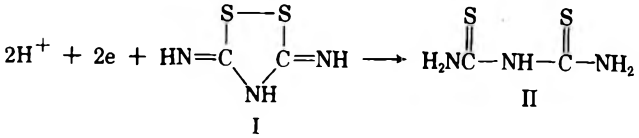
JOSEPH F. ROESLER, JAMES LESLIE, AND GEORGE GORIN

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

Received October 23, 1963

The reaction of 3,5-diimino-1,2,4-dithiazoline (DS_2) with cysteine, glutathione, and 2-aminoethanethiol is first order in DS_2 and second order in mercaptan; the specific rate constants are 9.4, 6.9, and 17.0 × 10^3 moles^2 l.$^{-2}$ min.$^{-1}$, respectively, at pH 4.60 and 30°. At pH 4.6–3.5, the rate is approximately proportional to the reciprocal of hydrogen ion activity. A mechanism is proposed.

This paper is part of a series[2] dealing with the interaction of disulfide and mercapto compounds, particularly those of importance in biochemistry. 3,5-Diimino-1,2,4-dithiazoline (DS_2, I) is a cyclic disulfide of unusual constitution, and a study of its reaction with cysteine and some cysteine derivatives was undertaken in the hope of finding some novel and useful results. DS_2 and dithiobiuret (II) possess the important property of forming a thermodynamically reversible half-cell (E_0 = +0.251 v. at pH 0).[3] The potential of other mercaptan–disulfide systems, which do not give reversible half-cells and are still to some extent uncertain,[4]



I II

might be determined if an equilibrium between them and DS_2–dithiobiuret could be established and measured.

This possibility has not yet been realized, principally for the reason that the reaction is very slow at the pH and concentrations that might otherwise be suitable. The present paper reports measurements of the reaction rates, and some deductions concerning the reaction mechanism.

Experimental

Materials.—Dithiobiuret, from the American Cyanamid Co., New York, N. Y., was recrystallized three times from hot 0.01 *M* hydrochloric acid, washed with ethanol, and dried *in vacuo*. 3,5-Diimino-1,2,4-dithiazoline hydrochloride was prepared as described by Preisler and Bateman.[3] 2-Aminoethanethiol (β-mercaptoethylamine), from Evans Chemical Co., New York 17, N. Y., was recrystallized from methanol and dried *in vacuo*. L-Cysteine hydrochloride hydrate, from California Corporation for Biochemical Research, Los Angeles 63, Calif., and glutathione, from Schwarz Laboratories, Mt. Vernon, N. Y., were used as obtained. All other chemicals were of reagent grade. The water used in the preparation of all solutions was distilled, passed through a column of Amberlite MB-1 ion-exchange resin, boiled for 20–25 min., cooled with a stream of nitrogen passing through, and stored under nitrogen for no longer than 2 days.

The buffers of pH 4.6–3.8 contained acetic acid–sodium acetate of total concentration 0.1 *M*; the buffers of pH 3.7 – 3.5 were prepared similarly from chloroacetic acid.

Apparatus.—Spectral measurements were done with a Beckman DU spectrophotometer, in 1-cm. silica cells. Measurements of pH were done with a Beckman Model GS pH meter, standardized with commercial buffers.

Kinetic Measurements.—Solutions of DS_2 and mercaptan were prepared in air-free buffer shortly before the measurements; in many but not all cases, the solutions were also made 10^{-3} *M* in ethylenedinitrilotetraacetic acid. Appropriate amounts were mixed to give about 5 × 10^{-5} *M* DS_2 and the desired mercaptan ratio, and an aliquot portion was transferred to a spectrophotometer cell. The absorbance at 246 and 282 mμ was then measured at intervals, against a blank solution containing mercaptan and buffer. The temperature was maintained at 30 ± 0.5°

(1) This work was supported by Contract AT(11-1)-71, No. 8, from the Division of Biology and Medicine, U. S. Atomic Energy Commission.

(2) See preceding papers: *J. Org. Chem.*, **29**, 1480, 1484 (1964).

(3) P. W. Preisler and M. M. Bateman, *J. Am. Chem. Soc.*, **69**, 2632 (1947).

(4) W. M. Clark, "Oxidation-Reduction Potentials of Organic Systems," Williams and Wilkins, Baltimore, Md., 1960, pp. 471–487.

with the aid of an attachment which has been described elsewhere.[5] Whenever it was desired to continue the measurements for longer than 15 min., the cell contents were renewed from the stock reaction mixture, which was kept in a thermostat under nitrogen.

Results

DS_2 is a base with ionization constants $10^{-7.4}$ and *ca.* 10^{-3}. It, therefore, exists as the cation $(DS_2H)^+$ in the pH range 4.6–3.5 employed in the experiments. $(DS_2H)^+$ has an absorption maximum at 246 mμ; dithiobiuret has a maximum at 282 mμ.[6] The molar absorbancies at these wave lengths are as follows.

	246 mμ	282 mμ
$(DS_2H)^+$	16,540	6,010
Dithiobiuret	4,100	19,630

When $(DS_2H)^+$ was mixed with excess cysteine or other mercaptan (RSH) in buffer, the absorbance at 246 mμ decreased and that at 282 mμ increased. If $(DS_2H)^+$ and dithiobiuret are the only absorbing species present, one can write for the absorbance at 246 or 282 mμ

$$A = A_{SS}[(DS_2H)^+] + A_{SH}\{[(DS_2H)^+]_0 - [(DS_2H)^+]\} \quad (1)$$

where A_{SS} and A_{SH} are the respective molar absorbancies and $[(DS_2H)^+]_0$ is the initial concentration. Rearrangement of the equation gives

$$[(DS_2H)^+] = \{A - A_{SH}[(DS_2H)^+]_0\}/(A_{SS} - A_{SH}) \quad (2)$$

Rate measurements were conducted in the presence of a large excess of mercaptan, the molar ratio $[RSH]/[(DS_2H)^+]$ being 20, 35, and 50. In these conditions it might be expected that the disappearance of $(DS_2H)^+$ would follow the first-order law, *i.e.*

$$\log [(DS_2H)^+]/[(DS_2H)^+]_0 = -kt/2.303 \quad (3)$$

so that a plot of $-\log \{A - A_{SH}[(DS_2H)^+]_0\}$ against t would be a straight line of slope $k/2.303$. This was in fact found experimentally; a representative set of data is shown in Fig. 1.

Table I summarizes the results ($= k'$) obtained by dividing the pseudo-first-order rate constants obtained at various mercaptan ratios by the mercaptan concentration squared. It can be seen that the results are constant for any given mercaptan, indicating that the rate is directly proportional to $[RSH]^2$. Ethylenedinitrilotetraacetic acid (EDTA) was added in some of the experiments, because this substance has been found effective in retarding autoxidation; however, it did not have an appreciable effect.

Table II summarizes the results obtained at 50:1 cysteine–$(DS_2H)^+$ ratio and pH values from 4.6 to 3.5. Measurements were not made at higher pH because DS_2 is reportedly unstable above pH 5,[3] while the lower limit was determined by the length of time required. The range covers a tenfold increase in hydrogen ion activity, and the rate decreases somewhat more rapidly than if it were inversely proportional to this quantity.

(5) H. J. Martin and G. Gorin, *Anal. Chem.*, **32**, 892 (1960).

(6) G. Baudo and G. Gorin, Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, p. 28-C. The assistance of Mr. Baudo in some of the early experiments is acknowledged with thanks.

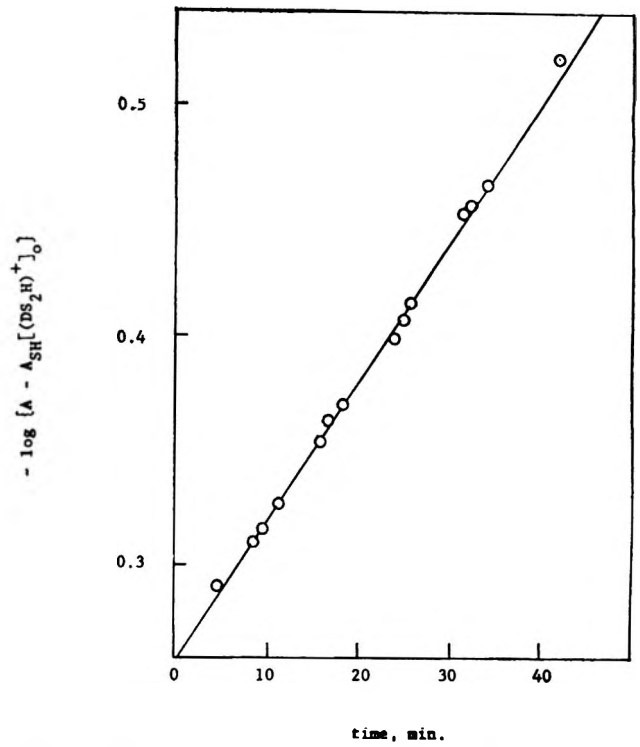


Fig. 1.—First-order rate equation plot for reaction of cysteine at 30°, pH 4.2. Initial concentrations are $[DS_2] = 4.54 \times 10^{-5}$, [cysteine] $= 2.26 \times 10^{-3}$ *M*.

TABLE I

THIRD-ORDER RATE CONSTANTS FOR REACTION OF $(DS_2H)^+$ WITH MERCAPTANS[a]

Mercaptan	Initial RSH-$(DS_2H)^+$ ratio 20:1	35:1	50:1	Mean
Cysteine	9.53[b]	8.75	9.83	
	8.89	9.12	10.22	9.4 ± 0.5
		9.21[b]	8.96	
			10.13[b]	
2-Aminoethanethiol	17.2[b]	17.8[b]	16.73[b]	
	17.3[b]	16.9[b]	16.9	17.0 ± 0.3
		16.5		
Glutathione	7.02[b]	6.84[b]	6.68[b]	
	6.91	7.00	6.93	6.9 ± 0.9

[a] pH 4.60, 30°; units of k' are 10^3 l.^{2} mole^{-2} min.$^{-1}$. [b] Denotes ethylenedinitrilotetraacetic acid added.

TABLE II

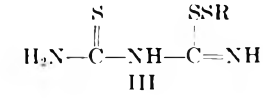
pH DEPENDENCE OF RATE CONSTANTS[a]

pH	$10^{-3}\,k'$, l.^{2} mole^{-2} min.$^{-1}$	$k'[H^+]$,[b] l. mole^{-1} min.$^{-1}$
4.60	9.40	0.235
4.30	4.14	0.211
4.00	1.75	0.175
3.70	0.96	0.192
3.50	0.58	0.186

[a] [Cysteine–$(DS_2H)^+$] = 50, 30°. [b] $[H^+] = 10^{-pH}$.

Discussion

The following mechanism is approximately in accord with the results reported in the preceding section. It is postulated that $(DS_2H)^+$ reacts with mercaptan to form the mixed disulfide (III, dithiobiuret = DTB).



III

$$(DS_2H)^+ + RSH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} III + H^+ \quad (a)$$

$$III + RSH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (DTB) + RSSR \quad (b)$$

It is further postulated that III is an unstable intermediate, whose concentration remains small and nearly constant throughout the reaction, so that one can write to a good approximation

$$d[(III)]/dt = k_1[(DS_2H)^+][RSH] - k_{-1}[(III)][H^+] - k_2[(III)][RSH] \cong 0 \quad (4)$$

whence

$$[(III)] = \{k_1[(DS_2H)^+][RSH]\}/\{k_{-1}[H^+] + k_2[RSH]\} \quad (5)$$

Finally, it is postulated that $k_{-1}[H^+] >> k_2[RSH]$. Since, in the conditions, the reversal of eq. b is negligible, one can write

$$-d[(DS_2H)^+]/dt = d[(DTB)]dt = k_2[(III)][RSH] = \{k_1k_2[(DS_2H)^+][RSH]^2\}/k_{-1}[H^+] \quad (6)$$

In the presence of a large excess of RSH and at constant pH, one can equate

$$k_1k_2[RSH]^2/k_{-1}[H^+] = k \quad (7)$$

The resulting expression can be integrated to give eq. 3. The specific rate constants reported in Tables I and II are related in the following ways

$$k_1k_2/k_{-1} = k'[H^+] = k[H^+]/[RSH]^2 \quad (8)$$

(in view of the approximate nature of the analysis, the distinction between hydrogen ion concentration and activity is not considered).

In other mercaptan–disulfide reactions it has been found that the equilibrium constants[2] for the reactions corresponding to eq. a and b are not very different from unity, from which one can conclude that the rate constants are usually of the same order of magnitude. Also, convincing evidence has been produced that the mechanism involves the reaction of disulfide with RS^-.[7] The mechanism proposed above for $(DS_2H)^+$ implies two principal points of difference. First, it is postulated that the rate of reversal of eq. a is greater than the forward rate of b; this can be rationalized on the grounds that, in the former case, the participating groups are held in close proximity at all times, the reaction being an intramolecular one. Secondly, $(DS_2H)^+$ must be more susceptible to S–S bond fission than ordinary disulfides, since the former can be attacked by RSH and the latter only by the more strongly nucleophilic RS^-. It should be noted that, in the pH range in question, $[RS^-]$ is very small; *i.e.*, it is not implied that $(DS_2H)^+$ cannot react with RS^-, only that the reaction is not important in the conditions employed. As a matter of fact, a likely explanation for the fact that the rate of reaction increases somewhat more rapidly with pH than predicted by eq. 6–8 is that RS^- makes an appreciable contribution to the over-all reactions at the higher pH values. The reaction with RS^- cannot be the principal one, however, as this would lead to a dependence of the rate on $1/[H^+]^2$, which is clearly not the case.

A degree of uncertainty attaches to the above analysis, because the spectrum of the mixed disulfide is not known. Owing to this, one cannot be sure that the mixed disulfide would not be produced in appreciable amounts, its presence escaping detection by a fortuitous compensation of the absorbances. However, this is not likely. The mechanism proposed, though speculative, provides a reasonable explanation for the experimental findings.

(7) O. Foss in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, pp. 87–90.

The Solvolysis of 3-Hydroxyestr-5(10)-en-17-one Sulfonates

WILLIAM F. JOHNS

Division of Chemical Research, G. D. Searle and Company, Chicago 80, Illinois

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Solvolyses of the sulfonates of 3α- and 3β-hydroxyestr-5(10)-en-17-one (**2a**, **6a**) yield the cyclosteroids **4** and **8**, respectively. Other products of the solvolyses include the diene **11a** and the *inverted* alcohols. The mechanisms involved in the synthesis of these compounds are discussed.

i-Steroids, both in structural determination and the mechanism of formation, have been the basis of a fascinating story through several decades of organic chemistry.[1] Investigation in this area continues, in recent years concentrated largely on determination of the steric requirements necessary for the synthesis of these compounds[2] and on a more precise definition of the nonclassical cation intermediate in their formation.[3] Pertinent to both problems, the present work reports the results of experiments dealing with the C-3 sulfonates of $\Delta^{5(10)}$-steroids.[4] These compounds, containing both the participating double bond and the oxygen function in the *same* (unbridged) ring, represent a structural type whose solvolyses have not been investigated heretofore. Numerous examples exist of bridge 3-cyclohexenol sulfonate solvolyses.[5] How-

(1) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 314; a recent list of *i*-steroid syntheses has been given by L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross [*J. Am. Chem. Soc.*, **85**, 1851 (1963)].

(2) For leading references see the following: W. J. A. Vandenheuvel and E. S. Wallis, *J. Org. Chem.*, **27**, 1233 (1962); C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc.*, 3261 (1961); R. M. Moriarty and R. M. deSousa, *J. Org. Chem.*, **28**, 3072 (1963).

(3) (a) S. Winstein and E. M. Kosower, *J. Am. Chem. Soc.*, **81**, 4399 (1959) and references cited there; (b) G. H. Whitham, *Proc. Chem. Soc.*, 422 (1961).

(4) Portions of this work are included in U. S. Patents 2,944,067 (1960), 2,944,068 (1960), and 3,087,943 (1963). Work along similar lines has been recently reported by S. G. Levine, N. H. Eudy, and E. C. Farthing [*Tetrahedron Letters*, 1517 (1963)].

(5) J. A. Berson, "Molecular Rearrangements," P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 192, and references contained there.

ever, the corresponding reaction in the unbridged 3-cyclohexenol, Δ^9-octalol-2, or analogous polycyclic systems has escaped investigation.[6]

Although $\Delta^{5(10)}$-steroids are routinely obtained in the metal–ammonia reduction of compounds with an aromatic A-ring,[7] they are labile intermediates usually transformed to the corresponding conjugated ketone derivatives. Among the few reports dealing with the reactions of the 3-keto-$\Delta^{5(10)}$-steroids is Hartman's reduction of 17-hydroxyestr-5(10)-en-3-one,[8] this work attesting to the possibility of reduction of the carbonyl group without isomerization of the double bond. Following this precedent, the preparation of 3-hydroxyestr-5(10)-en-17-one was undertaken. The starting material, estr-5(10)-ene-3,17-dione,[9] was reduced carefully with sodium borohydride. The marked difference in the reactivity of the C-3 and C-17 carbonyl groups, previously described in the androstanes,[10] allowed reduction to occur selectively without appreciable attack at the C-17 carbonyl. In addition, no isomerization of the double bond was seen. The resultant product contained two hydroxy ketones (**2a** and **6a**) in a 5:1 ratio. A more stereoselective reduction was effected with lithium tri-*t*-butoxyaluminohydride[11] which afforded the same ketones in a 15:1 ratio.

The general structure of each hydroxy ketone was shown by its infrared spectrum: absorption of both the secondary hydroxyl group and a five-membered ring carbonyl group was present. The n.m.r. spectra of these compounds showed no vinyl proton absorption indicating their respective double bonds had remained in a ditertiary position.

To prove the configuration of the C-3 hydroxyls in this pair of hydroxy ketones, the major component was converted by hydride reduction to the 3,17-diol (**2b**), identical with that prepared by Hartman.[8] Hydrogenation of this material under vigorous conditions afforded a good yield of 5α,10α-estrane-3α,17β-diol (**1**) and a minor amount of the corresponding 5β,10β-derivative.[12] Similarly, the minor component of the borohydride reduction product was converted to its diol (**6b**) and this in turn was hydrogenated to 5α,-10α-estrane-3β,17β-diol (**9**). Since no change at C-3 can occur during hydrogenation, these experiments constitute a direct chemical proof of the configuration of **2a**: the major reduction product of the 3-keto-$\Delta^{5(10)}$-steroid has a C-3α hydroxyl group. This is contrary to the assignment made by analogy to the reduction of the C-3 carbonyl function in the normal steroids.[8,10,13]

The C-3 tosylate of the hydroxy ketone **2a**, prepared in good yield, was solvolyzed in buffered aqueous acetone following the classical procedure[14] and the products were separated readily by chromatography. The least polar material obtained (60% of the weight) was a mixture of dienes resulting from a simple elimination reaction. This same diene mixture could be formed by more conventional procedures such as passing the tosylate over activated alumina[15] or heating it in pyridine. Although the conjugated isomer **10**, having the extra stability conferred by resonance, was expected to predominate, it constituted less than 20% of the diene fraction as determined from the ultraviolet spectrum. The major component was a nonconjugated diene whose structure is most probably that shown in formula **11a**. The n.m.r. spectrum of the purified material showed vinyl proton absorption with an intensity equivalent to two protons, ruling out the several diene structures having three protons attached to olefinic bonds. A heteroannular relationship of these bonds was considerable improbable, not only because of the unnecessary complexity of the requisite reaction path, but also because of the ready oxidation of the diene to 3-desoxyestrone[16] with chromic acid–pyridine (among other reagents). The formation of the diene is presumably a kinetically controlled process; that isomerization of the double bonds does not occur during the reaction was shown by a separate demonstration of their marked stability to acid or base treatment. It should be noted however, that the nonconjugated isomer may have a thermodynamic stability very close to that of the conjugated isomer, for it possesses a strong stabilization provided by overlap of the π-electron clouds in 1,4-cyclohexadiene systems.[17] The steric factors involved in this reaction superficially favor neither direction of elimination, since both the C-2 and C-4 protons have similar steric accessibilities and both lie in the proper plane with the C-3 sulfonate for ready elimination. The conjugated diene component, although not isolated in pure form, almost certainly has the structure represented by structure **10**, the product of simple elimination of sulfonate and C-4 proton.

A normal component of the diene mixture was desoxyestrone (**12**), formed in the several reactions in which sulfonate elimination occurred. Especially large amounts of this material (30% of the product) were formed from the mesylate **3b** on activated alkaline alumina. Presumably this aromatic material was formed by autoxidation of the diene, although attempts to oxidize the diene mixture with oxygen in the presence of platinum catalyst effected no change in either diene component (**10** or **11a**).

Lithium–ammonia treatment of the crude diene effected reduction of the carbonyl function as well as of the conjugated double bonds of the contaminant **10**, providing the readily purified dienol **11b** (R′ = H) as the major product (see Chart I). Addition of acetylene proceeded normally to give the adduct **11b** (R′ = C≡CH). Hydrogenation of the ethynyl compound afforded smoothly the vinyl derivative **11b** (R′ =

(6) After the submission of this manuscript a solvolytic synthesis of bicyclo[3.1.0]hexan-2-ol appeared by M. Hanack and W. Keberle [*Chem. Ber.*, **96**, 2937 (1963)]. See also N. A. Nelson and G. A. Mortimer, *J. Org. Chem.*, **22**, 1146 (1957), for other synthetic routes to this bicyclohexanol system. None of the corresponding bridged decalin analogs have been prepared.

(7) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(8) J. A. Hartman, *ibid.*, **77**, 5151 (1955).

(9) F. B. Colton, U. S. Patent 2,729,654 (1956).

(10) E. Elisberg, H. Vanderhaeghe, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2814 (1952).

(11) O. H. Wheeler and J. L. Mateos, *Chem. Ind.* (London), 395 (1957); J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

(12) R. E. Counsell, *Tetrahedron*, **15**, 202 (1961). We wish to thank Dr. Counsell for providing several infrared spectra for comparison.

(13) Dr. S. G. Levine, Research Triangle Institute, has kindly pointed out this reversal of configurations contained in the patents on this subject (see ref. 4).

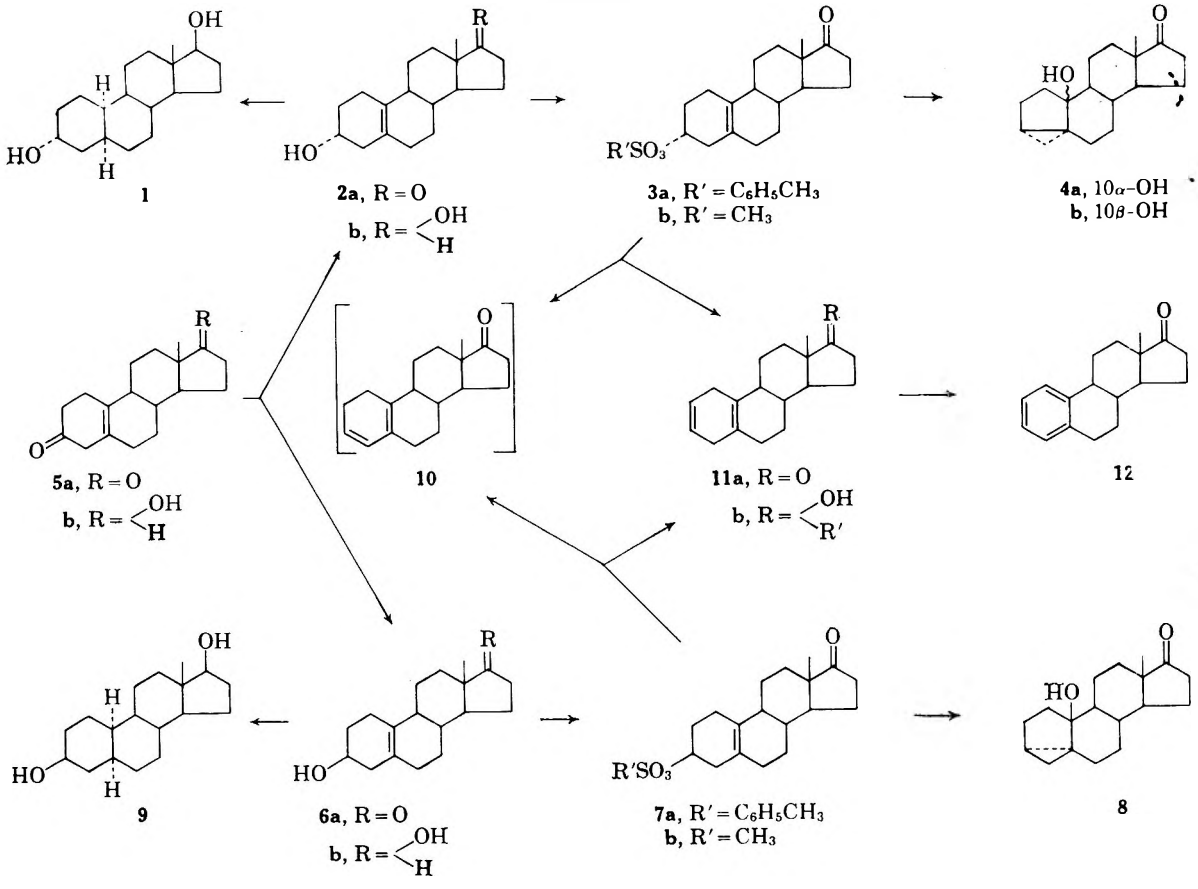
(14) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956).

(15) F. C. Chang and R. T. Blickenstaff, *Chem. Ind.* (London), 590 (1958); G. H. Douglas, P. S. Ellington, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 1720 (1959).

(16) This sample was kindly supplied by Dr. A. H. Goldkamp. See E. Caspi, E. Cullen, and P. K. Grover, *ibid.*, 212 (1963).

(17) R. B. Bates, R. H. Carnighan, and C. E. Staples, *J. Am. Chem. Soc.*, **85**, 3030 (1963).

CHART I



$CH{=}CH_2$). Further hydrogenation, however, was complicated by concomitant dehydrogenation of the A-ring.

The second product from solvolysis of the C-3α sulfonate exhibited signals in the n.m.r. spectrum at 7, 10, and 15 c.p.s. with an integrated area equivalent to three protons; these bands are most reasonably attributed to protons attached to a cyclopropyl ring.[18] The infrared spectrum of this compound showed the presence of a cyclopentanone carbonyl as well as a hydroxyl group. The latter group was determined to be tertiary by virtue of its stability to the usual acetylation or oxidation conditions. These facts are consistent with the formation of the *i*-steroid **4** expected from the positions of the double bond and hydroxyl group in the starting material. In agreement with this conclusion was the ready acid-catalyzed regeneration of the pure starting alcohol **2a**. The gross structural features of this compound are unique insofar as no cyclosteroids yet synthesized have either a tertiary hydroxyl group adjacent to the cyclopropane ring or a hydroxyl group as a substituent of the bridged cyclohexane ring. Solvolysis of the corresponding mesylate **3b** gave improved yields of the cyclosteroid **4** (30% instead of 20%). This may be due, in part, to a slower rate of the simple elimination reaction as suggested by a lower yield of accompanying dienes.

The cyclosteroid **4** was hydrogenated in an attempt to prove the configuration of its hydroxyl group.[19] The resulting noncrystalline mixture showed broadened methyl signals in the n.m.r. indicative of nonselective attack at the three cyclopropyl bonds. Under modified conditions, another hydrogenation attempt provided a product that was largely aromatic (**12**).

A hydroxy ketone fraction obtained from solvolysis of tosylate **3a** contained a third product, the inverted alcohol **6a**, in approximately 10% yield. This material is the result of a typical SN2 displacement of the sulfonate group (without rearrangement or participation of the double bond). Thus in the case of the estrenyl sulfonate, displacement and especially elimination reactions compete strongly with the rearrangement. In contrast, the hydrolysis of cholesteryl tosylate provides no products of simple displacement or elimination. This difference is readily ascribed to the difference in the geometry of the two systems.

Although the inverted alcohol **6a** was the main constituent of the hydroxy ketone fraction, the epimer **2a** was also present. The ratio of nucleophilic attack at C-3–C-10 of the nonclassical intermediate ion is expected to be a consequence of both steric and electronic factors. The small amounts of materials involved did not allow a good measure of this ratio or its comparison to the cholesteryl case (C-3–C-6 = 12:85).[3]

As a poorly crystalline, minor component of the borohydride reduction product, the 3β-alcohol **6a** could not be separated efficiently by chromatography and recrystallization. To obtain sufficient quantities of this compound for solvolysis studies, the mixture of alcohols was benzoylated; the desired benzoate was separated by fractional crystallization and saponified

(18) See D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Am. Chem. Soc.*, **85**, 3218 (1963), and references cited there.

(19) C. W. Shoppee and G. H. R. Summers [*J. Chem. Soc.*, 3361 (1952)] have reported the analogous hydrogenation of *i*-cholesterol.

to form the pure alcohol **6a**. In addition, the nucleophilic displacement of the C-3α tosylate in dimethylformamide[20] followed by saponification afforded the diene mixture (**10**, **11a**) and the inverted alcohol **6a**. Additional quantities of this compound were also realized from the chromatography of the mesylate **3b** on alkaline alumina.[15]

Solvolysis of the C-3β tosylate **7a** in buffered aqueous acetone provided three components in roughly the same relative proportions as formed in the reaction of the epimer **3**. The first product, formed by sulfonate elimination, consisted of a mixture of dienes (**10**, **11a**) and aromatic material (**12**). The second component in the solvolysis of the β-tosylate was a new *i*-steroid (**8**); supporting this assignment were the signals in the n.m.r. spectrum at 39, 42, and 47 c.p.s., the presence of a tertiary hydroxyl, and the acid-catalyzed conversion to starting material (**6a**). The final material obtained in the solvolysis of the β-tosylate was the product of inversion, the 3α-alcohol **2a**. The relative absence of starting alcohol (**6a**) again points to a preference of this system to undergo the Sn2 displacement as compared to that found in the case of cholesterol.

Whereas the gross structural features of the cyclosteroids **4** and **8** are dictated by the positions of the double bond and hydroxyl group of the starting materials, at present the configurations of the carbon–carbon bridge and the C-10 hydroxyl groups can only be inferred by consideration of mechanism and several pertinent facts. In cholesteryl derivatives, the equatorial leaving group (3β) can undergo the *i*-steroid rearrangement, but the axial (3α) epimer fails completely.[21] This is ascribed, for the equatorial isomer, to the geometrically favorable overlap of the π-electrons of the double bond with the carbonium ion, affording anchimeric assistance in the solvolysis.[3] The axial epimer, lacking this π-electron overlap, undergoes a different course of reaction and forms no *i*-steroid. In sharp contrast to this more rigid system is the flexibility of the cyclohexene system in the $\Delta^{5(10)}$-steroids; here *both* epimers (C-3α and C-3β sulfonates) can assume readily an equatorial conformation. Thus, for both epimers the rearrangement occurs starting with an equatorial sulfonate, the conformer which meets the steric requirements of the reaction.

The departure of the sulfonate group in cholesteryl derivatives is assisted by the electron pair of the double bond, in effect causing an inversion at C-3 and producing the incipient cyclopropyl bond.[3] Precisely the same situation is present in the 3β-derivative **7** and no change in the stereochemistry of the bridge need be considered. However, in the case of the 3α-sulfonate **3**, the opposite situation exists; inversion at C-3 by the electron pair of the double bond should produce a C-3β–C-5 bridge.[22] That the difference in these 10-hydroxy *i*-steroids (**4**, **8**) is due to the configuration of the bridge rather than that of the 10-hydroxyl is clear from the acid-catalyzed reversal of these compounds: each forms only its starting alcohol. If the difference were due solely to the configuration of the hydroxyl, the intermediate carbonium ion in this reaction would be one common to both compounds and a single alcohol would result. This is demonstrated in the acid-catalyzed formation of cholesterol from both *i*-cholesterol and *epi-i*-cholesterol.[23]

The configuration of the C-10 hydroxyl is a more complex question. In the normal *i*-steroid rearrangement the β-configuration of the C-6 hydroxyl is a result of an axial attack at the point of maximum overlap of the π-orbitals with the incoming anion. The reaction of the 3β-derivative **7** is closely analogous, axial attack at C-10 occurring from the β-face yielding a C-10β hydroxyl group. Again by analogy, the solvolysis of the C-3α tosylate **3a** should form a C-10α hydroxyl group. However, inspection of the molecular models shows that the B-ring of a C-10α hydroxy cyclosteroid is required to assume an energetically disfavored boat conformation. Even with conformational modification by twisting,[24] the molecule remains in a form presumably more strained than the 10β-hydroxy cyclosteroid. The formation of this molecule from its sulfonate should occur in lower yields than the analogous formation of the 10β-hydroxy cyclosteroid **8**; consequent enhanced yields of the products of the competing substitution and elimination reactions should be realized. That no appreciable difference in yields of the cyclosteroids is seen leads to the surprising implication that no appreciable energy difference exists in the formation of cyclosteroids **4** and **8**.

An interpretation of the reaction course which circumvents this unusual conclusion can be delineated. In the *i*-steroids previously synthesized, the rigidity of the systems involved allows only one possible direction of axial attack by the incoming anion. An inference which might be drawn from these examples is that the entering and leaving groups in the cyclosteroid rearrangement must be *cis*. However, no compelling mechanistic argument supports this thesis. Axial attack of the homoallylic double bond should cause expulsion of an equatorial leaving group from either face of the molecule despite the *cis* or *trans* relationships of the two groups involved. In the present case, due to the intracyclic position of the double bond, axial attack at the double bond can be *trans* (β-face approach) to the C-3α leaving group, considering the B-ring as plane of reference. This route would provide the C-10β hydroxyl derivative **4b** in which the B-ring can readily assume the energetically favored chair conformation. Thus the hydroxyl group can be produced theoretically in either the 10α- or 10β-position. In the absence of concrete evidence to this point this configuration is left unassigned.

(20) F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

(21) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955); E. J. Becker and E. S. Wallis, *J. Org. Chem.*, **20**, 353 (1955).

(22) This structural type has been recently demonstrated in steroids as the result of a photochemical reaction [*cf.* W. G. Dauben and F. G. Wiley, *Tetrahedron Letters*, 893 (1962); W. G. Dauben and J. A. Ross, *J. Am. Chem. Soc.*, **81**, 6521 (1959)].

(23) A. F. Wagner and E. S. Wallis, *ibid.*, **72**, 1047 (1950). Since the configuration of the alcohol in the reverse rearrangement normally derives from the nucleophile attacking the C-3–C-5 bond to produce over-all inversion at C-3, it is not unreasonable to expect that the product derived from a C-3β–C-5 bridge would have a C-3α hydroxyl group. However, Dauben (ref. 22) observed an A-nor product on acid treatment of his 3β,5-cyclosteroid. One interpretation of this difference in products is due to the possible configurational differences in the oxygen functions in Dauben's cyclosteroid (β) and that reported here (α?). We wish to thank the referee for offering this explanation as well as several other valuable comments.

(24) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *ibid.*, **83**, 607 (1961).

Experimental[25]

3α-Hydroxyestr-5(10)-en-17-one (2a). A. Sodium Borohydride Reduction.—To an efficiently stirred solution of 86 g. of estr-5(10)-ene-3,17-dione (**5a**) in 2 l. of methanol at 10° was added a cooled solution of 3.18 g. of sodium borohydride in 65 ml. of water over a 10-min. period. After an additional 5 min. the solution was poured into 4 l. of water containing 20 ml. of acetic acid. The resulting precipitate was collected on a filter and washed with water. This material (75 g.) was adsorbed on 1.7 kg. of silica (60–200 mesh). Elution with 10% ethyl acetate in benzene afforded 7.7 g. of the starting diketone. The following fractions contained 58 g. of the two epimeric alcohols, the α-isomer (**2a**) being in pure form in the earlier fractions. Analysis by paper chromatography[26] showed the isomers to be present in a 5:1 ratio (α–β). Recrystallization from methanol gave 31.2 g. of dense prisms, m.p. 183–188°, which were recrystallized from acetone–ether to give the pure compound, m.p. 192–194°, λ_{max} 2.74 and 5.74 μ, $[\alpha]_D$ 263°.[27]

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.54; H, 9.82.

Careful fractional recrystallization of the later hydroxy ketone fractions from cyclohexane and from acetonitrile provided a sample of the epimeric C-3β derivative **6a**, identical with the material described below.

Elution of the column with ethyl acetate yielded 8 g. of the crude diol (**2b, 6b**), recrystallized to give a pure sample of estr-5(10)-ene-3α,17β-diol, m.p. 206–213°, identical with an authentic sample.[28]

B. Lithium Tri-*t*-butoxyaluminohydride Reduction.[29]—To a solution of 86 g. of the dione **5a** in 1 l. of tetrahydrofuran at 5° was added a solution of 176 g. of lithium tri-*t*-butoxyaluminohydride in 1 l. of tetrahydrofuran over a 1-hr. period. The cooling bath was removed and the reaction mixture was stirred for an additional 4 hr. at ambient temperature. The product was precipitated by pouring the solution slowly with stirring into 16 l. of water containing 100 ml. of acetic acid. This material was washed with water and dissolved in benzene. The resulting solution was washed with water, dried, and evaporated. The crystalline residue was shown by paper chromatography to consist of the 3α-hydroxy derivative **2a** contaminated with 5–8% of the 3β-hydroxy ketone **6a** and 3–4% of the 17-hydroxy derivatives **2b** and **6b**. Recrystallization from acetone gave 44 g., m.p. 175–181°, and 15 g., m.p. 172–175°, of the hydroxy ketone **2a**.

Lower yields obtained in other runs were probably due to prereduction isomerization of the double bond.

3α-Acetoxyestr-5(10)-en-17-one.—The hydroxy ketone **2a** (50 mg.) was heated in 2 ml. of pyridine and 1 ml. of acetic anhydride at 100° for 10 min. The cooled reaction was diluted with water. The resulting precipitate was separated by filtration and recrystallized from methanol, giving the pure acetate, m.p. 156–158°, λ_{max} 5.77 μ, $[\alpha]_D$ 240°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.20; H, 8.88.

3α-Benzoyloxyestr-5(10)-en-17-one.—The hydroxy ketone **2a** (0.30 g.) was heated in 10 ml. of pyridine containing 1 ml. of benzoyl chloride at 100° for 15 min., was cooled and diluted with water, and then was heated again at 100° for 20 min. The mixture was cooled and filtered. Recrystallization of the product from methanol gave 0.23 g. of the pure material, m.p. 176–180°, λ_{max} 5.72 and 5.80 μ, $[\alpha]_D$ 196°. The C-3β proton had a half-height width of 14 c.p.s., centered at 307 c.p.s.

Anal. Calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.24; H, 8.13.

5(10)-Estrene-3α,17β-diol (2b).—A solution of the hydroxy ketone **2a** (0.20 g.) and lithium tri-*t*-butoxyaluminohydride (1 g.) in 30 ml. of tetrahydrofuran was allowed to stand at room temperature for 18 hr. The solution was poured into 300 ml. of water containing 20 ml. of acetic acid. The precipitate which formed was collected on a filter and recrystallized from acetone–ethyl acetate providing 0.12 g. of material (**2b**), m.p. 210–213°, $[\alpha]_D$ 187°, identical with an authentic sample.[28]

Sodium borohydride reduction of **5b** also gave a good yield of the same diol (**2b**).

Hydrogenation of Estr-5(10)-ene-3α,17β-diol (2b).—The estradiol **2b** (2.0 g.) and ruthenium oxide (2.0 g.) in 50 ml. of ethanol (3A) was stirred at 100° and 1600 p.s.i. for 8 hr. The uptake of hydrogen could not be accurately measured because of the small size of the sample relative to the volume of the apparatus. The solution, after filtration of the catalyst, was concentrated to dryness under reduced pressure.[30] The residue was crystallized from acetone–ethyl acetate to yield 1.05 g. of material, m.p. 219–222°, identical in the infrared with an authentic sample of 5α,10α-estrane-3α,17β-diol (**1**, lit.[12] m.p. 223–225°). The mother liquors of the reaction (0.9 g.) were submitted to chromatography on 100 g. of silica. Elution with 10% ethyl acetate in benzene provided an additional 0.59 g. of crude *cis*-α-diol **1**, recrystallized to yield 0.30 g. of the pure compond, m.p. 209–215° (identical in the infrared with the above sample). Elution with more polar solvents gave 0.13 g. of crude crystalline material recrystallized from acetone to yield 20 mg. of product, m.p. 209–211°, identical in the infrared with an authentic sample of 5β,10β-estrane-3α,17β-diol.[12]

Rhodium–alumina catalyst (5%, 5 g.) also effected hydrogenation of the diol (1.0 g.) in acetic acid (1600 p.s.i., 67°, 8 hr.), affording, after saponification, 0.42 g. of the *cis*-diol **1**, m.p. 225–226°.

3α-Tosyloxyestr-5(10)-en-17-one (3a).—To a solution of 8.65 g. of the hydroxy ketone **2a** in 500 ml. of pyridine at 0° was added 15 g. of *p*-toluenesulfonyl chloride. The solution was removed from the cooling bath and allowed to stand at room temperature for 16 hr. Aqueous potassium bicarbonate was added and the mixture was stirred for 10 min. The solution was partitioned between water and benzene. The organic layer was separated and washed with water and twice with excess 10% hydrochloric acid. A routine extraction procedure[31] yielded an oil which was crystallized from ether–methanol, providing 7.55 g., m.p. 128–134°, and 2.50 g., m.p. 132–134°, of the tosylate **3a**. Recrystallization from methylene chloride–methanol gave the analytically pure material, m.p. 134–136°, λ_{max} 5.76 μ, $[\alpha]_D$ 182°.

Anal. Calcd. for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53. Found: C, 69.96; H, 7.38.

Chromatography on silica caused considerable decomposition of the tosylate, leading to noncrystalline mixtures.

3α-Mesyloxyestr-5(10)-en-17-one (3b).—To a stirred solution of 40 g. of the hydroxy ketone **2a** in 500 ml. of pyridine at −10° was added dropwise 20 ml. of methanesulfonyl chloride over a 5-min. period. The reaction mixture was allowed to warm slowly. After 2 hr. (final temperature, 10°), the reaction mixture was poured into aqueous potassium bicarbonate. The resulting product was collected on a filter, yielding 43 g. of mesylate, m.p. 127–128°. Recrystallization from ether gave 34.0 g. of the pure mesylate, m.p.129–130°; λ_{max} 5.75, 7.37, 7.49, and 8.51 μ; Δν 183 c.p.s. (SO_2CH_3).

Anal. Calcd. for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.00. Found: C, 64.52; H, 8.10.

The mesylate, like the tosylate, was unstable to chromatography on silica.

Estra-2,5(10)-dien-17-one (11a).—A solution of 1.0 g. of the tosylate **3a** in 50 ml. of 1:1 benzene–petroleum ether was adsorbed on a column of Woelm cationotropic alumina, causing the immediate appearance of a bright yellow band. Elution with benzene yielded 0.48 g. of material which was recrystallized from methanol to yield 0.21 g. of the diene **11a**, m.p. 133–134°, and 0.20 g., m.p. 130–133°, λ_{max} 5.75 μ, $[\alpha]_D$ 238°. The n.m.r. showed a strong peak at 344 c.p.s. with a weaker absorption at 346 c.p.s. (total width at half-height, 3 c.p.s.).

(25) Infrared spectra and rotations (1%) were determined in chloroform and ultraviolet spectra in methanol. N.m.r. spectra were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc., at 60 Mc., using tetramethylsilane as in internal standard (Δν = 0 c.p.s.). Petroleum ether refers to the fraction with b.p. 63–68°. Melting points are uncorrected.

(26) Effective product analysis throughout this work was accomplished routinely by paper chromatography. We wish to thank Dr. E. G. Duskalakis and staff for these separations as well as for all the column chromatography described here.

(27) We are indebted to Dr. R. T. Dillon and staff for the spectra and analyses reported here.

(28) We wish to thank Mr. L. N. Nysted for this comparison; see U. S. Patent 2,705,721 (1955) and ref. 8.

(29) We wish to acknowledge the assistance of Mr. R. Mayne who conducted the experiments with this reagent.

(30) We are grateful to Mr. W. M. Selby and staff for performing the hydrogenations and the autoxidation described in this paper.

(31) This procedure generally involved washing a benzene solution of the crude reaction product with water, aqueous potassium bicarbonate, and water, drying the solution over anhydrous magnesium sulfate, and distilling the solvent under reduced pressure (temperature less than 50°).

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.43; H, 9.12.

The conjugated diene **10** was a contaminant of the diene **11a**, as was seen in the ultraviolet spectrum of the crude product [λ_{max} 265 mμ (ϵ 16000)].[32] In addition the crude diene contained 5–10% of **12** as indicated by n.m.r. and paper chromatography.

The same elimination reaction was effected by boiling the tosylate for 6 hr. in pyridine.

The mesylate **3b** also underwent an elimination on Woelm basic alumina (activity grade 1) although in this case 30% of the product had aromatized as evidenced by the typical n.m.r. signals in the 420–440 c.p.s. region. With Merck alumina, 1.0 g. of mesylate **3b** afforded 0.56 g. of the diene (**10**, **11a**), λ_{max} 264 mμ (ϵ 1100), containing no discernible amounts of the aromatic compound. Also obtained in this case was 0.11 g. of hydroxy compound **6a**, shown to contain none of the isomeric alcohol **2a** by paper chromatography.

The stability of the double bonds in the unconjugated position was demonstrated by treating a sample of the diene **11a** in refluxing methanol containing aqueous hydrochloric acid for 20 hr. The product was largely unchanged, exhibiting less than 20% of the strong ultraviolet spectrum typical of the 3,5-diene system. The diene showed no change after being boiled for 2 hr. in methanol containing aqueous potassium hydroxide.

Oxidation of the Diene.—A solution of 14.8 g. of the diene mixture (**10**, **11a**) in 300 ml. of pyridine was added to 15 g. of chromic acid slurried[33] in 300 ml. of pyridine at 10°. After 90 min., the solution was diluted with water, and the product was separated by extraction with ether in the usual way.[31] The residue was recrystallized from methylene chloride–methanol to yield 10.8 g. of estra-1,3,5(10)-trien-17-one (**12**), m.p. 144–145°, identical with an authentic sample[16] by comparison of the usual criteria. An additional 1.56 g. of the same material, m.p. 137–144°, was obtained by chromatography of the mother liquors.

Dehydrogenation was effected also when the diene **11a** was mixed with 5% palladium–charcoal catalyst and heated to 180° for 5 min.; this procedure tended to produce more highly aromatized materials as by-products than did direct oxidation. N-Bromosuccinimide in carbon tetrachloride reacted readily with the diene giving the aromatic compound and an unstable brominated product, the mixture being converted by treatment in refluxing pyridine to a total of 50% of desoxyestrone.

The diene **11a** in ethyl acetate underwent no change when stirred with oxygen in presence of palladium or platinum catalyst at atmospheric pressures.[30]

Estra-2,5(10)-dien-17β-ol.—A solution of 1.40 g. of the crude diene (**10**, **11a**) in 20 ml. of ethanol was added dropwise to a solution of 1 g. of lithium wire in 600 ml. of ammonia and 30 ml. of ethanol. An additional 4 g. of lithium wire was added in three portions over a 1-hr. period. The ammonia was distilled from the colorless solution and replaced with ether–benzene. Water was added (carefully at first) and the product was isolated by benzene extraction.[31] The product was crystallized from acetone, 0.30 g., m.p. 139–141°; a second crop was obtained from petroleum ether, 0.64 g., m.p. 139–141°. The analytical sample of **11b** (R′ = H) was obtained by recrystallization from acetone, m.p. 139–141°.

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.77; H, 10.25.

Estra-2,5(10)-dien-17β-ol propionate was prepared by treating the hydroxydiene with propionic anhydride–pyricine at 100° and had m.p. 88–90° on recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.11; H, 9.72.

The diene was also preparable by selective tosylation of the diol **2b** (1 mole equiv. of *p*-toluenesulfonyl chloride, 5°). The product was passed over Woelm basic alumina (activity grade I) forming a mixture which consisted of roughly equal parts of a diene C-17-tosylate, the desired product **11b** (R′ = H), and starting material.

17α-Ethynylestra-2,5(10)-dien-17-ol.—Through a stirred solution of 3.0 g. of potassium metal in 40 ml. of *t*-amyl alcohol at 5° was passed a stream of acetylene gas (passed through water and concentrated sulfuric acid washing towers). After saturation of the solution with acetylene, 2.0 g. of the diene **11a** (no solvent) was added to the reaction mixture. A slow stream of acetylene was passed over the reaction at 5° for 6 hr. The mixture was stoppered and stored at 0°. After 18 hr. the solution was diluted with 100 ml. of water containing 20 g. of ammonium chloride. The product was extracted with benzene in the usual way,[31] affording 2.55 g. of an oil that was chromatographed on 60 g. of silica. The material eluted with 70% benzene–petroleum ether afforded, on recrystallization from petroleum ether, 0.24 g. of the pure product, m.p. 98.0–98.5°: λ_{max}^{KBr} 2.81, 2.95, and 3.03 μ; [α]D 1.3.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 85.34; H, 9.08.

A second crop (0.95 g., m.p. 97–99°) was also obtained.

17α-Vinylestra-2,5(10)-dien-17-ol.—A solution of 0.56 g. of the ethynyl derivative (**11b**, R′ = C≡CH) in 30 ml. of pyridine and 0.28 g. of 5% palladium–calcium carbonate catalyst were stirred in an atmosphere of hydrogen for 25 min. The mixture, filtered and concentrated, yielded a residue (0.56 g.) which was chromatographed on 40 g. of silica. The fractions obtained with 70% benzene–petroleum ether were combined to yield 0.50 g. of material, recrystallized from aqueous methanol to give the analytical sample of **11b** (R′ = CH=CH$_2$), m.p. 106–108°, λ_{max}^{KBr} 2.97 and 6.08 μ, [α]D 117°.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.17; H, 9.81.

Attempts to reduce the vinyl double bond in the presence of palladium–carbon catalyst led to a mixture from which ring-A aromatic derivatives were isolated and identified by infrared and n.m.r. spectra.

3β-Hydroxyestr-5(10)-en-17-one (6a).—A solution of 5.0 g. of the tosylate **3a** in 50 ml. of dimethylformamide was heated at 65° for 68 hr. The product (3.3 g.), isolated by dilution with water and benzene extraction,[31] was saponified by boiling in 50 ml. of methanol containing 15 ml. of 10% aqueous potassium hydroxide in a nitrogen atmosphere for 2 hr. The reaction mixture was diluted with water, and the product was isolated by benzene extraction.[31] The residue (3.1 g.) was chromatographed on 300 g. of silica. The initial eluates (5% ethyl acetate in benzene) provided 0.60 g. of a mixture of dienes (**11a** and **10**) containing 20% of aromatic material **12** (n.m.r. analysis). Elution with 8% ethyl acetate in benzene gave a total of 1.0 g. of material, shown by paper chromatography to contain 15% of the epimer **2a**. The product was recrystallized from cyclohexane (Darco) to yield 0.68 g. of the 3β-hydroxy ketone **6a**, m.p. 137–140°, λ_{max} 2.75 and 5.72 μ, [α]D 202°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.97; H, 9.47.

Treatment of the mesylate **3b** with dimethylformamide under these conditions caused reaction of only 70% of the starting material in 68 hr. by n.m.r. assay. Added sodium benzoate helped little.[34]

3β-Benzoyloxyestr-5(10)-en-17-one.—The benzoate was prepared in the same manner as its epimer. Recrystallization of the crude product from methylene chloride–methanol gave the pure benzoate, m.p. 136–138°, λ_{max} 5.75 and 5.82 μ, [α]D 135°. The C-3α proton had an n.m.r. signal centered at 322 c.p.s. (half-height width, 18 c.p.s.).

Anal. Calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.24; H, 8.13.

The same compound could be obtained from a mixture of the 3α- and 3β-benzoates, obtained by benzoylation of the crude borohydride product. Chromatography of the mixture on silica was followed by fractional crystallization of the material eluted at 1% ethyl acetate in benzene, giving the pure 3β-isomer, m.p. 136–138°.

Estr-5(10)-ene-3β,17β-diol (6b).—A solution of 1.05 g. of the hydroxy ketone **6a** in 50 ml. of tetrahydrofuran containing 3.0 g. of lithium tri-*t*-butoxyaluminohydride was allowed to stand at room temperature for 18 hr. The solution then was poured into aqueous acetic acid, and the resultant precipitate was collected on a filter. Recrystallization of the product from acetonitrile and

(32) Preparation of this diene system (**11**) has not been described in the literature. Near analogs are estra-2,4-dien-17-ol acetate, λ_{max} 268 mμ (ϵ 5270) [P. N. Rao and H. R. Goldberg, *Chem. Ind.* (London), 1317 (1961)], and several androsta-2,4-dienes, λ_{max} 266 mμ (ϵ 6500) [B. Berkoz, A. D. Cross, M. E. Adams, H. Carpio, and A. Bowers, *J. Org. Chem.*, **28**, 1976 (1963)].

(33) For precautions, see G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(34) *Cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **24**, 1618 (1959).

from aqueous methanol gave 0.44 g. of the pure diol **6b**, m.p. 137–138° as a monohydrate, λ_{max}^{KBr} 3.05 μ.

Anal. Calcd. for $C_{18}H_{28}O_2 \cdot H_2O$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.13.

Hydrogenation of Estr-5(10)-ene-3β,17β-diol (6b).—A solution of 0.43 g. of the diol **6b** in ethanol (50 ml.) and ruthenium oxide catalyst (1.0 g.) were heated in an atmosphere of hydrogen at 100°, 1600 p.s.i. for 8 hr. The solution was filtered and concentrated, yielding a residue which was recrystallized from aqueous methanol to yield 0.22 g. of 5α,10α-estrane-3β,17β-diol (**9**), m.p. 171–175°, identical with an authentic sample in the infrared.[12]

10ξ-Hydroxy-3β,5-cycloestran-17-one (4). A. Tosylate Solvolysis.—A solution of 9.2 g. of the tosylate **3a** in 300 ml. of acetone and 100 g. of potassium acetate in 500 ml. of water were stirred together at the boiling point for 18 hr. (Later experiments showed this time could be reduced to 3 hr.) The solution was concentrated to half volume and the product was extracted with benzene.[31] The semicrystalline residue (7.0 g.) was adsorbed onto 300 g. of Merck chromatographic alumina (alkaline). Elution with benzene gave 3.4 g. of crystalline material, recrystallized from methanol to provide the diene **11a**, m.p. 133–134°. Elution of the column with 1 and 2% ethyl acetate in benzene gave 1.3 g. (19%) of material, recrystallized from acetone–petroleum ether to yield 1.15 g. of the pure *i*-steroid **4**, m.p. 193–195°; $\lambda_{max}^{CCl_4}$ 2.78 and 5.75 μ; $\Delta\nu$ 7, 10, and 15 c.p.s. (cyclopropane protons); $[\alpha]_D$ 115°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.92; H, 9.42.

Acetylation of this material failed to occur with pyridine–acetic anhydride at 100° for 10 min. Treatment with 4 *N* chromic acid in acetone at room temperature effected no reaction.

Further elution of the column with 10 and 20% ethyl acetate in benzene gave a crude product containing about 5% of the 3α-alcohol (by paper chromatogram); recrystallization from cyclohexane afforded 0.60 g. of the major constituent, the 3β-alcohol, m.p. 133–136°.

B. Mesylate Solvolysis.—A slurry of the mesylate **3b** (7.0 g.) in 250 ml. of acetone and 250 ml. of water containing 18 g. of potassium acetate was stirred at the reflux temperature. The initially present crystals dissolved slowly giving way to an oily precipitate. After 2.5 hr. the solution was concentrated *in vacuo*, producing a crystalline solid (4.85 g.) which was collected on a filter. Extraction of the filtrate with benzene afforded an additional 0.6 g. of material. Neither product contained mesylate as seen clearly from the n.m.r. spectra. Chromatography showed the product to consist of 2.0 g. (40%) of the diene [λ_{max} 260 mμ (ϵ 1000)] containing 3–6% of aromatic material (n.m.r. analysis). Also obtained was 1.8 g. (33%) of the crude cyclosteroid **4**, recrystallized to give 1.0 g., m.p. 187–191°, and 0.35 g., m.p. 178–182°, of **4**. Later fractions contained 0.57 g. (12%) of the hydroxy ketone **6a**.

Acid-Catalyzed Rearrangement of the Cyclosteroid 4.—A solution of 50 mg. of the cyclosteroid **4** in 20 ml. of 98% formic acid containing 0.2 ml. of triethylamine was allowed to stand at room temperature for 18 hr. The solution was diluted with water and the precipitate was collected on a filter. The product (42 mg). was dissolved in 10 ml. of methanol containing 0.5 ml. of 5% aqueous potassium hydroxide, and the solution was heated at reflux for 30 min. The methanol was distilled and replaced with water, yielding a crystalline material which was collected and washed on a filter. The product, 40 mg. of **2a**, m.p. 186–190°, was identical in the infrared with an authentic sample. A paper chromatogram of this material showed it to be free of any contaminant including the 3β-hydroxy compound **6a**.

Hydrogenation of the Cyclosteroid 4.—A solution of 0.20 g. of the cyclosteroid **4** in 15 ml. of dioxane and 0.8 ml. of acetic acid was stirred at room temperature under hydrogen for 27 hr.[19] The mixture absorbed *ca.* 1 mole equiv. of gas. The product, isolated by filtration of the catalyst and evaporation of the solvent, was chromatographed on 4 g. of silica. The fractions, all amorphous, were combined into three groups and each was examined by n.m.r.; the spectra showed marked broadening of the methyl group signals, implying that the hydrogenation had produced new methyl groups.

In a subsequent run, the same procedure was followed except the acid was omitted. The product from 0.90 g. of cyclosteroid **4** was chromatographed on alumina and afforded 0.58 g. of a semicrystalline material. Crystallization from petroleum ether yielded 60 mg., m.p. 105–115°, and 50 mg., m.p. 123–125°, of desoxyestrone **12**, as seen from comparison of n.m.r. and infrared spectra. No other crystalline products were obtained. In another experiment, palladium-on-carbon catalyst caused increased pressure in the system due to release of hydrogen.

3β-Tosyloxyestr-5(10)-en-17-one (7a).—A solution of 0.95 g. of the 3β-hydroxy compound **6a** and 1.5 g. of *p*-toluenesulfonyl chloride was allowed to stand at 15° for 18 hr. The solution was diluted with aqueous potassium bicarbonate and the resulting precipitate was separated by filtration and washed with water, yielding 1.0 g. of product, m.p. 135–138°. Recrystallization of this material from acetone–petroleum ether gave the pure sample, m.p. 140–142°, λ_{max} 5.75 μ, $[\alpha]_D$ 138°.

Anal. Calcd. for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53. Found: C, 69.91; H, 7.32.

The same compound was isolated readily as a second crop from a mixture of 3α- and 3β-tosylates. This afforded an additional method of separating reasonably pure 3β-derivatives.

Passage of the tosylate **7a** (0.20 g.) over 6 g. of Woelm basic alumina gave 0.13 g. of crude diene **11a** [λ_{max} 266 mμ (ϵ 1200)].

10β-Hydroxy-3α,5-cycloestran-17-one (8).—A solution of 2.0 g. of the tosylate **7a** in 100 ml. of acetone and 10 g. of potassium acetate in 80 ml. of water was stirred at room temperature for 6 hr. The solution then was heated at reflux for 24 hr., cooled, and diluted with water. The product, isolated by benzene extraction,[31] amounted to 1.40 g. of an oil which was chromatographed on 40 g. of silica. The early fractions, eluted with 2% ethyl acetate in benzene, amounted to 0.42 g. of the crude diene (infrared correlation). Elution with 10% ethyl acetate in benzene provided 0.21 g. of the crude *i*-steroid, recrystallized from acetone–petroleum ether to provide the analytical sample, m.p. 173–176°; $\lambda_{max}^{CCl_4}$ 2.78 and 5.75 μ; $\Delta\nu$ 39, 42, and 47 c.p.s.; $[\alpha]_D$ 138°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.94; H, 9.43.

Later eluents provided 0.23 g. of the 3α-alcohol **2a** contaminated with 10–15% of the 3β-alcohol **6a**; the latter epimer probably was derived largely from the epimeric tosylate **3a** present in the starting material.

The mesylate **7b**, an amorphous material prepared in the same manner as the epimer **3b**, was solvolyzed under the same conditions as described for **3b**. The product from 1.4 g. of **7b** was chromatographed to yield the following crude fractions: 0.31 g. of the diene **11a** [λ_{max} 266 mμ (ϵ 1060)], 0.39 g. of the cyclosteroid **8** (37%), and 0.20 g. of the alcohol **2a** (containing 8–10% of the epimer **6a**).

Acid-Catalyzed Rearrangement of the Cyclosteroid 8.—A solution of 30 mg. of the cyclosteroid **8** in 5 ml. of formic acid and 0.05 ml. of triethylamine was allowed to stand at room temperature for 16 hr. The solution was diluted with water, and the product was isolated by extraction with benzene.[31] The residue, 32 mg. of an oil, was boiled in 10 ml. of methanol containing 2 ml. of 10% aqueous potassium hydroxide for 30 min. The product was isolated by dilution with water and extraction with benzene. The resulting material, 34 mg., was adsorbed on 3 g. of silica. Elution with 10% ethyl acetate in benzene provided 30 mg. of material which was crystallized from petroleum ether to yield the 3β-isomer **6a**, m.p. 134–138°. Analysis of total product by paper chromatography showed the presence of 85% of the 3β-epimer and 10% of the 3α-epimer. The latter compound arose from the epimeric cyclosteroid **4a** shown by paper chromatography to be present in the starting material.

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Ionic Reactions Occurring in Sulfuric Acid. III. The Sulfuric Acid-Catalyzed Self-Alkylation of Isobutane with C_3–C_6 Olefins

J. E. HOFMANN

Process Research Division, Esso Research and Engineering Company, Linden, New Jersey

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Quantitative data have been obtained for the acid-catalyzed self-alkylation of isobutane with branched and normal olefins ranging from propene to hexenes. It has been found that self-alkylation increases with both increasing molecular weight and branching of the olefin. At least two mechanistic schemes are required to interpret the data. The first, a classical protonation–hydride transfer sequence predominates with *n*-olefins while an alkylation–fission sequence is preferred for isoolefins.

The abnormal reaction of isobutane with certain olefins, particularly C_{5+} branched olefins, has been known for almost as long as the alkylation reaction itself.[1] The over-all reaction involves the combination of 2 moles of the isoparaffin and thus came to be known as "self-alkylation" (reaction 1) or hydrogen transfer.

$$2i\text{-}C_4H_{10} + C_nH_{2n} \longrightarrow i\text{-}C_8H_{18} + C_nH_{2n+2} \quad (1)$$

With isobutane as the isoparaffin, the octanes formed are similar to that observed when isobutene is employed as the reactant olefin.

The mechanism for self-alkylation has been explained in terms of familiar carbonium reactions.[2] The olefin is protonated (reaction 2) and the resulting carbonium

$$C_nH_{2n} + H^+ \rightleftharpoons C_nH^+_{2n+1} \quad (2)$$

is saturated by hydride transfer with the isoparaffin (reaction 3). The *t*-butyl cation is in equilibrium with

$$C_nH^+_{2n+1} + i\text{-}C_4H_{10} \longrightarrow C_nH_{2n+2} + t\text{-}C_4H_9^+ \quad (3)$$

isobutylene (reaction 4), and the isobutylene thus

$$t\text{-}C_4H_9^+ \rightleftharpoons H^+ + i\text{-}C_4H_8 \quad (4)$$

formed is alkylated to form the trimethylpentyl cation (reaction 5).

$$t\text{-}C_4H_9^+ + i\text{-}C_4H_8 \longrightarrow (CH_3)_3CCH_2\overset{+}{C}(CH_3)_2 \quad (5)$$

Despite the general knowledge available, only limited quantitative data have appeared in the literature. McAllister[1] presents evidence that self-alkylation increases with molecular weight and increased branching, while Schmerling[3] reports on the reaction between propylene and isobutane using aluminum chloride monomethanolate as the catalyst. Such data are of interest from both a process point of view as well as from mechanistic considerations. Process wise, product quality will certainly be a function of the degree of self-alkylation while mechanistically it is important to compare observed results with the reaction scheme described previously. This paper discusses quantitative data for olefins ranging from C_3 through C_6 (including C_4-olefins).

Experimental

All experiments were carried out in a 1-l. magnetically agitated autoclave. Isobutane (3.8 moles) and 220 g. of concentrated (97.7 wt. %) sulfuric acid were charged to the autoclave. Approximately 2 wt. % acid sludge was added to minimize any induction period.[4] After equilibrating the autoclave at 10°, 0.35 mole of olefin was added continuously over a 2-hr. period. At the end of this period, the total of the hydrocarbon phase was sampled and analyzed by gas chromatography using a Perkin-Elmer Model 154 gas chromatograph equipped with a 21-ft. column of Dow Corning (DC-200) silicone oil at 75°.

Concentrated sulfuric acid from American Cyanamide and Matheson research grade isobutane were employed throughout this study. Phillips pure grade olefins were used in all cases except for propylene which was Matheson C.P. grade.

Results

Alkylate compositions on a pentane and higher basis are shown in Table I for each of the olefins studied. Moles of C_8 and moles of saturated paraffin of the same carbon number as the reactant olefin were calculated from the total hydrocarbon composition as determined by the gas chromatographic analysis. The degree of self-alkylation, as determined by octane formation, as a function of carbon number of the reactant olefin is shown in Fig. 1. Figure 2 contains a comparison of octane formation with the amount of olefin that was saturated to a paraffin at the same carbon number.

Discussion

Figure 1 shows the trend of self-alkylation with increasing molecular weight and is similar to what has been observed in the past.[1] That is, self-alkylation increases with increasing molecular weight and increased branching of the olefin. The data presented for the C_4-olefins, 1-butene and isobutylene, were obtained during studies of the alkylation of C^{14}-labeled olefins.[5] Experimentally, these data were obtained under slightly different conditions, principally continuous *vs.* batch operation, but the over-all conditions were close enough to make a reasonable comparison.

For simplicity, data interpretation can be broken into two separate categories:

Effect of Molecular Weight.—It is clear from Fig. 1 that self-alkylation increases with increasing carbon number for both the normal and branched olefins. If one adopts as a mechanism for self-alkylation the reactions previously outlined (reactions 2–5), then one step must be favored as the olefin molecular weight increases. Within a given series, *i.e.*, branched or normal, it is not likely that the rate of protonation (reaction 2) or equilibrium would change markedly from olefin to olefin. Likewise, relative rates of hydride transfer (reaction 3) should not vary appreciably for a given series. Since the mechanism, particularly with regard

(1) S. H. McAllister, J. Anderson, S. A. Ballard, and W. E. Ross, *J. Org. Chem.*, **6**, 647 (1941).

(2) L. Schmerling, "The Chemistry of Petroleum Hydrocarbons," Vol. 3, Reinhold Publishing Corp., New York, N. Y., 1955, p. 375.

(3) L. Schmerling, *J. Am. Chem. Soc.*, **68**, 275 (1946).

(4) J. E. Hofmann and A. Schriesheim, *ibid.*, **84**, 953 (1962).

(5) J. E. Hofmann and A. Schriesheim, *ibid.*, **84**, 957 (1962).

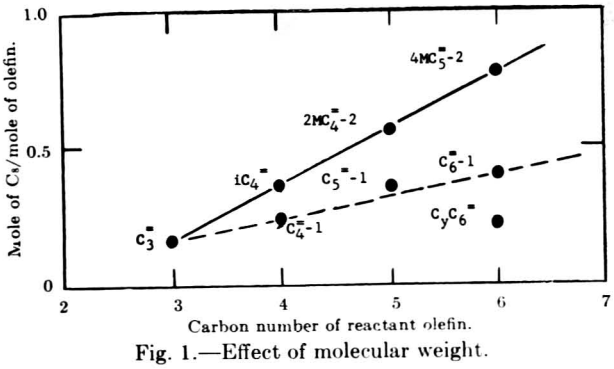


Fig. 1.—Effect of molecular weight.

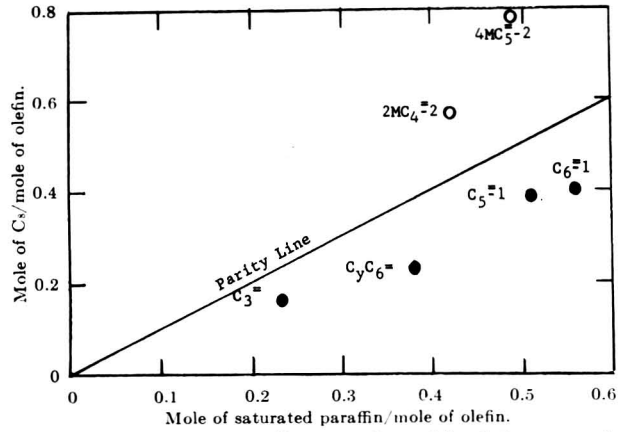


Fig. 2.—Comparison of C_8 formation with olefin saturation (the saturated paraffin having the same carbon number as the reactant olefin).

to normal olefins, appears to be proper, it is apparent that some other phenomenon must be operative. This could be physical and involve more rapid extraction of the higher molecular species into the hydrocarbon phase. However, any rigorous explanation at this time would be premature.

Effect of Branching.—Comparison of branched *vs.* normal olefins is somewhat more obvious. Protonation of a branched olefin leads to a tertiary carbonium ion as compared to a secondary ion for a normal olefin. The enhanced stability of tertiary ions drives protonation (reaction 2) to the right, and this in turn leads to more self-alkylation *via* the subsequent steps. An interesting point that must also be considered in this comparison is the fact that the product from self-alkylation of normal olefins is always predominantly the corresponding isoparaffin. For instance, from Table I it can be seen that isopentane is formed from 1-pentene, 2- and 3-methylpentane from 1-hexene, and a large amount of methylcyclopentane from cyclohexene. This has been observed in the past[3] and most likely arises because a secondary ion, once formed, rapidly rearranges to a more stable tertiary ion (reaction 6).

$$\text{C—C—}\overset{+}{\text{C}}\text{—R} \xrightarrow[\text{fast}]{} \text{C—}\overset{+}{\underset{\text{C}}{\text{C}}}\text{—R} \qquad (6)$$

This still leaves the rate at which the original normal olefin is protonated at the limiting factor which differentiates between normal and isoolefins.

General Mechanistic Considerations.—Although the mechanism outlined in reactions 2–5 explains the normal products of self-alkylation, it does not allow for by-product formation. (By-products are defined as those hydrocarbons that have carbon numbers other than the carbon number of the olefin, a C_8, or the normal alkylation product of the olefin and isobutane.) Alkylation of the normal olefins leads to only a small amount of by-products and does no equire additional interpretation. However, during alkylation of the two isoolefins, a relatively large amount of by-products are formed (isohexanes from the methylbutene; isopentane and isoheptanes from the methylpentene). Explanation of these materials requires additional reactions, and these in turn have direct bearing on the mechanism of self-alkylation.

If, during β-fission, only fragments of C_4 and larger can be formed, then formation of a C_6 from isobutane and a C_5-olefin must arise from a C_{10} or larger. Likewise, formation of C_5 and C_7 compounds from isobutane and a C_6-olefin requires at least some C_{11} or higher as intermediates. Formation of these higher molecular weight intermediates requires olefin dimerization or at least two successive alkylation steps. The rapid rate at which isobutylene tends to polymerize and undergo nonselective cracking was noted during our tracer studies.[5] A similar alkylation–fission sequence has been demonstrated during the sulfuric acid-catalyzed isomerization of isoparaffins.[6] Rapid dimerization of a C_5-olefin leads to a C_{10}, which in turn can crack to fragments of C_6 and C_4 or C_5 and C_5. In the latter case, differentiation between the classical mechanism for self-alkylation and this mechanism is impossible. However, if both the normal and isoolefins were initially dimerized, one can expect similar nonselective cracking patterns. Since only the isoolefins show a large amount of by-product formation, it is likely that they are also the only ones that participate in the alkylation–fission scheme[7] to any great extent.

By material balance and mass action, the buildup of higher molecular weight intermediates followed by nonselective fission must be accompanied by the formation of isobutylene and subsequently octanes (as long as isobutane is in large excess). This is illustrated graphically in Fig. 2. The normal olefins and cyclohexene all fall below the parity line, while the two isoolefins are above the line. Below the line is indicative of less than 1 mole of C_8 for each mole of saturated paraffin of the same carbon number as the olefin. Since isobutylene itself would not be alkylated to C_8 with 100% selectivity, this situation could arise from reaction sequence 2–5 accompanied by the normal alkylation of isobutylene with about 70% selectivity. A point above the line requires that more octanes be formed than saturated paraffins of the same carbon number as the reactant olefin. For the isoolefins, this is a consequence of the aforementioned by-product formation. Reaction 7 is presented as one possible example of reaction

$$2C_6H_{12} + 5i\text{-}C_4H_{10} \longrightarrow 2C_5H_{12} + C_6H_{14} + 2C_8H_{18} \qquad (7)$$

stoichiometry which yields 2 moles of C_8 for each mole of C_6-olefin that is saturated to a C_6-paraffin.

This is only one of a number of over-all equations that could be written and each will require several addition and fission reactions. However, as long as by-products between C_5 and C_7 are formed, there will

(6) G. J. Karabatsos and F. M. Vane, *J. Am. Chem. Soc.*, **85**, 729 (1963).

(7) In this sense, alkylation could be the addition of *t*-butyl cation to an olefin or the addition of protonated olefin to another olefin, *i.e.*, olefin dimerization.

TABLE I
ALKYLATE COMPOSITIONS

	Experiment					
Alkylate composition, mole %	1 Propylene	2 2-Methyl-2-butene	3 1-Pentene	4 4-Methyl-2-pentene	5 1-Hexene	6 Cyclohexene
Isopentane	3.1	36.2	31.6	22.4	8.3	1.3
n-Pentane	...	...	2.3	...	...	...
2,3-Dimethylbutane	2.4	5.7	1.2	3.3	0.7	1.2
2-Methylpentane	...	...	...	14.9	24.1	...
3-Methylpentane	...	1.3	0.1	4.5	12.8	...
n-Hexane	...	...	...	...	1.8	...
2,4-Dimethylpentane	21.9	1.5	0.5	2.1	1.0	...
2,3-Dimethylpentane, 2-methylhexane	52.2	1.8	0.2	3.5	0.3	...
Methylcyclopentane	...	...	...	...	...	30.5
Cyclohexane	...	...	...	...	...	...
2,2,4-Trimethylpentane	11.4	23.6	14.8	18.1	16.9	15.3
2,2,3-Trimethylpentane, 2,4- + 2,5-dimethylhexane	0.6	5.3	1.9	4.7	1.7	1.8
2,3,3- + 2,3,4-Trimethylpentane, 2,3-dimethylhexane	8.4	18.8	8.9	12.7	10.0	13.1
C_9	...	5.9	38.2	9.3	...	...
C_{10}	...	...	...	4.5	22.4	13.4[a]
Mole of paraffin[b]/mole of olefin	0.23	0.42	0.51	0.49	0.56	0.38
Mole of C_8/mole of olefin	0.16	0.57	0.38	0.78	0.40	0.23

[a] Possibly contains alkylated naphthenes. [b] Saturated paraffin having the same carbon number as the reactant olefin.

be an increase in octane formation. Since paraffins with the same carbon number as the reactant olefin are also formed by the alkylation–fission scheme, it is impossible to say how much is formed by this mechanism as compared to straight self-alkylation. It is clear, however, that considerably more alkylation–fission occurs with the isoolefins than with the normal olefins.

It is apparent from the preceding discussion that all the reaction products can be explained on the basis of classical carbonium ion reactions. However, the specific mechanistic route will depend to a large degree upon the reactant olefin. With normal olefins, the straight self-alkylation mechanism (reactions 2–5) appears to predominate. A normal hexene is particularly illustrative of this because alternative mechanisms would predict the formation of fairly large amounts of non-C_6 products. With isoolefins, an alkylation–fission sequence becomes increasingly important. This is borne out by the observed nonselectivity of the reactions with both the methylbutene and the methylpentene. Unfortunately, the general complexity makes it impossible to assess just how much of each mechanism is applicable to the different olefins.

Acknowledgment.—The author wishes to thank the Esso Research and Engineering Co. for permission to publish this work.

Identification of the Disultone from Sulfuryl Chloride and 1-Propanol

J. HODGE MARKGRAF,[1a] B. ANDES HESS, JR.,[1b] CHARLES W. NICHOLS,[1b] AND ROY W. KING[1c]

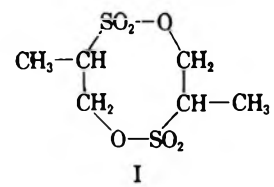
Departments of Chemistry, Williams College, Williamstown, Massachusetts, and Iowa State University, Ames, Iowa

Received December 23, 1963

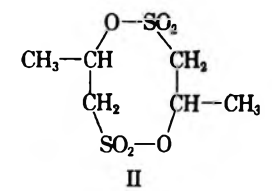
The crystalline product from the reaction of sulfuryl chloride with 1-propanol is assigned structure II on degradative and spectroscopic evidence. The mode of its formation is rationalized.

In 1952 Manecke[2] reported that sulfuryl chloride treatment of 1-propanol led to an eight-membered cyclic product to which he assigned structure I. Analytical and molecular weight data established the formula as $C_6H_{12}O_6S_2$, but it does not appear that alternate structures for the disultone were considered. Although hydrolytic and degradative reactions were reported, the structures of such products were not confirmed.

We have reinvestigated this reaction and established that the product is actually 4,8-dimethyl-1,5-dioxa-2,6-dithiacyclooctane 2,2,6,6-tetraoxide (II).[3] Repetition of Manecke's procedure afforded the same material in an over-all yield of 3% (the yield was not reported originally); modifications increased the yield



I



II

(1)(a) To whom inquiries should be addressed at Williams College; (b) based in part on the Honors theses of B.A.H., Jr. (1962), and C.W.N. (1960), Williams College; (c) Iowa State University.

(2) G. Manecke, *Chem. Ber.*, **85**, 160 (1952).

(3) The correct structure was originally proposed to us by Professor W. von E. Doering; his interest and encouragement in this work are gratefully acknowledged.

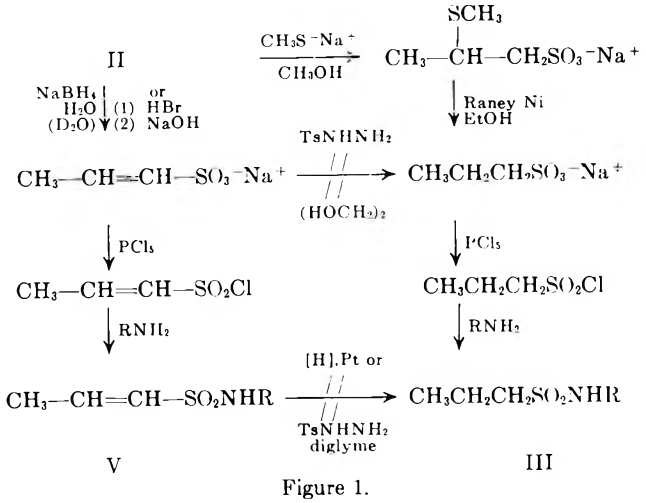


Figure 1.

to 25%. There is no doubt we have obtained the same compound, since analytical, molecular weight, and melting point data are in agreement. Manecke did not comment on the mode of formation of I, and it seemed to us that structure II may be mechanistically more reasonable.

Confirmation of structure II was obtained by degradation of the disultone to derivatives of 1-propanesulfonic acid. Authentic samples of sulfonamide derivatives (III and IV) of the isomeric propanesulfonic acids were prepared by known methods. Reductive

$CH_3CH_2CH_2SO_2NHR$ (III) $(CH_3)_2CHSO_2NHR$ (IV)

a, R = *p*-tolyl
b, R = α-naphthyl

cleavage of the disultone with sodium borohydride appeared to be a satisfactory route to propanesulfonic acid derivatives. However, conversion of the sodium sulfonate to sulfonamide afforded material different from both III and IV. The infrared spectrum exhibited absorption similar to that for IIIb and, in addition, contained a peak at 10.5 μ characteristic of *trans* olefins.[4] The bromine test for unsaturation was positive. The compound was assigned the *trans*-N-aryl

$CH_3—CH=CH—SO_2NHR$
V

1-propene-1-sulfonamide structure (V) on the basis of its n.m.r. spectrum which was consistent only with a 1-propenesulfonamide: an ABX_3 system[5] similar to that worked out by Fessenden and Waugh.[6]

The chemistry of the 1-propenesulfonamide derivatives was interesting in regard to both the mechanism of generation and the resistance to reduction. Thus, hydrogenation of Vb → IIIb failed to occur with Adams catalyst. Furthermore, the attempted diimide reductions of Va and sodium 1-propene-1-sulfonate with tosylhydrazine by the method of van Tamelen[7] were unsuccessful; the unsaturated compound was recovered in each case. The fact that borohydride effected elimination rather than reduction raised the possibilities of a concerted process or a reversible formation of an intermediate carbanion. That the latter pathway was not operative was shown by the absence of deuterium in the product (*i.e.*, no $CH_3—CH=CD—SO_2NHR$) obtained from the disultone and sodium borohydride in deuterium oxide. This constitutes a sufficient condition for the concerted process since the degrees of freedom in the eight-membered ring permit a *trans* (E2) elimination to occur, regardless of the configuration (*vide infra*).[8,9] Hydrolysis of the disultone by hydrobromic acid also yielded the unsaturated acid. The generation of the olefinic linkage by acid catalysis must have occurred during ring opening because Marvel and Weil[10] used the same reagent to convert sodium 2-hydroxy-1-propanesulfonate to sodium 2-bromo-1-propanesulfonate.

Cleavage of the eight-membered ring without concomitant elimination was obtained with sodium methylmercaptide, which functioned as an effective nucleophile.[10] The resulting sodium 2-methylmercapto-1-propanesulfonate was converted to IIIa. These reactions are summarized in the accompanying flow chart (Fig. 1). Thus the assignment of structure II was unambiguous.[11]

The n.m.r. spectrum of the disultone was consistent with the assigned structure. Since both I and II would have the same coupling between protons, the chemical shift afforded the only basis for differentiation. In dimethyl sulfoxide the disultone showed a methyl doublet at τ 8.57 (J = 6.7 c.p.s.) and CH_2 and CH multiplets centered at τ 6.15 and 4.80, respectively. Irradiation of the methyl peak with a radiofrequency field of approximately 4.5 mgauss simplified the CH multiplet to four lines (Fig. 2). Their positions were found by replacing each one by a 1:3:3:1 quartet with the observed CH_3–CH coupling constant and thus assigning each peak of the original multiplet to its corresponding quartet. The four line positions obtained by averaging these quartets were analyzed with the methylene multiplet as an ABX system, giving ν_A = 233 c.p.s., ν_B = 229 c.p.s., ν_X = 312 c.p.s., J_{AB} = 14.8 c.p.s., J_{AX} = ±1.3 c.p.s. and J_{BX} = ± 9.5 c.p.s. It was interesting that in this case, where $\nu_A - \nu_B$ was fortuitously equal to $\frac{1}{2}|J_{AX} - J_{BX}|$, one of the two quartets usually associated with the AB region collapsed to an intense singlet. In carbon tetrachloride solution the α-methylene protons of 1-propyl methanesulfonate and methyl 1-propanesulfonate appeared at τ 5.89 and 7.00, respectively, and the methine proton of 2-propyl methanesulfonate appeared at τ 5.15. The disultone methylene resonance at τ 6.15 might be consistent with either structure I or II. The methine protons, however, were at slightly lower field

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 40.

(5) The vinyl–vinyl coupling constant (15.0 c.p.s.) showed these protons to be *trans* as in *trans*-propenylbenzene.[6]

(6) R. W. Fessenden and J. S. Waugh, *J. Chem. Phys.*, **30**, 944 (1959).

(7) E. E. van Tamelen, R. S. Dewey, M. F. Lease, and W. H. Pirkle [*J. Am. Chem. Soc.*, **83**, 4302 (1961)] successfully reduced allyl disulfide by this method: we thank Professor van Tamelen (private communication) for experimental details.

(8) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York, N. Y., 1962, pp. 253–254.

(9) The possibility of a two-stage mechanism involving formation of a carbanion in a rate-determining and irreversible step seems remote in the present case. Such an interpretation has been offered for *cis*-eliminations in some cyclic sulfones [H. L. Goering, D. I. Relyea, and K. L. Howe, *J. Am. Chem. Soc.*, **79**, 2502 (1957)], but not in the case of others [F. G. Bordwell and P. S. Landis, *ibid.*, **79**, 1593 (1957)].

(10) C. S. Marvel and E. D. Weil, *ibid.*, **76**, 61 (1954).

(11) Subsequent to the completion of this work a report appeared from which this structural assignment could be inferred. H. Schmitz, H. Grosspietsch, H. Kaltenhäuser, and H. Wendt [*Angew. Chem.*, **75**, 299 (1963)] observed that the barium salt of 1-hydroxy-2-propanesulfonic acid exhibited an infrared spectrum different from that of the hydroxypropanesulfonic acid obtained from the hydrolysis of "Manecke's" disultone. The latter compound was shown to be the isomeric 2-hydroxy-1-propanesulfonic acid.

than in 2-propyl methanesulfonate whereas, by analogy with the 1-propyl compounds, they should have been at considerably higher field if adjacent to sulfur instead of oxygen.

The preparation of a disultone from 1-propanol and sulfuryl chloride must proceed by the initial formation of 1-propyl chlorosulfonate (VI) as suggested by Manecke. We have isolated VI from the reaction

$$CH_3CH_2CH_2OH + SO_2Cl_2 \xrightarrow[-HCl]{0^\circ} \underset{VI}{CH_3CH_2CH_2OSO_2Cl} \quad (1)$$

mixture and subsequently converted the pure compound to II in enhanced yield. The transformation of VI to a system containing a primary carbon–sulfur linkage can be rationalized by an elimination–addition–dimerization sequence. The first two steps (eq. 2 and 3) have been postulated by Nazarova and Tsukervanik[12] to account for the product obtained from the thermal decomposition of 1-propyl chlorosulfonate (eq. 5).[13] From the gaseous products evolved

$$VI \xrightarrow[\Delta]{} HCl + SO_3 + CH_3{-}CH{=}CH_2 \quad (2)$$

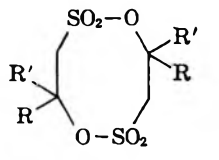
$$CH_3{-}CH{=}CH_2 \xrightarrow{SO_3} [CH_3{-}\overset{+}{C}H{-}CH_2{-}SO_2{-}O^-] \quad (3)$$

$$[CH_3{-}\overset{+}{C}H{-}CH_2{-}SO_2{-}O^-] \longrightarrow II \quad (4)$$

$$VI \xrightarrow[(2)\ H_2O\ (3)\ PbCO_3]{(1)\ 80^\circ} [CH_3{-}CH(OH){-}CH_2SO_3]_2Pb \quad (5)$$

from the similar decomposition of isobutyl chlorosulfonate, these same authors isolated isobutylene (dibromide derivative). The reaction of olefins with sulfur trioxide (eq. 3) has been studied extensively.[14] Repeated attempts were made to test the postulated sequence (eq. 2–4) by the reaction of 2-propanol with sulfuryl chloride. The crude 2-propyl chlorosulfonate (VII) could not be purified, and its thermal decomposition afforded no disultone. The instability of VII has been noted previously,[12] however, and the greater tendency for isopropyl derivatives of related systems to decompose has been observed.[12,15]

It is interesting to note that the disultone can exist as diastereomers. The configuration in which the methyl groups are *trans* is *meso* (onefold alternating axis of symmetry), while an enantiomeric pair is possible for the *cis* isomer (twofold axis of symmetry). Resolution studies were not undertaken with compound II.



VIII. R = R' = H
IX, R = H; R' = Ph
X, R = R' = CH_3

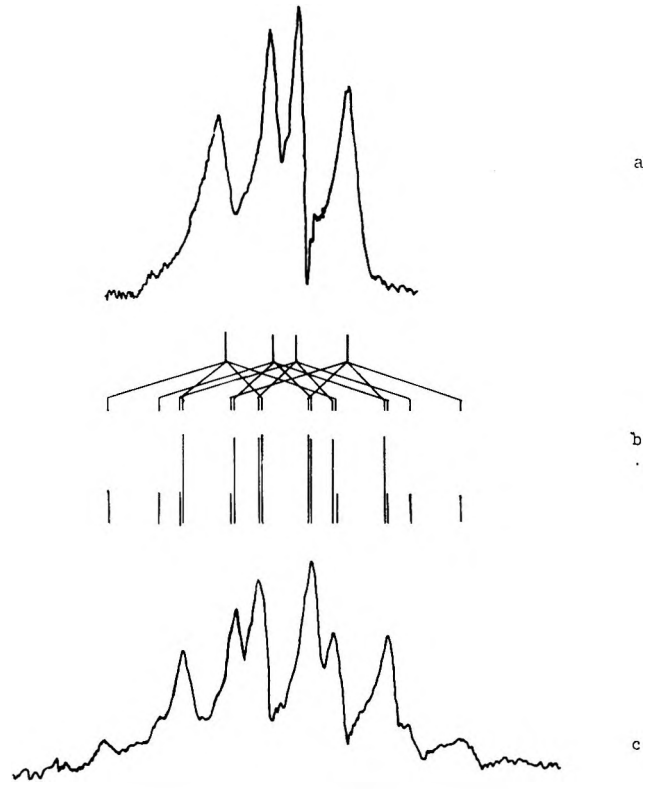


Fig. 2.—(a) N.m.r. spectrum at 60 Mc. of methine protons of disultone with CH_3 irradiated with 4.5 mgauss radiofrequency field; (b) theoretical spectrum of CH region; and (c) observed multiplet.

Only two other examples of eight-membered disultones have been reported. Manecke and Danhäuser[16] prepared the disultone of isethionic acid (VIII) by the vacuum distillation of bis(2-sulfoethyl) ether. Bordwell, *et al.*,[14b] isolated the relatively unstable compound IX from the sulfonation of styrene. From the thermal decomposition of isobutyl chlorosulfonate Nazarova and Tsukervanik[12] obtained the lead salt of a hydroxybutanesulfonic acid which, when allowed to stand 3 weeks over sulfuric acid, was reported to form an unidentified anhydride. The structure of this compound could be X, although their data were ambiguous.[17]

Experimental[18]

4,8-Dimethyl-1,5-dioxa-2,6-dithiacyclooctane 2,2,6,6-Tetraoxide (II). A.—The method of Manecke[2] was followed. To sulfuryl chloride (42.8 g., 0.317 mole) contained in a three-necked flask fitted with a drying tube, thermometer, and addition funnel, and cooled by an ice–salt bath, 1-propanol (19.7 g., 0.328 mole) was added dropwise with magnetic stirring. The reaction mixture, which was maintained below 0° during the addition, was permitted to warm to room temperature. After 5 days, excess water was added to the dark, two-phase system and crystalline material was formed. The solid was collected, washed with water, and dried in a vacuum desiccator to yield 1.1 g. (2.8%) of II. The crude material was recrystallized twice from absolute ethanol, m.p. 189.2–189.3° dec., lit.[2] m.p. 192–

(12) Z. N. Nazarova and I. P. Tsukervanik, *J. Gen. Chem. USSR*, **18**, 430 (1948).

(13) In one decomposition a white solid (m.p. 163°) was obtained; this material may have been crude disultone.

(14) For a recent review see E. E. Gilbert, *Chem. Rev.*, **62**, 549 (1962). The following references are particularly pertinent: (a) C. M. Suter, P. B. Evans, and J. M. Kiefer, *J. Am. Chem. Soc.*, **60**, 538 (1938); (b) F. G. Bordwell, M. L. Peterson, and C. S. Rondestvedt, Jr., *ibid.*, **76**, 3945 (1954); (c) F. G. Bordwell and M. L. Peterson, *ibid.*, **76**, 3952 (1954).

(15) (a) F. W. Bushong, *Am. Chem. J.*, **30**, 212 (1903); (b) F. C. Wagner and E. E. Reid, *J. Am. Chem. Soc.*, **53**, 3407 (1931).

(16) G. Manecke and J. Danhäuser, *Angew. Chem.*, **70**, 745 (1958).

(17) The anhydride was reported only as $C_8H_{18}S_2O_6$ (mol. wt. 274). The disultone X requires $C_8H_{16}S_2O_6$ (mol. wt. 272). The anhydride or the isomeric sulfonate requires $C_8H_{18}S_2O_7$ (mol. wt. 290).

(18) Melting and boiling points are uncorrected. Infrared spectra were taken as chloroform solutions with a Perkin-Elmer Infracord Model 137 spectrophotometer. Analyses were made by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. and Galbraith Laboratories, Inc., Knoxville 21, Tenn.

193° dec. The molecular weight was determined cryoscopically in purified[19] *p*-dioxane.

Anal. Calcd. for $C_6H_{12}O_6S_2$: C, 29.50; H, 4.95; S, 26.25; mol. wt., 244. Found: C, 29.47; H, 5.15; S, 26.04; mol. wt., 253, 200, 247.

B.—The same procedure was followed for the addition of reagents. Directly after the addition, the reaction mixture was heated on the steam bath until a vigorous exothermic reaction ensued. Crystalline material was obtained upon the addition of water to the dark, viscous residue. Yields of II were 3–4% in a series of runs.

C.—Method B was modified. Careful application of a steam bath and cooling bath permitted the exothermic reaction to be moderate and self-sustaining with the liquid phase at 95°. Yields of II were increased to 25%.

1-Propyl Chlorosulfonate (VI).—The reaction solution obtained at 0° from the addition of 1-propanol (34.5 g., 0.574 mole) to sulfuryl chloride (75.0 g., 0.556 mole) was distilled *in vacuo* to yield 42 g. (48%) of 1-propyl chlorosulfonate, b.p. 52–53° (10 mm.), $n^{20}D$ 1.4218; lit.[20] b.p. 53.2° (10 mm.), $n^{20}D$ 1.422. 1-Propyl chlorosulfonate (29.5 g., 0.186 mole) was converted by method B to 1.7 g. (7.5%) of II.

Attempted Preparation of 2-Propyl Chlorosulfonate (VII).—The reaction solution obtained at 0° from the addition of 2-propanol (46 g., 0.77 mole) to sulfuryl chloride (100 g., 0.74 mole) was decomposed thermally by method C (above). Despite the cautious application of heat, violent bumping occurred under conditions that were adequate for VI. No crystalline material was obtained in a series of such reactions.

Several attempts were made to isolate the intermediate 2-propyl chlorosulfonate by vacuum distillation. Decomposition of the distilland occurred each time without distillation.

N-Aryl 1-Propanesulfonamides (III).—1-Propanesulfonyl chloride was prepared by the method of Pantlitshko and Salvenmoser.[21] A mixture of 1-bromopropane (55 g., 0.45 mole), ammonium sulfite (93 g., 0.69 mole), and water (170 ml.) was stirred and heated at reflux until the system was homogeneous (3.2 hr.). The solution was concentrated to dryness at reduced pressure. The residual ammonium 1-propanesulfonate was treated with phosphorus pentachloride (187 g., 0.90 mole) and the reaction mixture was worked up as described[21] to yield 2.6 g. (4.1%) of 1-propanesulfonyl chloride, b.p. 79–81° (15 mm.), $n^{25}D$ 1.4524; lit.[22] b.p. 76–77° (12 mm.), $n^{20}D$ 1.4540. The sulfonyl chloride was converted by the method of Mel'nikov, *et al.*,[23] to 1-propanesulfon-*p*-toluidide (IIIa), m.p. 68.2–69.0° from aqueous ethanol, lit.[24] m.p. 67.0–67.8°. The method of Shepherd[25] was used to convert the sulfonyl chloride to 1-propanesulfon-α-naphthylide (IIIb), m.p. 82.8–83.6° from aqueous ethanol, lit.[26] m.p. 84°.

N-Aryl 2-Propanesulfonamides (IV).—Sodium 2-propanesulfonate monohydrate (15 g., 0.091 mole) was converted with phosphorus pentachloride (36 g., 0.18 mole) to 10 g. (80%) of 2-propanesulfonyl chloride. The crude sulfonyl chloride was converted to 2-propanesulfon-*p*-toluidide (IVa), m.p. 98.2–98.8° from aqueous ethanol.

Anal. Calcd. for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.03. Found: C, 56.50; H, 7.39; N, 6.31; S, 14.94.

The sulfonyl chloride was also converted to 2-propanesulfon-α-naphthylide (IVb), m.p. 133.8–134.8° from aqueous ethanol, lit.[26] m.p. 154°.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: S, 12.86. Found: S, 13.16.

Degradation of Disultone (II). A. With Sodium Borohydride–Water.—To a magnetically stirred solution of sodium borohydride (0.31 g., 0.0082 mole) in 25 ml. of water at room temperature was added solid disultone (1.00 g., 0.0041 mole) over a 10-min. period; copious gas evolution accompanied the addition of each portion. The two-phase mixture was stirred until the system was homogeneous (1.3 hr.). The solution was stirred an additional hour at 90°, and then concentrated to dryness with a rotary evaporator at reduced pressure and steam bath temperature.

The residual white solid (1.27 g.) was treated with phosphorus pentachloride (2.08 g., 0.010 mole) in the manner previously described to give 0.40 g. (35%) of 1-propene-1-sulfonyl chloride.

The crude sulfonyl chloride was refluxed with α-naphthylamine (0.81 g., 0.0057 mole) in 15 ml. of dry benzene to give 0.28 g. (14% over-all from II) of 1-propene-1-sulfon-α-naphthylide (Vb), m.p. 104.4–107.4° from aqueous ethanol.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66; S, 12.97. Found: C, 63.24; H, 5.50; N, 5.48; S, 13.17.

The bromine test for unsaturation was positive. The infrared spectrum contained absorption at 10.5 μ, not present in authentic IIIb.

B. With Sodium Borohydride–Deuterium Oxide.—In an analogous reaction, disultone (0.18 g., 0.0073 mole) was added to a stirred solution of sodium borohydride (0.056 g., 0.0015 mole) in 5 ml. of deuterium oxide (assay 99.7%; General Dynamics Corporation, Liquid Carbonic Division). Gas evolution was less vigorous, and homogeneity was not achieved until 3.5 hr. Work-up was by the previously described procedure.

The white residual solid was converted in the normal fashion to the sulfonyl chloride and then to 1-propene-1-sulfon-α-naphthylide (Vb), m.p. 104–106°, in 24% over-all yield from II. The bromine test for unsaturation was positive. The infrared spectrum, which contained no absorption characteristic of vinyl deuterium,[27] was identical with that for Vb prepared by method A.

C. With Hydrobromic Acid.—A mixture of disultone (0.69 g., 0.0028 mole), 47.5% hydrobromic acid (1.00 g., 0.0059 mole), and water (10 ml.) was stirred and heated at 95–100° until the system was homogeneous (4 hr.). The cooled reaction solution was titrated to a phenolphthalein endpoint with 1.000 *N* sodium hydroxide (11.0 ml., 0.0110 mole); the equivalents of base required for neutralization indicated the product was most likely 1-propene-1-sulfonic acid. The bromine test for unsaturation was positive.

D. With Sodium Methylmercaptide.—To a nitrogen-swept 5-ml. ampoule containing disultone (0.56 g., 0.0023 mole) was added a methanolic solution of sodium methylmercaptide prepared by the addition of sodium (0.10 g., 0.0043 mole) to 4 ml. of methanol containing methyl mercaptan (0.3 g., 0.006 mole). The sealed ampoule was heated at 95–105° for 25 hr. The reaction solution was concentrated to dryness at reduced pressure, and the white residual solid was dried in a vacuum desiccator over phosphorus pentoxide to give 0.65 g. (74%) of sodium 2-methylmercapto-1-propanesulfonate.

Desulfurization of the above compound was carried out by the procedure of Marvel and Weil.[10] To the solid (0.65 g., 0.0034 mole) were added Raney nickel[28] (approximate weight 6–8 g. in aqueous slurry, washed with absolute ethanol prior to use) and absolute ethanol (20 ml.). The reaction mixture was stirred and heated at reflux for 6.5 hr., filtered, and evaporated to dryness with a rotary evaporator at reduced pressure and steam bath temperature to give 0.43 g. (87%) of sodium 1-propanesulfonate.

The white crystalline solid (0.43 g., 0.0029 mole) was treated with phosphorus pentachloride (0.73 g., 0.0035 mole) in the normal manner. The crude sulfonyl chloride was converted to 0.21 g. (21% over-all from II) of 1-propanesulfon-*p*-toluidide (IIIa), m.p. 66.6–67.5° from aqueous ethanol, m.m.p. 67.4–68.4° with authentic IIIa. The infrared spectrum was identical with that for authentic IIIa.

Attempted Reductions of 1-Propenesulfonic Acid Derivatives. A. Sodium 1-Propene-1-sulfonate.—The diimide reduction procedure of van Tamelen was used.[7] The white residual solid (0.82 g., containing 0.59 g., 0.0041 mole of sodium 1-propene-1-sulfonate), obtained from the reaction of the disultone with aqueous sodium borohydride solution, was dissolved in 25 ml. of warm ethylene glycol. To the stirred solution at 80–90° was added solid *p*-toluenesulfonyl hydrazine (2.29 g., 0.0123 mole) over a 30-min. period; gas evolution accompanied the addition of each portion. The stirred reaction solution was heated at 85° for an

(19) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 245.

(20) W. W. Binkley and E. F. Degering, *J. Am. Chem. Soc.*, **60**, 2810 (1938).

(21) M. Pantlitschko and F. Salvenmoser, *Monatsh.*, **89**, 285 (1958).

(22) G. Geisler and P. Laue, *Chem. Ber.*, **95**, 867 (1962).

(23) N. N. Mel'nikov, E. M. Sokolova, and P. P. Trunov, *Zh. Obshch. Khim.*, **29**, 529 (1959).

(24) P. H. Latimer and R. W. Bost, *J. Org. Chem.*, **5**, 24 (1940).

(25) R. B. Shepherd, *ibid.*, **12**, 275 (1947).

(26) M. Duguet, *Bull. Acad. Roy. Belg.*, 87 (1906); *Chem. Zentr.*, 1529 (1906).

(27) M. F. Zinn, T. M. Harris, D. G. Hill, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 71 (1963).

(28) (a) Kindly supplied by Dr. R. E. Boucher, Anken Chemical & Film Corporation. (b) Contrary to most specifications for freshly prepared Raney nickel, this sample had been stored 9 months under tap water at pH 8.3.

additional 2.5 hr. The solvent was removed by distillation at reduced pressure. The residual solid was extracted exhaustively with ethyl ether, and the remaining white solid (0.49 g.) was dried in a vacuum desiccator. The solid was converted by the normal procedures to the N-*p*-tolylsulfonamide derivative, m.p. 53–55°. The infrared absorption and elemental analysis indicated that the compound was 1-propene-1-sulfon-*p*-toluidide (Va).

Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.18. Found: C, 57.13; H, 6.40; N, 6.67; S, 15.06.

B. 1-Propene-1-sulfon-*p*-toluidide (Va).—The diimide reduction of Va was unsuccessful. A solution of Va (0.22 g., 0.0010 mole) and *p*-toluenesulfonyl hydrazine (0.39 g., 0.0021 mole) in 13 ml. of freshly distilled diglyme was refluxed for 1.5 hr. The solvent was removed at reduced pressure, and the residual oil was chromatographed in chloroform on alumina. No material corresponding to IIIa was recovered.

C. 1-Propene-1-sulfon-α-naphthylide (Vb).—The catalytic hydrogenation of Vb was unsuccessful. A solution of Vb in absolute ethanol was shaken with Adams catalyst for 3.5 hr. in a Parr apparatus under 2.5 atm. of hydrogen. Starting material was recovered unchanged.

1-Propyl Methanesulfonate.—The product, b.p. 103° (12 mm.), lit.[29] b.p. 115° (21 mm.), was obtained in 60% yield by the method of Ross and Davis.[29]

Methyl 1-Propanesulfonate.—The product, obtained in 7% yield by the same procedure,[29] was distilled *in vacuo* twice, b.p. 93° (12 mm.), and chromatographed in chloroform on alumina.

Anal. Calcd. for $C_4H_{10}O_3S$: S, 23.20. Found: S, 23.30.

2-Propyl Methanesulfonate.—The product, b.p. 86–88° (12 mm.), $n^{25}D$ 1.4219, was prepared by the same procedure.[29]

N.m.r. Spectra.—Measurements were obtained with a Varian HR-60 instrument at 60 Mc. and 14,100 gauss. Tetramethylsilane was used as internal standard. Spin decoupling experiments were done by a modification of the method of Johnson.[30]

Acknowledgment.—The authors are indebted to Professor C. H. DePuy for assistance with the n.m.r. spectra. We thank Mr. N. E. Fersen, Williams College, for Russian translations.

(29) W. C. J. Ross and W. Davis, *J. Chem. Soc.*, 2420 (1957).

(30) L. F. Johnson, "Proton-proton Spin Decoupling Using the Varian V-3521 Integrator," Varian Associates, Palo Alto, Calif., 1962.

Skeletal Rearrangement Accompanying the Reaction of 2-Phenyl-1-propanol, 1-Phenyl-2-propanol, and 2-Phenyl-ethanol-1-C^{14} with Brominating and Chlorinating Reagents[1]

HERMAN PINES AND FREDERICK SCHAPPELL[2]

Ipatieff High Pressure and Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois

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Under conventional brominating procedures employing phosphorus tribromide or aqueous hydrobromic acid, 2-phenyl-1-propanol is shown to produce up to 85% 1-phenyl-2-bromopropane. Bromination of 1-phenyl-2-propanol yields only small amounts of isomeric bromides. The mechanism of the rearrangement is discussed. The reaction product of 2-phenylethanol-1-C^{14} with the brominating agents consisted of 2-phenyl-1-bromoethane-1-C^{14} containing 0.1 to 6.3% of the rearranged bromide, 2-phenyl-1-bromoethane-2-C^{14}. 2-Phenyl-1-propanol upon treatment with thionyl chloride and pyridine produced 9.3% of the rearranged product, 1-phenyl-2-chloropropane. The same alcohol on reaction with phosphorus trichloride formed the normal and rearranged products in a ratio of 1.3 to 1.

In conjunction with the study of some base-catalyzed reactions being carried out in this laboratory it became necessary to synthesize 2-phenyl-1-bromopropane. The usual procedure for converting alcohols to bromides consists of reacting the alcohol with phosphorus tribromide or with concentrated aqueous hydrobromic acid in the presence of sulfuric acid. When applied to secondary alcohols this reaction is accompanied by isomerization. It was found that either 2- or 3-pentanol gives a mixture of 2- and 3-bromopentanes.[3,4]

These procedures were considered to be safe for the synthesis of primary bromides although Whitmore and Rothrock[5] reported that neopentyl alcohol underwent extensive rearrangement to pentyl bromides when treated with hydrobromic acid.

In the present study we found that the primary alcohol, 2-phenyl-1-propanol, undergoes extensive rearrangement upon bromination with either phosphorus tribromide or 48% hydrobromic acid; however, the secondary alcohol, 1-phenyl-2-propanol, rearranges very little upon treatment with either reagent.

In order to determine the effect the methyl group in 2-phenyl-1-propanol may have upon the extent of skeletal isomerism, it was decided to study the reaction of 2-phenylethanol-1-C^{14} with phosphorus tribromide and hydrobromic acid.

Results

I. 2-Phenyl-1-propanol and 1-Phenyl-2-propanol with Phosphorus Tribromide and with Hydrobromic Acid. 1. Reactions with Phosphorus Tribromide.—The bromination of 2-phenyl-1-propanol by conventional procedures[6,7] yields, besides 2-phenyl-1-bromopropane, from 16 to 34% 1-phenyl-2-bromopropane (Table I). The other isomeric bromides, which would be expected to be formed had the rearrangement proceeded by carbonium ion mechanisms 1 and 2, were essentially absent (see p. 1504).

The tertiary bromide, 2-phenyl-2-bromopropane, which would be produced by mechanism 1, was found to be unstable in the presence of water or base, or on

(1) This research was supported in part by the National Science Foundation Grant NSF-G14503.

(2) Monsanto Chemical Co. Predoctoral Fellow, 1962–1963.

(3) H. Pines, A. Rudin, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **74**, 4063 (1952).

(4) J. Casor and J. J. Correia, *J. Org. Chem.*, **26**, 3645 (1961).

(5) F. C. Whitmore and H. S. Rothrock, *J. Am. Chem. Soc.*, **71**, 3431 (1932).

(6) C. R. Noller and R. Dinsmore, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 358.

(7) P. A. Levene, R. E. Marker, and A. Rothen, *J. Biol. Chem.*, **100**, 589 (1953).

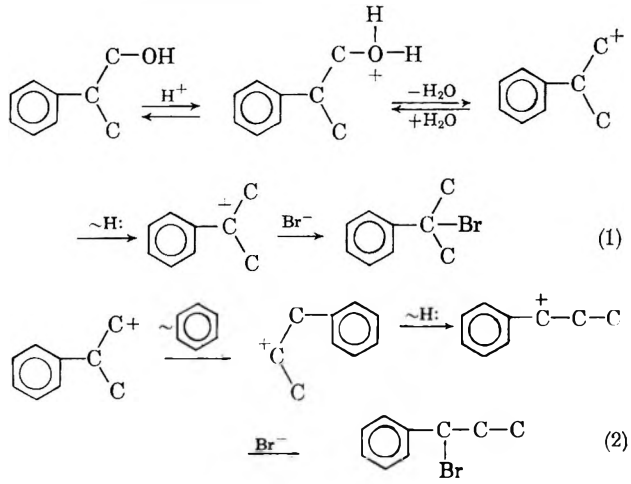
TABLE I

BROMINATION OF PHENYLPROPANOL

	Experiment[a]									
	1[c]	2	3a[d]	3b[e]	3c[f]	4	5[m]	6[n]	7	8
Alcohol used; kind[b]	2-Ph-1-P	2-Ph-1-P		2-Ph-1-P		1-Ph-2-P	2-Ph-1-P	2-Ph-1-P	2-Ph-1-P	1-Ph-2-P
Alcohol used; g. (mole)	10 (0.07)	8.3 (0.06)		10 (0.07)		20 (0.15)	9.5 (0.07)	9.5 (0.07)	9.5 (0.07)[o]	13.6 (0.1)
PBr_3 used; g. (mole)	15 (0.05)	5.8 (0.02)		7.3 (0.07)		14.6 (0.05)				
Aqueous HBr, 48%, g.							38	38	38	43
	Product Formed, Mole%[h]									
Ph—C—C—C	1.1[i]	(3.0)		0.8	2.7			2.0[j]	7.6[k] (1.5)	6.1[e] (2.8)
Ph—C(=C)—C		2.5					0.9			(1.3)
Ph—C(=C—Br)—C	64.7 (63.8)	79.3 (73.6)	84.4	71.4	70.2	(1.7)	13.6	16.2 (12.9)	17.7 (13.3)	3.0 (4.0)
Ph—C—CBr—C	34.2 (34.1)	19.8 (20.4)	15.6	27.8	27.3	100 (93.5)	85.5	81.8 (83.2)	74.7 (75.7)	90.2 (83.4)
Ph—CBr—C—C	(2.1)	(0.5)				(4.8)		(3.9)	(9.5)	(9.5)

[a] Unless indicated the procedures used are those described in the Experimental part. [b] 2-Ph-1-P corresponds to 2-phenyl-1-propanol; 1-Ph-2-P corresponds to 1-phenyl-2-propanol. [c] The reagents were mixed at 0° and the mixture was allowed to stand overnight and then heated to 100° and maintained at this temperature for 1 hr. This procedure was analogous to that of Levene, *et. al.*[7] [d] This sample was analyzed immediately after the PBr_3 addition was complete. The unchanged materials found were alcohol, 45.5%; phosphites, 29.5%. [e] The product was analyzed after the reaction mixture was allowed to stand for 20 hr. at room temperature. Unchanged material in the form of organophosphites composed 11.8% of the reaction product. [f] After distillation. [g] Sulfuric acid, 96%, was used in amounts equivalent to the moles of alcohol used. [h] The data given in the parentheses are based on n.m.r. analysis; those without parentheses were obtained from gas chromatography. [i] Composed of allylbenzene, 0.2%; *trans*-β-methylstyrene, 0.9%. [j] Composed of *cis*-β-methylstyrene, 1.4%; *trans*-β-methylstyrene, 0.6%. [k] Composed of *cis*-β-methylstyrene, 2.0%; *trans*-β-methylstyrene, 5.6%. [l] Composed of allylbenzene, 0.2%; *trans*-β-methylstyrene, 5.9%. [m] The bromide was washed with sulfuric acid during work-up. [n] When this reaction was carried out without sulfuric acid an 80% rearrangement was observed. The product distribution was 1-phenyl-2-bromopropane, 60%; allylbenzene, 1%; β-methylstyrene, 19%.

gas chromatographic analysis. Hence, its presence could be detected only as a stable decomposition product, namely as α-methylstyrene; this compound was generally absent from all reactions.



The isomeric bromide which could arise from mechanism 2 was found to occur to the extent of 2.1% at a maximum; its formation could also be ascribed, however, to a noncarbonium ion mechanism, as described below.

All the reactions with phosphorus tribromide gave high yields of brominated products. Using the usual brominating procedure and an internal standard, it was found by gas chromatography that 93% of the 2-phenyl-1-propanol reacted with an 83% conversion to the bromides, and only 6.1% of the starting alcohol could not be accounted for.

The effect of the ratio of phosphorus tribromide to 2-phenyl-1-propanol used was investigated. It was found that the ratio 2-phenyl-1-bromopropane to the rearranged bromide, 1-phenyl-2-bromopropane, decreases with the amount of phosphorus tribromide used (Table II). Upon standing, after the addition of a stoichiometric amount of phosphorus tribromide, this ratio decreases (Table I, expt. 3). However, neither of these effects can be explained on the basis of isomerization of the bromides since under identical brominating conditions preformed 2-phenyl-1-bromopropane did not rearrange.

TABLE II

RATIOS OF 2-PHENYL-1-BROMOPROPANE FORMED AS A FUNCTION OF PHOSPHORUS TRIBROMIDE TO 2-PHENYLPROPANOL USED

Theoretical amount of PBr_3 used[a]	1/3	2/3	1
2-Phenylpropanol reacted, mole %	17	53	93
Ratio of $\frac{\text{2-Phenyl-1-bromopropane}}{\text{1-Phenyl-2-bromopropane}}$ formed	8.1	4.3	3

[a] For experimental conditions see Experimental.

The bromination of 1-phenyl-2-propanol (expt. 4) went essentially to completion. The reaction product consisted mainly of 1-phenyl-2-bromopropane. In this reaction 4.8% of the bromides was composed of 1-phenyl-1-bromopropane, a product resulting probably from a carbonium ion mechanism, and only 1.7% of the skeletally rearranged 2-phenyl-1-bromopropane was produced.

2. Reactions with Hydrobromic Acid–Sulfuric Acid.—When 2-phenyl-1-propanol was refluxed with 48% hydrobromic acid and sulfuric acid, according to conventional procedures,[8a,b] a rearrangement to 1-phenyl-2-bromopropane was found to occur to the extent of about 76% and to 1-phenyl-1-bromopropane to the extent of 9.5% (expt. 7).

(8) (a) O. Kamm and C. S. Marvel, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 30; (b) B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

In order to ascertain whether the 1-phenyl-2-bromopropane was a primary reaction product or whether it arose from the isomerization of 2-phenyl-1-bromopropane, a series of experiments was carried out in which the reaction time was varied from 1 min. to 2 hr. It was found that 1-phenyl-2-bromopropane formed immediately in the reaction in large excess over the expected product. At 2-hr. reaction time, the reaction had gone 99% to completion, material balance had been maintained, and the ratio of the normal and rearranged products was essentially that found in the longer reactions (Fig. 1).

When preformed 2-phenyl-1-bromopropane was refluxed with a threefold excess of 48% hydrobromic acid, it was found that some loss of product occurred after 70-min. reaction time. However, at this point only 13.8% of the 2-phenyl-1-bromopropane had isomerized. This rate of isomerization is far too slow to account for the rapid buildup of 1-phenyl-2-bromopropane early in the reaction.

The absence of a carbonium ion character in the brominations employing 48% hydrobromic acid–sulfuric acid was strikingly illustrated by reaction of 1-phenyl-2-propanol (expt. 8, Table I). This alcohol reacted to form only 9.5% carbonium ion products in the form of 1-phenyl-1-bromopropane. The product of a phenyl migration, 2-phenyl-1-bromopropane, was found to the extent of 4.0%, while bromination went to completion.

Discussion

From the data presented in Table I it is obvious that the bromination of phenylpropanol, unlike that of 2- and 3-pentanol,[3] does not proceed *via* a classical carbonium ion mechanism. The bromination reaction of 2-phenyl-1-propanol resembles very much the solvolysis and rearrangement of 2-phenyl-1-propyl-*p*-benzenesulfonate described by Winstein and Schreiber,[9] and could probably be explained by an SN1 process, *via* a phenonium intermediate, or by a competition of SN1 and SN2 processes.

The observation that in the bromination reaction the ratio of 2-phenyl-1-bromopropane to the rearranged bromide isomer decreases as a function of phosphorus tribromide to 2-phenylpropanol used can be explained by a consideration of the reactive species present at various times in the reaction and/or the change in the dielectric constant of the medium. The effect of variation in medium upon the rate of participation was found to influence the rate of solvolytic reactions.[10]

The rearrangement occurring during the bromination of 2-phenyl-1-propanol with hydrobromic acid sulfuric acid can also be explained by the mechanism described above. The bromides once formed undergo little rearrangement; this is indicated by Fig. 1.

The very small participation of the classical carbonium ion mechanism in the bromination of phenylpropanols was not predictable in view of the early work on the bromination of 2- and 3-pentanols by means of either phosphorus tribromide or hydrobromic acid.[3,4,11] In each case a mixture of 2- and 3-bromopentane was obtained. On the other hand the bromination of 2-butanol formed the unrearranged *sec*-butyl bromide, as determined by the use of carbon-14.[12,13] These incongruous results were rationalized by a steric argument, bromination of *sec*-butyl alcohol being less sterically hindered to the transition state of an SN2 reaction.[4] However, neopentyl alcohol was converted to neopentyl bromide in the presence of an excess of quinoline.[14] When a base was not present extensive rearrangement was found to occur. Similarly, the bromination of neopentyl alcohol with hydrobromic acid leads to isomeric pentyl bromides.[5]

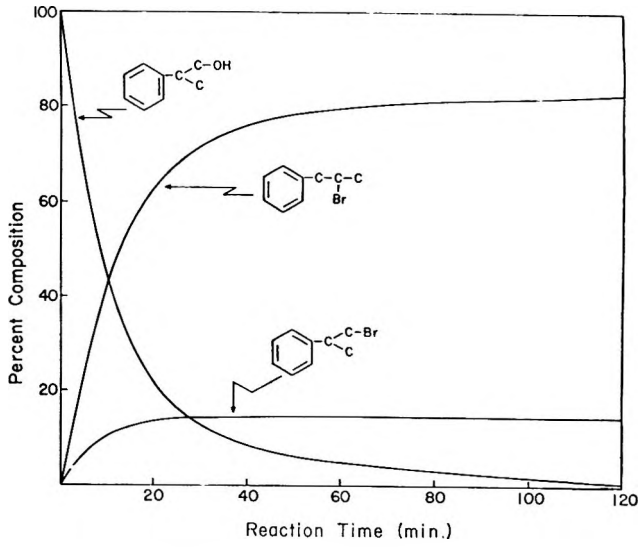


Fig. 1.—Composition of product from 2-phenyl-1-propanol with hydrobromic acid–sulfuric acid at 123°.

II. 2-Phenylethanol-1-C^{14}.—The reactions of the title compound with hydrobromic acid, hydrobromic acid sulfuric acid, and with phosphorus tribromide were made under experimental conditions described above. In each case over 95% of the alcohol was converted to 2-phenyl-1-bromoethane; the only impurity detected was styrene, which ranged from 0.2 to 1.1%. The isomeric bromide 1-phenyl-1-bromoethane was not detected among the products of the reaction.

The reaction product consisted of 2-phenyl-1-bromoethane-1-C^{14} containing smaller amounts of the rearranged product 2-phenyl-1-bromoethane-2-C^{14}. The extent of isomerization (Table III) was determined by oxidizing the phenylethyl bromide to benzoic acid by means of alkaline potassium permanganate solution. The activity of the benzoic acid, as compared with the parent bromide, gave the measure of the degree of rearrangement. Before counting, the bromide was purified from small amounts of the unreacted phenylethanol by passing it over a column of alumina powder: the alcohol was retained by the alumina.

A comparison of the present results with those obtained from the reaction of 2-phenyl-1-propanol (Table III) demonstrates the effect of the methyl group upon the extent of isomerization. These observations are in agreement with the relative stabilities

(9) S. Winstein and K. C. Schreiber, *J. Am. Chem. Soc.*, **74**, 217 (1952).
(10) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).
(11) J. Cason and R. H. Mills, *J. Am. Chem. Soc.*, **73**, 1351 (1951).
(12) A. T. Shulgin, *ibid.*, **77**, 2338 (1955).
(13) P. S. Skell, R. G. Allen, and G. L. Helmkamp, *ibid.*, **82**, 410 (1960).
(14) L. H. Sommer, H. D. Blankman, and P. C. Miller, *ibid.*, **76**, 803 (1954).

TABLE III

THE REARRANGEMENT OF 2-PHENYLETHANOL-1-C^{14} UPON REACTION WITH BROMINATING REAGENTS[a]

	Reagent		
	48% HBr	48% HBr-H_2SO_4	PBr_3
Activity[b] of 2-phenylethyl bromide $\times 10^{-3}$ μc./mmole	2107	2146	2000
Activity of benzoic acid, $\times 10^{-5}$ μc./mmole	102	136	2.8
Per cent rearrangement	4.7	6.3	0.14
Per cent rearrangement of 2-phenyl-1-propanol to 1-phenyl-2-bromopropane	60	76	20

[a] The activity of the 2-phenylethanol-1-C^{14} used as a starting material for all experiments was 2129 $\times 10^{-3}$ μc./mmole. [b] All activities are corrected for a background radiation of 1.11 $\times 10^{-15}$ amp.

of the nonsymmetrical phenonium ions mentioned previously and by other investigators.[15]

The phenyl migration accompanying the reaction of 2-phenylethanol-1-C^{14} was in accord with the observations made by Lee and Spinks,[16] who observed 5.3–7.0% isomerization on treatment of the cited alcohol with hydrobromic acid, and about 50% with thionyl chloride.

As was already discussed above, a symmetrical phenonium ion cannot explain the results of the reaction; however, a competition between an Sn2 process and a symmetrical phenonium ion could explain the results of the bromination of phenylethanol. Similarly, Roberts and Regan[15] were able to explain the deamination of 2-phenylethyl-1-C^{14} amine in terms of a mechanism in which the symmetrical phenonium ion was a transition state rather than an intermediate.

However, the small amount of hydride migration products found in this work, in the reactions of phenylpropanols described above, and in the work of Roberts and Regan[15] is somewhat puzzling if one assumes an ionization step prior to the formation of the phenonium ion. Hence, it seems that either the unsymmetrical phenonium ion forms directly without any hydride migration or perhaps a concerted mechanism is involved in the competition with the Sn2 process.

It was reported that the reaction of 2-phenylethanol-1-C^{14} [16] and 2-*p*-anisylethanol-1-C^{14} [17] with thionyl chloride is accompanied by 46–50% of skeletal isomerization involving phenyl migration. When the reaction was carried out in the presence of pyridine as a solvent less than 0.5% rearrangement occurred.

III. 2-Phenyl-1-propanol with Thionyl Chloride.—As would be expected in the light of the existing data, 2-phenyl-1-propanol, upon treatment with thionyl heloride and pyridine according to the procedure of Whitmore and Karnatz,[18] produced 9.3% of the rearranged product 1-phenyl-2-chloropropane (Table IV). This experiment confirms the observation that a methyl group attached to the β carbon atom in phenylethanol exerts an effect upon phenyl migration.

It is interesting to note that phosphorus trichloride treatment of 2-phenyl-1-propanol produced a reaction

(15) J. D. Roberts and C. M. Regan, *J. Am. Chem Soc.*, **75**, 2069 (1953).
(16) C. C. Lee and J. W. T. Spinks, *Can. J. Chem.*, **32**, 1005 (1954).
(17) C. C. Lee, D. Newman, and D. P. Thornhill, *ibid.*, **41**, 620 (1963).
(18) F. C. Whitmore and F. A. Karnatz, *J. Am. Chem. Soc.*, **60**, 2536 (1938).

TABLE IV

COMPOSITION OF PRODUCTS FROM THE REACTIONS OF 2-PHENYL-1-PROPANOL WITH THIONYL CHLORIDE AND PHOSPHORUS TRICHLORIDE

	Reagent		
Products	$SOCl_2$-pyridine	$SOCl_2$-$CHCl_3$	PCl_3
2-Phenyl-1-chloropropane	90.7	5.3	33.7
1-Phenyl-2-chloropropane	9.3	32.6	26.6
Olefins		10.1	12.7
2-Phenyl-1-propanol		32.2	27.0
High boiling compounds		19.8	

mixture containing a normal to rearranged chloride ratio of 1.27. The reaction of this alcohol with thionyl chloride in chloroform solution in the absence of pyridine showed a normal to rearranged chloride ratio of only 0.163 (Table IV).

Analytical Procedure. A.—Gas chromatography was carried out on an F and M Model 300 gas chromatograph (F and M Scientific Corporation, Avondale, Pennsylvania). When the analyses were performed using the standard siliceous solid supports, the bromides underwent extensive dehydrobromination to form aryl olefins. In order to minimize this reaction pretreated Tide (commercial detergent) was used as a solid support.[19]

The experimental conditions of analysis and relative retention times are given in Table V.

TABLE V

RELATIVE RETENTION TIMES OF PHENYLBROMOPROPANES[a]

Compound	Relative retention times
n-Hexylbenzene	1.00
1-Phenyl-1-bromopropane	2.59
1-Phenyl-2-bromopropane	2.60
2-Phenyl-1-bromopropane	3.06
3-Phenyl-1-bromopropane	4.18
2-Phenyl-2-bromopropane	decomposes

[a] Column, 6 mm. × 4 m. filled with 10% Carbowax 20M on 40–60-mesh pretreated Tide; temp. 100°; carrier gas, helium with a flow rate of 156 ml./min.

B. Nuclear Magnetic Resonance.—This technique allowed the quantitative determination of 1-phenyl-1-bromopropane in the presence of 1-phenyl-2-bromopropane since these isomers were inseparable by gas chromatography. It also served as a check on the amount of decomposition which took place upon gas chromatographic analysis. Quantitative measurements were accomplished by cutting and weighing of the peaks.

τ-Values[20] of the phenylbromopropanes and of methylstyrenes are listed in Table VI.

C. Infrared Analysis.—Since uncomplicated analytical bands did not occur for the bromides involved in this research, infrared analysis served only to determine the presence of olefins or unchanged alcohols and phosphite esters in the reaction mixture.

D. Radioactivity Assay.—Both the phenylethyl bromide and the benzoic acid resulting from the alkaline potassium permanganate oxidation of this compound were converted to gaseous carbon dioxide by

(19) A. W. Decora and G. U. Denneen, U. S. Department of Interior, Bureau of Mines, Report of Investigations 5768.
(20) G. V. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

TABLE VI

N.M.R. ANALYSIS. τ-VALUES OF PURE BROMIDES AND OLEFINS

Compound	Peak assignment	τ-value
2-Phenyl-1-bromopropane	$-CH_3$	8.61[a]
1-Phenyl-2-bromopropane	$-CH_3$	8.38[a]
	—CHBr—	5.85[a]
1-Phenyl-1-bromopropane	$-CH_3$	8.87[b]
		9.02[c]
	—CHBr—	4.77[c]
3-Phenyl-1-bromopropane	$-CH_2Br$	6.68[c]
α-Methylstyrene	$-CH_3$	7.92
β-Methylstyrene	$-CH_3$	8.22[d]

[a] Calculated from the midpoint of the adsorbance. [b] Calculated from the lowest peak of the absorbance. [c] Calculated from the central peak of the absorbance. [d] Calculated from the upper peak of the absorbance.

wet combustion according to the procedure of Van Slyke.[21,22]

The apparatus and techniques employed for measuring the radioactivity of carbon dioxide have been described previously.[23]

Experimental

1. Preparation of Alcohols. A.—2-Phenyl-1-propanol was prepared by hydrogenation of hydrotropaldehyde with an equal volume of ethanol as solvent with 10% by weight copper chromite as catalyst. The reaction was carried out in a 1350-ml. rocking autoclave at 170° and an initial hydrogen pressure of 100 atm. The alcohol distilled at 92–93° (4 mm.), $n^{25}D$ 1.5245.

B.—1-Phenyl-2-propanol was obtained by hydrogenation of phenylacetone at 118° according to the procedure described above; b.p. 82° (9 mm.), $n^{25}D$ 1.5194.

C.—1-Phenyl-1-propanol was prepared from propiophenone by hydrogenation, according to the above described procedure. The alcohol distilled at 90–91° (6 mm.), $n^{25}D$ 1.5212.

D.—2-Phenyl-2-propanol was synthesized by a Grignard reaction from 47.4 g. (0.3 mole) of bromobenzene, 6.9 g. (0.3 g.-atom) of magnesium, and 16.5 g. (0.28 mole) of acetone; the complex was decomposed with an ammonium chloride solution. The alcohol, 52% yield, distilled at 71° (7 mm.), $n^{25}D$ 1.5206.

E.—2-Phenylethanol-1-C^{14} [24].—**Phenylacetic acid-1-C^{14}** was prepared by the reaction of benzylmagnesium chloride and carbon dioxide C^{14} obtained from barium carbonate C^{14}. **2-Phenylethanol-1-C^{14}** was prepared from the phenylacetic acid obtained above by reduction with lithium aluminum hydride. A 60% yield of this alcohol was received based on the amount of barium carbonate used.

2. Preparation of Bromides. A.—2-Phenyl-1-bromopropane was prepared by treating 184 g. (2.4 moles) of benzene with 88 g. (1.36 moles) of allyl bromide in the presence of 41 ml. of 96% sulfuric acid, according to the procedure of Adams and Garber.[25] The bromide was over 95% pure according to gas chromatography; b.p. 99.5° (11 mm.), $n^{25}D$ 1.5470.

B.—1-Phenyl-2-bromopropane was synthesized by treating the tosyl ester of 1-phenyl-2-propanol with calcium bromide. The tosylate was prepared from 7.3 g. of the alcohol with 22.8 g. of *p*-toluenesulfonyl chloride in pyridine solvent, according to the procedure of Streitwieser, *et al.*[26] The crude ester, 88% yield, was then treated with calcium bromide using dimethylformamide as a solvent.[27] A 33% yield of pure 1-phenyl-2-bromopropane was obtained, $n^{25}D$ 1.5418.

C.—1-Phenyl-1-bromopropane was prepared from 8.3 g. (0.06 mole) of 1-phenyl-1-propanol with 5.8 g. (0.02 mole) of phosphorus tribromide, according to Noller and Dinsmore.[6] The bromide, 85% yield, distilled at 89.5° (6 mm.), $n^{25}D$ 1.5494.

D. 2-Phenyl-2-bromopropane.—Several attempts were made to prepare the bromide from 2-phenyl-2-propanol with either phosphorus tribromide, 48% hydrobromic acid, or hydrogen bromide. In the latter case the water liberated from the reaction was already sufficient to cause the decomposition of the bromide to α-methylstyrene and to the starting alcohol.

Similarly, the reaction of hydrogen bromide with α-methylstyrene in the presence and absence of acetic acid failed to form pure 2-phenyl-2-bromopropane.

Bromination Procedure. A. Phosphorus Tribromide.—The bromination reactions, unless otherwise indicated in Table I, were carried out in a 100-ml., three-necked, round-bottom flask following the procedure of Noller and Dinsmore.[6] The phosphorus tribromide was added dropwise to the alcohol which was cooled to −5°. The rate of addition was controlled for the temperature of the reaction not to exceed 0°. Stirring was maintained throughout the reaction and for 30 min. after the addition of the phosphorus tribromide was completed.

The reaction mixture, which was allowed to warm to room temperature and to stand overnight, was decomposed by pouring it over ice. The organic phase was diluted with benzene, separated, neutralized with 10% aqueous sodium bicarbonate, and dried over potassium carbonate; the benzene was stripped under reduced pressure in the presence of anhydrous potassium carbonate.

B. Hydrobromic Acid (48%)-Sulfuric Acid (96%).—Brominations with the title reagent were carried out according to the procedure of Kamm and Marvel.[8]

The alcohol to be brominated was refluxed with a solution containing a threefold excess of hydrobromic acid and an amount of sulfuric acid equivalent to the moles of alcohol used. After 4-hr. refluxing at 123° the aqueous phase was diluted with water and the organic phase was diluted with benzene, separated, washed with a 10% aqueous sodium bicarbonate until neutral, and dried over potassium carbonate. The benzene was then removed under reduced pressure in the presence of anhydrous potassium carbonate.

C. Miscellaneous Reactions. 3-Phenyl-1-propanol, 2-Phenyl-1-bromopropane, and Phosphorus Tribromide.—Following the general procedure, 8.3 g. (0.06 mole) of the alcohol and 5.8 g. (0.02 mole) of phosphorus tribromide were treated in the presence of 3.8 g. of preformed 2-phenyl-1-bromopropane. The final reaction product showed a 90% yield of 3-phenyl-1-bromopropane and none of the 2-phenyl-1-bromopropane initially present in the reaction had isomerized.

Use of Variable Amounts of PBr_3 on Bromination of 2-Phenyl-1-propanol.—Following the general procedure, 20 g. (0.15 mole) of 2-phenyl-1-propanol was treated with 14.6 g. (0.054 mole) of phosphorus tribromide in the presence of an internal standard (1,2,3,4-tetrahydronaphthalene, 6.7 g.). Samples were taken from the reaction mixture for analysis when the addition of PBr_3 was one-third complete, two-thirds complete, and complete. These samples were allowed to stand at room temperature for 20 hr. After this time, all the samples were decomposed and analyzed. Analysis of the third sample showed the yield of bromides to be 83.1%. Only 6.1% of the material could not be accounted for. Analytical results are summarized in Table II.

2-Phenyl-1-bromopropane and HBr–H_2SO_4.—A solution of preformed 2-phenyl-1-bromopropane containing 8% 1-phenyl-2-bromopropane was refluxed with a threefold excess of 48% hydrobromic acid and sulfuric acid for periods of time ranging from 30 min. to 5 hr. After 70 min., substantial material was lost through charring. However, in this period of time only 13.8% of the preformed 2-phenyl-1-bromopropane had undergone isomerization.

(21) D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940).

(22) D. D. Van Slyke, J. Plazin, and T. R. Weisiger, *ibid.*, **191**, 299 (1951).

(23) H. Pines and G. Benoy, *J. Am. Chem. Soc.*, **82**, 2483 (1960).

(24) Prepared by J. Herling of this laboratory.

(25) R. Adams and J. J. Garber, *J. Am. Chem. Soc.*, **71**, 525 (1949).

(26) A. Streitwieser, R. H. Jagow, R. C. Bahey, and S. Suzurti, *ibid.*, **80**, 2326 (1958).

(27) G. L. Jennkins and J. C. Kellett, Jr., *J. Org. Chem.*, **27**, 624 (1962).

The Synthesis and Hydrolysis of 2′,3′-Dideoxyuridine

K. E. PFITZNER AND J. G. MOFFATT

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Treatment of 2′-deoxy-3′-O-methanesulfonyl-5′-O-trityluridine with sodium iodide in 1,2-dimethoxyethane gave 2′,3′-dideoxy-3′-iodo-5′-O-trityluridine. After acid detritylation, the resulting 2′,3′-dideoxy-3′-iodouridine was hydrogenated in the presence of a palladium catalyst and triethylamine to give crystalline 2′,3′-dideoxyuridine in good yield. The relative rates of acidic hydrolysis of uridine, 2′-deoxyuridine, 2′,3′-dideoxyuridine, and of the corresponding thymidine derivatives have been determined and related to current views on the mechanism of hydrolysis of nucleosides.

In recent years a number of analogs of deoxynucleosides have been prepared in which the normal 2-deoxyribofuranosyl moiety is replaced by other deoxy and polydeoxypentoses. These compounds, which have been prepared both as exercises in organic synthesis and in order to provide possible antimetabolites for biological screening, have been obtained by several routes. In one approach, a deoxy sugar is condensed, by conventional routes, with a heterocyclic base as in the synthesis of 5′-deoxyadenosine.[1] More frequently, a sugar hydroxyl group in a pre-existing ribo- or deoxyribonucleoside is converted into a halogen- or sulfur-containing derivative and subsequently removed by metal-catalyzed hydrogenolysis. Thus, 3′-deoxyadenosine,[2] 3′-deoxyuridine,[3] 5′-deoxyuridine,[4] 3′-deoxythymidine,[5] 5′-deoxythymidine,[5] and 3′,5′-dideoxythymidine[5] have been prepared with varying success.

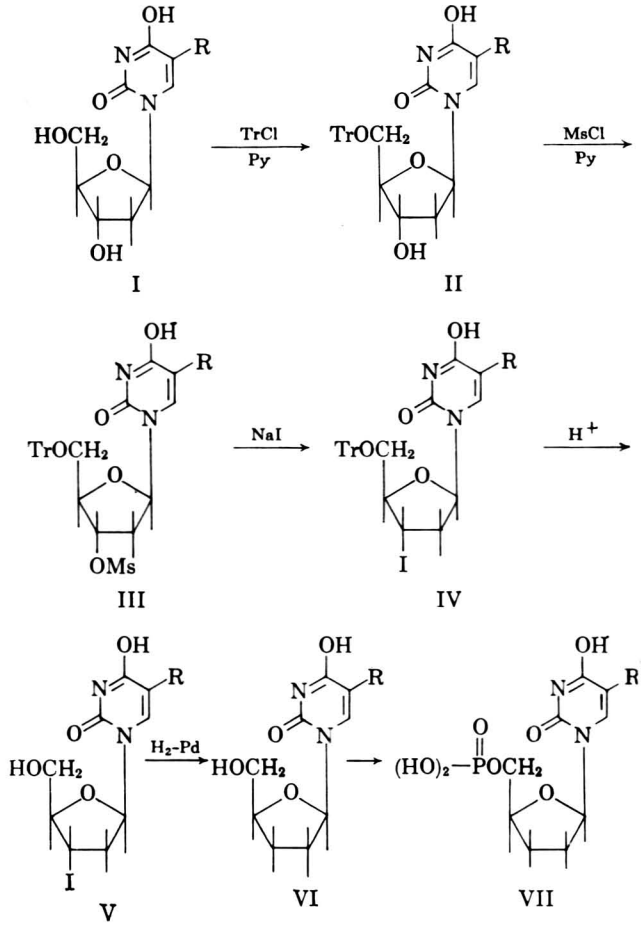
As part of another project in this laboratory,[6] we have recently had need to obtain samples of 3′-deoxythymidine 5′-phosphate (VII, R = CH_3) and 2′,3′-dideoxyuridine 5′-phosphate (VII, R = H). A synthesis of VII (R = CH_3) has recently been briefly mentioned by Ikehara and Ohtsuka[7] through phosphorylation of 3′-deoxythymidine[5] (VI, R = CH_3) with P¹-diphenyl P²-morpholinophosphorochloridate. Neither 2′,3′-dideoxyuridine (VI, R = H) nor its 5′-phosphate has, however, been previously described and in this paper we provide details of their synthesis. A study of the relative rates of acidic hydrolysis of the ribo-, 2′-deoxy-, and 2′,3′-dideoxynucleosides derived from uracil and thymine is also included.

The route to 3′-deoxythymidine (VI, R = CH_3) previously described by Michelson and Todd[5] and outlined in Chart I has been repeated with minor variations and the over-all results are quite comparable. The yields obtained in the various steps are summarized in the Experimental section and the changes made have been incorporated into the presently described synthesis of 2′,3′-dideoxyuridine (VI, R = H).

Throughout these and other reactions dealing with substituted nucleosides, the utility of thin layer chromatography on Silica G or Alumina G as a qualitative or quantitative diagnostic tool cannot be over emphasized. This is particularly so when a phosphor (see Experimental section for details) is added to the adsorbant before application to the glass plates. The addition of a phosphor such as Radelin GS-115 (Type P-1) permits the detection of extremely small quantities of nucleosides by ultraviolet examination. Since in the 200–400-mμ region the pre-extracted phosphor itself has only a very weak end adsorption at 200 mμ, it is possible to obtain quantitative and undistorted ultraviolet spectra from single spots on the plate by scraping off the silica layer and extracting the product with methanol. This technique has found wide applicability in this laboratory and it has been possible to demonstrate excellent accuracy and reproducibility.

The reaction of 2′-deoxyuridine (I, R = H) with a slight excess of trityl chloride (TrCl) in pyridine (py)

CHART I



(1) H. M. K. Kissman and B. R. Baker, *J. Am. Chem. Soc.*, **79**, 5534 (1957).

(2) (a) A. Todd and T. L. V. Ulbricht, *J. Chem. Soc.*, 3275 (1960); (b) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 1906 (1961).

(3) D. M. Brown, D. B. Parihar, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).

(4) (a) I. Wempen, I. L. Doerr, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 1624 (1960); (b) J. Smrt, *Collection Czech. Chem. Commun.*, **27**, 1056 (1962).

(5) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(6) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963), and unpublished results.

(7) M. Ikehara and E. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **10**, 997 (1962).

at 100° for 45 min.[8] gave crystalline 2′-deoxy-5′-O-trityluridine (II, R = H) in 75% yield.

Mesylation of II (R = H) with an excess of methanesulfonyl chloride in pyridine resulted in the quantitative formation of 2′-deoxy-3′-O-methanesulfonyl-5′-O-trityluridine as judged by thin layer chromatography. In spite of repeated attempts, however, it was not possible to obtain this product in crystalline form even after chromatography on a column of silicic acid. A similar lack of crystallinity has been observed previously by others (and in this laboratory) for the thymidine analog of this compound (III, R = CH_3). A totally acceptable analysis was not obtained: but, in view of the thin layer chromatographic homogeneity of this compound, it was used directly in the next step. Thus III (R = H) was treated with an excess of sodium iodide in refluxing 1,2-dimethoxyethane for several hours giving 2′,3′-dideoxy-3′-iodo-5′-O-trityluridine (IV, R = H) in 64% yield (including retreatment of some unchanged starting material). The use of dimethoxyethane as the solvent for this reaction proved to be convenient rather than using acetone in a sealed tube at 100° as described by Michelson and Todd.[5] It was, however, necessary first to reflux the dimethoxyethane over lithium aluminum hydride to avoid serious coloration of the reaction, presumably due to the liberation of iodine in the presence of peroxides. By analogy with the established over-all retention of configuration during conversion of 5′-O-acetyl-2′-O-tosyluridine to 5′-O-acetyl-2′-deoxy-2′-iodouridine,[9] it is likely that IV (R = H) also has the structure indicated with the iodine atom in the *ribo* configuration.

Removal of the trityl group from IV (R = H) was readily accomplished by treatment with 80% acetic acid at 100° for 45 min. This is a somewhat longer time than is usually necessary for the removal of 5′-trityl groups under these conditions, but examination of the mixture by thin layer chromatography indicated that a little starting material was still present after 30 min. The resulting crystalline 2′,3′-dideoxy-3′-iodouridine (V, R = H) was hydrogenated at room temperature in the presence of a commercial 10% palladium-on-carbon catalyst[10] and 2 equiv. of triethylamine. Hydrogen uptake was very rapid and, after removal of the catalyst, the free iodide ion was removed by passing the reaction mixture through a small column of Dowex 2 (HCO_3^-) resin and evaporation of the resulting triethylammonium bicarbonate. This procedure was found to be very much more convenient and efficient than hydrogenation in the presence of ammonium hydroxide,[5] in which case complete removal of ammonium iodide was difficult. It is also worth noting that, in the absence of a base, almost complete reduction of the 5,6-double bond in the uracil ring occurred with the catalyst used. The resulting 2′,3′-dideoxyuridine was obtained in crystalline form in 83% yield but even under these mild conditions was contaminated by 4% uracil which was not readily removed by recrystallization. A completely pure sample was obtained by preparative paper chromatography followed by crystallization.

(8) Essentially the method used by J. P. Horwitz, J. A. Urbanski, and J. Chua [*J. Org. Chem.*, **27**, 3300 (1962)] for the tritylation of thymidine.

(9) D. M. Brown, D. B. Parihas, and A. R. Todd, *J. Chem. Soc.*, 4242 (1958).

(10) Obtained from Matheson Coleman and Bell.

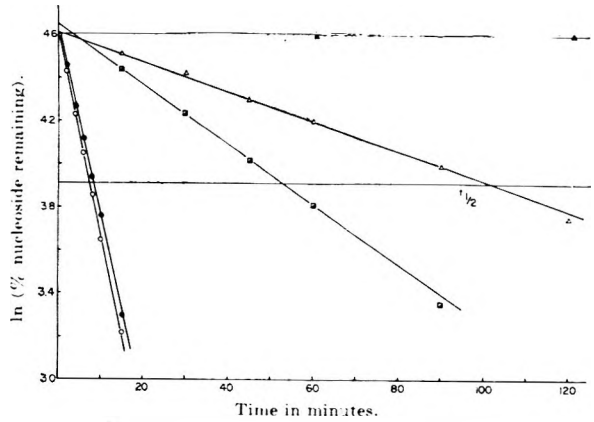


Fig. 1.—Kinetics of the hydrolysis of ribo-, 2-deoxyribo-, and 2′,3′-dideoxyribonucleosides in 1 *N* HCl at 100°: ▲, uridine; △, 2-deoxyuridine; ◪, thymidine; ●, 2′,3′-dideoxyuridine; ○, 3′-deoxythymidine.

Phosphorylation of 2′,3′-dideoxyuridine and of 3′-deoxythymidine by the method of Tener[11] resulted in the ready isolation of the respective 5′-phosphates (VII) in good yield. Some further reactions of these compounds will be described in a future paper.

While it is well recognized that the N-glycosidic bond in a 2′-deoxynucleoside is very much more susceptible to acid hydrolysis than is that in the corresponding ribonucleoside, few quantititave comparative studies have been described.[12] With the availability of 2′,3′-dideoxyuridine and 3′-deoxythymidine, it was of interest to determine whether the removal of yet another hydroxyl group from the 3′-carbon would lead to a further labilization. Accordingly, samples of uridine, 2′-deoxyuridine, 2′,3′-dideoxyuridine, thymidine, and 3′-deoxythymidine were treated under identical conditions with 1 *N* hydrochloric acid in sealed capillaries at 100°. The rates of hydrolysis were determined by spectral examination of the individual aliquots in 1 *N* alkali. The ratio of the optical densities at the absorption maxima of the pyrimidine base and of the nucleoside (276 mμ 263 mμ for the uracil nucleosides and 281 mμ/267 mμ for the thymine nucleosides) was found to provide a sensitive measure of the degree of hydrolysis, and good first-order kinetics were obtained for all the deoxynucleosides up to 65–75% hydrolysis. Under these conditions, uridine was virtually unaffected, only 2% hydrolysis being detected in 5 hr. The kinetic results are shown in Fig. 1 from which it can be seen that thymidine is hydrolyzed roughly twice as fast ($k_1 = 2.33 \times 10^{-4}$ sec.$^{-1}$; $t_{1/2}$ = 56 min.) as 2′-deoxyuridine ($k_1 = 1.14 \times 10^{-4}$ sec.$^{-1}$; $t_{1/2}$ = 104 min.). 3′-Deoxythymidine and 2′,3′-dideoxyuridine were, however, much more labile, the rates being 1.55×10^{-3} sec.$^{-1}$ ($t_{1/2}$ = 7.5 min.) and 1.45×10^{-3} sec.$^{-1}$ ($t_{1/2}$ = 8.2 min.), respectively. Thus the removal of the hydroxyl group from C-3′ does indeed result in a considerably increased rate of hydrolysis. This observation is quite consistant with those made earlier on the relative rates of hydrolysis of ethyl glucopyranoside, ethyl 2-deoxyglucopyranoside, and ethyl 2,3-dideoxyglucopyranoside by Butler,

(11) G. M. Tener, *J. Am. Chem. Soc.*, **83**, 159 (1961).

(12) See *e.g.* (a) A. Wacker and L. Trager, *Z. Naturforsch.*, **18b**, 13 (1963); (b) W. Pollman and G. Schramm, *ibid.*, **16b**, 673 (1961); (c) F. Micheel and A. Heesing, *Chem. Ber.*, **94**, 1814 (1961).

et al.,[13] and of the anilides of glucose and 2-deoxyglucose by Richards.[14]

The mechanism of hydrolysis of nucleosides is not altogether clear, but the suggestion has been made by Kenner [15] and amplified by Dekker[16] that the site of effective protonation is the ring oxygen of the sugar rather than the glycosidically bound nitrogen. Further, it has been suggested by Richards[14] that the relative stability of normal glycosides as compared with the 2-deoxyglycosides is due to the competitive protonation of the relatively acidic hydroxyl group at C-2 which then electrostatically opposes further protonation at either of the acetal oxygens.[17] The pronounced increase in lability on further removal of the hydroxyl groups at C-3′ of 2-deoxyuridine and thymidine lends some support to Kenner's suggestion[15] of protonation on oxygen rather than nitrogen. Thus, it is somewhat difficult to explain the increased lability by a decrease in electrostatic shielding of the rather remote N-1 of the uracil ring, but it is quite compatible with decreased shielding of the sugar ring oxygen which is roughly equidistant from the hydroxyl groups on both C-2′ and C-3′.

It is intended to make a more comprehensive study of the rates of hydrolysis of other deoxy- and polydeoxynucleosides now being prepared in this laboratory in order to gain clear knowledge of the mechanism of these reactions.

Experimental[18]

General Techniques.—Thin layer chromatography was performed on 0.25-mm. layers of Merck Silica G evenly spread on glass plates with a Desaga applicator. In order to detect ultraviolet absorbing products with a high degree of sensitivity, Radelin GS-115 (Type P-1) phosphor[19] (25 mg.) was mixed for 30–45 sec. with the Silica G (50 g.) and water (100 ml.) in a Waring Blendor prior to application to the glass plates.[20] The phosphor was first continually extracted for 12 hr. with boiling methanol in a Soxhlet extractor in order to remove a small amount of ultraviolet absorbing impurity. Compounds detected on such plates under an ultraviolet lamp may be quantitatively eluted with methanol and spectrally examined. Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer, and infrared spectra were obtained from potassium bromide pellets on a Perkin-Elmer Model 237 spectrophotometer. Paper chromatography was performed by the descending technique on Schleicher and Schuell No. 589 orange ribbon paper using solvent I, 2-propanol–concentrated ammonium hydroxide–water (7:1:2).

2′-Deoxy-5′-O-trityluridine (II, R = H).—2′-Deoxyuridine (4.56 g., 20 mmoles) was dissolved in anhydrous pyridine (50 ml.) containing triphenylchloromethane (6.67 g., 24 mmoles) and heated at 100° for 45 min. with exclusion of moisture. After cooling, the solution was poured slowly into 1 l. of vigorously stirred ice–water, and after 30 min. the precipitated solid was removed and washed with water. The crude product was dried *in vacuo* and crystallized from acetone–benzene giving a product of m.p. 192–196° which still contained a little triphenylcarbinol. One further crystallization from acetone–benzene gave 5.40 g. of pure 2′-deoxy-5′-O-trityluridine of m.p. 204–205°. A further 1.64 g. of pure product (total yield 75%) was recovered from the mother liquors by chromatography on a column of silicic acid.[21] The trityl ether was eluted with chloroform–acetone (19:1).

Anal. Calcd. for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.95. Found: C, 71.60; H, 5.61; N, 5.98.

2′-Deoxy-3′-O-methanesulfonyl-5′-O-trityluridine (III, R = H).—Methanesulfonyl chloride (5 ml.) was added slowly to an ice-cooled solution of 2′-deoxy-5′-O-trityluridine (5.47 g., 11.6 mmoles) in anhydrous pyridine (25 ml.). After storage overnight at 0°, water (2 ml.) was added and the solution was slowly poured into 2 l. of well-stirred ice–water. The precipitate was filtered, washed well with water, and dried *in vacuo*. It was then dissolved in hot ethanol (100 ml.), treated with carbon (1 g. of Darco G-60), and poured into a large excess of ice water. The amorphous precipitate was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide giving a quantitative yield of 2′-deoxy-3′-O-methanesulfonyl-5′-O-trityluridine which was homogeneous by thin layer chromatography (chloroform–ethyl acetate, 1:1) but could not be obtained in crystalline form and did not give acceptable analyses.

2′,3′-Dideoxy-3′-iodo-5′-O-trityluridine (IV, R = H).—2′-Deoxy-3′-O-methanesulfonyl-5′-O-trityluridine (5.48 g., 10 mmoles) and sodium iodide (15 g., 0.1 mole) were dissolved in 1,2-dimethoxyethane[22] (100 ml.) and refluxed for 5 hr. The solvent then was evaporated, and the residue was partitioned between methylene chloride and water. The organic layer then was extracted twice with 5% sodium thiosulfate, once with water, and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was dissolved in benzene–methylene chloride (1:1) and applied to a column containing 300 g. of silicic acid.[21] After removal of 0.4 g. of unidentified material with methylene chloride–ether (9:1), 2′,3′-dideoxy-3′-iodo-5′-O-trityluridine was eluted with methylene chloride–ether (3:1) and crystallized from hot methanol (2.65 g., 46%, m.p. 138–140°). Continued elution with the same solvent gave a further 2.26 g. of unchanged mesylate (III, R = H) which was retreated as above with sodium iodide in 1,2-dimethoxyethane. The total yield was 3.65 g. (64%) and after one further recrystallization from acetone–methanol, the melting point was raised to 142–143° with excellent recovery.

Anal. Calcd. for $C_{28}H_{25}IN_2O_4$: C, 57.94; H, 4.34; I, 21.87; N, 4.83. Found: C, 57.36; H, 4.42; I, 21.40; N, 4.65.

2′,3′-Dideoxy-3′-iodouridine (V, R = H).—2′,3′-Dideoxy-3′-iodo-5′-O-trityluridine (2.08 g., 3.58 mmoles) was dissolved in 80% acetic acid (100 ml.) and heated at 100° for 45 min. After cooling to room temperature, the solvent was evaporated *in vacuo* and last traces of acetic acid were removed by coevaporation with methanol several times. The residue was dissolved in methylene chloride–ethyl acetate (1:1) from which pure, crystalline 2′,3′-dideoxy-3′-iodouridine (0.58 g., 45%, m.p. 161° dec.) quickly separated. The mother liquors were directly applied to a column containing 200 g. of silicic acid.[21] Triphenylcarbinol and a small amount of an unidentified impurity were removed with methylene chloride–ethyl acetate (1:1) and subsequent elution with ethyl acetate gave a further 0.3 g. of the desired product. The combined products were recrystallized from acetone giving 0.79 g. (62%) of chromatographically pure (ethyl acetate) 2′,3′-dideoxy-3′-iodouridine of m.p. 162° dec., $\lambda_{max}^{0.1\ N\ HCl}$ 263 mμ (ϵ_{max} 11,300), $\lambda_{max}^{0.1\ N\ NaOH}$ 263 mμ (ϵ_{max} 8720).

Anal. Calcd. for $C_9H_{11}IN_2O_4$: C, 31.95; H, 3.29; N, 8.28. Found: C, 32.15; H, 3.47; N, 8.11.

2′,3′-Dideoxyuridine (VI, R = H).—2′,3′-Dideoxy-3′-iodouridine (730 mg., 2.15 mmoles) was dissolved in 50% aqueous methanol (100 ml.) containing triethylamine (0.7 ml., 5 mmoles) and vigorously stirred in an atmosphere of hydrogen in the presence of 10% palladium on carbon (200 mg.)[10] Hydrogen uptake was complete within 15 min. at room temperature. After removal of the catalyst by filtration, the filtrate and washings were evaporated to dryness *in vacuo*. The residue was then dissolved in aqueous methanol and passed through a small column containing 10 ml. of Dowex-2 (HCO_3^-) resin. The resin was washed with water until it was free of ultraviolet absorbing material, and the combined eluates were evaporated to dryness

(13) K. Butler, S. Laland, G. W. Overend, and M. Stacey, *J. Chem. Soc.*, 1433 (1950).

(14) G. N. Richards, *Chem. Ind.* (London), 228 (1955).

(15) G. W. Kenner in Ciba Foundation Symposium, Chemistry and Biology of Purines, Little, Brown and Co., Boston, Mass., 1957, p. 312.

(16) C. A. Dekker, *Ann. Rev. Biochem.*, **29**, 463 (1960).

(17) As applied to pyranosides, this has been explained as a conformational phenomena by J. T. Edward [*Chem. Ind.* (London), 1102 (1955)]. Such an explanation seems to be less satisfactory when applied to the relatively planar furanose system in nucleosides.

(18) Melting points are uncorrected and elemental analyses were obtained by Midwest Microlabs, Inc., Indianapolis, Ind.

(19) U. S. Radium Corp., Morristown, N. J.

(20) J. S. Matthews, A. L. Pereda, and A. Aguilera, *J. Chromatog.*, **9**, 331 (1962).

(21) Davidson Chemical Co., Baltimore, Md., grade 923, 100–200 mesh.

(22) 1,2-Dimethoxyethane was purified by distillation from lithium aluminum hydride.

in vacuo. The residue was crystallized from acetone–petroleum ether (b.p. 30–60°) giving 2′,3′-dideoxyuridine (375 mg., 83%) of m.p. 115°. This product contained 4% uracil which was difficult to remove by crystallization. A completely pure product was, however, readily obtained by preparative paper chromatography in solvent I which gave material of m.p. 116–117° after crystallization from acetone–ether, $\lambda_{max}^{0.01\ N\ HCl}$ 263 mμ (ϵ_{max} 10,050), $\lambda_{max}^{0.01\ N\ NaOH}$ 263 mμ (ϵ_{max} 7220).

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.90; H, 5.70; N, 13.20. Found: C, 50.81; H, 5.75; N, 13.22.

3′-Deoxythymidine.—This compound was prepared *via* the same sequence of steps as described above for 2′,3′-dideoxyuridine, except that the starting material was 5′-O-tritylthymidine.[8] The procedure is a direct adaptation of that described by Michelson and Todd[5] and the intermediates prepared were as follows: 3′-O-methanesulfonyl-5′-O-tritylthymidine (100%, amorphous), 3′-deoxy-3′-iodo-5′-O-tritylthymidine (70%, m.p. 147–148°), 3′-deoxy-3′-iodothymidine (79%, m.p. 166° dec., 3′-deoxythymidine (61%, m.p. 147–149°).

2′3′-Dideoxyuridine 5′-Phosphate (VII, R = H).—A mixture of pyridinium cyanoethyl phosphate[11] (0.2 mmole) and 2′,3′-dideoxyuridine (0.1 mmole) was rendered anhydrous by three evaporations with 2-ml. portions of dry pyridine. The final residue was dissolved in anhydrous pyridine (1 ml.) and dicyclohexylcarbodiimide (124 mg., 0.6 mmole) was added. After 24 hr. at room temperature, a small amount of water (0.5 ml.) was added and, after a further 30 min., the solvent was evaporated *in vacuo*. The residue was well stirred with water (5 ml.) and ether (5 ml.) and filtered to remove crystalline dicyclohexylurea. The water layer was extracted once more with ether, made 0.5 *M* with lithium hydroxide, and heated at 100° for 1 hr. After cooling in ice, the precipitated lithium phosphate was removed and the filtrate and washings (with 0.01 *M* LiOH) were passed through a column containing 3 ml. of Dowex-50 (H^+) resin. The eluates gave a single spot on paper with solvent I (R_f 0.11, while dideoxyuridine itself had R_f 0.63) and, based upon the ultraviolet spectrum, the yield was 80%. The pH of the solution was brought to 8.0 with barium hydroxide and after removal of a trace of barium phosphate the volume was reduced to 3–4 ml. The addition of three volumes of ethanol gave a white precipitate which was washed with ethanol and dried *in vacuo*. The barium salt of 2′,3′-dideoxyuridine 5′-phosphate thus obtained was spectrally shown to be a tetrahydrate and was poorly soluble in water, λ_{max} 263 (pH 2) and 263 mμ (1 *N* lithium hydroxide).

Anal. Calcd. for $C_9H_{11}BaN_2O_7P\cdot 4H_2O$: P, 6.20, P/dideoxyuridine, 1.0. Found: P, 6.51; P/dideoxyuridine, 1.05.

3′-Deoxythymidine 5′-Phosphate (VII, R = Me).—Phosphorylation of 3′-deoxythymidine (0.1 mmole) was carried out in identical manner to that of 2′,3′-dideoxyuridine above. The yield of chromatographically pure product (R_f 0.14; *cf.* 3′-deoxythymidine, R_f 0.72 in solvent I) was 85% and the barium salt was an octahydrate.

Anal. Calcd. for $C_{10}H_{13}BaN_2O_7P\cdot 8H_2O$: P, 5.30; P/deoxythymidine, 1.0. Found: P, 5.70; P/deoxythymidine, 1.08.

Kinetics of Acid Hydrolyses. A. Uracil Nucleosides.—Samples of uridine, 2′-deoxyuridine, and 2′,3′-dideoxyuridine (2.0 mg.) were separately dissolved in 0.5-ml. portions of cold, 1.0 *N* hydrochloric acid. Approximately 20-μl. aliquots of these solutions were sealed in capillary tubes and placed in a boiling water bath. At intervals the tubes were removed and, if necessary, stored in Dry Ice. The tubes were then broken and the contents were mixed directly with approximately 1.5 ml. of 1 *N* lithium hydroxide in a quartz spectrophotometer cell. The extent of the hydrolysis was followed by the ratio of the optical densities at 276 and 263 mμ: O.D. 276/263 = 0.556 for uracil nucleosides, 276/263 = 1.29 for uracil in 1 *N* lithium hydroxide.

B. Thymine Nucleosides.—The procedure in A was repeated exactly, except that thymidine and 3′-deoxythymidine were used in place of the uracil nucleosides. The extent of hydrolysis was determined from the optical density ratios at 281 and 267 mμ: 281/267 = 0.596 for thymidine and 3′-deoxythymidine, and 1.184 for thymine in 1 *N* lithium hydroxide. The results are shown in Fig. 1, the various deoxynucleosides all obeying first-order kinetics until 60–75% hydrolysis had occurred.

Alkylbenzenes. XIII. Rearrangements and Reorientations of C¹⁴-Labeled *n*-Propyltoluenes and *n*-Propylxylenes

ROYSTON M. ROBERTS, ALI ALI KHALAF, AND JAMES E. DOUGLASS

Department of Chemistry, The University of Texas, Austin, Texas

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The reactions of *p*-*n*-propyl-α-C¹⁴-toluene and 1,3-dimethyl-4-*n*-propyl-β-C¹⁴-benzene with aluminum chloride at temperatures from 23 to 98° were studied. At lower temperatures the main reactions were reorientation to *m*-*n*-propyltoluene and 1,3-dimethyl-5-*n*-propylbenzene, respectively; at higher temperatures a complex mixture of products was formed by competing reactions which included reorientation of methyl as well as propyl groups, and rearrangements of *n*-propyl groups to isopropyl groups and to *n*-propyl groups in which C¹⁴ was interchanged between α- and β-positions of the side chains. The results of the present work and previous work lead to the conclusion that the susceptibility toward aluminum chloride-induced rearrangement of *n*-propyl side chains decreases in the series *n*-propylbenzene, *n*-propyltoluene, and *n*-propylxylene. An explanation for this order is suggested.

Reorientation reactions of the type *p*-xylene → *m*-xylene[1,2] and *p*-ethyltoluene → *m*-ethyltoluene[3] take place under milder conditions than those which produce rearrangements of side chains in propyl-[4] and butylbenzenes.[5] However, in some studies of reorientation reactions,[6,7] conditions were similar to those which produce rearrangement; it thus seemed worthwhile to determine the extent to which rearrangements may occur in these systems.

Nightingale and Shackelford[7] reported that the major products of reaction of 1,3-dimethyl-4-*n*-propylbenzene and 1,3-dimethyl-4-*n*-butylbenzene were 1,3-dimethyl-5-*n*-propylbenzene and 1,3-dimethyl-5-*n*-butylbenzene, respectively, but they stated that it was quite possible that their products contained minor amounts of side chain-rearranged isomers. We particularly were interested in investigating the C¹⁴-labeled *n*-propyl case, since rearrangements could be detected with more precision in this system than the butyl. This paper reports the results of investigation of the reaction of 1,3-dimethyl-4-*n*-propyl-β-C¹⁴-benzene and of the structurally related *p*-*n*-propyl-α-C¹⁴-toluene with aluminum chloride.

(1) G. Baddeley, G. Holt, and D. Voss, *J. Chem. Soc.*, 100 (1952).

(2) (a) D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **74**, 6246 (1952); (b) H. C. Brown and H. Jungk, *ibid.*, **77**, 5579 (1955).

(3) R. H. Allen, *ibid.*, **82**, 4856 (1960).

(4) R. M. Roberts and J. E. Douglass, *J. Org. Chem.*, **28**, 1225 (1963); *cf.* references to previous papers.

(5) R. M. Roberts, Y. W. Han, C. H. Schmid, and D. A. Davis, *J. Am. Chem. Soc.* **81**, 640 (1959).

(6) G. Baddeley and J. Kenner, *J. Chem. Soc.*, 303 (1935).

(7) (a) D. V. Nightingale and J. M. Shackelford, *J. Am. Chem. Soc.*, **76**, 5767 (1954); (b) **78**, 1225 (1956).

TABLE I

REACTIONS OF 1,3-DIMETHYL-4-*n*-PROPYLBENZENE WITH ALUMINUM CHLORIDE

Temp., °C.	30 ± 2	30 ± 2	30 ± 2[a]	80 ± 2	98 ± 2[a]	98 ± 2
Time, hr.	4	4	8	2.5	4	4
$AlCl_3$/hc[b]	0.24	0.48	0.48	0.24	0.24	0.48
$AlCl_3/H_2O$	...	...	...	...	...	2
Products[c]						
Toluene	Tr.	Tr.	Tr.	1	2	4
Xylenes	18	18	13	8	11	19
Mesitylene	tr.	tr.	tr.	5	9	12
Pseudocumene	2	3	5	10	13	17
n-Propyltoluenes	5	5	8	18	17	17
1,3-Dimethyl-4-*n*-propylbenzene	57	38	28	21	...[d]	...[d]
1,2-Dimethyl-4-*n*-propylbenzene	...[d]	...[d]	...[d]		18	12
1,3-Dimethyl-5-*n*-propylbenzene	18	36	46	34	25	13
1,3-Dimethyl-5-isopropylbenzene	...	...	...	3[e]	5[e]	6[e]
Residue[f]	...	...	25	...	20	32
Per cent C^{14} in α-carbon of 1,3-dimethyl-5-*n*-propylbenzene			0		4.5 ± 0.2[g]	36 ± 1[g]

[a] 1,3-Dimethyl-4-*n*-propyl-β-C^{14}-benzene was the starting material. See Experimental section for details. [b] Molar ratio of $AlCl_3$/hydrocarbon. [c] Mole %, determined by integration of v.p.c. recordings of crude product mixtures. [d] These isomers were not resolved on the v.p.c. column, but their infrared spectra were sufficiently distinctive to indicate the absence of any more than trace amounts of the 1,2-dimethyl isomer in the first three experiments and of the 1,3-dimethyl isomer in the last two. [e] Estimated within ±5% from shoulder peaks, since this isomer was not completely resolved from 1,3-dimethyl-5-*n*-propylbenzene by the v.p.c. column. [f] Distillation residues, b.p. >210°, are given in wt. % of starting material for three experiments. [g] Confidence limits based on a maximum error of 4% in radioassays.

Results and Discussion

In preparation for the work with the C^{14}-labeled molecules, several experiments were carried out with ordinary 1,3-dimethyl-4-*n*-propylbenzene at different temperatures and with different proportions of catalysts. These experiments and their results, as well as those with radioactive materials, are summarized in Table I. At 30° a complex mixture resulted from reorientation and disproportionation reactions. The major products were 1,3-dimethyl-5-*n*-propylbenzene and xylenes (probably mainly the *meta* isomer[8]) as reported previously.[7b] Reorientation was incomplete, considerable starting material remaining even after 8 hr. No rearrangement of the *n*-propyl side chain to isopropyl was found.

The experiment of column five, Table I, duplicated the one reported by Nightingale and Shackelford.[7b] In addition to those found in the lower temperature experiments, several new products appeared in appreciable amounts: toluene, mesitylene, psuedocumene, *n*-propyltoluenes, 1,2-dimethyl-4-*n*-propylbenzene, and 1,3-dimethyl-5-isopropylbenzene. It is to be noted that several of these result from removal and reorientation of methyl groups, as well as propyl groups. Some rearrangement of *n*-propyl to isopropyl side chains occurred.

In order to determine the amount of rearrangement of C^{14} in the *n*-propyl groups in the experiments utilizing labeled starting material, the crude reaction mixtures were subjected to fractional distillation, and dimethylpropylbenzene cuts were taken for degradation to trimesic acid. These cuts were shown by v.p.c. analysis to be free of 1,3-dimethyl-5-isopropyl benzene (see below); they contained 1,3-dimethyl-5-*n*-propylbenzene and 1,3-dimethyl-4-*n*-propylbenzene (experiment of column three) or 1,2-dimethyl-4-*n*-propylbenzene (experiments of columns five and six). The trimellitic acid resulting from oxidation of the latter two isomers was easily separated from trimesic acid by recrystallization. In order to ensure that the radioactivity of the trimesic acid arose from oxidation of 1,3-dimethyl-5-*n*-propyl-α-C^{14}-benzene only and *not* 1,3-dimethyl-5-isopropyl-α-C^{14}-benzene, the latter labeled isomer was synthesized and mixed with nonradioactive 1,3-dimethyl-5-*n*-propylbenzene, and the mixture was oxidized to trimesic acid. Radioassay of the purified trimesic acid showed that only 6% of the 1,3-dimethyl-5-isopropyl-α-C^{14}-benzene was oxidized to trimesic acid. Since the v.p.c. analysis of the dimethylpropylbenzene cuts would have detected as much as 5% of the isopropyl isomer, the error in radioassay produced by the presence of the isopropyl isomer in trace amounts and its oxidation to trimesic acid would have been insignificant. The extent of rearrangement of C^{14} calculated from the radioassays of trimesic acid is shown at the bottom of Table I.

p-*n*-Propyl-α-C^{14}-toluene also was synthesized and its reactions with Lewis acids were studied. In toluene solution at 23°, with aluminum bromide–hydrogen bromide, complete reorientation to the *meta* isomer occurred in 30 min. The same reactants in a sealed tube at 100° for 30 min. gave a mixture so complex that recovery of pure propyltoluene was impossible. A third experiment carried out with aluminum chloride and water cocatalysts gave a mixture somewhat more amenable to separation and analysis.

The *m*-*n*-propyltoluene recovered from the first experiment was oxidized to isophthalic acid and this was converted to the dimethyl ester for radioassay. The radioassay indicated loss of only 1.9 ± 0.5% of C^{14} from the α-carbon of the *n*-propyl side chain. The propyltoluene distillation fraction from the third experiment was not pure *m*-*n*-propyltoluene (infrared analysis), but it gave isophthalic acid upon oxidation, as did a higher boiling fraction which contained *m*-di-*n*-propylbenzene. At the time these experiments with

(8) Nightingale and Shackelford[7b] identified *m*-xylene by means of a derivative. *p*-Xylene would not have been resolved from *m*-xylene by our v.p.c. column, but *o*-xylene was; it made up 10–20% of the xylene mixtures produced.

p-*n*-propyl-α-C14-toluene were carried out, v.p.c. analysis of the products was not feasible. When the experiments with *n*-propyldimethylbenzenes were carried out at a later date, a sample of the dipropylbenzene distillation fraction (e) was still available and was analyzed by v.p.c., but none of the propyltoluene fraction (c) remained. Since the v.p.c. analysis of the higher boiling fraction showed that it contained *m*-*n*-propyltoluene, it is reasonable to assume that the lower boiling cut contained some *m*-di-*n*-propylbenzene. From the proportions of *m*-*n*-propyltoluene and *m*-di-*n*-propylbenzene determined in the higher boiling fraction by v.p.c. and the radioassay of the dimethyl isophthalate obtained from this fraction, the per cent loss of C^{14} from the α-positions of the *n*-propyl side chains was calculated to be about 17%.[9] Making the reasonable assumption that the lower boiling fraction contained 10 mole % *m*-di-*n*-propylbenzene, and, using the radioassay of the dimethyl isophthalate obtained from this fraction, the per cent loss of C^{14} from the α-positions of the *n*-propyl side chains also was calculated to be about 17%.

In view of the complexity of the mixture obtained from reaction of *p*-*n*-propyl-α-C14-toluene with aluminum chloride at 98° and the assumption necessitated by the fragmentary data, the extent of isotopic rearrangement calculated for this hydrocarbon must be considered indicative rather than conclusive.

Although accurate comparisons can not be made with the data available, we are tempted to comment on the apparent relative susceptibility of an *n*-propyl side chain toward rearrangement by aluminum chloride in an aromatic hydrocarbon having it as the only side chain with ones having in addition one or two methyl groups attached to the same benzene ring. Under similar conditions of time, temperature, and catalyst to hydrocarbon ratio, the approximate extent of rearrangement of *n*-propyl groups is in *n*-propylbenzene about 30%,[4] in *p*-*n*-propyltoluene about 17%, and in 1,3-dimethyl-4-*p*-propyltoluene about 5%. We have pointed out in previous papers[4,10] that rearrangements of alkylbenzene side chains induced by aluminum chloride and similar catalysts are subject to inhibition by disproportionation products such as polyalkylbenzenes, owing to the deactivation of the Lewis acid catalyst by complex formation with these products, which are stronger Lewis bases than the original monoalkylbenzene.[11] A reasonable explanation of the decreasing extent of rearrangement of *n*-propyl side chains in the series *n*-propylbenzene, *p*-*n*-propyltoluene, and 1,3-dimethyl-4-*n*-propylbenzene appears to lie in the fact that the catalyst would be progressively less active toward rearrangement of the di- and trialkylbenzenes, particularly after reorientation to the 1,3 and 1,3,5 isomers has occurred. The reorientation and rearrangement reactions are probably entirely independent of one another (the reorientation of *p*-*n* propyltoluene to *m*-*n*-propyltoluene was complete in 30 min. at room temperature with no accompanying side chain rearrangement) so that the rearrangements observed are probably subsequent rearrangements of the rapidly formed reorientation products, *m*-*n*-propyltoluene and 1,3-dimethyl-5-*n*-propylbenzene.

The greater extent of rearrangement in the experiment of column six, Table I, also is understandable in terms of (lesser) deactivation of the catalyst by the trialkylbenzene, since in this experiment the ratio of aluminum chloride to hydrocarbon was twice that of the experiment of column five. The effect of water as a cocatalyst[4,5] was an additional factor favoring rearrangement, of course.

The mechanisms of rearrangement of the *n*-propyl side chains of *m*-*n*-propyltoluene and 1,3-dimethyl-5-*n*-propylbenzene to isopropyl side chains and to *n*-propyl side chains in which the α- and β-carbon atoms have been interchanged are undoubtedly the same as those of *n*-propylbenzene, which have been considered previously.[4]

The reorientation of the methyl groups (production of 1,2-dimethyl-4-*n*-propylbenzene) is interesting. Additional examples of methyl shifts of this type will be discussed in a forthcoming publication.[12] We note that Nightingale and Shackelford reported their products from 1,3-dimethyl-4-*n*-propylbenzene contained 28% of "1,3,4-trialkylbenzene."[7b] It now appears, from our results, that the "1,3,4-trialkylbenzene" was mainly 1,2-dimethyl-4-*n*-propylbenzene.

Experimental

Materials.—Ethyl-1-C^{14} iodide was purchased from Tracerlab, Inc.[13] Aluminum chloride was commercial anhydrous sublimed reagent grade, taken from freshly opened bottles. The following authentic hydrocarbons used for v.p.c. and infrared identification and analysis were prepared by standard, unequivocal syntheses by Dep Shiengthong, in connection with another problem[12]: 1,3-dimethyl-4-*n*-propylbenzene, 1,3-dimethyl-5-*n*-propylbenzene, 1,2-dimethyl-4-*n*-propylbenzene, 1,3-dimethyl-5-isopropylbenzene, 1,3-dimethyl-4-isopropylbenzene, and 1,2-dimethyl-4-isopropylbenzene. Authentic *p*- and *m*-*n*-propyltoluene were prepared by standard, unequivocal syntheses from *p*- and *m*-toluidines (recrystallized in the free amine and hydrochloric acid salt forms, respectively). *m*- and *p*-di-*n*-propylbenzene were produced by low temperature disproportionation of *n*-propylbenzene.

Analytical Procedures.—Radioassays were made as described previously.[4] Infrared analysis was done with Beckman IR5A and Baird Model 4-55 double-beam instruments, using sodium chloride cells. Vapor-phase chromatographic (v.p.c.) analysis was made using a Beckman GC2A instrument with a 12-ft. silicone gum rubber-on-firebrick column.

Synthesis of Radioactive Materials.—1,3-Dimethyl-4-*n*-propyl-β-C^{14}-benzene was synthesized from ethyl-1-C^{14} iodide *via* sodium propionate-2-C^{14} and 2,4-dimethylpropiophenone-2′-C^{14}, in a manner analogous to that used for *n*-propyl-β-C^{14}-benzene.[14] The 2,4-dimethylpropiophenone-2′-C^{14}, after fractional distillation (b.p. 102–103° at 6 mm.), was pure according to v.p.c. analysis. It was radioassayed in the form of its semicarbazone derivative, 0.86 μc./mmole. The ketone was hydrogenated to 1,3-dimethyl-4-*n*-propyl-β-C^{14}-benzene in glacial acetic acid containing a little perchloric acid using 5% palladium-on-carbon catalyst[15]; the hydrocarbon was pure by v.p.c. and infrared analysis, b.p. 204–207°, $n^{22}D$ 1.4972.

1,3-Dimethyl-5-isopropyl-α-C^{14}-benzene was synthesized from 2-propanol-2-C^{14} *via* 2-chloro-2-C^{14}-propane, which was used to alkylate *m*-xylene by standard procedures.[16] The product was fractionally distilled and a cut boiling at 195.5–197.5° was shown (infrared and v.p.c. analysis) to contain less than 2% of 1,3-

(9) See Experimental.

(10) R. M. Roberts, E. K. Baylis, and G. J. Fonken, *J. Am. Chem. Soc.*, **85**, 3454 (1963).

(11) D. A. McCaulay and A. P. Lien, *ibid.*, **73**, 2013 (1951).

(12) R. M. Roberts and D. Shiengthong, paper in preparation.

(13) On allocation from the U. S. Atomic Energy Commission.

(14) R. M. Roberts and S. G. Brandenberger, *J. Am. Chem. Soc.*, **79**, 5484 (1957).

(15) R. M. Roberts, G. A. Ropp, and O. K. Neville, *ibid.*, **77**, 1764 (1955).

(16) D. Nightingale and B. Carton, Jr., *ibid.*, **62**, 280 (1940).

dimethyl-4-isopropylbenzene. The hydrocarbon was radioassayed in the form of the trinitro derivative, m.p. 116–117°,[7b] 0.75 μc./mmole.

p-*n*-**Propyl-α-C^{14}-toluene** was synthesized from $BaC^{14}O_3$ (Oak Ridge National Laboratory[13]) *via* sodium propionate-1-C^{14} and *p*-methylpropiophenone-1-C^{14} in a manner analogous to that previously reported for *n*-propyl-α-C^{14}-benzene.[4] Infrared analysis showed that no *ortho* isomer was present in the product. The hydrocarbon was radioassayed in the form of dimethyl terephthalate, m.p. 139–140.5°, produced by permanganate oxidation to the acid, conversion to the acid chloride with phosphorus pentachloride, followed by reaction with methanol; 0.614 μc./mmole.

Reactions of 1,3-Dimethyl-4-*n*-propylbenzene with Aluminum Chloride.—All reactions were carried out on 10 g. (0.068 mole) of hydrocarbon and either 2.15 g. (0.0161 mole) or 4.30 g. (0.0322 mole) of aluminum chloride. In one experiment 0.29 g. (0.016 mole) of water also was added. The reactants were stirred by a Teflon-covered magnet in a flask equipped with a reflux condenser protected by a calcium chloride tube. The temperature of the reaction was controlled by an electrically heated oil bath. The conditions for six experiments are given in Table I. After the reaction period was completed, the contents of the flask were cooled in an ice bath and decomposed with 6 *N* hydrochloric acid. The organic products were extracted into ether; the ether solution was washed with 5% sodium bicarbonate solution and water and then dried over calcium chloride. The crude organic mixture was analyzed by v.p.c. with the results shown in Table I.

In the case of the experiments with radioactive materials, the reaction mixture was subjected to fractional distillation through a 100-cm. Nichrome spiral column using a reflux ratio of 99:1. The dimethylpropylbenzene fractions were analyzed by infrared and v.p.c. The fractionations were apparently effective in separating 1,3-dimethyl-5-isopropylbenzene (b.p. 194.5°[17]) from 1,3-dimethyl-5-*n*-propylbenzene (b.p. 202.2°[17]) and 1,2-dimethyl-4-*n*-propylbenzene (b.p. 208.9°[17]) because the shoulder or peak corresponding to the first isomer disappeared from the v.p.c. recordings of the fractions from the 98° reactions which were taken for degradation to trimesic acid.

Reactions of *p*-*n*-Propyl-α-C^{14}-toluene with Aluminum Bromide and Aluminum Chloride.—A mixture of 15.7 g. (0.0292 mole, as Al_2Br_6) of aluminum bromide and 15.7 ml. of dry toluene were shaken until all the solid had disappeared. Hydrogen bromide was bubbled through the mixture until a homogeneous solution was obtained. *p*-*n*-Propyl-α-C^{14}-toluene, 4.0 g. (0.030 mole), was added; the vessel was capped, inverted several times to ensure complete mixing, and placed in a water bath at 23° for 30 min. The reaction mixture was then decomposed with water and worked up in the usual way. A fraction which boiled at 178–181° had an infrared spectrum identical with that of authentic *m*-*n*-propyltoluene.

A mixture of 15.9 g. (0.119 mole) of *p*-*n*-propyl-α-C^{14}-toluene, 3.9 g. (0.030 mole) of aluminum chloride, and 0.13 g. (0.0071 mole) of water was heated with stirring at 98 ± 2° for 4 hr. The reaction mixture was worked up as before and distilled through a 75-cm. Nichrome spiral column. The following fractions were collected: (a) b.p. 109–114°, 0.76 g.; (b) b.p. 114–181°, 2.00 g.; (c) b.p. 181–185°, 1.35 g.; (d) b.p. 185–196°, 0.61 g.; b.p. 196–221°, 3.75 g. Fractions c and e were degraded for radioassay, as described below.

Degradations for Radioassays. 1,3-Dimethyl-4-*n*-propyl-β-C^{14}-benzene (starting material) was shown to have no C^{14} in the α-position of the side chain by oxidation (basic permanganate at reflux for 10 hr., followed by acidification and reflux for 2 hr.) to trimellitic acid. Recrystallized from aqueous ethanol, it melted at 237–238°; it gave no radioactivity above background. (Mixture of this product with trimellitic acid prepared by oxidation of pseudocumene gave no melting point depression.)

A. Dimethylpropylbenzenes.—A distillation fraction, b.p. 201–209°, obtained from the reaction at 30° (column three, Table I) was shown by v.p.c. and infrared analysis to consist of 1,3-dimethyl-4-*n*-propylbenzene, 35 ± 5%, and 1,3-dimethyl-5-*n*-propylbenzene, 65 ± 5%. Oxidation with basic and acidic permanganate, as described above, gave trimesic acid, m.p. 364–370°; a mixture with authentic trimesic acid obtained by oxidation of mesitylene had the same melting point. This product showed no radioactivity above background.

A distillation fraction, b.p. 195–205°, obtained from the reaction at 98° (column five, Table I) was shown by v.p.c. and infrared analysis to consist of 1,3-dimethyl-5-*n*-propylbenzene, 67 ± 5%, and 1,2-dimethyl-4-*n*-propylbenzene, 33 ± 5%. Oxidation gave trimesic acid, m.p. 365–370°; recrystallized from water, m.p. 365–368°. Radioassay gave 0.039 μc./mmole, corresponding to 4.5 ± 0.2% rearrangement of C^{14} to the α-position of the *n*-propyl side chain (Table I).

A distillation fraction, b.p. 198–208°, obtained from the reaction at 98° (column six, Table I) was shown by v.p.c. and infrared analysis to consist of 1,3-dimethyl-5-*n*-propylbenzene, 60 ± 5%, and 1,2-dimethyl-4-*n*-propylbenzene, 40 ± 5%. Oxidation gave trimesic acid, m.p. 364–370°; after recrystallization from water, radioassay gave 0.31 μc./mmole, corresponding to 36 ± 1% rearrangement of C^{14} to the α-position of the *n*-propyl side chain (Table I).

A prepared mixture of 1,3-dimethyl-5-isopropyl-α-C^{14}-benzene (0.636 g., 0.753 μc./mmole), 1,3-dimethyl-5-*n*-propylbenzene (1.80 g.), and 1,3-dimethyl-4-*n*-propylbenzene (1.20 g.) was oxidized in the usual way. The crude acid was recrystallized from water to give 600 mg. of trimesic acid, m.p. 365–368°. Recrystallization to constant radioactivity gave 0.012 μc./mmole; this corresponded to 6.0 ± 0.2% of the molecular radioactivity which could have been obtained by complete oxidation of the α-C^{14}-labeled isopropyl side chain.

B. *m*-*n*-Propyltoluene.—The *m*-*n*-propyltoluene fraction, b.p. 178–181°, from the reaction of *p*-*n*-propyl-α-C^{14}-toluene with aluminum bromide–hydrogen bromide at 23° was oxidized by permanganate to isophthalic acid. This was converted to the dimethyl ester as described for the *para* isomer (starting material) and recrystallized from 30% aqueous methanol, m.p. 66–67°. Recrystallization to constant melting point (67°) and radioactivity gave 0.602 μc./mmole. This corresponded to a loss of 1.9 ± 0.5% of the C^{14} from the α-position of the *n*-propyl side chain.

Fraction c, b.p. 181–185°, from the reaction of *p*-*n*-propyl-α-C^{14}-toluene with aluminum chloride at 98°, gave upon oxidation isophthalic acid which was converted to dimethyl isophthalate (m.p. 67°), recrystallized to a constant radioactivity of 0.562 μc./mmole. The infrared spectrum of fraction c was not identical with that of authentic *m*-*n*-propyltoluene. The impurities present were probably *m*-di-*n*-propylbenzene, unchanged *p*-*n*-propyltoluene, and isopropyltoluene isomers, judging from the v.p.c. analysis of fraction e (see below). The latter two would not interfere with the radioactivity analysis, since they would not oxidize appreciably to isophthalic acid.[18] Assuming 10 mole % *m*-di-*n*-propylbenzene and 90 mole % *m*-*n*-propyltoluene responsible for the dimethyl isophthalate radioassayed, the extent of rearrangement away from the α-position of the *n*-propyl side chains was calculated to be about 17%.[19]

Fraction e from the same reaction was also oxidized to isophthalic acid and converted to dimethyl isophthalate which was recrystallized to constant radioactivity, 0.763 ± 0.003 μc./mmole. Analysis of fraction e by v.p.c. showed it to contain *m*-*n*-propyltoluene and *m*-di-*n*-propylbenzene in about a 1:1 ratio.[19] Other products (three peaks) such as *m*- and *p*-diisopropylbenzene, *m*- and *p*-propylisopropylbenzene, and dipropyltoluenes also were present, but none of these would oxidize appreciably to isophthalic acid.[18] From the radioactivity of the dimethyl isophthalate and the proportion of *m*-*n*-propyltoluene and *m*-di-*n*-propylbenzene, the extent of rearrangement of C^{14} from the α-positions of the *n*-propyl side chains was calculated to be about 17%.[19]

Acknowledgment.—We are grateful to the Robert A. Welch Foundation and the National Science Foundation for generous support of this research.

(17) F. R. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun, and G. C. Pimentel, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburgh, Pa., 1953, p. 74.

(18) The *para* isomers, of course, could not oxidize to isophthalic acid. The failure of isopropyl groups to oxidize to an appreciable extent was demonstrated in the case of 1,3-dimethyl-5-isopropylbenzene, as described earlier in Experimental.

(19) The precision of the v.p.c. analysis was not better than ±5%; this is responsible for the approximate value indicated for the extent of C^{14} rearrangement in this experiment.

The Friedel–Crafts Alkylation with 2-Aryl Ethyl-1-C^{14} Chlorides[1]

MATTHEW A. MCMAHON[1] AND STANLEY C. BUNCE

Walker Laboratory, Rensselaer Polytechnic Institute, Troy, New York

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The reaction of toluene with 2-phenylethyl-1-C^{14} chloride using aluminum chloride as catalyst gives β-tolylethylbenzene in which 52.0–52.3% of the carbon-14 is contained in the α-position, while 2-phenylethyl chloride recovered from contact with aluminum chloride in toluene had no isotope position rearrangement. The formation of a symmetrical intermediate, whose rate of reaction with toluene is subject to an intramolecular isotope effect, is indicated. The reaction of toluene with 2-(4-nitrophenyl)ethyl-1-C^{14} chloride gives only 8% isotope position rearrangement, while alkylation of naphthalene and of phenol with 2-phenylethyl-1-C^{14} chloride gave 48.7 and 52.7% of the carbon-14 in the α-position.

The Friedel–Crafts alkylation reaction of primary halides continues to present interesting problems. The rearrangements which result in the formation of a large proportion of *sec*-alkyl benzenes were first explained on the basis of a simple carbonium ion mechanism, although some experimental observations could not be interpreted in this way.[2–4] Studies of catalyst complexes and extensive kinetic studies of Friedel–Crafts alkylations led Brown to conclude that alkylations with primary halides proceed by displacement.[5]

The extent of rearrangement which is a significant part of the Friedel–Crafts reaction of most primary halides has been studied by examining the relative amounts of the normal and branched alkylation products. While results described in the older literature often indicate a single product, more refined analytical techniques usually demonstrate the presence of several products, including considerable proportions of those of unrearranged structure.[6,7]

These reactions have also been studied by measuring the extent of carbon-14 isotope position rearrangement. For example, the alkylation of anisole with 2-phenylethyl-1-C^{14} chloride gave a reaction product with nearly equal distribution of carbon-14 in the two alkyl carbons.[8]

In most of these studies, the possibility that halides might rearrange prior to alkylation (a rearrangement which is known to be important in the absence of arenes) has not been excluded.[6,9] The possibility that rearrangement of an alkyl benzene may take place subsequent to reaction has generally been considered slight, since most disproportionations and alkyl group migrations occur with little or no skeletal isomerization.[7,10] Yet, in one instance, partial isotope position rearrangement in an alkyl benzene, without isomerization, was demonstrated to accompany disproportionation.[11a]

There is presently no simple rationalization of many of these observations.[12] The simultaneous operation of SN1 and SN2 pathways, rearrangement prior to or subsequent to alkylation or rearrangement within a π-complexed carbonium ion,[13] may be required to explain these results.

Alkylations with 2-phenylethyl halides, which have been little studied, seemed to us to provide opportunity for determining the relative contributions of SN1 and SN2 pathways and the extent of phenyl participation to form a symmetrical ion. Studies of reaction kinetics, of isotope position rearrangement, and of the effect of substituents on rates of reaction and rearrangement might all be used to elucidate the mechanism of reaction.

This paper reports studies of isotope position rearrangement in alkylations with 2-phenylethyl-1-C^{14} chloride and 2-(4-nitrophenyl)ethyl-1-C^{14} chloride, using aluminum chloride as a catalyst. The reaction of 2-phenylethyl-1-C^{14} chloride with phenol was first investigated; the high temperatures and long reaction times required led to experiments with alkylation of naphthalene and then of toluene.

Results and Discussion

The reaction of 2-phenylethyl chloride, excess toluene, and aluminum chloride was found to be homogeneous when less than 0.15 mole of aluminum chloride per mole of 2-phenylethyl chloride was used, and to have a rate such that the reaction was more than half complete in 10 min. at 0°.[14] Isotope position rearrangement in this reaction of 2-phenylethyl-1-C^{14} chloride and 2-(4-nitrophenyl)ethyl-1-C^{14} chloride was then studied.

(1) Abstracted from the Ph.D. thesis of M. A. McMahon, Rensselaer Polytechnic Institute, 1962; Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962.

(2) V. N. Ipatieff, H. Pines, and L. Schmerling, *J. Org. Chem.*, **5**, 253 (1940).

(3) H. Pines, L. Schmerling, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **62**, 2901 (1940).

(4) G. Baddeley, *Quart. Rev.* (London), **8**, 355 (1954).

(5) (a) H. C. Brown and M. Grayson, *J. Am. Chem. Soc.*, **75**, 6285 (1953); (b) H. C. Brown and H. Jungk, *ibid.*, **78**, 2182 (1956); (c) H. Jungk, C. R. Smoot, and H. C. Brown, *ibid.*, **78**, 2185 (1956).

(6) R. N. Roberts and D. Shiengthong, *ibid.*, **82**, 732 (1960).

(7) (a) D. V. Nightingale and J. M. Shackelford, *ibid.*, **78**, 1225 (1956); (b) S. H. Sharman, *ibid.*, **84**, 2945 (1962).

(8) C. C. Lee, A. G. Forman, and A. Rosenthal, *Can. J. Chem.*, **35**, 220 (1957).

(9) H. C. Brown and W. Wallace, *J. Am. Chem. Soc.*, **75**, 6268 (1953).

(10) (a) D. A. McCaulay and A. P. Lien, *ibid.*, **75**, 2411 (1953); (b) R. E. Kinney and L. A. Hamilton, *ibid.*, **76**, 786 (1954).

(11) (a) R. M. Roberts and S. G. Brandenberger, *ibid.*, **79**, 5484 (1957); (b) R. M. Roberts, Y. W. Han, C. H. Schmid, and D. A. Davis, *ibid.*, **81**, 640 (1959).

(12) K. L. Marsi and S. H. Willen, *J. Chem. Educ.*, **40**, 214 (1963).

(13) A. Streitwieser, Jr., W. D. Schaeffer, and S. Andreades, *J. Am. Chem. Soc.*, **81**, 1113 (1959).

(14) The kinetics of the reaction in excess toluene were studied by gas chromatographic analysis of the change in concentration of 2-phenylethyl chloride with time. Values for the pseudo-first-order reaction rate constant, calculated by substitution of the peak heights of 2-phenylethyl chloride in the integrated form of the first-order rate expression following,

$$k_1 = \frac{2.303}{t_2 - t_1} \log \frac{C_{t_1}}{C_{t_2}}$$

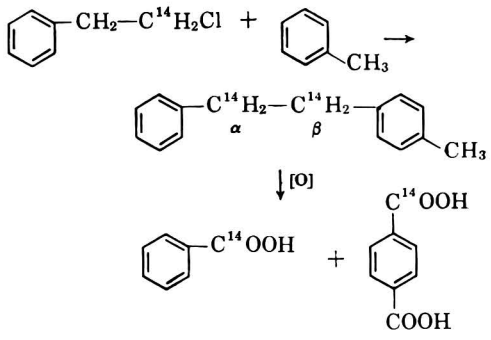
decreased with time. Typical values for the reaction of 2-phenylethyl chloride (1.00 mole/l. of toluene solution) and aluminum chloride (0.014 mole/l. of toluene solution) at −10° were k_1 = 0.0051 sec.$^{-1}$ at 150 sec., 0.0035 sec.$^{-1}$ at 295 sec., 0.0026 sec.$^{-1}$ at 415 sec., and 0.0018 sec.$^{-1}$ at 752 sec. The decrease of k_1 with time may be due to the formation of the loose σ-complex, $C_6H_5CH_3 + HCl + Al_2Cl_6 \rightarrow CH_3C_6H_6^+Al_2Cl_7^-$, which has been observed at −45°.[5a]

TABLE I

REACTION OF TOLUENE WITH 2-ARYL ETHYL-1-C^{14} CHLORIDES. RADIOACTIVITY ANALYSES[a]

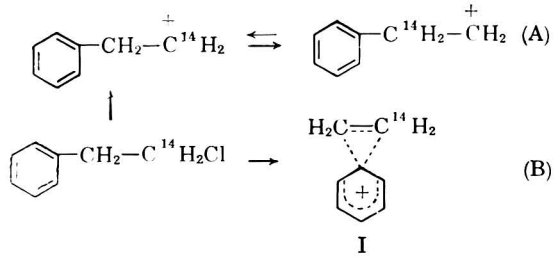
Compound counted	Obsd. c.p.m.	Corrected c.p.m./mmole	Rearrangement, %	$\frac{k^{14}}{k^{12}}$
Reaction 1				
p-$CH_3C_6H_4CH_2CH_2C_6H_5$[b]	1197 ± 11	9.82×10^4		
	576 ± 10	10.09×10^4		
p-$HOOCC_6H_4COOH$	667 ± 7	4.91×10^4		
C_6H_5COOH	683 ± 7	5.30×10^4	52.0	0.92 ± 0.02
Reaction 2				
$C_6H_5CH_2CH_2Cl$[c]	678 ± 6	3.72×10^4		
p-$HOOCC_6H_4COOH$	490 ± 4	1.74×10^4		
	461 ± 4	1.78×10^4		
C_6H_5COOH	568 ± 4	1.96×10^4	52.7	0.90 ± 0.02
Reaction 3				
p-$O_2NC_6H_4CH_2CH_2C_6H_4CH_3$	2117 ± 12	2.014×10^5		
	2478 ± 13	2.003×10^5		
p-$HOOCC_6H_4COOH$	2065 ± 14	1.873×10^5		
	1859 ± 13	1.787×10^5	8.6	

[a] All compounds were counted in the gas phase as carbon dioxide by the general method described by R. C. Anderson, Y. Delabarre, and A. A. Bothner-by, *Anal. Chem.*, **24**, 1298 (1952). [b] Analyses of this compound were poor owing to difficulty in combustion of the liquid. [c] Counted as the urethane derivative of the alcohol from which it was prepared.



The results of radiocarbon assay of the products and their degradation products are given in Table I.

It is evident that a 1,2-phenyl shift has taken place at some stage in the alkylation. 2-Phenylethyl-1-C^{14} chloride which had been in contact with aluminum chloride in toluene was recovered and oxidized; the benzoic acid produced was not radioactive. The formation of a simple carbonium ion (or ion pair) and equilibration of that with one in which a phenyl has shifted (reaction path A) is, therefore, not a possible explanation, unless the reaction of these carbonium ions with toluene is very much faster than their recombination with chloride.



If such were the mechanism of the reaction, one might expect a distribution of activity approaching and perhaps equaling 50% rearrangement. Also, the loss of chloride from 2-phenylethyl-1-C^{14} chloride would presumably be rate-controlling; it would then be subject to an intermolecular isotope effect[15,16] leading, if the reaction were incomplete, to an observation of lowered specific activity of the combined reaction products as compared with starting materials.

In fact in reaction 2, which proceeded to the extent of approximately 60% reaction, no intermolecular isotope effect is observed; instead, an intramolecular isotope is evident in reactions 1 and 2. Thus the distribution of activity is such as to require a different interpretation.

If a symmetrical intermediate (I) is formed, the atomically unsymmetrical ion will produce β-tolylethylbenzene which is carbon-14 rich in the α-position. The magnitude of the observed isotope effect agrees favorably with that expected for an intramolecular isotope effect.

Melander[17] has calculated that an isotope effect should be about half as strong for an Sn1 type reaction as for an Sn2 type. Although the magnitude of these calculated isotope effects is subject to great uncertainty because of the neglect of solvolytic effects, data on some reactions do show such a difference. The reaction of nucleophiles with methyl-C^{14} iodide showed isotope effects in the range $k^{14}/k^{12} = 0.88$–0.92,[18] while for the hydrolysis of 2-chloro-2-methylpropane-2-C^{14} in weakly alkaline solution, $k^{14}/k^{12} = 0.97$.[19]

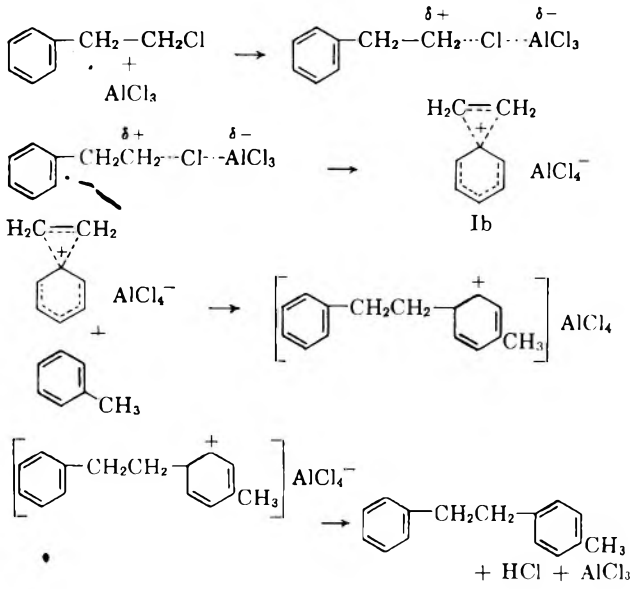
The observation of an intramolecular isotope effect in the reaction of 2-phenylethyl-1-C^{14} chloride with toluene indicates discrimination in a bond-breaking step in a symmetrical intermediate; the magnitude of this effect, $k^{14}/k^{12} = 0.92$ (calculable only approximately from these results), indicates that a nucleophilic displacement reaction of this intermediate may be involved.

The mechanism of the reaction must then be as shown in Scheme I.

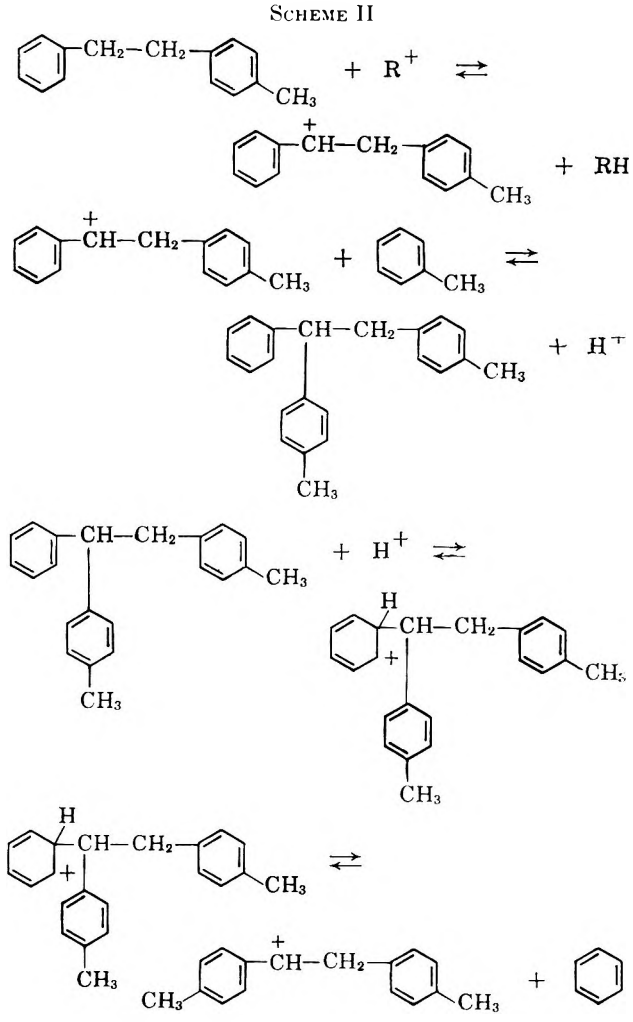
The extent of reversibility of the first step is not known. The second step must be irreversible since 2-phenylethyl-1-C^{14} chloride after contact with aluminum chloride in toluene contained no 2-phenylethyl-2-C^{14}

(15) A. Roe and M. Hellmann, *J. Chem. Phys.*, **19**, 660 (1951).
(16) G. A. Ropp and V. F. Raaen, *J. Am. Chem. Soc.*, **74**, 4992 (1952).
(17) L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1960.
(18) M. L. Bender and D. F. Hoeg, *J. Am. Chem. Soc.*, **79**, 5649 (1957); G. J. Buist and M. L. Bender, *ibid.*, **80**, 4308 (1958).
(19) M. L. Bender and G. J. Buist, *ibid.*, **80**, 4304 (1958).

SCHEME I



SCHEME II



chloride. This fact also lends support to a mechanism which involves a stabilized intermediate. If it is assumed that chloride ion becomes a relatively poor nucleophile when involved in the $AlCl_4^-$ complex, this nucleophile will be discriminated against more readily by a stabilized intermediate than by an unstabilized one. Thus the intermediate will react preferentially with toluene, and none of the recovered alkyl halide will be rearranged.

A kinetic study of the aluminum bromide-catalyzed isomerization of 2-phenylethyl-1-C^{14} bromide to 2-phenylethyl-2-C^{14} bromide in carbon disulfide by Adema and Sixma[20] led to the conclusion that the rate-determining step in this fast reaction involved the reaction of a $C_8H_9BrAlBr_3$ particle and an ion formed by ionization of $C_8H_9BrAl_2Br_6$. Their data are not inconsistent with the formulation of $C_8H_9BrAlBr_3$ as a relatively stable ion pair like Ib.

This reaction pathway is unusual in that a first ionization step is not rate determining; because of the slower reaction of the phenonium ion with toluene, the reaction should be first order in 2-phenylethyl chloride and in toluene. Attempts to study the kinetics of this reaction[14] were successful only in part, and gave no certain answer on this point. Other reactions of phenylethyl derivatives may indeed follow different pathways; both displacement[21] and rate-controlling ionization mechanisms (both to bridged[22] or to classical[23] carbonium ions) are known.

It was considered that the observed rearrangement might be attributed to an alternate mechanism involving reversible hydride transfers and alkylations. Reactions of the types involved in this reaction sequence (Scheme II) are known to take place, although they may require higher temperatures, catalyst concentrations, and reaction times.[24]

It is evident that biphenyl could be produced by a similar path. These transformations would lead to oxidation products with specific activities indicating 1,2-phenyl shifts.

The product of the reaction of 2-phenylethyl-1-C^{14} chloride with toluene was isolated by distillation; although it was free of chloride, it could not readily be crystallized and it was assayed without further purification. Examination of infrared spectra of the reaction product, of bibenzyl, of pure 4-methylbibenzyl, and of 4,4′-dimethylbibenzyl as solutions in carbon disulfide showed that there was no important amount of 4,4′-dimethylbibenzyl present in the reaction product, whose spectrum differed from that of 4-methylbibenzyl only by weak absorptions at 11.1, 12.8, and 13.9 μ which are attributable to small amounts of the *ortho* and *meta* isomers.[25]

Gas chromatography gave confirmation that no significant amounts of bibenzyl or 4,4′-dimethylbibenzyl were present in the reaction product. In a mixture of bibenzyl, 4-methylbibenzyl, and 4,4′-dimethylbibenzyl, all three components gave well-separated peaks (retention volumes 368, 572, and 810 cc., respectively) at 208° using an Apiezon M liquid phase (10% on Chromosorb P); the reaction product gave a single peak corresponding to 4-methylbibenzyl. It

(20) E. H. Adema and F. L. Sixma, *Rec. trav. chim.*, **81**, 323, 336 (1962).

(21) (a) H. Hart and H. S. Eleuterio, *J. Am. Chem. Soc.*, **76**, 516 (1954); (b) H. Hart, W. L. Spliethoff, and H. S. Eleuterio, *ibid.*, **76**, 4547 (1954).

(22) (a) D. J. Cram, *ibid.*, **74**, 2159 (1952), and earlier papers; (b) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2165 (1952), and earlier papers.

(23) C. J. Collins, W. A. Bonner, and C. T. Lester, *ibid.*, **81**, 466 (1959).

(24) (a) H. Pines and J. T. Arrigo, *ibid.*, **80**, 4369 (1958); (b) L. Schmerling, J. P. Luvisi, and R. W. Welch, *ibid.*, **81**, 2718 (1959); (c) A. Streitwieser, Jr., and L. Reif, *ibid.*, **82**, 5003 (1960); (d) A. Streitwieser, Jr., and W. J. Downs, *J. Org. Chem.*, **27**, 625 (1962); (e) E. Unseren and P. Wolf, *ibid.*, **27**, 1509 (1962).

(25) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

was estimated that 1.0% of bibenzyl or 4,4′-dimethylbibenzyl would have been detected.

It is not likely that randomization of carbon-14 in 4-methylbibenzyl could occur by processes involving reversible alkylations and be followed by the exclusive formation of 4-methylbibenzyl at equilibrium.

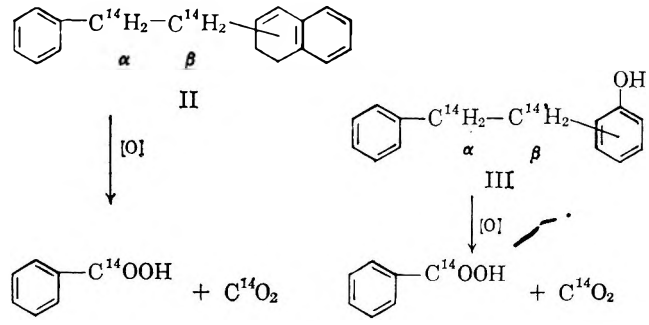
A second way in which apparent scrambling of carbon-14 between α- and β-positions might occur is represented by an intramolecular migration of both phenyl and *p*-tolyl in protonated 4-methylbibenzyl. A reaction of this type was postulated[11] to explain a partial rearrangement of *n*-propylbenzene-β-C^{14} to *n*-propylbenzene-α-C^{14}, and the interconversion of *sec*-butylbenzene and isobutylbenzene. This reaction was found to be significant, in the case of *n*-propylbenzene, only with large amounts of aluminum chloride at reflux for several hours, and it was accompanied by the formation of a relatively large amount of di-*n*-propylbenzene. At room temperature where isotopic position rearrangement of *n*-propylbenzene-β-C^{14} was slight after 6.5 hr., disproportionation was still extensive. The absence of biphenyl and bi-*p*-tolyl and the fact that the reaction products included less than 11% of higher boiling material makes it unlikely that a reaction of this type could explain the distribution of carbon-14 activity in the 4-methylbibenzyl.

The results of the alkylation of toluene with 2-(4-nitrophenyl)ethyl-1-C^{14} chloride indicate a considerably smaller contribution from a symmetrical ion, whose stability would be decreased by the electron withdrawing group. In this case, a displacement reaction or a reaction of a nonrearranging open carbonium ion (evidence from kinetic studies[26] indicates the former) competes importantly with the formation of the symmetrical intermediate.

Experiments with aluminum chloride-catalyzed alkylations of naphthalene and of phenol,[27] which preceded the study of the alkylation of toluene, indicate (although not unequivocally) that a similar mechanism obtains in these cases also.

Naphthalene reacted with 2-phenylethyl chloride sufficiently rapidly that catalysis by aluminum chloride in benzene solution at 0–5° for 30 min. gave 19% of a solid mixture of 2-phenylethylnaphthalenes, after removal of reactants and other products by reduced pressure distillation. The competing alkylation of benzene gave a large amount of bibenzyl in this case.

Chromic acid oxidation of the product (II) formed from 2-phenylethyl-1-C^{14} chloride and naphthalene converted it to benzoic acid and carbon dioxide, which was swept by a stream of nitrogen into a trap cooled by liquid nitrogen. Benzoic acid, obtained from the oxidation mixture by dilution and purified by vacuum sublimation, was found to have 48.7% of the radioactivity; the carbon dioxide, 51.3%.



The reaction of 2-phenylethyl chloride with excess phenol in the presence of catalytic amounts of aluminum chloride was accomplished only by long heating at 180–190°. After distillation of phenol from the reaction mixture, the residue was dissolved in base and precipitated by addition of acid. In a typical experiment the yield of mixed 2-phenylethylphenols (III) was 66%.

Degradation of the product of the reaction of phenol with 2-phenylethyl-1-C^{14} chloride was also accomplished by chromic acid oxidation. The purified benzoic acid contained 49.6% of the activity of the reaction product and the carbon dioxide contained 44.8%. These results are comparable with the nearly symmetrical distribution of carbon-14 in the ethane carbons found in the product of the alkylation of anisole with 2-phenylethyl-1-C^{14} chloride at intermediate temperatures,[8] which was reported after our study with phenol was initiated.

These results are those of single experiments with the labeled materials and are not precise, but they show approximately the distribution of activity which is expected if a symmetrical bridged ion is an intermediate.

It should be pointed out that in neither of these cases was it found possible to isolate unchanged 2-phenylethyl-1-C^{14} chloride under the reaction conditions, and it is therefore possible that a prior rearrangement of 2-phenylethyl-1-C^{14} chloride may have given a symmetrical distribution of activity in the ethane carbon atoms of the products.

Experimental[28]

Phenylacetic Acid-1-C^{14}.—The reaction of carbon dioxide generated from 23 mg. of $BaC^{14}O_3$ with 56 mmoles of benzylmagnesium chloride, followed by addition of inactive solid carbon dioxide gave a 78% yield (25% radiochemical yield) of phenylacetic acid-1-C^{14}.[29]

2-Phenylethanol-1-C^{14}.—Lithium aluminum hydride (10.5 g., 0.29 mole) was added to 150 ml. of ether in a 2-l. flask fitted with a stirrer, condenser, and addition funnel. A solution of 33 g. (0.244 mole) of phenylacetic acid-1-C^{14} in 350 ml. of ether was added to the slurry during 2 hr. The reaction mixture was stirred for an additional 4 hr., and the excess lithium aluminum hydride was decomposed by the dropwise addition of water, followed by 15% sulfuric acid. The clear layers were separated, and the aqueous layer was extracted with two 250-ml. quantities of ether. The ether solutions were combined and washed with saturated

(26) A kinetic study of the reaction of 2-(4-nitrophenyl)ethyl bromide with toluene in 1,2,4-trichlorobenzene catalyzed by aluminum bromide will be separately reported. The reaction exhibits marked retardation after 25–35% reaction, attributed in this case to removal of toluene by separation of the insoluble σ-complex, $CH_3C_6H_6^+Al_2Br_7^-6C_6H_5CH_3$.[9] In the early stages of the reaction the rate was shown to be proportional to the concentrations of both 2-(4-nitrophenyl)ethyl bromide and toluene. This result, together with the relatively small amount of isotope position rearrangement found in alkylation of toluene with 2-(4-nitrophenyl)ethyl chloride, suggests that the reactions of the 4-nitrophenylethyl halides follow a displacement mechanism for the greater part.

(27) This part of the work is a portion of the B.S. theses of E. Umgelter (1957) and R. Lorenz (1958) at Rensselaer Polytechnic Institute.

(28) All reactions with carbon-14 compounds were conducted first with inactive compounds. Elemental analyses for carbon were routinely performed on all samples combusted for radioassay; results agreed within 0.5% with the calculated value. Boiling points are uncorrected; melting points are corrected [S. C. Bunce, *Anal. Chem.*, **25**, 825 (1953)]. For gas chromatography, a Perkin-Elmer 154C vapor fractometer was used.

(29) W. G. Dauben, *J. Org. Chem.*, **13**, 313 (1948).

sodium chloride solution and 8% sodium bicarbonate solution. After drying over sodium sulfate, the ether was distilled, and the residual liquid was distilled at reduced pressure through a 10-in. Vigreux column. 2-Phenylethanol, 26.5 g. (85%), was collected at 110° (17 mm)., lit.[30a] b.p. 104° (14 mm.).

2-Phenylethanol-1-C^{14} (0.5 g.) was converted[31] to the phenylurethane for isotopic assay. The crude derivative was dissolved in petroleum ether (b.p. 70–90°), treated with Norit A, and filtered. After three recrystallizations, the material melted at 78.0–79.5°, lit.[30a] m.p. 79°.

2-Phenylethyl-1-C^{14} Chloride.[32]—A solution of 25 g. (0.2 mole) of 2-phenylethanol in 100 ml. of pyridine was placed in a 300-ml. flask fitted with a thermometer, addition funnel, and mechanical stirrer. The contents of the flask were cooled to 0° while 50 ml. (0.7 mole) of purified thionyl chloride was added slowly. The solution was then heated on a steam bath for 5 min., cooled to room temperature, and allowed to stand for 30 min. The reaction was quenched by the slow addition of ice–water, while the solution was cooled in an ice bath. The aqueous solution was extracted with two 300-ml. portions of ether and the ether solutions were combined and washed successively with water, dilute hydrochloric acid, saturated sodium chloride, 6% sodium bicarbonate, and water. After drying over sodium sulfate, the ether was distilled, and the residual liquid was distilled at reduced pressure through a 15-in. Vigreux column. The product, 24.5 g. (83.5%), was collected at 88° (18 mm.), n^{21}D 1.5284; lit.[30b] b.p. 91° (20 mm.), n^{20}D 1.5294.

Oxidation of 2-Phenylethyl-1-C^{14} Chloride.—2-Phenylethyl chloride (2.0 g., 0.014 moles) was added to 250 ml. of 3% potassium permanganate containing 0.5 g. of potassium hydroxide. The reaction mixture was stirred at reflux for 4 hr. The solution was cooled to room temperature, filtered, and acidified with 20 ml. of 20% sulfuric acid. The benzoic acid, 0.51 g. (29.2%), was filtered and washed with ice–water. After drying and vacuum sublimation, it melted at 121.1–122.1°. It was found to be inactive, a 2-mg. sample having 100 ± 4 c.p.m. while background was 101 ± 4 c.p.m.

Alkylation of Toluene with 2-Phenylethyl-1-C^{14} Chloride.—A solution of 6 g. (42 mmoles) of 2-phenylethyl-1-C^{14} chloride in 50 ml. of reagent grade toluene was cooled to 0° in a three-necked flask equipped for mechanical stirring and protected by drying tubes. To this solution was added 0.802 g. (5.9 mmoles) of sublimed aluminum chloride. The solution became yellow and then orange. After allowing the reaction to stir for 20 min., it was quenched by the addition of 100 ml. of ice–water. The layers were separated, and the organic layer was washed with saturated salt solution and 8% sodium bicarbonate until neutral. After drying, the toluene was distilled. The residual liquid was then distilled through a 12-in. Vigreux column. Two fractions were collected: less than 155° (13 mm.), 3.3 g.; 155–156°, 4 g., n^{20}D 1.5628.

A second run was performed in a similar manner. Two fractions were collected: less than 148° (12 mm.), 1 g.; 148–151° (12 mm.), 5 g. The highest boiling fraction was redistilled, and three fractions were collected: 137–147° (11 mm.), 2 g.; 147° (11 mm.), 2 g., n^{20}D 1.5629; 147° (11 mm.), 2 g., n^{20}D 1.5629. Pure 4-methylbibenzyl had n^{20}D 1.5635.

Alkylation of Toluene with 2-Phenylethyl-1-C^{14} Chloride and Isolation of Unchanged 2-Phenylethyl Chloride.—In a three-necked flask equipped with a mechanical stirrer and drying tubes at all openings, were placed 80 g. of toluene and 13.6 g. (96 mmoles) of 2-phenylethyl-1-C^{14} chloride. This solution was cooled to −6°. While the stirrer was in motion, 0.31 g. (2.3 mmoles) of sublimed aluminum chloride was added. The solution became a deep orange, the temperature rose to −4° and was maintained at −5° for the remainder of the reaction. After 10 min., the reaction was quenched by the addition of ice–water. The organic phase which was separated remained yellow. It was washed with two 75-ml. portions of 8% sodium bicarbonate and with water, and dried. The toluene was distilled through a 15-in. Vigreux column. Three higher boiling fractions were then collected: 105° (50 mm.), 6.5 g.; 105–130° (50 mm.), 4.3 g., $n^{21.5}$D 1.5251; 130–135° (50 mm.), 2.2 g. $n^{21.5}$D 1.5267. These were distilled again through the same column and three fractions were collected: 87° (14 mm.); 88–91° (14 mm.), $n^{22.4}$D 1.5287; 100–105° (14 mm.). The reported[30b] physical constants of 2-phenylethyl chloride are b.p. 89° (10 mm.), n^{20}D 1.5294. When the sample, b.p. 88–91° (14 mm.), was oxidized to benzoic acid, the acid was found to be inactive (3-mg. sample, 94 ± 4 c.p.m.; background, 93 ± 4 c.p.m.). The specific activity of the 2-phenylethyl chloride-1-C^{14} which was oxidized was 10.50×10^4 c.m.p./mmole.

4-Methylbibenzyl.—Benzyl *p*-tolyl ketone, m.p. 108.6–109.6° (lit.[30c] m.p. 110°), was prepared[33] in 51% yield by the reaction of benzylmagnesium chloride and *p*-tolunitrile.

A mixture of 2.1 g. (10 mmoles) of the ketone, 2.1 g. (30 mmoles of hydrazine hydrate, and 2.2 g. (30 mmoles) of potassium hydroxide in 30 ml. of diethylene glycol was slowly heated from 121 to 225° while a small amount of volatile material distilled. After 3 hr., the clear solution was cooled, diluted with water, and extracted three times with ether. The combined ether solutions were washed with dilute hydrochloric acid, dried, and distilled. The residue, 1.7 g. (87%) of crude 4-methylbibenzyl, crystallized at low temperature. Recrystallization from ethanol at 0° gave 0.7 g., m.p. 33.5–34.5°, lit.[34] m.p. 27°.

4,4′-Dimethylbibenzyl.—The oxidation of 24 g. (0.25 mole) of *p*-xylene with 33 g. (0.12 mole) of potassium persulfate[35] gave 14 g. (50%) of 4,4′-dimethylbibenzyl, m.p. 78–79° after recrystallization from ethanol, lit.[35] m.p. 80–81°.

2-(4-Nitrophenyl)ethyl-1-C^{14} Chloride.—Into a 500-ml. flask equipped with a thermometer, addition funnel, and a mechanical stirrer was placed 200 ml. of concentrated nitric acid (Sp. Gr. 1.42). This was stirred at 85–90° while 21 g. (0.15 mole) of 2-phenylethyl-1-C^{14} chloride was added over a period of 1 hr. After allowing the reaction to continue for an additional 15 min., it was poured into 600 ml. of ice–water. Water was extracted with two 250-ml. quantities of ether. The ether was washed with 8% sodium bicarbonate and saturated salt solution. After drying over sodium sulfate, the ether was evaporated; the residual orange oil was dissolved in ethanol. The oily crystals which formed on cooling were recrystallized four times from ethanol. The yield was 8.4 g. (31%), m.p. 47.0–47.3°, lit.[36] m.p. 48°.

Alkylation of Toluene with 2-(4-Nitrophenyl)ethyl-1-C^{14} Chloride.—A solution of 7.2 g. (39 mmoles) of 2-(4-nitrophenyl)ethyl-1-C^{14} chloride in 100 ml. of dry toluene was added over a 10-min. period to a slurry of 11 g. (83 mmoles) of aluminum chloride in 150 ml. of toluene. The temperature rose 1°, but remained constant thereafter. The reaction was stirred at room temperature for 2.5 hr., then quenched by the addition of ice–water. The layers were separated, the aqueous layer was extracted with 250 ml. of ether, and the combined organic layers were washed with saturated salt solution and 8% sodium bicarbonate solution. After drying over sodium sulfate, the toluene and ether were distilled and the residual liquid was distilled at reduced pressure. Three fractions were collected: 120–170° (3 mm.), 3 g.; 170–192° (3 mm.), 1. g.; 192–203° (3 mm.), 3.5 g. The highest boiling fraction was an oil at room temperature. It was crystallized in ethanol, and recrystallized eight times yielding 150 mg. of 4-nitro-4′-methylbibenzyl, m.p. 68.0–68.5°.[37]

Anal.[38] Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27. Found: C, 74.93; H, 6.03.

Oxidation of 4-Methylbibenzyl.—4-Methylbibenzyl-C^{14} (2.0 g., 0.01 mole) was added to 500 ml. of 3% potassium permanganate containing 4 g. of potassium hydroxide. This mixture was stirred at reflux for 120 hr. After cooling to room temperature, the manganese dioxide was filtered from the solution. The filtrate was acidified with 20% sulfuric acid, cooled, and filtered. The resulting crystals were washed with ice–water and air dried. The white powder was extracted with two 100-ml. quantities of carbon tetrachloride. The carbon tetrachloride was decanted and evaporated to dryness. The residue (5.3 mg.) melted at 110–117°. The original acidic aqueous solution was extracted

(30) (a) I. Heilbron and H. Bunbary, "Dictionary of Organic Compounds," Vol. IV, Oxford University Press, New York, N. Y., 1953, p. 125; (b) Vol. I, p. 500; (c) Vol. III, p. 363.

(31) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 227.

(32) C. C. Lee, M. C. Hamblin, and N. James, *Can. J. Chem.*, **36**, 1597 (1958).

(33) E. E. Turner, *J. Chem. Soc.*, **107**, 1459 (1915). We are indebted to R. Brown for this preparation.

(34) W. Mann, *Ber.*, **14**, 1645 (1881).

(35) C. Moritz and R. Wolffenstein, *ibid.*, **32**, 2531 (1899). We are indebted to S. D. Clemans for this preparation.

(36) H. Sobotka, *ibid.*, **62B**, 2191 (1929).

(37) Preparation of the nonradioactive compound, on which the analysis is reported, gave 4%, m.p. 68.5–69.0° after six recrystallizations.

(38) Analysis by Dr. G. Weiler and Dr. F. B. Strauss, Analytical Laboratory, 164 Banbury Road, Oxford, England.

with three 150-ml. quantities of carbon tetrachloride. The carbon tetrachloride was evaporated and the residue was extracted with 75 ml. of hot water. After decanting and cooling, white crystals resulted. Upon filtering and drying, 60 mg. of material melting at 110–117° was isolated. The total crude benzoic acid isolated corresponded to a 5% yield. Vacuum sublimation gave material with m.p. 119.5–121.0°.

The solid material which was insoluble in carbon tetrachloride was heated and stirred for 2 hr. in ethanol. After filtering and cooling, 0.2 g. of white crystals was isolated. An additional 0.11 g. was obtained as second and third crops. This crude yield (19%) of terephthalic acid was further purified by vacuum sublimation.

Oxidation of 4-Nitro-4′-methylbibenzyl.—To a solution of 75 ml. of saturated potassium permanganate containing 0.5 g. of potassium hydroxide was added 140 mg. (0.58 mmole) of 4-nitro-4′-methylbibenzyl-C^{14}. This mixture was stirred at reflux for 120 hr. The basic solution was acidified with 20% hydrochloric acid, filtered, and the manganese dioxide was extracted with two 50-ml. quantities of 10% sodium hydroxide. Acidification of the solution gave 15 mg. of white powder. The acidified filtrates were combined and extracted with two 200-ml. quantities of ether. The ether was evaporated to 50 ml. and extracted with 50 ml. of 10% sodium hydroxide. This yielded 30 mg. of solid material upon acidification and filtration. All of the solid material was combined and extracted with three 50-ml. portions of ether. When the ether was evaporated to dryness, approximately 2–3 mg. of oily material remained. The solid which remained after ether extraction was extracted with two 30-ml. quantities of hot ethanol. Evaporation of the ethanol extracts and cooling resulted in a first crop of white crystals (approximately 10 mg.); further concentration gave 4 mg., and evaporation to dryness yielded an additional 3 mg. of material. The first crop of crystals would not sublime, but the second two crops yielded 4 mg. of terephthalic acid after sublimation. *p*-Nitrobenzoic acid was not isolated.

Alkylation of Naphthalene.—A solution of 12.8 g. (0.1 mole) of naphthalene in 150 ml. of benzene was stirred at 0° while 13.2 g. (0.1 mole) of aluminum chloride and 14.0 g. (0.1 mole) of 2-phenylethyl-1-C^{14} chloride in 15 ml. of benzene were added. The addition required 6 min. and the mixture was stirred for a total time of 30 min. at 0–5°, then poured onto ice. The benzene layer was washed thoroughly, dried with calcium chloride, and distilled. After removal of benzene and naphthalene at reduced pressure, 1.5 g. (19%) of the product, b.p. 140–144° (2.5 mm.), was obtained. Recrystallization from alcohol and from petroleum ether to constant specific activity gave material of 132×10^3 c.p.m./mmole.

Chromic Acid Oxidation.—To a mixture of 10 ml. of water, 5.5 ml. of concentrated sulfuric acid, and 4.5 g. (15 millimoles) of potassium dichromate there was added 0.16 g. (0.7 millimole) of reaction product. Nitrogen was used to flush the lines which led to a Dry Ice-cooled water trap and a liquid nitrogen trap; after addition the mixture was heated to reflux for 3 hr. The carbon dioxide in the nitrogen trap was purified by transfers on a vacuum line then counted by proportional counting in the gas phase.[39] The activity was 61.3×10^2 c.p.m./mmole, compared with an activity of $132 \times 10^3 \div 11$, or 120×10^2 c.p.m./mmole, to be expected if all of the carbon-14 were in the β-position. After dilution, the oxidation mixture was extracted with ether and the ether solution was extracted with 10% sodium hydroxide. The benzoic acid obtained by acidification was in turn extracted with ether; after drying and removal of the solvent, two vacuum sublimations gave material of 64.2×10^3 c.p.m./mmole, compared with 132×10^3 c.p.m./mmole to be expected if all of the carbon-14 were in the α-position.

Alkylation of Phenol.—In preliminary investigations of the reaction of 2-phenylethyl chloride (0.1 mole) with phenol (0.12 mole) and aluminum chloride (0.24 mole), no reaction was noted at 25° in nitroethane, nitrobenzene, or *n*-heptane solution. Slow evolution of hydrogen chloride was noted at 180° when excess phenol was used as the solvent. A mixture of 56.5 g. (0.6 mole) of phenol, 18 g. (0.127 mole) of 2-phenylethyl-1-C^{14} chloride (282×10^3 c.p.m./mmole), and 0.3 g. of aluminum chloride was heated at 180–190° for 78 hr. After cooling, the mixture was dissolved in ether and washed with dilute hydrochloric acid. After distillation of the ether, phenol was separated by distillation from a Claisen flask (b.p. 95° at 35 mm.). The cooled solid residue was dissolved in dilute sodium hydroxide solution, washed with ether, treated with decolorizing carbon, and filtered. Addition of hydrochloric acid at 0° gave 16.8 g. (66%), m.p. 70–75°, 240×10^3 c.p.m./mmole. Both the melting point and infrared spectra indicated that this product was a mixture, including *ortho*, *para*, and probably some *meta* isomers. Oxidation with chromic acid gave carbon dioxide with activity 15.4×10^3 c.p.m./mmole, compared with an activity of $240 \times 10^3 \div 7$ or 34.3×10^3 c.p.m./mmole to be expected if all the carbon-14 were in the β-position. The acid fraction, obtained as previously described, except that sodium bicarbonate rather than sodium hydroxide was used, gave benzoic acid which, after sublimation, had m.p. 120° and an activity of 118×10^3 c.p.m./mmole.

Acknowledgment.—Support of the junior author, M. A. M., by a Sterling–Winthrop Research Institute fellowship is acknowledged with gratitude.

(39) See footnote *a* in Table I.

Anchimerically Accelerated Bond Homolysis. IV.[1] Participation of a Neighboring Olefinic Double Bond in the Decomposition of a *t*-Butyl Perester

T. W. KOENIG[2] AND J. C. MARTIN

Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

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First-order rate constants for the decompositions of a series of *o*-vinyl-substituted benzoyl peroxides and *t*-butyl perbenzoates have been determined. All compounds studied decompose faster than unsubstituted benzoyl peroxide or, in the case of the peresters, *t*-butyl perbenzoate. The accelerations are ascribed to neighboring group participation by the olefinic groups in the homolytic cleavage of the O–O bond. Solvent and substituent effects support the postulated charge separation in the transition state. Products isolated from one of the peresters and one of the peroxides are compatible with the proposed bonding interaction in the transition state leading to free-radical fragments.

Previous studies[3,4] have shown that the first-order rate constants observed in the thermal decomposition of *o*-methylthio-, *o*-iodo-, and *o*-phenylthio-substituted *t*-butyl perbenzoates are unusually large. This acceleration has been attributed to a stabilization of the transition state leading to radical intermediates by means of a bonding interaction between the perester group and the neighboring group. The postulation of charge separation in the transition state for the decomposition of the *o*-phenylthio perester has been well supported by studies of the variation in the first-order

(1) For paper III, see D. L. Tuleen, W. G. Bentrude, and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 1938 (1963).

(2) National Science Foundation Cooperative Fellowship, 1962–1963.

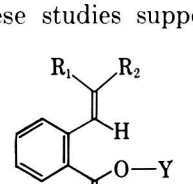
(3) W. G. Bentrude and J. C. Martin, *J. Am. Chem. Soc.*, **84**, 1561 (1962).

(4) W. G. Bentrude and J. C. Martin, *Chem. Ind.* (London), 192 (1959).

rate constants with substituents,[5] solvent ionizing power,[5,6] and ionic strength of the decomposition medium.[5]

During the course of this work Lamb and co-workers[7] reported kinetic evidence for an acceleration of the first-order decomposition of *trans*-γ-benzylidenebutyryl peroxide, presumably involving an interaction with the olefinic double bond. The rate of decomposition of this diacyl peroxide is also dependent on solvent composition, varying in a manner qualitatively correlated with solvent ionizing power. The decompositions of the *t*-butyl perester[8] and the diacyl peroxide[9] of *endo*-norbornene-5-carboxylic acid give lactone products which may be a result of some assisted cleavage of the O–O bonds.

This paper reports the synthesis and complete results of kinetic studies on the decompositions of peresters I and II, peroxides III–VIII, and the products of the decompositions of I and VI in chlorobenzene solution. The results of these studies support the previously



I, $R_1 = R_2 = C_6H_5$; Y = $OC(CH_3)_3$
II, R_1R_2C = fluorenylidene; Y = $OC(CH_3)_3$
III, $R_1 = R_2 = p\text{-}NO_2C_6H_4$; Y = $C_6H_5CO_2$
IV, R_1 = H; $R_2 = C_6H_5$; Y = $C_6H_5CO_2$
V, R_1 = H; $R_2 = m\text{-}NO_2C_6H_4$; Y = $C_6H_5CO_2$
VI, R_1 = H; $R_2 = p\text{-}NO_2C_6H_4$; Y = $C_6H_5CO_2$
VII, R_1 = H; $R_2 = p\text{-}NOC_6H_4$; Y = $p\text{-}NO_2C_6H_4CO_2$
VIII, R_1 = H; $R_2 = p\text{-}NO_2C_6H_4$; Y = $p\text{-}CH_3OC_6H_4CO_2$

mentioned[6] conclusion (for compound I) that neighboring olefinic groups can participate in the acceleration of the O–O bond cleavage in a manner formally identical with that postulated[3] for the neighboring sulfur in the decomposition of *t*-butyl *o*-(phenylthio)perbenzoate.

Experimental[10]

Materials.—The purification of chlorobenzene, pentane, pyridine, and *t*-butyl hydroperoxide and the preparation of galvinoxyl have been described.[3]

***o*-(2,2-Diphenylvinyl)benzoic Acid.**—A Grignard sequence similar to that described by DeTar[11] was used to prepare *o*-(2,2-diphenylvinyl)bromobenzene, m.p. 75–76° (63%).

Anal. Calcd. for $C_{20}H_{15}Br$: C, 71.66; H, 4.50. Found: C, 71.92; H, 4.66.

A solution of tetrahydrofuran (150 ml.) containing *o*-(2,2-diphenylvinyl)bromobenzene (80 g., 0.23 mole) was added to a flask containing tetrahydrofuran (30 ml.) and magnesium turnings (5.3 g., 0.23 g.-atom). Addition of the bromide was complete in 30 min. after the reaction was initiated and the mixture was boiled for an additional 2.5 hr. and poured into a Dry Ice–ether slurry. The acid was recrystallized from dilute acetic acid to yield 40 g., 0.14 mole, 56%, m.p. 166–168°, lit. m.p. 169°.[12] The infrared and n.m.r. spectra were identical with those of the same acid prepared in 5% yield by the method of Loewenthal and Pappo.[12] The acid chloride was prepared by refluxing the acid in excess thionyl chloride for 2 hr. (70%, m.p. 115–116.5°).

Anal. Calcd. for $C_{21}H_{13}ClO$: C, 79.14; H, 4.71. Found: C, 78.87; H, 4.96.

***t*-Butyl *o*-(2,2-Diphenylvinyl)perbenzoate (I).**—This perester was prepared by the published procedure[3] using ether solvent. Recrystallization from pentane gave a 42% yield of perester, a white solid, m.p. 74–75°.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.63; H, 6.54. Found: C, 80.84; H, 6.48.

***o*-Carboxybenzalfluorene.**—The ψ-methyl ester of *o*-phthaladehydic acid (45 g., 0.27 mole) was boiled for 12 hr. in a methanol solution of fluorene (45 g., 0.30 mole) and sodium methoxide (from 6.9 g., 0.30 g.-atom, of sodium) under nitrogen.[13] The solvent was evaporated and the residue was dissolved in water and extracted with chloroform and ether. Acidification of the aqueous phase and recrystallization of the precipitated solid from ethanol gave 55 g. (0.16 mole, 60%) of the pure acid, m.p. 187–189°.

Anal. Calcd. for $C_{21}H_{14}O_2$: C, 84.59; H, 4.79. Found: C, 84.61; H, 4.83.

The acid was converted in 73% yield to the acid chloride by boiling with thionyl chloride for 1 hr.

***t*-Butylperoxy *o*-Carboxybenzalfluorene (II).**—Treatment of the acid chloride by the same procedure gave a 16% yield of the pure perester, m.p. 76–78°.

Anal. Calcd. for $C_{25}H_{22}O_3$: C, 81.05; H, 5.99. Found: C, 80.94; H, 6.11.

***trans*-Stilbene-2-carboxylic Acid.**—This acid was prepared by the literature method[10] in 48% yield, m.p. 162.5–163° (lit.[10] m.p. 158–160°).

Wittig Reaction.—*o*-(Carbomethoxy)benzyltriphenylphosphonium bromide was prepared by the addition *o*-(carbomethoxy)-benzyl bromide to a benzene solution of triphenylphosphine. The solid phosphonium salt was added to a stirred solution of the reaction product of sodium hydride in dimethyl sulfoxide.[14] To the resulting bright orange solution was added the appropriate carbonyl compound (*p*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, or *p,p'*-dinitrobenzophenone) in solid form. The exothermic reaction resulted in a color change from orange to green. The solution was stirred under nitrogen for 2 hr., the mixture was poured onto ice–hydrobromic acid, and the precipitated mass was recrystallized. The crude yield of the methyl esters obtained in this way varied from 53–87%. These esters were converted to the acids by basic hydrolysis. The melting points and analytical data for these compounds are given in Table I. The assignment of geometry to the products isolated from these reactions, when aldehydes were used, was made on the basis of the n.m.r. spectra (*cis* isomers, doublet at τ 3.4; *trans* isomers, doublet at τ 3.1). The two isomers were found to be formed in roughly equal amounts.

Diacyl Peroxides.—The diacyl peroxides listed in Table I were prepared by addition of an acetone solution of the appropriate acid chloride to a cold aqueous solution of the appropriately substituted sodium perbenzoate. The peroxides precipitated after 15–45 min. and were filtered, washed with cold 5% aqueous bicarbonate and methanol, and recrystallized from benzene–pentane. The only exception to this procedure was that of the synthesis of *o*-(*trans*-2-phenylvinyl)benzoyl peroxide. In this case, the acid chloride was added in cyclohexane solution and stirred for 3 hr. The peroxide crystallized from the cyclohexane solution on cooling overnight.

3-Benzhydrylidenephthalide.—Phthalic anhydride (10.5 g., 0.071 mole) and diphenylacetic acid (15.0 g., 0.071 mole) were heated together with freshly fused sodium acetate (0.4 g., 0.006 mole) to 280° in a sand bath according to the general method of Weiss.[15] This temperature was maintained until water ceased to distil from the reaction vessel. The resulting brown mixture was dissolved in chloroform and extracted with 10% aqueous sodium hydroxide. The solid residue from evaporation of the chloroform was recrystallized from absolute ethanol. Chromatographic purification of this material on silica gel afforded a colorless crystalline solid, m.p. 151.5–152°, 9 g., 0.032 mole, 45%.

(5) D. L. Tuleen, J. C. Martin, and W. G. Bentrude, *J. Am. Chem. Soc.*, **85**, 1938 (1963).

(6) J. C. Martin, D. L. Tuleen, and W. G. Bentrude, *Tetrahedron Letters*, 229 (1962).

(7) R. C. Lamb, F. F. Rogers, Jr., G. D. Dean, and F. W. Voight, *J. Am. Chem. Soc.*, **84**, 2635 (1962).

(8) M. M. Martin and D. C. DeJongh, *ibid.*, **84**, 3526 (1962).

(9) H. Hart and F. J. Chloupek, *ibid.*, **85**, 1155 (1963).

(10) We thank Mr. Joseph Nemeth for the microanalysis and molecular weight determinations and Mr. Richard Johnson for n.m.r. and infrared spectra. Spectra are reproduced in full in the Ph.D. thesis of T. W. Koenig, available from University Microfilms, Inc., Ann Arbor, Mich.

(11) D. F. DeTar and L. A. Carpino, *J. Am. Chem. Soc.*, **78**, 475 (1956).

(12) H. J. E. Loewenthal and R. Pappo, *J. Chem. Soc.*, 4799 (1952).

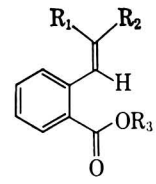
(13) E. D. Bergmann, *Bull. soc. chim.* (France), 703 (1952).

(14) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(15) R. Weiss, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 61.

TABLE I

SYNTHESIS OF



Compound	R_1	R_2	R_3	M.p., °C.	Anal., % Calcd. C	Anal., % Calcd. H	Anal., % Found C	Anal., % Found H
	p-$NO_2C_6H_4$	p-$NO_2C_6H_4$—	H—	198–199	64.61	3.61	64.55	3.77
	H	p-$NO_2C_6H_4$—	H—	207–208	66.91	4.12	66.66	4.22
	H	m-$NO_2C_6H_4$—	H—	212–214	66.91	4.12	66.54	4.19
III	p-$NO_2C_6H_5$	p-$NO_2C_6H_4$—	$C_6H_5CO_2$—	114 dec.	65.88	3.55	66.15	3.81
IV	H	C_6H_5—	$C_6H_5CO_2$—	58–59	76.73	4.68	77.01	4.84
V	H	m-$NO_2C_6H_4$—	$C_6H_5CO_2$—	114 dec.	67.86	3.88	67.67	4.14
	H	C_6H_5—	p-$NO_2C_6H_4CO_2$—	95 dec.	67.86	3.88	68.38[a]	4.25[a]
VI	H	p-$NO_2C_6H_4$—	$C_6H_5CO_2$—	114 dec.	67.86	3.88	67.95	3.86
VII	H	p-$NO_2C_6H_4$—	p-$NO_2C_6H_5CO_2$—	114 dec.	60.83	3.25	61.00	3.42
VIII	H	p-$NO_2C_6H_4$—	p-$CH_3OC_6H_8CO_2$—	110–112	65.86	4.09	66.07	4.17

[a] This compound is extremely unstable. We were, therefore, unable to obtain a sample with the desired degree of purity.

Anal. Calcd. for $C_{21}H_{14}O_2$: C, 84.55; H, 4.73. Found: C, 84.83; H, 4.69.

The ultraviolet spectrum of this material in chloroform [λ_{max} 343 mμ (log ε 4.26), 310 (4.13), and 298 (4.12)] was nearly identical with that of 3-benzylidenephthalide.[16]

3-Benzhydrylphthalide.—Crude 3-benzhydrylidenephthalide (5.0 g., 0.017 mole) was boiled for 3 hr. in a mixture of 15% aqueous potassium hydroxide (20 ml.) and 2 g.-atoms of zinc dust. After cooling and filtration, the solution was extracted with chloroform and the acidified with 20% aqueous hydrochloric acid. Recrystallization from ether–pentane gave 3 g. (0.010 mole, 59%) of the pure lactone, m.p. 149–149.5°.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 84.20; H, 5.47.

The n.m.r. spectrum of this material showed doublets at τ 5.78 and 3.78 (relative area 1) and an aromatic multiplet (relative area 14). The ultraviolet spectrum was typical of a phthalide structure [λ_{max} 282 and 275 mμ (log ε 3.20)].

3-(Diphenyl-*t*-butoxymethyl)phthalide.—Recrystallization of a sample of the perester which had stood for several weeks at room temperature gave a material which was insoluble in pentane. Recrystallization of this material from ether–pentane gave a white solid, m.p. 184°.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.63; H, 6.54. Found: C, 80.21; H, 6.45.

The structure of this material was assigned on the basis of its microanalysis and comparison of its infrared, ultraviolet, and n.m.r. spectra with those of 3-benzhydrylphthalide.

***p*-Nitrobenzylphthalide.**—A solution of *o*-[*trans*-2-(*p*-nitrophenyl)-vinyl]benzoic acid (1 g.) in 100 ml. of 10% hydrobromic acid in acetic acid was refluxed for 16 hr. Evaporation of solvent and recrystallization of the residue from ethanol gave 200 mg., 20% yield, of the pure lactone, m.p. 165–166° (lit.[17] m.p. 162–163°).

Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.90; H, 4.12. Found: C, 66.73; H, 4.17.

***p*-Nitrobenzylidenephthalide.**—The substituted benzalphthalide was prepared by the known[18] method in 22% yield, m.p. 226–227° (lit.[18] m.p. 223–223.5°).

Product Studies.—The procedures and apparatus used in the determination of products from the decomposition of this perester were similar to those described earlier.[3]

Products of the Decomposition of *t*-Butyl *o*-(2,2-Diphenylvinyl)-perbenzoate. A. Gaseous Products.—The gaseous products from decomposition of 1.02 g. (2.74 mmoles) of the perester in chlorobenzene at 90° were methane (480 ml. at 30° and 12 mm., 0.31 mmole, 11%) and carbon dioxide (less than 3%) detected by absorption on Ascarite. The methane was identified by comparison of its infrared spectrum with published A.P.I. spectrum.[19]

B. Volatile Products.—The amounts of acetone and *t*-butyl alcohol could be measured by decomposition of the perester in a sealed n.m.r. tube and determining the ratio of the area of acetone or *t*-butyl alcohol n.m.r. peaks to the total area of nonaromatic protons. The amount of acetone found in this manner from the decomposition of 0.269 mmole of perester in 0.5 ml. of chlorobenzene was 0.156 mmole or 58%. The amount of *t*-butyl alcohol was 0.073 mmole or 27%. These values were in agreement with amounts of acetone and *t*-butyl alcohol determined by n.m.r. analysis of the distillate collected by a bulb-to-bulb distillation at high vacuum.

The n.m.r. of this distillate also showed peaks attributable to toluenes. An authentic mixture of toluene and *o*-chlorotoluene in chlorobenzene gives only one peak (τ 7.78) as does a solution of *m*-chlorotoluene and *p*-chlorotoluene in chlorobenzene (τ 7.93). The total area of these two peaks either in the distillate or the crude reaction mixture corresponds to a 24% yield.

C. Nonvolatile Products.—The nonvolatile residue from the decomposition of the perester (1.09 g., 2.93 mmoles) amounted to 0.860 g. The infrared spectrum of this solid mixture in chloroform solution was very similar to that of a mixture of 3-benzhydryl- and 3-benzhydrylidenephthalides. There was very little absorption in the carbonyl region below 1750 cm.$^{-1}$. The n.m.r. spectrum of this crude product mixture shows doublets characteristic of benzhydrylphthalide (τ 3.78 and 5.68). In addition there is a sharp singlet at τ 8.86 characteristic of 3-(diphenyl-*t*-butoxymethyl)phthalide. These peaks in the n.m.r. spectrum were used to estimate the amounts of the compounds corresponding to them by using an accurately weighed internal standard (3-benzhydrylphthalide, 35%; 3-(diphenyl-*t*-butoxymethyl)phthalide, 10%). The ultraviolet absorption of the product mixture at 343 mμ was used to estimate the amount of 3-benzhydrylidenephthalide (16%, a maximum value).

Chromatographic separation of the product mixture (285 mg.) using silica gel and eluting with chloroform gave 42 mg. or 15% of pure 3-benzhydrylidenephthalide in the first fraction. This compound was identified by comparison of infrared and ultraviolet spectra and mixture melting point with an authentic sample. The succeeding fractions from the chromatographic separation had infrared and ultraviolet spectra which were very similar to those of the 3-benzhydrylphthalide, but single compounds could not be obtained from them.

3-Benzhydrylidenephthalide and 3-benzhydrylphthalide could be separated by g.l.p.c. using an Aerograph Hi Fi gas chromatograph with flame ionization detection. The column used was packed with 5% SE-30 on Chromosorb-W. This method was used to estimate the amounts of the two phthalides using an internal standard technique. The product mixture contained 15%

(16) E. D. Bergmann, *J. Org. Chem.*, **21**, 461 (1956).
(17) G. Berti, *Ann. chim.* (Rome), **51**, 675 (1961).
(18) H. G. Krey, *Pharmazie*, **13**, 619 (1958).
(19) "Catalogue of Infrared Spectral Data," American Research Institute Project 44, National Bureau of Standards, Vol. 2, No. 538.

TABLE II

KINETICS OF THE DECOMPOSITION OF PERESTER I IN CHLOROBENZENE

Run	Wave length	Scavenger concn., M	Perester concn., M	Temp., °C.	$k \times 10^4$ sec.$^{-1}$	$n/2$[a]
1	8.40 μ	None	0.06	89.8	1.16 ± 0.01	
2	8.40 μ	None	0.6	90.0	1.32 ± 0.00	
3	316 mμ	None	1×10^{-6}[d]	90.0	1.29	
4	8.40 μ	0.2, S[b]	0.06	90.0	0.86 ± 0.00	
5	8.40 μ	None	0.06	100.0	3.27 ± 0.05	
6	8.40 μ	None	0.06	115.0	13.7 ± 0.3	
7	575 mμ	1.4×10^{-3}, G[c]	1×10^{-2}	90.3	0.745 ± 0.00[d]	0.76
8	575 mμ	1.0×10^{-3}, G[c]	0.4×10^{-3}	90.4	0.985 ± 0.02	0.76
9	575 mμ	1.3×10^{-3}, G[c]	0.7×10^{-3}	105.5	4.64 ± 0.05	0.86
10	575 mμ	1.4×10^{-3}, G[c]	0.5×10^{-3}	119.3	15.4 ± 0.02	0.91
11[e]	575 mμ	1.0×10^{-3}, G[c]	0.7×10^{-3}	90.4	23	0.7
12[e]	316 mμ	None	1.5×10^{-4}	90.4	21.6	
13[f]	316 mμ	None	1.5×10^{-4}	90.0	0.35	
14[g]	316 mμ	None	1.5×10^{-4}	90.0	3.75	
15[e,g]	316 mμ	None	1.5×10^{-4}	90.0	24.7	

[a] Trapping efficiency. [b] S means styrene. [c] G means galvinoxyl. [d] $(n/2)k_d$. [e] In methanol. [f] In cyclohexane. [g] Fluorenyl perester (II).

benzhydrylidenephthalide and 33% benzhydrylphthalide as analyzed by this method.

The average molecular weight of the nondistillable residue as determined by osmometry in benzene and in chloroform was 360. This value is compatible with a mixture of 65% monomer (mol. wt., 300) and 35% dimer (mol. wt., 600). Sublimation of the product mixture (1.03 g.) gave 0.658 g. of sublimate (64%) and 0.378 g. of nonvolatile residue (36%). G.l.p.c. analysis of the sublimate showed it to contain a total of 70% 3-benzhydrylphthalide and 3-benzhydrylidenephthalide. The average molecular weight of this sublimate was 307. The average molecular weight of the residue was 700. The n.m.r. spectrum of the residue had no characteristic absorption other than the aromatic multiplet. Its infrared spectrum showed carbonyl absorption at 1760 and phthalide lactone absorption at 1290 cm.$^{-1}$. The material was not further purified.

Products of the Decomposition of Benzoyl *o*-[*trans*-2-(*p*-Nitrophenyl)vinyl]benzoyl Peroxide. A. Gaseous Products.—Decomposition of this diacyl peroxide (90 mg., 0.231 mmole) in chlorobenzene (1.8 ml.) gave 131 ml. of carbon dioxide at 27° and 8.5 mm. (0.06 mmole or 0.26 mole/mole of peroxide). Decomposition of the peroxide in a solution of 10% 1,4-cyclohexadiene in chlorobenzene gave no detectable gaseous products.

B. Nonvolatile Residue.—The peroxide (3.142 g., 8.11 mmoles) was heated at 70° for 12 hr. in a mixture of chlorobenzene (27 ml.) and 1,4-cyclohexadiene (3 ml.). Extraction of the chlorobenzene solution with aqueous sodium carbonate gave, upon acidification of the extract, *o*-[*trans*-2-(*p*-nitrophenyl)vinyl]-benzoic acid, 300 mg. (14%), m.p. 198–204 (m.m.p. 200–204°). The n.m.r. spectrum of this material showed no detectable amount of *cis* isomer.

Chloroform extractions of acidified sodium carbonate extract gave 602 mg. (62%) of benzoic acid.

Chromatography, on Fluorisil, of the product mixture from decomposition of 5.60 mmoles of peroxide gave 345 mg. (23%) of a material, m.p. 239–240°, which was assigned the structure 3-(*p*-nitrophenyl)isocoumarin on the basis of its nonidentity with the isomeric 3-(*p*-nitrobenzylidene)phthalide (m.m.p. 180–190°) and its infrared and n.m.r. spectra.

Anal. Calcd. for $C_{15}H_9NO_4$: C, 67.04; H, 3.39; N, 5.24. Found: C, 67.18; H, 3.30; N, 5.43.

A second chromatographic fraction contained a mixture of two substances which were obtained pure by fractional recrystallization from ether–pentane. One of these was shown to be 3-(*p*-nitrobenzyl)phthalide, m.p. 164–165° (m.m.p. 164–165°). The second, m.p. 149–150°, is considered to be 2-(*p*-nitrophenyl-benzoyloxymethyl phthalide.

Anal. Calcd. for $C_{22}H_{15}NO_6$: C, 67.98; H, 3.96. Found: C, 67.98; H, 3.96.

The n.m.r. spectra of these two pure components were used in the interpretation of the spectrum of the mixture in a determination of the relative amounts of the two present in the unresolved chromatographic fraction.

Methanol elution provided a further fraction with an average molecular weight (osmometric) of 558. No pure constituents of the mixture were isolated.

Kinetics.—The procedure for the kinetic runs analyzed by infrared spectroscopy was the same as that given in ref. 3 except that the frequency used was 1190 cm.$^{-1}$. The procedure for the measurement of the rate of disappearance of galvinoxyl involved degassing the solution carefully. The flask used in this procedure was fitted with a manifold which was used to distribute the solution to sample tubes which were sealed under vacuum giving twelve aliquots of the same solution, identically degassed. Blank solutions degassed as outlined previously changed in optical density by less than 3% under the conditions of the kinetic runs. Optical densities were measured at 575 and 313 mμ on a Bausch and Lomb Spectronic 505 spectrophotometer.

Results

Kinetic Studies.—The rates of decomposition of compound I were measured by the published[3] method using infrared spectroscopy, except that the wave length used was 8.40 (1190) instead of 5.68 μ (1760 cm.$^{-1}$). The rates obtained by this method follow first-order rate laws for more than three half-lives. Styrene (0.2 M) causes a decrease of 34% in the rate constant observed for the decomposition of this perester. This probably reflects the inhibition by styrene of a small amount of radical chain-induced decomposition.

The rates of decomposition of all of these *o*-vinyl-substituted peroxides were measured by ultraviolet spectroscopy using the adsorption at ~320 mμ. The rate of decomposition of compound I at 90°, measured by the latter method, agrees very well with that found by the infrared method, though there was a more than 1000-fold variation in initial perester concentration (Table II). This agreement indicates that any induced decomposition is probably first order in peroxide.

Rate constants for the decompositions of these compounds also were determined by following the decolorization (575 mμ) of the colored scavenger "galvinoxyl" which has been shown to be an efficient trap for *t*-butoxy and 2-cyano-2-propyl radicals.[20] At scavenger concentrations in excess of the minimum required to trap all of the free radicals produced by complete destruction of the peroxide, the rate law for disappearance

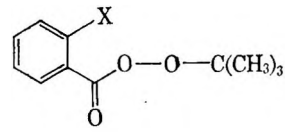
(20) P. D. Bartlett and Toshio Funahashi, *J. Am. Chem. Soc.*, **84**, 2596 (1962).

of the scavenger is pseudo first order, using a measured value for the infinity absorption, and gives a measure of R_d (the rate constant for thermal decomposition). A rate constant so obtained is free from error resulting from contributions of radical chain-induced decomposition[21] processes. Under these conditions of initial peroxide and scavenger concentrations, the total change in scavenger concentration from zero to infinite reaction times can be used to estimate the fraction of the reaction which gives scavengeable radicals (n 2).[7] The product (n 2)k_d can be determined by following the pseudo-zero-order disappearance of the scavenger in the presence of a large excess of radical source.[3,21]

The results of the kinetic studies of compounds I and II by one or more of these methods are summarized in Table II. The galvinoxyl run in methanol (run 11 in Table II) can only be regarded as semiquantitative since the scavenger reacts slowly with solvent at 90°. This reaction could not be eliminated by more elaborate degassing, but it was slow enough that the very fast disappearance of the scavenger in the presence of the perester was approximately first order for the first three half-lives.

Activation parameters and relative rates of these and related peresters are given in Table III.

TABLE III

DECOMPOSITION OF 

IN CHLOROBENZENE

ortho substituent X	Rel. rate[a] at 60°	H^*, kcal./mole	S^*, e.u.
—S-C_2H_5	2.05×10^5[b]	23.0[c]	−3.4[b]
—S-CH_3	1.41×10^5[b]	22.6[c]	−5.5[b]
—CH:$C(C_6H_5)_2$	67.0	26.3[c,d]	−5.0[c,e]
—CH:C[*o,o'*-$(C_6H_4)_2$]	200		
—I	43.4	28.0[b]	−0.8[b]
—$C(CH_3)_3$	3.0	34.2[b]	12.5[b]
—H[f]	1	34.1[g]	10.0[g]

[a] Calculated using values for H^* and S^* given in this table. [b] Determined in the absence of scavenger. [c] Determined in excess galvinoxyl. [d] ±0.7. [e] ±1.6 e.u. [f] Values from ref. 1. [g] Determined in the presence of 0.2 *M* sytrene.

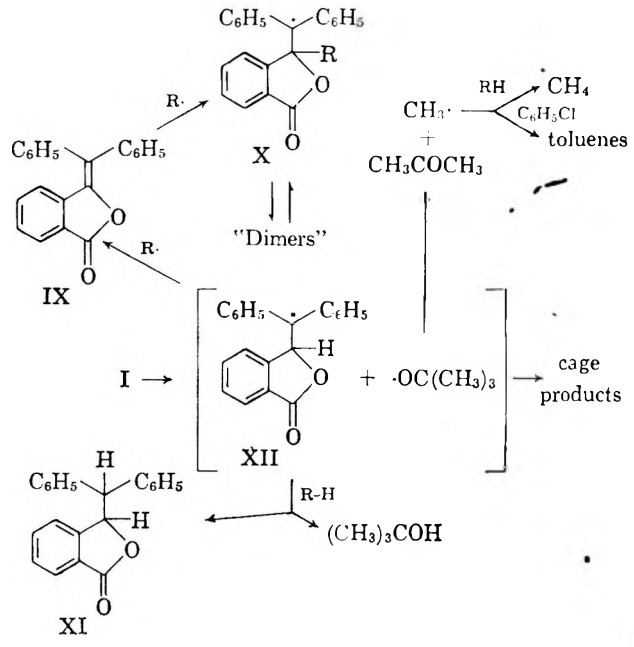
The results of kinetic studies of the diacyl peroxides (compounds III–VIII) are summarized in Table IV.

Product Studies.—The products of decomposition of *t*-butyl *o*-(2,2-diphenylvinyl)perbenzoate (I) in chlorobenzene at 90° are summarized in Table V. A similar product study for one of the diacyl peroxide decompositions is described in Table VI.

Discussion

Peresters.—The first-order rate constants observed for the decomposition of *t*-butyl *o*-(2,2-diphenylvinyl)-perbenzoate show a definite acceleration in comparison with the unsubstituted perester (a factor of ~10^3 in methanol). The entropy of activation is similar in magnitude to other *ortho*-substituted *t*-butyl perbenzoates, already investigated,[3] which undergo anchimerically accelerated decomposition. The relatively large solvent effect observed for the decomposition of this perester (faster in methanol than in cyclohexane by a factor of 62 at 90°) also is expected by analogy with these earlier studies.

CHART I



The radical nature of the intermediates is supported both by the decolorization of galvinoxyl solutions and by the products observed in the decomposition of this perester. All of the products can be explained by postulating the formation of the *t*-butoxy and benzhydrylphthalidyl radicals as intermediates in the reaction.

The presence of methane, *t*-butyl alcohol, and 3-benzhydrylphthalide can be explained as the result of the reactions of intermediate radicals which function as hydrogen abstractors. The total yield of these products is 0.75 mole/mole of perester. The toluenes and 3-benzhydrylidenephthalide can be explained as the result of the reactions of intermediate radicals which functioned as hydrogen donors. The 3-benzhydrylidenephthalide could very well function as a radical scavenger[22] giving rise to radical species which could dimerize. This "dimeric material" would then represent the final product of reactions of a compound which has functioned as a hydrogen donor. These hydrogen donor products also amount to approximately 0.75 mole/mole of perester.

It is interesting to note that an electron spin resonance (e.s.r.) signal is detected on heating to 100° a sample of compound I in chlorobenzene solution. The intensity of this signal is temperature dependent disappearing with cooling to room temperature and reappearing as the temperature is again raised to 100–140°. At temperatures greater than 140°, the signal rapidly and permanently disappears. The lack of hyperfine structure attributable to the aliphatic proton in XII suggests that the primary source of this radical is the addition of reactive radicals to IX to give X (Chart I).

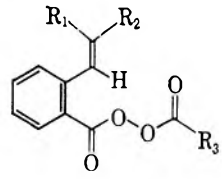
The best explanation for all these observations appears to be a bonding interaction between the perester group and the neighboring olefin in a transition state

(21) C. E. H. Bawn and D. Verdin, *Trans. Faraday Soc.*, **56**, 815 (1960).

(22) 3-Benzylidenephthalide can be copolymerized with styrene using radical initiators: D. T. Mowry (to Monsanto Chemical Co.), U. S. Patent 2,475,150 (July 5, 1949); *Chem. Abstr.*, **43**, 7753 (1949).

TABLE IV

RATES OF DECOMPOSITIONS OF



Run no.	Compound	R_1	R_2	R_3	Temp., °C.	Solvent	$k \times 10^4$ sec.$^{-1}$	k (rel.)[a]	$n/2$
16	IV	H	C_6H_5—	C_6H_5—	35.0	CH_3OH	9.77[c]	2.57×10^b	...
17		H	C_6H_5—	p-$NO_2C_6H_4$—	35.0	C_6H_5Cl	8.09[c]	2.13×10^b	0.02[d]
18	IV	H	C_6H_5—	C_6H_5—	35.0[b]	C_6H_5Cl	0.942[c]	2.48×10^g	0.13[d]
	Benzoyl peroxide				35.0	C_6H_6	0.00038[e]	1	...
19	IV	H	C_6H_5—	C_6H_5—	70.0[b]	C_6H_5Cl	30.21[f]	387	0.11[g]
20	V	H	m-$NO_2C_6H_4$—	C_6H_5—	70.0	C_6H_5Cl	1.87[f]	24	0.15[g]
21	VI	H	p-$NO_2C_6H_4$—	C_6H_5—	70.0	C_6H_5Cl	1.18 ± 04[f]	150	0.39[g]
22	VII	H	p-$NO_2C_6H_4$—	p-$NO_3C_6H_4$—	70.0	C_6H_5Cl	3.81 ± 12[f]	49	0.34[g]
23	VIII	H	p-$NO_2C_6H_4$—	p-$CH_3OC_6H_4$—	70.0	C_6H_5Cl	0.606 ± 0.008[f]	7.8	0.41[g]
24	III	p-$NO_2C_6H_4$	p-$NO_2C_6H_4$—	C_6H_5—	70.0	C_6H_5Cl	15.4	198	0.13[d]
25	VI	H	p-$NO_2C_6H_4$—	C_6H_5—	70.0	Tetrahydrofuran	0.62[h]	8.0	...
	Benzoyl peroxide				70.0	C_6H_6	0.078[e]	1	...

[a] Relative to benzoyl peroxide at the same temperature. [b] Rates at 35 and 70° allow the determination of $\Delta H^* = 20.2$ kcal./mole and $\Delta S^* = -8.7$ e.u. [c] Measured without scavenger by ultraviolet spectroscopy, 320 mμ. [d] Estimate from measurement of the change in absorbance at 575 mμ of a solution of excess galvinoxyl and peroxide after complete decomposition of peroxide (one point). [e] Extrapolated from the data of P. D. Bartlett and K. Nozaki, *J. Am. Chem. Soc.*, **68**, 1686 (1946). [f] Measured with excess galvinoxyl, *i.e.*, pseudo-first-order disappearance of scavenger at 575 mμ. [g] From the amount of galvinoxyl decolorized during the kinetic run. [h] Measured with excess peroxide, $(n/2)k_d$.

TABLE V

PRODUCTS OF THE DECOMPOSITION OF *t*-BUTYL *o*-(2,2-DIPHENYLVINYL)PERBENZOATE AT 90° IN CHLOROBENZENE (5×10^{-3} *M*)

Product	Mole/mole of perester
CO_2	0.02
CH_4	0.11
t-Butyl alcohol	0.29
Toluenes	0.24
Acetone	0.58
3-Benzhydrylphthalide	0.35 (0.59)[a]
3-Benzhydrylidenephthalide	0.16 (0.16)[a]
3-(Diphenyl-*t*-butoxymethyl)phthalide	(0.10)[b]
Dimeric material	35% by weight of the solid residue

[a] Determined by g.l.p.c. from decomposition of the perester in 10% 1,4-cyclohexadiene in chlorobenzene at 70°. [b] Inferred from the n.m.r. spectrum of the product mixture.

TABLE VI

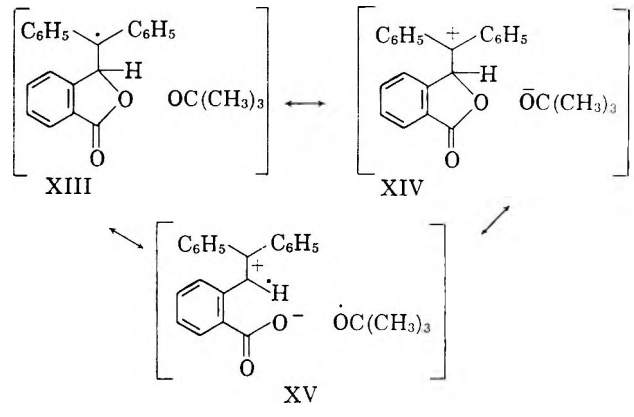
DECOMPOSITION PRODUCTS FROM BENZOYL *o*-[*trans*-2-(*p*-NITROPHENYL)VINYL]BENZOYL PEROXIDE IN 10% 1,4-CYCLOHEXADIENE IN CHLOROBENZENE AT 70°

Product	Mole/mole of peroxide
CO_2[a]	0.26
CO_2	0.02
Benzoic acid	0.62
o-[*trans*-2-(*p*-Nitrophenyl)vinyl]benzoic acid	0.14
3-*p*-Nitrophenylisocoumarin	0.23
3-*p*-Nitrobenzylphthalide	0.08
3-(*p*-Nitrophenylbenzoyloxymethyl)phthalide	0.13
Higher mol. wt. residue	25% by weight of the residue

[a] Without 1,4-cyclohexadiene.

formally identical with the one already proposed for the *o*-phenylthio, *o*-methylthio, and *o*-iodo peresters. The transition state for the decomposition of *o*-(2,2-diphenylvinyl)perbenzoate is postulated to be a dipolar singlet represented by canonical structures such as XIII, XIV, and XV (Chart II).

CHART II



XIII XIV XV

Decomposition of the fluorenylidene perester (II) is somewhat faster at 90° in chlorobenzene than that of I, but the rates are quite similar in methanol. This apparent lesser sensitivity of perester II to solvent may be interpreted as indicating that the contribution from a canonical form such as XIV is less important in the transition state for decomposition of II, reflecting its resemblance to a fluorenyl cation.

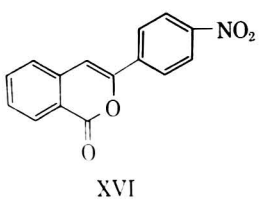
Diacyl Peroxides.—All of the peroxides of Table IV decompose faster than unsubstituted benzoyl peroxide. The fraction of the reaction which gives scavengable free radicals is rather low for compounds III, IV, and V. As mentioned in a previous publication,[3] there are several possible explanations for inefficient radical production in peroxide decompositions, all of which could apply here. The fractions of radicals trapped for compounds VI, VII, and VIII are nearer to those observed in other cases,[3,7] though they do not approach the values observed in the decomposition of the *o*-vinyl-substituted perester (I). In spite of low free-radical efficiencies observed here, the conclusion that *o*-vinyl substituents do participate in the radical decompositions of these diacyl peroxides seems valid.

The variation of solvents used as media for the decompositions of the diacyl peroxides was limited by the insolubility of many of the compounds. Compound IV shows an acceleration in its rate of decomposition of approximately ten (at 35°) on going from chlorobenzene to methanol solvent. The rates of radical production in the decomposition of VI in tetrahydrofuran and in chlorobenzene are almost identical at 70°. These solvent effects are smaller than those observed for the *o*-vinyl-substituted peresters and much less pronounced than the effect observed for the decomposition of *t*-butyl *o*-(phenylthio)perbenzoate.[5,6]

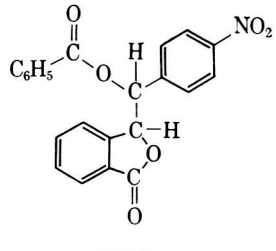
The products of the decomposition of benzoyl *o*-[*trans*-2-(*p*-nitrophenyl)vinyl]benzoyl peroxide are compatible with the proposed mechanism. The formation of carbon dioxide in the absence of cyclohexadiene and its elimination from the products in the presence of hydrogen donor are consistent with a radical decomposition. The formation of benzoic acid would be expected to result from hydrogen abstraction by benzoyloxy radical and a lower concentration of hydrogen donor would increase the importance of decarboxylation of this intermediate. The benzoic acid could, of course, also arise by an ionic path or by some secondary decomposition of initially formed products.

The *o*-substituted benzoic acid in the product mixture could have its genesis in an unassisted O–O bond cleavage to give unbridged carboxy radicals which might either abstract hydrogen or undergo ring closure to the bridged radical. The relatively small acceleration (a factor of fifteen, run 21) attributed to bridging in this reaction would make it possible to account for a part of the acid by this route. A small amount of radical chain-induced decomposition involving cyclohexadiene also might give this acid *via* decomposition of the initially formed unstable cyclohexadienyl ester.

The 3-(*p*-nitrobenzyl)phthalide is expected by analogy with the products of the perester decomposition. It is surprising that the corresponding 3-(*p*-nitrobenzylidene)phthalide was not isolated. There was meager evidence that it was present in small amount from the ultraviolet spectra of some chromatography fractions. An isomeric compound was isolated in relatively high yield. This material was shown not to be the same as the *trans*-3-(*p*-nitrobenzylidene)phthalide obtained by the literature preparation. The compound was not changed by boiling overnight in chloroform with a trace of trifluoroacetic acid, an indication that it is probably not *cis*-3-(*p*-nitrobenzylidene)phthalide. On the basis of infrared and ultraviolet spectra, the structure proposed is XVI.



XVI

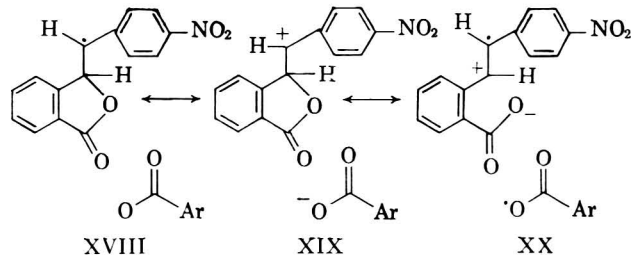


XVII

Another sharp melting compound was obtained from the product mixture after chromatography and fractional crystallization. From the twin carbonyl peaks at 1760 and 1720 cm.$^{-1}$ in the infrared spectrum, the microanalysis, and the n.m.r. spectrum, the structure proposed for this material is XVII.

The latter two products could be formed by a number of mechanisms both radical and ionic. Without more extensive studies on the formation of these products under varying conditions, any statement as to their origin is rather speculative.

Substituent Effects.—The relative rates of decomposition of peroxides IV, V, and VI in chlorobenzene at 70° correlate with σ^+-constants with a ρ of -1.8. The rates of radical production ($n/2 \cdot k_d$) for the same compounds gives a poorer correlation (ρ -1.2). The rates of decomposition of compounds VI, VII, and VIII correlate with σ-constants with a ρ of $+0.7$. The rates of radical production, $(n/2)k_d$, by the latter three compounds also correlate with the same substituent constants with a ρ of $+0.6$. Although the small value of ρ indicates a small sensitivity to substituent polarity it is significant that the sign of this reaction constant is opposite that observed for the decompositions of *meta*- and *para*-substituted benzoyl peroxides (ρ -0.4[23]) and *t*-butyl perbenzoates (ρ -0.6[24]). The positive sign is an expected result if stabilization of a negative charge on the leaving group contributes to the stability of the transition state (*i.e.*, structure XIX).



XVIII XIX XX

Greene and co-workers[25] have reported similar substituent effects in the bimolecular reactions of stilbenes and benzoyl peroxides. The reaction constant for the substituted *trans*-stilbene–benzoyl peroxide reactions is -1.0 and that for *trans*-stilbene-substituted benzoyl peroxide reactions is $+0.8$. These authors found that the rate of scavengable free-radical production with olefin present was greater than that from the peroxide alone under identical conditions. The explanation given to these observations was the formation of an olefin–peroxide complex which could give rise to radical intermediates.

The explanation given by Lamb[7] for the acceleration in the rate of decomposition of *trans*-γ-benzylidenebutyryl peroxide and its sensitivity to solvent polarity, compared to the saturated analog, involved the postulation of a structure analogous to XX for the transition state leading to free-radical formation. The substituent effects observed in the *o*-vinyl-substituted benzoyl peroxides of this work indicate that this structure cannot be the sole contributor to the transition state. At least part of the negative charge is shared by the leaving group (*i.e.*, structure XIX is also important). There is no real evidence for or against a contribution from XX.

Conclusion.—We may summarize our results by saying that *o*-vinyl substituents can participate in the

(23) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *J. Am. Chem. Soc.*, **72**, 5426 (1950).
(24) A. T. Blomquist and A. F. Ferris, *ibid.*, **73**, 3408 (1951).
(25) F. D. Greene, W. Adam, and J. E. Cantrill, *ibid.*, **83**, 3461 (1961).

homolysis of the O–O bond in *t*-butyl perbenzoates and benzoyl peroxides in a manner formally identical with that already postulated for neighboring sulfur and iodine. The 2,2-diphenylvinyl group is a better neighboring group than iodide (see Table III) but not so effective as the phenylthio group in anchimeric acceleration of perester O–O bond homolysis. Substituent effects are compatible with the postulated dipolar transition state involving a five-membered ring with a concentration of positive charge on the neighboring group involved in the displacement on oxygen and a negative charge on the oxygen leaving group (see structures XIV or XIX).

Acknowledgment.—We are indebted to the Rohm and Haas Company for a fellowship to T. W. K., 1960–1961. We thank the Alfred E. Sloan Foundation for a fellowship for J. C. M., 1962–1964. This research was supported in part by a grant from the U. S. Army Research Office, Durham, North Carolina.

Chlorination and Bromination of Alkyl *s*-Triazines

FRED C. SCHAEFER AND JOSEPH H. ROSS

Exploratory Research Department, Central Research Division, American Cyanamid Company, Stamford, Connecticut

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Liquid-phase chlorination or bromination of alkyl *s*-triazines produced exclusively α-substitution by an acid-catalyzed process regardless of the halogenation reagent used. Nuclear halogenation of mono- and dialkyl *s*-triazines does not compete. Special emphasis has been given to the development of synthetic procedures using elementary chlorine and bromine for the preparation of mono- and polyhalogenation products from trimethyl- and triethyl-*s*-triazine. The chemistry of the wide variety of products has been explored to provide an insight into their potentialities as reactive intermediates.

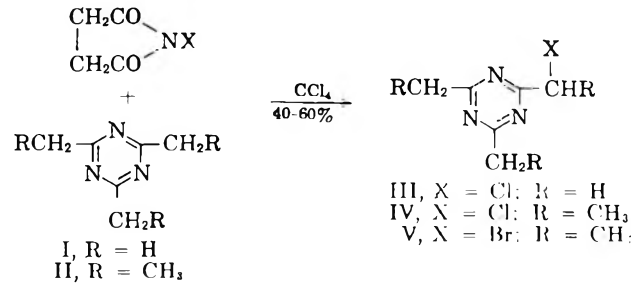
Perhaps the most promising opportunities for exploitation of the newly available alkyl *s*-triazines[1-3] lie in the study of their halogenation products. The work reported here was undertaken to explore the range of compounds which could be obtained in preparatively useful processes. Principal attention has been given to the particularly practical use of 2,4,6-trimethyl-*s*-triazine (I) and 2,4,6-triethyl-*s*-triazine (II) as substrates for chlorination or bromination, and a surprising number of different types of products has been obtained in good yield. Somewhat less work has been done with 2-alkyl *s*-triazines where unsubstituted nuclear positions are available and might have been competitive sites for halogenation. An exploratory study of the chemistry of the halogenation products was also carried out.

A substantial amount of work on the synthesis of chloro- and bromoalkyl *s*-triazines has been reported, but the bulk of this deals with compounds prepared by synthesis of the *s*-triazine system from reagents containing the halogenated alkyl group.

Only a very small number of references report the direct halogenation of an alkyl *s*-triazine group.[4] The work of Reinhardt and Schiefer, who prepared mono- and dibrominated and -chlorinated derivatives from 2-ethyl-4,6-diphenyl-*s*-triazine by direct halogenation is particularly pertinent to the present study.[5] Also significant is the reaction of 2,4-dichloro-6-methyl-*s*-triazine with elemental chlorine under rather strenuous conditions to give 2-trichloromethyl-4,6-dichloro-*s*-triazine.[6]

The halogenation of alkyl groups attached to electron-withdrawing substituents has received a great deal of attention in recent years.[7,8] The experimental work in this field provides an excellent basis for the selection of reaction procedures. The literature did not permit prediction of the reactivity of alkyl *s*-triazines, but combined with the present findings gives a satisfactory basis for interpretation of the results.

Monochlorination and Bromination.—N-Chloro- and N-bromosuccinimide (NBS) were used as halogenating agents in the initial experiments because of their wide applicability for the monosubstitution of methyl aromatics.[7,9,10] Reactions under conventional conditions were sluggish, but 2-chloromethyl-4,6-dimethyl-*s*-triazine (III), 2-(1-chloroethyl)-4,6-diethyl-*s*-triazine (IV), and 2-(1-bromoethyl)-4,6-diethyl-*s*-triazine (V) were obtained in moderate yield. Bromination of I with NBS was impractically slow. Small amounts of



I, R = H
II, R = CH_3

III, X = Cl; R = H
IV, X = Cl; R = CH_3
V, X = Br; R = CH_3

dihalogenation products were also obtained in these reactions, but it is clear that loss of the desired compounds through side reactions was the major obstacle to higher yields. It was found that III itself is surprisingly stable to N-chlorosuccinimide (NCS).

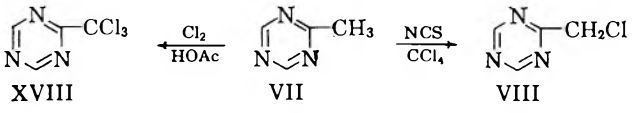
(1) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).
(2) F. C. Schaefer, *ibid.*, **27**, 3362 (1962).
(3) F. C. Schaefer, *ibid.*, **27**, 3608 (1962).
(4) Reaction of N-bromosuccinimide with 2-methyl-4,6-bisphenylamino-*s*-triazine is reported to give the bromomethyl derivative [H. K. Reimschuessel and N. T. McDevitt, *J. Am. Chem. Soc.*, **82**, 3756 (1960)]. However, it is clear from the published infrared spectrum that the product is in fact 2-(*p*-bromophenylamino)-4-methyl-6-phenylamino-*s*-triazine. See related work by C. G. Overberger and S. L. Shapiro, *ibid.*, **76**, 93, 1061 (1954).
(5) H. Reinhardt and F. Schiefer, *Chem. Ber.*, **90**, 2643 (1957).
(6) E. Kober and C. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959).
(7) See C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 8.
(8) (a) B. R. Brown, D. L. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, 1145 (1951); (b) B. R. Brown, D. L. Hammick, B. H. Thewlis, and D. J. Walbridge, *ibid.*, 1369 (1953); (c) G. M. Bennett and G. H. Willis, *ibid.*, 1960 (1928).
(9) (a) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948); (b) B. H. Walker, *J. Org. Chem.*, **25**, 1047 (1960); (c) H. Gershon, K. Dittmer, and R. Braun, *ibid.*, **26**, 1874 (1961).
(10) (a) N. P. Buu-Hoi, *Ann.*, **556**, 1 (1944); (b) A. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 2356 (1961).

Although these experiments were moderately successful, various considerations suggested that the reactions might be following predominantly an acid-catalyzed path. If such were the case, no apparent advantage could be gained with the elegant selective halogenating reagents. We therefore concentrated on the use of elemental chlorine and bromine.[11]

Direct chlorination and bromination of several alkyl *s*-triazines has proven to be an easy process. Reactions are rapid at moderate temperatures and yields of monohalogenated products have been at least equal to those obtained with N-halosuccinimides. A particular improvement was the synthesis of 2-bromomethyl-4,6-dimethyl-*s*-triazine (VI) in 50% yield. Acetic acid is an excellent medium, but successful reactions have also been carried out in chloroform or carbon tetrachloride.

Chlorination of I with an equimolar amount of chlorine in acetic acid at 55° gave mono- and dichlorinated products in approximately a 1:1 ratio. It was both interesting and useful to find that the presence of an equimolar amount of sodium acetate in the reaction mixture shifted this product ratio to 1.7:1.0 with consequent greater conversion of I. In this case the yield of III was 54% based on unrecovered I.[12] Monobromination, however, was not appreciably influenced by the presence of sodium acetate.

Chlorination of 2-methyl-*s*-triazine (VII) with NCS was sluggish but gave 2-chloromethyl-*s*-triazine (VIII) in low yield. 2-Ethyl-*s*-triazine and 2-isopropyl-*s*-triazine reacted with chlorine in hot carbon tetrachloride to give the α-chloroalkyl derivatives. In none of these cases was nuclear chlorination detectable.[13]

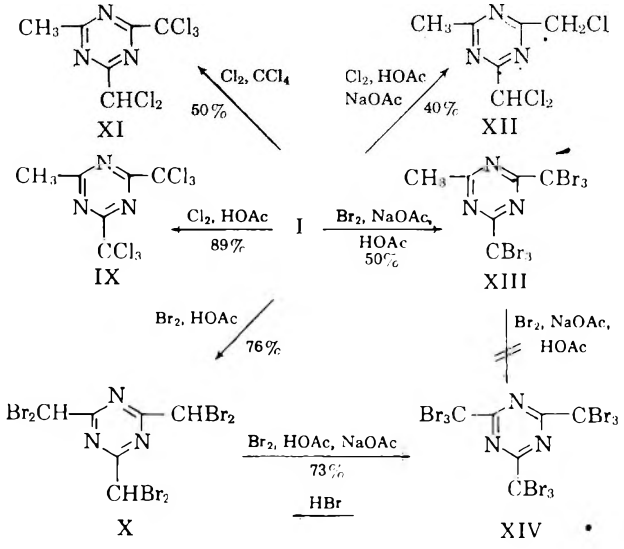


XVIII VII VIII

The halogenation of an ethyl substituent could not safely be assumed to occur exclusively at the α-carbon although this has been found to be the case. Successful reactions with I demonstrated that α-substitution was possible, but the published work on alkane nitriles and similar compounds suggested that β-attack would be probable if a free-radical mechanism were involved.[7] Reinhardt and Schiefer had reported the preparation of 2-(1-haloethyl)-4,6-diphenyl-*s*-triazines,[5] but these authors believed that dihalogenation gave the 1,2-dihaloethyl compounds. In the present work we have used n.m.r. spectroscopy and independent syntheses to obtain unequivocal proof of exclusive α-substitution in all cases, regardless of the degree of halogenation, and incidentally have found Reinhardt and Schiefer's products to be the 2-(1,1-dihaloethyl)-4,6-diphenyl-*s*-triazines.

CHART I

POLYHALOGENATION PRODUCTS FROM 2,4,6-TRIMETHYL-*s*-TRIAZINE



Polychlorination and Bromination.—The end products of the reactions of alkyl *s*-triazines with excess chlorine or bromine are strongly dependent on the reaction system used. A wide variety of products may be obtained in excellent yield. It appears that glacial acetic acid is a particularly useful reaction medium, probably acting as an acid catalyst, and substantially different results can be obtained in many cases through the inclusion of sodium acetate in the reaction mixture. Reactions are much the same in chloroform or carbon tetrachloride but are much slower.

The principal products derivable by polyhalogenation of I are indicated in Chart I.

Also useful was the formation of 2-dichloromethyl-4,6-dimethyl-*s*-triazine (XIX) and 2,4-dimethyl-6-trichloromethyl-*s*-triazine (XXII) as the major products when I reacted with about 1.7 moles of chlorine in acetic acid. By recycling by-product III and unchanged I, compounds XIX and XXII could be prepared as a mixture in high yield. By recycling XIX also, compound XXII could be obtained quite practically.

It is striking that 2-methyl-4,6-bis(tribromomethyl)-*s*-triazine (XIII) is the major product of bromination in the presence of sodium acetate, although a small amount of 2,4,6-tris(tribromomethyl)-*s*-triazine (XIV) was also isolated. It was not possible to brominate XIII further under these conditions. On the other hand, X was easily further brominated to XIV in the presence of sodium acetate.

Several additional halogenation products of I were isolated in the course of the work and are described in the Experimental section.

Bromination of II in hot acetic acid gave a nearly quantitative yield of 2,4,6-tris(1,1-dibromoethyl)-*s*-

(11) NCS probably is equivalent to free chlorine in any case [P. S. Goldfinger, P. A. Gosselain, and R. H. Martin, *Nature*, **168**, 30 (1951); K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958)].

(12) Such experiments which make evident the effects of variables on the relative rates of the successive reactions, should not be taken as optimized synthetic procedures. The relative and absolute yields of these products depend upon the extent to which conversion of I is carried. For the preparation of III, most practical results might be obtained by running the reaction at the most selective conditions to relatively low conversion and recycling unconverted I.

(13) Nuclear halogenation of the *s*-triazine ring, a highly "deactivated" system toward electrophilic reagents,[14] would be expected to be difficult if observable at all. Nevertheless, Grundmann and Kreutzberger[15] have demonstrated the formation of polyhalogenation products from *s*-triazine itself. The remarkably easy nuclear chlorination of 2-methyl- and 2,5-dimethylpyrazine reported recently[10, 16] further illustrates our inability to predict with confidence the course of such reactions. Perhalides may well occur as intermediates with unforeseeable consequences.[15,17]

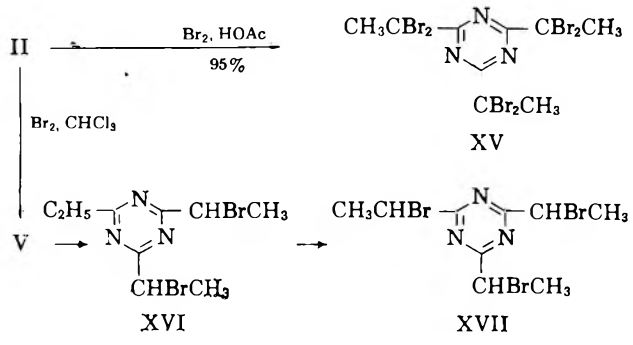
(14) L. Paoloni, *Gazz. chim. ital.*, **84**, 729 (1954).

(15) C. J. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **77**, 44 (1955); U. S. Patent 2,777,847 (1957).

(16) H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

(17) (a) R. D. Brown and R. D. Harcourt, *J. Chem. Soc.*, 3451 (1959); (b) J. Eisch, *Chem. Ind.* (London), 1449 (1959).

triazine (XV). The course of this reaction is indicated by the fact that reaction of II with an equimolar amount of bromine in chloroform gave in addition to V isolable amounts of 2,4-bis(1-bromoethyl)ethyl-*s*-triazine (XVI) and 2,4,6-tris(1-bromoethyl)-*s*-triazine (XVII), but that no 1,1-dibromoethyl derivative was detectable.



The expected product, 2-trichloromethyl-*s*-triazine (XVIII), was obtained from VII under conditions for exhaustive chlorination. Similarly the 2-(1,1-dihaloethyl)-*s*-triazines were obtained in our early work by bromination or chlorination of 2-ethyl-*s*-triazine. The yields were low in these cases, but probably can be substantially improved.

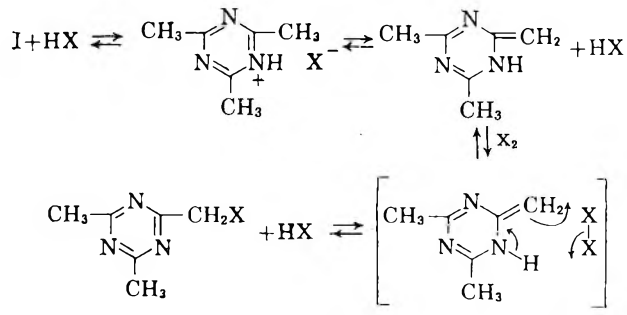
The use of n.m.r. spectroscopy was of invaluable assistance in establishing the structures of several products. The most significant features of the spectra for this purpose were the chemical shifts established as characteristic of the protons of the CH_3-, CH_2X-, and CHX_2 groups which have τ-values in the ranges 7.02–7.52, 4.15–4.56, and 3.45–3.57, respectively, measured using 10% solutions of the compounds in carbon tetrachloride.

The Mechanism of the Halogenation Reactions.— Several observations support the conclusion that free-radical processes take little part in these halogenation reactions. The reactions are essentially unaffected by ultraviolet illumination or radical catalysis but are strongly responsive to hydrohalide concentration or the presence of a base. Moreover, easy substitution at the position α to the strongly electronegative *s*-triazine ring to the exclusion of β-substitution is contrary to the observed orientation in established free-radical halogenations of other polar molecules.[7] An ionic mechanism such as these observations seem to demand and which is consistent with numerous other aspects of the reactions can be formulated along lines closely related to ketone halogenation and to the work of Brown and Hammick on quinaldine and the picolines.[8]

Regardless of the reaction conditions, the predominant halogenation process is believed to proceed by acid catalysis, perhaps following an induction period in which a slow radical reaction generates the acid. The alkyl *s*-triazine, I for example, is presumably converted to an enol analog which reacts with a halogen molecule to give the halomethyl-*s*-triazine hydrohalide, a process conveniently represented as analogous with the model for acid-catalyzed ketone bromination proposed by Newman.[18]

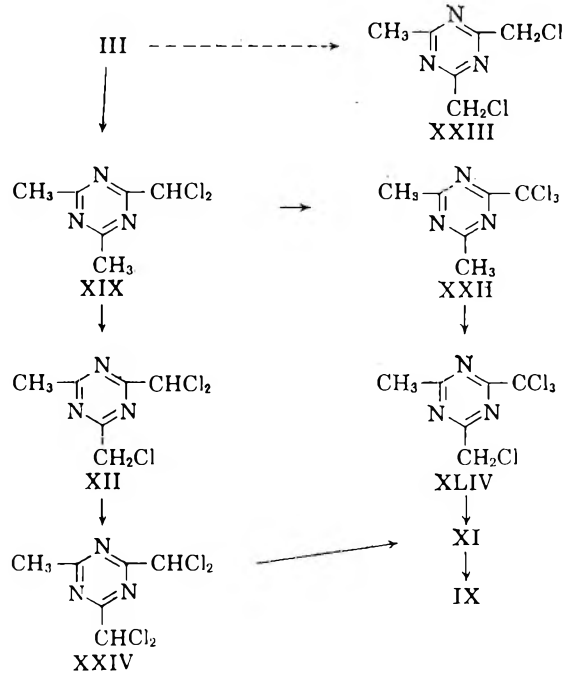
As a consequence of the greater acidity of the chloromethyl group, the predominant dichlorination product is 2-dichloromethyl-4,6-dimethyl-*s*-triazine (XIX)

(18) M. S. Newman, *J. Am. Chem. Soc.*, **73**, 4993 (1951).



under all conditions tried. However, bromination differs in that conditions of relatively high hydrogen bromide concentration tend to cause 2,4-bis(bromomethyl)-6-methyl-*s*-triazine (XX) to be the major, if not exclusive, product. This is the result of the reversibility of the dibromomethyl-*s*-triazine formation in the presence of hydrogen bromide which causes thermodynamic rather than kinetic control of the product distribution.[19] If sodium acetate is present during the reaction, the hydrogen bromide is removed and the isomeric dibromination products, XX and 2-dibromomethyl-4,6-dimethyl-*s*-triazine (XXVI), are produced in about equal amounts.

Examination of the product mixtures obtained in reactions of I with varying amounts of chlorine has made it possible to identify the predominant sequence of chlorination steps in the presence of hydrogen chloride.

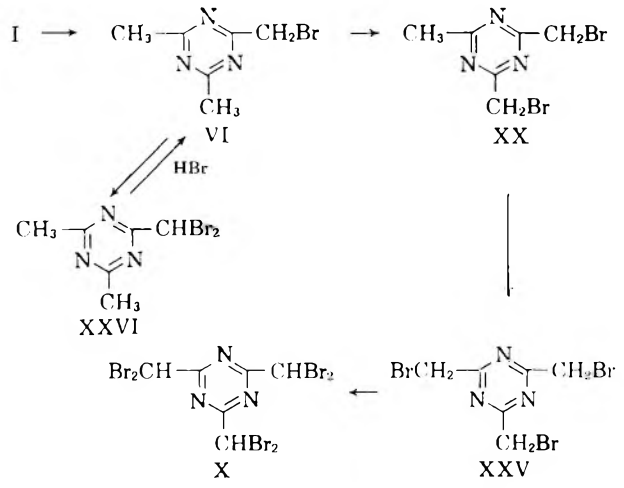


It is very clear from several experiments that the dichloro isomer, XIX, is favored over 2,4-bis(chloromethyl-*s*-triazine (XXIII) by a factor of at least ten. Further chlorination gives principally XXII, but an appreciable amount of XII is also formed despite the much greater acidity of the dichloromethyl group compared with an unsubstituted methyl group. This may be taken as evidence of appreciable steric inhibition of the XIX → XXII step. Compound XXII

(19) The analogous situation in acid-catalyzed bromination of ketones has been studied by F. Kröhnke, *et al.*, [*Ber.*, **68**, 615,921 (1936); **86**, 1559 (1953)]. In contrast, chlorination is substantially irreversible (see ref. 26).

shows more resistance to higher chlorination than does XII and can be obtained in substantial amount. Further chlorination of IX at 60° in acetic acid saturated with hydrogen chloride proceeded at a barely perceptible rate.

Bromination of I has a much stronger tendency to give at each stage the product of least "positive halogen" character.



Reaction stops at X because tribromomethyl groups are unstable in the presence of hydrogen bromide. Reaction of XIV with hydrogen bromide does, in fact, cause reduction to X.[20] Bromination of II proceeds similarly.

When chlorination of I in acetic acid is carried out in the presence of sodium acetate, the hydrogen chloride is removed as formed. Continued reaction then depends on the relatively weak catalytic effect of acetic acid rather than responding autocatalytically to a developing hydrogen chloride concentration. The reduced reaction rate is not of importance, however, except at high chlorination stages. A more important and useful consequence is a greater selectivity in the reaction as the weaker acid has less tendency to protonate the weaker *s*-triazine bases.[21] This causes an increase in the rate of chlorination of I with respect to III and is responsible for the increase in the molar ratio of mono- to dichlorination products which obtains when reaction of I with an equimolar amount of chlorine is carried out in the presence of sodium acetate. The effect is slightly greater when a threefold excess of acetate is used. In those reactions where chloroform or carbon tetrachloride was used as the medium, the starting *s*-triazine itself probably played a role analogous to that of sodium acetate in the acetic acid system. Separation of insoluble hydrohalide salts usually occurred, the reactions were sluggish, and the products were those typical of weak acid catalysis.

An additional effect of the sodium acetate is found in the ratio of the isomeric dichlorination products, XIX–XXIII, obtained when it is used. Reaction of I with an equimolar amount of chlorine in acetic acid in the absence of sodium acetate gave these by-products in a ratio of greater than 10:1. When 1 equiv. of sodium acetate was present, this ratio was about 7:1, and with 3 equiv. it was strongly reduced to 2:1. These results suggest that the acetate ion plays a part in the reaction as a basic cocatalyst, possibly facilitating the enolization step.[22] The slightly greater crowding at the chloromethyl group in III compared to a methyl group could cause the observed reduction in selectivity. The same argument can be made in connection with the more dramatic effect on the XII–XXII ratio at the trichlorination stage.

When exhaustive bromination of I was carried out in acetic acid in the presence of sodium acetate, the reaction led nearly exclusively to XIII, which is quite analogous to the work of Hammick and others,[8] with methylpyridines, quinaldines, and 2-methylquinoxaline. This result, when the reducing activity of hydrogen bromide is eliminated, is evidently equivalent to that obtained in chlorination.

The very sluggish chlorination of I to give IX in an acetic acid–sodium acetate system and the complete failure of an attempt to brominate the residual methyl group in XIII under similar conditions are reflections of the low catalytic activity of acetic acid with the less basic, highly halogenated compounds. Ready bromination of X to XIV under the same conditions is easily seen to be consistent with the expected much higher proton lability in X.

The Reactivity of 1-Haloalkyl *s*-Triazines.—The strongly electronegative character of the *s*-triazine ring is responsible for striking differences between the chemistry of the 1-haloalkyl *s*-triazines and that of the superficially similar benzyl halides. The ability of the nucleus to stabilize an α-anion is apparent in the positive halogen character of the 1-monohaloalkyl compounds, which are readily reduced by an acidic acetone solution of sodium iodide.[23]

On the other hand, reactions of SN1 type which require stabilization of a positive charge at the α-position have not been observed.[24] Such reactivity would be expected to be inhibited by the highly electrophilic character of the carbon atoms of the *s*-triazine ring.[14] Perhaps this inhibition of ionization of an α-halogen atom is responsible for the complete absence of an elimination reaction when V reacted with ethanolic potassium hydroxide. The sole product was 2-(1-ethoxyethyl)-4,6-diethyl-*s*-triazine (XXVII). Nuclear magnetic resonance spectroscopy was used to show that the product was not the isomeric 2-(2-ethoxyethyl)-*s*-triazine which could arise by base-catalyzed addition of ethanol to the expected 2,4-diethyl-6-vinyl-*s*-triazine (XXVIII). It seems reasonable to interpret this reaction as the result

(20) C. Broche [*J. prakt. Chem.*, [2]**50**, 97 (1894)] reported the preparation of XII by trimerization of tribromoacetonitrile with hydrogen chloride or hydrogen iodide. The melting point given was 129°. This compound was undoubtedly X, found in this work to melt at 129–131°; authentic XIV has m.p. 158–159°.

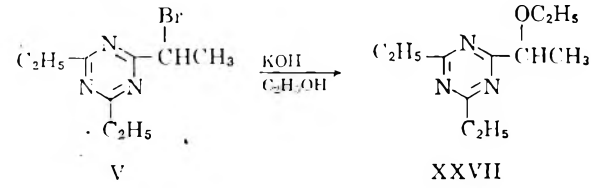
(21) This interpretation has no established precedent in ketone halogenation where the kinetics have been studied with strong acid catalysis and ketone–acid equilibration specifically discounted as a rate-determining factor [L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2785, 2791 (1939)].

(22) This is probably particularly important in the absence of a stronger acid catalyst. In the bromination of ω,ω-dibromoquinaldine under similar conditions, sodium acetate has been shown not to be involved in a rate-determining step.[14b] This difference may be ascribed to the greater protonation in acetic acid of the quinaldine derivative compared to the *s*-triazines concerned.

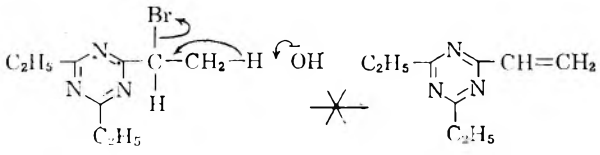
(23) S. L. Shapiro and C. G. Overberger, *J. Am. Chem. Soc.*, **76**, 97 (1954).

(24) Attempted silver ion-catalyzed hydrolysis of IX and other polyhalogenated compounds in aqueous acetic acid or ethanol were unsuccessful under conditions which are useful with α-halo derivatives of quinaldine,[8a] α-picoline,[8a] and 4-methylpyrimidine.[25] With silver nitrate incomplete halide elimination took place, but destruction of the product by the liberated nitric acid ensued. With silver acetate no reaction was obtained.

(25) H. Bredereck, W. Jentzsch, and G. Morlock, *Chem. Ber.*, **93**, 2405 (1960).



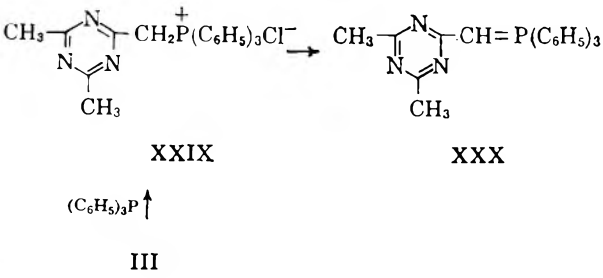
V XXVII



XXVIII

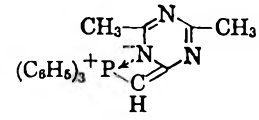
of inability of the *s*-triazine substituent to stabilize the transition state for bimolecular elimination.[26]

This reaction of V with ethanolic hydroxide takes place readily at room temperature and is an example of normal SN2 reactivity.[27] Other examples were demonstrated in the displacement of bromide ion from V by acetate ion to give 2-(1-acetoxyethyl)-4,6-diethyl-*s*-triazine, the easy reaction of 2-bromomethyl-4,6-dimethyl-*s*-triazine with pyridine to give the quaternary salt, and the reaction of 2-chloromethyl-4,6-dimethyl-*s*-triazine (III) with triphenylphosphine to give the salt XXIX.



XXIX XXX III

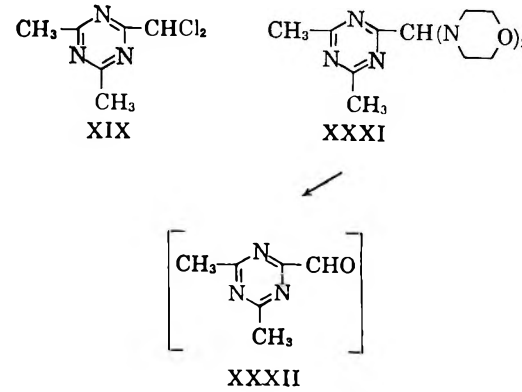
The quaternary phosphonium salt XXIX had somewhat exceptional properties. Its infrared spectrum exhibited a band at 2420 cm.$^{-1}$, believed to be the C–H stretching frequency of the acidic methylene group. This is the lowest frequency that was observed in a large group of triphenylphosphonium salts which included acylmethyl derivatives.[28] The position of this band can presumably be taken as a measure of the acidity of the methylene group. This indication is confirmed by the great ease of conversion of XXIX to the ylid XXX by aqueous sodium carbonate.[29] An unexpected result of n.m.r. study of XXX was evidence that the two methyl groups were not equivalent. Measurements at both 40 and 60 Mc. showed this was not a case of long range splitting due to the phosphorus atom. This result has led to the suggestion that the unsymmetrical structure XXXa may have considerable stability. Reaction of XXX with *p*-dimethylamino-



XXXa

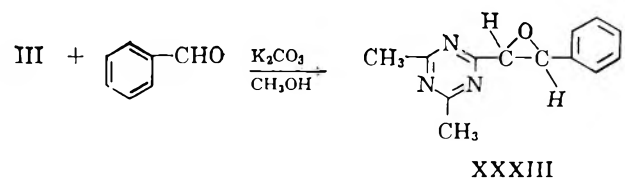
benzaldehyde was extremely sluggish, although the formation of a small amount of 2,4-dimethyl-6-(*p*-dimethylaminostyryl)-*s*-triazine was demonstrated.

Reaction of XIX with morpholine took place readily under the conditions used by Kerfanto with a variety of dihalomethyl compounds[30] to give 2,4-dimethyl-6-dimorpholinomethyl-*s*-triazine (XXXI). Hydrolysis of this product apparently proceeded normally but 4,6-dimethyl-2-*s*-triazinecarboxaldehyde (XXXII) was not recovered, probably because of solvation and high solubility in water.[31] However, XXXI is a useful generator of the aldehyde and reacted readily with thiosemicarbazide and with 2,4-dinitrophenylhydrazine to give the expected aldehyde derivatives.



XIX XXXI XXXII

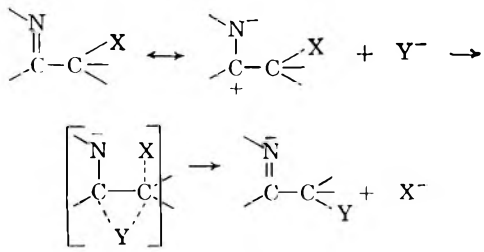
2-Choromethyl-4,6-dimethyl-*s*-triazine (III) reacted normally with benzaldehyde under the conditions of the Darzens condensation[32] to give *trans*-2-(4,6-dimethyl-2-*s*-triazinyl)-3-phenyloxirane (XXXIII).[33]



XXXIII

(26) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 420.

(27) By analogy with α-halonitriles and carbonyl compounds, enhanced SN2 reactivity would be expected in these *s*-triazine derivatives over benzyl halides because of neighboring group participation in the transition state.



It seems unnecessary to invoke an α-elimination and carbene mechanism for any of these reactions, although the potentiality for such processes in the mono- and dihalomethyl-*s*-triazines appears to be substantial.

(28) Unpublished work of Mr. N. B. Colthup and Mrs. I. Chenzoff.

(29) This is comparable to the preparation of triphenylphosphinebenzoylmethylene by F. Ramirez and S. Dershowitz [*J. Org. Chem.*, **22**, 41 (1957)].

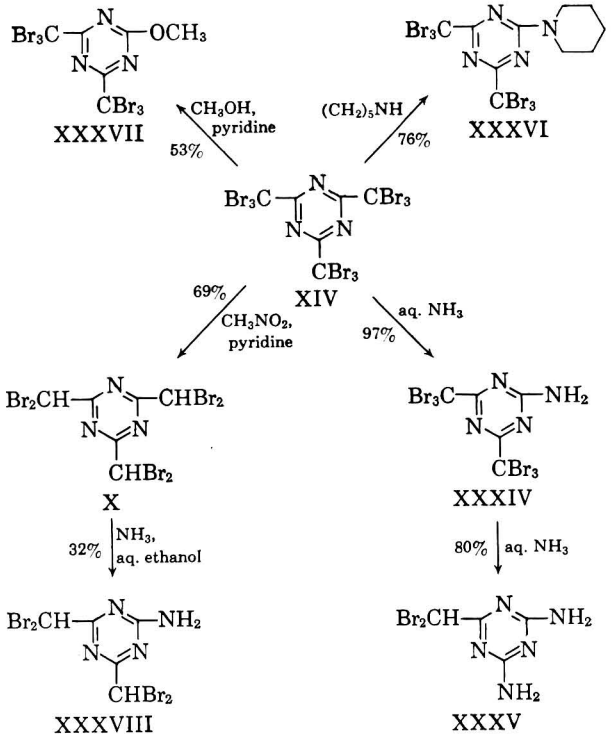
(30) M. Kerfanto, *Compt. rend.*, 493 (1962).

(31) E. Kober and C. Grundmann, *J. Am. Chem. Soc.*, **80**, 5547 (1958).

(32) (a) M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949); (b) E. Kleucker, *Ber.*, **55**, 1634 (1922).

(33) The stereochemistry of such reactions has recently been discussed [see H. Kwart and L. G. Kirk, *J. Org. Chem.*, **22**, 116 (1957), and H. Dahn and L. Loewe, *Chimia* (Aarau), **11**, 98 (1957)].

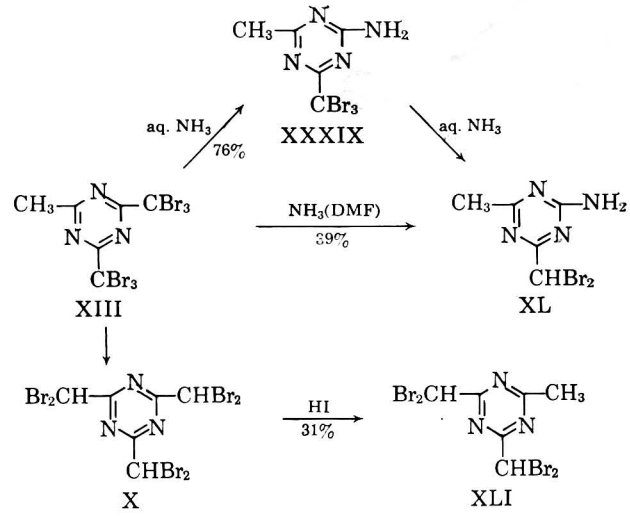
Several publications during recent years[34] have greatly enlarged much earlier reports of the reactivity of trichloromethyl-*s*-triazines. We have now found comparable reactivity in the tribromomethyl-*s*-triazines although a more complex situation arises because of easy reduction to the dibromomethyl compounds in some circumstances. Reaction of 2,4,6-tris(tribromomethyl)-*s*-triazine (XIV) with aqueous ammonia to displace one substituent is very fast at room temperature, producing the monoamine XXXIV. Further reaction was slower and accompanied by reduction, giving a high yield of 2,4-diamino-6-dibromomethyl-*s*-triazine (XXXV) as the final product. Reaction of XIV with 2 equiv. of piperidine in methoxyethanol gave only the monopiperidino-*s*-triazine, XXXVI. Displacement of a single tribromomethyl group from XIV by boiling methanol in the presence of pyridine gave XXXVII, although pyridine apparently does not catalyze such reactions with 2,4,6-tris(trichloromethyl)-*s*-triazine.[34c]



Attempts to displace a tribromomethyl group from XIV with the anions of nitromethane or malonitrile in the presence of pyridine led instead to the reduced product, *i. e.*, 2,4,6-tris(dibromomethyl)-*s*-triazine (X). Reaction of this compound with ammonia in aqueous ethanol gave the monoamine XXXVIII in low yield. 2,4,6-Tris(1,1-dibromoethyl)-*s*-triazine was unreactive toward ammonia or amines.

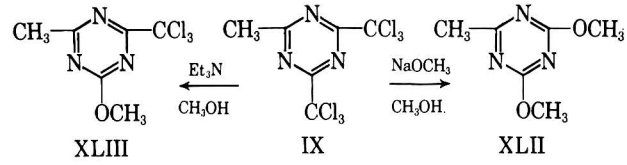
The reactions of XIII with aqueous ammonia were comparable to those observed with XIV. Displacement of one tribromomethyl group gave XXXIX and subsequent reduction gave a small amount of XL. The latter was obtained in substantial yield by reaction of XIII with ammonia in hot dimethylformamide (DMF).

An extreme example of the oxidation-reduction reactions which can occur with these polybromides is found in the unexpected reaction of XIII with dimethylformamide and 2,4-diamino-6-methyl-*s*-triazine to give X. Compound X also was reduced rapidly in a remarkable fashion by sodium iodide and acetic acid in acetone to give 2,4-bis(dibromomethyl)-6-methyl-*s*-triazine (XLI). Prolonged treatment with this reagent at room temperature caused complete reduction to I.



Reports of the efficient use of hexachloroacetone for generation of dichlorocarbene[35] led us to evaluate 2-methyl-4,6-bis(trichloromethyl)-*s*-triazine (IX) for this purpose under similar conditions. Some dichlorocarbene was obtained by reaction with sodium methoxide in cyclohexene, but the yield was only about 5%, the major product being 2-methyl-4,6-dimethoxy-*s*-triazine (XLII).

Compound XLII was also obtained by methoxide-catalyzed methanolysis of IX. The intermediate XLIII was obtained by adaptation of the method of Kober.[34c]



Experimental[36]

2-Chloromethyl-4,6-dimethyl-*s*-triazine (III). Chlorination of I with N-Chlorosuccinimide.—A mixture of 5.0 g. (0.040 mole) of I, 5.6 g. (0.040 mole) of NCS, 0.72 g. (0.003 mole) of benzoyl peroxide, and 50 ml. of carbon tetrachloride was heated at reflux for 4 hr. Filtration gave a 92% yield of succinimide. Distillation of the filtrate gave 2.3 g. of recovered I and 3.5 g. of crude III, b.p. 92–120° (20 mm.), *ca.* 60% yield based on unrecovered I. Redistillation gave a fraction boiling at 97–98° (20 mm.), $n^{25}D$ 1.5032. This was 94.5 mole % III as judged by mass spectrometry. It was essentially identical with III prepared by reaction of chloroacetamidine hydrochloride with ethyl acetimidate.[3]

Chlorination of I with Chlorine in Acetic Acid.—Chlorine (68 g., 0.96 mole) was passed into a solution of 123 g. (1.0 mole) of I in 500 ml. of glacial acetic acid at 50–55° during 1.0 hr. Anhydrous sodium acetate (1.0 mole) then was added, and the mix-

(34) (a) A. Kreutzberger, *J. Am. Chem. Soc.*, **79**, 2629 (1957); (b) H. Schroeder, *ibid.*, **81**, 5658 (1959); (c) E. Kober, *J. Org. Chem.*, **25**, 1728 (1960).

(35) (a) P. K. Kadaba and J. O. Edwards, *ibid.*, **25**, 1431 (1960); (b) F. W. Grant and W. B. Cassie, *ibid.*, **25**, 1433 (1960).

(36) Melting points are uncorrected. Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck and Dr. J. H. Deonarine. Gas-liquid chromatographic separations were carried out on a silicone column. The cooperation of Dr. R. Feinland and his associates was helpful in this aspect of the work.

TABLE I

COMPOSITION OF PRODUCT MIXTURES FROM CHLORINATION OF I IN ACETIC ACID[a]

Component of mixture	Molar ratio of chlorine to I				Molar ratio of chlorine to sodium acetate to I			
	1.0	1.3	1.7	2.5	1:1:1	1:3:1	3:3:1	4.8:9:1
I	60	46	8[b]	3	37	29		
III	19	22	29	18	37	43		
XIX	20	19	29	43	21	18	9	
XXIII		1	1	4	3	8	18	
XXII	1	11	27	16	1.4	2	9	
XII		1	5	9	<1		46	15
XXIV				3			10	14
XLIV			1	2			7	29
XI				2				28
IX								14

[a] Approximate mole % based on g.l.c. and mass spectrometry data. Acetic acid was present in all samples, but the data have been normalized to show only the s-triazine ratios. [b] An indefinite amount of I was codistilled with the acetic acid and not recovered.

ture was cooled overnight. The acetic acid solution was subsequently filtered from precipitated sodium chloride and distilled. Analysis of the total distillate by mass spectrometry gave data showing 54% recovery of starting I, a 38% yield of III (27 g.), a 39% yield of dichlorinated material (35 g.), and a 2% yield of trichloride. These yields are based on unrecovered I; the yield of III based on starting I was 17%.

Purification of III was difficult because of the close boiling points of the by-products. However, the bulk of this compound was recovered as a fraction boiling at 111–112° at 24 mm., $n^{26}D$ 1.5037, which was estimated to be 97% pure by mass spectrometry. Examination of the higher boiling fractions and comparison with authentic samples[3] by g.l.c. proved that the dichlorination product was almost exclusively 2-dichloromethyl-4,6-dimethyl-s-triazine (XIX), b.p. 123–125° at 24 mm. A distilled fraction, b.p. *ca.* 129° at 24 mm., rich in **2,4-dimethyl-6-trichloromethyl-s-triazine** (XXII) crystallized on standing. The crystals were washed with petroleum ether (b.p. 30–60°) and recrystallized from methanol or hexane to give analytically pure material, m.p. 72–74°.

Chlorination of I with Chlorine in Acetic Acid Containing Sodium Acetate.—Chlorine (40 g., 0.56 mole) was passed into a mixture of 68.5 g. (0.55 mole) of I, 45.1 g. (0.55 mole) of sodium acetate, and 150 ml. of glacial acetic acid over a period of 1 hr. while the temperature was held at 55–60°. The precipitated sodium chloride was filtered after the mixture had been chilled, and the solution was distilled. After a forerun containing only the bulk of the acetic acid, the remainder was distilled rapidly as completely as possible giving a mixture which was analyzed by g.l.c. and mass spectrometry. The yields of monochloride (III) and dichloride (XIX plus XXIII) were approximately 54% (30 g.) and 31% (22 g.), respectively, based on unrecovered I.

The yield of III based on starting I was 35% in this experiment, with 35% recovery of I. When a threefold excess of sodium acetate was used, the yield of III was 38% on the same basis and 27% of I was recovered.

Dichlorination of Trimethyl-s-triazine.—A mixture of 40.6 g. (0.33 mole) of I, 122 g. of acetic acid, and 6 g. of acetic anhydride was treated with chlorine at 55–60° until the weight increase was 42 g. Escape of hydrogen chloride was apparent toward the end of the reaction. The mixture was cooled to room temperature and 0.8 mole of sodium acetate was added slowly with cooling. After time to complete separation of the resulting sodium chloride, the mixture was diluted with an equal volume of ether and filtered. The insoluble salts were found to contain 0.60 equiv. of chloride ion, corresponding to 21.9 g. of hydrogen chloride in the reaction mixture. Taking this into account, the weight gain on chlorination corresponded to 1.7 moles of chlorine reacted per mole of I.

The filtrate from the reaction mixture was distilled after addition of 10 ml. of methanol. After a forerun containing most of the acetic acid, a 62-g. fraction was obtained, b.p. 70° (130 mm.). The distillation residue was negligible. Mass spectrometry and g.l.c. data (see Table I) showed the yields of the major products to be as follows (based on starting I): III, 22%; XIX, 22%; and XXII, 20%.

Trichlorination of Trimethyl-s-triazine.—Chlorine was passed over a stirred mixture of 40.6 g. (0.33 mole) of I, 81.2 g. (0.99 mole) of anhydrous sodium acetate, 122 g. of acetic acid, and 6 g. of acetic anhydride held at 55–60° until 69 g. (0.97 mole) had been absorbed (2.5 hr.). After cooling to room temperature the mixture was diluted with an equal volume of ether, and the insoluble salts were removed by filtration. The solution was treated with 10 ml. of methanol and distilled. A fraction was obtained, b.p. 78 (130 mm.)–135° (5 mm.), which weighed 78 g.; there was virtually no residue. This crude product, containing a small amount of acetic acid, was analyzed by mass spectrometry and by g.l.c. with the results shown in Table I. The indicated yield of **2-chloromethyl-4-dichloromethyl-6-methyl-s-triazine** (XII) was 40% based on starting I.

Separation of the products by fractional distillation was very difficult because of the closeness of their boiling points and because of decomposition during prolonged distillations. With the aid of a 24-in. spinning band column, 25 g. of XII of over 85% purity was separated, b.p. 123–125° (3.5 mm.). Material of higher purity was obtained by very slow distillation, b.p. 157° (18 mm.), but loss due to decomposition was substantial. A sample of 97% purity for mass spectrometry standardization was obtained by preparative g.l.c. The structure was confirmed by n.m.r. spectroscopy.

Miscellaneous Experiments on the Chlorination of I in Acetic Acid.—In Table I are collected data on the compositions of product mixtures obtained when the amounts of chlorine and sodium acetate used per mole of I were varied over a wide range. The reaction temperature was 50–60° and concentrations were in the range used in the preparations described above. Table II gives additional analytical data.

2-Methyl-4,6-bis(trichloromethyl)-s-triazine (IX).—Chlorine was passed into a stirred solution of 123 g. (1.00 mole) of I in 500 ml. of acetic acid at 45° until approximately 6.3 moles had reacted; the weight gain was corrected for dissolved hydrogen chloride which was determined by Volhard titration. The reaction mixture was then diluted with ice–water. The crude product was washed with water and air-dried to yield 295 g. (89%), m.p. 86–88°. Recrystallization from hexane raised the melting point to 95–96°, lit.[37] m.p. 96°. The n.m.r. spectrum of this compound consisted of a single peak at τ 7.02.

The mother liquors from several such crystallizations were combined and distilled to obtain a small amount of **2-chloromethyl-4,6-bis(trichloromethyl)-s-triazine**, b.p. 120–125° (0.1 mm.), m.p. 63–64° (from methanol).

Anal. Calcd. for $C_5H_2Cl_7N_3$: C, 19.78; H, 0.55; Cl, 68.13; N, 11.54. Found: C, 19.92; H, 0.90; Cl, 68.34; N, 11.63.

This compound was difficult to remove from IX by crystallization. It was convenient to avoid the problem by treating the crude product with excess sodium iodide in hot acetone containing a little acetic acid. This accomplishes reduction of any monochloromethyl groups to methyl[23] and gives a crude product melting at 93–95°.

In a similar preparation, most of the product IX, was crystallized from the acetic acid directly, and the mother liquor was distilled. Examination of the high boiling fraction (b.p. 140–190° at 3 mm.) by g.l.c. and mass spectrometry showed that hepta-, octa-, and nonachloro derivatives were present, totaling approximately 5–8% yield.

2-Dichloromethyl-4-methyl-6-trichloromethyl-s-triazine (XI).—Chlorine was bubbled for 2.5 hr. through a refluxing solution of 9.7 g. of I in 30 ml. of carbon tetrachloride under illumination

(37) C. Grundmann, G. Weisse, and S. Seide, *Ann.*, **577**, 77 (1952).

TABLE II

ANALYTICAL DATA FOR NUMBERED COMPOUNDS

Structure	Formula	Calcd., % C	H	N	X	Found, % C	H	N	X
IV	$C_9H_{14}ClN_3$	54.13	7.07		17.76	54.17	7.13		17.53
V	$C_9H_{14}BrN_3$	44.27	5.79	17.21	32.73	44.31	5.97	17.48	32.79
VI	$C_6H_8BrN_3$	35.66	3.99	20.80	39.55	35.47	4.08	20.93	39.74
VIII	$C_4H_4ClN_3$	37.06	3.11	32.43	27.36	37.49	3.31	32.59	27.51
X	$C_6H_3Br_6N_3$	12.08	0.51	7.04	80.37	12.28	0.50	7.28	80.02
XIII	$C_6H_3Br_6N_3$[a]	12.08	0.51	7.04	80.37	12.32	1.31	7.30	79.0
XIV	$C_6H_3Br_9$	8.65	0.00	5.04	86.31	8.84	0.10	5.10	85.95
XV	$C_9H_9Br_6N_3$	16.92	1.42	6.58	75.08	16.53	1.47	6.87	74.87
XVI	$C_9H_{13}Br_2N_3$	33.46	4.06	13.01	49.48	33.44	4.61	12.96	49.18
XVII	$C_9H_{12}Br_3N_3$	26.89	3.01	10.54	59.64	26.72	2.64	10.36	59.72
XX	$C_6H_7Br_2N_3$	25.66	2.51	14.96	56.89	26.01	2.21	14.96	56.93
XXII	$C_6H_6Cl_3N_3$	31.81	2.67	18.55		31.95	2.79	18.65	
XXIV	$C_6H_5Cl_4N_3$	27.61	1.93		54.35	27.86	2.11		54.90
XXVI	$C_6H_7Br_2N_3$	25.66	2.51	14.96	56.89	25.24	2.56	14.60	56.13
XXIX	$C_{24}H_{23}ClN_3P\cdot C_6H_6$	72.3	5.82	8.43		71.35	5.85	8.40	
XXX	$C_{24}H_{22}N_3P$	75.17	5.78	10.96	(P, 8.09)	75.12	5.78	11.10	(P, 8.18)
XXXI	$C_{14}H_{23}N_5O_2$	57.32	7.90	23.87		57.72	8.29	23.91	
XXXIII	$C_{13}H_{13}N_3O$	68.71	5.76	18.49		68.68	5.61	18.11	
XXXIV	$C_5H_2Br_6N_4$	10.05	0.34	9.38		10.58	0.96	9.95	
XXXV	$C_4H_5Br_2N_5$	16.98	1.78	24.76	56.49	17.96	1.89	24.26	54.60
XXXVI	$C_{10}H_{10}Br_6N_4$	18.04	1.51	8.42	72.03	18.15	1.80	8.71	70.80
XXXVII	$C_6H_3Br_6N_3O$	11.76	0.49	6.86	78.27	11.94	0.80	6.32	79.05
XXXVIII	$C_5H_4Br_4N_4$	13.65	0.92	12.74	72.69	13.91	1.06	12.41	72.70
XXXIX	$C_5H_5Br_3N_4$	16.64	1.40	15.53	66.44	16.90	1.86	16.18	65.09
XL	$C_5H_6Br_2N_4$	21.30	2.14	19.87	56.69	21.45	2.43	19.82	56.27
XLI	$C_6H_5Br_4N_3$[b]	16.42	1.15	9.58	72.85	17.29	1.69	9.55	71.74
XLII	$C_6H_9N_3O_2$	46.44	5.85	27.08		46.16	6.05	27.42	

[a] Mol. wt.: calcd., 596.60; found, 529, 580. [b] Mol. wt.: calcd., 438.78; found, 451.8.

from a Hanovia Type 16200 ultraviolet lamp. The reaction mixture was added to excess aqueous sodium bicarbonate and extracted with methylene dichloride. Distillation of a portion of the extract gave a colorless oil, b.p. 80–96° (0.1 mm.), from which a 7% yield of 2,4-bis(dichloromethyl)-6-methyl-*s*-triazine (XXIV) was crystallized, m.p. 82–86°. The crude product extracted by methylene dichloride was reduced with sodium iodide–acetic acid in acetone[23] to remove monochloromethyl groups. It was then washed with aqueous sodium bisulfite, extracted with ether, and treated with excess concentrated aqueous ammonia in a little ethanol.[38] **2-Amino-4-dichloromethyl-6-methyl-*s*-triazine** crystallized directly from the reaction mixture; the crude yield was 50%, m.p. 160–170°, based on the original I used. After recrystallization from ethanol the product melted at 173–174°. The n.m.r. spectrum of this compound was essentially identical with that of XL.

Anal. Calcd. for $C_5H_6Cl_2N_4$: Cl, 36.74; N, 29.03. Found: Cl, 37.09; N, 28.97.

Collected samples of 2,4-bis(dichloromethyl)-6-methyl-*s*-triazine (XXIV) from similar examples were recrystallized from ethanol and hexane for analysis, m.p. 86–87°. This compound was unaffected by aqueous alcoholic ammonia under the conditions above and did not react with acidified sodium iodide.

2-Bromomethyl-4,6-dimethyl-*s*-triazine (VI).—A solution of 1.0 mole of I in 500 ml. of glacial acetic acid was held at 60° while 1.0 mole of bromine was added dropwise during 15 min. The mixture was then cooled to 25° and 1.0 mole of sodium acetate was added. The precipitated salt was removed by filtration and the filtrate was distilled. Analysis of the total distillate by g.l.c. indicated approximately a 20% recovery of I and 50 and 12% yields of VI and XX, respectively, based on unrecovered I. Virtually no XXVI was obtained. Fractional redistillation gave 80 g. (0.40 mole) of VI, b.p. 93–95 (10 mm.), $n^{25}D$ 1.5304. Mass spectrometry showed this material to be 99.5% pure.

A 26-g. fraction of higher bromination products boiling at 61–126° at 0.5 mm. was also obtained. Partial crystallization of this material gave 17 g. of XX, m.p. 54–57°.

When bromination was carried out under the conditions above but with an equimolar amount of sodium acetate present, VI was obtained in about the same yield, 46% based on starting I. However, both XX and XXVI were obtained, their respective fields being 9 and 12%.

Bromination of 2-Bromomethyl-4,6-dimethyl-*s*-triazine.—Reaction of VI with 0.5 mole of bromine per mole in boiling carbon tetrachloride gave a mixture of the isomeric dibromo compounds. There was some decomposition during the isolation procedure, but the ratio of recovered XXVI to XX was approximately 4:1. Perhaps this does not correctly represent the original product ratio.

2-Dibromomethyl-4,6-dimethyl-*s*-triazine (XXVI) boiled at 74–75° (0.2 mm.), $n^{27.5}D$ 1.5652, m.p. 20°. This compound was confirmed by its n.m.r. spectrum.

2,4-Bis(bromomethyl)-6-methyl-*s*-triazine (XX) had b.p. *ca.* 100° (0.5 mm.), m.p. 58–59° from ethanol or hexane. The n.m.r spectrum of this compound was consistent with the structure assigned.

2,4,6-Tris(dibromomethyl)-*s*-triazine (X).—Bromine (180 ml., 3.5 moles) was added in 45 min. to 62 g. (0.50 mole) of I in 600 ml. of acetic acid at 60°. The resultant mixture was filtered cold and the product was washed with acetic acid and ethanol and dried in air to yield 230 g. (76%), m.p. 125–129°. Recrystallization from acetonitrile gave m.p. 129–131°, lit.[39] m.p. 127–129°.

2-Methyl-4,6-bis(tribromomethyl)-*s*-triazine (XIII).—A mixture of 61.5 g. (0.50 mole) of I, 410 g. (5.0 moles) of sodium acetate, and 1000 ml. of acetic acid was heated to 70°, and 225 ml. (5.0 moles) of bromine was added gradually (65 min.). The mixture was heated for an additional hour at 90°, cooled, diluted with water, and allowed to stand overnight. The crystalline product was washed with water and air-dried, yielding 210 g., m.p. 120–150°. Recrystallization from acetonitrile gave 105 g., m.p. 157–158.5° (35% yield). Examination of the mother liquors by infrared showed that XIII and 2,4,6-tris(tribromomethyl)-*s*-triazine (XIV) were both present in substantial amount. After tedious recrystallizations XIV was isolated in approximately 6% yield, m.p. 152–155° and an additional 15% of XIII was recovered.

The n.m.r. spectrum of XIII showed a single proton peak which had very nearly the same chemical shift (τ 7.04) as that for 2-methyl-4,6-bis(trichloromethyl)-*s*-triazine.

(38) This reactivity of the trichloromethyl-*s*-triazine structure is well defined by A. Kreutzberger [*J. Am. Chem. Soc.*, **79**, 2629 (1957)]. We find that XXIV is inert under these conditions.

(39) E. Ghigi, *Gazz. chim. ital.*, **71**, 641 (1941).

On long standing, the aqueous acetic acid solution from the reaction mixture deposited crystals of 2-acetoxymethyl-4,6-bis(tribromomethyl)-*s*-triazine, m.p. 142–144° (from cyclohexane).

Anal. Calcd. for $C_8H_3Br_6N_3O_2$: C, 14.68; H, 0.77; Br, 73.24; N, 6.42. Found: C, 15.01; H, 1.00; Br, 72.8; N, 6.43.

2,4,6-Tris(tribromomethyl)-*s*-triazine (XIV).—A mixture of 216 g. (0.36 mole) of X, 178 g. (2.17 moles) of sodium acetate, and 1450 ml. of acetic acid was stirred at 109°, and 84 ml. (1.63 moles) of bromine was added over a period of 20 min. Heating was continued for an additional hour. The product which crystallized rapidly was collected after cooling, washed with acetic acid and water, and air-dried. The crude yield was approximately quantitative, m.p. 140–160°. Recrystallization from acetonitrile gave a 73% yield of material melting at 156–159°. The analytical sample had m.p. 158–159° (heptane).

N.m.r. and infrared examination of XIV confirmed the absence of hydrogen atoms.

Reduction of 2,4,6-Tris(tribromomethyl)-*s*-triazine.—Hydrogen bromide was passed into a solution of XIV in chloroform at 25° for 6 hr. Bromine production was evident. The solution was evaporated and the residue was triturated with petroleum ether. The crystalline product was then washed with ethanol and air-dried. The yield of 2,4,6-tris(dibromomethyl)-*s*-triazine, m.p. 119–125°, was 50%. This material was essentially identical with analytically pure X by infrared examination.

2-(1-Chloroethyl)-4,6-diethyl-*s*-triazine (IV).—Chlorine (0.10 mole) was passed into a solution of 0.10 mole of II in 30 ml. of carbon tetrachloride at 60–65°. After a brief holding period, the mixture was cooled and run into an excess of aqueous bicarbonate. The organic phase was separated, dried with potassium carbonate, and rapidly distilled as completely as possible. Analysis of the total distillate by g.l.c. showed approximately 17% recovery of II and a 58% yield of IV. Dichlorination products amounted to 10%. Yields are based on unrecovered II.

Distillation of a larger quantity of similar crude IV gave material boiling at 70° (1 mm.), $n^{25}D$ 1.4850.

2-(1-Bromomethyl)-4,6-diethyl-*s*-triazine (V).—Bromine (1.0 mole) was added dropwise during 1.5 hr. to a solution of 1.0 mole of II in 500 ml. of chloroform. The mixture was held at gentle reflux during most of the addition. There was no apparent evolution of hydrogen bromide, and the solution remained clear. (Reaction in carbon tetrachloride led to a gummy mass.) The reaction mixture was treated with aqueous carbonate, and the organic phase was separated. Distillation after drying gave 35 g. (0.21 mole) of recovered II, b.p. 68–72° (7 mm.), and 122 g. (0.50 mole) of V, b.p. 98–100° (4 mm.), $n^{25}D$ 1.5065.

From the higher boiling fractions were recovered 37 g. (0.11 mole) of **2,4-bis(1-bromoethyl)-6-ethyl-*s*-triazine (XVI)**, b.p. *ca.* 95° (0.22 mm.), $n^{25}D$ 1.5412; and 3.0 g. of **2,4,6-tris(1-bromoethyl)-*s*-triazine (XVII)**, b.p. *ca.* 110° (0.2 mm.). The latter compound crystallized on cooling and after recrystallization from petroleum ether melted at 53.5–55°.

No material having a $-CBr_2CH_3$ group could be detected in the fractions containing the dibromo compound above by n.m.r. spectroscopy.

2,4,6-Tris(1,1-dibromoethyl)-*s*-triazine (XV).—To a solution of 83 g. (0.50 mole) of II in 500 ml. of acetic acid at 42° was added 105 ml. of bromine. Because reaction did not begin spontaneously, a small portion of the reaction mixture was removed and heated to about 70°. This caused a vigorous reaction, after which the material was returned to the main portion where exothermic reaction began quickly. The temperature rose spontaneously to 70° and hydrogen bromide was evolved liberally. The remainder of 205 ml. of bromine (4.0 moles) was added in portions over the following hour, the temperature remaining at 65–70°. The mixture was filtered after cooling, and the product was washed with acetic acid, ethanol, and water. The crude material weighed 302 g. (95%), m.p. 122–126°. Recrystallization from acetonitrile, ethanol, and heptane gave an analytical sample melting at 133–134°.

2-Chloromethyl-*s*-triazine (VIII).—2-Methyl-*s*-triazine and N-chlorosuccinimide (9.08 mole each) were heated in 100 ml. of boiling carbon tetrachloride in the presence of benzoyl peroxide (2.5 mmoles added in several portions) for 10 hr. Reaction was incomplete. The solution was then cooled and filtered. Fractional distillation gave 2.3 g. of VIII, b.p. 43–46° (0.5 mm.), in 22% yield. This material was identical by infrared comparison with VIII prepared by reaction of 2-chloroacetamidine hydrochloride with *s*-triazine.[40]

This compound is a severe skin irritant and has poor storage stability.

2-(1-Chloro-1-methylethyl)-*s*-triazine was prepared by passing 0.20 mole of chlorine into a solution of 0.40 mole of 2-isopropyl-*s*-triazine[41] in 200 ml. of carbon tetrachloride at 65–78°. The yield was 20 g., 64% based on chlorine, b.p. 70–74° (10 mm.), $n^{25}D$ 1.4965.

Anal. Calcd. for $C_6H_8ClN_3$: C, 45.72; H, 5.12; Cl, 22.50; N, 26.66. Found: C, 45.71; H, 5.57; Cl, 22.20; N, 26.76.

2-Trichloromethyl-*s*-triazine[42] (XVIII) was obtained in 22% yield by reaction of VII with excess chlorine in acetic acid containing acetic anhydride at 100°.

2-(1-Chloroethyl)-*s*-triazine and 2-(1,1-dichloroethyl)-*s*-triazine were obtained in approximately 10 and 18% yields, respectively, when 0.5 mole of chlorine per mole was passed into a carbon tetrachloride solution of 2-ethyl-*s*-triazine at 50–70° over a 1-hr. period.

2-(1-Chloroethyl)-*s*-triazine boiled at 93° (29 mm.), $n^{25}D$ 1.5047. Its infrared spectrum was identical with that of a sample prepared in 37% yield by the reaction of *s*-triazine with 2-chloropropionamide hydrochloride.[42]

2-(1,1-Dichloroethyl)-*s*-triazine boiled at 83–84° (10 mm.), $n^{24}D$ 1.5195. This product was spectroscopically identical with a sample obtained in 24% yield as a by-product from the reaction of *s*-triazine with 2-chloropropionamidine hydrochloride. Gas–liquid chromatography showed the compound to be approximately 96% pure. Its identity was confirmed by mass spectrometry and n.m.r. spectroscopy.

2-(1,1-Dibromoethyl)-*s*-triazine was recovered in 9% yield after reaction of 2-ethyl-*s*-triazine with bromine in hot acetic acid, b.p. 110–112° (10 mm.), $n^{24}D$ 1.5803.

Anal. Calcd. for $C_5H_5Br_2N_3$: C, 22.50, H, 1.88; Br, 59.88; N, 15.74. Found: C, 23.02; H, 2.04; Br, 59.31; N, 15.31.

2-(1-Ethoxyethyl)-4,6-diethyl-*s*-triazine (XXVII).—Reaction of V (22.8 g., 0.092 mole) with an equivalent amount of potassium hydroxide in ethanol at 25–35° for 2 hr. gave about 90% of the theoretical amount of potassium bromide. Distillation of the solution gave as the major fraction 7.4 g., b.p. *ca.* 122° (15 mm.), $n^{25}D$ 1.4728. Mass spectrometric analysis indicated that this was chiefly 2-(1-ethoxyethyl)-4,6-diethyl-*s*-triazine with some of the original bromide present; 2,4-diethyl-6-vinyl-*s*-triazine could not be detected. Examination by n.m.r. spectroscopy confirmed that this material was a 3:1 mixture of XXVII and V. In further confirmation of this result, **2-(2-ethoxyethyl)-4,6-diethyl-*s*-triazine** was prepared by reaction of 2,4-diethyl-6-vinyl-*s*-triazine[43] with ethanol containing a catalytic amount of sodium ethoxide, b.p. 120–125° (12 mm.). The structure of this product and its nonidentity with XXVII were established by infrared spectroscopy, n.m.r. examination, and mass spectrometry (*ca.* 99% purity indicated).

2-(1-Acetoxyethyl)-4,6-diethyl-*s*-triazine.—A mixture of 299 g. (1.23 moles) of V, 151 g. (1.84 moles) of anhydrous sodium acetate, 307 ml. of glacial acetic acid, and 25 ml. of acetic anhydride was heated at reflux for 18 hr. After hot filtration to remove the precipitated potassium bromide (94%), potassium iodide (12 g., 0.073 mole) was added and the mixture was heated at 90° for 30 min. to reduce residual V to triethyl-*s*-triazine (the acetate and V are very difficult to separate by distillation). Water and ether were then added, and the mixture was neutralized with sodium hydroxide and sodium carbonate. The ether phase was separated, dried, and distilled. The product acetate, collected at 139–146° (19 mm.), weighed 180 g. (68.5%). Redistillation gave material boiling at 96.0–96.5° (3 mm.), $n^{25.5}D$ 1.4670.

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.68; N, 18.82. Found: C, 59.27; H, 7.82; N, 18.64.

Mass spectrometric analysis showed the product to be free of compound V.

(4,6-Dimethyl-2-*s*-triazinyl)methylpyridinium Bromide.—Reaction of VI with a 50% excess of pyridine in acetone solution at room temperature for 4 hr. gave a 70% yield of the crystalline pyridinium salt, m.p. 199–202°. Recrystallization from acetonitrile gave material melting at 204–206°.

Anal. Calcd. for $C_{11}H_{13}BrN_4$: C, 46.99; H, 4.66; N, 19.93; Br, 28.42. Found: C, 47.36; H, 4.78; N, 19.62; Br, 28.71.

(40) Prepared by Dr. K. R. Huffman using the general method of ref. 42.

(41) Prepared by the general method of ref. 42, b.p. 153°, $n^{25}D$ 1.4684. *Anal.* Calcd. for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.40; H, 7.27; N, 34.05.

(42) F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

(43) The synthesis of this compound will be reported separately.

(4,6-Dimethyl-2-*s*-triazinyl)methyltriphenylphosphonium Chloride (XXIX).—Reaction of 9.5 g. (0.060 mole) of III with 15.7 g. (0.060 mole) of triphenylphosphine in 35 ml. of benzene at room temperature for 4 days gave the phosphonium salt in approximately 90% yield. The product was adequately purified by washing with benzene. It tended to retain the solvent strongly, however. It was extremely soluble in more polar solvents such as acetonitrile and chloroform. A sample dried *in vacuo* at 65° melted at 195–198° if heated normally, but melted with gas evolution and resolidification if placed in a melting point bath at 180°.

(4,6-Dimethyl-2-*s*-triazinyl)methylenetriphenylphosphorane (XXX).—A mixture of 6.2 g. (0.012 mole) of XXIX (benzene complex), 2.0 g. (0.019 mole) of sodium carbonate, 15 ml. of water, and 20 ml. of benzene was stirred for 1.5 hr. The benzene phase then was separated, dried, and evaporated. The residue, 5.0 g. (88%), was recrystallized from ethyl acetate, m.p. 161.5–163°.

2,4-Dimethyl-6-(*p*-dimethylaminostyryl)-*s*-triazine.—A mixture of 12.3 g. (0.10 mole) of I, 14.9 g. (0.10 mole) of *p*-dimethylaminobenzaldehyde, 1 g. of potassium hydroxide and 50 ml. of methanol was allowed to stand for 2 days. The crystals which separated, 17 g., m.p. 128–135°, were recrystallized from acetonitrile and from benzene to give analytically pure material, m.p. 143–145°; the crude yield was 67%.[44]

Anal. Calcd. for $C_{15}H_{18}N_4$: C, 70.63; H, 6.94; N, 21.68. Found: C, 70.83; H, 7.13; N, 22.03.

A mixture of equimolar amounts of XXX and *p*-dimethylaminobenzaldehyde in tetrahydrofuran gave no detectable reaction in 4 days at room temperature. After 3 days at reflux a slight amount of triphenylphosphine oxide was detectable by infrared. Thereafter, the solvent was evaporated and the residue was heated for 6 hr. at 160–170°. Extraction of the reaction mixture with ether left substantially pure triphenylphosphine oxide undissolved. The ether-soluble material contained considerable 2,4-dimethyl-6-(*p*-dimethylaminostyryl)-*s*-triazine as was determined by infrared comparison with an authentic sample.

2,4-Dimethyl-6-dimorpholinomethyl-*s*-triazine (XXXI).—A mixture of 13 g. of approximately 85% XIX (*ca.* 0.07 mole) and 50 ml. of morpholine was heated for 2 hr. on the steam bath. It then was allowed to cool slowly, and the crystallized morpholine hydrochloride was filtered out. The solution was distilled to remove essentially all unchanged morpholine, and the residue was extracted with ether. Evaporation of the ether solution gave 10.3 g. of crude XXXI, m.p. 106–115 (*ca.* 50% yield). Recrystallization from hexane raised the melting point to 121–123°.

4,6-Dimethyl-2-*s*-triazinecarboxaldehyde 2,4-dinitrophenylhydrazone was obtained by boiling a mixture of XXXI and a slight excess of 2,4-dinitrophenylhydrazine in ethanol for 2 hr., m.p. 235–237° from benzene.

Anal. Calcd. for $C_{12}H_{11}N_7O_4$: C, 45.42; H, 3.50; N, 30.91. Found: C, 45.77; H, 3.60; N, 30.56.

4,6-Dimethyl-2-*s*-triazinecarboxaldehyde thiosemicarbazone was prepared by refluxing an ethanol solution of equivalent amounts of XXXI and thiosemicarbazide for 6 hr., m.p. 230–232° from ethanol.

Anal. Calcd. for $C_7H_{10}N_6S$: C, 39.99; H, 4.79; N, 39.98; S, 15.25. Found: C, 39.90; H, 4.51; N, 39.82; S, 14.86.

2-(4,6-Dimethyl-2-*s*-triazinyl)-3-phenyloxirane (XXXIII).—A mixture of 10.0 g. of 2-chloromethyl-4,6-dimethyl-*s*-triazine of 80% purity (≈0.051 mole), 5.4 g. (0.051 mole) of benzaldehyde, 7 g. of anhydrous potassium carbonate, and 20 ml. of methanol was stored at room temperature for 3 days with occasional shaking. The mixture then was filtered and the solution was evaporated. The residue was extracted with ether, and the extract was re-evaporated to a sirup. Extraction of this material with petroleum ether left undissolved a small amount of gum. The extract was again evaporated as completely as possible, leaving a residue of 11.3 g. which crystallized readily when refrigerated. The crystals were washed with a small amount of petroleum ether to remove some unchanged benzaldehyde and other minor impurities. The crude product weighed 7.0 g., m.p. *ca.* 50°. Lower melting material (4.0 g.) recovered from the wash solution was estimated to be 75–80% pure by infrared spectroscopy. The total yield was approximately 90%.

A sample of XXXIII recrystallized from hexane melted at 55–60°.

In the n.m.r. spectrum of this product which was in full accord with the assigned structure, the oxirane proton resonances at τ 5.71 and 6.20 showed a coupling of 2.9 c.p.s., characteristic of a *trans* configuration.[45] Examination of the less pure fractions showed that the oxirane content was identical with this pure compound and therefore exclusively of the *trans* configuration.

2-Amino-4,6-bis(tribromomethyl)-*s*-triazine (XXXIV).—2,4,6-Tris(tribromomethyl)-*s*-triazine (8.3 g.) was covered with 25 ml. of concentrated aqueous ammonia and the reactants were ground together with a stirring rod. After 5 min. the mixture was filtered, and the solid was washed with water and with petroleum ether. The product weighed 5.8 g. (97%), m.p. 202–208. Recrystallization from toluene or acetonitrile gave m.p. 218.5–219.5°. The n.m.r. spectrum of this product showed only the resonance of an amino-*s*-triazine group at τ 1.23.

This compound has been reported to melt at 184–185° by Broche.[20] Although the analytical data given were excellent, it is probable that his product was XXXVIII.[46]

2,4-Diamino-6-dibromomethyl-*s*-triazine (XXXVI).—A mixture of 12.1 g. (0.020 mole) of XXXIV and 60 ml. of concentrated ammonia was allowed to stand for 30 hr. The recovered solid (80% yield) was recrystallized from butanol, m.p. 220° dec. (lit.[46] m.p. 223°). Analytical data on this product were very erratic, merely showing the approximate composition.

The n.m.r. spectrum of a solution of this product in deuterated dimethyl sulfoxide had a strong peak at the chemical shift characteristic of the dibromomethyl-*s*-triazine group.

2-Piperidino-4,6-bis(trisbromomethyl)-*s*-triazine (XXXVI).—Reaction of 0.012 mole of XIV with 0.024 mole of piperidine in 70 ml. of methoxyethanol was allowed to proceed for 10 min. The mixture was then diluted with water, chilled, and filtered. The crystals obtained had m.p. 164–165° dec., 6.1-g. (76%) yield. Recrystallization from acetonitrile gave m.p. 166° dec.

2-Methoxy-4,6-bis(tribromomethyl)-*s*-triazine (XXXVII).—A mixture of 5.0 g. of XIV, 5 ml. of pyridine, and 100 ml. of methanol was heated under reflux for 3 hr. The solution was then concentrated and diluted with water to obtain 2.7 g. (53%) of crystals, m.p. 116–119°. Recrystallization from hexane gave m.p. 122.5–123°.

Reduction of XIV to X.—A mixture of 1.0 g. of XIV, 25 ml. of nitromethane, and 2 ml. of pyridine was allowed to stand for 16 hr. at room temperature. Dilution with 50 ml. of methanol and 100 ml. of water caused crystallization of 0.5 g. of X, m.p. 130–132° (69%).

Malononitrile plus pyridine in ether reacted similarly with XIV. Without the basic catalyst, no reaction occurred between XIV and boiling nitromethane.

When hydrogen bromide was passed into a solution of 8.3 g. of XIV in 20 ml. of chloroform for 6 hr. at room temperature, bromine was liberated and X was recovered in 50% yield.

2-Amino-4,6-bis(dibromomethyl)-*s*-triazine (XXXVIII).—Concentrated aqueous ammonia (250 ml.) was added at room temperature to a solution of 15 g. of X in 500 ml. of ethanol. After 15 min., 3 l. of water was added and the precipitated product was filtered. The crude material, 4.2 g., was recrystallized from ethanol, giving 3.5 g. (32%), m.p. 171–173°.

2-Amino-4-methyl-6-tribromomethyl-*s*-triazine (XXXIX).—Reaction of 5.0 g. of XIII with 100 ml. of aqueous ammonia for 7 hr. gave 3.6 g., m.p. 155–180°. Extraction of this material with boiling chloroform left 1.0 g. undissolved. This was found by infrared examination to be a mixture of 2,4-diamino-6-methyl-*s*-triazine[47] and XL. From the chloroform extract, 2.3 g. of XXXIX was obtained, m.p. 153–158°, 76% yield. Recrystallization from methanol and from acetonitrile gave material melting at 157–160°.

The n.m.r. spectrum of this compound exhibited proton resonances attributable to amino- and methyl-*s*-triazine groups with very weak peaks at the chemical shifts characteristic of XL.

2-Amino-4-dibromomethyl-6-methyl-*s*-triazine (XL).—Ammonia was passed through a solution of 5.0 g. of XIII in 10-ml. of dimethylformamide for 1 hr. without heating (25–60°) and then for 1 hr. at 100°. The mixture then was filtered and the filtrate

(44) This synthesis was carried out by Mrs. G. P. Papp.

(45) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **32**, 1378 (1960).

(46) A. Ostrogovich prepared 2,4-diamino-6-dibromomethyl-*s*-triazine (XXXV) and 2,4-diamino-6-tribromomethyl-*s*-triazine by bromination of 2,4-diamino-6-methyl-*s*-triazine with bromine in acetic acid. His melting point of 210° for the tribromo derivative similarly refutes Broche's reported preparation of this compound, m.p. 300° [*Bull. soc. sci. Bucharest*, **14**, 49 (1905); *Chem. Zentr.*, **II**, 1358 (1905)].

(47) M. Nencki, *Ber.*, **7**, 775 (1874).

was diluted with 25 ml. of water. The precipitated product weighed 0.9 g. (39%), m.p. 193° dec. Recrystallization from methanol raised the melting point to 201° dec.

The n.m.r. spectrum of this compound in dimethyl sulfoxide-d_6 was essentially identical with that of 2-amino-4-dichloromethyl-6-methyl-*s*-triazine.

Isomerization of XIII to X.—A mixture of 6.0 g. of XIII, 1.2 g. of 2,4-diamino-6-methyl-*s*-triazine, and 25 ml. of dimethylformamide was heated for 45 min. at 100°. Water then was added to the point of beginning crystallization. The crude product obtained was triturated with methoxyethanol which left 1.0 g., m.p. 126–130°, identified by infrared comparison as X.

Reduction of X to XLI.—A solution of 15 g. (0.025 mole) of X in 100 ml. of acetone was added to 150 g. (1.0 mole) of sodium iodide in 50 ml. of acetic acid and 500 ml. of acetone. After 6 min. at room temperature the reaction mixture was added to 25 g. of sodium bisulfite in 1 l. of ice–water. By extraction with ether, 7.2 g. of a dark oil was recovered. This was crystallized in part from ethanol, giving 3.4 g. of crude XLI, m.p. 79–85° (31% yield). Recrystallization from cyclohexane raised the melting point to 87–88.5°.

The n.m.r. spectrum of this compound was consistent with the structure XLI, although there was evidence for a minor amount of an impurity containing $-CH_2Br$.

2,4-Dimethoxy-6-methyl-*s*-triazine (XLII).—A solution of 16.5 g. (0.050 mole) of IX and 5.4 g. (0.10 mole) of sodium methoxide in 115 ml. of methanol was stored at room temperature for 60 hr. Only 1.2 g. of sodium chloride was obtained. The solution was saturated with carbon dioxide to precipitate the residual alkoxide, was filtered, and then was evaporated as completely as possible. The residue was extracted with an ether–petroleum ether mixture from which 4.7 g. of crystals were recovered, m.p. 45°. Recrystallization from hexane raised the melting point to 62–64°; the crude yield was 61%.

2-Methoxy-4-methyl-6-trichloromethyl-*s*-triazine (XLIII).—A mixture of 15 g. of IX, 18 ml. of triethylamine, and 75 ml. of methanol was heated at reflux for 6 hr. The solvent then was evaporated, and the residue was extracted with ether. The ether solution was distilled, giving 5.5 g. of product boiling at about 120° (6 mm.). The product was shown to be the expected[3,4c] XLIII by n.m.r. spectroscopy. (About 5% of the dimethoxy derivative XLII was found as an impurity.) The yield of XLIII was 45%.

Dichlorocarbene from IX.—A solution of 33.0 g. (0.10 mole) of IX in 50 g. of cyclohexene was added dropwise to a stirred suspension of 10.8 g. (0.20 mole) of sodium methoxide in 32 g. of cyclohexene at 5–10° over a period of 2 hr. Stirring was continued for 3 hr. longer at 5–10° and for 18 hr. at room temperature. The black mixture then was filtered and the low-boiling material was distilled. Analysis of the distillate by g.l.c. showed that about 25% of the theoretical yield of chloroform was present. The less volatile material (9 g.) then was distilled at low pressure. The fraction boiling at 65–75° (8 mm.) weighed 2.0 g. and was found to contain about 50% 2,2-dichlorobicyclo-[4.1.0]heptane by mass spectrometry and g.l.c. The yield of this product was only 3–5%. The major product, *ca.* 4.5 g., b.p. 80–90° (5 mm.), m.p. 65–67°, was 2-methyl-4,6-dimethoxy-*s*-triazine (XLII).

N.m.r. Examination of Halogenation Products from 2-Ethyl-4,6-diphenyl-*s*-triazine.—2-Ethyl-4,6-diphenyl-*s*-triazine was mono- and dichlorinated and brominated as described by Reinhardt and Schiefer, and the four products were found to have the melting points reported.[5] The n.m.r. spectra of the two monohalides showed the expected quartet and doublet resonances for the methine and methyl groups, respectively, of the $-CHXCH_3$ structure. The n.m.r. spectra of the two dihalides showed single resonances due to the $-CX_2CH_3$ group rather than the complex pattern that would result from the $-CHXCH_2X$ structure. Thus there is no doubt that only α-halogenation of the ethyl group is significant.

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Reactions of Benzaldehyde with *o*-Nitroaniline[1]

GARDNER W. STACY, BRUCE V. ETTLING,[2] AND ANTHONY J. PAPA

Department of Chemistry, Washington State University, Pullman, Washington

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When benzaldehyde and *o*-nitroaniline (I) are heated under reflux in toluene for varying lengths of time, not only is the anticipated product N-benzylidene-*o*-nitroaniline (II) formed but also N,N-benzylidenedi(*o*-nitroaniline) (III). Prolonged reaction time effects heterocyclization to give 1-hydroxy-2-phenylbenzimidazole (V) and 2-phenylbenzimidazole (IV). The structure of V was substantiated by its reduction to IV and by an alternate synthesis from N-benzyl-*o*-nitroaniline. Some intermediate conversions of interest were observed. The Schiff base II added *o*-nitroaniline to form III. Also, both II and III react with benzaldehyde to give V.

The reaction of aromatic aldehydes with aromatic amines usually proceeds without complication to form Schiff bases.[3] We have examined a case, however, where several subsequential reactions of interest occurred and found that control of experimental conditions was important in governing the outcome.

When *o*-nitroaniline was heated with an excess of benzaldehyde in toluene, the Schiff base, N-benzylidene-*o*-nitroaniline (II), was in fact obtained as the major product (see Chart A[4]); however, its separation and purification from the reaction mixture was made difficult by the presence of small amounts of N,N-benzylidenedi(*o*-nitroaniline) (III) and 1-hydroxy-2-phenylbenzimidazole (V).

N-Benzylidene-*o*-nitroaniline (II) on standing at room temperature will react with traces of moisture to form III (presumably the process involves initial hydrolysis to benzaldehyde and *o*-nitroaniline with subsequent addition of the latter to unchanged II). However, II is stable at 0° and may be stored at this temperature without evidence of transformation to III.

N,N-Benzylidenedi(*o*-nitroaniline) (III) was obtained as the sole product when benzaldehyde was heated with excess *o*-nitroaniline. Crude III displayed odd behavior on attempted purification. Recrystallization from several solvents gave materials of variable melting point. Although examination of these modi-

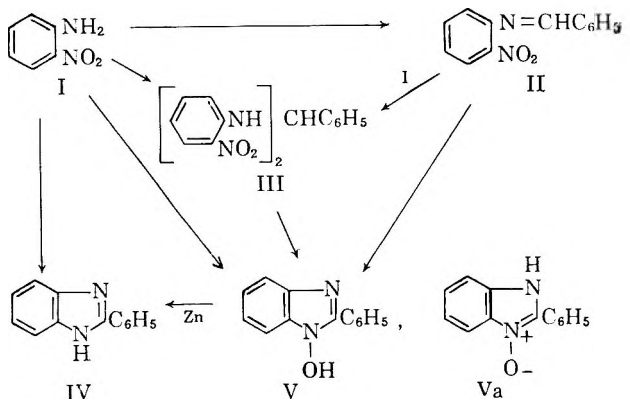
(1) Presented in part at the 1961 Northwest Regional Meeting of the American Chemical Society, Portland, Ore., June, 1961.

(2) In part abstracted from a thesis submitted by B. V. Ettling in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Washington State University, June, 1958. Public Health Service Research Fellow of the National Institute of Neurological Diseases and Blindness, 1956–1958.

(3) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(4) Unless otherwise indicated the reactant is benzaldehyde.

CHART A



fications was not complete, it was found that they all had the same bright orange-yellow color and quite similar infrared spectra but frequently varied in composition as indicated by elemental analysis. It finally was observed that, if the crude product was simply washed with several portions of cold toluene, a substance of constant melting point and purity was obtained. It appeared that the erratic melting point behavior might reflect heat lability of III. Acidic hydrolysis of III resulted in its decomposition to *o*-nitroaniline and benzaldehyde.

The ease of formation of III is consistent with the enhanced electron deficiency of the carbon atom of the carbon–nitrogen double bond of II which is influenced by the strongly electron-attracting *o*-nitro group. Thus, as expected, *o*-nitroaniline readily added to N-benzylidene-*o*-nitroaniline to yield III. There appears to be only one previous report of a stable compound of this type, N,N-trichloroethylidenedi(*o*-nitroaniline) which was obtained by condensing chloral with *o*-nitroaniline.[5]

A more convenient method for the preparation of II was developed.[6] When *o*-nitroaniline was heated with an equimolar quantity of N-benzylideneaniline under

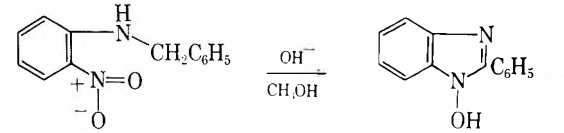
$$\underset{\text{I}}{o\text{-}O_2NC_6H_4NH_2} + C_6H_5N{=}CHC_6H_5 \rightleftharpoons \underset{\text{II}}{o\text{-}O_2NC_6H_4N{=}CHC_6H_5} + C_6H_5NH_2$$

reduced pressure (0.4 mm.), the free aniline which was displaced distilled, and the residue in the distilling flask was recrystallized from benzene–heptane. The infrared spectrum of the product showed as expected a strong band at 1629 cm.$^{-1}$ corresponding to the carbon–nitrogen double bond, whereas the spectrum of III did not have a band between 1800 and 1605 cm.$^{-1}$.

A somewhat higher temperature and a longer period of reflux promoted heterocyclization in the reaction of *o*-nitroaniline and benzaldehyde. Thus, when equimolar amounts were heated in xylene for seven days, 2-phenylbenzimidazole(IV) was isolated. When these reactants (1:2) were heated for three days in toluene, 1-hydroxy-2-phenylbenzimidazole(V) was obtained. The ultraviolet and infrared spectra of IV and V were quite similar, and V was converted to IV by heating with zinc dust. A comparison of infrared spectra also was made to the known 1-hydroxybenzimidazole[7] and again the agreement was quite good. 1-Hydroxy-2-phenylbenzimidazole (V) might also exist as an N-oxide structure (Va), a modification which has been favored recently for 1-hydroxybenzimidazole by Kew and Nelson.[8] Although these authors concluded that an N-oxide structure best explained the experimental results they describe, it would seem that an N-hydroxy structure would be just as valid.

We have determined n.m.r. spectra for 1-hydroxybenzimidazole and 1-hydroxy-2-phenylbenzimidazole-(V) in trifluoroacetic acid with a trace of tetramethylsilane added as an internal reference. If the N-oxide structure were the structure of choice, a broad peak due to the NH_2^+ ion probably would have been observed. Also, like phenylhydroxylamine, 1-hydroxy-2-phenylbenzimidazole(V) is photosensitive,[9] while the esterified (benzoyl) derivative is not. On the basis of these observations and considering that a noncharged structure would be more stable, it is felt that the N-hydroxy form V is the preferred tautomeric structure for benzimidazoles carrying the oxygen function in the 1-position.

To confirm the structure of V, an alternate method of formation was sought. Attempted peracid oxidation of 2-phenylbenzimidazole under a variety of conditions and concentrations failed. An attempt to cyclize *o*-nitrobenzanilide by the method of Niementowski[7] also was unsuccessful. Finally, the desired V was obtained by the base-catalyzed cyclization of N-benzyl-*o*-nitroaniline(VI). Base-catalyzed cyclizations involving condensation of nitro groups have been reported previously.[10]



VI V

Not only was it possible to form 1-hydroxy-2-phenylbenzimidazole (V) from *o*-nitroaniline (I), but it was obtained also by heating N-benzylidene-*o*-nitroaniline (II) or N,N-benzylidenedi(*o*-nitroaniline) (III), respectively, with benzaldehyde in toluene. Of course, this does not necessarily mean that II and III are intermediates in the formation of V.

Experimental[11]

N-Benzylidene-*o*-nitroaniline (II) from Benzaldehyde and *o*-Nitroaniline (I).—A solution of 6.90 g. (0.05 mole) of *o*-nitroaniline and 10.6 g. (0.10 mole) of benzaldehyde[12] in 10 ml. of dry

(5) P. Grammaticakis, *Bull. soc. chim. France*, **17**, 158 (1950).

(6) This procedure was similar to that employed by Reddelien for preparing ketimines [G. Reddelien, *Ber.*, **54**, 3121 (1921)].

(7) S. Niementowski, *ibid.*, **43**, 3012 (1910).

(8) D. J. Kew and P. F. Nelson, *Australian J. Chem.*, **15**, 792 (1962).

(9) D. M. McQueen, U. S. Patent 2,426,894 (1947); *Chem. Abstr.*, **41**, 7290 (1947).

(10) (a) C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wotring, and E. A. Pacofsky, *J. Org. Chem.*, **25**, 736 (1960); (b) G. Heller and C. Spielmeyer, *Ber.*, **58**, 834 (1925); (c) F. Arndt, *ibid.*, **46**, 3522 (1913).

(11) All melting points are corrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn., and by Weiler and Strauss Laboratories, Oxford, England. The infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. The samples were prepared as potassium bromide pellets (3 mg. of sample per 1 g. of potassium bromide).

(12) This was purified by washing commercial benzaldehyde with 10% sodium bicarbonate solution, drying over anhydrous potassium carbonate, and distilling under reduced pressure. It was stored in the absence of light and repurified every 2–3 months.

toluene was added under reflux for 32 hr. Most of the solvent was removed by distillation, and the residual solution was allowed to cool. A small amount of V (5%) crystallized and was separated. The remaining solvent was removed from the filtrate, and the oil was extracted with four 10-ml. portions of heptane to remove excess benzaldehyde. The oil was allowed to stand at −5°, and crude III crystallized and was removed by filtration, yielding 1.47 g. (16%), m.p. 105–109°. The filtrate again was extracted with 10 ml. of heptane, and the remaining oil was allowed to stand at −5°. Crystalline II was obtained after addition of a seed crystal and recrystallized from heptane–benzene, yielding 3.47 g. (31%), m.p. 76–77°.[13]

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.45; N, 12.39. Found: C, 69.34; H, 4.52; N, 12.30.

The infrared spectrum showed a band assignable to C=N at 1629 (s) cm.$^{-1}$.

N,N-Benzylidenedi(*o*-nitroaniline) (III) from Benzaldehyde and *o*-Nitroaniline (I).—A solution of 6.90 g. (0.05 mole) of recrystallized *o*-nitroaniline and 3.20 g. (0.03 mole) of purified benzaldehyde in 10 ml. of dry toluene was heated under reflux for 9 hr., during which time 0.3 ml. of water was collected in a Dean–Stark trap. After the reaction mixture had been cooled in a refrigerator, the product was separated by filtration and washed with one 5-ml. portion of cold toluene, yielding 8.39 g. (92%), m.p. 68–72°. Recrystallization of this material from hot benzene led to material with variable melting points (94–118°) and which did not give satisfactory analyses. On the other hand, washing the product with five 5-ml. portions of toluene at room temperature yielded 3.10 g. (34%) of pure, bright orange-yellow crystals of N,N-benzylidenedi(*o*-nitroaniline), m.p. 94.5–95°.

Anal. Calcd. for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.43; N, 15.38. Found: C, 62.69; H, 4.36; N, 15.21.

The infrared spectrum indicated bands assignable to N–H stretching vibrations (3345 cm.$^{-1}$, m) and NH deformation vibrations (1510 cm.$^{-1}$, s), characteristic of secondary amines.

Conversion of N-Benzylidene-*o*-nitroaniline (II) to N,N-Benzylidenedi(*o*-nitroaniline) (III).—In 5 ml. of heptane–benzene was placed 452 mg. (2.0 mmoles) of II, some of which, but not all, dissolved in the solvent. After standing for 1 week, the crystals had turned orange-yellow in color. This material was removed by filtration, yielding 353 mg. (97%), m.p. 114–116°. This substance proved to be identical with some of the material of variable melting point that was observed in the procedure above.

Addition of *o*-Nitroaniline to N-Benzylidene-*o*-nitroaniline (II).—A solution of 226 mg. (1.0 mmole) of II in 5 ml. of dry benzene was added to a solution of 138 mg. (1.0 mmole) of *o*-nitroaniline. The reaction mixture was heated at 80° for 1 hr., and then most of the solvent was removed by distillation under reduced pressure. The mixture was allowed to stand overnight in a freezer, during which time the product crystallized and was isolated by filtration, yielding 0.30 g. (83%), m.p. 100–101°. Washing with two 3-ml. portions of benzene at room temperature afforded a bright orange-yellow product, m.p. 95°, mixture melting point with the product obtained from the above procedure was 94.5–95°. The infrared spectra were also identical.

Anal. Calcd. for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.43; N, 15.38. Found: C, 62.72; H, 4.65; N, 15.22.

Acidic Hydrolysis of N,N-Benzylidenedi(*o*-nitroaniline) (III).—A sample of 364 mg. (1.0 mmole) of III was added to aqueous ethanol and warmed gently. A solution of 250 mg. of 2,4-dinitrophenylhydrazine sulfate in ethanol–water was added, and the mixture was warmed at about 80° for 10 min. After the reaction mixture was cooled, a solid product was obtained by filtration. Recrystallization from benzene afforded orange benzaldehyde-2,4-dinitrophenylhydrazone, 283-mg. (96%) yield, m.p. 239–240°.

The filtrate from the recrystallization was concentrated and mixed with water. It and the filtrate from the hydrolysis were extracted with ether. The ether was removed from the combined extracts, and the residual *o*-nitroaniline (I) was recrystallized from heptane–benzene (5:1), yielding 229 mg. (83%), m.p. 70–71°; mixture melting point with authentic I was 70–71°.

N-Benzylidene-*o*-nitroaniline (II) from N-Benzylideneaniline and *o*-Nitroaniline (I).—In a 10-ml. flask assembled for distillation were introduced 4.14 g. (0.03 mole) of *o*-nitroaniline and 5.43 g. (0.03 mole) of N-benzylideneaniline. The reaction mixture was heated under reduced pressure (0.8 mm.) by means of an oil bath maintained at 150°. Over a period of 13 hr., 6 g. of an orange oil was distilled (b.p. 95–115°). The residue was placed in a freezer for 1 day during which time N-benzylidene-*o*-nitroaniline (II) crystallized; this was recrystallized twice from benzene–heptane (1:10) to give 3.85 g. (53%) of II, m.p. 76–78°; mixture melting point with material prepared by the alternate method described above was 76–77°.

2-Phenylbenzimidazole (IV).—A solution of 6.90 g. (0.05 mole) of *o*-nitroaniline and 5.30 g. (0.05 mole) of benzaldehyde in 50 ml. of xylene was heated under reflux until no more water was evolved (7 days). The reaction mixture was allowed to stand at room temperature, and the crystalline product which formed was isolated by filtration, yielding 2.50 g. (20%), m.p. 292–294°. Recrystallization of the crude product from ethanol–benzene (1:1) gave gray monoclinic prisms, m.p. 293–294°, lit.[14] m.p. 291°; mixture melting point with an authentic sample of IV[15] was 293–294°. The infrared spectrum indicated bands assignable to NH at 3100 (w) and aromatic C=C at 1560 (w) and 1450 (s) cm.$^{-1}$.

1-Hydroxy-2-phenylbenzimidazole (V).—A solution of 13.8 g. (0.10 mole) of *o*-nitroaniline and 21.2 g. (0.20 mole) of benzaldehyde in 20 ml. of dry toluene was heated under reflux for 3 days during which time 2.2 ml. of water was collected in a Dean–Stark trap. After the reaction mixture had been cooled, 18.9 g. of product was obtained by filtration. This crude product was purified by treatment with boiling ethanol, yielding 18.0 g. (86%), m.p. 220° dec., λ_{max}^{EtOH} 298 mμ (ε 21,500).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.80; N, 13.33. Found: C, 74.47; H, 4.75; N, 13.50.

The infrared spectrum indicated bands assignable to OH at 3120 (w) and aromatic C=C at 1540 (w) and 1450 (s) cm.$^{-1}$.

1-Hydroxy-2-phenylbenzimidazole (V) by Cyclization of N-Benzyl-*o*-nitroaniline.—A solution of 4.56 g. (0.02 mole) of N-benzyl-*o*-nitroaniline[16] and 4.0 g. of sodium hydroxide in 80 ml. of dry methanol was heated under reflux on a steam bath for 5 hr. The reaction mixture then was concentrated to a volume of 30 ml. by distillation. The solution was neutralized with dilute hydrochloric acid, and the product was collected by filtration yielding 3.30 g. (79%), m.p. 220° dec. The mixture melting point with the product obtained from the reaction of *o*-nitroaniline and benzaldehyde gave a 15° depression, and the elemental analysis was inconsistent with that for V. However, brief treatment of this material with boiling water led to the formation of 1-hydroxy-2-phenylbenzimidazole (V), 2.30-g. (71%) yield, m.p. 220° dec.; mixture melting point with V obtained previously showed no depression (220° dec.), and the infrared spectra were identical.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.80; N, 13.33. Found: C, 74.09; H, 4.63; N, 13.02.

A **benzoyl derivative** was obtained from a mixture of 1.05 g. (5.0 mmoles) of 1-hydroxy-2-phenylbenzimidazole (V), 1.50 g. of benzoyl chloride, and 0.5 ml. of pyridine, which was heated at about 90° for 0.5 hr. and then allowed to cool. Water was added, and the resultant oil was removed by extraction with ether. The ether solution was shaken successively with dilute sodium bicarbonate solution and with hydrochloric acid. Evaporation of the ether followed by recrystallization of the residue from heptane gave colorless crystals, 1.13-g. (72%) yield, m.p. 116–118°.

Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.67; H, 4.45; N, 9.01.

The infrared spectrum indicated an absorption band at 1766 cm.$^{-1}$ assignable to an ester C=O.

A **methyl derivative** was obtained from a solution of 210 mg. (1.0 mmole) of 1-hydroxy-2-phenylbenzimidazole (V) in methanol, to which an ether solution of diazomethane was added dropwise until rapid gas evolution ceased. The mixture was allowed to stand for 1 hr., and the solvent was removed by evaporation

(13) C. K. Ingold and H. A. Piggott [*J. Chem. Soc.*, **121**, 2793 (1922)] reported the preparation of II by this method. Although the elemental analysis was consistent with II, it was orange-yellow, and the melting point reported was 118°, which is suggestive of III. Because II and III both occur in the same crude product and because II readily is converted to III on standing at room temperature, it is understood how a discrepancy could be encountered in reporting these results.

(14) H. Franzen, *Ber.*, **40**, 903 (1907).

(15) Prepared by the method of R. Walther and T. von Pulawski, *J prakt. Chem.*, [2]**59**, 249 (1899).

(16) Prepared in 80% yield by the method of M. S. Gibson [*J. Chem. Soc.*, 1076 (1956)].

The residue was recrystallized twice from diisopropyl ether to give 175 mg. (78%) of product, m.p. 102–104°.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.79; H, 5.64; N, 12.31.

Zinc Dust Reduction of 1-Hydroxy-2-phenylbenzimidazole (V).—A mixture of 210 mg. (1.0 mmole) of V and 200 mg. (3.0 mg.-atoms) of zinc dust was heated at 240° for 2 hr. The mixture was allowed to cool and was extracted with warm ethanol. After the ethanol had been decanted, the residue was dissolved in dilute hydrochloric acid. The resulting solution was filtered, and the filtrate was made slightly basic. The basic filtrate then was extracted with three 15-ml. portions of warm chloroform. The chloroform was removed by distillation, and the residue was recrystallized from ethanol–benzene to yield 113 mg. of IV (58%), m.p. 292–294°, m.m.p. 293–294.5°.

Conversion of N-Benzylidene-*o*-nitroaniline (II) to 1-Hydroxy-2-phenylbenzimidazole (V).—A solution of 452 mg. (2.0 mmoles) of II and 212 mg. (2.0 mmoles) of benzaldehyde in 3 ml. of dry toluene was heated under reflux for 72 hr. The reaction mixture was allowed to stand in the freezer for 3 days, and the resulting crystalline precipitate was removed by filtration and purified by boiling toluene to give V in a 82-mg. yield (20%, m.p. 220° dec.). Identity was established by mixture melting point determination and infrared spectrum.

Conversion of N,N-Benzylidenedi(*o*-nitroaniline) (III) to V.—A solution of 364 mg. (1.0 mmole) of III and 318 mg. (3.0 mmoles) of benzaldehyde in 3 ml. of dry toluene was heated under reflux for 2 days. From the mixture was obtained 200 mg. of crude product which upon recrystallization from ethanol gave 117 mg. (56%) of V, m.p. 220° dec.

Acknowledgment.—We wish to express thanks to Varian Associates for assistance in determination and interpretation of n.m.r. spectra. This investigation was supported in part by a grant (G 1100) from the National Science Foundation.

Oxidation by Solids. III. Benzalanilines from N-Benzylanilines and Related Oxidations by Manganese Dioxide

ERNEST F. PRATT AND TERRENCE P. MCGOVERN[1,2]

Department of Chemistry, University of Maryland, College Park, Maryland

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A variety of benzalanilines are readily obtained in excellent yield upon heating a suspension of manganese dioxide in a benzene solution of the corresponding N-benzylaniline in an apparatus equipped with a water trap. Close to theoretical yields of the by-product water collect at a rate which measures the rate of the oxidation. The effect of changes in structure of the reactants on the rate indicates that the process proceeds *via* free radicals. N-*t*-Alkyl benzylamines are also oxidized smoothly. Quinoline is obtained in good yield from 1,2,3,4-tetrahydroquinoline under the same conditions, and indole and acridine are readily prepared from 2,3-dihydroindole and acridane. The oxidation of a number of hydrazobenzenes to the azobenzenes proceeds rapidly in nearly quantitative yield, and, under modified conditions, azobenzenes are also obtained in good yield from a variety of anilines.

It has been found that, when a solution of an N-benzylaniline in benzene is heated under reflux with manganese dioxide in an apparatus equipped with a Bidwell–Sterling water trap, excellent yields of the corresponding benzalanilines and approximately theoretical yields of the by-product water are ordinarily obtained (Table I). These mild, anhydrous conditions prevent the further oxidation or hydrolysis of the product which often occurs when other methods of oxidation are used.[3,4]

$$p\text{-}RC_6H_4CH_2NHC_6H_4R'\text{-}p + MnO_2 \longrightarrow p\text{-}RC_6H_4CH{=}NC_6H_4R'\text{-}p + MnO + H_2O$$

A plot of the yield of water *vs.* time gives smooth curves of constantly decreasing slope which are closely reproducible and which show no tendency to cross one another as the reactant is varied. The times required for 50% of the theoretical yield of water to collect ($t_{50\%}$) are, therefore, valid measures of the relative reaction rates.

Data in the first and fourth sections of the table show that shifting a methoxyl group from the *para* to the *meta* to the *ortho* position or a methyl group from the *para* to the *ortho* position decreases the rate. The decrease in rate is reasonably ascribed to an increase in steric hindrance and as expected on this basis the shift of the methyl group has less effect than the shift of the larger methoxyl group.

It is of interest that dibenzylamine (fifth section) was oxidized at about the same rate as N-benzylaniline although only the latter compound gives a product in which the new double bond is conjugated with both aromatic rings. The oxidation also proceeded smoothly, although much more slowly, when the anilino ring of N-benzylaniline was replaced by tertiary alkyl groups.

No well-defined products were isolated when attempts were made to oxidize benzylamine, N-methylbenzylamine, N-isopropylbenzylamine, N-methylaniline, N-butylaniline, dibutylamine, or piperidine under the standard conditions. Apparently, unstable Schiff bases, which reacted further, were formed, since in all these cases water was collected in over 80% yield. Some of these amines have been oxidized by manganese dioxide under other conditions,[5,6] and, although in

(1) From the Ph.D. thesis of T. P. McGovern, April, 1962.

(2) For the preceding paper in this series, see E. F. Pratt and S. P. Suskind, *J. Org. Chem.*, **28**, 638 (1963).

(3) (a) P. Friedlander, "Fortschritte der Theerfarbenfabrikation," Vol. 4, Julius Springer, Berlin, 1899, p. 129 (German Patent 91503); (b) p. 131 (German Patent 92084); (c) R. Hubner, *Ber.*, **35**, 731 (1902); (d) C. M. Rosser and J. J. Ritter, *J. Am. Chem. Soc.*, **59**, 2179 (1937); (e) F. W. Newman and C. W. Gould, *Anal. Chem.*, **25**, 751 (1953); (f) J. T. Edwards, *J. Chem. Soc.*, 1464 (1954); (g) A. A. Bolandin and N. A. Vasyunina, *Dokl. Akad. Nauk SSSR*, **103**, 831 (1955); *Chem. Abstr.*, **50**, 9283 (1956).

(4) E. A. Braude, A. G. Brook, and R. P. Linstead [*J. Chem. Soc.*, 3574 (1954)] describe a procedure employing diphenylpicrylhydrazyl for the conversion of N-benzylaniline to benzalaniline which is of considerable theoretical, but limited preparative, interest.

(5) (a) R. J. Highet and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 4399 (1955); (b) H. B. Henbest and A. Thomas, *J. Chem. Soc.*, 3032 (1957).

(6) M. Z. Barakat, M. F. Abdel-Wahab, and M. M. El Sadr, *ibid.*, 4605 (1956).

TABLE I

OXIDATION OF N-BENZYLANILINES, HYDRAZOBENZENES, AND RELATED COMPOUNDS[a]

Reactant	$t_{50\%}$, min.	H_2O, %	Product, %
N-Benzyl-*p*-Substituted Anilines			
$C_6H_5CH_2NHC_6H_4OCH_3$-*p*	48	113	80
$C_6H_5CH_2NHC_6H_4CH_3$-*p*	65	110	82
$C_6H_5CH_2NHC_6H_4C_6H_5$-*p*	68	110	91
$C_6H_5CH_2NHC_6H_4Cl$-*p*	96	105	83
$C_6H_5CH_2NHC_6H_5$	98	101	84
$C_6H_5CH_2NHC_6H_4NO_2$-*p*	130	103	73
N-(*p*-Substituted benzyl)anilines			
p-$O_2NC_6H_4CH_2NHC_6H_5$	59	109	82
p-$CH_3OC_6H_4CH_2NHC_6H_5$	82	109	69[b]
$C_6H_5CH_2NHC_6H_5$	98	101	84
p-$CH_3C_6H_4CH_2NHC_6H_5$	99	103	64[b]
p-$ClC_6H_4CH_2NHC_6H_5$	103	110	76
p,p'-Disubstituted N-Benzylanilines			
p-$CH_3OC_6H_4CH_2NHC_6H_4OCH_3$-*p*	50	101	77
p-$ClC_6H_4CH_2NHC_6H_4Cl$-*p*	85	111	86
$C_6H_5CH_2NHC_6H_5$	98	101	84
p-$O_2NC_6H_4CH_2NHC_6H_4NO_2$-*p*	103[c]	103	85
Other Benzylanilines			
$C_6H_5CH_2NHC_6H_4OCH_3$-*m*	136	102	70
$C_6H_5CH_2NHC_6H_4CH_3$-*o*	146	97	78
$(C_6H_5)_2CHNHC_6H_5$	149	104	89
$C_6H_5CH_2NHC_6H_4OCH_3$-*o*	162	96	78
N-Substituted Benzylamines			
$C_6H_5CH_2NHCH_2C_6H_5$	103	106	62
$C_6H_5CH_2NHC(CH_3)_2CH_2C(CH_3)_3$	173	106	85
$C_6H_5CH_2NHC(CH_3)_3$	250	97	80
Heterocyclic Amines			
o-$C_6H_4CH_2CH_2NH$	40	134	59[d]
$C_6H_4CH_2C_6H_4NH$[e]	46	117	93
o-$C_6H_4CH_2CH_2CH_2NH$	72[f]	100[f]	79[f]
p-Substituted Hydrazobenzenes			
p-$CH_3OC_6H_4NHNHC_6H_5$	34	111	96
$C_6H_5NHNHC_6H_5$	40	100	97
p-$ClC_6H_4NHNHC_6H_5$	46	109	96
p-$CH_3C_6H_4NHNHC_6H_5$	55	107	96
p,p'-Disubstituted Hydrazobenzenes			
p-$CH_3C_6H_4NHNHC_6H_4CH_3$-*p*	39	116	99
$C_6H_5NHNHC_6H_5$	40	100	97
p-$ClC_6H_4NHNHC_6H_4Cl$-*p*	44	101	91

[a] Standard conditions: 0.05 mole of amine, 0.40 mole of manganese dioxide, and 500 ml. of benzene stirred magnetically while distilling the by-product water at 81°. [b] The yield of these low melting products could probably be raised 10 to 15% if isolated by distillation instead of crystallization. [c] This value may be low since reactant was not completely soluble. [d] Yield could probably be raised by stopping reaction when yield of water reaches 100%. [e] Acridine. [f] Product is quinoline and yield of water and $t_{50\%}$ value are recorded on this basis.

certain cases evidence of the formation of Schiff bases was obtained, none were isolated.

Oxidation under the standard conditions proved to be an excellent way to convert 1,2,3,4-tetrahydroquinoline to quinoline; two molecules of water per molecule of reactant were rapidly evolved (sixth section). Indole and acridine were also readily obtained from their dihydro precursors.

Results in the last two sections of the table show that a variety of hydrazobenzenes are oxidized in 96% average yield to the azobenzenes. For a number of the hydrazobenzenes, the rate differences were too small to be significant. In all cases the reaction proceeded markedly faster than for the corresponding N-benzylanilines. On the other hand, starting material was recovered in 90% yield when the oxidation of dibenzyl was attempted.

In numerous cases correlation, on even a qualitative basis, of the rate data in the first three sections of Table I with the relative ability of the *para* substituents to attract electrons[7,8] is impossible. This lack of correlation and the relatively small changes in rate resulting from changes in these substituents indicate that the reaction proceeds *via* free-radical rather than ionic intermediates. It seems improbable that changes in the ease of absorption of the reactants on the manganese dioxide resulting from changes in the *para* substituents would interfere with correlations of rate with electron-attracting ability of these substituents to the extent found here. The evidence that this reaction proceeds *via* free radicals is re-enforced by the previously reported evidence that the oxidation of phenylcarbinols[9] and of diphenylmethanes,[2] under similar conditions, are homolytic processes; the effects of varying the *para* substituents found in these two earlier studies are not unlike those summarized in Table I. Although ionic reactions are often catalyzed by acids or bases, *p*-toluenesulfonic acid (0.001 mole) had no appreciable effect on the rate of oxidation of N-benzylaniline. Oxidations by diphenylpicrylhydrazyl are certainly homolytic processes[4] and the fact that both this hydrazyl and manganese dioxide oxidize hydrazobenzene more rapidly and dibenzyl more slowly than they oxidize N-benzylaniline suggests that these oxidations by manganese dioxide are also homolytic reactions. A mechanism analogous to those of the related preceding studies[2,9] is, therefore, proposed.

$$RCH_2NHR' + O{=}Mn^{+4}{=}O \longrightarrow RCH_2\dot{N}R' + HO{-}Mn^{+3}{=}O$$

$$RCH_2\dot{N}R' + HO{-}Mn^{+3}{=}O \longrightarrow RCH{=}NR' + HO{-}Mn^{+2}{-}OH$$

$$HO{-}Mn^{+2}{-}OH \longrightarrow H_2O + Mn^{+2}{=}O$$

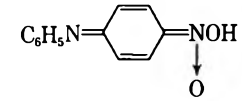
Some of the product could result from disproportionation of the intermediate radical, as shown below,

$$2RCH_2\dot{N}R' \longrightarrow RCH{=}NR' + RCH_2NHR'$$

but the tendency for the concentration of active radicals to be low ordinarily minimizes their interaction.[10]

It is well-recognized that, when a radical can be formed by loss of a hydrogen atom from either nitrogen or carbon, loss from nitrogen ordinarily takes precedence, and the remaining steps tend to require less energy.[4,11] The interpretation that the odd electron first appears on the nitrogen is in agreement with the fact that N-benzylaniline is oxidized more rapidly than dibenzyl

(7) The rate-decreasing effect of the nitro group would be a logical result of the existence of an appreciable proportion of the compound in the tautomeric form.



(8) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 188–197; (b) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(9) E. F. Pratt and John F. Van de Castle, *J. Org. Chem.*, **26**, 2973 (1961).

(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, New York, N. Y., 1959, p. 692.

(11) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 53.

and more slowly than hydrazobenzene, and also with the fact that a substituent tends to have a greater effect when on the anilino than when on the benzyl group of N-benzylaniline (Table I).

Attempts to oxidize aniline under the standard conditions for the experiments of Table I gave only a 47% yield of azobenzene; when, however, the manganese dioxide was not dried (by distilling the water from a suspension of it in benzene) before the aniline was added, a 91% yield of azobenzene was obtained. Since under these modified conditions the water evolved from the oxidation was accompanied by about three times as much water from the dehydration of the manganese dioxide, it was impractical to determine differences in rates of oxidation of various anilines.

Good yields of azobenzenes were obtained from a variety of anilines under the modified conditions. The compounds oxidized and the yields obtained were as follows: *p*-chloroaniline, 96%; aniline, 91%; *p*-phenylaniline, 76%; *p*-toluidine, 71%; *p*-anisidine, 60%; *p*-nitroaniline, 55%; *m*-nitroaniline, 50%; γ-aminopyridine, 49%; *o*-nitroaniline, 21%; and *p*-cyanoaniline, 18%. This method, because of its facility and generality, is in many cases an improvement upon previously described methods.[6,12,13]

Experimental[14,15]

Starting Materials.—The manganese dioxide for the experiments of Table I was prepared by a modified Attenburrow[16] procedure. A solution of 281 g. of manganous sulfate monohydrate (Mallinckrodt, A.R.) in 500 ml. of water was added concurrently with 390 ml. of 40% aqueous sodium hydroxide to a mechanically stirred solution of 320 g. of potassium permanganate (Mallinckrodt, A.R.) in 2 l. of water. The permanganate solution was warmed to 80° at the start, and during the additions the temperature gradually rose to 90°; the mixture was stirred at this temperature for 1 hr. after the additions were completed. It was found that the precipitate could be washed much more rapidly if the manganese sulfate was added over a 60-min. period while the addition of the sodium hydroxide extended over only the first 45 min. of this period. After the hot mixture was filtered, the precipitate was washed in the filter with copious amounts of hot water until the filtrate was neutral to litmus. The manganese dioxide was dried at 125° for 24 hr. and ground to pass a 60-mesh sieve. A number of batches were thoroughly mixed to give a single large batch which was used for all experiments of Table I. The manganese dioxide was allowed to equilibrate with atmospheric moisture by exposing it in 3/8-in.-thick layers to the room atmosphere for 5 days during which it was thoroughly mixed at about 5-hr. intervals; the gain in weight amounted to over 5%. The dioxide was then weighed into 0.4-mole (34.78-g.) portions and stored at −20° in tightly closed containers until used. It was found that this equilibration of the dioxide with the atmospheric moisture markedly improved the reproducibility of the reaction rates.

N-Benzyl-*m*-anisidine [b.p. 226–227° (27 mm.), $n^{20}D$ 1.6080] and N-benzyl-*o*-anisidine [b.p. 211–212° (27 mm.), $n^{20}D$ 1.6053] were prepared, in 90 and 60% yields, by a method described for the *para* isomer.[17] N-*p*-Chlorobenzylaniline, m.p. 60–61°, was obtained from N-*p*-chlorobenzalaniline upon reduction with sodium borohydride,[18] and *p*-methoxyhydrazobenzene, m.p. 74–75°, was obtained from the corresponding azobenzene.[19] *p*-Hydrazotoluene, m.p. 129.5–131°, was prepared from *p*-nitrotoluene.[19] Results of ultimate analyses were satisfactory in all cases.

All other components of the reaction mixtures were purchased or prepared by previously published procedures and purified by standard methods until their refractive index or melting point agreed closely with the literature values.

Experiments of Table I.—Except for readily apparent modifications, the previously described procedure was used.[9] During the 5 hr. of refluxing to dry the manganese dioxide, before the amine was added, 2.53 ± 0.05 ml. of water ordinarily collected. Frequent readings of water volume, time, and temperature were taken until the reaction was 80% complete. Heating was ordinarily continued overnight to complete the reaction.

With only a few minor exceptions, the temperature for the 10 to 80% portion of the relatively slow reactions in the fourth and fifth sections of Table I was 81.8 ± 0.2°, while for the reactions in the other sections it was 81.0 ± 0.2°. It was found that the $t_{50\%}$ values, which were read from the plots of the yield of water *vs.* time, were readily reproducible to within 5%.

The reaction mixture was filtered through a Celite mat, and the mat was washed with benzene. Most of the solvent was removed from the combined filtrate and washings under reduced pressure and the residues were freed of the remainder of the solvent in an air stream. The products were purified by standard crystallization and distillation procedures until their melting points or refractive indices agreed satisfactorily with the literature values except for the following six products which had the indicated refractive indices: N-benzal-*p*-toluidine, $n^{21}D$ 1.6432; N-benzal-*m*-anisidine, $n^{21}D$ 1.6374; N-benzal-*o*-toluidine, $n^{21}D$ 1.6272; N-benzal-*o*-anisidine, $n^{21}D$ 1.6439; N-benzal-*t*-butylamine, $n^{20}D$ 1.5156; and N-benzal-1,1,3,3-tetramethylbutylamine, $n^{20}D$ 1.5130.

When, under conditions otherwise identical with those for the fifth experiment of the table, the amount of manganese dioxide was decreased from 0.4 to 0.3 to 0.2 mole, the yields of pure benzalaniline decreased from 84 to 66 to 0%; when the temperature was decreased from 111 to 81 to 52° (by changing the solvent) the yields were 70, 84, and 60%.

The oxidation of the hydrazobenzenes (last two sections of the table) was carried out with the standard 0.4 mole (34.78 g.) of manganese dioxide in order to facilitate comparison with the N-benzylanilines. Less manganese dioxide gave equally good yields of product, however, and the reaction tended to proceed even faster, probably because of increased efficiency of the stirring. Thus, when the amount of manganese dioxide was increased from 0.2 to 0.3 to 0.4 mole, the $t_{50\%}$ values were 24, 40, and 40 min., respectively. The total yields of water were 86, 96, and 100%, and the yields of product were 98, 97, and 97%.

Azobenzenes from Anilines.—When aniline and *p*-chloroaniline were oxidized under the standard conditions given for Table I, the yields of water were 100 and 112%, but the yields of the pure azobenzenes were only 47 and 72%; black tarry material was also produced. It was found that higher yields of product were obtained if the dehydration of the manganese dioxide (by refluxing for 5 hr. before the amine was added) was omitted. For the oxidation of anilines, the standard procedure was, therefore, modified by adding both the 0.05 mole of the aniline and the 0.4 mole of manganese dioxide after the 30 min. of refluxing to dry the apparatus. In all cases, heating was continued for 24 hr., at which time water evolution had virtually ceased. The total volume of water was ordinarily 3.25 to 3.50 ml. When the yield of the azobenzene was less than 60%, starting material was ordinarily recovered in 20 to 35% yield. The manganese dioxide employed for oxidation of the anilines was prepared as previously described[9] except that, after the final heating of the oxide, it was allowed to come into equilibrium with the moisture in the air as described above.

(12) (a) G. B. Barlin, K. H. Pausacker, and N. V. Riggs, *J. Chem. Soc.*, 3122 (1954); (b) K. H. Pausacker and J. G. Scroggie, *ibid.*, 4003 (1954); (c) E. Baer and A. L. Tosoni, *J. Am. Chem. Soc.*, **78**, 2857 (1956); (d) A. P. Terent'ev and Ya. D. Magilyanski, *Dokl. Akad. Nauk SSSR*, **103**, 91 (1955); *Chem. Abstr.*, **50**, 4807 (1956); (e) P. S. Raman, *Proc. Indian Acad. Sci.*, **45A**, 65 (1957); *Chem. Abstr.*, **51**, 13,795 (1957).

(13) K. H. Pausacker [*J. Chem. Soc.*, 1989 (1953)] proposes a free-radical mechanism for the oxidation of aniline to azobenzene by phenyliodosoacetate in benzene; hydrazobenzene is assumed to be an intermediate.

(14) All melting points are corrected.

(15) We wish to thank Dr. Franz Kasler for the microanalyses reported here.

(16) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(17) Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 3207 (1956).

(18) J. H. Billman and A. C. Riesing, *J. Org. Chem.*, **22**, 1068 (1957).

(19) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., Inc., New York, N. Y., 1961, pp. 631, 632.

When the amount of manganese dioxide employed for the oxidation of aniline was decreased from 0.4 to 0.3 to 0.2 mole, the yield of azobenzene decreased from 91 to 75 to 48%. When the temperature was decreased from 111 to 81 to 52°, by changing the solvent, the corresponding yields of azobenzene were 85, 91, and 76%.

Acknowledgment—It is a pleasure to acknowledge financial support by the National Science Foundation, the Union Carbide Corporation, and the National Institutes of Health which greatly aided the progress of this work.

Ring Closure of Ylidenemalononitriles. III.[1] Formation of Six-Membered Rings and Related Chemistry[2]

E. CAMPAIGNE, DONALD R. MAULDING,[3a] AND WENDELL L. ROELOFS[3b]

Contribution No. 1198 from the Chemistry Laboratories of Indiana University, Bloomington, Indiana

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Several γ-aryl ylidenemalononitriles, including that of a phenylacetaldehyde derivative, were cyclized in concentrated sulfuric or polyphosphoric acid to 1-naphthylamine derivatives. Surprisingly, ylidenemalononitriles derived from α-acetonaphthalene did not form six-membered rings *via* cyclization to the 8-position. Hydration to the *trans*-cyanoamide was the principal reaction in these cases. The ring closure was shown to proceed by attack of a protonated nitrile group, rather than an amido group, on the aromatic ring, by cyclizing *cis*-2-cyano-3-methyl-4-phenyl-2-butenamide, a reaction which failed for the *trans* isomer. The configuration of the isomers was established by n.m.r. studies. The ultraviolet absorption spectra of the hindered and unhindered 2-cyano- and 2-carboxamido-1-naphthylamines produced by these cyclizations are discussed.

Substituted indenones and indanones can be produced by strong acid treatment of the appropriate ylidenemalononitriles.[1,4] From the ring closure of these dinitriles, compounds containing newly formed five-membered rings were obtained. The study of this facile ring closure has now been extended to ylidenemalononitriles leading to six-membered rings.

Cyclizations of aromatic derivatives of nitriles to form six-membered cyclic ketones and aromatic amines are well known. Atkinson and Thorpe[5] prepared a series of 1,3-diaminonaphthalene derivatives by ring closing various derivatives of ethyl β-imino-α-phenylbutyrate in sulfuric acid. *o*-Biphenylacetonitrile and its derivatives have been converted to phenanthrylamines or phenanthrones by an intramolecular cyclization in sulfuric acid.[6] Howell and Taylor[7] prepared 1,2,3,4-tetrahydrofluoren-1-one from γ-3-indenylbutyronitrile in the presence of anhydrous zinc chloride and hydrogen chloride. Several other papers[8] report cyclizations involving nitrile groups to form six-membered heterocyclic compounds. The conversion of γ-(1-cyclohexenyl)butyronitrile to Δ^9-1-octalone in polyphosphoric acid[9] showed that ring closure of a nitrile can also occur by electrophilic attack on an olefinic double bond.

Only two reports have been found describing the cyclization of an ylidenemalononitrile to form a six-membered ring. Dufraisse and Etienne[10] accomplished the bicyclization of 1,3-diphenylisopropylidenemalononitrile to 11,12-diaminonaphthacene in a phosphoric acid–sulfuric acid–phosphorus pentoxide mixture. Jaeger[11] describes the ring closure of 2-(cyclohexylidene)cyclohexylidenemalononitrile to 10-amino-9-cyano-1,2,3,4,5,6,7,8-octahydrophenanthrene in sulfuric acid.

As shown by earlier results,[4] good yields of α-carboxamido-α,β-unsaturated ketones were obtained from the ring closure of certain α-cyano-β-substituted cinnamonitriles. In most instances, the second nitrile was hydrated during cyclization. It was of interest to investigate cyclizations of ylidenemalononitriles which could lead to six-membered cyclic compounds having the partial structure **1**, especially since this structure is present in certain antibiotics.

It was found that treatment of several ylidenemalononitriles (**2**) with sulfuric acid gave good yields of newly formed six-membered rings. The ring closure of ylidenemalononitrile **2a** to 2-cyano-3,4,4-trimethyl-1-keto-1,4-dihydronaphthalene (**4**) has already been reported.[4b] Ylidenemalononitriles (**2**), with R^1 = H, were prepared (Table I) and were all ring closed to derivatives of 1-naphthylamine (Table II).

A good yield of 2-cyano-3-methyl-1-naphthylamine (**3a**, Z = CN) was obtained when phenylisopropylidenemalononitrile (**2b**) was allowed to stand in concentrated sulfuric acid at room temperature for 1 hr. It was interesting to note that the amine was isolated from the acid solution after the reaction mixture was poured over ice. No further product was isolated when the mother liquor was made basic. The second nitrile group resisted hydration similar to that of **4** mentioned above. However, when the sulfuric acid solution was heated for 1 hr. at 90°, only the hydrated product **3a**

(1) Previous paper II: E. Campaigne, R. Subramanya, and D. R. Maulding, *J. Org. Chem.*, **28**, 623 (1963).

(2) This investigation was supported in part by Public Health Service Fellowship No. GPM-18,661 from the Division of General Medical Sciences, in part by Public Health Service Research Grant GM 10366-01, and in part by a grant from the Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y.

(3) Taken in part from the (a) Ph.D. thesis of D. Maulding, June, 1962, Bristol Predoctoral Fellow, 1960–1962; (b) Ph.D. thesis to be submitted by W. Roelofs, National Institute of Health Predoctoral Fellow, 1962–1964.

(4) (a) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, and D. R. Maulding, *J. Org. Chem.*, **27**, 4428 (1962); (b) E. Campaigne and D. R. Maulding, *ibid.*, **28**, 1391 (1963).

(5) E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1906 (1906).

(6) C. K. Bradsher, D. J. Beavers, and E. D. Little, *J. Am. Chem. Soc.*, **76**, 948 (1954); **78**, 2153 (1956).

(7) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.* 3011 (1957).

(8) (a) A. Schaarschmidt, *Ann.*, **409**, 59 (1915); (b) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27**, 1659 (1962); (c) C. R. Hauser and J. G. Murray, *J. Am. Chem. Soc.*, **77**, 2851 (1955); (d) M. Lamant and M. Le Moine, *Bull. soc. chim. France*, 2150 (1962); (e) W. Baker, A. Pollard, and R. Robinson, *J. Chem. Soc.*, 1468 (1929).

(9) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).

(10) C. Dufraisse and A. Etienne, *Compt. rend.*, **239**, 1744 (1954); **240**, 265 (1955).

(11) H. Jaeger, *Chem. Ber.*, **95**, 242 (1962).

TABLE I

PREPARATION AND PROPERTIES OF YLIDENEMALONONITRILES

Compound	Reaction time, hr.	Yield, %	B.p. (mm.) or m.p., °C.	$n^{24}D$	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
2b	8	78	120 (0.4)	1.5518	$C_{12}H_{10}N_2$			15.38			15.51
2c	12	74	67–68[a]		$C_{12}H_{14}N_2$						
2d	5	75	93–94 (0.01)	1.5442	$C_{12}H_{10}N_2$	79.09	5.53	15.38	78.80	5.57	15.53
2e	15	70	142–143 (0.05)	1.5446	$C_{16}H_{18}N_2O$	75.59	7.13	11.02	75.46	7.21	11.26
5a	3	90	168–169[b]		$C_{14}H_8N_2$						
5b	24	40	73–74		$C_{15}H_{10}N_2$	82.52	4.62	12.84	82.68	4.50	13.24

[a] J. G. Murphy [*J. Org. Chem.*, **26**, 3104 (1961)] reported m.p. 67–68° and a 97% yield. [b] H. G. Sturz and C. R. Noller [*J. Am. Chem. Soc.*, **71**, 2949 (1949)] report m.p. 170–171.5°; B. B. Corson and R. W. Stoughton [*ibid.*, **50**, 2825 (1928)] report m.p. 173.5–174.5°.

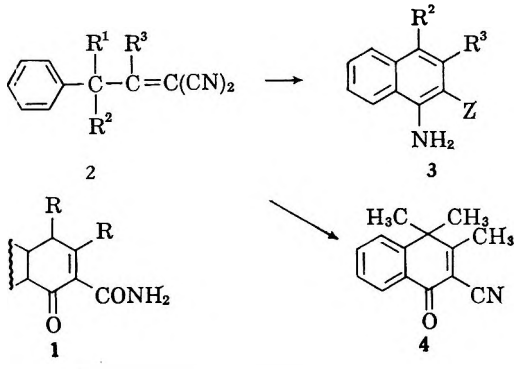
TABLE II

RING CLOSURE OF YLIDENEMALONONITRILES TO NAPHTHYLAMINE DERIVATIVES

Reactant	Reaction time, hr.[a]	Temp., °C.	% yield of 3, Z = CN	% yield of 3, Z = $CONH_2$
2b	1	25[b]	73	0
	1	90	0	72
2c	6	25	80	0
	0.33	90	22	1
	4[c]	90	0	62
2d	1	5	63	0
	1	25	57	28
	0.125	90	0	44,[d] 45
2e	0.33[c]	120	10	0

[a] In sulfuric acid unless otherwise stated. [b] Room temperature, approximately 25°. [c] In polyphosphoric acid. [d] Bisulfate salt.

(Z = $CONH_2$) was isolated. In this case, the product precipitated only after basification of the dilute acidic solution.



2a, $R^1 = R^2 = R^3 = CH_3$
b, $R^1 = R^2 = H$; $R^3 = CH_3$
c, $R^1 = H$; R^2-R^3 = $—CH_2CH_2CH_2CH_2—$
d, $R^1 = R^3 = H$; $R^2 = CH_3$
e, p-OCH_3, $R^1 = H$; $R^2 = R^3 = C_2H_5$

3a, $R^2 = H$; $R^3 = CH_3$
b, R^2-R^3 = $—CH_2CH_2CH_2CH_2—$
c, $R^2 = CH_3$; $R^3 = H$
d, 7-OCH_3, $R^2 = R^3 = C_2H_5$; Z = CN

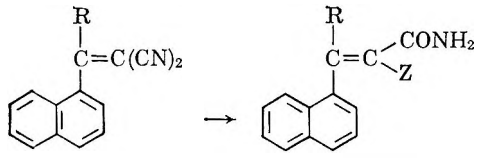
Cyclization of 2-phenylcyclohexylidenemalononitrile (**2c**) in concentrated sulfuric acid at room temperature gave 9-amino-10-cyano-1,2,3,4-tetrahydrophenanthrene (**3b**, Z = CN) as the sole product. Again this cyano derivative was isolated from the dilute acidic solution. Heating the reaction mixture on the steam bath for several hours gave the cyano derivative as the major product, but basification of the mother liquor yielded a small amount of the hydrated product **3b** (Z = $CONH_2$). Reaction in polyphosphoric acid on a steam bath for 4 hr. afforded the hydrated compound as the only product.

In the formation of five-membered rings[4] it was found that a bulky group on the α-position of the ylidenemalononitrile was necessary for ring closure. It was suggested that this group provided distortion of the ring-deactivating conjugated resonance system between the protonated nitrile and the aromatic ring, thus facilitating electrophilic attack by the $-C^+=NH$ group. In the present system, the protonated nitrile is not conjugated with the aromatic ring and, therefore, ring closure should be feasible with malononitrile adducts of phenylacetaldehyde derivatives containing only hydrogen on the α-position. The condensation of phenylacetaldehyde with malononitrile could not be effected due to side reactions involving the highly reactive methylene group of the aldehyde. The condensation with malononitrile was successful when one of the methylene hydrogens of the aldehyde was replaced by a methyl group, giving the adduct **2d**. The cyclization of **2d** is the first described for an aldehyde–malononitrile adduct. Treatment with sulfuric acid at 5° gave only 2-cyano-4-methyl-1-naphthylamine (**3c**, Z = CN), but, at room temperature, a mixture of the above cyano derivative and the hydrated product **3c** (Z = $CONH_2$) was obtained. Again the cyano derivative was isolated from the acidic solution and the hydrated product after basifying. Treatment in sulfuric acid at 90° followed by dilution with water caused the bisulfate salt of the hydrated product **3c** (Z = $CONH_2$) to precipitate from the acidic solution, and some free hydrated product was obtained on basification of the mother liquor. The bisulfate salt was readily converted to **3c** by stirring in an alkaline solution.

Ylidenemalononitrile **2e**, in which a methoxy group on the aromatic ring is so positioned that ring closure will occur at the *meta* position rather than the more active *ortho* or *para* positions, when treated with sulfuric acid, yielded a black tar when the reaction mixture was poured over ice, which could not be crystallized from organic solvents nor purified by column chromatography. Cyclization in polyphosphoric acid yielded a red solid, which proved to be the cyanoamine **3d**.

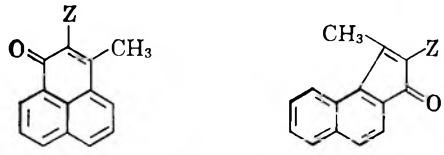
An attempt to extend the ring-closure reaction to ylidenemalononitriles of α-naphthyl derivatives was not successful. α-Naphthylmethylidenemalononitrile (**5a**) did not cyclize to form either a five- or six-membered ring when heated in concentrated sulfuric acid, but instead was hydrated to the cyanoamide **6a**. This is analogous to the results of strong acid treatment of benzylidenemalononitrile.[4a] In this case, ring closure might have occurred at the 8-position, forming a new

six-membered ring. The substitution of a methyl group for R on compound **5** did not enhance ring closure to the 8-position to form the six-membered ring compound **7**. Instead, treatment of compound **5b** with concentrated sulfuric acid produced a small amount of



5a, R = H
b, R = CH_3

6a, R = H; Z = CN
b, R = CH_3; Z = CN
c, R = CH_3; Z = $CONH_2$



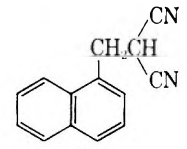
7a, Z = CN
b, Z = $CONH_2$

8a, Z = CN
b, Z = $CONH_2$

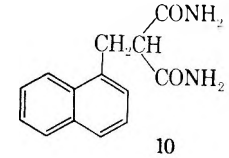
ring-closed product which appeared to be a mixture of **8a** and **b**. The products were separated by preparative thin layer chromatography (t.l.c.), but could not be purified by recrystallization. A small amount of pure red crystals was obtained by sublimation and assigned the structure **8a**. The analysis and the downfield shift of the methyl group resonance in the n.m.r. spectra to 2.74 p.p.m. (from tetramethylsilane) are consistent with either structure **7a** or **8a**. The carbonyl absorption, however, at 1710 cm.$^{-1}$ corresponds to that of a five-membered ring ketone. The compound isolated by t.l.c. and assigned structure **8b** also had carbonyl absorption corresponding to a five-membered ring ketone at 1695 cm.$^{-1}$. The carbonyl absorption of compounds analogous to the six-membered ring ketone of structure **7** has been reported to be in the range of 1632–1637 cm.$^{-1}$.[12]

Only hydration occurred on treating adduct **5b** in polyphosphoric acid, giving the diamide **6c** on prolonged heating, and the cyanoamide **6b** under milder conditions. The cyanoamide **6b** was also obtained when **5b** was treated with concentrated sulfuric acid in dimethylformamide. Only one isomeric form of the cyanoamides **6a** and **6b** was obtained in the above reactions as evidenced by movement as a single spot on thin layer chromatography plates. Structure **6**, with carboxamide *trans* to naphthyl, represents the least hindered configuration and, in the case of **6b**, was supported by n.m.r. data. The methyl group resonance of **6b** is shifted 0.15 p.p.m. downfield from that of **5b**, (δ 2.63), analogous to data from compound **15a**, also possessing carboxamide *cis* to methyl (see later discussion). The n.m.r. spectrum of **6a** could not be obtained because of low solubility.

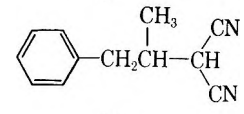
It was thought that the ring closure might be effected if the double bond were reduced and resonance between the naphthalene ring and cyano groups eliminated. The reduction was accomplished quite smoothly by hydrogenation of **5a** over platinum oxide. The reduced adduct **9** gave only water-soluble products, probably the



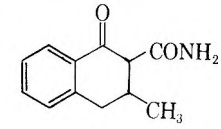
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10



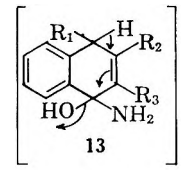
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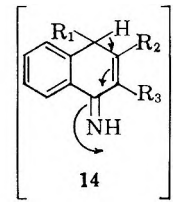
12

result of sulfonation, when treated with concentrated sulfuric acid, but formed the hydrated diamine **10** when treated with polyphosphoric acid. However, a six-membered ring was readily formed when the reduced adduct **11** was cyclized in concentrated sulfuric acid, forming the α-tetralone derivative **12**.

In discussing the mechanism of the ring closure of ylidenemalononitriles to six-membered rings, two possibilities must be considered. One possible mechanism involves the hydration of a cyano group and ring closure of the resulting amide.[8c] While by this mechanism one would expect naphthol as a result of ammonia elimination (apparent $k_{NH_3^+} >> k_{OH}$),[13a] still elimination of water from **13** could lead to the aromatic amine. The other mechanism would require ring closure by



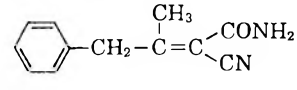
13



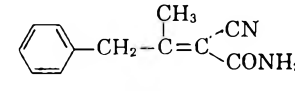
14

attack of protonated nitrile on the aromatic ring to give an imine intermediate **14**. Evidence supporting the latter mechanism has now been obtained.

The two isomers obtained from the condensation of cyanoacetamide with phenylacetone were isolated by fractional crystallization and preparative t.l.c. The physical data (Table III) are in accord with the assignment of the *cis* and *trans* structures **15a** and **b**. Isomer

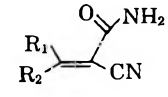


15a



15b

15a, with carboxamide *trans* to benzyl, would be the least hindered, which would account for the higher yield of **15a** from the condensation reaction and its lower solubility in ethyl acetate. The most conclusive evidence, however, is obtained from the n.m.r. data. The isomers can be assumed to be in the planar *S-cis* conformation **16** in which the carbonyl group will cause maximum deshielding of R_1.[13b] The methyl group of



16

(12) a) R. D. Campbell and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 3456 (1957); (b) N. H. Cromwell, D. B. Capps, and S. E. Palmer, *ibid.*, **73**, 1226 (1951).

(13) (a) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 139; (b) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 122–123.

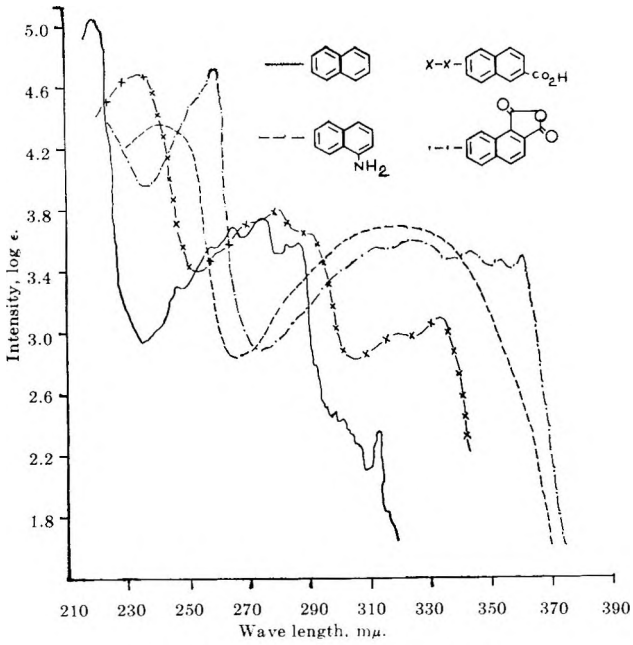


Fig. 1.—Ultraviolet spectra in ethanol.

isomer **15a** resonates 0.14 p.p.m. downfield from that of isomer **15b**, and the methylene group of isomer **15b** resonates 0.36 p.p.m. downfield from that of isomer **15a**. The magnitude of deshielding is less with the methyl group resonance because of its free rotation.[13b] The fact that the difference of chemical shifts is due to a deshielding downfield shift rather than a shielding upfield shift is supported by the corresponding δ-values of the dicyano compound **2b** (CH_3, 2.1; and $-CH_2-$, 3.8). These values agree quite well with the chemical shifts of the groups *trans* to the deshielding carbonyl group, therefore, indicating that it is the *cis* groups which are affected.

TABLE III

PROPERTIES OF ISOMERS 15a AND b

Isomer	M.p., °C.	R_f in ether	%[a] in crude product	n.m.r. peaks[b] CH_3	$-CH_2-$	Ar
15a	140–141	0.62	56	2.29	3.85	7.2
15b	135.5–136.0	0.75	44	2.15	4.21	7.26

[a] Calculated from the n.m.r. spectrum of crude condensation material using the ratio of peak areas. [b] Parts per million downfield from tetramethylsilane.

Isomer **15a** (cyano *cis* to aryl) was cyclized quite readily in concentrated sulfuric acid at 5° to the carboxamidoamine **3a** (Z = $CONH_2$). Isomer **15b** (carboxamido *cis* to aryl) could not be ring closed, even though it was treated at a higher temperature. These facts support the theory that the nitrile group is directly involved in the ring closure and not hydrated first to an amide.

The Ultraviolet Spectra of Substituted 1-Naphthylamines.—The cyclization of ylidenemalononitriles has made available a series of 1-naphthylamines (**3**) containing conjugatable substituents on the 2-position. A carboxamido group on the 2-position would be subject to steric hindrance by alkyl groups on the 3-position and cause inhibition of its resonance interaction with the aromatic nucleus. Such inhibition of resonance would modify the effects of extending conjugation on the various bands in the ultraviolet absorption spectra.

It has been shown that extension of conjugation in a given direction will primarily affect a band polarized in that direction. The polarization of the three bands of naphthalene (Fig. 1) are summarized in Table IV.[14]

TABLE IV

POLARIZATION OF NAPHTHALENE BANDS

Band	Polarization	Wave length, mμ	Log ε
$^1L_{b_1}$ (A)	Longitudinal[a]	221	4.98
^1L_a (B)	Transverse[b]	286	3.62
$^1L_{b_2}$ (C)	Longitudinal	312	2.40

[a] Parallel to the long axis of the molecule. [b] Perpendicular to the long axis of the molecule.

It was further shown that a conjugatable substituent at position 1 extends conjugation in a transverse direction (species **17**) and causes bathochromic and hyperchromic effects, especially in the 285-mμ band (see 1-naphthylamine, Fig. 1). A conjugated substituent at



17 **18**

position 2 (species **18**) will extend conjugation in a longitudinal direction, producing bathochromic and hyperchromic effects in the two longitudinal-polarized bands, especially the C band (see 2-naphthoic acid,[15] Fig. 1).

The spectra obtained from naphthalene derivatives with conjugatable substituents in the 1- and 2-positions have been discussed by Hirschberg and Jones[15] using naphthalene-1,2-dicarboxylic acid anhydride (in *n*-heptane, Fig. 1), and various derivatives. It is evident from Fig. 1 that the spectrum of the anhydride must result from a mixture of species **17** and **18** giving the resulting red shift and intensification to all three bands of naphthalene. Bands A and C then should decrease in intensity and be shifted to shorter wave lengths in the ultraviolet spectra of compounds containing a conjugatable substituent in the 1-position and a sterically hindered conjugatable substituent in the 2-position.

In the present study, it was found that the ultraviolet spectra of the aminonitriles (Fig. 2, I–III) were similar to that of naphthalene-1,2-dicarboxylic acid anhydride. This shows the lack of inhibition of resonance in compounds II and III owing to linearity of the cyano group. The spectrum of the unhindered aminoamide (Fig. 2, IV) was found to be quite analogous to those of the aminonitriles and the anhydride. The remaining two aminoamides (V and VI) containing an alkyl group on the 3-position gave different absorption spectra. The C band found at 355–365 mμ in the spectra of the unhindered amide and nitriles was missing in the spectra of the amides V and VI, probably because of fusion with band B, which had no significant shift. Band A, at 268 mμ in the unhindered aminoamide IV, exhibited a hypsochromic shift of 30 mμ for

(14) H. H. Jaffe and Milton Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 305–307.

(15) Y. Hirschberg and R. Norman Jones, *Can. J. Research*, **27B**, 437 (1949).

the most hindered aminoamide V, and 19 mμ for VI. These data are in accord with the fact that a loss of conjugation at the 2-position will alter the longitudinal-polarized bands A and C.

Further evidence for the steric hindrance of the 2-carboxamide group was obtained from the ultraviolet spectra of the amine salts (Fig. 3, Ia–VIa). In the salt form, the unshared pair of electrons of the amine are protonated and, therefore, cannot interact with those of the nucleus. The quaternary amine then produces inductive effects analogous to those of a methyl group.[16] In the present study, the production of an amine salt would eliminate the resonance interaction of species **17** and leave only the resonance interaction of the 2-substituent. Steric hindrance of the 2-substituent would cause the absorption spectrum to approach that of an alkyl-substituted naphthalene, with a low intensity C band.

In accord with these facts, the aminonitrile salts Ia–IIIa gave absorption spectra quite analogous to that of 2-naphthoic acid (Fig. 1). Similar to the results from the free bases, the spectrum of the unhindered aminoamide salt IVa was almost identical with that of the corresponding aminonitrile salt Ia. The spectra of the hindered aminoamide salts Va and VIa, however, exhibit hypochromic and hypsochromic effects in the C band along with a large shift to shorter wave lengths in the A band.

Although the most hindered carboxamido-containing compounds V and Va absorb at shorter wave lengths for most of the peaks than the corresponding less hindered compounds VI and VIa, this would not necessarily constitute evidence for greater steric hindrance, since the difference in absorption may be due to the increased alkyl substitution of compounds VI and VIa.

Experimental[17]

Preparation of the Ylidenemalononitriles.—The method used was the same as that described in previous papers[4] following the procedure of Mowry.[1,8] The reaction conditions and physical properties of the dinitriles are listed in Table I.

Ring Closure of Phenylisopropylidenemalononitrile (2b). A.—Two grams of **2b** was dissolved in 20 ml. of concentrated sulfuric acid and allowed to stand at room temperature for 1 hr. The dark green solution was poured over 200 g. of ice and the solid was collected by filtration. Recrystallization from methanol gave 1.45 g. (73%) of **3a** (Z = CN), m.p. 146–147°; ν_{max}^{KBr} 3525, 3410, and 3250 (NH), and 2203 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.87; H, 5.68; N, 15.47.

B.—Two grams of **2b** was dissolved in 20 ml. of concentrated sulfuric acid and heated at 90° for 1 hr., then poured over ice. No precipitate was obtained until the solution was made basic with 15% sodium hydroxide. The white solid was collected by filtration to yield 1.6 g. (73%) of **3a** (Z = $CONH_2$), m.p. 210–213°. Recrystallization from methanol gave an analytical sample, m.p. 214–215°; ν_{max}^{KBr} 3350 and 3140 (NH), and 1640 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.05; N, 4.00. Found: C, 71.91; H, 5.94; N, 14.19.

(16) R. Norman Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(17) Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord and n.m.r. spectra were determined in deuteriochloroform at 60 Mc. with a Varian A-60 spectrometer, employing tetramethylsilane as an internal reference. Chemical shifts are given in parts per million downfield from tetramethylsilane. The ultraviolet absorption spectra were determined with a Cary Model 14 recording spectrometer using 1-cm. sample cells.

(18) D. T. Mowry, *J. Am. Chem. Soc.*, **67**, 1050 (1945).

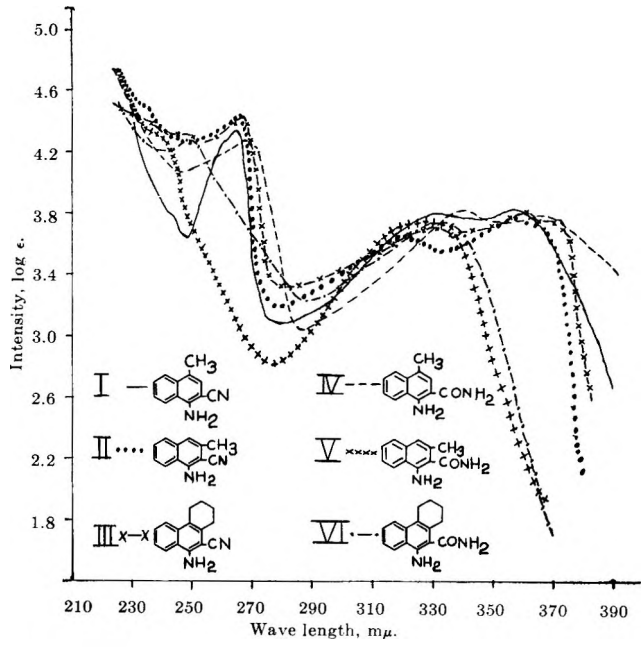


Fig. 2.—Ultraviolet spectra in 95% ethanol.

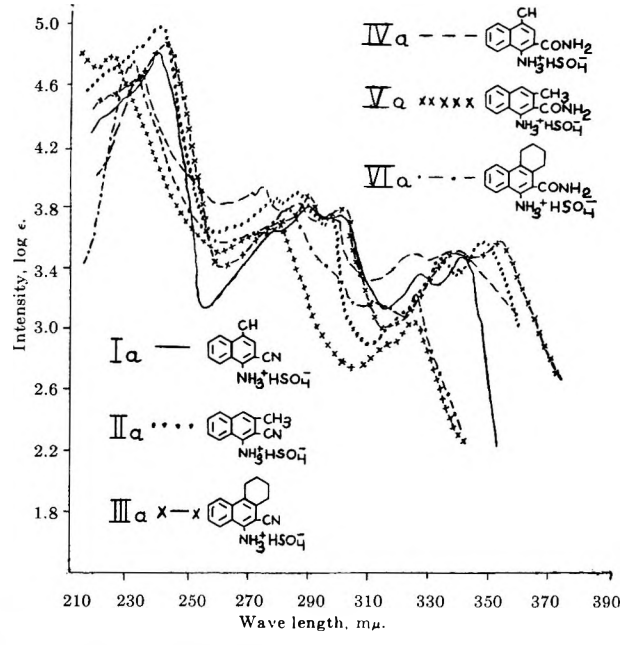


Fig. 3.—Ultraviolet spectra in 50% sulfuric acid.

Ring Closure of 2-Phenylcyclohexylidenemalononitrile (2c). A.—Two grams of **2c** was dissolved in 20 ml. of concentrated sulfuric acid and allowed to stand at room temperature for 6 hr. before pouring over ice. Filtration and subsequent recrystallization from methanol yielded 1.6 g. (80%) of **3b** (Z = CN) as colorless crystals, m.p. 165–166°; ν_{max}^{KBr} 3510, 3410, and 3290 (NH), and 2200 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.10; H, 6.41. Found: C, 80.92; H, 6.55.

B.—Two grams of **2c** treated with 20 ml. of concentrated sulfuric acid at 90° for 20 min., then poured over ice, gave 0.44 g. (22%) of **3b** (Z = CN). Basification of the acidic solution precipitated 0.02 g. (1%) of the hydrated product **3b** (Z = $CONH_2$). Recrystallization from methanol gave colorless crystals, m.p. 265–268°; ν_{max}^{KBr} 3415 and 3225 (NH), and 1630 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.98; H, 6.89; N, 11.50.

Two grams of **2c** mixed with 80 g. of polyphosphoric acid and heated at 90° for 4 hr. gave 1.3 g. (62%) of the hydrated product **3b** (Z = $CONH_2$) when poured into 500 ml. of water.

Ring Closure of 2-Phenylpropylidenemalononitrile (2d). A.—Two grams of 2d was dissolved in concentrated sulfuric acid at 5° and kept at 5–10° for 1 hr. before pouring over ice. The white solid was collected and recrystallized from methanol to give 1.25 g. (63%) of **3c** (Z = CN), m.p. 120–121°; ν_{max}^{KBr} 3450, 3360, and 3240 (NH), and 2200 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.99; H, 5.30; N, 15.55.

B.—Two grams of 2d placed in 20 ml. of concentrated sulfuric acid for 1 hr. at room temperature gave 1.14 g. (57%) of **3c** (Z = CN) when poured over ice. Basification of the acidic solution with 15% sodium hydroxide gave a white precipitate, which from methanol gave 0.62 g. (28%) of the hydrated product **3c** (Z = $CONH_2$), m.p. 222–224°. An analytical sample melted at 226.5–227.5°; ν_{max}^{KBr} 3410, 3320, and 3150 (NH), and 1640 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.05; N, 14.00. Found: C, 72.18; H, 6.21; N, 14.22.

C.—Two grams of 2d was dissolved in 20 ml. of concentrated sulfuric acid and heated for 10 min. at 90°. After pouring the reaction mixture over ice, a white solid was collected by filtration. Recrystallization from methanol gave 1.32 g. (44%) of the bisulfate salt of **3c** (Z = $CONH_2$), m.p. 222–223°.

Anal. Calcd. for $C_{12}H_{14}N_2O_5S$: C, 48.32; H, 4.73; N, 9.40. Found: C, 48.38; H, 4.63; N, 9.65.

Basification of the mother liquor gave 1 g. (45%) of **3c** (Z = $CONH_2$), m.p. 223–225°. This carboxamido amine was also obtained by stirring the bisulfate salt in a solution of potassium carbonate or sodium hydroxide.

2-Cyano-3,4-diethyl-7-methoxy-1-naphthylamine (3d).—One gram of 2e was mixed with 20 ml. of polyphosphoric acid and heated at 120° for 20 min. After cooling to 80°, the deep red solution was poured into 50 ml. of ice–water. Filtration gave 0.4 g. of red-brown solid. Neutralization of the acidic solution gave no further product. The solid was dissolved in chloroform and placed on a column packed with activated alumina. Elution with chloroform–methanol (95:5) gave 0.1 g. (10%) of red crystals, m.p. 170–180°. Recrystallization from benzene–hexane gave an analytical sample, m.p. 189–191°; ν_{max}^{KBr} 3350 and 3370 (NH), and 2200 cm.$^{-1}$ (CN); $\lambda_{max}^{95\%\ ethanol}$ mμ (log ε): 220–230 sh (4.09), 246 (4.14), 260 sh (4.07), and 345–350 (3.99).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.13; N, 11.02. Found: C, 75.46; H, 7.31; N, 11.12.

Attempted Cyclization of α-Naphthylmethylidenemalononitrile (5a).—Three grams of 5a was dissolved in 30 ml. of concentrated sulfuric acid, heated on a steam bath for 10–15 min., and then poured over 300 g. of crushed ice. The solid that formed was collected by filtration. Ether extraction and neutralization of the acidic solution produced no other material. Recrystallization of the solid from benzene gave white plates, 1.5 g. (45%), of 6a, m.p. 194–196°; ν_{max}^{KBr} 3535 and 3255 (NH), 2240 (CN), and 1670 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.67; H, 4.51; N, 12.61. Found: C, 75.37; H, 4.59; N, 12.66.

The mixture melting point of 6a and the condensation product from α-naphthaldehyde and cyanoacetamide was not depressed.

Attempted Cyclization of 1-(α-Naphthyl)ethylidenemalononitrile (5b). A.—Two grams of 5b was added to 20 ml. of concentrated sulfuric acid and allowed to stand at room temperature for 1 hr. before pouring over ice. The orange solid (2 g.) was collected by filtration and placed on a column packed with silica gel. Elution with chloroform gave 160 mg. of a dark red-brown solid, m.p. 110–115°. Further elution with chloroform–methanol solutions produced 1.12 g. of uncharacterized tars. The dark red-brown solid was purified on preparative t.l.c. plates using Silica Gel H developed with chloroform to give 90 mg. (4%) of a yellow powder, m.p. 140–150°. It could not be recrystallized from various organic solvents. The infrared spectrum indicates the powder to be compound **8b**: $\nu_{max}^{CHCl_3}$ 3390 and 3310 (NH), 1695 (CO), and 1660 and 1640 cm.$^{-1}$ (amide CO).

B.—The crude product obtained from a reaction carried out under conditions similar to part A was sublimed at 100° (1 mm.). A red solid was obtained and recrystallized from acetic acid to give 40 mg. (2%) of red crystals, m.p. 67–69°. The infrared spectrum supports the assignment of structure 8a: ν_{max}^{KBr} 2210 (CN) and 1710 cm.$^{-1}$ (CO). The n.m.r. spectrum showed a peak at δ 2.74 (CH_3) along with a complex multiplet for the aromatic hydrogens at δ 7.5–8.2.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 82.21; H, 4.14. Found: C, 82.40; H, 4.49.

C.—One gram of 5b was heated in 20 g. of polyphosphoric acid on a steam bath for 3 hr. and poured over ice. Polymeric material melting above 300° was obtained by filtration. Extraction of the diluted acidic solution with chloroform yielded 140 mg. of white **6c**, m.p. 229–231° (from ethanol); ν_{max}^{KBr} 3401 and 3160 (NH), and 1665 and 1645 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.98.

D.—One gram of 5b was heated in 20 g. of polyphosphoric acid on a steam bath for 1 hr. and poured over ice. Chloroform extraction of the acidic solution gave 50 mg. of **6b**, m.p. 208–210° (from ethanol); ν_{max}^{KBr} 3410 and 3200 (NH), 2217 (CN), and 1665 cm.$^{-1}$ (amide CO). The n.m.r. spectrum showed a peak at δ 2.81 for 3 protons.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.08. Found: C, 75.92; H, 5.24.

E.—A solution of 2 g. of 5b, 10 ml. of dimethylformamide, and 10 ml. of concentrated sulfuric acid was stirred for 1 hr. at room temperature. The dark solution was poured over ice, and the resulting precipitate was collected by filtration. Unchanged starting material (1.5 g.) was obtained by washing the precipitate with ether and evaporating the ether extract. The residue not soluble in ether was recrystallized from ethanol to give 0.24 g. of colorless crystals of **6b**, m.p. 209–210°. The mixture melting point with the sample obtained in part D was undepressed.

α-Naphthylmethylmalononitrile (9).—A mixture of 10 g. of α-naphthylmethylidenemalononitrile (5a), 0.4 g. of platinum oxide, and 250 ml. of absolute ethanol was subjected to 45 p.s.i. of hydrogen for 3 hr. The catalyst was filtered, and the solvent was evaporated *in vacuo* to leave 9.5 g. of a dark oil. The oil crystallized on cooling and was recrystallized from 95% ethanol to give 7.23 g. (72%) of **9**, m.p. 63–64°. An analytical sample had m.p. 67–68°; ν_{max}^{KBr} 2210 and 2290 cm.$^{-1}$ (CN); the n.m.r. spectrum showed AB_2 pattern[19] centered at δ 3.82 and 3.69.

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.52; H, 4.89; N, 13.59. Found: C, 81.57; H, 5.10; N, 13.21.

Attempted Ring Closure of 9. A.—One gram of 9 was dissolved in concentrated sulfuric acid and allowed to stand at room temperature for 2 hr. before it was poured over ice. No product could be obtained by extraction of the acidic solution with chloroform or by adding base and extracting the basic solution.

B.—Two grams of 9 was placed in 40 g. of polyphosphoric acid and heated at 120° for 0.5 hr. It was cooled to 80° and poured over ice. The precipitate was collected by filtration and recrystallized from methanol to give 1.4 g. (60%) of **10**, m.p. 255–260°. Further recrystallizations from acetic acid–water gave colorless crystals, m.p. 267–269°; ν_{max}^{KBr} 3400 and 3210 (NH), and 1670 and 1650 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 68.84; H, 5.89; N, 10.93. Found: C, 69.16; H, 5.96; N, 11.57.

2-Cyano-3-methyl-4-phenylbutyronitrile (11).—A solution of 10 g. of phenylisopropylidenemalononitrile (**2b**) in 200 ml. of absolute ethanol was shaken under hydrogen at 3 atm. with 0.4 g. of platinum oxide in a Parr low-pressure hydrogenation apparatus. The catalyst was filtered and the solvent was evaporated *in vacuo* to yield an oil residue. Distillation under reduced pressure gave 8.1 g. (80%) of a colorless liquid, b.p. 103–105° (0.01 mm.); ν_{max}^{film} 2280 and 2270 cm.$^{-1}$ (CN); n.m.r. spectrum showed a doublet at δ 1.3 (J = 6 c.p.s., 3 protons), complex multiplet from 2.16–2.58 (1 proton), doublet at 2.8 (J = 6 c.p.s., 2 protons), doublet at 3.54 (J = 5 c.p.s., 1 proton), and complex multiplet from 7.17–7.42 (5 protons).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.21; H, 6.57; N, 15.21. Found: C, 78.27; H, 6.45; N, 15.50.

2-Carboxamido-3-methyl-1-tetralone (12).—Two grams of 9 was stirred in 15 ml. of concentrated sulfuric acid for 4 hr. and poured over ice. The orange solid was collected by filtration and recrystallized from 95% ethanol to give 1.31 g. (60%) of **12**, m.p. 182–183°. An analytical sample had m.p. 183–184°; ν_{max}^{KBr} 3400 and 3200 (NH), 1670 (CO), and 1640 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.45; N, 6.90. Found: C, 71.18; H, 6.35; N, 6.97.

The **2,4-Dinitrophenylhydrazone** of 12 melted at 225–227°.

Anal. Calcd. for $C_{18}H_{17}N_5O_5$: N, 18.27. Found: N, 18.48.

Condensation of Cyanoacetamide with Phenylacetone to Give 15a and 15b.—A mixture of 80 g. (0.6 mole) of phenylacetone, 50.4 g. (0.6 mole) of cyanoacetamide, 4.62 g. of ammonium acetate, 7.2 g. of glacial acetic acid, and 60 ml. of benzene was refluxed overnight in a system with a Dean–Stark trap. The

(19) Ref. 13, p. 93, Fig. 6.7c.

reaction mixture was cooled and filtered to yield 104 g. of crude product, m.p. 75–87°. Concentration of the mother liquor afforded another 10 g. of product. Development of the crude product on Silica Gel G plates with ether gave two spots, R_f 0.62 and 0.75. Recrystallization of the crude product from ethyl acetate–hexane five times gave only the less soluble isomer **15a**, m.p. 140–141°; R_f 0.62; ν_{max}^{KBr} 3390, 3300, and 3200 (NH), 2210 (CN), and 1680 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.05; N, 14.00. Found: C, 71.97; H, 6.04; N, 14.30.

The soluble isomer **15b** was obtained by evaporating the mother liquor from the recrystallizations of isomer **15a** and placing 100 mg. of the residue on preparative Silica Gel G plates (1.5 mm. thick). Development with ether and extraction of the top band with acetone gave 50 mg. of isomer **15b**, m.p. 135.5–136°, R_f 0.75. The mixture melting point with isomer **15a** was 105–109°. The infrared spectrum in chloroform was identical with that of isomer **15a** in chloroform, but the spectrum of the KBr mull differed: ν_{max}^{KBr} 3410, 3350, 3300, and 3160 (NH), 2210 (CN), and 1680 cm.$^{-1}$ (amide CO).

Ring Closure of Isomer 15a.—One gram of isomer **15a** was dissolved in 5 ml. of concentrated sulfuric acid at 5° and maintained between 5–10° for 15 min. The green solution was poured over ice. No precipitation occurred until the solution was neutralized with 15% sodium hydroxide. The white solid (0.98 g., m.p. 175–190°) was collected by filtration and recrystallized from methanol to give 0.48 g. (48%) of **3a** (Z = $CONH_2$). A mixture melting point with a sample obtained by ring closure of **2b** was undepressed and their infrared spectra were identical.

Attempted Ring Closure of Isomer 15b.—A solution of 0.47 g. of isomer **15b** and 4 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 2.5 hr. before pouring over ice. The precipitate was collected to give 0.27 g. of starting material, m.p. 115–120°. This was confirmed by identical infrared spectra and R_f values on t.l.c. Neutralization of the acidic mother liquor did not yield any precipitate.

A New Sesquiterpene Lactone with Analgesic Activity from *Helenium amarum* (Raf.) H. Rock

R. A. LUCAS, S. ROVINSKI, R. J. KIESEL, L. DORFMAN, AND H. B. MACPHILLAMY

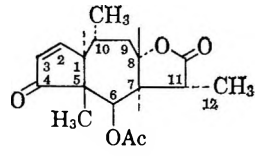
Research Department, Ciba Pharmaceutical Company, Division of Ciba Corporation, Summit, New Jersey

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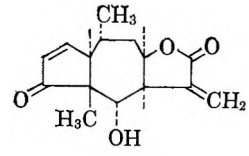
A new sesquiterpene lactone with potent analgesic activity has been isolated from *Helenium amarum* (Raf.) H. Rock. The structure of this substance has been shown to be Ia by correlation with another accompanying lactone (III), which in turn was related to desacetyldihydroisotenulin (XII). The activity of a number of related substances was investigated.

In connection with our general medicinal plant screening program, we had occasion to submit a crude extract of *Helenium amarum* (Raf.) H. Rock[1] to broad pharmacological investigation.[2] On subcutaneous administration, this material was found to have an analgesic activity in mouse tail flick test[3] which was not antagonized by nalorphine. It was also shown to inhibit the writhing syndrome in mice induced by the intraperitoneal injection of acetic acid. Further, the extract demonstrated no anticonvulsant properties nor did it cause any alteration in spinal reflexology in cats.

The above combination of biological properties seemed to warrant an attempt to identify the chemical individual responsible for this activity. The use of solvent distribution and of chromatographic techniques led to the isolation of two new substances. One, which we have called amaralin, $C_{15}H_{20}O_4$, m.p. 195–198°, $[\alpha]^{25}D$ +5°, was responsible for the major part of the analgesic action. The other, later shown to be identical with aromaticin,[4] $C_{15}H_{18}O_3$, m.p. 234–236°, $[\alpha]^{26}D$ +14°, was inactive. There also was a relatively large quantity of tenulin known to be the main sesquiterpene lactone of *Helenium amarum* (Raf.) H. Rock.[5] The empirical formulas of the two new substances indicated that they, too, were probably sesquiterpenes and, therefore, possibly related structurally to isotenulin or to helenalin.[6]



Isotenulin



Helenalin

That amaralin had one hydroxyl group could be inferred from its infrared absorption at 3430 cm.$^{-1}$ and by the formation of a monoacetate (Ib), which no longer had an infrared absorption in the hydroxyl region. This was further supported by the observed downfield shift of the n.m.r. signal at 3.81 p.p.m. in amaralin to 4.71 p.p.m. in the acetate (Table I). Such a shift would be expected for a proton attached to a carbon bearing a secondary alcohol.

Another band in the amaralin infrared spectrum at 1736 cm.$^{-1}$ could be attributed to a cyclic ketone or to a γ-lactone containing a conjugated exocyclic methylene, a grouping which is characteristic of many of these sesquiterpene lactones.[5] That this system was actually present in amaralin was further indicated by infrared bands at 1660 and 940 cm.$^{-1}$ (exocyclic double bond α

(1) The plant material was collected and identified by Harry E. Ahles, Botany Department, University of North Carolina, Chapel Hill, N. C., to whom our sincere thanks are due.

(2) We wish to express our appreciation to Dr. A. Plummer and his associates of our Macrobiology Division for the biological tests and for their kind permission to include some of their results in this paper.

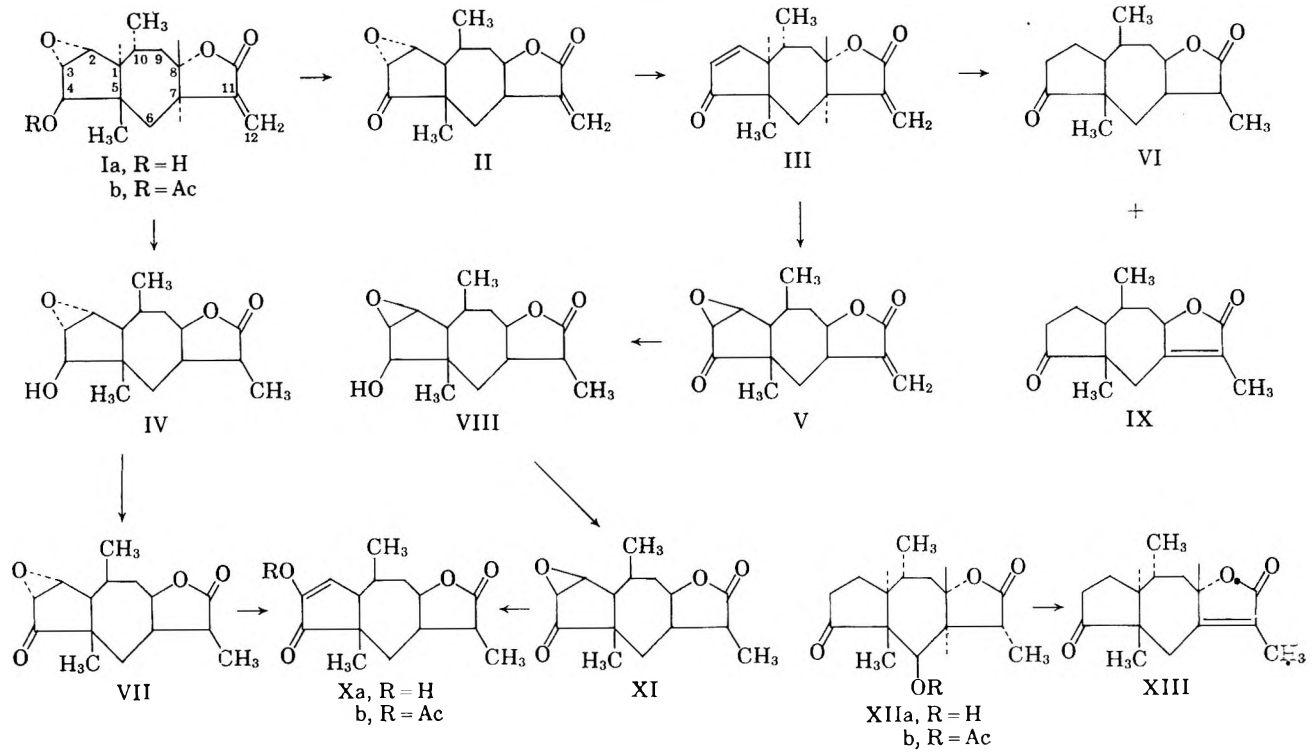
(3) L. Witkin, C. Huebner, F. Galdi, E. O'Keefe, P. Spitaletta, and A. Plummer, *J. Pharmacol. Exptl. Therap.*, **133**, 400 (1961).

(4) During the preparation of the manuscript of this paper, an article by J. Romo, P. Joseph-Nathan, and F. Diaz A. [*Chem. Ind.* (London), 1839 (1963)] appeared in which the isolation and structure of a new sesquiterpene lactone, aromaticin, was described. The physical properties of this substance corresponded with our second lactone and the methods of structure proof were exactly the same. A comparison sample of aromaticin kindly supplied by Dr. Romo through the courtesy of Dr. W. I. Taylor was shown to be identical with our substance by the usual criteria.

(5) For a review of the excellent and comprehensive work already done on the constituents of this and related species, see (a) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Am. Chem. Soc.*, **85**, 19 (1963); (b) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963); and (c) W. Herz, *J. Org. Chem.*, **27**, 4043 (1962), and related papers.

(6) For simplicity in the development of our structural arguments we will assume this relationship, later to be demonstrated, and use the numbering system shown when referring to particular carbon and hydrogen atoms.

SCHEME I



to a carbonyl) and by the existence of the low-field doublets in the n.m.r. spectra at 6.17 and 5.46 p.p.m. which have been previously associated with this conjugated methylene.[5a] The presence of a broad single proton multiplet extending for 27 c.p.s. at approximately 4.3 p.p.m. was interpretable on the basis of a guaianolide skeleton as representing the proton attached to the carbon bearing the lactonized hydroxyl function. The complexity of this signal provided evidence which indicated that the lactone in amaralin was probably attached at C-8 as in isotenulin and helenalin, rather than at C-6 as is the case in some of the other natural sesquiterpene lactones. In that event the coupling of this proton would have resulted in a simple doublet.[7] Furthermore, this C-8 multiplet, ABXY type, can be analyzed as two overlapping quartets which seemed to imply that the stereochemistry at C-8 in amaralin was like that of the tenulin series (C-8 β-H), rather than like that of the helenalin series (C-8 α-H) where this signal is a triplet split again into doublets.[5a]

Hydrogenation of amaralin yielded a dihydro derivative (IV) which had only one infrared carbonyl band at 1770 cm.$^{-1}$ (unconjugated γ-lactone) and no longer had the band associated with the double bond. Nor did it exhibit the n.m.r. signals for the conjugated methylene, but did show a doublet signal in the methyl region at 1.20 p.p.m. indicative of a secondary methyl group.

A consideration of the above facts in the light of the wealth of information on the sesquiterpene lactones already provided by Herz and his collaborators[5] led to the postulation that dihydroamaralin was probably related to desacetyldihydroisotenulin (XIIa), but with some as yet unidentified difference in the fourth oxygen function. The presence of a ketone in amaralin seemed unlikely because of the lack of any appropriate absorption or of any reaction with the usual ketone reagents. In fact the nonreactivity of this fourth oxygen led us to consider some type of oxide bridge. Structures of this nature have been published[3] for some of the natural sesquiterpene lactones of the "normal" or guaianolide type (CH_3 at C-4), but so far as we are aware none belonging to the "abnormal" or pseudoguaianolide series (CH_3 at C-5) have been reported.

An insight into the further details of the structure of amaralin was had by the oxidation of its dihydro derivative (IV) with chromium trioxide to give ketone VII, whose infrared spectrum showed bands at 1765 (γ-lactone) and 1746 cm.$^{-1}$ (cyclopentanone).[9] Treatment of VII with base yielded a conjugated hydroxy ketone which exhibited a characteristic ultraviolet absorption spectrum: λ_{max} 261 mμ (ϵ 7000), λ_{max}^{KOH} 300 mμ (ϵ 6000), λ_{max}^{HCl} 259–261 mμ (ϵ 5600). These data seemed best explained on the basis of an enolic α-diketone structure such as Xa. Furthermore, reaction of VII with acetic anhydride and *p*-toluenesulfonic acid in acetic acid and subsequent work-up resulted in the isolation of two products, Xa and its acetate, Xb; the ultraviolet absorption spectrum of the latter showed a hypsochromic shift of 30 mμ expected for the acetate of an enolic conjugated ketone. These reactions can best be explained by assigning an α,β-epoxy ketone structure to VII.[10]

Assuming structure VII to be correct, then amaralin itself must contain an α-hydroxy epoxide, most prob-

(7) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).

(8) V. Procházka, Z. Čekan, and R. Bates, *Collection Czech. Chem. Commun.*, **28**, 1202 (1963); R. Bates, Z. Čekan, V. Procházaka, and V. Herout, *Tetrahedron Letters*, **No. 17**, 1127 (1963); F. Sánchez-Viesca and J. Romo, *Tetrahedron*, **19**, 1285 (1963).

(9) A cycloheptanone could not be excluded. See D. Barton and P. de Mayo, *J. Chem. Soc.*, 142 (1956).

(10) For an analogy to the base-catalyzed reaction, see S. Winstein and R. Henderson, "Heterocyclic Compounds," Vol. 1, R. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 52, and for one to the acid reaction, see H. House and R. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).

TABLE I

N.M.R. SIGNALS[a]

	C-1 H	C-2 H[b] C-3 H	C-4 H[c]	C-5 CH_3	C-8 H	C-10 CH_3	C-11 CH_3	C-12 H[d]
Ia[e]		3.42 q ($H_{2,3}$ 3.7)	3.81 d (H_{OH} 5.3)	1.15	4.33 oq (H_7 *ca.* 11, H_9 *ca.* 9,3)	1.26 d (5.7)		6.17 d, 5.46 d (3.3)
Ib[h]		3.43 q ($H_{2,3}$ 3.7)	4.71	1.16	4.29 oq (H_7 *ca.* 9.5, H_9 *ca.* 9,3)	1.27 d (5.6)		6.14 d, 5.43 d (3.4)
II		3.65 q ($H_{2,3}$ 2.3)		1.18	4.31 oq (H_7 *ca.* 9, H_9 *ca.* 9,3)	1.28 d (5.4)		6.12 d, 5.44 d (3.3)
III[e]	2.80 ddd (H_2 2, H_3 3, H_{10} 10)	7.70 dd 6.17 dd (H_3 6, H_1 3) (H_2 6, H_1 2)		1.21	4.55 oq (H_7 9.6, H_9 8,3)	1.26 d (6.8)		6.21 d, 5.55 d (3.3)
IV[e]		3.35 q ($H_{2,3}$ 3.7)	3.70 d (H_{OH} 5.4)	1.11	4.25 oq (H_7 *ca.* 9, H_9 *ca.* 8.5,3)	1.20 d (5.7)	1.16 d (5.4)	
V[f]		3.86 q 3.35 d (H_3 2.6, H_1 1.2) (H_2 2.6)		1.24	4.32 oq (H_7 *ca.* 9, H_9 *ca.* 9,3.6)	1.29 d (6.6)		6.05 d, 5.73 d (3.3)
VI				1.04	4.31 oq (H_7 *ca.* 8.5, H_9 *ca.* 8,3)	1.20 d (6.7)	1.08 d (5.0)	
VII		3.64 q ($H_{2,3}$ 2.5)		1.19	4.34 oq (H_7 *ca.* 11, H_9 *ca.* 8,3.5)	1.28 d (5.1)	1.18 d (6.4)	
Xb	2.69 dd ($H_2$2, H_{10} 9.8)	7.20 d (H_1 2)		1.26	4.47 oq	1.20 d (7.3)	1.20 d (7.3)	
XIII[g]				1.00	5.02 d (H_9 *ca.* 11.8)	1.05 d (5.8)	1.73 q[g]	

[a] Spectra determined on a Varian A-60 spectrometer in deuteriochloroform. Values are given in p.p.m. relative to tetramethylsilane as internal standard. Numbers in parentheses denote coupling constants in c.p.s. of the hydrogen at top of column with the one indicated in parenthesis: H_2 means the hydrogen at C-2. Multiplicity of signals are designated as follows: d, doublet; q, quartet; oq, overlapping quartet. [b] Where a single signal is reported for C-2 H and C-3 H, it is the midpoint of a narrow quartet. [c] The signal of the hydroxyl hydrogen in Ia and IV is a doublet at 2.97 and 2.41 p.p.m., respectively, which in both cases becomes a singlet on the addition of deuterium oxide. [d] The signal for the vinyl proton oriented toward the carbonyl group of the lactone is at lower field. [e] We wish to thank Professor E. Wenkert for the decoupling studies on this compound and on certain helenalin derivatives. [f] The large chemical shift, 30 c.p.s., between hydrogens on C-2 and C-3 in the β-oxide was also observed for helenalin oxide. However, in the case of the compounds containing the α-oxide the shift was approximately 5 c.p.s. [g] The signal for the hydrogens at C-6 is split into an AB quartet centered at 2.63 p.p.m. (J = 20.4 c.p.s.). That for the hydrogens of the C-11 methyl group is split into a quartet by long-range coupling with C-8 H and with C-6 H, however, the constants for this (J = 1.5, 3 c.p.s.) have not been resolved. This long range coupling further results in a broadening of the C-8 H signal. [h] The signal of the acetyl methyl protons is at 2.17 p.p.m.

ably in the five-membered ring as shown in Ia. Additional evidence confirming this point was had by oxidizing amaralin to ketone II, which on reduction with chromous chloride yielded an α,β-unsaturated cyclopentenone identical with our second isolated product (III).

Certain possible structural features of III could be inferred from spectral data: ν 1768 (γ-lactone), 1707, 1590 (conjugated cyclopentenone), 1665, and 940 cm.$^{-1}$ (double bond); n.m.r. signals at 6.17 and 7.70 p.p.m. (α- and β-protons of cyclopentenone), 5.55 and 6.21 p.p.m. (conjugated exocyclic methylene); λ_{sh} 217 mμ (ϵ 14,000), combination of cyclopentenone and unsaturated lactone chromophores.[11] Catalytic reduction of III yielded a mixture from which a tetrahydro derivative (VI) could be isolated as the main product; ν 1760 (γ-lactone) and 1742 cm.$^{-1}$ (cyclopentanone); λ_{max} 218 mμ (ϵ 1070) (impurity, probably IX). The n.m.r. signals at 6.13 and 7.65 and at 5.52 and 6.18 p.p.m. were no longer present, but a new doublet appeared at 1.20 p.p.m. (C-11 CH_3). Epoxidation of III with alkaline peroxide formed an oxide (V) which was not identical with the corresponding substance (II) prepared from amaralin. However, treatment of its dihydro derivative (XI) with base did yield X which had already been derived from the corresponding amaralin derivative (VII) by a similar reaction. The patterns of the n.m.r. signals attributed to the C-8 protons in Ia, II, and V were practically identical and, hence, it is probable that no epimerization at this center took place during the transformation of Ia to II or of II to III or of III to V. But the nature of the reactions involved in converting II to III and VII to X is such that epimerization at C-1 cannot be excluded. However, in a reaction comparable to that involved in going from II to III, helenalin oxide[12] was reduced with chromous chloride to yield helenalin. Since no epimerization at C-1 apparently occurred in this case, it would seem unlikely that it did in the preparation of III from II. Hence II and V and, therefore, VII and XI must differ only in the configuration of the epoxide. These data were consistent with our postulated structure for III and a definite correlation with desacetyldihydroisotenulin was now necessary.

Having placed the oxygen functions in III at C-4 and C-8 it seemed to us that this correlation could best be accomplished by the removal of the C-6 oxygen function in desacetyldihydroisotenulin (XIIa). However, this was never accomplished in spite of numerous efforts to place appropriate groups in this substance at C-6 which might be removed by any of the well-known methods. We, therefore, resorted to the synthesis of a known compound which could be compared to IX. It has already been shown[5a] that in helenalin and similar substances, the exocyclic double bond of the lactone system undergoes isomerization during catalytic hydrogenation to yield an endocyclic conjugated lactone with a stable double bond at C-7–C-11. It has been previously mentioned that hydrogenation of III yielded, in addition to the tetrahydro derivative, another substance (IX) which when purified by chromatography had the ultraviolet and infrared absorption spectra

(11) G. Buchi and D. Rosenthal, *J. Am. Chem. Soc.* **78**, 3860 (1956).

(12) R. Adams and W. Herz, *ibid.*, **71**, 2551 (1949).

expected for such a system: λ_{max} 219 mμ (ε 16,000); ν 1755 (γ-lactone), 1739 (cyclopentanone), and 1668 cm.$^{-1}$ (conjugated double bond). Correlation of this substance and, therefore, III and amaralin with the tenulin series could be had by a comparison of its properties with those of anhydrodesacetyldihydroisotenulin (XIII) prepared by the literature method.[13] When this was done, it was found that IX was indeed identical with XIII. This identity confirmed the postulated skeletal structure for III and defined its stereochemistry as shown, because the C-7 hydrogen is considered to be α in all known cases.[5b] Since III has been related to amaralin, its structure and the stereochemistry of all of its asymmetric centers can now be assigned as shown in Ia, with the exception of those in the cyclopentane ring, and an inspection of the n.m.r. data permits a proposal for these.

Since the doublet at 3.81 p.p.m. (C-4 proton) collapsed to a singlet, 3.78 p.p.m., on the addition of D_2O, it must have been coupled to the hydroxyl proton and only minimally with C-3 H. Hence, the dihedral angle between C-3 H and C-4 H must approximate 90°. The two proton signal at 3.42 p.p.m., which is unaffected by the addition of D_2O, can now be assigned to the hydrogens on C-2 and C-3. The shape of this signal can best be described as a collapsed AB quartet, $J_{2,3}$ = 3.7 c.p.s., and, hence, not what would be expected if there were appreciable coupling between these hydrogens and either C-1 H or C-4 H. This is in agreement with the above stated relationship between C-3 H and C-4 H and further indicates that the dihedral angle between C-1 H and C-2 H must also approximate 90°.

An inspection of a Dreiding model of the various structures possible for this molecule showed that in only two were the above conditions all satisfactorily met. One corresponded to that shown in Ia and the other required that rings A and B be *cis* joined. Since we have already presented evidence that epimerization at C-1 was unlikely as a result of the reactions used in the correlation of amaralin with a substance of known *trans* structure, we prefer Ia as a representation of its stereochemistry, especially since this conforms in general with that already established for other members of this family of substances.

One of the reactions carried out early in our work in an attempt to gain knowledge about the nature of the fourth oxygen function in amaralin, led to a rather unexpected result. When this substance was treated with sodium borohydride, the product, formed in good yield, was found to be identical with dihydroamaralin (IV) produced by catalytic hydrogenation. In fact the metal hydride procedure was preferred since the product was free of the usual contaminating endocyclic unsaturated lactone isomerization by-product. So far as we are aware, this type of reduction of the exocyclic double bond of similarly unsaturated lactones has not been previously mentioned. However, a somewhat similar case has been reported for iresin.[14]

When this same reduction method was applied to helenalin acetate, we found that not only was the exocyclic methylene double bond reduced as in the case of amaralin, but also the α,β-unsaturated ketone was apparently reduced to a saturated alcohol mixture, which on reoxidation yielded the known tetrahydrohelenalin acetate with no spectral evidence for the regeneration of the conjugated ketone. The same result was obtained whether or not acid was used in the work-up.[15] Similar reductions of conjugated ketones are of course known in the steroids,[16] although the saturated alcohol is usually not the sole product.

Table II presents the biological activity of amaralin (Ia) and a number of related substances.

TABLE II

ANALGESIC ACTIVITY[a] OF SESQUITERPENE LACTONES

Compound	Dose mg./kg.[a]	Increase, %
Ia	10	64
	25	133
IV	100	92
III	100	None
V	100	28
Helenalin[b]	25	60
Helenalin oxide[c]	100	61
Tetrahydrohelenalin oxide[c]	100	None
Tenulin[d]	100	101
Isotenulin[d]	100	100
Isotenulin oxide[e]	100	64
XIIb[d]	100	51

[a] Drugs administered subcutaneously. [b] See ref. 5a. Material kindly supplied by Dr. W. I. Taylor. [c] See ref. 12. [d] See ref. 13. [e] See Experimental.

Experimental

All melting points are uncorrected. Ultraviolet spectra were determined in 95% ethanol unless otherwise indicated on a Beckman DK-1 spectrophotometer; infrared spectra were run in Nujol on a Perkin-Elmer Model 21 spectrophotometer. Rotations were measured in chloroform solution unless stated otherwise.

Isolation of Amaralin (Ia).—A 3.2-kg. sample of finely ground leaves and stems of *Helenium amarum* (Raf.) H. Rock was extracted twice with 12 l. of boiling methanol and once with 12 l. of hot water. The combined extract was evaporated *in vacuo* to a thick paste and partitioned in countercurrent fashion between 1-butanol and water, using portions of 1, 0.5, and 0.5 l. each. Evaporation of the 1-butanol fraction *in vacuo* yielded 236 g. of crude extract.

A 100-g. portion of the above was finely powdered and digested with 400 ml. of boiling benzene for 2 hr. After filtration of the hot solution to remove 27 g. of insoluble material, the filtrate was concentrated to a volume of 250 ml. and allowed to crystallize at room temperature overnight, yielding 17 g. of crude crystalline tenulin. The benzene filtrate was chromatographed on 1350 g. of Woelm grade II–III neutral alumina. The column was eluted with 10 l. of benzene, 9 l. of benzene–CH_2Cl_2 (50%), and 16 l. of CH_2Cl_2. The final 10 l. of CH_2Cl_2 eluate yielded 1.14 g. of amaralin,[17] m.p. 195–198° after crystallization from benzene; $[\alpha]^{25}D$ +5°; ν 3430 (hydroxyl), 1736 (γ-lactone), 1660, and 940 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.48; H, 7.40; mol. wt. (mass spectroscopy), 264.

Isolation of III.—The benzene eluates from a number of chromatograms used for the isolation of Ia were combined, evaporated to a pasty solid (35 g.) and dissolved by refluxing in 50 ml. of cyclohexane. The solution was allowed to crystallize overnight at 0–5°, yielding crude III. Recrystallization from cyclohexane and from ethyl acetate–CH_2Cl_2 yielded 2 g. of material, m.p. 234–236°; $[\alpha]^{26}D$ +14°; ν 1768 (γ-lactone), 1707, 1590 (cyclopentenone), 1655, and 940 cm.$^{-1}$ (double bond).

(13) W. Herz, W. Rohde, K. Rabindran, P. Jayaraman, and V. Viswanathan, *J. Am. Chem. Soc.*, **84**, 3857 (1962).

(14) C. Djerassi and W. Rittel, *J. Am. Chem. Soc.* **79**, 3528 (1957).

(15) J. Marshall and W. Johnson, *J. Org. Chem.*, **28**, 595 (1963).

(16) F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. Ind.* (London), 1482 (1954); D. Kupfer, *Tetrahedron*, **15**, 193 (1961).

(17) A recent repetition of this isolation procedure using plant material collected a year later has so far not yielded any amaralin.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.16; H, 7.53.

The melting point of a mixture of III and aromaticin[4] showed no depression and the infrared spectra of the two substances were identical.

Amaralin Acetate (Ib).—Ia (100 mg.) was acetylated with pyridine (1 ml.) and acetic anhydride (1 ml.) at room temperature. The reaction mixture was poured into ice–water (10 ml.), made basic with 2 ml. of aqueous ammonia, and extracted with CH_2Cl_2. After washing and drying, the extract was evaporated and the residue was warmed with ether yielding 50 mg. of crude crystalline acetate. Recrystallization from cyclohexane–CH_2Cl_2 afforded 20 mg. of Ib, m.p. 140–142°; $[\alpha]^{26}D$ −16°; ν 1761 (γ-lactone), 1741, 1245 (acetate) 1662, and 940 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.84; H, 7.38.

Dihydroamaralin (IV). A. Catalytic Reduction.—A solution of 200 mg. of Ia in 30 ml. of methanol was hydrogenated over 200 mg. of 10% palladium on carbon (presaturated with hydrogen). Approximately 1 molar equiv. of hydrogen was absorbed during 2 hr. Filtration of catalyst and evaporation *in vacuo*, followed by crystallization of the residue from ethyl acetate yielded 80 mg. of IV, m.p. 218–219°, ν 1770 cm.$^{-1}$.

B. Sodium Borohydride Reduction.—Ia (200 mg.) in methanol (8 ml.) was treated with 200 mg. of sodium borohydride in 4 ml. of methanol at room temperature. After 1 hr. the mixture was diluted with water, acidified with hydrochloric acid, and extracted four times with 25-ml. portions of CH_2Cl_2. The combined extracts were dried and evaporated *in vacuo*. Crystallization of the residue from CH_2Cl_2–ethyl acetate yielded 135 mg. of IV, m.p. 223–225°, $[\alpha]^{26}D$ +23°, ν 3446 (hydroxyl) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.08; H, 8.29.

Oxidation of IV to VII.—A solution of 100 mg. of IV in 4 ml. of acetone was cooled to 0°, stirred vigorously, and treated with 5 drops of 8 *N* chromic acid[18] which imparted a persistent orange color to the solution. After 1 min. the mixture was diluted with 40 ml. of water and extracted with three 20-ml. portions of CH_2Cl_2. The solvent after drying was evaporated *in vacuo* and the residue was crystallized from ethyl acetate–CH_2Cl_2 yielding 77 mg. of VII, m.p. 238–240°, $[\alpha]^{26}D$ +116°, ν 1765 (γ-lactone) and 1746 cm.$^{-1}$ (cyclopentanone).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.70; H, 7.59.

Preparation of Xa.—A suspension of 100 mg. of VII in 2.7 ml. of 5% sodium hydroxide was heated on the steam bath for 0.5 hr. effecting gradual solution. It was cooled, acidified with 2 *N* hydrochloric acid, and after a short time yielded 65 mg. of needles which on crystallization from ethyl acetate–CH_2Cl_2 had m.p. 245–246°; $[\alpha]^{26}D$ +89°; λ_{max} 261 mμ (ϵ 7000), λ_{max}^{KOH} 300 mμ (ϵ 6000), λ_{max}^{HCl} 259–261 mμ (ϵ 5600); ν 3345 (hydroxyl), 1750 (γ-lactone), 1700 (ketone), and 1650 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.37; H, 7.77.

Reaction of VII with Acetic Anhydride, *p*-Toluenesulfonic Acid.—A mixture of 60 mg. of VII, 150 mg. of *p*-toluenesulfonic acid, 1.2 ml. of acetic anhydride, and 2.4 ml. of acetic acid was heated at 60–65° for 3 hr. and then allowed to stand overnight at room temperature. At the end of this time it was partially evaporated *in vacuo*, diluted with 20 ml. of water, and extracted several times with CH_2Cl_2. The combined, water-washed CH_2Cl_2 extracts were evaporated *in vacuo*, leaving an oily product which could not be crystallized. It was chromatographed in benzene solution on 3 g. of Woelm activity II–III neutral alumina. Benzene eluted 36 mg. of solid which crystallized from hexane–CH_2Cl_2 as shiny needles of Xb, 26 mg., m.p. 191–192°; λ_{max} 230–232 mμ (ϵ 8700) and 315 mμ (ϵ 60), λ_{min} 280 mμ (ϵ 30), λ_{max}^{KOH} 298–300 mμ (ϵ 6300), λ_{max}^{HCl} 244–248 mμ; ν_{CHCl_3} 1764 (γ-lactone and enol acetate) and 1719 cm.$^{-1}$ (unsaturated ketone).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.01; H, 7.23.

The above column was then eluted with increasing amounts of CH_2Cl_2 and finally CH_2Cl_2 and 4% methanol yielded 17 mg. of a second substance which after crystallization from CH_2Cl_2–hexane weighed 12 mg., m.p. 235–238°. This substance was shown to be identical with Xa previously prepared.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.21; H, 7.51.

Oxidation of Amaralin.—A solution of 52 mg. of Ia in 2 ml. of acetone was cooled to 5° and oxidized with the chromic acid mixture as described for the preparation of VII. The experiment yielded 35 mg. of II, m.p. 244–245° after crystallization from methanol–CH_2Cl_2; $[\alpha]^{26}D$ +101°; ν 1757 (γ-lactone), 1739 (cyclopentanone), and 1660 sh cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.68; H, 6.86.

Reduction of II to III with Chromous Chloride.—A mixture of II (21 mg.) in 1 ml. of acetic acid was warmed slightly to effect solution, cooled to room temperature, and treated with 0.5 ml. of 0.4 *N* chromous chloride solution. After 0.5 hr. the mixture was diluted with water and the product was extracted with CH_2Cl_2. Chromatography of the 19 mg. of crude substance on 700 mg. of Woelm II–III neutral alumina afforded from the benzene eluate 5 mg. of solid. This was recrystallized from cyclohexane–CH_2Cl_2, yielding 1.37 mg. of crystals, m.p. 225–228°. A comparison of the infrared spectrum of this substance with that of isolated III demonstrated their identity, and the melting point of a mixture showed no depression.

Reduction of III.—A mixture of 800 mg. of III and 800 mg. of 10% palladium on carbon in 160 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature with very slow and interrupted periods of stirring. During the course of 4 hr., 160 ml. of hydrogen was consumed. The product was worked up in the usual way to obtain a mixture of VI and IX. Repeated chromatography on Woelm II–III and III–IV neutral alumina afforded from the cyclohexane–benzene (2:1) eluates 65 mg. of VI, m.p. 135–136°; λ_{max} 218 mμ (ϵ 1070), indicates some contamination with IX; ν 1760 (γ-lactone) and 1742 cm.$^{-1}$ (cyclopentanone).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.29; H, 8.83.

The slower moving IX was eluted with 1:1 cyclohexane–benzene. Even after repeated chromatography the latter compound was slightly contaminated with VI. The purest sample of IX had m.p. 140–143°, $[\alpha]^{26}D$ +164° (EtOH), λ_{max} 219 mμ (ϵ 16,000). This substance was later shown to be identical with anhydrodesacetyldihydroisotenulin (XIII) by the usual criteria.

Epoxidation of III.—A solution of 200 mg. of III in 5 ml. of CH_2Cl_2 plus 5 ml. of methanol was cooled to 0° and allowed to react with a cold mixture of 0.5 ml. of 30% hydrogen peroxide, 0.5 ml. of 4 *N* sodium hydroxide, and 0.5 ml. of water. After stirring for 20 min. at 0° the mixture was poured into 20 ml. of water and acidified with dilute hydrochloric acid. It was extracted with CH_2Cl_2. Work-up in the usual way and crystallization from CH_2Cl_2–methanol yielded 160 mg. of V, m.p. 188–189°; $[\alpha]^{26}D$ +29°; ν 1766 (γ-lactone), 1741 (cyclopentanone), and 1666 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.76; H, 6.88.

Reduction of V.—A slurry of 70 mg. of V in 4 ml. of methanol was treated at 0° with 70 mg. of sodium borohydride in 2 ml. of methanol. At the end of 1 hr. the solution was diluted with 20 ml. of ice–water and acidified with hydrochloric acid. Extraction with CH_2Cl_2 in the usual manner yielded crystalline VIII, m.p. 180–195°, ν 3500 (hydroxyl) and 1743 cm.$^{-1}$ (γ-lactone).

Oxidation of VIII.—The above compound (70 mg.) in 3 ml. of acetone was oxidized with chromic acid in the way described for the preparation of VII. There was obtained 60 mg. of XI, m.p. 158–160° after recrystallization from CH_2Cl_2–ether, ν 1772 (γ-lactone) and 1741 cm.$^{-1}$ (cyclopentanone).

Base Treatment of XI.—A 35-mg. sample of XI was treated with sodium hydroxide and worked up as described for the preparation of X from VII, yielding 30 mg. of needles, m.p. 245–246° after recrystallization from ethyl acetate–CH_2Cl_2. A mixture melting point with the basic rearrangement product (X) obtained from VII exhibited no depression and the infrared and ultraviolet absorption curves were practically superimposable.

Isolation of Tenulin.—The 17 g. of crude tenulin obtained from benzene crystallization during the isolation of amaralin was purified by filtration in CH_2Cl_2 through a short column of Woelm activity II–III neutral alumina. Crystallization from ethyl acetate–petroleum ether gave 12 g. of tenulin, m.p. 214–216°, lit.[9] m.p. 215°; $[\alpha]^{26}D$ −22°; λ_{max} 226 mμ (ϵ 8500); ν 3407 (hydroxyl), 1772 (γ-lactone), and 1713 cm.$^{-1}$ (cyclopentenone).

(18) A. Bowers, T. Halsall, E. Jones, and A. Lemin, *J. Chem. Soc.*, 2555 (1953)

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.47; H, 7.20.

Isotenulin.—The method of Barton[8] was followed using tap water to convert 2 g. of tenulin to isotenulin, yielding 1.8 g., m.p. 161–163°, lit.[9] m.p. 160–161°; $[\alpha]^{26}D$ +9° (EtOH); λ_{max} 225 mμ (ε 8800); ν 1775 (γ-lactone), 1705 and 1590 (cyclopentenone), 1750, and 1230 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.52; H, 7.14.

Dihydroisotenulin.—Isotenulin (2.1 g.) was reduced catalytically over 200 mg. of 10% palladium on carbon in methanol yielding 1.9 g. of dihydroisotenulin, m.p. 147–149° crystallized from cyclohexane–CH_2Cl_2 (lit.[9] m.p. 148–149°.

Anhydrodesacetyldihydroisotenulin.—Dihydroisotenulin (2 g.) was converted[13] through the intermediates desacetyldihydroisotenulin and its methanesulfonyl ester to anhydrodesacetyldihydroisotenulin (0.75 g.), m.p. 130–132°. Further crystallization from ether, filtration in benzene through Woelm activity II–III neutral alumina, and crystallization from hexane–CH_2Cl_2 raised the melting point to 143–144°, lit.[13] m.p. 143.5–144°; $[\alpha]^{26}D$ +170° (EtOH); λ_{max} 218–220 mμ (ε 14,800); ν 1755 (γ-lactone), 1739 (cyclopentanone), and 1668 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H, 8.08.

Isotenulin Oxide.—To 500 mg. of isotenulin in 12 ml. of methanol, cooled to −7°, was added a mixture of 0.5 ml. of 30% hydrogen peroxide, 0.5 ml. of water, and 106 mg. of sodium carbonate. The mixture was stirred for 10 min. before the addition of 20 ml. of water to complete precipitation of the solid. After filtering and drying, it weighed 400 mg. and melted indistinctly at 85–95°. It resisted all attempts at recrystallization and had ν 1750–1780, sh 1715 cm.$^{-1}$; λ_{max} 225 mμ (ε 1950).

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.52; H, 6.82.

Reduction of Helenalin Oxide to Helenalin with Chromous Chloride.—An 18-mg. sample of helenalin oxide[12] was reduced with 0.4 *N* chromous chloride solution in exactly the same manner as described for the reduction of I. The crude reaction product crystallized from the CH_2Cl_2 extract and after recrystallization from CH_2Cl_2 afforded 10 mg. of substance, m.p. 164–166°, which was shown to be identical with a known sample of helenalin by the usual criteria.

Acknowledgment.—We wish to express our appreciation to Dr. E. Schlittler for his interest and encouragement during our work on this problem. Thanks are due to various members of the Technical Services Section for the microanalyses and for spectroscopic and rotational determinations. We are especially indebted to Professor E. Wenkert of Indiana University for stimulating discussions and for making available to us decoupling n.m.r. data on certain of the substances mentioned.

Benzene Extractives of Lodgepole Pine Bark. Isolation of New Diterpenes[1]

JOHN W. ROWE AND JONNELL H. SCROGGINS

Forest Products Laboratory,[2] Forest Service, U. S. Department of Agriculture, Madison, Wisconsin

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Lodgepole pine bark is unique in that over one-fourth is soluble in benzene. The benzene extract has been fractionated and the neutral materials extensively investigated. These consist of esterified wax and fatty acids, homologous wax alcohols, *n*-paraffins, sterols, and diterpenes. The most significant discovery is that 21% of the benzene extract consists of the new diterpene alcohol, 13-epimanool (1) ($\Delta^{8(20),14}$-labdadien-13α-ol). Three other new diterpenes with the labdane skeleton, hydroxyepimanool (2), contortolal (3), and contortadiol (4), were also isolated.

Pinus contorta Dougl., commonly known as lodgepole pine, is an important commercial western tree and one of the oldest species on the North American continent.[3] It grows from Alaska and the Yukon Territory to Baja California, Mexico, and from the Pacific Coast to the eastern edge of the Rocky Mountains. Some botanists have claimed there are a number of varieties of lodgepole pine, especially the inland form, which shows some difference from the coastal form.[4] The "Checklist of Native and Naturalized Trees of the United States (Including Alaska)," however, lists all varieties as *P. contorta*.[5]

Lodgepole pine has a thin brown bark with many loose scales. Hergert has investigated this bark[6] and found it to be a rich source of flavonoids, especially myricetin, whose isolation from this bark has been patented.[7] Quercetin, dihydroquercetin, dihydromyricetin, aromadendrin, and pinobanksin were also found in lesser amounts. A low yield of a good tannin has also been obtained from this bark.[8]

The turpentine of lodgepole pine has been investigated and found to consist almost entirely of *l*-β-phellandrene with small amounts of *l*-α-pinene sometimes present.[4] Hergert has also identified small amounts of β-pinene, Δ^3-carene, and β-camphene in the turpentine by gas chromatography.[9] Schorger reported that the oleoresin contains abietadienic acids, and that the needle and twig oil contains *l*-α-pinene, *l*-β-pinene, *l*-phellandrene, camphene, dipentene, *l*-borneol, bornyl acetate, methylchavicol (?), cadinene, and a trace of furfural.[10]

During a study of the chemical composition of common North American pulpwood barks,[11] it was found

(1) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 10D of abstracts. Part of these results are included in the undergraduate thesis of J. H. S. at the University of Wisconsin. Previous paper in this series: W. C. Nickles and J. W. Rowe, *Forest Prod. J.*, **12**, 374 (1962).

(2) Maintained at Madison, Wis., in cooperation with the University of Wisconsin.

(3) D. A. Zischke, "Lodgepole Pine," U. S. Forest Products Laboratory Rept. No. 2052, 1956.

(4) N. T. Mirov, "Composition of Gum Turpentines of Pines," U.S.D.A. Tech. Bull. No. 1239, U. S. Government Printing Office, Washington, D. C., 1961, p. 117, and references cited therein.

(5) E. L. Little, Jr., U.S.D.A. Handbook No. 41, U. S. Government Printing Office, Washington, D. C., 1953, p. 263.

(6) H. L. Hergert, *J. Org. Chem.*, **21**, 534 (1956).

(7) H. L. Hergert, U. S. Patent 2,870,165 (Jan. 20, 1959); Canadian Patent 612,236 (Jan. 10, 1961).

(8) Oregon State Board of Forestry, Biennial Report of State Forester to Governor, 1948/49–1949/50, 1950, p. 65.

(9) H. L. Hergert, private communication.

(10) A. W. Schorger, *J. Ind. Eng. Chem.*, **7**, 24 (1915).

(11) Y.-P. Chang and R. L. Mitchell, *Tappi*, **38**, 315 (1955).

that lodgepole pine bark from the Rocky Mountains was unique in that 28.7% was soluble in benzene whereas most softwood barks contain only 2–5% benzene extractives.[12] This intriguing property led us to include lodgepole pine in a survey being made at the U. S. Forest Products Laboratory on the benzene extractives of pine bark. Chemotaxonomic indications had suggested that pines might be rewarding as a source for new diterpenes. The ubiquity of diterpene resin acids in pines was significant since biosynthetic theory indicates that diterpene alcohols should be the precursors of resin acids.[13] Expectations were amply fulfilled when it was found that new diterpene alcohols, all possessing the labdane skeleton,[14] were major constituents of lodgepole pine bark.

The benzene extract was fractionated as shown in Fig. 1. The unsaponifiable fraction of the benzene extract, the sterol fraction, the terpenoid fraction, and an ethanol extract of the benzene-extracted bark were submitted to the Cancer Chemotherapy National Service Center. No confirmable activity was found.

Thorough extraction of the benzene extract with alkali removed the free acids.[15] No attempt was made to prevent saponification of labile esters, which are undoubtedly present, especially as triglycerides. Saponification yielded the combined acids. The sodium salts of the wax acids produced by saponification were quite insoluble in water and satisfactory extraction could be carried out only after precipitation and filtration.

The combined acids were readily fractionated into three groups by treatment with urea to form the channel inclusion complex.[16] Table I gives the combined

TABLE I

LODGEPOLE PINE BARK COMBINED ACIDS

Saturated acid	%	Unsaturated acid	%
Myristic	0.2	Palmitoleic	1.4
Palmitic	5.2	Oleic	16.8
Stearic	0.4	Linoleic	19.1
Arachidic	7.4	5,9,12-Octadeca-trienoic	10.7
Heneicosanoic	0.1		
Behenic	7.9	Linolenic	1.4
Tricosanoic	0.1	Complex unsaturated higher acids	22.2
Lignoceric	5.1		
Cerotic	0.4		
Total	26.8	Total	71.6

analysis of this fraction. Apparently two different sets of acids are present. The first are long chain wax acids, especially behenic and lignoceric acids (Table II), which are probably part of the waxes in the suberized cell walls of the corky periderm. The second are typical fatty acids, which are most likely present as triglycerides in the phloem. The presence of only traces of stearic acid is usual in tree fats.[17] Some of the unsaturated acids are of higher molecular weight and

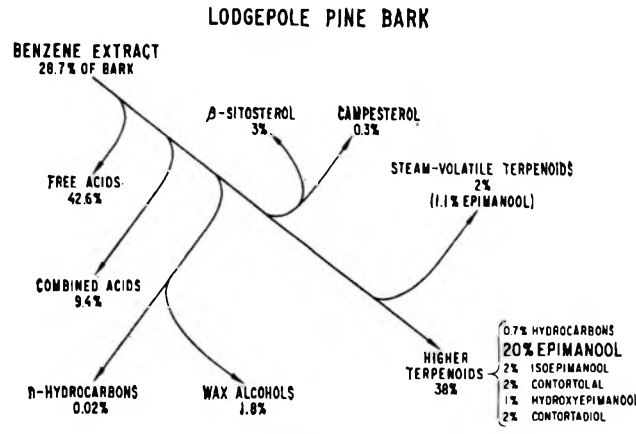


Figure 1.

may consist of a mixture of unsaturated wax and terpenoid acids. One major component of the unsaturated acids was shown to be the recently discovered *cis*-5,9,12-octadecatrienoic acid, a major component in tall oil and pine wood.[18] The unsaturated fatty acids were further confirmed by classical permanganate oxidation,[19] and the saturated acids were further confirmed by infrared analysis of the band progression frequencies of their barium salts.[20] The ultraviolet spectrum indicated that a small amount (~2% of the combined acids) of conjugated trienic acids were also present, perhaps formed by the alkaline rearrangement of double bonds in linolenic acid during saponification.[19]

TABLE II

SATURATED *n*-ALIPHATICS FROM LODGEPOLE PINE BARK

C_n	Paraffins, %	Wax alcohols, %	Combined wax acids, %
C_{16}			19
C_{18}	0.3	0.1	1.4
C_{19}	3.9		
C_{20}	3.8	24	28
C_{21}	17	0.3	0.4
C_{22}	8.6	47	30
C_{23}	26	0.4	0.4
C_{24}	8.9	27	19
C_{25}	9.8		
C_{26}	5.9	0.9	1.4
C_{27}	6.1		
C_{28}	3.5		
C_{29}	1.8		

The *n*-aliphatics were separated from the unsaponifiable fraction by formation of the urea channel inclusion complex.[16] Chromatography separated this into a small amount of *n*-paraffins and a major amount of wax alcohols. No trace of unsaturated or carbonyl components was detected. Gas chromatography showed

(12) However, Hergert[6] found that the amount of benzene extract from three samples of West Coast lodgepole pine varied from 5.7–9.8%.

(13) L. Ruzicka, *Pure Appl. Chem.*, **6**, 493 (1963), and references cited therein.

(14) Nomenclature is based on the unknown hydrocarbon labdane [J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 4262 (1956)].

(15) The free acids will be the subject of a future paper when research on the development of a gas chromatographic method for the quantitative analysis of mixed fatty and resin acids is completed. See initial paper: F. H. M. Nestler and D. F. Zinkel, *Anal. Chem.*, **35**, 1747 (1963).

(16) H. Schlenk and R. T. Holman, *J. Am. Chem. Soc.*, **72**, 5001 (1950).

(17) D. B. Mutton, "Wood Extractives and Their Significance to the Pulp and Paper Industries," W. E. Hillis, Ed., Academic Press, New York, N. Y., 1962, p. 331; M. A. Buchanan, "The Chemistry of Wood," B. L. Browning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p. 335.

(18) Y. Aho, O. Harva, and S. Nikkilä, *Teknillisen Kemian Aikakausilehti*, **19**, 390 (1962); O. Lehtinen, V. Karkkainen, and M. Antila, *Suomen Kemistilehti*, **35B**, 179 (1962); E. Elomaa, T. Lehtinen, and J. Alhojarvi, *ibid.*, **36B**, 52 (1963).

(19) M. L. Meara, "Modern Methods of Plant Analysis," Vol. II, K. Paech and M. V. Tracey, Ed., Springer-Verlag, Berlin, 1955, pp. 337–339, 354–357.

(20) R. A. Meiklejohn, R. J. Meyer, S. M. Aronovic, H. A. Schuette, and V. A. Meloche, *Anal. Chem.*, **29**, 329A (1957); V. F. Wenzel and U. Schiedt, *Z. Naturforsch.*, **12B**, 71 (1957).

that both fractions consisted of a mixture of homologs, as shown in Table II. The hydrocarbon chromatogram also showed five minor peaks totaling 1.3% which could correspond to paraffins with a small amount of branching. The wax alcohols and the esterified wax acids have a similar distribution with the even chain lengths predominating, as is to be expected. The paraffins, on the other hand, have a similar distribution but with the odd chain lengths predominating, as is to be expected for a biogenesis *via* decarboxylation of wax acids.

The sterols were readily separated from the unsaponifiable fraction *via* precipitation of the digitonides. β-Sitosterol is the major sterol, although, surprisingly, pure β-sitosterol has apparently been obtained only very recently.[21] The β-sitosterol, as well as all available comparison samples, showed about 10% of a lower molecular weight impurity on gas chromatography. This ubiquitous impurity in β-sitosterol preparations has recently been identified as campesterol,[22] and comparison with an authentic sample indicated that this was indeed the minor sterol. Another peak in the gas chromatogram of the lodgepole sterols had a retention time identical with an authentic sample of α_1-sitosterol.[23,24] No trace of stigmasterol could be detected. No attempt was made to detect saturated sterols which are normally present in small amounts in sitosterol preparations.[25a] Strong indications were also found of two β-sitosterol autoxidation products, stigmasta-3,5-dien-7-one[26] and 7-keto-β-sitosterol. Formation of these from β-sitosterol parallels the behavior of cholesterol on autoxidation.[25b]

To summarize, the 3.9% of sterols in the benzene extract consists of 2.9% β-sitosterol, 0.2% campesterol, 0.1% α_1-sitosterol, 0.1% 7-keto-β-sitosterol, and 0.01% stigmasta-3,5-dien-7-one.

Steam distillation of the remaining part of the unsaponifiable fraction removed only a small amount of material. Chromatography separated this into 17% of hydrocarbons and 83% of polar compounds. Gas chromatography of the hydrocarbons by Dr. E. von Rudloff at the Prairie Regional Laboratory, National Research Council, Saskatoon, indicated that they were a mixture of sesquiterpenes. At least three cadinenes (one predominates) and lesser amounts of α- and β-caryophyllene and cedrene were tentatively identified by retention characteristics on Apiezon N, Carbowax 20M, and neopentylglycol adipate polyester. The infrared spectrum suggests the presence of compounds such as γ- and γ_1-cadinene.[27] The polar fraction was shown to consist of one major component identical with 13-epimanool (**1**) which was later isolated from the nonvolatile higher terpenoids.

The oily, nonvolatile, pale yellow, higher terpenoids constitute 38% of the benzene extract and, therefore, contribute significantly to the high benzene solubility of this bark. Column chromatography succeeded in separating these into six major fractions, each of which was shown by gas and thin layer chromatography to contain a major diterpene component. These major components are shown in the order of elution in Fig. 1.

The oily hydrocarbon fraction can not be dehydration products of **1** since the ultraviolet spectrum showed only a high end absorption, while dehydration products of **1** must contain a conjugated diene. Since no crystalline hydrochloride could be obtained and the gas chromatogram indicated that this small fraction was a complex mixture, no further work was carried out on it.

The oily epimanool fraction constituted half of the nonvolatile terpenoids and was shown by gas and thin layer chromatography to be quite pure. Its infrared spectrum clearly indicated a tertiary allylic hydroxyl plus an exocyclic methylene and a vinyl group in a typically terpenic skeleton whose retention time on gas chromatography was as expected for a diterpene alcohol. The n.m.r. spectrum of the 3,5-dinitrobenzoate was most informative, clearly showing three tertiary methyl groups, a typical vinyl AB_2 system, the twin bands for an exocyclic methylene, and an unsplit band for a methyl geminal to oxygen. A proton count indicated an empirical formula of $C_{20}H_{34}O$ for the alcohol, which is as expected for a diterpene alcohol with two rings and two double bonds. These properties strongly suggested a compound like manool, a supposition strongly supported when manool trihydrochloride, identical with an authentic sample,[28] was formed on treatment with hydrogen chloride in acetic acid. Repeated attempts to crystallize this fraction had failed, but seeding with authentic manool resulted in the immediate formation of crystals which were recrystallized to constant melting point and optical rotation from hexane and acetone. However, these physical properties differed from those reported for manool (**7**).[29-33]

It was originally thought that the sample was merely impure since the infrared and ultraviolet spectra were identical with those of authentic manool, the mixture melting point was undepressed, and thin layer chromatograms of the product and authentic manool under a variety of conditions were identical, as were gas chromatograms under a variety of conditions including those in which decomposition occurred. However, the 3,5-dinitrobenzoate was found to be definitely different from that prepared from authentic manool, although their n.m.r. spectra were identical. Since the hydrochlorides were identical and preparation of the hydrochloride has been shown to lead to allylic rearrangement of the side chain,[28] the product can only be 13-epimanool. The absolute configuration of sclareol (**10**) has been determined,[34] and, since sclareol has been

(21) J. A. Steele and E. Mosettig, *J. Org. Chem.*, **28**, 571 (1963).

(22) M. J. Thompson, S. J. Louloudes, W. E. Robbins, J. A. Waters, J. A. Steele, and E. Mosettig, *Biochem. Biophys. Res. Commun.*, **9**, 113 (1962).

(23) K. Schreiber and G. Osske, *Experientia*, **19**, 69 (1963).

(24) α_1-Sitosterol has also been reported in the tall oil of *Pinus densiflora* [S. Ito, *Nippon Daigaku Kogaku Kenkyusho Iho*, **No. 13**, 114 (1956)].

(25) F. Radt, "Elsevier's Encyclopaedia of Organic Chemistry," Vol. 14, Elsevier Publishing Co., New York, N. Y., 1954-1959: (a) p. 1827s; (b) pp. 2682s, 2695s, and 2454s.

(26) R. A. Abramovitch and R. G. Micetich, *Can. J. Chem.*, **40**, 2017 (1962).

(27) V. Herout and V. Sykora, *Tetrahedron*, **4**, 246 (1958).

(28) R. M. Carman, *ibid.*, **18**, 285 (1962). Manool trihydrochloride is a mixture of C-13 epimers; $[\alpha]_D$ varies from +20 to +40° and the melting point runs as high as 128°.

(29) G. Büchi and K. Biemann, *Croat. Chem. Acta*, **29**, 163 (1957).

(30) G. Ohloff, *Helv. Chim. Acta*, **41**, 845 (1958); *Ann.*, **617**, 134 (1958).

(31) C. Enzell, *Acta Chem. Scand.*, **15**, 1303 (1961); H. S. Barreto and C. Enzell, *ibid.*, **15**, 1313 (1961).

(32) C. Enzell and H. Erdtman, *ibid.*, **11**, 902 (1957).

(33) J. R. Hosking and C. W. Brandt, *New Zealand J. Sci. Technol.*, **17**, 750 (1936).

(34) M. Soucek and P. Vlad, *Chem. Ind.* (London), 1946 (1962); *Collection Czech. Chem. Commun.*, **28**, 1211 (1963).

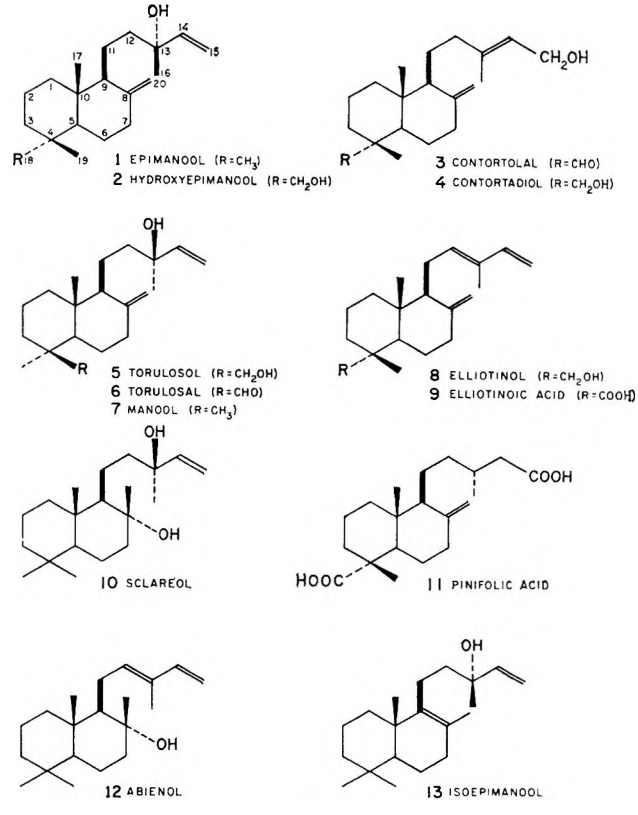
converted into manool,[29] the absolute configuration of 13-epimanool must, therefore, be **1** ($\Delta^{8(20),14}$-labdadien-13α-ol) which has a 13*S* configuration.

The mass spectrum of **1** provided further confirmation.[35] It was practically identical with that of manool.[31] The intensities of peaks formed by cleavage at C-13, however, showed definite differences in agreement with the difference in configuration. Epimanool has a more positive rotation than manool ($\Delta[M]_D$ +52°). A change from a 13*R* to a 13*S* configuration has been observed to result in a higher rotation in analogous cases. Thus, (*R*)-(−)-linalool → (*S*)-(+)-linalool has $\Delta[M]_D$ +70°; (13*R*)-sclareol (**10**) → (13*S*)-13-episclareol has $\Delta[M]_D$ +49°.[36,37] Unfortunately an attempted synthesis[36] of 13-epimanool was unsuccessful so that no definite correlation is possible.

The third fraction following 13-epimanool on the chromatogram was an oily mixture whose infrared spectrum was similar to that of 13-epimanool except that the band characteristic of the exocyclic methylene was absent while a new band appeared at 1380 cm.$^{-1}$ characteristic of a vinylic methyl.[36] In addition, the intensity of the end absorption in the ultraviolet was increased. The major diterpene component is assumed to be 13-epiisomanool (**13**), an oily compound which is known synthetically.[36] This could be either a native constituent of lodgepole pine bark, or an artifact produced by migration of the exocyclic double bond into the ring during fractionation of the benzene extract.

The fourth fraction was a small amount of oily mixture with bands in the infrared for an aldehyde, hydroxyl, and exocyclic methylene. The major component was named contortolal and isolated in the form of its semicarbazone. The semicarbazone gave a very characteristic n.m.r. with bands for two tertiary methyls a vinylic methyl, a single vinylic proton, and a doublet for an exocyclic methylene. Another doublet suggested a vinylic CH_2O group in which a single peak expected for two equivalent hydrogens was being split by an adjacent vinylic proton. That this is indeed the case was confirmed by spin–spin decoupling at 100 Mc.,[38] which showed that the triplet for the vinylic proton collapsed to a sharp singlet when irradiated with the frequency of the CH_2O, and that the doublet for the CH_2O collapsed to a singlet when irradiated with the frequency of the vinylic proton. The vinylic proton showed no indication of coupling with any other protons, especially those of the vinylic methyl that must be on the same double bond. Likewise, the vinylic methyl was a sharp singlet whose τ-value was the same at both 60 and 100 Mc. That the adjacent vinylic methyl and vinylic proton do not couple indicates the biogenically preferable *trans* relationship of these two groups as illustrated in **3**. In confirmation, the chemical shift of the vinylic methyl is exactly as has been predicted from model systems in which the vinylic

CHART I



methyl and proton are *trans* rather than *cis*.[39] Phytol has a similar side chain and the n.m.r. resonances for the vinylic proton, vinylic methyl, and vinylic CH_2O of phytol[40] have the same form and position as in contortolal semicarbazone. Another resonance in the n.m.r. was characteristic for one uncoupled proton on a carbon–nitrogen double bond. The resonances due to NH and NH_2 of the semicarbazone were readily identified since they exchanged with deuterium.

Taken all together, the proton count coupled with the analytical and spectral data show that contortolal is a dicyclic diterpene containing an exocyclic methylene, two tertiary methyls, a tertiary aldehyde group, and a *trans*-$C(CH_3)=CH—CH_2OH$ grouping. This strongly suggests a labdane type of skeleton in which the side chain is allylicly rearranged from the vinyl carbinol as present in **1**. A structure such as **3** (15-hydroxy-$\Delta^{8(20),13}$-labdadien-18-al) satisfactorily incorporates all the available data and, although unknown as a natural product, possesses structural similarities with several labdane diterpenes and is biogenetically attractive. Placement of the tertiary aldehyde group at 4α rather than 4β or at 10 is done solely on the basis that all known pine diterpenes, such as the resin acids, have oxidized methyl groups only at this position. It should be possible to correlate this suggested structure with other labdane diterpenes, especially contortadiol (**4**).

(35) A paper on the mass spectrum of carbodicyclic diterpenes is being prepared by C. Enzell.

(36) D. B. Bigley, N. A. J. Rogers, and J. A. Barltrop, *J. Chem. Soc.*, 4613 (1960); *Chem. Ind.* (London), 1570 (1962).

(37) D. P. Popa and G. V. Lazur'evskii, *Zh. Obshch. Khim.*, **33**, 303 (1963).

(38) N. S. Bhacca, M. E. Wolff, and R. Kwok, *J. Am. Chem. Soc.*, **84**, 4976 (1962), and references cited therein.

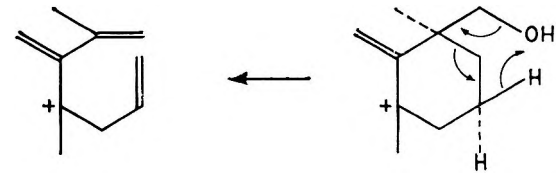
(39) R. B. Bates, R. H. Carnighan, R. O. Rakutis, and J. H. Schauble *Chem. Ind.* (London), 1020 (1962).

(40) Compare 2,2,4-trimethylpentane-1,3-diol. N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 217, phytol, No. 346. E. Wenkert and P. Beak [*Tetrahedron Letters*, **No. 11**, 358 (1961)] also report that axial and equatorial CH_2OH groups at C-4 both give AB quartets, but with different chemical shifts.

The fifth fraction was a small amount of an oil from which crystals could be obtained. The infrared spectrum strongly resembled 13-epimanool except that additional bands were present at 3643 and 1017 cm.$^{-1}$ characteristic of a primary hydroxyl group. The n.m.r. spectrum showed bands characteristic of two tertiary methyls, a vinyl AB_2 system, an allylic methyl, an exocyclic methylene, and a typical AB quartet for a tertiary CH_2O group. This strongly suggests a hydroxymanool or hydroxy-13-epimanool. A compound of this type, torulosol (**5**), has been reported by Enzell in *Cupressus torulosa*.[31] It co-occurs with the corresponding aldehyde, torulosal (**6**), and manool. Comparison of torulosol and our compound was most interesting. They have a similar optical rotation and R_f, and have almost identical infrared, mass and n.m.r. spectra. Although the melting points are almost the same, a mixture melting point is, however, sharply depressed. The mass spectra differ from one another mainly in small differences in intensity such as would be explained if our compound were epimeric with torulosol at both C-13 and C-4.[35] Thus, the axial 4β-CH_2OH group of torulosol appears to be more readily lost than the equatorial 4α-CH_2OH group of the hydroxyepimanool, while the axial 4-methyl of hydroxyepimanool appears to be more readily lost than the equatorial 4-methyl in torulosol. Similarly, the n.m.r. spectra are identical except that the signals for the 4-CH_2O and 4-methyl show a different chemical shift, although this is only by 2 c.p.s. Dr. Enzell attributed the nonequivalence of the 4β-CH_2O protons in torulosol to hindered rotation caused by the 10β-methyl, but according to Dr. Hollis of Varian Associates, 4α-CH_2O protons would also be expected to be nonequivalent due to steric hindrance at the adjacent carbon.[40] Thus, this compound would appear to be best described as 18-hydroxy-13-epimanool **2** ($\Delta^{8(20),14}$-labdadiene-13α,18-diol). Assignment of a 13*S* epimeric configuration as in the 13-epimanool is mostly by analogy. However, 13-episclareol has been recently found to co-occur with sclareol (**10**) in *Salvia sclarea*.[37] Future research should allow this to be correlated with both 13-epimanool and contortadiol (**4**) below. Dehydration should lead to elliotinol[41] from *Pinus elliottii*, which we believe should have the structure **8**. The corresponding acid, elliotinoic acid, was also recently reported in the same species[42]; we believe this should have the structure **9**. This is the 4-epimer of communic acid ($\Delta^{8(20),12,14}$-labdatrien-19-oic acid) from *Juniperus* spp. barks.[43]

The sixth and last fraction was a complex oily mixture of alcohols from which the major crystalline component was isolated *via* its di-*p*-phenylazobenzoate. The infrared spectrum indicated that the ester had no free hydroxyl groups, but did have an exocyclic methylene. The n.m.r. spectrum of the ester was similar to that of hydroxymanool and contortolal semicarbazone, showing two tertiary methyls, a doublet for the exocyclic methylene, the typical AB quartet for a tertiary CH_2O group, a vinylic methyl, a vinylic proton, and a doublet for a vinylic CH_2O as before. Spin–spin decoupling at 100 Mc.[38] clearly showed that the single vinylic proton was coupled to the vinylic CH_2O, but that there was no coupling to the vinylic methyl, thus indicating a *trans* $-C(CH_3)=CH-CH_2OR$ grouping. This, together with a proton count and the analytical data, clearly suggests a structure such as **4**, possessing the allylicly rearranged side chain as in contortolal and the biogenetically preferable 4α-CH_2OH as in **2**. In analogy with contortolal, we have named this compound contortadiol ($\Delta^{8(20),13}$-labdadiene-15,18-diol). It is thus the C-4 epimer of agathadiol ($\Delta^{8(20),13}$-labdadiene-15,19-diol), which is formed from torulosol by allylic rearrangement of the side chain.[31]

Comparison of contortadiol and agathadiol was most informative. According to physical properties, mixture melting point, infrared spectra, and thin layer chromatography, these two compounds are identical. However, the mass spectra, although very similar, did show definite differences in intensity. Of particular significance, the intensity of the *m/e* 135 peak is about five times as great ($\Sigma\%$ basis) in agathadiol as is to be expected since this peak is due to an ion originating by a dehydration which is more favorable for an axial CH_2OH group.[35]



It is significant to note that since the stereochemistry at C-4 apparently has no effect on the optical rotation the similarity of $\Delta[M]_D$ (**7** → **1**) +57° and $\Delta[M]_D$ (**5** → **2**) +37° supports the assigned stereochemistry at C-13 in 18-hydroxy-13-epimanool.

The genus *Pinus* is characterized by the presence of mono- and diterpenes. Although most pine diterpenes possess the tricyclic abietane or pimarane skeleton, the presence of dicyclic labdane diterpenes is to be expected biogenetically.[13] In addition to elliotinol and elliotinoic acid, which were mentioned previously, two further labdane diterpenes have been reported in pines, pinifolic acid (**11**)[44] and abienol (**12**),[45] both found in *P. sylvestris*.

This is the first reported isolation of 13-epimanool, 18-hydroxyepimanool, contortolal, and contortadiol, although current investigations indicate that these new labdane diterpenes are present in other pine barks as well. Manool itself has not been previously reported in the Pinaceae. It is normally considered characteristic of many *Dacrydium* spp. where it is found together with related labdane diterpenes as well as the primarane diterpenes, isopimaric acid and rimuene, and the abietane diterpenes, ferruginol and sugiol.[46] Manool has also been reported in *Cupressus sempervirens*[32] and *C. torulosa*.[31]

(41) E. M. Roberts and R. V. Lawrence, Abstracts of Papers, Division of Organic Chemistry, 131st National Meeting of the American Chemical Society, Miami, Fla., April, 1957, p. 20-O.

(42) N. M. Joye and R. V. Lawrence, *J. Org. Chem.*, **28**, 3274 (1963).

(43) V. P. Arya, C. Enzell, H. Erdtman, and T. Kubota, *Acta Chem Scand.*, **15**, 225 (1961).

(44) C. Enzell and O. Theander, *ibid.*, **16**, 607 (1962).

(45) G. V. Pigulevskii, V. G. Kostenko, and L. D. Kostenko, *Zh. Obshch. Khim.*, **31**, 3143 (1961).

(46) W. Karrer, "Konstitution und Vorkommen der organischen Pflanzenstoffe," Birkhäuser Verlag, Basel, 1958, pp. 782–788.

Experimental

Unless otherwise stated, melting points were determined in evacuated capillaries in a copper block and are corrected, optical rotations were determined with a Rudolph Model 80 polarimeter in chloroform, ultraviolet spectra with a Beckman DK-2 recording ratio spectrometer in ethanol, infrared spectra with a Baird Atomic spectrophotometer as a liquid film or in potassium bromide, and the n.m.r. spectra in deuteriochloroform at 60 Mc. with tetramethylsilane as an internal standard. Gas chromatographic data were mostly supplied by Mr. Robert F. Sweeny, Applied Science Laboratories, State College, Pa. Column chromatography was carried out using thirty times the amount of Woelm alumina, neutral, activity II.

Isolation of the Neutral Benzene Extract of Lodgepole Pine (*Pinus contorta* Dougl.) Bark.—Bark was collected at the Kremmling, Colo., sawmill of the Nebraska Bridge Co. from the upper portion of butt logs that were cut 2 days before on the eastern side of the summit of Gor Pass in Arapaho National Forest, Colo. After partial air drying, the bark was reduced on a hammer mill with a 4-mm. screen, air-dried to approximately 5% moisture, and exhaustively extracted in a Lloyd extractor with benzene. The benzene extract was filtered through Celite and then extracted with warm 1 *N* sodium hydroxide. Both the aqueous phase, which contained suspended solids and emulsion, and the benzene phase were washed several times with fresh solvent. The combined aqueous phases and the combined benzene phases were worked up as usual to yield free acids and neutrals in the ratio 1:1.35.

Isolation and Fractionation of the Combined Acids.—The neutral fraction of the benzene extract (115.2 g.) was saponified by refluxing for 5 hr. with 1 l. of 2 *N* ethanolic sodium hydroxide. The solution was then concentrated under vacuum and 1.2 l. of benzene and 1.2 l. of a saturated sodium chloride solution were then added with vigorous agitation. The mixture was filtered and the precipitated sodium salts thoroughly washed with benzene and salt solution.

The benzene layer of the filtrate was washed with dilute alkali removing benzene-soluble sodium salts, and worked up in the usual way to yield 88.5 g. of the unsaponifiable fraction. The precipitated sodium salts were suspended in aqueous acid and similarly extracted with benzene to yield 4.76 g. The combined aqueous layers from the filtration analogously yielded 16.07 g. No phlobaphenes were produced.

The acid fractions were combined and added to a refluxing solution of 250 g. of urea in 1200 ml. of 95% ethanol. Benzene (600 ml.) was slowly added to the refluxing solution which was then allowed to cool overnight. The urea complex was filtered, washed with fresh benzene, suspended in water, and extracted with benzene as usual to yield 4.185 g. of combined wax acid fraction.

The filtrate was concentrated to 200 ml. and cooled overnight in the refrigerator. Filtration of the complex and working up as before yielded 5.62 g. of combined fatty acid fraction. The filtrates were poured into water and extracted with benzene to yield 9.85 g. of combined unsaturated acid fraction.

Combined Wax Acids.—The white, crystalline, combined wax acid fraction was crystallized from hexane and methanol and dried for analysis, m.p. 68–71°. The infrared spectrum was identical with that of behenic acid. The infrared spectrum of the barium salt indicated behenic acid plus homologs.[20] The ultraviolet spectrum showed only a very weak end absorption, and the iodine number was 0.2.

Anal. Calcd. for $C_{22}H_{44}O_2$: C, 77.58; H, 13.02; neut. equiv., 340.6. Found: C, 77.57; H, 13.12; neut. equiv., 339.4.

Gas chromatography of the methyl esters on 7% ethylene glycol isophthalate (EGiP) on Gas Chrom P at 224° gave the following results (methyl ester, t_R' in minutes, % total area): C_{18}, 7.5, 0.2; C_{20}, 12.0, 35.4; C_{21}, 15.3, 0.5; C_{22}, 19.8, 37.5; C_{23}, 25.5, 0.6; C_{24}, 33.1, 24.0; C_{26}, 58, 1.8. Peak assignments were checked against known wax acid esters.

Combined Fatty Acids.—The combined fatty acid fraction was an almost colorless mobile oil that solidified in the refrigerator. It gave a brown color with tetranitromethane, and had an iodine number of 118 and a neut. equiv. of 224. The infrared spectrum was identical with oleic acid. The ultraviolet spectrum showed a strong end absorption plus weak peaks at 259, 268, and 279 mμ ($E^{1\%}_{1cm}$ 30, 39, and 31, respectively). Gas chromatography of the methyl esters on 15% ethylene glycol succinate (EGS) on Gas Chrom P at 188° gave the following results (methyl ester, t_R' in minutes, % total area): myristate, 3.8, 0.7; palmitate, 5.9, 17.9; palmitoleate, 7.0, 4.7; stearate, 9.5, 1.1; oleate, 11.0, 57.9; linoleate, 13.2, 11.7; unsaturated lignocerate (?), 42, 0.7; unsaturated cerotate (?), 90, 5.2; and traces of laurate, lauroleate, and linolenate. Retention times for the major components were checked against known samples.

A portion of the acids (2.268 g.) was dissolved in 1 l. of ice–water containing 6 g. of potassium hydroxide and crushed ice. The solution was stirred while 300 ml. of 1% potassium permanganate solution were added rapidly. Sulfurous acid and dilute hydrochloric acid were added after 5 min. and the product was filtered, dried, and placed in a Soxhlet extractor. Extraction with petroleum ether (b.p. 30–80°) yielded 426 mg. of saturated fatty acids; extraction with ethyl acetate yielded 1.329 g. of dihydroxy fatty acids; and extraction with water and with ethanol yielded 55 mg. of tetrahydroxy fatty acids.

The colorless saturated fatty acids, m.p. 52–53.5°, neut. equiv. 283, iodine number 6, had no absorption in the ultraviolet. The acid and its barium salt had infrared spectra identical to those of palmitic acid and its salt.[20]

The dihydroxy fatty acids were recrystallized from ethyl acetate to yield colorless crystals, m.p. 122–126° (reported[19] for *cis*-9,10-dihydroxystearic acid, 133°), which had an infrared spectrum (Nujol) as expected and gave no color with tetranitromethane.

Anal. Calcd. for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47; neut. equiv., 317. Found: C, 68.19; H, 11.36; neut. equiv., 319.

The colorless tetrahydroxy fatty acids, m.p. 172.5–174.5° (reported[19] for *cis*-9,10,12,13-tetrahydroxystearic acid, 172°), had the expected infrared spectrum (Nujol).

Anal. Calcd. for $C_{18}H_{36}O_6$: C, 62.04; H, 10.41; neut. equiv., 349. Found: C, 61.90; H, 10.51; neut. equiv., 350.

Combined Unsaturated Acids.—The combined unsaturated acid fraction was a dark viscous oil which gave only a very strong end absorption in the ultraviolet, iodine number 166.5, neut. equiv. 291. Its infrared spectrum resembled that of oleic acid. Gas chromatography of the methyl esters on 15% EGS on Gas Chrom P at 188° gave the following results (methyl ester, t_R' in minutes, % total area): unknown, 7.9, 3.5; linoleate, 13.1, 31.4; *cis*-5,9,12-octadecatrienoate, 14.8 21.4; linolenate, 16.9, 2.8; plus a series of eight unknown peaks with longer retention times totaling 40.8%. Retention times were checked against known samples of each of the C_{18} esters.

Hydrogenation of the methyl esters (Adams' catalyst in acetic acid), followed by rechromatography as before, gave the following results (methyl ester, t_R' in minutes, % total area): C_{16}, 5.9, 1.0; C_{18}, 9.5, 56.9; C_{20}, 15.7, 10.1, C_{22}, 27.5, 4.2; unknown, 29.4, 10.5; unknown, 41, 8.6; unknown, 72, 8.7. Peak assignments were checked with known fatty acid esters.

***n*-Aliphatics from Unsaponifiable Fraction.**—The unsaponifiable fraction (17.2 g.) in 200 ml. of benzene was added to 50 g. of finely powdered urea moistened with 10 ml. of methanol. The mixture was shaken intermittently for 48 days after which the crystals were filtered washed with benzene, and recrystallized from benzene–ethanol. The complex and filtrate were worked up as usual by extraction with benzene from an aqueous suspension to yield 685 mg. of white waxy *n*-aliphatics and 65 mg. of impure *n*-aliphatics, respectively.

The filtrate from the treatment with urea was shaken for 10 days with 20 g. of active expanded urea.[47] The mixture was filtered and both crystals and filtrate worked up by adding to water and extracting with benzene to yield 20 mg. of impure *n*-aliphatics and 16.0 g. of *n*-aliphatic-free unsaponifiables.

The pure *n*-aliphatics (685 mg.) gave no color with tetranitromethane and showed no carbonyl absorption in the infrared. Chromatography on alumina yielded 16 mg. of hydrocarbons eluted with petroleum ether and 663 mg. of wax alcohols eluted mostly with benzene.

The hydrocarbon fraction was absorbed onto 1.4 g. of alumina (alkaline, activity 1) and eluted with petroleum ether to yield 6 mg. of pure *n*-paraffins. This was crystallized from benzene–methanol for analysis, m.p. 50–56.5°.

Anal. Found: C, 85.05; H, 14.74.

The infrared spectrum was as expected with a strong band progression doublet at 729 and 719 $cm.^{-1}$. There was no absorption in the ultraviolet (isooctane). The gas chromatographic

(47) M. H. Gorin and L. Rosenstein, U. S. Patent 2,785,151 (March 12, 1957).

analysis (6% EGiP on Gas Chrom P at 220°) gave the following results (hydrocarbon, t_R' in minutes, % total area): C_{18}, 0.7, 0.3; C_{19}, 0.9, 3.9; C_{20}, 1.3, 3.8; C_{21}, 1.8, 17.1; C_{22}, 2.5, 8.6; C_{23}, 3.4, 25.7; unknown, 4.5, trace; C_{24}, 5.0, 8.9; unknown, 6.5, 0.3; C_{25}, 7.0, 9.8; unknown, 9.3, 0.4; C_{26}, 10.0, 5.9; unknown, 13.4, 0.4; C_{27}, 14.4, 6.1; unknown, 19.4, 0.25; C_{28}, 21.0, 3.5; unknown, 28.2, trace; C_{29}, 30.5, 1.8; C_{30}, 44.9, 1.85; C_{31}, 65.4, 1.55. The slope of the log plot was checked against several standards, and cochromatography with known C_{24} was used to establish definite identification.

The wax alcohols were crystallized from hexane for analysis, m.p. 69–70°.

Anal. Calcd. for $C_{29}H_{46}O$: C, 80.90; H, 14.20. Found: C, 81.22; H, 14.36.

The infrared spectrum was identical with that of behenyl alcohol. Gas chromatographic analysis (0.75% G.E. SE-30 silicone gum rubber on Gas Chrom P at 200°) gave the following results (alcohol, t_R' in minutes, % total area): C_{18}, 3.0, 0.07; C_{20}, 4.9, 24.3; C_{21}, 6.6, 0.3; C_{22}, 8.9, 47.2; C_{23}, 12.0, 0.4; C_{24}, 15.9, 26.7; C_{26}, 29, 0.9. Peak assignments were confirmed by chromatography of pure behenyl and lignoceryl alcohols.

Sterols from Unsaponifiable Fraction.—The *n*-aliphatic-free unsaponifiables (16.0 g.) were added to a solution of 5.2 g. of digitonin in 400 ml. of 95% ethanol. The solution was taken to dryness under vacuum and 400 ml. of benzene added to the residue. After refluxing for 1 hr., the fine suspension of digitonin and digitonides was filtered and washed thoroughly with fresh benzene. The filtrate was again treated with digitonin (recovered from first precipitation) similarly to yield 14.3 of *n*-aliphatic- and sterol-free unsaponifiables (terpene fraction).

The digitonin precipitates were each refluxed briefly with 50 ml. of pyridine, cooled, and 400 ml. of ether–benzene then added with thorough shaking. After settling for 1 hr., the supernate was decanted and the gelatinous precipitate of digitonin was filtered and thoroughly washed with benzene. The ether–benzene solutions of the sterols were washed with dilute acid, dilute alkali, and water yielding 1.10 g. of sterols from the first precipitation and 90 mg. from the second.

The sterols were purified by reprecipitation of the digitonide as before. They showed a high end absorption in the ultraviolet plus shoulders at 281 mμ (ε 71) [reported[26] for stigmasta-3,5-dien-7-one, λ_{max} 278 mμ (ε 20,000)] and at 232 mμ (ε 379) [predicted[25b] for 7-keto-β-sitosterol, λ_{max} 237 mμ (ε 13,000)]. The infrared spectrum was completely identical with that of β-sitosterol. No trace of a peak at 968 cm.$^{-1}$ as expected for the *trans* disubstituted double bond of stigmasterol could be seen.[48] Gas chromatography (1% SE-30 on Gas Chrom P at 228°) showed 90% of a single component with the same elution time (27.5 min.) as pure β-sitosterol, 6% of a peak eluted earlier with the same elution time (22 min.) as campesterol, and 4% of a peak eluted later with the same elution time (35 min.) as α_1-sitosterol.[23] No peak was present at the position (24 min.) expected for stigmasterol.

A portion of the sterols (260 mg.) were chromatographed on alumina. Petroleum ether–benzene mixtures eluted 17 mg. with λ_{max} 282 mμ (ε 2260), ν_{max} 1653 cm.$^{-1}$ (conj. C=O). Methylene chloride–95% ethanol eluted 29 mg. of material with λ_{max} 236 mμ (ε 2075), ν_{max} 1672 cm.$^{-1}$ (conj. C=O). The main fraction (202 mg.) eluted with benzene gave infrared and ultraviolet spectra identical with those of β-sitosterol. The center cut was recrystallized from methanol for analysis, m.p. 139–140°, $[\alpha]^{23}D$ −30° (*c* 1.4), reported[21] for pure β-sitosterol, m.p. 139–140°, $[\alpha]D$ −33°. A mixture melting point was undepressed. Gas chromatography as before showed 94% β-sitosterol plus 6% campesterol.

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.82; H, 12.23.

Steam-Volatile Terpenoids.—The terpene fraction free of sterols and *n*-aliphatics (14.3 g.) was steam distilled for 5 hr. The distillate was extracted with benzene in the usual manner to yield 675 mg. of a pale yellow oil whose ultraviolet spectrum showed only a strong end absorption. Chromatography on 125 g. of alumina (activity I) readily separated this into 113 mg. of colorless oily methanol-insoluble hydrocarbons and 556 mg. of a pale yellow polar oil.

The hydrocarbons had very strong bands for methylene and a trisubstituted double bond, ν_{max} 3067, 1646, 885, 833, 792 cm.$^{-1}$; a sharp doublet at 1384 and 1365 cm.$^{-1}$ indicated an isopropyl group. Gas chromatography (SE-30) indicated a mixture of mostly sesquiterpenes with a major component constituting about one-quarter of the fraction. The polar fraction had an infrared spectrum almost identical with 13-epimanool. Gas chromatography as below showed 68% 13-epimanool as the only major constituent.

Chromatography of Nonvolatile Terpenoids.—The nonvolatile terpenoids (50 g.) were chromatographed on alumina. Petroleum ether eluted 1.0 g. of a colorless oily hydrocarbon fraction. The ultraviolet spectrum showed only a very strong end absorption at 210 mμ ($E^{1\%}_{1cm}$ 1084). The infrared spectrum had characteristic bands at 1387, 1376, 1368 (CH_3), 3056, 1641, 1410, 995 910 (–CH=CH_2), and 961 cm.$^{-1}$ (*trans* –CH=CH–). Gas chromatography (10% G.E. XE-60 nitrile silicone gum on Gas Chrom P, temperature programmed) showed this fraction to be a complex mixture with diterpenes predominating. No crystalline product could be obtained when this fraction in glacial acetic acid was treated with anhydrous hydrogen chloride for 5 hr. at 15°.

The second fraction, eluted with petroleum ether–benzene mixtures, was 24 g. of pale yellow oily epimanool (1) fraction. The ultraviolet spectrum showed only a strong end absorption at 210 mμ (ε 3110). The infrared spectrum had characteristic bands at 1643, 1406, 992, 916, 886 (–CH=CH_2 and >C=CH_2), and 1385 and 1364 cm.$^{-1}$ (>C(CH_3)$_2$). A single-beam, double-pass infrared spectrum in carbon tetrachloride was run on a Perkin-Elmer 112 spectrophotometer using a calcium fluoride prism. A single, strong, sharp hydroxyl band was present at 3610 cm.$^{-1}$ for the tertiary allylic hydroxyl; a single sharp vinylic C–H stretching band was present at 3084 cm.$^{-1}$. Gas and thin layer chromatography under a variety of conditions as below showed this fraction to be essentially homogeneous. All attempts to crystallize this fraction failed until a hexane solution was seeded with authentic manool. Repeated recrystallization from both hexane and from acetone failed to change the melting point or optical rotation significantly. An analytical sample of 13-epimanool (1) had m.p. 36.5–38.5°, $[\alpha]^{23}D$ +51° (*c* 1.3); reported[29-33] for manool, m.p. 53°, $[\alpha]D$ +30 to 33°. A mixture of two parts 13-epimanool and one part authentic manool melted at 41–49°.

Anal. Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.72; H, 11.68.

The infrared spectrum was unchanged from that of the oily epimanool fraction and was identical with that of authentic manool. Thin layer chromatography of the epimanool, authentic manool, and a mixture of the two at varying concentrations on alumina and silica gel plates gave identical R_f values of 0.6 and 0.8, respectively, when developed with 4:1 benzene–anhydrous ether; no separation of the mixture could be detected. Gas chromatography of the epimanool, authentic manool, and a mixture of the two on 3% SE-30 on Gas Chrom P at 150 (t_R' 45 min.), 170 (t_R' 22 min.), and 185° (t_R' 12 min.), and on 3% ethylene glycol succinate silicone (EGSS-X) on Gas Chrom P, temperature programmed, all gave a single peak with the same retention time for all three samples. Gas chromatography on 3% and 10% XE-60 on Gas Chrom P at 150 and 210° caused considerable decomposition, especially at the higher temperature, but the decomposition patterns were identical for all three samples. The mass spectrum of 13-epimanool was practically identical with that of manool itself[34] except that the intensities of those peaks arising from cleavage at C-13 were altered. In particular, the intensity of the *m/e* 71 ion (CH_3–$\overset{+}{C}$(OH)–CH=CH_2) was markedly lower in 13-epimanool than in manool.[35]

The third fraction eluted from the chromatogram with benzene was 6.0 g. of oily isoepimanool (13) fraction. The ultraviolet spectrum showed only a strong end absorption at 210 mμ (ε 7090). The infrared spectrum had characteristic bands at 3023, 1632, 1401, 996, and 913 (–CH=CH_2), 1380 (=C–CH_3), and 3291 cm.$^{-1}$ (OH). Thin layer chromatography showed a major and two minor spots more polar than 13-epimanool. Gas chromatography (10% XE-60 on Gas Chrom P) indicated that this fraction contained one major and eight minor constituents.

The fourth fraction, eluted from the chromatogram with benzene–ether mixtures, was 3.1 g. of yellow oily contortolal (3) fraction. The ultraviolet spectrum showed only a strong end absorption at 210 mμ (ε 5640). The infrared spectrum had characteristic bands at 3077, 1645, 870 (>C=CH_2), and 1712 and 2710 cm.$^{-1}$ (–CHO). Thin layer and gas chromatography

(48) J. A. Campbell, D. A. Shepherd, B. A. Johnson, and A. C. Ott, *J. Am. Chem. Soc.*, **79**, 1127 (1957).

indicated that this fraction contained one major and one minor constituent.

The fifth fraction, eluted from the chromatogram with ether and 100:1 ether–methanol, was 2.7 g. of yellow oily hydroxy-epimanool (2) fraction. Although thin layer chromatography showed only a single spot, gas chromatography (10% XE-60 on Gas Chrom P) indicated six minor coproducts in addition to the major constituent. Careful crystallization from heptane–methylene chloride yielded the major constituent, 18-hydroxy-13-epimanool (2), as white crystals which were recrystallized from heptane–methylene chloride and methanol–methylene chloride to constant melting point for analysis, m.p. 113–114.5°, $[\alpha]^{22}D$ +43° (*c* 1.3).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.71; H, 11.26.

The ultraviolet spectrum showed only a strong end absorption at 210 mμ (ε 3265). The infrared spectrum had ν_{max} 3050, 1640, 1410, 999, 919, 890 (–CH=CH_2 and >C=CH_2), and 3302 and 1017 cm.$^{-1}$ (–OH). An infrared spectrum in carbon tetrachloride was run on a Perkin-Elmer 421 spectrophotometer, ν_{max} 3085 (=CH_2), and a doublet at 3643 and 3617 cm.$^{-1}$ (C-18 and C-13 OH, respectively). Except for the bands at 3643 and 1017 cm.$^{-1}$ for primary hydroxyl,[49] the spectra were very similar to those of 13-epimanool. The spectrum was also very similar to that of torulosol (5), m.p. 110–111°, $[\alpha]D$ +31°.[31] However, a mixture melting point was depressed to 89–101°. Thin layer chromatography on alumina of these two compounds gave identical results (R_f 0.59 when developed with 100:1 benzene–methanol). The mass spectra of both compounds were practically identical except for minor differences in intensity for those peaks resulting from cleavage at C-13 or from removal of one of the groups at C-4.[35]

The n.m.r. spectrum indicated 34 protons, was practically identical with that of torulosol, and showed only the expected differences from that of manool. Characteristic resonances were present at τ 9.32 and 9.03 (C-17 and C-19 methyls), τ 8.67 (C-16 allylic methyl), and τ 5.19 and 5.48 (C-20 exocyclic methylene). A typical vinyl AB_2 system was present between τ 3.8 and 5.1, while a typical AB quartet was observed for the C-18 CH_2O group at τ 6.16, 6.34, 6.53, and 6.72.

The sixth and last fraction, eluted from the chromatogram with ether–95% ethanol, was 13 g. of yellow oily contortadiol (4) fraction. The ultraviolet spectrum showed only a strong end absorption at 210 mμ (ε 6100). The infrared spectrum had characteristic bands at 3041, 1637, 886 (>C=CH_2), and 3436 and 1027 cm.$^{-1}$ (–CH_2OH). Although thin layer chromatography indicated that this fraction had a major and one minor constituent, gas chromatography (10% XE-60 on Gas Chrom P) indicated that this fraction was more complex with five minor constituents in addition to the major one.

Manool Trihydrochloride.—Crude 13-epimanool (568 mg.) in 10 ml. of glacial acetic acid was saturated with anhydrous hydrogen chloride for 5 hr. at 15°. The white precipitate was filtered and washed with 10:1 glacial acetic acid–concentrated hydrochloric acid to yield 451 mg., m.p. 114–119°. Repeated recrystallization from hexane yielded an analytical sample, m.p. 118–120.5°, $[\alpha]^{23}D$ +22° (*c* 0.8). A mixture melting point with authentic manool trihydrochloride, m.p. 117–121°, was undepressed. No color was produced with tetranitromethane, the Beilstein test was positive, and the infrared spectrum was superimposable on that of authentic manool trihydrochloride.[28]

Anal. Calcd. for $C_{20}H_{35}Cl_3$: C, 62.90; H, 9.24. Found: C, 63.10; H, 9.32.

Manool and 13-Epimanool 3,5-Dinitrobenzoates.—The 13-epimanool ester was prepared in the usual fashion with an excess of 3,5-dinitrobenzoyl chloride in pyridine at room temperature for 3 days. The product was recrystallized from methylene chloride–methanol and methylene chloride–hexane to constant melting point, m.p. 116.5–118° with decomposition, $[\alpha]^{22}D$ +33° (*c* 1.0). Owing to instability of the ester at 100°, it was at no time heated above 60°.

Anal. Calcd. for $C_{27}H_{36}O_6N_2$: C, 66.92; H, 7.49; N, 5.78; mol. wt., 485. Found: C, 66.25; H, 7.90; N, 5.80; mol. wt. (vapor pressure osmometer), 461.

Manool 3,5-dinitrobenzoate was prepared similarly except that the crude ester was first purified by chromatography on alumina. The product was subsequently crystallized to constant melting point as before, m.p. 95–96° without decomposition, $[\alpha]^{22}n$ +8° (*c* 1.3); reported[30] melting point for manool 3,5-dinitrobenzoate is 95–97°.

The infrared spectra of both esters resembled each other closely. Comparison thin layer chromatography on alumina gave spots with an identical R_f 0.75 when developed with 1:1 petroleum ether–benzene. However, a mixture melting point was sharply depressed to 79–80.5°.

The n.m.r. spectra were identical. Three tertiary methyl peaks were present at τ 9.32, 9.20, and 9.12, while a fourth methyl group at τ 8.25 was characteristic of a tertiary methyl geminal to oxygen. A doublet was present at τ 5.45 and 5.13 for the exocyclic methylene group. A typical vinyl AB_2 pattern was present at τ 3.60, 3.77, 3.90, 4.07, 4.60, 4.65, 4.82, and 4.88. The ninth AB_2 line that would be expected around τ 5.64 could not be detected, but this resonance is normally very low when δ_ν/J_{AB} is high as in the present case. The total number of protons was 36, three of which were represented by aromatic protons of the 3,5-dinitrobenzoate group and appeared well downfield. Brief heating at 140° decomposed 13-epimanool 3,5-dinitrobenzoate *via* elimination of 3,5-dinitrobenzoic acid. The n.m.r. spectrum indicated that extensive rearrangement of the double bonds occurred concurrently.

Contortolal Semicarbazone.—The contortolal fraction (3.1 g.) in ethanol was refluxed for 1 hr. with an excess of semicarbazide hydrochloride and sodium acetate. The reaction mixture was cooled, poured into water, and extracted with benzene to yield 4.0 g. of product which was chromatographed on alumina (activity III). Benzene–methanol 10:1 eluted 1.5 g. of an essentially pure derivative which was crystallized with difficulty from benzene–acetonitrile to constant melting point for analysis, m.p. 157–159°, $[\alpha]^{21}D$ +22° (*c* 1.2). Thin layer chromatography on alumina gave a single spot, R_f 0.80, when developed with 5:1 benzene–methanol; ν_{max} 3280–3510 (OH and NH), 1681 (C=O), 1580 (C=C and C=N), 995 (primary OH), 885 (>C=CH_2), and 763 cm.$^{-1}$ (CH=N).

Anal. Calcd. for $C_{21}H_{35}N_3O_2$: C, 69.77; H, 9.76; N, 11.62. Found: C, 69.93; H, 9.74; N, 11.56.

The n.m.r. spectrum confirmed the presence of 35 protons. Characteristic resonances were present at τ 9.45 and 8.97 (C-17 and C-19 methyls), τ 8.33 (C-16 vinylic methyl), τ 5.82 and 5.94 (C-15 vinylic CH_2O), τ 5.16 and 5.48 (C-20 exocyclic methylene), triplet at τ 4.63 (C-14 vinylic proton), and a sharp singlet at τ 3.98 (C-18 CH=N). The amide nitrogens resonated at τ 1.2 (NH) and 4.5 (NH_2) and were identified by the fact that they exchanged with deuterium in deuterium oxide. The NH exchanged very rapidly, while the NH_2 was completely exchanged after 1 hr. at room temperature. The hydroxyl proton was not visible, being no doubt hidden among the high field resonances as would be expected in the case where hydrogen bonding is not likely. The n.m.r. spectrum at 100 Mc. was very informative. The NH_2 and the vinylic proton triplet were now cleanly resolved from one another. Spin-spin decoupling clearly showed that this triplet for one vinylic proton was coupled with the vinylic CH_2O doublet at τ 4.82 and 5.94. Irradiating at τ 5.88 caused the triplet for a vinylic proton to collapse to a sharp singlet. Likewise, irradiating at τ 4.63 caused the doublet for the vinylic CH_2O to collapse to a singlet. The τ-values for the two angular methyls and even for the vinylic methyl were unchanged and no indication of coupling between the adjacent vinylic proton and vinylic methyl could be observed.

Contortadiol Di-*p*-phenylazobenzoate.—The contortadiol fraction (2.2 g.) was dissolved in 120 ml. of pyridine. *p*-Phenylazobenzoyl chloride (16 g.) was added and the solution heated on the steam bath for 4 hr. Cooling, destruction of the excess acid chloride with water, and extraction in the usual way yielded 4.1 g. of product that was chromatographed on 410 g. of alumina. Benzene eluted 0.49 g. of a crystalline product which was homogeneous according to infrared spectra and thin layer chromatography on alumina (R_f 0.60 when developed with 2:1 benzene–petroleum ether). No other major crystalline product was obtained. The ester was crystallized from benzene–heptane and benzene–methanol to constant melting point for analysis, m.p. 170–173° with decomposition, $[\alpha]^{22}D$ −11° (*c* 1.1); ν_{max} 1713 (C=O), and 1406 and 889 cm.$^{-1}$ (>C=CH_2).

Anal. Calcd. for $C_{46}H_{36}N_4O_4$: C, 76.42; H, 6.97; N, 7.75. Found: C, 75.97; H, 7.11; N, 7.55.

The n.m.r. spectrum confirmed the presence of 50 protons, 18 of which appeared well downfield in the region for aromatic protons. Characteristic resonances were present at τ 9.23 and

(49) A. R. H. Cole, G. T. A. Müller, D. W. Thornton, and R. L. S. Willix, *J. Chem. Soc.*, 1218 (1959).

8.91 (C-17 and C-19 methyls), and τ 5.15 and 5.43 (C-20 exocyclic methylene). An AB quartet was present at τ 5.38, 5.56, 5.81, and 5.99 for a C-18 CH_2O as in 18-hydroxy-13-epimanool (2), but further downfield owing to formation of the ester group. A multiplet for a single C-14 vinylic proton was present at τ 4.6 as in contortolal semicarbazone. Analogously, the C-16 vinylic methyl appeared at τ 8.21, and a doublet appeared at τ 5.08 and 5.19 for the vinylic C-15 CH_2 in which the signal for the two equivalent protons was being split by coupling to the adjacent vinylic proton at C-14. This was confirmed as before by spin–spin decoupling at 100 Mc. in which irradiation at τ 5.13 (the midpoint of the C-15 doublet) caused the multiplet for the single C-14 vinylic proton to collapse to a sharp singlet, while irradiation at τ 4.55 caused the C-15 doublet to collapse to a singlet at τ 5.13 which overlapped one of the exocyclic methylene resonances. Again no indication of coupling was observed between the C-16 vinylic methyl and the C-14 vinylic proton.

Saponification of Contortadiol Di-*p*-phenylazobenzoate.—The ester (1.652 g.) in 80 ml. of benzene was added to a solution of 6.95 g. of sodium hydroxide in 200 ml. of 95% ethanol. The mixture was refluxed for 2 hr. under nitrogen and cooled; the precipitated sodium *p*-phenylazobenzoate was filtered and washed with benzene. The filtrates were extracted as usual to yield 0.708 g. of an almost colorless oil.

This was crystallized from methylene chloride–hexane and acetone to constant melting point for analysis, m.p. 106–107.5°, $[\alpha]^{22}D$ +31° (*c* 0.9).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.56; H, 11.41.

The ultraviolet spectrum showed only a strong end absorption, 210 mμ (ϵ 5600). The infrared spectrum had characteristic bands at 3270 and 1027 ($-CH_2OH$), and 3050, 1641, and 898 cm.$^{-1}$ ($>C{=}CH_2$). An infrared spectrum in carbon tetrachloride was run on a Perkin-Elmer 421 spectrophotometer, ν_{max} 3078 ($=CH_2$), and a doublet at 3634 and 3617 cm.$^{-1}$ (C-18 and C-15 OH, respectively).

Comparison with a sample of agathadiol (m.p. 107–108° $[\alpha]D$ +31°)[31] showed that the mixture melting point was undepressed and the infrared spectra were superimposable. Thin layer chromatography on alumina (R_f 0.83) and on silica gel (R_f 0.57) showed no difference between them, and mixtures were not separated. The plates were developed with 3:1 benzene–1,2-dimethoxyethane and the spots were detected with iodine vapor. However, the mass spectra, although very similar, did show definite differences. On a Σ% basis, the peaks at *m/e* 55, 82, 86, 96, 122, and 160 are clearly more intense in the spectrum of contortadiol, whereas the peaks at *m/e* 135, 277, and 306 are more intense in the spectrum of agathadiol.

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Preparation and Reactions of Hydrazino Perfluoroaromatic Compounds

DEWEY G. HOLLAND,[1] GEORGE J. MOORE, AND CHRIST TAMBORSKI

Nonmetallic Materials Division, Air Force Materials Laboratory, Wright-Patterson Air Force Base, Ohio

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Nucleophilic attack by hydrazine on perfluoroaromatic systems has yielded versatile, difunctional, hydrazino perfluoroaromatic intermediates which have been employed in the synthesis of several disubstituted perfluoroaromatic compounds.

Nucleophilic attack by hydrazine on hexafluorobenzene has been reported[2,3] to yield pentafluorophenylhydrazine. In our studies, disubstitution was encountered when 4 moles of anhydrous hydrazine were employed (Table I).

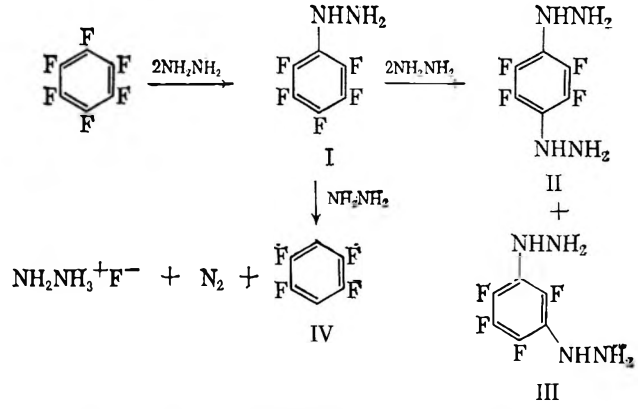
TABLE I

PRODUCTS OBSERVED[a]

Solvent	I	II	III	IV	N_2
Dioxane	24	12.5	12.5	Detected	27
Tetrahydrofuran	32	35	0	Detected	23

[a] Mole %.

When the reaction was conducted in *p*-dioxane, a 25% yield of 1:1 mixture[4] of the isomeric dihydrazinotetrafluorobenzenes II and III was obtained. An efficient means of separation of this nearly intractable mixture has not been found. When tetrahydrofuran (THF) was employed as the solvent, a 35% yield of only one isomer, *p*-dihydrazinotetrafluorobenzene (II), was realized. Pentafluorophenylhydrazine (I) was isolated from both of these reactions and was shown to be the intermediate, since it yielded the same products in essentially the same ratio when treated with additional anhydrous hydrazine.



The low yield of disubstituted product(s) has been attributed to the consumption of hydrazine, which is capable of acting as a base rather than a nucleophile, in the intramolecular oxidation–reduction of the intermediate pentafluorophenylhydrazine (I). Nitrogen and 1,2,4,5-tetrafluorobenzene (IV) are shown by us

(1) This work was reported at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) G. M. Brooke, J. Burdon, M. Stacey, and J. Tatlow, *J. Chem. Soc.*, 1768 (1960).

(3) J. M. Birchall, R. N. Haszeldine, and A. R. Parkinson, *ibid.*, 4966 (1962).

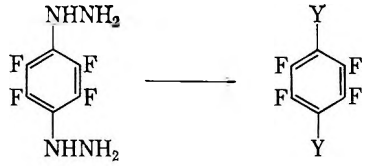
(4) As determined by F^{19} n.m.r.

elsewhere[5] to be the major products of the reaction of pentafluorophenylhydrazine (I) with 3 *N* sodium hydroxide.

Several reactions, analogous with those reported for pentafluorophenylhydrazine by Birchall, *et al.*,[3] were conducted with 1,4-dihydrazinotetrafluorobenzene (II) to extend these oxidation, reduction, and free-radical reactions to the preparation of difunctional compounds. The conditions for optimum yields have not yet been determined.

When the nearly intractable 1:1 mixture of isomeric dihydrazino compounds II and III was oxidized with bromine in acetic acid, the only product isolated was 1,4-dibromotetrafluorobenzene (V, 42%).

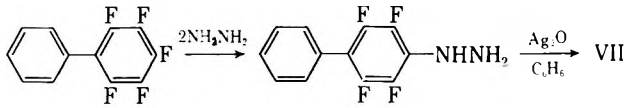
The sole product isolated from the hydriodic acid reduction of compound II was 2,3,5,6-tetrafluorophenylenediamine (VI, 18%). The oxidation of compound II with silver oxide in benzene afforded, through a free-radical process, 1,4-diphenyltetrafluorobenzene (VII, 24%).



II

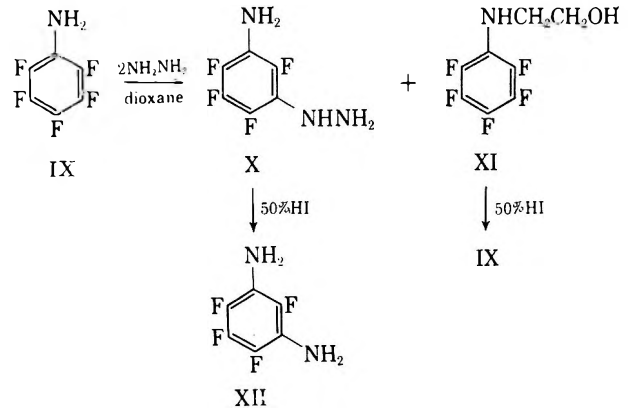
V, Y = Br
VI, Y = NH_2
VII, Y = C_6H_5

On reaction with anhydrous hydrazine, 2,3,4,5,6-pentafluorobiphenyl[3] yielded 4-hydrazino-2,3,5,6-tetrafluorobiphenyl (VIII, 76%). Oxidation of VIII with silver oxide in benzene also produced the terphenyl VII (21%).



VIII

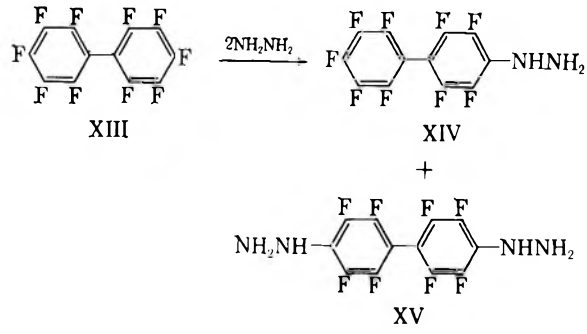
Reaction between pentafluoroaniline (IX) and anhydrous hydrazine was not observed when ethanol or THF was employed as the solvent. In *p*-dioxane, the aniline IX yielded both the *meta*-substitution product, 3-hydrazinotetrafluoroaniline (X, 24%), and 2-(pentafluoroanilino)ethanol (XI, 40%). The yield of the former product may be increased to 78% when only a small amount of *p*-dioxane is employed as the solvent. The latter product is believed to arise through cleavage of the solvent, since it was observed even in specially purified[6] *p*-dioxane.



XII

The anilinoethanol XI was cleaved to pentafluoroaniline (IX) on reaction with 50% hydriodic acid. The hydrazinoaniline X afforded 2,4,5,6-tetrafluorophenylenediamine (XII, 32%) on reaction with hydriodic acid.

Only *para*-substitution products were observed in the reaction of decafluorobiphenyl (XIII) with anhydrous hydrazine. 4,4′-Dihydrazinooctafluorobiphenyl (XV, 18%) was isolated, as well as the anticipated product, 4-hydrazinononafluorobiphenyl (XIV, 72%).



XIII XIV XV

Experimental[7]

The Reaction of Hexafluorobenzene with Hydrazine. In Dioxane.—Hexafluorobenzene (37.2 g., 0.20 mole) and 95+% anhydrous hydrazine (38.4 g., 1.20 moles) were heated in 125 ml. of *p*-dioxane. After 16 hr. at reflux temperature approximately 1200 cc. (27%) of nitrogen had been evolved. Distillation from the reaction solution yielded a fraction (b.p. 88–92°) boiling below the solvent. A vapor phase chromatogram[8] showed this distillate to be a mixture of hexafluorobenzene (13.4%), pentafluorobenzene (7.6%), and 1,2,4,5-tetrafluorobenzene (IV, 78.9%).

The cooled reaction mixture was stirred with 400 ml. of ligroin (b.p. 60–90°). The intractable tan solid (10.5 g., 25%, m.p. 156.5–162° dec.) was removed by filtration. Recrystallization three times from toluene afforded a small amount of pale yellow needles, m.p. 148.5–152.5° dec.

Anal. Calcd. for $C_6H_6F_4N_4$: C, 34.29; H, 2.88; F, 36.2; N, 26.66. Found: C, 34.56; H, 2.92; F, 36.3; N, 26.76.

The F^{19} n.m.r. spectrum of the intractable tan solid in dimethylformamide showed it to be a 1:1 mixture of 1,4- and 1,3-dihydrazinotetrafluorobenzenes. Absorption at 74.7, 88.7 (doublet), and 93.9 (triplet) p.p.m. is attributed to the *meta* isomer, while a single absorption at 83.0 p.p.m. is attributed to the *para* isomer. The spectrum of the sample recrystallized from toluene exhibited similar absorption with the approximate molar isomeric ratio of 12.5:1.0 *meta–para*.

The crude mixture yielded a bis-1,4-acetophenone hydrazone derivative, white needles (from ethanol), m.p. 167.5–168°.

Anal. Calcd. for $C_{22}H_{18}F_4N_4$: C, 63.76; H, 4.38; F, 18.3; N, 13.52. Found: C, 63.82; H, 4.40; F, 18.6; N, 13.60.

The F^{19} n.m.r. spectrum of the bishydrazone in acetone exhibits absorption at 79.8 p.p.m.

The ligroin filtrate was stripped under vacuum, and the resulting solid was recrystallized from ligroin (b.p. 90–120°). This process yielded 9.6 g. (24%) of pentafluorophenylhydrazine, m.p. 73–75°, lit.[2] m.p. 76.0–77.5°.

In Tetrahydrofuran.—Hexafluorobenzene (93.0 g., 0.5 mole) and 95+% anhydrous hydrazine (70.5 g., 2.2 moles) were stirred and refluxed for 45 hr. in 400 ml. of anhydrous tetrahydrofuran. Evolved nitrogen, 2576 cc. (23%), was measured on a wet test meter. A yellow hygroscopic precipitate was filtered from the reaction mixture. Washing, by stirring with water, yielded 17.4 g. of tan, crystalline product. The tetrahydrofuran filtrate

(5) D. G. Holland, G. J. Moore, and C. Tamborski, in press.

(6) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

(7) Melting points are corrected.

(8) F & M Model 500 programmed vapor phase chromatograph, employing a 6-ft. (0.25-in.) diisodecylphthalate (20%) Chromasorb P column.

was concentrated by distilling the solvent. 1,2,4,5-Tetrafluorobenzene was detected[8] in the distillate. On cooling, a tan solid was precipitated. After filtration and drying, pentafluorophenylhydrazine (12.7 g., 32%) was separated from this mixture by four 250-ml. extractions with hot ligroin (b.p. 60–90°). The undissolved solid was combined with the product previously obtained to give 36.5 g. (35%) of nearly intractable 1,4-dihydrazinotetrafluorobenzene, m.p. 152–158° dec. A sample, recrystallized from a large volume of toluene, afforded white crystals, m.p. 168.5–170.5° dec.

The F^{19} n.m.r. spectra (in dimethylformamide) of the crude product and of the recrystallized sample showed both to be exclusively the *para* isomer through their singular absorption at 82.6 p.p.m.

The Reaction of Pentafluorophenylhydrazine with Hydrazine.—Pentafluorophenylhydrazine (21.8 g., 0.11 mole) and 95+% anhydrous hydrazine (6.7 g., 0.22 mole) were refluxed for 16 hr. in 80 ml. of *p*-dioxane. One hundred milliliters of ligroin (b.p. 60–90°) was added to the cooled reaction mixture. After vigorous stirring, the mixture was filtered yielding 6.4 g. (28%) of a 1:1 mixture (as shown by F^{19} n.m.r.) of 1,4- and 1,3-dihydrazinotetrafluorobenzenes (II and III), m.p. 156–160° dec. The ligroin filtrate was evaporated, yielding 3.2 g. (15%) of unchanged starting material.

1,4-Dibromotetrafluorobenzene (V).—Three-hundredths of a mole (6.3 g.) of crude 1,4- and 1,3-dihydrazinotetrafluorobenzenes (II and III, a 1:1 mixture) in 100 ml. of glacial acetic acid was stirred as 19.2 g. (0.12 mole) of bromine in 25 ml. of acetic acid was slowly added. Stirring was continued for 16 hr. At the end of this time, hydrogen bromide evolution was still evident. The mixture was then refluxed for 16 hr. It was then decanted into 500 ml. of water. The precipitate, after collection by filtration, was recrystallized from dilute methanol. 1,4-Dibromotetrafluorobenzene (1.6 g.) was collected by filtration. This compound was identical with an authentic sample, m.p. and m.m.p. 75.5–78.5°, lit.[9] m.p. 76–77°. The aqueous filtrate was extracted with two 100-ml. portions of ether. After neutralizing the ether extracts with 10% sodium bicarbonate, they were evaporated. An additional 0.3 g. of the same product was obtained in this manner. The combined yield was 1.9 g. (42%, based on II). No other product was observed.

2,3,5,6-Tetrafluorophenylenediamine (VI).—To crude 1,4-dihydrazinotetrafluorobenzene (10.5 g., 0.05 mole) was cautiously added 70 ml. of 50% hydriodic acid. The resulting solution was refluxed for 2 hr. The mixture was treated with solid sodium metabisulfite until a starch–potassium iodide test was negative for iodine. Water was added and the solution was steam distilled. The distillate was made basic with sodium hydroxide pellets. The crystalline precipitate was separated and recrystallized once, from benzene, to yield 1.6 g. (18%) of 2,3,5,6-tetrafluorophenylenediamine as white needles, m.p. 142–144°, lit.[2] m.p. 143.5–144°.

Further work-up failed to yield any other tractable product.

4-Hydrazino-2,3,5,6-Tetrafluorobiphenyl (VIII).—2,3,4,5,6-Pentafluorobiphenyl (17.5 g., 0.072 g.) and 95+% anhydrous hydrazine (5.16 g., 0.153 mole) were stirred and refluxed in 85 ml. of *p*-dioxane for 1.5 hr. The resulting reaction mixture was evaporated under vacuum. The residual solid was steam distilled, yielding the product, which, after recrystallization from 90–120° ligroin, afforded 13.9 g. (76%) of pale tan platelets, m.p. 140–142°. Two further recrystallizations from ligroin (b.p. 60–90°) gave the analytical sample as white platelets, m.p. 141.5–142.5°.

Anal. Calcd. for $C_{12}H_8F_4N_2$: C, 56.25; H, 3.15; F, 29.7; N, 10.94. Found: C, 56.17; H, 3.14; F, 29.7; N, 10.90.

The F^{19} n.m.r. spectrum in dimethylformamide exhibited two sextets at 72.0 and 83.4 p.p.m. A crude sample (before steam distillation) exhibited no other fluorine environments.

1,4-Diphenyltetrafluorobenzene (VII). A.—To crude 1,4-dihydrazinotetrafluorobenzene (1.56 g., 0.0074 mole) in 75 ml. of reagent grade benzene was slowly added 3.48 g. (0.015 mole) of silver oxide. The reaction was stirred while vigorous nitrogen evolution was evident. Ice-bath cooling was occasionally necessary. The reaction mixture was then stirred for 3 hr. at room temperature and subsequently refluxed for 1 hr. The mixture was filtered through asbestos fiber and the solids were thoroughly washed with 50 ml. of benzene. The combined filtrates were stripped under vacuum. The residual yellow solid was recrystallized twice from benzene, employing decolorizing carbon, to yield 537 mg. (24%) of white, crystalline, 1,4-diphenyltetrafluorobenzene (VII), m.p. 250–253° (sublimes while melting).

Anal. Calcd. for $C_{18}H_{10}F_4$: C, 71.52; H, 3.33; F, 25.1. Found: C, 71.64; H, 3.66; F, 24.7.

B.—4-Hydrazino-2,3,5,6-tetrafluorobiphenyl (2.1 g., 0.011 mole) was dissolved in 65 ml. of reagent grade benzene. To the well-stirred solution was slowly added 2.6 g. (0.011 mole) of silver oxide. The resulting reaction mixture was stirred for 0.5 hr. at room temperature and then was refluxed for 1 hr. Filtration, through asbestos fiber, and evaporation of the filtrate yielded the crude product. Sublimation at 70° (0.2 mm.) yielded 700 mg. (21%) of pale yellow crystalline product, m.p. 251–253° (sublimes while melting). The infrared spectra of this product and 1,4-diphenyltetrafluorobenzene (VII), synthesized from 1,4-dihydrazinotetrafluorobenzene, were identical.

The Reaction of Pentafluoroaniline with Hydrazine in Dioxane.—Pentafluoroaniline (72.2 g., 0.4 mole) and 95+% anhydrous hydrazine (27.0 g., 0.8 mole) were refluxed for 26 hr. in 250 ml. of *p*-dioxane. Water (300 ml.) was added to the reaction solution and the resulting mixture was extracted four times with 150-ml. portions of ether, once with 150 ml. of ligroin (b.p. 60–90°), and once with 150 ml. of benzene. The combined ether extracts were stripped under vacuum, yielding 51.8 g. of crude, tan solid. Recrystallization from ligroin (b.p. 90–120°) afforded 45.2 g. of a pale tan solid, m.p. 107.5–109.5°. Evaporation of the ligroin (b.p. 90–120°) filtrate yielded 36.6 g. of another material, m.p. 54.5–56.5°. The ligroin (b.p. 60–90°) and benzene extracts were stripped under vacuum, giving an additional 3.7 g. of material melting at 108–110°.

The combined yield of material melting at 107.5–109.5° was 18.9 g. (24%). An additional recrystallization from ligroin (b.p. 90–120°) afforded the analytical sample of 3-hydrazinotetrafluoroaniline (X), m.p. 108.5–110°.

Anal. Calcd. for $C_6H_5F_4N_3$: C, 36.93; H, 2.58; N, 21.54. Found: C, 37.83; H, 2.78; N, 21.41.

The yield of 3-hydrazinotetrafluoroaniline may be raised to 78% if only 41 ml. of *p*-dioxane is employed in the above experiment.

The 36.6 g. (40%) of low melting product is 2-(pentafluoroanilino)ethanol (XI). Sublimation at 50° (0.25 mm.) afforded the analytical sample, m.p. 55–56.5°.

Anal. Calcd. for $C_8H_6F_5NO$: C, 42.30; H, 2.66; F, 41.8; N, 6.17. Found: C, 42.08; H, 2.66; F, 42.2; N, 7.34.

The anilinoethanol XI was refluxed in 50% hydriodic acid for 2 hr. Steam distillation from the acidic mixture yielded pentafluoroaniline (IX), m.p. and m.m.p. (with an authentic sample) 35–36°.

2,4,5,6-Tetrafluorophenylenediamine (XII).—Hydriodic acid (50%, 47.6 g.) was cautiously added to 6.0 g. (0.031 mole) of 3-hydrazinotetrafluoroaniline. The mixture was stirred and refluxed for 18 hr. Solid sodium metabisulfite was added to the resulting mixture until a positive test for iodine was no longer indicated with starch–potassium iodide test paper. The mixture was steam distilled. The aqueous distillate was extracted three times with 150-ml. portions of ether. The combined ether extracts were evaporated. The solid obtained was recrystallized from ligroin (b.p. 90–120°). 2,4,5,6-Tetrafluorophenylenediamine (1.8 g., 32%) was obtained as white needles, m.p. 127–130°, lit.[2] m.p. 129.5–131.0. No additional products were recovered from the reaction mixture.

4-Hydrazinononafluorobiphenyl (XIV).—Decafluorobiphenyl (33.4 g., 0.1 mole) and 95+% anhydrous hydrazine (6.7 g., 0.2 mole) were stirred and refluxed in 350 ml. of absolute ethanol for 23 hr. Half of the solvent was removed by distillation, and the remaining solution was decanted into 400 ml. of water. The precipitate was removed by filtration and was thoroughly washed with water. Recrystallization from benzene yielded, as the first precipitate, 6.5 g. (18%) of white, crystalline 4,4′-dihydrazinooctafluorobiphenyl (XV), m.p. 198.5–206.5°. Three recrystallizations from benzene–ethanol gave the analytical sample, m.p. 210.5–212.5°.

Anal. Calcd. for $C_{12}H_6F_8N_4$: C, 40.24; H, 1.69; F, 42.4; N, 15.64. Found: C, 41.02; H, 1.81; F, 42.6; N, 15.80.

The F^{19} n.m.r. spectrum in acetone exhibited multiplets at 63.7 and 77.7 p.p.m.

On cooling, 24.9 g. (72%) of tan, crystalline 4-hydrazinonafluorobiphenyl (XIV), m.p. 130–132°, precipitated from the

(9) M. Hellmann and A. J. Bilbo, *J. Am. Chem. Soc.*, **75**, 4590 (1953).

benzene filtrate. One recrystallization from absolute ethanol gave the analytical sample, m.p. 132–133.5°.

Anal. Calcd. for $C_{12}H_3F_9N_2$: C, 41.63; H, 0.87; F, 49.4; N, 8.09. Found: C, 41.81; H, 0.98; F, 49.2; N, 8.13.

The F^{19} n.m.r. spectrum in acetone exhibited multiplets at 61.8, 64.8, 76.2, 79.0, and 85.6 p.p.m. Two unidentified, weak fluorine environments (80.7 and 82.3 p.p.m.) appeared similar to the absorption at 79.0 p.p.m. which was assigned to the fluorine *ortho* to the hydrazino function. These may have arisen due to formation of the hydrazone in acetone solution.

F^{19} Nuclear Magnetic Resonance Data.—The F^{19} spectra were run on a Varian V-4300-2 D.P. spectrometer at 40.0 Mc./sec. Chemical shifts are reported in p.p.m. from trifluoroacetic acid.

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The Action of Acetic Anhydride on Osazones and Hydrazones

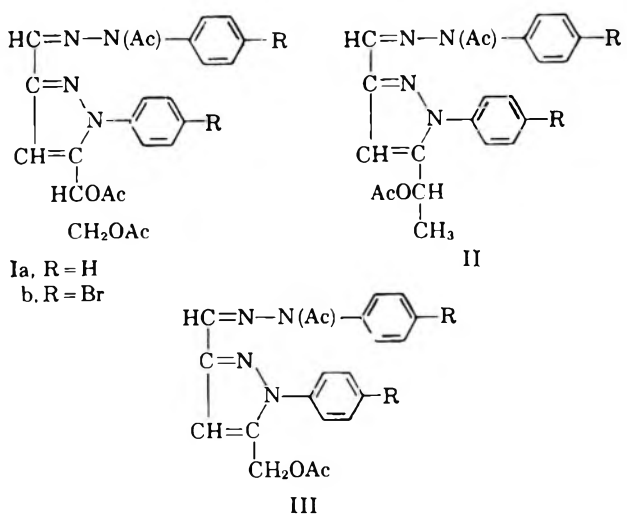
H. EL KHADEM,[1] Z. M. EL-SHAFEI, AND M. M. MOHAMMED-ALI

Chemistry Department, Faculty of Science, University of Alexandria, Egypt, U. A. R., and Department of Chemistry, The Ohio State University, Columbus 10, Ohio

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Like the phenyl derivatives, the *p*-bromophenylosazones obtained from D-galactose, L-rhamnose, and D-xylose, when refluxed with acetic anhydride, yielded dianhydro-*p*-bromophenylosazone acetates Ib, IIb, and IIIb, respectively. The phenylosazone from D-glucose yielded an acetylated monoanhydrophenylosazone (IV) in addition to the acetylated dianhydrophenylosazone Ia reported earlier. Compound IV on hydrolysis yielded 3,6-anhydro-D-*ribo*-hexose phenylosazone (V) from which it could also be prepared. D-Galactose phenylhydrazone and penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone yielded, on boiling with acetic anhydride, *N*-acetylpenta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone (VI).

It has been shown[2] that monosaccharide phenylosazones, when refluxed with acetic anhydride, yield colorless dianhydrophenylosazone acetates having pyrazole rings. Thus, hexoses of the D-series yielded Ia and 6-deoxy-L-hexoses IIa; and pentoses, whether D or L, yielded the optically inactive IIIa. We have now extended this reaction to the *p*-bromophenylosazones and obtained the corresponding acetylated dianhydro-*p*-bromophenylosazones. Thus D-*lyxo*-hexose *p*-bromophenylosazone (from D-galactose) yielded 5-(D-*glycero*-1,2-diacetoxyethyl)-1-(*p*-bromophenyl)-3-formylpyrazole *N*-acetyl-*p*-bromophenylhydrazone (Ib), and 6-deoxy-L-*arabino*-hexose *p*-bromophenylosazone (from L-rhamnose) yielded 5-(L-*glycero*-1-acetoxyethyl)-1-(*p*-bromophenyl)-3-formylpyrazole *N*-acetyl-*p*-bromophenylhydrazone (IIb). Similarly, D-*threo*-pentose *p*-bromophenylosazone (from D-xylose) yielded 5-acetoxymethyl-1-(*p*-bromophenyl)-3-formylpyrazole *N*-acetyl-*p*-bromophenylhydrazone (IIIb). This, like the previously investigated phenyl derivative, was hydrolyzed and treated with *p*-nitrophenylhydrazine to yield by *trans*-hydrazonation 1-(*p*-bromophenyl)-3-formyl-5-(hydroxymethyl)-pyrazole *p*-nitrophenylhydrazone.



D-*arabino*-Hexose phenylosazone, when refluxed with acetic anhydride, yielded in addition to 5-(D-*glycero*-1,2-diacetoxyethyl)-3-formyl-1-phenylpyrazole *N*-acetylphenylhydrazone (Ia) reported earlier,[2] a yellow product which proved to be *N*-acetyl-4,5-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose phenylosazone (IV). The structure of this compound was determined from combustion analysis and from *O*-acetyl[3] and total acetyl[4] determinations. The infrared spectrum of IV revealed both *N*- and *O*-acetyl groups at 1675 and 1725 cm.$^{-1}$, respectively, as well as the C=N group at 1600 cm.$^{-1}$. Deacetylation with either methanolic ammonia or methanolic *n*-butylamine yielded a monoanhydrophenylosazone which no longer possessed the amide or ester bands. This compound consumed one mole of periodate and was identical with Diels' monoanhydrophenylosazone[5] (V), obtained by refluxing D-*arabino*-hexose phenylosazone with methanolic sulfuric acid. Furthermore, acetylation of Diels' compound with boiling acetic anhydride afforded our initial *N*-acetyl-di-*O*-acetylanhydrophenylosazone (IV). Identity in both cases was established by mixture melting points and by comparison of infrared spectra. Since Diels' monoanhydrophenylosazone has been shown[6] to be 3,6-anhydro-D-*ribo*-hexose phenylosazone (V) formed by a Walden inversion on C-3, it was concluded that our product was the *N*-acetyl-4,5-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose phenylosazone (IV). The position of the *N*-acetyl group on the C-1 hydrazone has not been confirmed, but was allotted by analogy to I, II, and III.

(1) Visiting Fellow at The Ohio State University until July, 1964.

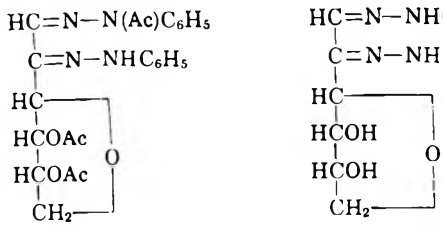
(2) H. El Khadem and M. M. Mohammed-Ali, *J. Chem. Soc.*, 4929 (1963).

(3) A. Kunz and C. S. Hudson, *J. Am. Chem. Soc.*, **48**, 1988 (1926).

(4) O. O. Hoffman and M. L. Wolfrom, *Anal. Chem.*, **19**, 225 (1947); see M. L. Wolfrom, M. Konigsberg, and S. Soltzberg, *J. Am. Chem. Soc.*, **58**, 490 (1936).

(5) O. Diels and R. Mayer, *Ann.*, **519**, 157 (1935).

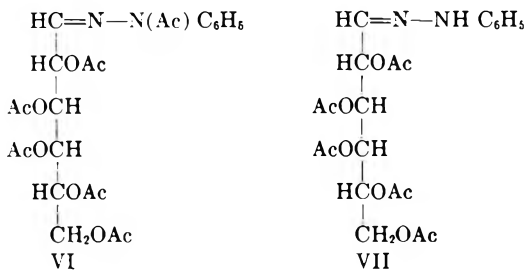
(6) E. Hardegger and E. Schreier, *Helv. Chim. Acta*, **35**, 232 (1957).



IV V

Acetylation of D-galactose phenylhydrazone with boiling acetic anhydride afforded a new hexaacetyl derivative VI which showed both *N*- and *O*-acetyl groups at 1700 and 1750 cm.$^{-1}$, respectively, and a C=N group at 1630 cm.$^{-1}$. Estimation of *O*-acetyl and total acetyl agreed with those calculated for a *N*-acetylpenta-*O*-acetylhexose phenylhydrazone. Hydrolysis with methanolic ammonia followed by treatment with phenylhydrazine yielded D-*lyxo*-hexose phenylosazone. Furthermore, acetylation of the known penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone[7] (VII) with boiling acetic anhydride afforded our product, which was therefore identified as *N*-acetyl penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone (VI).

The structures of the compounds described in this paper have been confirmed by study of their proton magnetic resonance spectra to be published later.



VI VII

From the above it seems that osazones and acyclic sugar hydrazones when acetylated with pyridine and acetic anhydride yield *O*-acetates,[4,7,8] whereas the more vigorous reaction with boiling acetic anhydride can lead to acetylation on both nitrogen and oxygen.

Experimental[9]

5-(D-*glycero*-1,2-Diacetoxylethyl)-1-(*p*-bromophenyl)-3-formylpyrazole *N*-Acetyl-*p*-bromophenylhydrazone (Ib).—D-*lyxo*-Hexose *p*-bromophenylosazone (20 g., from D-galactose) was refluxed for 1 hr. with acetic anhydride (100 ml.). The clear solution was poured onto crushed ice (500 g.) and left overnight. The aqueous solution was decanted and the residual oil was washed repeatedly with water; after several days it solidified and was crystallized from dilute ethanol as colorless needles soluble in ethanol, chloroform, and ether, and insoluble in water, m.p. 120°.

Anal. Calcd. for $C_{24}H_{22}Br_2N_4O_5$: C, 47.6; H, 3.7; N, 9.3. Found: C, 48.1; H, 4.1; N, 9.7.

5-(L-*glycero*-1-Acetoxyethyl)-1-(*p*-bromophenyl)-3-formylpyrazole *N*-Acetyl-*p*-bromophenylhydrazone (IIb).—6-Deoxy-L-*arabino*-hexose *p*-bromophenylosazone (5 g. from L-rhamnose) was refluxed with acetic anhydride (25 ml.) for 1 hr. and then poured onto ice (100 g.). The crystals that separated overnight were collected and crystallized from dilute ethanol as needles, m.p. 170°.

Anal. Calcd. for $C_{22}H_{20}Br_2N_4O_3$: C, 48.2; H, 3.7; N, 10.2. Found: C, 48.1; H, 3.9; N, 10.1.

5-(Acetoxymethyl)-1-(*p*-bromophenyl)-3-formylpyrazole *N*-Acetyl-*p*-bromophenylhydrazone (IIIb).—D-*threo*-Pentose *p*-bromophenylosazone (5 g. from D-xylose) was refluxed with acetic anhydride (25 ml.) for 1 hr., then poured onto crushed ice. The product crystallized from dilute ethanol as needles, m.p. 176°.

Anal. Calcd. for $C_{21}H_{18}Br_2N_4O_3$: C, 47.2; H, 3.4; N, 10.5. Found: C, 47.2; H, 3.7; N, 10.2.

1-(*p*-Bromophenyl)-3-formyl-5-(hydroxymethyl)pyrazole *p*-Nitrophenylhydrazone.—5-(Acetoxymethyl)-1-(*p*-bromophenyl)-3-formylpyrazole *N*-acetyl-*p*-bromophenylhydrazone (IIIb, 0.5 g.) was hydrolyzed with 20% ethanolic ammonia (50 ml.) overnight at room temperature. The product was evaporated to dryness, dissolved in ethanol (10 ml.), and treated with *p*-nitrophenylhydrazine (0.2 g.) in hot ethanol (10 ml.) and acetic acid (1 ml.). The mixture was refluxed for 1 hr and, on cooling, orange needles which were separated recrystallized from ethanol–water, m.p. 234°.

Anal. Calcd. for $C_{17}H_{14}BrN_5O_3 \cdot H_2O$: C, 47.0; H, 3.7; N, 16.2. Found: C, 46.9; H, 4.0; N, 16.8.

***N*-Acetyl-4,5-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose Phenylosazone (IV). A. From D-*arabino*-Hexose Phenylosazone.**—D-*arabino*-Hexose phenylosazone (20 g.) was refluxed with acetic anhydride (100 ml.) for 30 min. and then poured onto 1 kg. of crushed ice. After 3 days the product solidified yielding two types of crystals: colorless ethanol-soluble needles of Ia which were washed away with cold ethanol, and yellow, insoluble, prismatic needles which were filtered and recrystallized from hot ethanol, m.p. 172–173°, $[\alpha]^{21}D$ −108° (*c* 2.9, chloroform).

Anal. Calcd. for $C_{24}H_{26}N_4O_6$: C, 61.8; H, 5.6; N, 12.0; O, 20.6; total CH_3CO, 29.8; CH_3CO (OAc), 18.4. Found: C, 61.3; H, 5.9; N, 12.2; O, 20.7; total CH_3CO, 27.5; CH_3CO (OAc), 17.9.

B. From Diels' Anhydrophenylosazone (V).—Diels' anhydrophenylosazone (2 g.) prepared from D-*arabino*-hexose phenylosazone and methanolic sulfuric acid[5] was refluxed with acetic anhydride (50 ml.) for 2 hr. and then poured onto crushed ice (500 g.). After 24 hr. the crystals that separated were filtered, washed with water and ethanol, and crystallized from ethanol, m.p. and m.m.p. 172–173°.

Anal. Found: C, 61.8; H, 5.9; N, 12.0.

Hydrolysis of *N*-Acetyl-4,5-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose Phenylosazone.—Substance IV (1 g.) was either shaken overnight at room temperature with 50 ml. of methanol nearly saturated with ammonia or refluxed for 1 hr. with 50 ml. of methanol and 1 ml. of *n*-butylamine. The clear reaction product was evaporated to dryness in a vacuum desiccator, dissolved in hot ethanol, and crystallized by the addition of hot water to incipient turbidity. 3,6-Anhydro-D-*ribo*-hexose phenylosazone ("Diels'" anhydrophenylosazone, V) was obtained in the form of yellow needles, m.p. 175°, undepressed on admixture with an authentic specimen and with an infrared spectrum identical with that of the latter.

Anal. Calcd. for $C_{18}H_{20}N_4O_3$: C, 63.5; H, 5.9; N, 16.5. Found: C, 63.7; H, 6.2; N, 16.5.

***N*-Acetylpenta-*O*-acetyl-*aldehydo*-D-galactose Phenylhydrazone (VI). A. From D-Galactose Phenylhydrazone.**—D-Galactose phenylhydrazone (10 g.) was refluxed with acetic anhydride (150 ml.) for 1 hr. and the solution was then poured onto 1 kg. of crushed ice and left overnight. The clear solution was then extracted with ether and the latter washed with an aqueous solution of sodium hydrogen carbonate and dried. The residue obtained after ether removal was dissolved in 10 ml. of cold ethanol and crystallized by the addition of water (50 ml.). *N*-Acetylpenta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone crystallized in shining prisms, m.p. 135°, $[\alpha]^{21}D$ +37° (*c* 1, chloroform).

Anal. Calcd. for $C_{24}H_{30}N_2O_{11}$: C, 55.3; H, 5.8; N, 5.4; total CH_3CO, 49.4; CH_3CO (OAc), 41.2. Found: C, 55.0; H, 5.7; N, 5.7; total CH_3CO 49.3; CH_3CO (OAc), 43.2.

B. From Penta-*O*-acetyl-*aldehydo*-D-galactose (VII).—The pentaacetate[7] (1 g.) was refluxed with acetic anhydride (25 ml.) for 30 min. and the solution was then poured on 200 g. of crushed ice and left overnight. The water-soluble portion was extracted with ether, washed with aqueous sodium hydrogen carbonate, and dried. The residue obtained on solvent removal was crystallized as above, m.p. 135° undepressed on admixture with the above material. Both products had identical infrared spectra.

(7) M. L. Wolfrom and C. C. Christman, *J. Am. Chem. Soc.*, **53**, 3913 (1931).

(8) A. Gerecs, *Tetrahedron*, **19**, 1455 (1963); M. L. Wolfrom, G. Fraenkel, D. R. Lineback, and F. Komitsky, *J. Org. Chem.*, **29**, 457 (1964).

(9) Melting points are uncorrected; infrared spectra were measured with a Perkin-Elmer Infracord spectrophotometer. Microanalytical determinations were made by W. N. Rond, The Ohio State University, and A. Bernhardt, Max Plank Institut, Mülheim, Germany.

Deacetylation of VI and Conversion to D-*lyxo*-Hexose Phenylosazone.—*N*-Acetyl-penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone (1 g.) was treated with 50 ml. of methanol nearly saturated with ammonia and left overnight at room temperature, then evaporated to dryness in a vacuum desiccator. The residue was dissolved in water (20 ml.) and heated with phenylhydrazine (0.5 g.) and acetic acid (0.5 ml.) on the water bath for 1 hr. On cooling, D-*lyxo*-hexose phenylosazone separated in its characteristic crystalline shape and was identified by mixture melting point and comparative infrared spectra.

Acknowledgment.—H. El Khadem is indebted to the Educational and Cultural Exchange Program of the United States State Department for a Fulbright Grant to visit The Ohio State University where part of this work was carried out, to Professor M. L. Wolfrom for his valued advice and counsel, and to The Ohio State University for the laboratory facilities provided.

Infrared Spectra and Synthesis of Some Polyphenyls

RICHARD C. DOSS AND PAUL W. SOLOMON

Phillips Petroleum Company, Bartlesville, Oklahoma

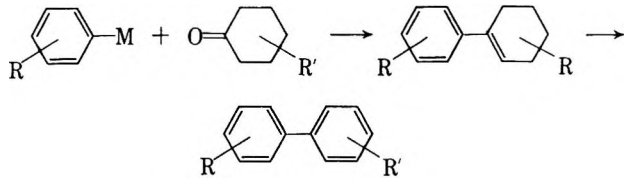
Received August 16, 1963

A general method of preparing polyphenyls by the addition of an aryl Grignard or an aryllithium to a substituted cyclic ketone followed by dehydration and aromatization was used to synthesize five polyphenyls heretofore unreported. These newly prepared polyphenyls are 3-bromo-*m*-terphenyl, 2,3′-di-(3-xenyl)biphenyl, 2,4-di(3-xenyl)biphenyl, 2,4-di(4-xenyl)biphenyl, and 3,5-diphenyl-4′-(3-xenyl)biphenyl. In addition, ten known polyphenyls were prepared, some by new routes. Infrared spectral correlations were developed which apply to *meta*- and *para*-type linkages in polyphenyls. These correlations are useful in indicating (a) the presence of single or consecutive *meta*- or *para*- and 1,3,5-substituted benzene rings in large polyphenyl molecules, and (b) the type of substitution present in the terminal groups of polyphenyls.

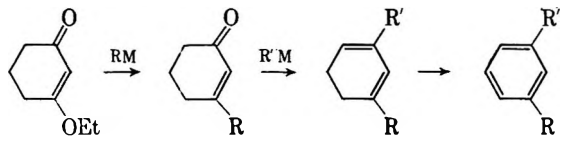
During a recent program under an Atomic Energy Commission Contract,[1] the need arose to prepare certain selected polyphenyls, particularly quaterphenyls and hexaphenyls. This was done for the most part by extending the methods of Woods and Scotti.[2] An examination of the infrared spectra of polyphenyls which are described in the literature and those obtained during the present study revealed certain characteristic shifts of assigned absorption bands in the 11.0- to 15.0-μ region. These band shifts were dependent upon the number and type of linkages involved.

Discussion

Syntheses.—The best general method found for the unambiguous synthesis of polyphenyls was that of the addition of an aryl Grignard or an aryllithium to an aryl cyclic ketone followed by dehydration and aromatization according to the following general scheme.

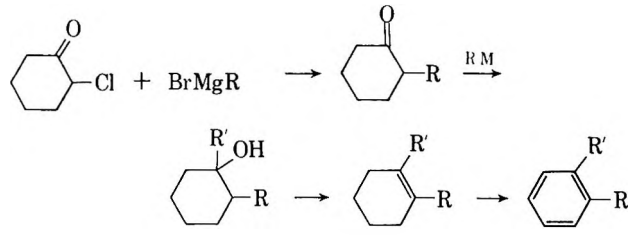


The introduction of internal *meta* linkages was accomplished by the method of Woods and Tucker,[3] whereby the monoethyl ether of dihydroresorcinol was treated (twice) with an aryl Grignard or an aryllithium followed by aromatization.



The compound 3-bromo-*m*-terphenyl was prepared by this method. 3-Ethoxycyclohex-2-en-1-one was added to 3-bromophenylmagnesium bromide, and the resulting 3-(3-bromophenyl)cyclohex-2-en-1-one added to phenylmagnesium bromide to give 3-bromodihydro-*m*-terphenyl. This was aromatized with bromine in chloroform to the desired 3-bromo-*m*-terphenyl.

The introduction of *ortho* linkages in positions other than terminal was brought about by the use of 2-chlorocyclohexanone.[2] An aryl Grignard was added to 2-chlorocyclohexanone, whereby rearrangement occurred giving the intermediate 2-aryl substituted cyclohexanone. This product was added to another aryl Grignard or aryllithium followed by hydrolysis, dehydration, and aromatization to the desired polyphenyl.



The Grignards of 3-xenyl bromide and 4-xenyl bromide were added to 2-chlorocyclohexanone to give the compounds 2-(3-xenyl)cyclohexane and 2-(4-xenyl)-cyclohexanone.[2] The butyllithium interchange products of 3-bromo-*m*-terphenyl and 4-bromo-*m*-terphenyl[4] were added to 2-(3-xenyl)cyclohexanone which after dehydration and aromatization gave, respectively, 2,3′-di(3-xenyl)biphenyl and 2,4′-di(4-xenyl)biphenyl. Lithio-*p*-terphenyl[5] was treated with 2-(4-xenyl)cyclohexanone in a similar manner to give 2,4′-di(4-xenyl)-biphenyl. Preparative details are given here only when the compounds were not found in the literature

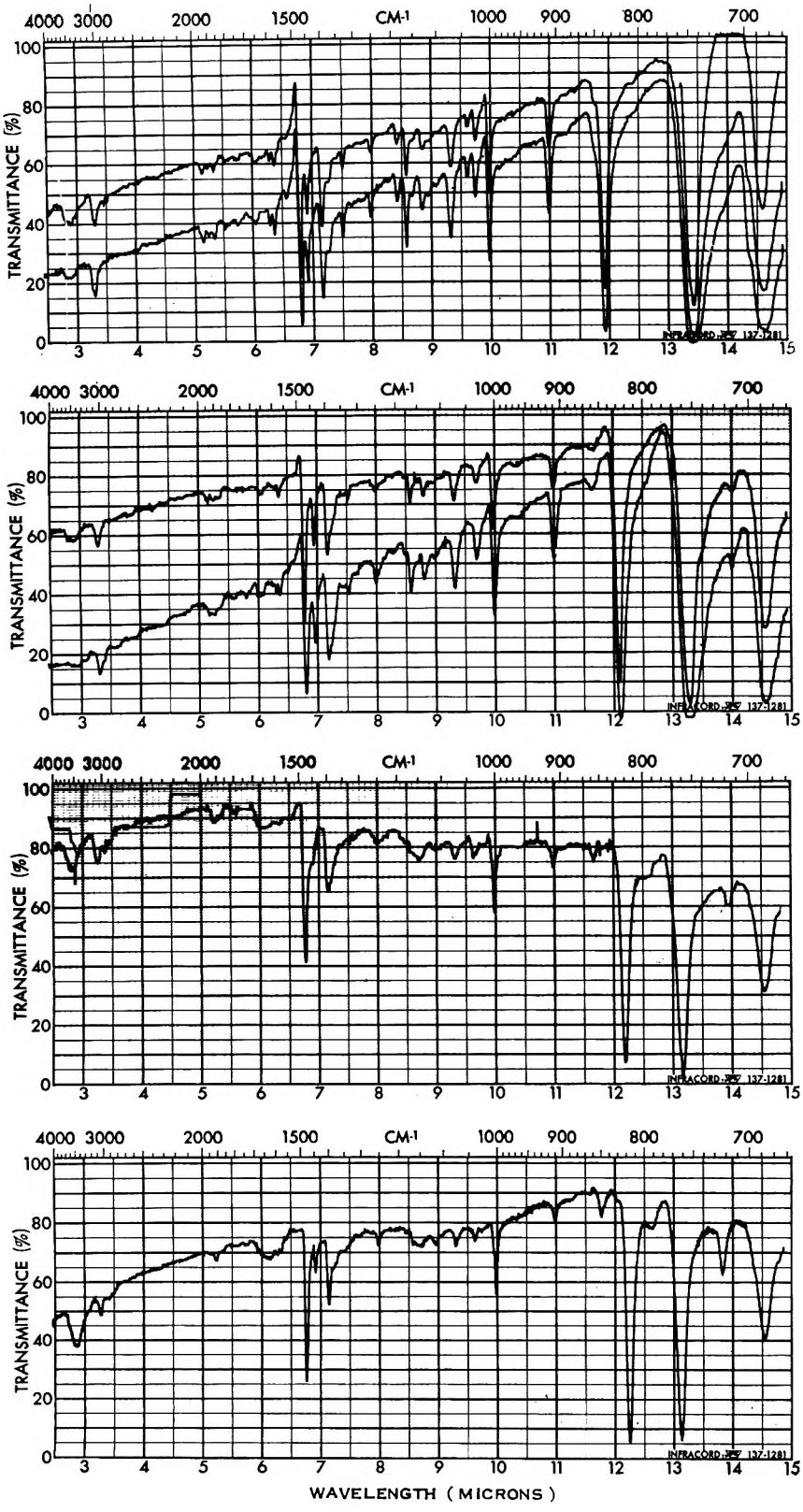
(1) U. S. Atomic Energy Commission Contract AT(10-1)-1080, Phillips Petroleum Co., Bartlesville, Okla.

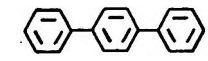
(2) G. F. Woods and F. Scotti, *J. Org. Chem.*, **26**, 312 (1961).

(3) G.F. Woods and I. W. Tucker, *J. Am. Chem. Soc.*, **70**, 3340 (1948).

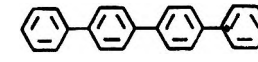
(4) G. F. Woods, J. P. Oppelt, and R. B. Isaacson, *ibid.*, **82**, 5227 (1960).

(5) J. A. Cade and A. Pilbeam, United Kingdom Atomic Energy Authority, AERE-R 3038, p. 3.

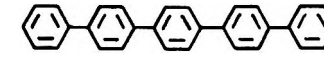




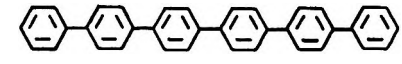
1. P-TERPHENYL



2. P-QUATERPHENYL



3. P-QUINQUEPHENYL



4. P-HEXAPHENYL

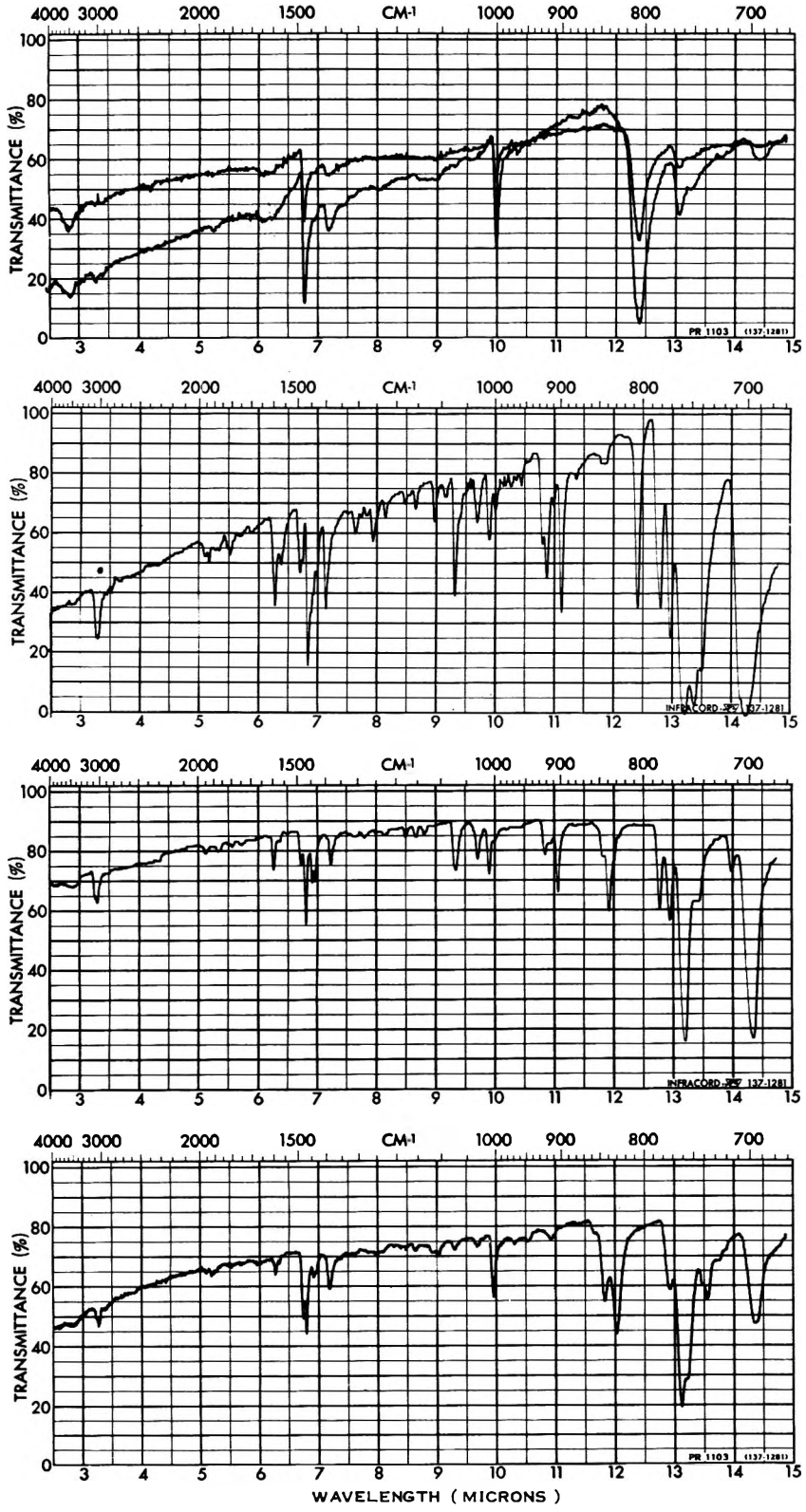
Fig. 1.—Infrared spectra of polyphenyls.

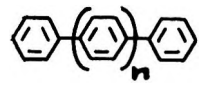
or when known compounds were prepared by a new method. Table I presents a list of these materials.

Infrared Correlations.—Bellamy[6] has noted the infrared correlations for CH out-of-plane deformations for variously substituted benzene rings found in Table II. These correlations have proved of considerable help in confirming the structure of the newly synthesized polyphenyls. With the availability of a number of spectra of these compounds, it was possible to refine and extend the correlations by limiting them to polyphenyl structures only (see Fig. 1–5).

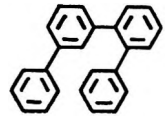
A. *para*-Type Substitution.—The normal band at 11.6–12.5 μ due to two adjacent hydrogens was found to shift according to the number of consecutive *para*-

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

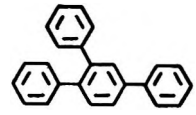




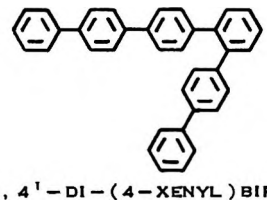
5. P-POLYPHENYL



6. 2,3'-DIPHENYLBIPHENYL



7. 1,2,4-TRIPHENYLBENZENE



8. 2,4'-DI-(4-XENYL)BIPHENYL

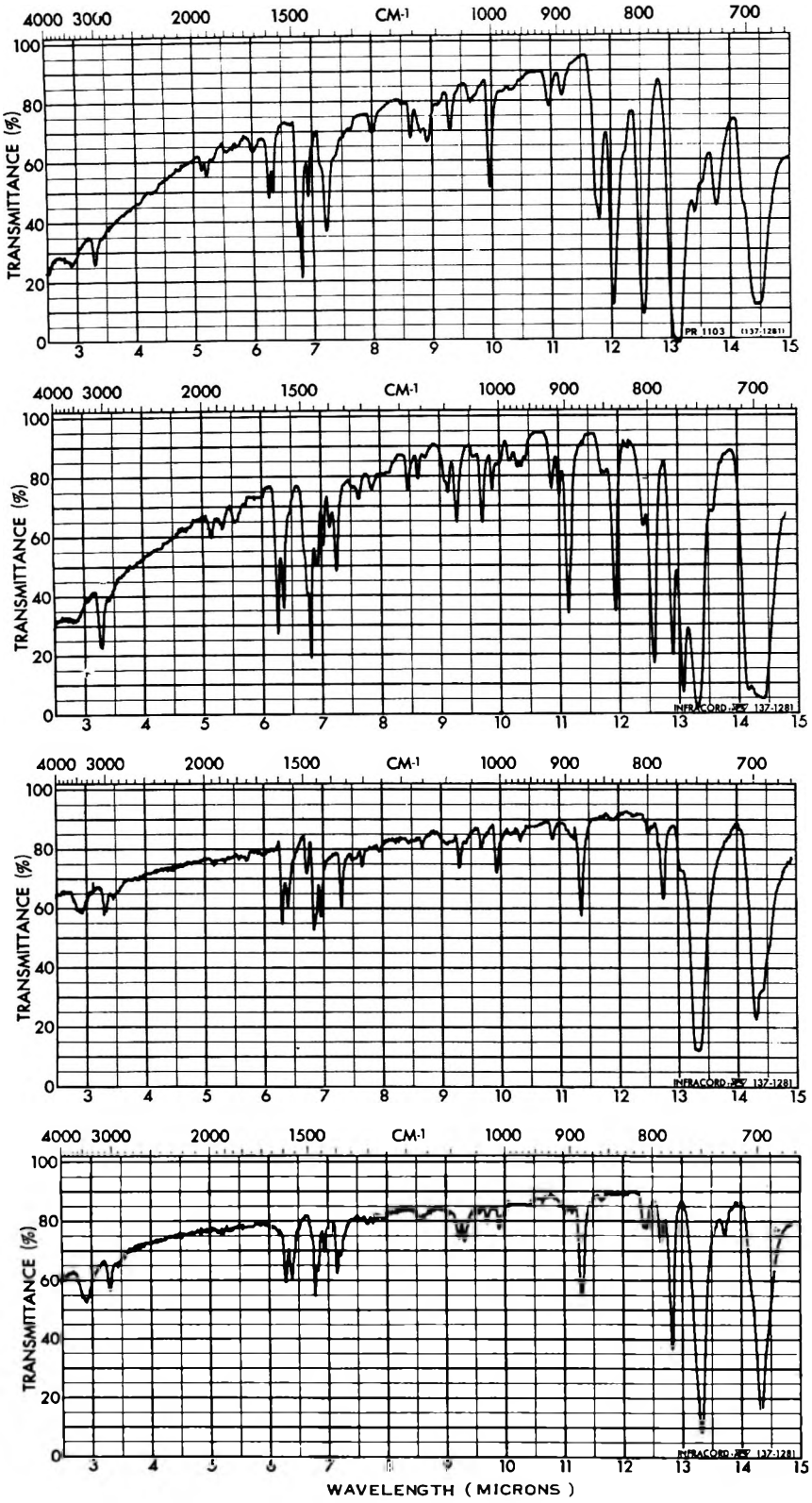
Fig. 2.—Infrared spectra of polyphenyls.

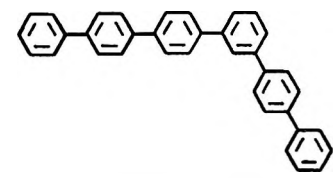
type linkages present (see Table III, also Fig. 6). When a single *para* linkage and two consecutive *para* linkages are present in the same molecule but separated by an *ortho*- or *meta*-linked phenylene group, both expected bands occur (see spectra 8 and 9). Two bands sometimes occur in the region where only one band would be expected (see spectra 16 and 19).

A shift can be noted in the 13.0–13.7-μ band due to monosubstituted phenyl structures when increasing consecutive *para* linkages are present. The band shifts from 13.45 μ for *p*-terphenyl to 13.05 μ for *p*-polyphenyl (see spectra 1–5). This correlation is only useful for all *para*-linked polyphenyls, however.

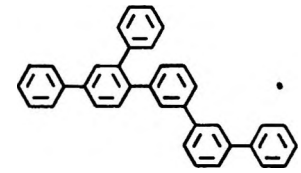
B. *meta*-Type Substitution.—The normal and at 12.3–13.3 μ was found to shift according to the umber of consecutive *meta* linkages present (Table IV, Fig. 6). This has been noted by Alexander[7] also. As with

(7) R. L. Alexander, Jr., *J. Org. Chem.*, **21**, 1464 (1956).

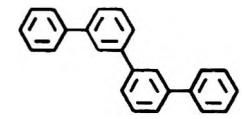




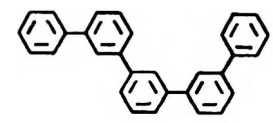
9. 3,4'-DI-(4-XENYL)BIPHENYL



10. 2,4-DIPHENYL-3'-(3-XENYL) BIPHENYL



11. M-QUATERPHENYL



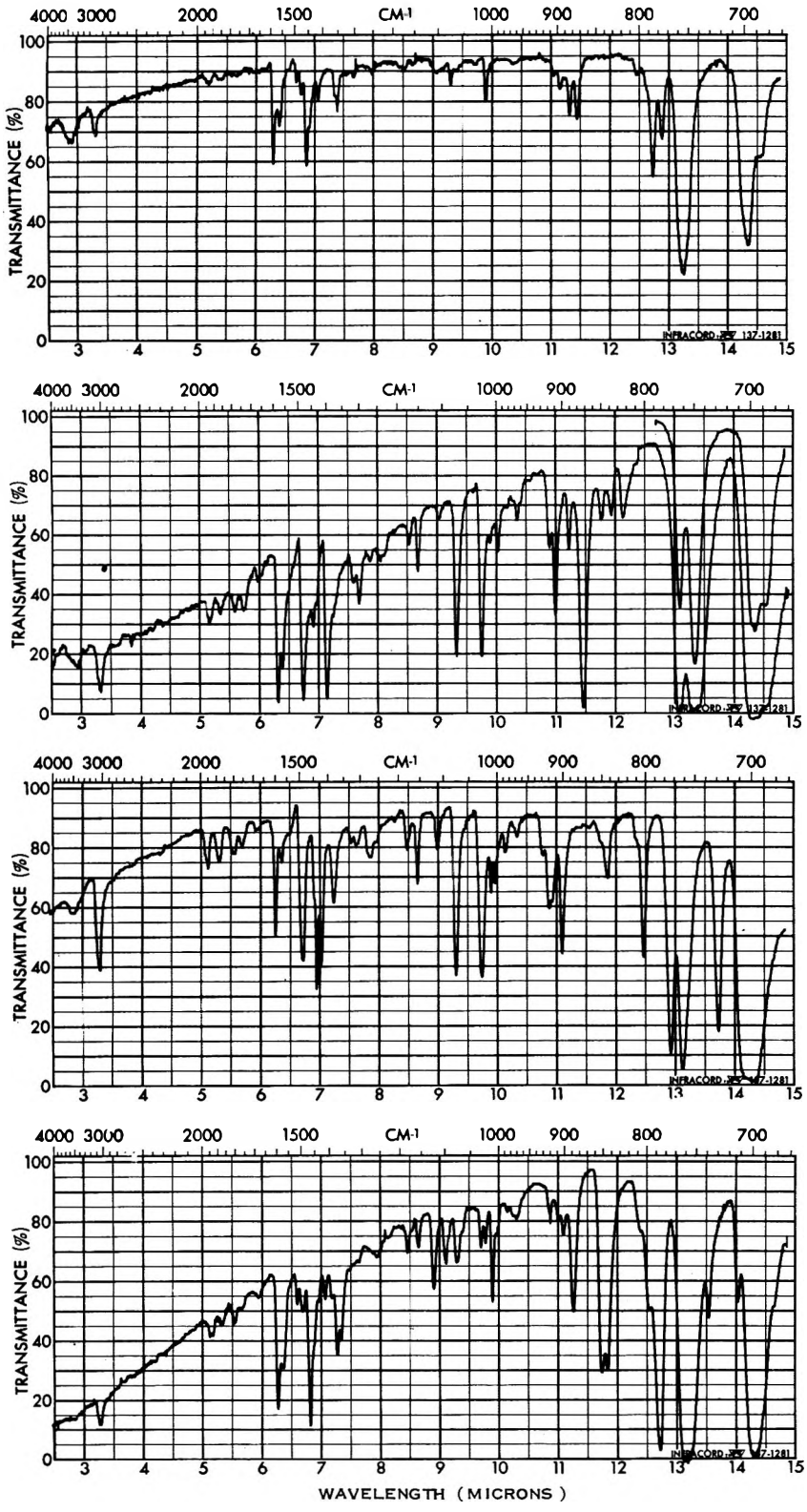
12. M-QUINQUEPHENYL

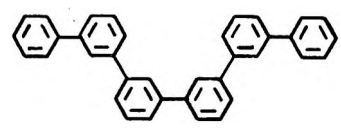
Fig. 3.—Infrared spectra of polyphenyls.

para linkages, these bands sometimes become multiple bands either when both mono- and poly-*meta* linkages are present (see spectra 16, 17) or when only a single type is present (see spectra 10, 12, 13).

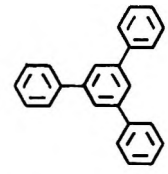
The band at 11.1–11.6 μ due to the single hydrogen present in this structure is displaced to longer wave length when it occurs in the special "*meta*" case of a 1,3,5-trisubstituted benzene ring (see Table V, Fig. 6). The latter correlation is not well established, as only two spectra of the 1,3,5-substitution type are available. Both types of bands are sometimes rather weak.

C. *ortho*-Type Substitution.—The band due to *ortho* substitution has not proved reliable as it tends to be hidden by the strong 13.0–13.6-μ band due to monosubstituted benzene. In some cases weak bands

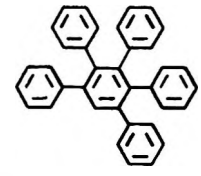




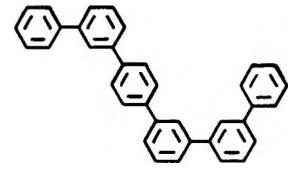
13. M-HEXAPHENYL



14. 1,3,5-TRIPHENYLBENZENE



15. PENTAPHENYLBENZENE



16. 3,4'-DI-(3-XENYL)BIPHENYL

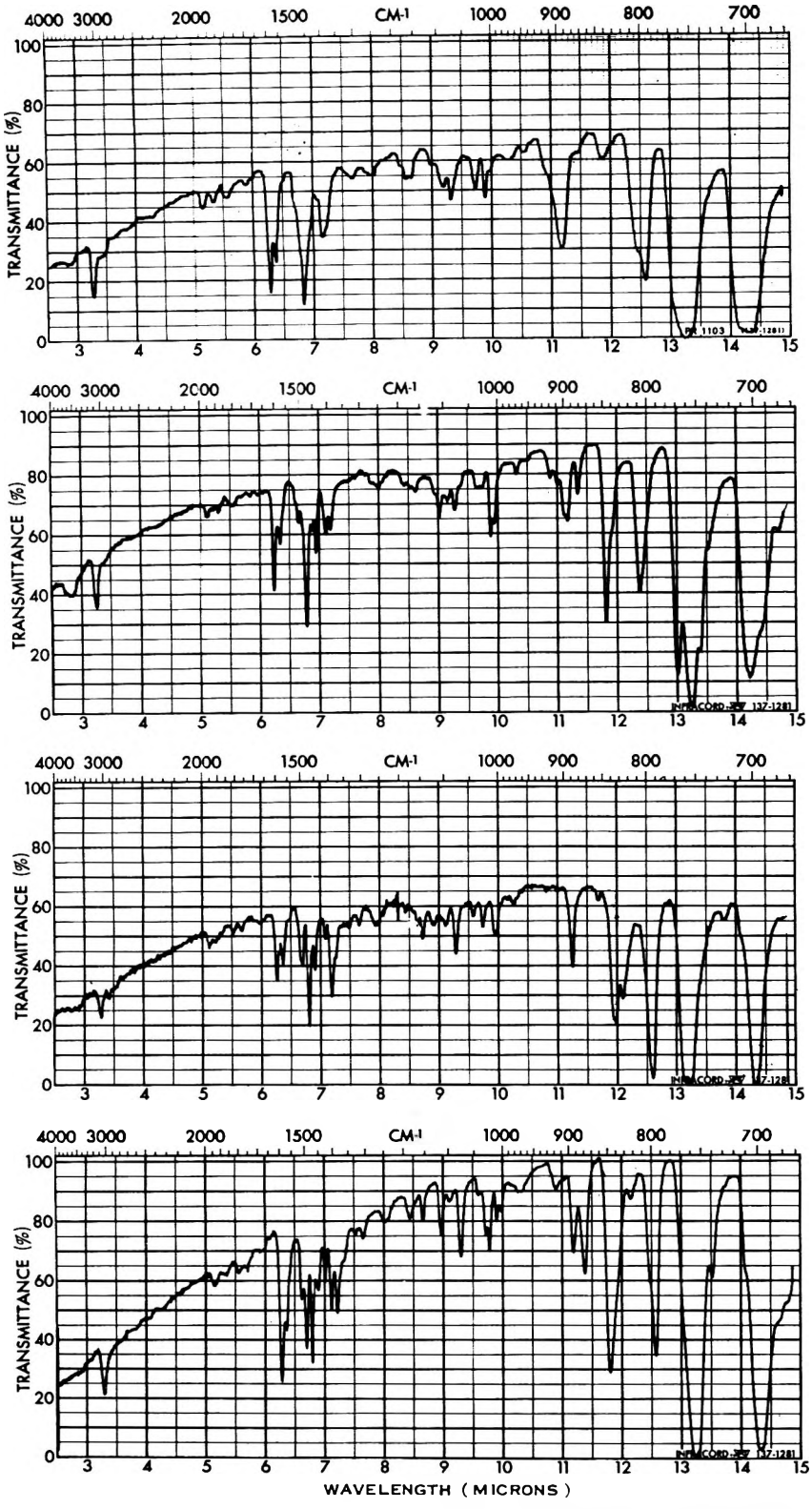
Fig. 4.—Infrared spectra of polyphenyls.

occur at 12.8–13.0 μ which may be due to this linkage. In a number of cases bands also occur in this last region when *ortho* linkages are absent.

D. Terminal Linkages.—The band at 14.1–14.5 μ due to monophenyl substitution is shifted in polyphenyls according to the type of terminal linkages present (see Table VI).

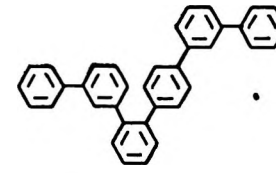
Experimental

An F & M Model 500 programmed temperature gas chromatograph was used to analyze the samples for purity. Unless otherwise noted, the indicated purity was 98.5% or better. Potassium bromide wafers were prepared with the polyphenyl samples and a Perkin-Elmer Corporation Model 137 Infracord spectrophotometer was used for recording infrared spectra. The completeness of aromatization was determined from these spectra.

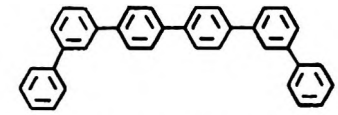




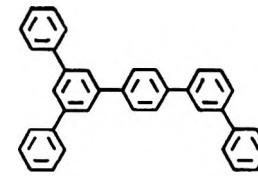
17. 2,3'-DI-(3-XENYL)BIPHENYL



18. 2,4'-DI-(3-XENYL)BIPHENYL



19. 4,4'-DI-(3-XENYL)BIPHENYL



20. 3,5-DIPHENYL-4'-(3-XENYL) BIPHENYL

Fig. 5.—Infrared spectra of polyphenyls.

The succeeding polyphenyls were prepared by methods described in the literature: *p*-polyphenyl,[8] 3,3'-diphenylbiphenyl,[9] 2,3'-diphenylbiphenyl,[9] pentaphenylbenzene,[10] and 4,4'-di(3-xenyl)biphenyl.[11] Additional compounds were made available for this study: *p*-terphenyl and *p*-quaterphenyl (Eastman), *m*- and *p*-quinquephenyl (Monsanto), 1,3,5-triphenylbenzene (Aldrich), and *m*-hexaphenyl (National Bureau of Standards). The following descriptions given are of the synthesis of various polyphenyls in their pure state.

3-Bromo-*m*-terphenyl.—Phenylmagnesium bromide prepared from 30 g. of bromobenzene and 3.6 g. of magnesium turnings in 150 ml. of ether was stirred and cooled to 15°. A solution was slowly added which contained 25.1 g. of 3-(3-bromophenyl)cyclohex-2-en-1-one[12] dissolved in 100 ml. of ether. The mixture was refluxed for 1 hr., hydrolyzed with cold dilute sulfuric acid, and steam distilled. The residue was dissolved in 100 ml. of ether and washed with dilute, aqueous sodium hydroxide and with water.

(8) P. Kovacic and C. Wu, *J. Polymer Sci.*, **47**, 45 (1960).
(9) G. F. Woods and F. Reed, *J. Am. Chem. Soc.*, **71**, 1348 (1949).
(10) W. Dilthey and G. Hurtig, *Chem. Ber.*, **67**, 2004 (1934).
(11) G. F. Woods, Wright Air Development Center, Technical Report 59-496, p. 112.
(12) G. F. Woods, Aeronautical Research Laboratory, Report 62-306.

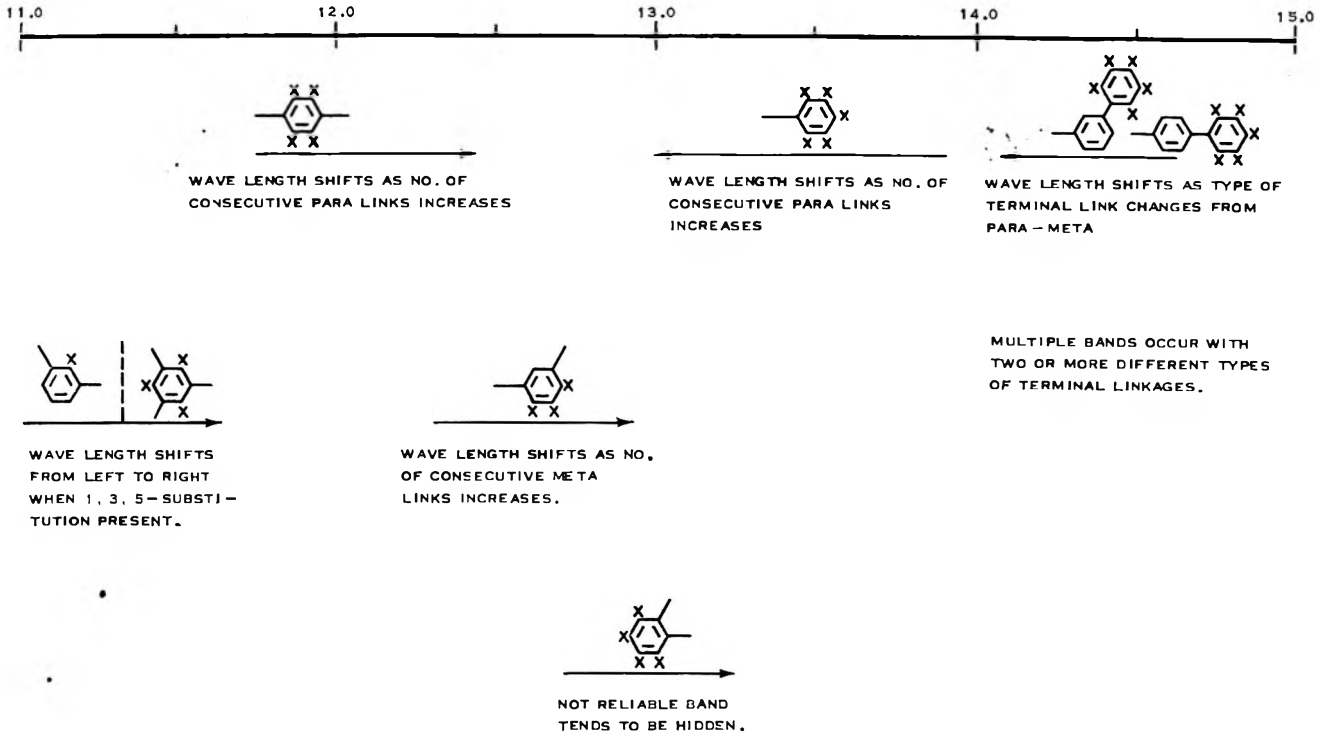


Figure 6.

TABLE I

POLYPHENYLS, NEW OR PREPARED BY A NEW ROUTE

Compound	Lit. m.p., °C.	Exptl. m.p., °C.
3-Bromo-*m*-terphenyl		200–205 (1.5 mm.)[a]
p-Hexaphenyl	465[b]	439–445
1,2,4-Triphenylbenzene	99–100[c]	96–97
3,4′-Di(3-xenyl)biphenyl	186–188[c]	192–195
2,4-Diphenyl-3′-(3-xenyl)biphenyl	145–146[c]	145–146
3,4′-Di(4-xenyl)biphenyl	312–314[b]	321–322
2,3′-Di(3-xenyl)biphenyl		58–60
2,4′-Di(3-xenyl)biphenyl		128–130
2,4′-Di(4-xenyl)biphenyl		231–232
3,5-Diphenyl-4′-(3-xenyl)biphenyl		155

[a] B.p., °C. [b] Ref. 5. [c] Ref. 11.

TABLE II

INFRARED CORRELATIONS

Number of adjacent hydrogen atoms on benzene ring	Band(s), μ
5	13.0–13.7 and 14.1–14.5
4	13.0–13.6
3	12.3–13.3
2	11.6–12.5
1	11.1–11.6

After drying the ether layer over magnesium sulfate, filtering, and evaporating the ether, 30 g. of a sirupy residue was obtained.

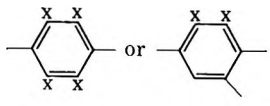
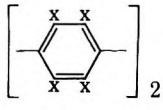
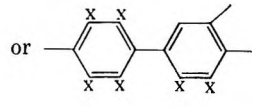
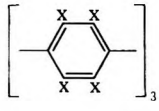
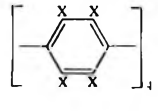
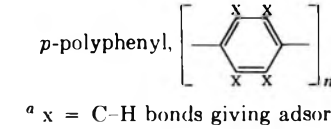
A solution which contained 30 g. of this sirupy residue and 20 g. of bromine dissolved in 200 ml. of chloroform was gently heated for 30 min. Upon distillation there was obtained 14.6 g. (45% yield) of a light yellow, viscous material boiling at 233–237° (4 mm.). The material was redistilled to obtain the product boiling at 200–205° (1.5 mm.) with a refractive index ($n^{20}D$) of 1.6786.

Anal. Calcd. for $C_{18}H_{13}Br$: C, 69.9; H, 4.2; Br, 25.8. Found: C, 69.5; H, 4.2; Br, 26.2.

p-Hexaphenyl.—*p*-Hexaphenyl was prepared by subjecting 9 g. of *p*-terphenyl to electron irradiation at 316° for 14 hr. at approximately 10^9 rads dosage. Repeated extractions of the irradiation product with boiling benzene gave 0.1 g. of an insoluble material which was analyzed by infrared as *p*-hexaphenyl.

TABLE III

CONSECUTIVE *para*-TYPE LINKAGES[a]

	Wave length of band, μ	Spectral examples (Fig. 1–5)
	11.7–12.0	1, 7, 8, 9, 10 16, 18, 20
		
	12.0–12.1	2, 8, 9, 19
	12.2	3
	12.25	4
	12.4	5

[a] x = C–H bonds giving adsorption bands.

1,2,4-Triphenylbenzene.—To a solution of 4′-lithio-*m*-terphenyl prepared from 25 g. of 4′-bromo-*m*-terphenyl[13] and 66.4 ml. of a 1.2 *M* solution of butyllithium in *n*-heptane was added 4 g. of cyclohexanone, and the solution was stirred for 2 hr. at 10°. The solution was hydrolyzed with aqueous ammonium chloride and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate, filtered, and distilled to give 7.8 g.

(13) J. J. E. Schmidt, J. A. Krimmel, and T. J. Farrell, Jr., Wright Air Development Center, Technical Report-207, part III.

TABLE IV

CONSECUTIVE *meta*-TYPE LINKAGES

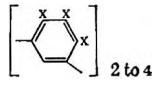
	Wave length of band, μ	Spectral examples (Fig. 1–5)
	12.4–12.7	6, 9, 16, 17, 18, 19, 20
 2 to 4	12.6–12.9	10, 11, 12, 13, 16, 17

TABLE V

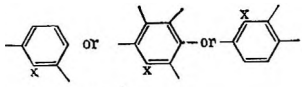
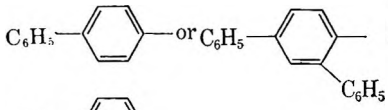
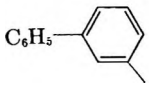
	Wave length of band, μ	Spectral examples (Fig. 1–5)
	11.0–11.35	6, 7, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20
	11.35–11.5	14, 20

TABLE VI

TERMINAL LINKAGES

	Wave length of bands(s), μ	Spectral examples (Fig. 1–5)
	14.35–14.6	1, 2, 3, 4, 5, 7, 8, 9
	14.2–14.35[a]	6, 11, 12, 13, 16, 17, 18, 19, 20

[a] Excluding *m*-Terphenyl.

of a viscous liquid which boiled at 225° (1.2 mm.). A small amount of this material was heated with 10% palladium–charcoal at 300° for 1 hr. The mixture was extracted with boiling *n*-hexane which, after evaporation of the solvent and recrystallization from *n*-hexane, gave the white crystalline product.

3,4′-Di(3-xenyl)biphenyl.—To a solution which contained 4-lithio-*m*-terphenyl in 100 ml. of ether prepared from 2.6 g. of 4-bromo-*m*-terphenyl[4] and 9.2 ml. of a 1.2 *M* solution of butyllithium–*n*-heptane was added 1.8 g. of 3(3-xenyl)cyclohex-2-en-1-one[9] dissolved in 30 ml. of ether. The mixture was stirred for 1.5 hr. at 10–20° and hydrolyzed with aqueous ammonium chloride; the ether layer was dried with magnesium sulfate and concentrated. The sirupy residue was heated at 260° for 30 min. with 10% palladium–charcoal. The mixture was extracted with hot *o*-xylene and after recrystallization from *o*-xylene gave 1.4 g. of the product.

2,4-Diphenyl-3′-(3-xenyl)biphenyl.—2,4-Diphenyl-3′-(3-xenyl)-biphenyl was prepared in a manner similar to the preceding procedure from 7.7 g. of 4′-bromo-*m*-terphenyl and 5.7 g. of 3-(3-xenyl)cyclohex-2-en-1-one followed by aromatization with 10% palladium–charcoal to give 1.5 g. of the desired polyphenyl.

3,4′-Di(4-xenyl)biphenyl.—3,4′-Di(4-xenyl)biphenyl was prepared in the same manner as that described for the preparation of 3,4′-di(3-xenyl)biphenyl, except that 4-bromo-*p*-terphenyl[5] and 3-(4-xenyl)cyclohex-2-en-1-one[3] were the reactants. Final purification was by sublimation at 360° (0.05 mm.).

Anal. Calcd. for $C_{36}H_{26}$: C, 94.3; H, 5.7. Found: C, 94.2; H, 5.7.

2,3′-Di(3-xenyl)biphenyl.—3-Lithio-*m*-terphenyl was prepared from 3.09 g. of 3-bromo-*m*-terphenyl dissolved in 100 ml. of ether and 10 ml. of a 1.2 *M* solution of butyllithium–*n*-heptane. After slowly adding at 10° with stirring a solution which contained 2.5 g. of 2-(3-xenyl)cyclohexanone dissolved in 50 ml. of ether, the mixture was stirred for 1 hr. and hydrolyzed with cold, dilute sulfuric acid. The ether layer was washed with aqueous sodium carbonate, dried over anhydrous magnesium sulfate, and concentrated to give 5.1 g. of a sirupy residue. The sirupy material was heated at 300° for 3 hr. with red phosphorus. The mixture was extracted with benzene and filtered; the filtrate was evaporated to dryness. This residue was dissolved in a 90:10 mixture of *n*-hexane and benzene and passed through a 12 × 700 mm. glass tube packed half full with F-20 activated alumina. Several fractions were obtained by eluting the column with graded concentrations of benzene–*n*-hexane. The desired material was eluted when the column was washed with a 60:40 mixture of *n*-hexane–benzene. The eluate was evaporated and the product was recrystallized from an ethanol–benzene mixture.

Anal. Calcd. for $C_{36}H_{26}$: C, 94.3; H, 5.7. Found: C, 94.4; H, 5.8.

2,4′-Di(3-xenyl)biphenyl.—A solution of 3.5 g. of 2-(3-xenyl)-cyclohexanone[2] in 50 ml. of ether was added to 4-lithio-*m*-terphenyl prepared from 4.0 g. of 4-bromo-*m*-terphenyl and 12 ml. of a 1.2 *M* solution of butyllithium–*n*-heptane, and the total mixture was stirred for 3 hr. at 25°. The mixture was hydrolyzed and the sirupy precursor was separated in the usual manner. A solution which contained 3.0 g. of the precursor dissolved in a chloroform–bromine mixture was gently heated on a steam bath for 1 hr. and then concentrated. The resulting residue was digested with *n*-hexane to give 0.8 g. of a white crystalline product.

Anal. Calcd. for $C_{36}H_{26}$: C, 94.3; H, 5.7. Found: C, 93.9; H, 5.8.

2,4′-Di(4-xenyl)biphenyl.—2,4′-Di(4-xenyl)biphenyl was prepared in the usual manner from 4-bromo-*p*-terphenyl and 2-(4-xenyl)cyclohexanone. Aromatization was effected with 10% palladium–charcoal.

Anal. Calcd. for $C_{36}H_{26}$: C, 94.3; H, 5.7. Found: C, 94.3; H, 5.7.

3,5-Diphenyl-4′-(3-xenyl)biphenyl.—The addition of the aryllithium prepared from 2.1 g. of 1,3-diphenyl-5-(4-bromophenyl)-benzene[11] to 0.86 g. of 3-phenylcyclohex-2-en-1-one[11] was carried out in the usual manner. The precursor (1.7 g.) was aromatized with bromine–chloroform, and the residue was purified by passing through an activated alumina column to give 0.5 g. of the product after recrystallization from ethanol–benzene.

Anal. Calcd. for $C_{36}H_{26}$: C, 94.3; H, 5.7. Found: C, 94.2; H, 5.8.

Reaction of Enol Ethers with Carbenes. II. 3-Chloro-2-methylthiochromone from 4-Ethoxy-3,4-thiochromene[1]

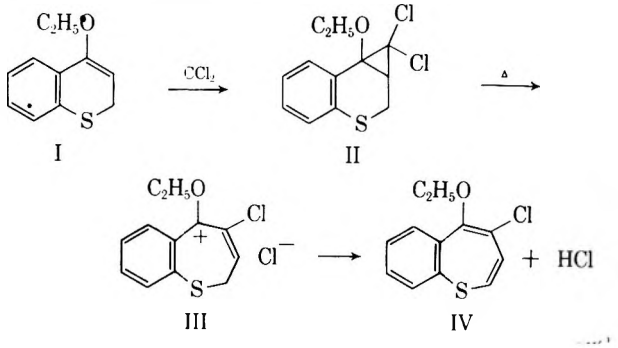
WILLIAM E. PARHAM AND M. D. BHAVSAR

Department of Chemistry, Institute of Technology, University of Minnesota, Minneapolis, Minnesota

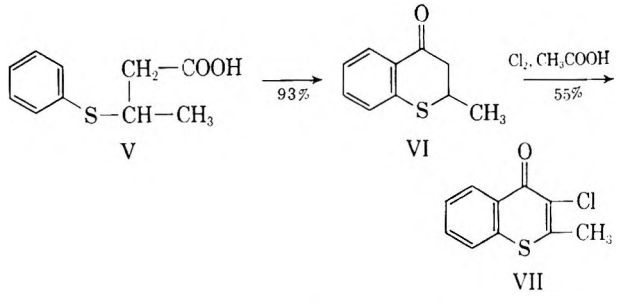
Received October 21, 1963

Decomposition of the dichlorocarbene adduct of 4-ethoxy-2H-1-benzothiapyran in hot quinoline leads to the formation of 3-chloro-2-methylthiochromone (VII); ethyl chloride also was shown to be a product of the thermal decomposition of the adduct. Evidence cited suggests that it is unlikely that the 2,3-benzothiepin ring system can be prepared by reactions which involve protonated intermediates with carbonium ion centers in the 2- and 3-positions.

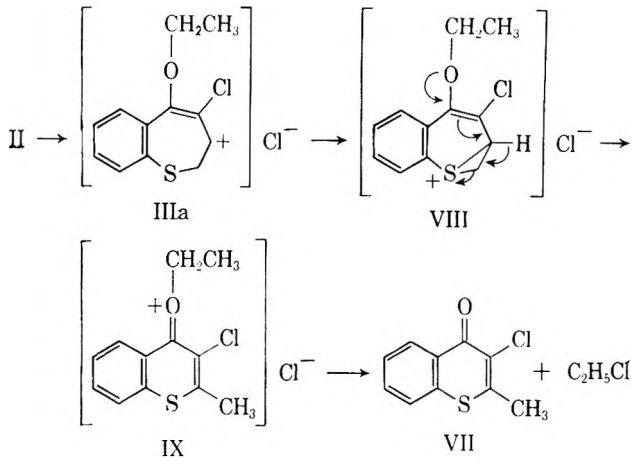
The facile conversion[2] of 1-ethoxycyclohexene into 1-ethoxy-1,3,5-cycloheptatriene, by ring expansion of the derived dichlorocarbene adduct, prompted us to explore the decomposition of 3,4-(dichloromethano)-4-ethoxythiochroman (II) as a route to the synthesis of 4-chloro-5-ethoxybenzthiepin (IV).



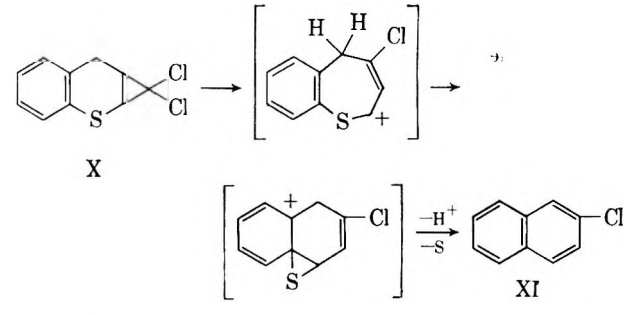
The benzothiapyran I was prepared in 88% yield from the corresponding thiochromanone and was converted into II in 33% yield by reaction with ethyl trichloroacetate and sodium methoxide.[3] The cyclopropane II was stable to hot acidic alcohol–water mixtures and stable in boiling pyridine; however, it decomposed to a solid (~48% yield), m.p. 153–154°, in hot (210°) quinoline. The composition of the solid, together with its infrared, ultraviolet, and nuclear magnetic resonance (n.m.r.) spectra (see Experimental) established that it was not the desired thiepin IV, but most probably the unknown 3-chloro-2-methylthiochromone (VII). The identity of the product as 3-chloro-2-methylthiochromone was confirmed by its independent synthesis as shown in V–VII.



The formation of VII is thought to occur in this sequence: III → IIIa → VIII → VII.[4] Ethyl chloride was shown to be one of the thermal decomposition products of II. The ring contraction IIIa → VIII → VII seems reasonable in view of the known rearrangements of sulfides substituted in the β-position in a manner which permits formation of three-membered cyclic sulfonium intermediates.[5]



In a previous paper[6] we reported that the decomposition of X in hot quinoline leads to 2-chloronaphthalene and suggested the reaction sequence as shown in X → XI. In view of these reactions it would appear unlikely that the 2,3-benzothiepin ring system can be



prepared by reactions which involve protonated intermediates with carbonium ion centers in the 2- or 3-positions.

Experimental

4-Ethoxy-2H-1-benzothiapyran (I).—A mixture of thiochromanone[7] (20.0 g., 0.121 mole), absolute alcohol (20 ml.), triethyl

(1) This work was supported by the Office of Ordnance Research, U. S. Army, Contract No. DA-ORD-31-124-61-G13.

(2) W. E. Parham, R. W. Soeder, and R. M. Dodson, *J. Am. Chem. Soc.*, **84**, 1755 (1962).

(3) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).

(4) For discussion and references related to the ring expansion of 1,1-dihalocyclopropanes, see W. E. Parham and E. E. Schweizer, *Org. Reactions*, **13**, 71 (1963).

(5) (a) *Cf.* W. E. Parham, J. Heberling, and H. Wynberg, *J. Am. Chem. Soc.*, **77**, 1169 (1955); (b) C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, pp. 9–15.

(6) W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961).

(7) J. C. Petropoulous, M. A. McCall, and D. S. Tarbell, *ibid.*, **75**, 1130 (1953).

orthoformate (40.0 g., 0.27 mole), and *p*-toluenesulfonic acid (~0.1 g., dried by azeotroping water with benzene) was added to a flask equipped with a magnetic stirrer, reflux condenser, and drying tube (calcium chloride). A slow stream of nitrogen gas was passed into the flask throughout the reaction. The mixture was stirred at room temperature for 24 hr. and then at the reflux temperature for 3 hr. The mixture was then concentrated at 70° (15–16 mm.) using a rotary evaporator. Additional dry *p*-toluenesulfonic acid (~0.1 g.) was added to the residue which was then heated under vacuum at 15–16 mm. in a flask equipped with a long (~18 in.) Claisen head. After some additional ethyl orthoformate had distilled, the temperature was raised slowly to 175°. At this point vigorous reflux, but no distillation, occurred. The mixture was cooled and distilled through a spiral wire column. 4-Ethoxy-2H-1-benzothiapyran was collected as a pale yellow oil, b.p. 105–107° (0.22 mm), $n^{25.8}$D 1.6113, 20.7 g., 88.4% yield. The product darkens in air and was stored under nitrogen at 0°.

Anal. Calcd. for $C_{11}H_{12}OS$: C, 68.75; H, 6.25. Found: C, 68.46; H, 6.24.

Infrared spectrum (neat liquid) showed strong absorption at 1630 cm.$^{-1}$ assigned to the olefinic band. Ultraviolet spectrum (in chloroform) was λ_{max} 256 mμ (ε 10,540) and 323 (1456). N.m.r. spectrum[8] (in carbon tetrachloride) was the following: aromatic CH (multiplets at 423.6 and 399.4 c.p.s.); =C—H (triplet at 279.7, 275.2, and 268.6 c.p.s., J = 5.7); OCH_2 (quartet at 224.7, 217.6, 210.4, and 203.8 c.p.s., J = 6.8); SCH_2 (doublet at 193.9 and 188.4 c.p.s., J = 7.5); CH_3 (triplet at 54.1, 77.5, and 69.8 c.p.s., J = 6.8).

3,4-(Dichloromethane)-4-ethoxythiochroman (II).—A mixture of 4-ethoxy-3,4-thiochromene (18.3 g., 0.095 mole), sodium methoxide (18.0 g., 0.33 mole), and olefin-free petroleum ether (b.p. 30–60°, 180 ml.) was cooled to 0–5° and ethyl trichloroacetate (46.0 g., 0.24 mole) was added all at once. The mixture was stirred (magnetic stirrer) under nitrogen at 0–5° for 8 hr. and then allowed to warm up slowly to room temperature overnight; a water condenser was employed to prevent evaporation of solvent. The dark brown mixture was filtered, the residue was washed with petroleum ether, and the combined organic layers were stirred vigorously with 200 ml. of 10% sodium hydroxide for 80 min. The ether layer was separated and the water layer was extracted with additional petroleum ether. The combined ether layers were dried (magnesium sulfate) and concentrated, and the dark-brown viscous liquid (29 g.) was chromatographed on aluminum (610 g., Alcoa, grade F-20) using petroleum ether (b.p. 30–60°) as eluent. Most of the fractions contained oils which partially or completely solidified when free of solvent. The principal product was II, isolated as white plates (8.7 g., 33% yield) melting at 68° from pentane.

Anal. Calcd. for $C_{12}H_{12}Cl_2OS$: C, 52.36; H, 4.36; Cl, 25.82; S, 11.63; mol. wt., 275. Found: C, 52.40; H, 4.57; Cl, 25.75; S, 11.69; mol. wt., 235 (cryoscopic in benzene).

Ultraviolet spectrum was λ_{max} (in 95% alcohol) 223 mμ (ε 13,650), 262 (6720), 295 (1222). N.m.r. spectrum[8] (in carbon tetrachloride) was the following: aromatic CH (multiplets at 422.6 and 403.2 c.p.s.); OCH_2 and SCH_2 (complex region with peaks at 206.1, 199.3, 191.4, 185.7, and 183.3 c.p.s.); –CH (triplet at 135.5, 127.6, and 119.6 c.p.s., J = 8.5); $-CH_3$ (triplet at 69.4, 62.6 and 55.8, J = 6.9).

A minor unidentified component of the mixture was isolated (~0.5 g.) from the earlier fractions of the chromatogram as colorless plates, m.p. 107–107.5° from pentane), which turned yellow on standing.

Anal. Found: C, 54.10; H, 4.86; S, 10.23.

Conversion of II to 3-Chloro-2-methylthiochromone.—A mixture of II (3.00 g., 0.0109 mole) in dry and refined quinoline (5.0 ml., 0.042 mole) was heated under nitrogen in a flask provided with an air condenser. The temperature was raised rapidly; the mixture darkened at 160° and boiled vigorously at 210–215°. The mixture was maintained for 2 min. at 210–215°, and was then cooled and diluted with ether (150 ml.). The ether solution was extracted with three 200-ml. portions of 2% hydrochloric acid and three 200-ml. portions of water, and was then dried and concentrated. The brown semisolid residue (~1.99 g.) was triturated with petroleum ether and the solid thus obtained (1.4 g.) was processed by sublimation at 50–155° (1.0 mm.). The pale yellow solid (1.1 g., 48% yield) gave white crystals of VII, m.p. 153–155°, by recrystallization from carbon tetrachloride. The product was identical (infrared, n.m.r., ultraviolet, and mixture melting point) with the authentic 3-chloro-2-methylthiochromone described below.

Thermal Decomposition of II.—A small sample of II (1.0 g.) was decomposed thermally in a round-bottom flask containing a short air condenser and distilling head in such a way that any highly volatile material such as ethyl chloride would be collected in a cold (ice–salt) solution of carbon tetrachloride (1 ml.) containing 0.5% tetramethylsilane. The sample turned brown at 170° and boiled vigorously with decomposition during a 2-min. heating period at 200°. The dark tarry residue was not processed. An n.m.r. spectrum of the carbon tetrachloride solution showed that it contained a high concentration of ethyl chloride.

2-Methylthiochromanone (VI).—A mixture of β-(phenylmercapto)-*n*-butyric acid[7,9] (39.7 g., 0.20 mole) and polyphosphoric acid (120 g.) was heated to 75–85° for 2 hr. with occasional stirring. The mixture was allowed to stand at room temperature for 5 hr., and was then diluted with water (240 ml.). The cooled mixture was extracted with ether (920-ml. total), and the ether extract was washed with two 200-ml. portions of water and two 125-ml. portions of 5% aqueous sodium bicarbonate. The ether extract was dried and distilled to give 33.4 g. (93% yield) of 2-methylthiochromanone, b.p. 93–95° (0.15 mm), $n^{26.5}$D 1.6083 [lit.[7,9] b.p. 146–147° (9 mm.), 152° (13 mm.); n^{20}D 1.6125]. The ketone showed strong absorption in the infrared at 1683 and 1673 cm.$^{-1}$, and gave a semicarbazone melting at 171–172° (lit.[7,9] m.p. 167–168° and 168–169°).

Conversion of VI to 3-Chloro-2-methylthiochromone (VII).—A solution of 2-methylthiochromanone (6.8 g., 0.038 mole) in glacial acetic acid (80.0 ml.) was placed in a 1-l. three-necked flask provided with a magnetic stirrer and a calcium chloride tube. The stirred mixture was cooled in a water bath (20–25°) and chlorine gas was admitted until approximately 2 molar equiv. of chlorine (5.4–5.5 g., 0.076 mole) had been adsorbed (~3 hr.). The solution was then stirred for 31 hr. at 30–34° and finally heated on a steam bath for 15 min. during which time hydrogen chloride was evolved. The resulting mixture was diluted with water and the pale yellow solid which precipitated (8.3 g.) was collected. Recrystallization of this solid from alcohol gave 3-chloro-2-methylthiochromone (VII) as pale yellow crystals (3.56 g., 43.4% yield, m.p. 152–154°). The thiochromone VII, m.p. 153–154° from carbon tetrachloride, gave a colorless solution in concentrated sulfuric acid with blue fluorescence in ultraviolet light.

Anal. Calcd. for $C_{10}H_7ClOS$: C, 57.00; H, 3.32; Cl, 16.86; S, 15.20; mol. wt., 210.5. Found: C, 57.06; H, 3.56; Cl, 16.85; S, 15.21; mol. wt., 182 (Rast in camphor).

Infrared spectrum was the following (perfluorocarbon mull): 3070 (w), 3025 (w), 1625 (s), 1586 (s), shoulder at 1570 (m), 1535 (m), 1450 (w), 1440 (s), shoulder at 1425 (m), 1380 (m), 1320 (s), and 1300 cm.$^{-1}$ (m); Nujol mull, 1625 (s), 1585 (s), shoulder at 1566 (m), 1535 (m), 1310 (s), 1300 (s), 1240 (w), 1160 (m), 1088 (s), 1068 (m), 1023 (m), 835 (s), 808 (s), 790 (m), 745 (s), shoulder at 730 (m), 680 (m), and 640 cm.$^{-1}$ (m). Ultraviolet spectrum (95% alcohol) was λ_{max} 215.5 mμ (ε 10,090), 226.5 (11,130), 250.5 (21,800), shoulder at 255 (21,590), 280 (3456), 291.5 (3046), 344 (10,810). N.m.r. spectrum[8] (deuteriochloroform) was the following: aromatic =CH (multiplets 478.3 and 423.9 c.p.s., τ 1.5 and 2.5) and CH_3 (singlet at 143.9 c.p.s., τ 7.44).

The alcoholic mother liquor was concentrated and ~0.5 g. of VII precipitated. Water was added to the residue and the solid that precipitated was recrystallized from petroleum ether. The solid thus obtained was recrystallized from petroleum ether (b.p. 60–68) and the pink solid (1.1 g.) was chromatographed on alumina (Alcoa, grade F-20). Three products were eluted: (A) with benzene, a product, m.p. 148–149°, with the composition in reasonable agreement for trichloro-2-methylthiochromanone [*Anal.* Calcd. for $C_{10}H_7Cl_3OS$: C, 42.93; H, 1.78. Found: C, 43.05; H, 1.98.]; (B) additional 3-chloro-2-methylthiochromone (4.46 g., 55.6% yield); and (C) an unidentified purple solid, sparingly soluble in alcohol.

(8) The n.m.r. spectra were determined on a Varian V 4302 at 56.44 Mc.

(9) F. Knollpfeiffer, H. Schultze, E. Schlumbohm, and E. Sommermeyer, *Ber.*, **58**, 1654 (1925).

Attempted Synthesis of 2,3-Epithioamides from Glycidamides and Dibromoamides

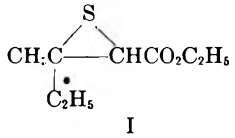
C. C. TUNG AND A. J. SPEZIALE

Research Department, Agricultural Division, Monsanto Company, St. Louis, Missouri

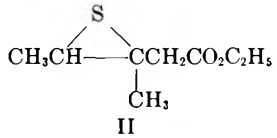
Received May 20, 1963

Attempts to synthesize 2,3-epithioamides failed. *trans*-Arylglycidamides with the thiourea produced *trans*-cinnamamides, urea, and sulfur. Under the same conditions, *cis*-arylglycidamides were recovered unchanged. Ethyl 2-acetylthio-3-chloro-2,3-dihydrocinnamate with base gave ethyl cinnamate, cinnamic acid, and sulfur. Two aliphatic 2,3-diacetylthioamides upon treatment with base afforded 1,4-dithianes.

Recently the first successful synthesis of a 2,3-epithio ester, ethyl 2,3-epithio-3-methylvalerate (I) was reported.[1] It was subsequently shown, however, that the compound was, in fact, the 3,4-epithio ester II.[2] In view of these and other failures[3,4] in the synthesis of 2,3-epithio esters, we wish to report our attempts in the preparation of 2,3-epithioamides from the corresponding epoxy amides and 2,3-dibromopropionamides.

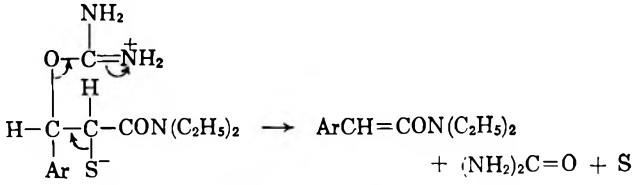


I

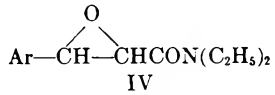


II

Ethyl *trans*-3-phenyl glycidate (III) with thiourea under a variety of conditions gave ethyl cinnamate, sulfur and urea.[3,4] Similarly *trans*-IVa, b afforded the corresponding N,N-diethylcinnamamides and sulfur.[5]



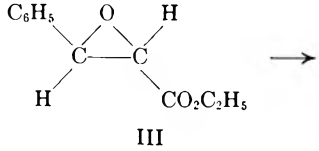
However, *cis*-IVb–d with thiourea in glacial acetic acid–dioxane solution were found to be unreactive; the epoxy amides were recovered unchanged.[7] Under conditions for the conversion of styrene epoxide to the episulfide,[8] IVa also remained unreactive. Since the action of thiourea on epoxyamides did not lead to



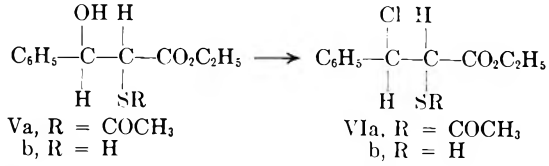
IV

a, Ar = C_6H_5 c, Ar = 2,6-$Cl_2C_6H_3$
b, Ar = 3-$NO_2C_6H_4$ d, Ar = 2,4-$Cl_2C_6H_3$

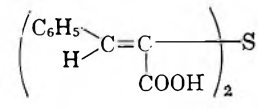
the desired episulfides, the use of thiolacetic acid and hydrogen sulfide was investigated. The action of thiolacetic acid in pyridine or hydrogen sulfide in alkaline methanol on ethyl *trans*-3-phenylglycidate (III) produced the corresponding hydroxythioacetate Va and hydroxythiol Vb which were converted to the chloro derivatives VIa and VIb with thionyl chloride.



III

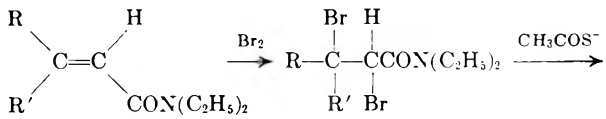


Unfortunately treatment of VI with alkali did not yield episulfides. VIa furnished ethyl cinnamate, cinnamic acid, and sulfur, whereas VIb gave VII (structure tentatively assigned) as the only isolable product. In view

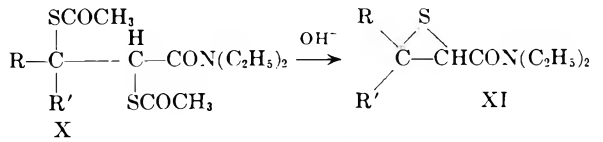


VII

of these failures we turned our attention to 2,3-dibromoamides as a route to episulfides. *erythro*-N,N-Diethylcinnamamide dibromide has been shown to undergo exclusively debromination to *trans*-N,N-diethylcinnamamide upon treatment with thiolacetate ion.[9] The aliphatic dibromides IX gave dithiolacetates X.



VIII IX



X XI

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

Treatment of Xa with aqueous alkali at room temperature afforded a 65% yield of VIIIa and an 80% yield of sulfur. However, under the same conditions, Xb, c each yielded a light yellow oil as the only product. Samples before and after purification through silica

(1) J. A. Durden, Jr., H. A. Stansbury, Jr., and W. A. Catlette, *J. Am. Chem. Soc.*, **81**, 1943 (1959).

(2) T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, 501, 656 (1962).

(3) C. C. J. Culvenor, W. Davis, J. A. MacLaven, P. F. Nelson, and W. E. Savige, *ibid.*, 2573 (1949).

(4) C. C. J. Culvenor, W. Davies, and N. S. Heath, *ibid.*, 278 (1949).

(5) It has been assumed[2,4,6] that the olefins arise from the thermal desulfurization of the episulfide. It also appears likely that in the case of *trans*-IVa, b, *trans*-III, and stilbene oxide, the episulfide is never formed, but instead an intermediate eliminates free sulfur directly.

(6) C. C. J. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, 4480 (1952).

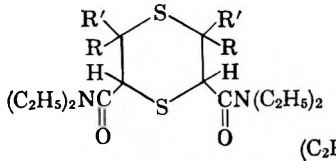
(7) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28**, 1514 (1963); C. C. Tung and A. J. Speziale, *ibid.*, **28**, 2009 (1963).

(8) C. O. Guss and D. L. Chamberlain, Jr., *J. Am. Chem. Soc.*, **74**, 1342 (1952).

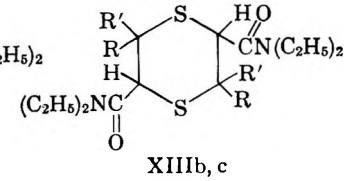
(9) A. J. Speziale and C. C. Tung, *J. Org. Chem.*, **28**, 1353 (1963).

gel gave elemental and infrared analyses consistent with the episulfides XIb, c. Molecular weight determinations, however, were consistent with a dimeric structure. The product derived from Xb reacted with triphenylphosphine but afforded only a 15% yield of triphenylphosphine sulfide and 15% yield of *trans*-N,N-diethylcrotonylamide (VIIIb). The product derived from Xc did not react with triphenylphosphine.

It appears that the action of base on Xb, c led to the stable dithianes XIIb, c or XIIIb, c, rather than the episulfides. Each could arise from the dimerization



XIIb, c



XIIIb, c

of Xb, c or the corresponding episulfides XIb, c. The conversion of a 3,4-epithio ester to a dithiane has been noted.[2]

Experimental

Ethyl 3-Hydroxy-2-acetylthiohydrocinnamate (Va).—To a stirred solution of 38.4 g. (0.20 mole) of ethyl *trans*-3-phenylglycidate (III) and 16.0 g. (0.21 mole) of freshly distilled thiolacetic acid, 16.6 g. (0.21 mole) of pyridine at 25° was added with cooling. The addition required about 1 hr. and the mixture was allowed to stand at room temperature overnight. The mixture, after washing with water, was dissolved in ether and dried over magnesium sulfate; the solvent was evaporated. The yield of light yellow viscous oil was 98%; $n^{25}D$ 1.5396. The product decomposed on distillation and the analysis was made on the crude product.

Anal. Calcd. for $C_{13}H_{16}O_4S$: C, 58.2; H, 6.0; S, 11.9. Found: C, 58.5; H, 5.9; S, 11.9.

Ethyl 2-Acetylthio-3-chloro-2,3-dihydrocinnamate (VIa).—To a stirred solution of 25.0 g. (0.094 mole) of Va in 75 ml. of benzene, 30 ml. of thionyl chloride was added dropwise at 25° over a period of 30 min. under nitrogen. The solution was then heated at reflux temperature (73°) for 2 hr., and the solvent and excess of thionyl chloride was removed *in vacuo*. The product, a light yellow viscous oil, $n^{25}D$ 1.5530, was obtained in 96% yield.

Anal. Calcd. for $C_{13}H_{15}ClO_3S$: C, 54.5; H, 5.3; Cl, 12.4; S, 11.2. Found: C, 54.4; H, 5.6; Cl, 12.0; S, 11.2.

A mixture containing 21.8 g. (0.076 mole) of VIa in 350 ml. of 0.5 *N* aqueous potassium hydroxide (0.17 mole) was heated at reflux temperature for 0.5 hr. The only products isolated were 5.8 g. (32.9% yield) of ethyl cinnamate, 3.9 g. (35% yield) of cinnamic acid, and 0.8 g. (32.8% yield) of sulfur.

Ethyl 3-Hydroxy-2-mercapto-2,3-dihydrocinnamate (Vb).—A slow stream of hydrogen sulfide was passed into a solution of 16.1 g. (0.40 mole) of sodium hydroxide in 142 ml. of methanol at −10 to 0° during 1.5 hr. The reaction mixture was allowed to stand at room temperature overnight, diluted with 400 ml. of water, cooled to 0°, and acidified with 5 *N* sulfuric acid (pH 2). The solution was extracted with 300 ml. of methylene chloride, and washed with 100 ml. of saturated sodium bicarbonate and 100 ml. of water. The methylene chloride extract, after drying over magnesium sulfate, was evaporated to dryness to give light yellow-colored oil. The yield of crude product was 82%; $n^{25}D$ 1.5500. It decomposed upon distillation under nitrogen atmosphere.

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 58.3; H, 6.2; S, 14.1. Found: C, 58.6; H, 6.0; S, 13.9.

Ethyl 2-Mercapto-3-chloro-2,3-dihydrocinnamate (VIb).—Thionyl chloride (74 ml., 1.0 mole) was added slowly to a stirred solution at 5–10° of Vb (51.0 g., 0.23 mole) in 150 ml. of benzene. The mixture was allowed to warm to 25° and stirred at that temperature for 2 hr. The solvent and unchanged thionyl chloride were removed *in vacuo* to give a light yellow oil ($n^{25}D$ 1.5771) in 91.0% yield. The product decomposed upon distillation and the analysis was made on crude material.

Anal. Calcd. for $C_{11}H_{13}ClO_2S$: C, 54.0; H, 5.4; Cl, 14.5; S, 13.1. Found: C, 54.6; H, 5.2; Cl, 14.8; S, 12.8.

To a solution of 21.9 g. (0.09 mole) of VIb in 150 ml. of methanol at 24°, 8.0 g. (1.20 moles) of sodium hydroxide in 40 ml. of water was added over a period of 35 min. The solution was stirred at room temperature for 10 hr., poured into 500 ml. of water, and extracted with chloroform. The chloroform extract was evaporated to dryness and the semisolid residue was stirred with 80 ml. of warm benzene. The benzene-insoluble material was collected and recrystallized from methanol. The cream-colored solid, after recrystallization from methanol, had m.p. 232–233°, yield 5.7 g.; 5.1 g. more of solid, m.p. 232–233°, was recovered from the benzene filtrate. The infrared data showed C=C band at 6.2 μ. The structure of this compound is tentatively assigned at 2,2′-thiodicinnamic acid (VII).

Anal. Calcd. for $C_{18}H_{14}O_4S$: C, 66.2; H, 4.3; S, 9.7; mol. wt., 326. Found: C, 66.8; H, 4.6; S, 9.6; mol. wt., 322.

N,N-Diethyl-2,3-dithioacetyl-3-methylbutyramide (Xa).—N,N-Diethyl-3,3-dimethylacrylylamide (VIIIa) was prepared from diethylamine and 3,3-dimethylacrylyl chloride.[10] The product, a colorless liquid, b.p. 41–42° (0.2 mm.), $n^{25}D$ 1.4697, was obtained in 92% yield.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.5; H, 11.0; N, 9.0.

The bromination of VIIIa in CCl_4 solution gave a 98% yield of N,N-diethyl-2,3-dibromo-3-methylbutyramide (IXa), m.p. 63.5–64.3°.

Anal. Calcd. for $C_9H_{17}Br_2NO$: C, 34.4; H, 5.4; Br, 50.7; N, 4.5. Found: C, 34.5; H, 5.5; Br, 50.7; N, 4.5.

Pyridine (20.5 g., 0.26 mole) was added dropwise to a solution of 23.1 g. (0.073 mole) of IXa and 19.7 g. (0.26 mole) of thiolacetic acid in 100 ml. of benzene. The temperature of the reaction mixture rose from 25 to 35° and solid separated slowly. The mixture was allowed to stand at room temperature for 2 days. The solid was collected by filtration, washed with benzene, and dried *in vacuo;* yield 25.3 g. (0.146 mole) of pyridine hydrobromide. The benzene filtrate was evaporated to dryness; the residue was redissolved in benzene and washed thoroughly with water. After removing solvent *in vacuo*, there was obtained a light yellow viscous oil, $n^{25}D$ 1.5054, in 92% yield.

Anal. Calcd. for $C_{13}H_{23}NO_3S_2$: C, 51.2; H, 7.6; N, 4.6; S, 21.0. Found: C, 51.2; H, 7.8; N, 4.9; S, 21.3.

A mixture of 6.4 g. (0.021 mole) of Xa and 250 ml. of 0.5 *N* potassium hydroxide (0.125 mole) was stirred vigorously at room temperature for 20 min. At the end of this period, the free sulfur was removed by filtration. The filtrate was saturated with salt, extracted with ether, washed with saturated brine solution, and dried over magnesium sulfate. After evaporation to dryness, there was obtained 2.9 g. of amber-colored oil (VIIIa) which was purified by distillation to a colorless liquid, b.p. 50–51° (0.4 mm.), $n^{25}D$ 1.4700, 2.1 g., 65% yield.

***erythro*-N,N-Diethyl-2,3-dithioacetylbutyramide (Xb).**—*trans*-N,N-Diethyl-3-methylacrylylamide (VIIIb)[11] was prepared from diethylamine and crotonyl chloride. The product, a colorless liquid, b.p. 47–48° (0.2 mm.), $n^{25}D$ 1.4737, was obtained in 98% yield.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.1; H, 10.7; N, 9.9. Found: C, 68.1; H, 10.7; N, 10.0.

Bromination of VIIIb in CCl_4 solution gave *erythro*-N,N-diethyl-2,3-dibromobutyramide (IXb) as a light yellow oil, b.p. 105–106° (0.5 mm.), $n^{25}D$ 1.5254, in theoretical yield.

Anal. Calcd. for $C_8H_{15}Br_2NO$: Br, 53.2. Found: Br, 52.7.

Treatment of 112.3 g. (0.37 mole) of IXb with 85.0 g. (1.02 moles) of pyridine as described above afforded a light yellow viscous oil Xb, $n^{25}D$ 1.5136, 94% yield.

Anal. Calcd. for $C_{12}H_{21}NO_3S_2$: C, 49.6; H, 7.2; N, 4.8; S, 22.0. Found: C, 49.6; H, 6.9; N, 4.7; S, 22.3.

2,3-Dimethyl-3,6-bis(diethylcarbamoyl)-1,4-dithiane (XIIb or XIIIb).—Treatment of 30.1 g. (0.10 mole) of Xb with 28.0 g. (0.50 mole) of KOH in 1000 ml. of water, as described for VIa, afforded a light yellow oil, $n^{25}D$ 1.5131, 10.0 g. (56% yield).

Anal. Calcd. for $C_{16}H_{30}N_2O_2S_2$: C, 55.5; H, 8.7; N, 8.1;

(10) L. I. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, **71**, 2671 (1949).

(11) The *trans* configuration was determined by n.m.r.: $J_{H_\alpha H_\beta}$ = 16.5 c.p.s.

S, 18.5; mol. wt., 346. Found: C, 54.8; H, 9.1; N, 7.5; S, 18.4; mol. wt., 334 (Rast method), 311 (Mechrolab osmometer in acetonitrile).

A solution of 5.0 g. (0.029 mole) of above product and 8.3 g. (0.031 mole) of triphenylphosphine in 50 ml. of chloroform was heated to reflux for 7 hr. Chloroform was removed; the residue was stirred with 130 ml. of hexane vigorously at room temperature. The hexane-insoluble material was collected and recrystallized from hexane. The crystalline solid, m.p. 161–162°, identified as triphenylphosphine sulfide (no depression in melting point with authentic sample) was obtained in 1.3-g. (0.0044 mole, 15%) yield. There was also isolated 0.7 g. (0.004 mole, 15.2%) of VIIIb from the hexane mother liquors. The very viscous oil was not distillable at 320° (0.15 mm.).

Infrared and elemental analysis of the sample, $n^{25}D$ 1.5131, after standing at room temperature for several months, did not change. However, its refractive index increased: $n^{25}D$ 1.5164. The compound after purification through silica gel gave a light yellow oil, $n^{25}D$ 1.5166, with no change in its infrared spectrum. Elemental analysis and molecular weight of the chromatogrammed sample remained essentially the same.

N,N-Diethyl-2,3-dithioacetylpropionamide (Xc).—N,N-Diethylacrylylamide (VIIIc) was prepared from diethylamine and acrylyl chloride in ether solution, b.p. 39–40° (0.2 mm.), $n^{25}D$ 1.4645, 97% yield.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.2; H, 10.2; N, 11.0. Found: C, 66.1; H, 10.1; N, 11.2.

Bromination of VIIIc in chloroform solution gave N,N-diethyl-2,3-dibromopropionamide (IXc) as a light yellow oil in quantitative yield, b.p. 124–125° (3 mm.), $n^{25}D$ 1.5270, 57% yield.

Anal. Calcd. for $C_7H_{13}Br_2NO$: C, 29.3; H, 4.5; N, 4.9; Br, 55.8. Found: C, 29.6; H, 4.4; N, 4.7; Br, 55.8.

The procedure as described for the preparation of Xa, b was used. The pyridine hydrobromide was obtained in 89.0% yield (based upon 2 mole equiv. of salt for 1 mole equiv. of IXc). The desired product, Xc, $n^{25}D$ 1.5194, was obtained in 94% yield.

Anal. Calcd. for $C_{11}H_{19}NO_3S_2$: C, 47.7; H, 6.9; N, 5.1; S, 23.1. Found: C, 47.3; H, 6.9; N, 5.0; S, 23.3.

2,5-[Bis(diethylaminocarbamoyl)]-1,4-dithiane (XIIc or XIIIc).—The procedure for the preparation of XIIb or XIIIb was used. The product, a light yellow oil, $n^{25}D$ 1.5110, was obtained in 48% yield.

Anal. Calcd. for $C_{14}H_{26}N_2O_2S_2$: C, 52.7; H, 8.2; N, 8.8; S, 20.1; mol. wt., 318. Found: C, 52.7; H, 8.4; N, 8.0; S, 19.2; mol. wt., 313 (Rast method), 291 (Mechrolab osmometer in acetonitrile).

The compound, after standing at room temperature for several days, did not react with triphenylphosphine.

Synthesis and Some Reactions of Triphenylphosphinamino- and (β-N-Disubstituted amino)imines

HANS ZIMMER AND GURDIAL SINGH

Department of Chemistry, University of Cincinnati, Cincinnati 21, Ohio

Received December 5, 1963

Triphenylphosphinamino- and (β-N-disubstituted amino)imines have been prepared by dehydrobromination of hydrazino- and (β-N-disubstituted hydrazino)triphenylphosphonium bromides, respectively. The aminophosphinimines have been treated further with methyl and ethyl iodides, and the structures of the resulting α-N-alkyl hydrazino- and (α-N-alkyl β-N-disubstituted hydrazino)triphenylphosphonium iodides have been confirmed through elemental analyses, hydrolysis to triphenylphosphine oxide and substituted hydrazines, and nuclear magnetic resonance studies. The hydrolysis of (α-N-alkyl β-N-disubstituted hydrazino)triphenylphosphonium iodides represents a new way for the synthesis of 1,1,2-trisubstituted hydrazines.

Recently we reported the preparation of some triphenylphosphinalkyl imines (I, R = alkyl)[1] and their successful utilization for the synthesis of sterically hindered dialkyl amines, such as *t*-butylmethylamine and *t*-butylethylamine, which are not easily available through conventional methods. It was also discovered that triphenylphosphine-*t*-butylamine (I, R = *t*-Bu)

$$Ph_3P{=}NR$$
I

was a very stable compound at ambient conditions. Triphenylphosphinisopropylimine (I, R = *i*-Pr) was less stable but sufficiently resistant towards moisture that an analytical sample could be prepared. All other triphenylphosphinalkyl imines decomposed rapidly to triphenylphosphine oxide and the corresponding alkyl amines when exposed to the atmosphere. Until then, the only stable triphenylphosphinimines known were resonance-stabilized ones,[2-8] such as $Ph_3P{=}NPh$.

A plausible explanation for the stability of triphenylphosphine-*t*-butylimine is that the *t*-butyl group, due to its bulk, exercises an effective shielding on the P=N bond.

These results made it appear desirable to study type I compounds further. It was of particular interest to investigate the effects of groups of different electronic and steric requirements on the reactivity of the phosphorus nitrogen double bond, and to investigate whether these phosphinimines could be used as tools in organic and inorganic syntheses. In this paper the synthesis and some properties of triphenylphosphinamino- and (β-N-disubstituted amino)imines (I, R = NH_2 or NXY), as well as their utilization for the preparation of trisubstituted hydrazines, are communicated.

Results and Discussion

Triphenylphosphine dibromide reacted with anhydrous hydrazine or 1,1-disubstituted hydrazines in the presence of triethylamine to give the hydrazino- or (β-N-disubstituted hydrazino)triphenylphosphonium bromides (eq. 1 and Table I).

Under the conditions employed, the free amino group of the hydrazinotriphenylphosphonium bromide (1) failed to react further with triphenylphosphine dibromide to give the diphosphonium bromide (eq. 2).

(1) H. Zimmer and G. Singh, *J. Org. Chem.*, **28**, 483 (1963).
(2) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
(3) H. Staudinger and E. Hauser, *ibid.*, **4**, 861 (1921).
(4) F. G. Mann and E. J. Chaplin, *J. Chem. Soc.*, 527 (1937).
(5) A. V. Kirsanov and G. I. Derkach, *Zh. Obshch. Khim.*, **26**, 2631 (1956); *Chem. Abstr.*, **51**, 1821 (1927).
(6) L. Horner and H. Oediger, *Ann.*, **627**, 142 (1959).
(7) V. I. Shevchenko and V. T. Stratienko, *Zh. Obshch. Khim.*, **30**, 1958 (1960); *Chem. Abstr.*, **55**, 6425 (1961).
(8) G. I. Derkach, E. S. Gubnitskaya, and A. V. Kirsanov, *ibid.*, **31**, 3679 (1961).

TABLE I

HYDRAZINO- AND (β-N-DISUBSTITUTED HYDRAZINO)TRIPHENYLPHOSPHONIUM BROMIDES

$[Ph_3PNHNXY]^+Br^-$

Compd. no.	X	Y	Formula	Color	M.p., °C.	Yield, %	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
1	H	H	$C_{18}H_{18}BrN_2P$	White	215[a]	83.5	57.91	58.31	4.82	4.90	7.51	7.28
2	CH_3	CH_3	$C_{20}H_{22}BrN_2P$	White	190–191 dec.	90.0	59.85	59.84	5.49	5.43	6.98	6.88
3	CH_3	C_6H_5	$C_{25}H_{24}BrN_2P$	White	213	87.3	64.79	64.38	5.22	5.05	6.04	6.18
4	C_6H_5	C_6H_5	$C_{30}H_{26}BrN_2P$[b]	Light yellow	249–250	98.5	68.57	68.57	4.98	4.92	5.33	5.33

[a] Ref. 6, m.p. 210–212°. [b] Calcd. for $C_{30}H_{26}BrN_2P$: Br, 15.21. Found: Br, 15.39.

$$Ph_3PBr_2 + H_2NNXY \xrightarrow{Et_3N} [Ph_3PNHNXY]^+Br^- + [Et_3NH]^+Br^- \quad (1)$$

1, X = Y = H
2, X = Y = CH_3
3, X = CH_3; Y = C_6H_5
4, X = Y = C_6H_5

$$[Ph_3PNHNH_2]^+Br^- + Ph_3PBr_2 \xrightarrow{Et_3N} [Ph_3PNHNHPPh_3]^{+2}2Br^- + [EtNH]^+Br^- \quad (2)$$

Hydrazino- and (β-N-disubstituted hydrazino)triphenylphosphonium bromides, obtained according to eq. 1, could be easily dehydrobrominated with sodamide in liquid ammonia to the corresponding triphenylphosphinamino- and (β-N-disubstituted amino)imines (eq. 3 and Table II).

TABLE II

TRIPHENYLPHOSPHINAMINO- AND (β-N-DISUBSTITUTED AMINO)IMINES

$Ph_3P{=}NNXY$[a]

Compd. no.	X	Y	M.p., °C.	Yield,[b] %	Color
5	H	H	115–116	90.0	Yellow
6	CH_3	CH_3	121–123	86.0	Light yellow
7	CH_3	C_6H_5	106–108	90.1	Light yellow
8	C_6H_5	C_6H_5	114–145 dec.	68.3	Light green

[a] Owing to their instability, no attempt was made to get analytically pure samples. [b] The yields were calculated on the assumption that no decomposition of the aminophosphinimines occurred.

$$[Ph_3PNHNXY]^+Br^- \xrightarrow[liq.\ NH_3]{NaNH_2} Ph_3P{=}NNXY + NaBr + NH_3 \quad (3)$$

Like triphenylphosphinalkyl imines,[1,9] the triphenylphosphinamino- and (β-N-disubstituted amino)imines described in this paper were bases and decomposed rapidly in air to give triphenylphosphine oxide and the corresponding hydrazines. The structures of the triphenylphosphinaminoimines and their nucleophilicity were confirmed by treating them with methyl and ethyl iodides and isolating the stable α-N-methylhydrazino- and (α-N-alkyl β-N-disubstituted hydrazino)triphenylphosphonium iodides (eq. 4 and Table III).

$$Ph_3P{=}NNXY + RI \longrightarrow [Ph_3PNNXY]^+I^- \quad (4)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |\ R$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad II$$

R = CH_3 or C_2H_5

The structures of these α-N-methylhydrazino- and (α-N-alkyl β-N-disubstituted hydrazino)triphenylphosphonium iodides (eq. 4 and Table III) were verified through elemental analyses, hydrolysis with alcoholic potassium hydroxide to triphenylphosphine oxide and the corresponding hydrazines (eq. 5), and nuclear magnetic resonance studies.

$$[Ph_3PNNXY]^+I^- \xrightarrow{alc.\ KOH} Ph_3PO + RHNNXY \quad (5)$$
$$\quad |\ R$$

Hydrolysis of compounds **10**, **11**, **12**, and **13** gave 1,1,-2-trimethylhydrazine, 1,2-dimethyl-1-phenylhydrazine, 1-methyl-2,2-diphenylhydrazine, and 1-ethyl-2,2-diphenylhydrazine, respectively, thus establishing that during the reactions of aminophosphinimines with alkyl iodides (eq. 4) the alkylation occurred at the α-nitrogen atom in agreement with structure II and not at the β-nitrogen atom as indicated in structure III.

$$[Ph_3P{=}NNXY]^+I^-$$
$$\quad |\ R$$
III

This sequence of reactions (1 → 3 → 4 → 5) represents a new and very convenient method for the preparation of 1,1,2-trisubstituted hydrazines in excellent yields and great purity (see Experimental).

N.m.r. data (see Table IV) obtained from **9**, **10**, **11**, and **12** furnished further evidence supporting structure II rather than III. In a recent paper[10] the occurrence of long-range P^{31}–H^1 coupling in systems such as PNCH and PNCCH was reported. The long-range coupling was not detectable in compounds containing the PNNCH system. Thus, if one considers the reaction between methyl iodide and triphenylphosphinaminoimines, two possible modes of addition might be discussed, namely, addition to the α-nitrogen atom to yield structure II-type compounds, or addition to the β-nitrogen atom to give structure of type III. As is evident from Table IV, **9**, **10**, **11**, and **12** showed the long-range coupling between phosphorus atom and the protons of the methyl group. This spin–spin coupling is only possible if the compounds in question possess structure II, since only it contains the PNCH system, which is capable of exhibiting the long-range coupling effect. Thus, structure II is supported by both physical evidence and chemical behavior.

Experimental[11]

Hydrazino- and (β-N-Disubstituted hydrazino)triphenylphosphonium Bromides (Table I).—A solution of anhydrous hydrazine or 1,1-disubstituted hydrazines (0.1 mole) in triethylamine (10.1 g., 0.1 mole) was added simultaneously, with stirring, to freshly prepared triphenylphosphine dibromide (42.2 g., 0.1 mole) in dry benzene (200 ml.) over a period of 0.5 hr. The stirring

(9) H. Zimmer and G. Singh, *Angew. Chem.*, **75**, 574 (1963).

(10) F. Kaplan, G. Singh, and H. Zimmer, *J. Phys. Chem.*, **67**, 2509 (1963).

(11) Melting points are uncorrected. Microanalyses were by A. Berhnardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany, and by Galbraith Laboratories, Knoxville, Tenn.

TABLE III

α-N-METHYLHYDRAZINO- AND (α-N-ALKYL β-N-DISUBSTITUTED HYDRAZINO)TRIPHENYLPHOSPHONIUM IODIDES

Compd. no.	X	Y	R	Formula	Color	M.p., °C.	Yield, %	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
9	H	H	CH_3	$C_{19}H_{20}IN_2P$	White	181–182 dec.	100	52.53	52.07	4.61	4.51	6.45	6.70
10	CH_3	CH_3	CH_3	$C_{21}H_{24}IN_2P$	White	143 dec.	98.0	54.54	53.92	5.20	5.12	6.06	6.01
11	CH_3	C_6H_5	CH_3	$C_{26}H_{26}IN_2P$	Light yellow	177 dec.	95.5	59.54	59.80	4.96	4.93	5.34	5.23
12	C_6H_5	C_6H_5	CH_3	$C_{31}H_{25}IN_2P$	Light yellow	179 dec.	80.0	63.51	63.72	4.78	4.99	4.78	4.96
13	C_6H_5	C_6H_5	C_2H_5	$C_{32}H_{30}IN_2P$	Light yellow	162 dec.	53.3	64.02	63.71	5.00	4.97	4.66	4.96

TABLE IV

N.M.R. DATA[a]

Compd. no.	Compound	δ_{CH_3}[b] PN-CH_3	δ_{CH_3}[b] PN-NCH_3	$J_{P,H}$ PN-CH_3	$J_{P,H}$ PN-NCH_3
2	$[Ph_3P—NH—N(CH_3)_2]^+Br^-$[c]		166.5		d
3	$[Ph_3P—NH—NCH_3Ph]^+Br^-$		190.2		d
6	$Ph_3P{=}N—N(CH_3)_2$[c]		192.5		d
9	$[Ph_3P—NCH_2—NH_2]^+I^-$[e]	199.9		9.0	
10	$[Ph_3P—NCH_2—N(CH_3)_2]^+I^-$[c]	187.0	150.9	8.8	d
11	$[Ph_3P—NCH_2—NCH_3Ph]^+I^-$[c]	193.6	187.8	7.8	d
12	$[Ph_3P—NCH_2—NPh_2]^+I^-$	202.0		7.1	

[a] Spectra were obtained in deuteriochloroform on a Varian A-60 spectrometer. [b] Chemical shifts were measured in c.p.s. from an internal reference of tetramethylsilane. [c] Data taken from ref 10. [d] Coupling between phosphorus and the protons of the methyl group were not observed. [e] The doublet of the NH_2 group appeared at 296.8 c.p.s. (J = 9.0 c.p.s.).

was continued for an additional hour and dry ether was added to precipitate completely the phosphonium bromide. After a little more stirring, the solid was collected by filtration, washed first with ice-cold water (50 ml.) to remove triethylammonium bromide and then with ether. Analytical samples were prepared by recrystallization from chloroform–ethyl acetate mixture.

Triphenylphosphinamino- and (β-N-Disubstituted amino)imines (Table II).—The appropriate phosphonium bromide (see Table I, 0.05 mole) and sodamide (2.05 g., 0.055 mole) were stirred in liquid ammonia (about 300 ml.) under anhydrous conditions. The ammonia then was allowed to evaporate, and the residue was extracted with ether which had been dried over sodium. After distilling the ether, the respective aminophosphinimine was left behind.

α-N-Alkyl Hydrazino- and (α-N-Alkyl β-N-Disubstituted hydrazino)triphenylphosphonium Iodides (Table III).—The appropriate aminophosphinimine (see Table II, 0.005 mole) was refluxed with 5 ml. of methyl or ethyl iodide for 2–3 hr. The reaction mixture was then cooled and an excess of dry ether or ethyl acetate was added to precipitate the phosphonium iodides. In the case of triphenylphosphinaminoimine and triphenylphosphine-β-N-dimethylaminoimine, the crude mixture containing sodium bromide was employed for reaction with methyl or ethyl iodide. The reaction mixture was diluted with chloroform (5 ml.) and filtered. The phosphonium iodides were precipitated from the filtrate by adding on excess of ether or ethyl acetate. Analytical samples were recrystallized from a mixture of chloroform and ethyl acetate.

1,1,2-Trimethylhydrazine.—α-N-Methyl-β-N-dimethyltriphenylphosphonium iodide (10, 4.62 g., 0.01 mole) and 50 ml. of 2% alcoholic potassium hydroxide solution were refluxed for 2 hr. The ethanol and 1,1,2-trimethylhydrazine were distilled. To the distillate was added an excess of a saturated solution of oxalic acid in dry ether. The oxalic acid salt, which separated as white precipitate, was collected by filtration; yield was 87.5%. An analytical sample, prepared by recrystallization from anhydrous ethanol and dry ether mixture, melted at 96–98°.

Anal. Calcd. for $C_3H_{10}N_2 \cdot C_2H_2O_4$: C, 36.59; H, 7.32; N, 17.08. Found: C, 36.60; H, 7.49; N, 16.96.

1,2-Dimethyl-1-phenylhydrazine.—A mixture of 5.24 g. (0.01 mole) of α-N-methyl-β-N-methyl-β-N-phenylhydrazinotriphenylphosphonium iodide (11) and 50 ml. of 2% alcoholic potassium hydroxide was refluxed for 2 hr. The ethanol was removed by distillation and the residue was extracted with ether. After drying the ether extract over anhydrous sodium sulfate, the ether was removed by distillation and 1,2-dimethyl-1-phenylhydrazine, which was left behind as a yellow liquid, distilled at 92 ± 1° (2 mm.)[12] as a colorless liquid,[13] $n^{23.5}D$ 1.5600; yield was 1.14 g. (88.0%).

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.59; H, 8.83; N, 20.59. Found: C, 70.91; H, 8.68; N, 20.51.

1-Methyl-2,2-diphenylhydrazine and 1-Ethyl-2,2-diphenylhydrazine.—They were prepared by hydrolysis of α-N-methyl-β-N-diphenylhydrazinotriphenylphosphonium iodide (12, 5.86 g., 0.01 mole) and α-N-ethyl-β-N-diphenylhydrazinotriphenylphosphonium iodide (13, 6.00 g., 0.01 mole), respectively, with 2% alcoholic potassium hydroxide (50 ml.) in a similar way as described above. 1-Methyl-2,2-diphenylhydrazine distilled at 150 ± 2° (3 mm.), yielding 1.79 g. (90.0%) of colorless liquid,[13] $n^{23}D$ 1.6284.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.79; H, 7.07; N, 14.14. Found: C, 79.35; H, 6.98; N, 13.46.

1-Ethyl-2,2-diphenylhydrazine distilled at 155 ± 2° (2 mm.), also as colorless liquid,[13] $n^{23}D$ 1.6284; yield was 1.74 g. (82.0%).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.24; H, 7.54. Found: C, 78.98; H, 7.15.

Acknowledgment.—Financial support by the U. S. Army Research Office, Durham, North Carolina, and the National Institutes of Health, Bethesda, Maryland, is gratefully acknowledged. The Varian A-60 spectrometer was purchased with grants provided by the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation.

(12) C. D. Harries [*Ber.*, **27**, 696 (1894)] reports b.p. 93–94° (7 mm.).
(13) This turned yellow on standing.

Enamines as 1,3-Dipolarophiles[1]

MARTIN E. KUEHNE, SANDRA J. WEAVER, AND PETER FRANZ[2]

Department of Chemistry, University of Vermont, Burlington, Vermont

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The reactions of benzhydroxamoyl chloride and N¹-α-chlorobenzylidene-N²-phenylhydrazine with a number of cyclic and acyclic enamines led to aminodihydroisoxazoles and a pyrrolidinodihydropyrrazole. Elimination of the tertiary amine from the substituted heterocycles gave the corresponding isoxazoles and tetrahydroisoindazoles.

Extensions of the Stork acylation and alkylation reactions of enamines[3,4] have led to the direct formation of four-[5] and six-membered[6] carbocyclic ring systems, as well as γ-pyrones.[7] In each instance the products arise by generation and collapse of a dipolar immonium anion intermediate, formed from uncharged precursors (*i.e.*, Chart I). Even in the reaction of an enamine with benzyne,[8] where addition of a proton source can prevent cyclization to a benzocyclobutene, this two-step reaction path is evident.

Direct formation of four-membered rings from reactions of enamines with ketenes,[9-11] with diethyl acetylenedicarboxylate,[12] and with alkyl sulfonyl chlorides[13,14] is also known.

The present study shows the direct formation of five-membered heterocyclic systems by reactions of enamines with two 1,3-dipolar species. While this work was in progress, syntheses of 1,2,3-triazoles were reported using other enamines and aryl and arylsulfonyl azides as alternative 1,3-dipolar reactants.[15-17]

As outlined by Huisgen,[18] the reaction of benzhydroxamoyl chloride (I) with base generates the 1,3-dipolar nitrile oxide II. When benzhydroxamoyl chloride (I) was added to 2 equiv. of the enamines III to X, the crystalline aminodihydroisoxazoles XII to XIX were formed in good yield. Alternatively, the reaction could be achieved with 1 equiv. of enamine and 1 equiv. of triethylamine as base. Only the morpholinodihydroisoxazole XX remained noncrystalline and had to be identified through the corresponding isoxazole XXII (see Chart II).

Pyrrolidine was readily eliminated on acid treatment of the aminodihydroisoxazoles XIII and XIV, derived from the six- and seven-membered carbocyclic enamines. However, the next lower homolog XII was stable in refluxing hydrochloric acid, and removal of the pyrrolidine ring could only be achieved by Hofmann degradation. The greater ease of elimination of pyrrolidine from the higher homologs XIII and XIV reflects greater flexibility of the four- and five-carbon bridges on the isoxazoles XXII and XXIII as compared with the more rigid three-carbon bridge in XXI, which imposes some steric strain on the isoxazole system. The decreasing strain on the heterocycle in the homologous series XXI, XXII, and XXIII is also reflected by the corresponding ultraviolet absorption maxima at 240, 236, and 229 mμ.

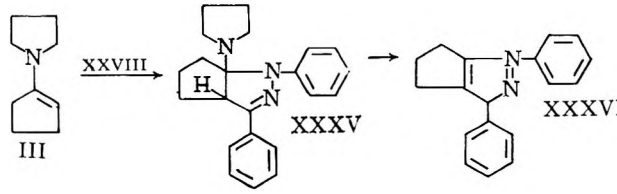
Preparation of the isoxazole XXII, derived from 1-pyrrolidinocyclohexene (IV) by the present route, now also allows structural assignment to the isoxazole obtained from 2-benzoylcyclohexanone XXV and hydroxylamine,[19] where the isomeric product XXVI with ultraviolet absorption at 266 mμ is obtained.



XXV XXVI

Addition of N¹-α-chlorobenzylidene-N²-phenylhydrazine (XXVII) to 1-pyrrolidinocyclohexene (IV), with triethylamine or excess enamine acting as base for liberation of the 1,3-dipolar diphenylnitrilimine XXVIII,[20] led directly to the diphenyltetrahydroisoindazole XXIX. Similarly, the enamines derived from piperidine and hexamethyleneimine and cyclohexanone VI and XXX gave the same product, and the pyrrolidine enamines of 4-benzoyloxycyclohexanone XXXI, cycloheptanone V, and benzyl phenyl ketone X gave the pyrazoles XXXII–XXXIV (see Scheme I).

Only from the reaction of 1-pyrrolidinocyclopentene III could the intermediate pyrrolidinodihydropyrazole XXXV be isolated. On mild acid treatment of this product, the trimethylenepyrazole XXXVI was formed. Again, as with the isoxazoles, the homologous series of pyrazoles fused to five-, six- and seven-membered carbocyclic rings shows decreasing ultraviolet absorption maxima in 287, 276, and 268 mμ.



III XXVIII XXXV XXXVI

(1) Taken in part from M.S. thesis in chemistry of S. J. Weaver, submitted May, 1963.

(2) Undergraduate research participant, Spring 1963.

(3) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(4) G. Stork and H. K. Landesman, *ibid.*, **78**, 5128, 5129 (1956).

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

(6) G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(7) S. Hünig, E. Benzing, and K. Hübner, *Ber.*, **94**, 486 (1961).

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

(9) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **26**, 4775 (1961); **28**, 1468 (1963).

(10) G. Opitz, H. Adolph, M. Kleemann, and F. Zimmermann, *Angew. Chem.*, **73**, 654 (1961).

(11) G. Opitz, M. Kleemann, and F. Zimmermann, *ibid.*, **74**, 32 (1962).

(12) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(13) G. Stork and I. Borowtiz, *J. Am. Chem. Soc.*, **84**, 313 (1962).

(14) G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962).

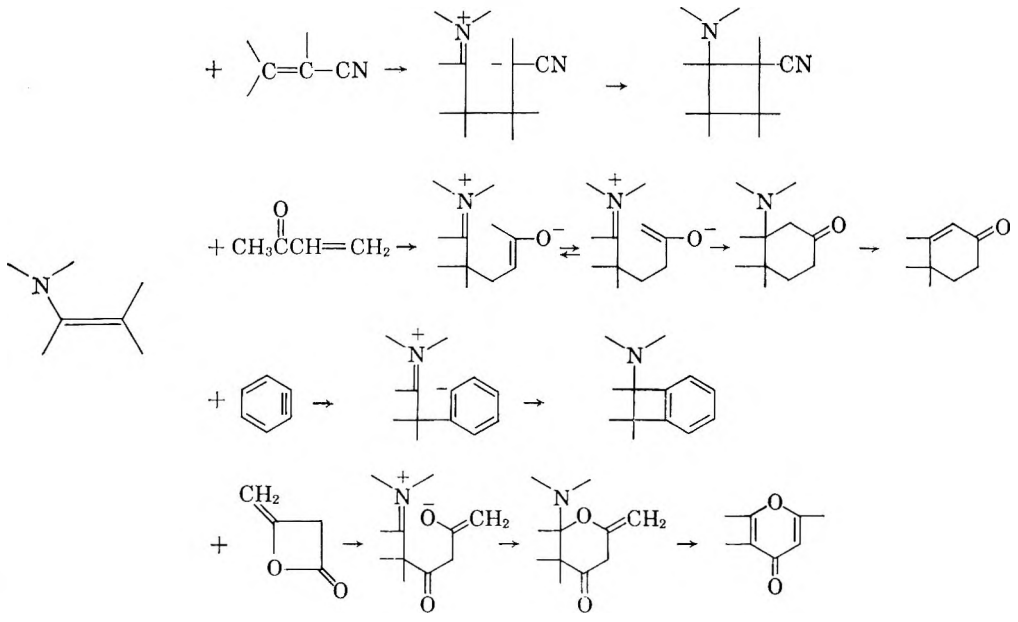
(15) (a) G. Nathanson, E. Testa, and N. Di Mola, *Experientia*, **18**, 57 (1962); (b) Morton E. Munk and Yung K. Kim, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 29Q.

(16) R. Fusco, G. Bianchetti, D. Pocar, and R. Ugo, *Ber.*, **96**, 802 (1963).

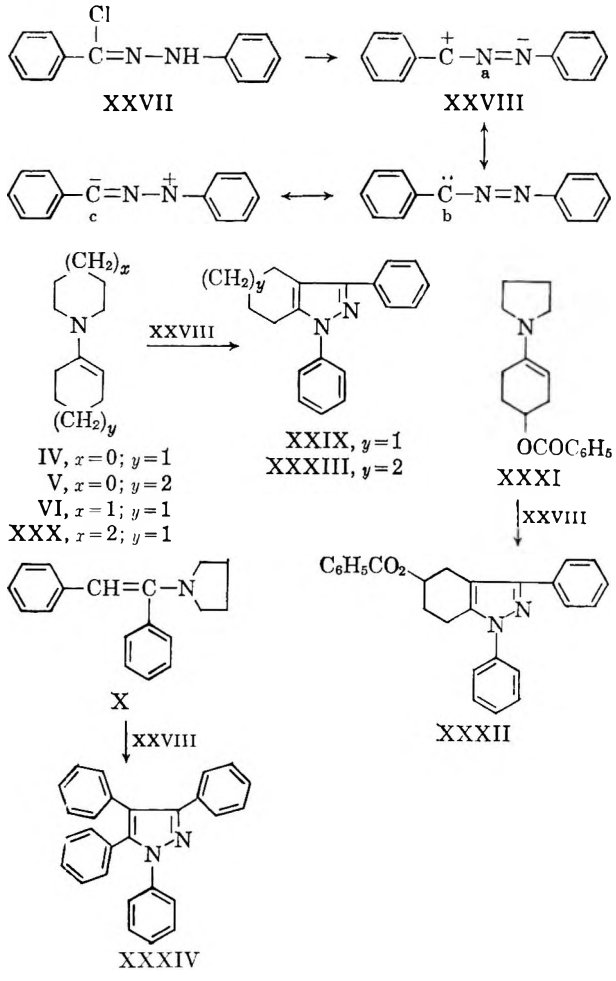
(17) R. Fusco, G. Bianchetti, D. Pocar, and R. Ugo, *Gazz. chim. ital.*, **91**, 849, 933 (1961); **92**, 1040 (1962).

(18) R. Huisgen, *Proc. Chem. Soc.*, 357 (1961).

CHART I

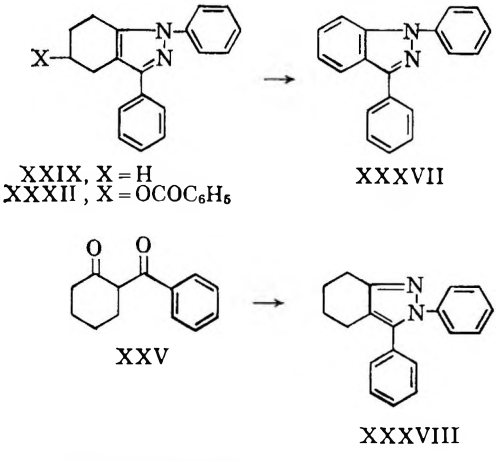


SCHEME I



Addition of the diphenylnitrilimine XXVIII to 1-pyrrolidinocyclohexene (IV) was also examined in a number of polar and nonpolar solvents under standard conditions. No significant changes in yields were apparent, suggesting a four-center mechanism rather than a polarized intermediate for this reaction.

Dehydrogenation of the tetrahydroisoindazoles XXIX, m.p. 131°, and XXXII to the known 1,3-diphenylisoindazole XXXVII and comparison of the tetraphenylpyrazole XXXIV with an authentic sample established the structures of these compounds. The present sequence also establishes the structure XXXVIII of the isomeric pyrazole, m.p. 11°, from 2-benzoylcyclohexanone XXV and phenylhydrazine.[19]

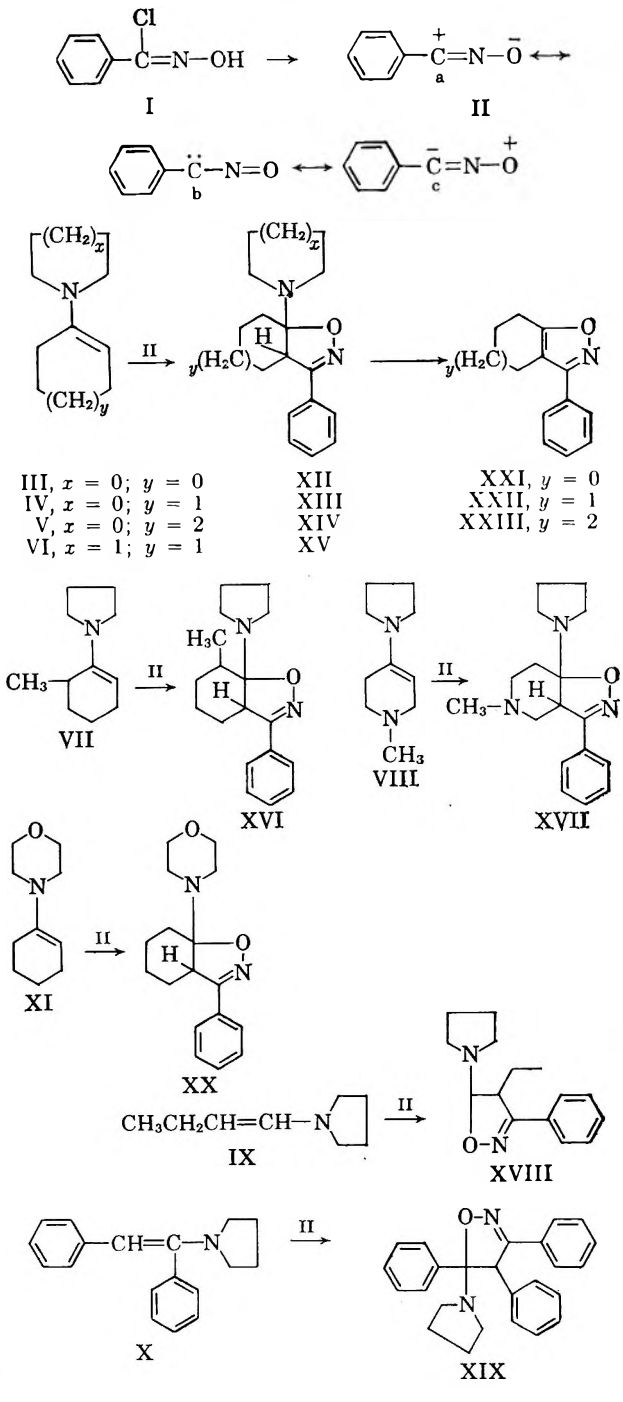


Although one might expect addition of the two dipolar species to enamines to proceed through a polarized stage with electron deficiency on carbon (IIa and XXVIIIa) rather than on oxygen or nitrogen (IIc and XXVIIIc), it was necessary to establish this mode of addition since it has been found that both additions to polarized double bonds are possible.[20] Structural assignments of the pyrrolidinodihydroisoxazoles and the pyrrolidinotrimethylenedihydropyrazole XXXV could be derived from n.m.r. spectra. The latter compound as well as the corresponding dihydroisoxazole XII showed the expected multiplets for the angular proton to have identical chemical shifts centered at τ 6.28. A difference in chemical shifts would be expected for the aminodihydroisoxazole and the aminodihydropyrazole if the alternative structures to XII

(19) E. Bauer, *Ann. chim.*, **1**, 393 (1914).

(20) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).

CHART II



and XXXV were present, with the angular hydrogen then on a carbon atom substituted by oxygen or nitrogen, respectively. Comparison of the trimethylenedihydroisoxazole XII with the tetramethylene compound XIII shows less deshielding of the angular proton, now centered at τ 6.57, in the higher homolog.

The chemical shifts of the angular protons compare favorably with the τ 6.38 value for the tertiary hydrogen multiplet of the isobutyrophenone oxime isomer, where phenyl and hydroxyl groups have the *anti* orientation.[21] The other isobutyrophenone oxime isomer,[21] with hydroxyl and phenyl groups *syn*, gave a tertiary hydrogen multiplet at τ 7.15. This difference in chemical shifts of the α-hydrogens between *syn* and *anti* isomers of the oxime, in accord with a recent report on a number of isomeric pairs[22] of oximes and hydrazones, was also found in the isobutyrophenone phenylhydrazone pair with chemical shifts of the tertiary hydrogen multiplet centered at τ 6.95 and 7.23. The fixed spacial orientation and identical chemical shift of the angular hydrogen in the dihydroisoxazole XII and the dihydropyrazole XXXV is not found in the analogous, but less rigid, butyrophenone oxime and phenylhydrazone.

(21) H. M. Kissman and J. Williams, *J. Am. Chem. Soc.*, **72**, 5223 (1950).

Experimental

The enamines used in the following experiments were prepared according to previous procedures.[8,23] The enamine 1-pyrrolidinobutene IX, b.p. 87–90° (65 mm.), 48% yield, was prepared according to the procedure of Opitz.[24]

Anal. Calcd. for $C_8H_{15}N$: C, 76.84; H, 12.08; N, 11.19. Found: C, 76.60; H, 12.01; N, 11.37.

The new enamine, 1,2-diphenyl-1-pyrrolidinoethylene (X), m.p. 42–43°, was prepared by Mr. Charles Bayha of this research group by azeotropic distillation of water from a benzene solution of equimolar amounts of desoxybenzoin and pyrrolidine, and crystallization from petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{18}H_{19}N$: C, 86.68; H, 7.68; N, 5.62. Found: C, 86.90; H, 7.70; N, 5.92.

4,5-Dihydro-4-pyrrolidino-3-phenyl-4,5-tetramethyleneisoxazole (XIII).—A solution of 0.60 g. (3.8 mmoles) of benzhydroxamoyl chloride[25] and 1.8 g. (12.0 mmoles) of 1-pyrrolidinocyclohexene in 30 ml. of dichloromethane was stirred at room temperature for 15 hr., the solvent evaporated, and about 20 ml. of water was added to the residue. Filtration and recrystallization from aqueous ethanol gave 1.0 g. (97% yield) of product, m.p. 103–104°. All other aminodihydroisoxazoles were prepared under the same conditions (see Table I).

3-Phenyl-4,5-tetra- and -pentamethyleneisoxazoles (XXII and XXIII.)—Solutions of 0.50 g. of the aminodihydroisoxazoles XIII and XIV in 5 ml. of methanol and 8 ml. of concentrated hydrochloric acid were boiled for 20 min., cooled, and neutralized with aqueous sodium bicarbonate. Filtration and recrystallization from aqueous ethanol gave 0.33 g. (91% yield) of XXII, m.p. 53–54°, ultraviolet absorption $\lambda_{max}^{cyclohexane}$ 236 mμ (log ε 4.18), and 0.35 g. (91% yield) of XXIII, m.p. 83–84°, ultraviolet absorption $\lambda_{max}^{cyclohexane}$ 229 mμ (log ε 4.09).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.32; H, 6.57; N, 7.03. Found: C, 77.92; H, 6.84; N, 6.36.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.86; H, 7.09; N, 6.57. Found: C, 78.65; H, 7.10; N, 6.76.

The crude oily morpholinodihydroisoxazole XX, from 1.0 g. of benzhydroxamoyl chloride and 2.7 g. of enamine XI gave 0.35 g. (28% over-all yield) of isoxazole XXII.

In comparison, a sample of the isoxazole XXVI,[19] prepared by refluxing equimolar quantities of 2-benzoylcyclohexanone, hydroxylamine hydrochloride, and excess sodium carbonate in aqueous ethanol showed m.p. 66–67°, ultraviolet absorption $\lambda_{max}^{cyclohexane}$ 226 mμ (log ε 4.32).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.32; H, 6.57; N, 7.03. Found: C, 78.60; H, 6.50; N, 7.12.

3-Phenyl-4,5-trimethyleneisoxazole (XXI).—A solution of 0.10 g. of the aminodihydroisoxazole XII in 5 ml. of methyl iodide was evaporated to dryness after 3 days at room temperature. After grinding with 0.30 g. of silver oxide, the mixture was heated to 220° at 0.05 mm. and the sublimed product was recrystallized from aqueous ethanol, m.p. 79–80°, ultraviolet absorption $\lambda_{max}^{cyclohexane}$ 240 mμ (log ε 4.07).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.82; H, 5.98; N, 7.56. Found: C, 77.83; H, 5.86; N, 7.58.

Reactions of Enamines with Diphenylnitrilimine XXVIII. 1,3-Diphenyl-4,5,6,7-tetrahydroisoindazole (XXIX).—To 0.61 g. (0.0027 mole) of N^1-α-chlorobenzylidene-N^2-phenylhydrazine (XXVII)[26] in 20 ml. of dichloromethane, under nitrogen, was added 1.1 ml. (0.0081 mole) of 1-pyrrolidinocyclohexene (IV).

(22) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *ibid.*, **85**, 2326, 2327 (1963).

(23) M. E. Kuehne, *ibid.*, **81**, 5400 (1959).

(24) G. Opitz and H. Mildenberger, *Ann.*, **649**, 26 (1961).

(25) A. Werner and H. Buss, *Ber.*, **27**, 2193 (1894).

(26) H. V. Pechman, *ibid.*, **27**, 320 (1894).

TABLE I

AMINODIHYDROISOXAZOLES

Compound	Empirical formula	M.p., °C.	Yield, %	Calcd., % / Found, % C	H	N
XII	$C_{16}H_{20}N_2O$	83–84	56	74.94	7.86	10.92
				74.64	7.71	10.82
XIII	$C_{17}H_{22}N_2O$	103–104	97	75.51	8.20	10.36
				75.23	8.00	10.23
XIV	$C_{18}H_{24}N_2O$	114–115	74	76.01	8.51	9.85
				75.65	8.78	9.59
XV	$C_{18}H_{24}N_2O$	132–133	64	76.01	8.51	9.85
				75.72	8.37	9.92
XVI	$C_{18}H_{24}N_2O$	163–164	64	76.01	8.51	9.85
				75.68	8.59	9.59
XVII	$C_{17}H_{23}N_3O$	118–119	82	71.54	8.12	14.73
				71.75	8.18	14.48
XVIII	$C_{16}H_{22}N_2O$	60–62	35	74.36	8.58	10.83
				74.12	8.40	10.70
XIX	$C_{25}H_{24}N_2O$	210–212	75	81.48	6.57	7.60
				81.34	6.60	7.44

TABLE II

FORMATION OF AMINODIHYDROPYRAZOLES

Reactant	Product	Empirical formula	M.p., °C.	Yield, %	Ultraviolet spectra,[a] λ, mμ (log ε)	Calcd., % / Found, % C	H	N
IV	XXIX	$C_{19}H_{18}N_2$	130–131	77	276 (4.36)	83.18	6.61	10.21
						83.07	6.71	10.50
VI	XXIX	$C_{19}H_{18}N_2$	130–131	13	276 (4.36)			
XXX	XXIX	$C_{19}H_{18}N_2$	130–131	58	276 (4.36)			
V	XXXIII	$C_{20}H_{20}N_2$	103–104	32	268 (4.22)	83.29	6.99	9.71
						82.97	7.00	9.71
XXXI	XXXII	$C_{26}H_{21}N_2O_2$	161–162	74	277 (4.50)	79.38	5.38	7.12
						79.18	5.74	7.11
X	XXXIV	$C_{27}H_{20}N_2$	217–218	21	238 (4.42) sh		[b]	
					273 (4.26) sh			

[a] In cyclohexane. [b] Identical mixture melting point and infrared spectra with authentic sample.

After 18 hr. at room temperature the solvent was evaporated under vacuum, the residue was washed with water and triturated with methanol, and the 0.56 g. (77% yield) of crystalline product was filtered, m.p. 130–131° after recrystallization from ethanol. Other enamines reacted with diphenylnitrilimine under the same conditions to give the compounds listed in Table II. Reactions of 1-pyrrolidinocyclohexene with diphenylnitrilimine, generated in different solvents, are listed in Table III. In these reactions equivalent amounts of enamine IV, chlorobenzylidene compound XXVII, and triethylamine were used.

TABLE III

FORMATION OF 1,3-DIPHENYL-4,5,6,7-TETRAHYDROISOINDAZOLE

Solvent system	Yield, %
Cyclohexane, room temp.	37
Dioxane, room temp.	27
Dimethylformamide, room temp.	37
Methylene chloride, room temp.	39
Benzene, reflux	4
Tetrahydrofuran, reflux	0

4,5-Dihydro-1,3-Diphenyl-5-pyrrolidyl-4,5-trimethylenepyrazole (XXXV) and 1,3-Diphenyl-4,5-trimethylenepyrazole (XXXVI).—Under the standard conditions above (Table II) 0.80 g. (0.0035 mole) of N^1-α-chlorobenzylidene-N^2-phenylhydrazine and 1.50 ml. (0.010 mole) of 1-pyrrolidinocyclopentene gave 0.92 g. (80% yield) of the aminodihydropyrazole XXXV, m.p. 99–100°, ultraviolet absorption $\lambda_{max}^{cyclohexane}$ 251 mμ (log ε 4.45), 299 (4.02). With equivalent amounts of enamine, chloro compound, and triethylamine, a 71% yield was obtained.

Anal. Calcd. for $C_{22}H_{25}N_3$: C, 79.71; H, 7.60; N, 12.68. Found: C, 79.42; H, 7.71; N, 12.76.

Refluxing a solution of 0.050 g. (0.00015 mole) of the aminodihydropyrazole XXXV in 5 ml. of ethanol and 10 ml. of 10% hydrochloric acid for 1 hr., cooling, and filtration gave 0.025 g. (64% yield) of the pyrazole XXXVI, m.p. 167–168° after recrystallization from ethanol, ultraviolet absorption $\lambda_{max}^{cyclohexane}$ 287 mμ (log ε 4.32).

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19; N, 10.76. Found: C, 82.80; H, 6.03; N, 10.48.

1,3-Diphenylisoindazole (XXXVII).—A mixture 50 mg. (0.18 mmole) of 1,3-diphenyl-4,5,6,7-tetrahydroisoindazole and 100 mg. of 10% palladium on charcoal was heated at 260–265° for 2 hr. Addition of dichloromethane to the cooled material, filtration, evaporation, and recrystallization from ethanol gave 35 mg. (71% yield), m.p. 101–102°, lit.[27] m.p. 100–101°.

Isobutyrophenone Phenylhydrazones.—A combination of equivalent amounts of phenylhydrazine and isobutyrophenone was treated after 24 hr. at 20° with petroleum ether. The mixture of phenylhydrazones, obtained in almost quantitative yield, was filtered and recrystallized from ligroin to m.p. 55–57°, lit.[28] m.p. 73°. The material was quite unstable. When left at room temperature, exposed to air, it quickly turned brown and after some hours to a black oil. A fresh solution in deuteriochloroform showed n.m.r. multiplets centered at τ 6.95 and 7.23 corresponding to the tertiary hydrogen of the isomeric phenylhydrazones. The methyl doublets of the isomeric phenylhydrazones were found at τ 8.78 and 8.86, respectively. After 24 hr. a solution of the phenylhydrazone mixture in carbon tetrachloride showed only the chemical shifts of one phenylhydrazone isomer at τ 6.95 and 8.78. All n.m.r. spectra were obtained with a Varian A-60 instrument.

(27) W. Borsch and W. Scriba, *Ann.*, **540**, 83 (1939).
(28) A. Klages, *Ber.*, **36**, 3688 (1903).

Acknowledgment.—These studies were generously supported by the National Science Foundation with Grant No. GP-225. Nuclear magnetic resonance spectra were kindly provided by Mr. L. Dorfman and associates, Ciba Pharmaceutical Company, Summit, New Jersey.

Photoisomerizations of 3,3′-Dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene

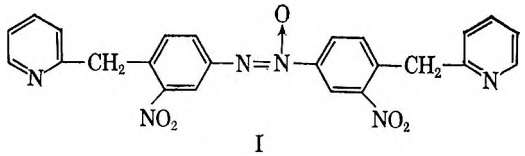
JULIUS WEINSTEIN, JOHN A. SOUSA, AND AARON L. BLUHM

Pioneering Research Division, U. S. Army Natick Laboratories, Natick, Massachusetts

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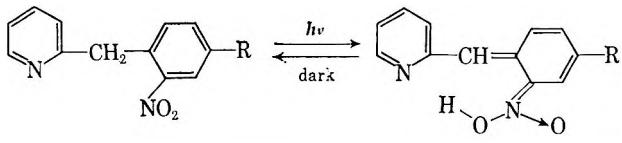
It is reported that, on irradiation with ultraviolet light, 3,3′-dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene (I) undergoes simultaneously *aci*-nitro–nitro tautomerization and geometrical isomerization. Kinetic data at several temperatures are reported for the dark reverse reactions. The thermodynamic properties of the dark reactions are also given.

In a previous paper,[1] the preparation of 3,3′-dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene (I) was reported. It was observed that, when cooled crystals are exposed to ultraviolet light, a photochromic change



I

from yellow to blue-green occurs. In room light the crystals fade to their original color. A reversible photochromism of cooled ethanol solutions of the compound was also noted. This behavior is similar to that observed for other *o*-nitrobenzylpyridines[1,2-6] and related compounds.[4,6-8] It is believed that the color change is due to the formation of the *aci*-nitro tautomer.[3-5,7]



In addition to the above structural change, I, on ultraviolet irradiation, might also undergo geometrical isomerization around the –N=N– bond. It was considered of interest to determine whether both photoisomerizations could be detected and isolated by spectrophotometric techniques, and, if so, to determine the kinetic and thermodynamic properties of the dark reactions.

Results and Discussion

Spectroscopic Studies.—The ultraviolet and visible spectra of an ethanol solution of I before and after exposure to ultraviolet light are shown in Fig. 1. The absorption band at 610 mμ, observed on irradiation of the cooled solution, is similar in shape to the visible band reported[3,4] for the photoisomer of 2-(2,4-dinitrobenzyl)pyridine. This band decays rapidly when the exciting radiation is removed.

In the ultraviolet spectrum of the unirradiated sample, absorption bands are observed at 330 and 260 mμ. The effect of ultraviolet light on these bands can be observed at room temperature. The band at 330 mμ decreases markedly in intensity, while the absorbance at 260 mμ increases slightly. After irradiation the spectrum slowly reverts to that originally observed. The ultraviolet spectra before and after exposure closely resemble those reported[9] for the pure *trans* and *cis* isomers, respectively, of azoxybenzene and several of its derivatives. This geometrical photoisomerization also occurs at low temperatures.

The ultraviolet spectra of unirradiated ethanol and cyclohexane solutions of I were not temperature dependent. In these solutions the compound exists essentially in the *trans* configuration. Evidence for an equilibrium mixture of *cis* and *trans* forms was observed in the spectrum of an unirradiated ethanol solution of azoxybenzene. Exposure to ultraviolet light enriched the solution with respect to the *cis* isomer. The original equilibrium was restored when irradiation was discontinued.

Kinetics.—First-order kinetics was observed for the fading reaction of the photoisomer of I absorbing at 610 mμ. Although many aromatic azoxy compounds undergo a molecular rearrangement to *o*-hydroxyazo compounds on prolonged irradiation with ultraviolet light,[10,11] and 2-(2,4-dinitrobenzyl)pyridine decomposes on extended exposure,[3,4] no detectable irreversible change occurred during the short exposure times utilized in the rate measurements reported in this study. For example, the same value for the first-order rate constant was obtained after each of several exposures of an ethanol solution to radiation in the flash photolysis experiments at room temperature.

The correlation of log k values with $1/T$, shown in Fig. 2, appears to be linear over a temperature range of 132°. The values of the Arrhenius activation energy, entropy of activation, and frequency factor were found to be 5.9 ± 0.1 kcal./mole, −39 e.u., and 4.2×10^4 sec.$^{-1}$, respectively. These values are consistent with those previously found for the thermal fading reaction

(1) A. L. Bluhm, J. Weinstein, and J. A. Sousa, *J. Org. Chem.*, **28**, 1989 (1963).
(2) A. E. Tschitchibabin, B. M. Kuindshsi, and S. W. Benewolenskaja, *Ber.*, **58**, 1580 (1925).
(3) R. Hardwick, H. S. Mosher, and P. Passailaigue, *Trans. Faraday Soc.*, **56**, 44 (1960).
(4) J. A. Sousa and J. Weinstein, *J. Org. Chem.*, **27**, 3155 (1962).
(5) H. S. Mosher, C. Souers, and R. Hardwick, *J. Chem. Phys.*, **32**, 1888 (1960).
(6) A. L. Bluhm, J. A. Sousa, and J. Weinstein, *J. Org. Chem.*, **29**, 636 (1964).
(7) G. Wettermark, *Nature*, **194**, 677 (1962).
(8) J. D. Margerum, *et al.*, *J. Phys. Chem.*, **66**, 2434 (1962).
(9) E. Müller and E. Hory, *Z. physik. Chem.*, **A162**, 281 (1932).
(10) W. M. Cumming and G. S. Ferrier, *J. Chem. Soc.*, 2374 (1925).
(11) G. M. Badger and R. G. Buttery, *ibid.*, 2243 (1954).

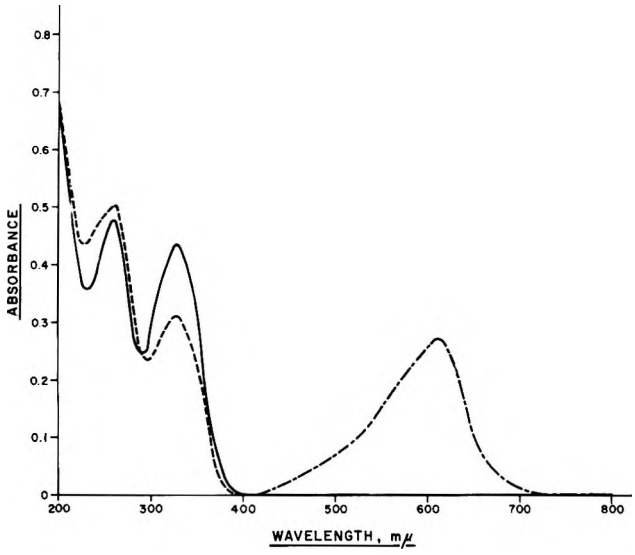


Fig. 1.—Absorption spectra of an ethanol solution of 3,3′-dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene: ———, ultraviolet and visible spectra before irradiation; – – – –, ultraviolet spectrum after irradiation for 3 min. at 25.0°; –·–·–, and visible spectrum after irradiation for 1 min. at −90.0°.

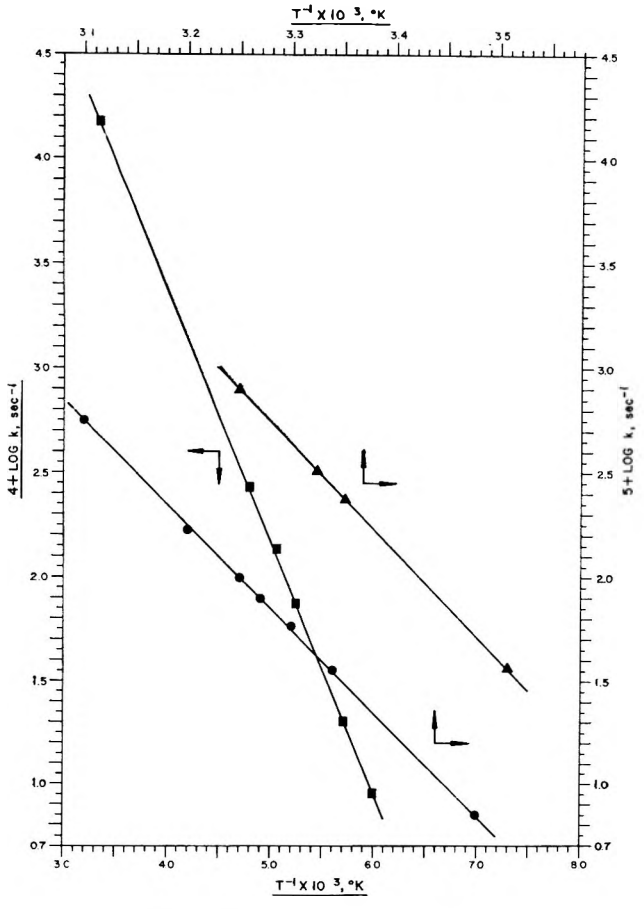


Fig. 2.—Plots of log k values *vs.* $1/T$ for 3,3′-dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene: □, *aci*-nitro–nitro tautomerization in ethanol (room temperature value is from flash photolysis experiments); O, *cis–trans* isomerization in ethanol; and Δ, in cyclohexane.

of the photoisomers of 2-(2,4-dinitrobenzyl)pyridine[4] and other *o*-nitrobenzyl compounds.[6]

The thermal *cis–trans* isomerization of I in ethanol and cyclohexane follows first-order kinetics. Log k values are given in Fig. 2 and thermodynamic data are presented in Table I.

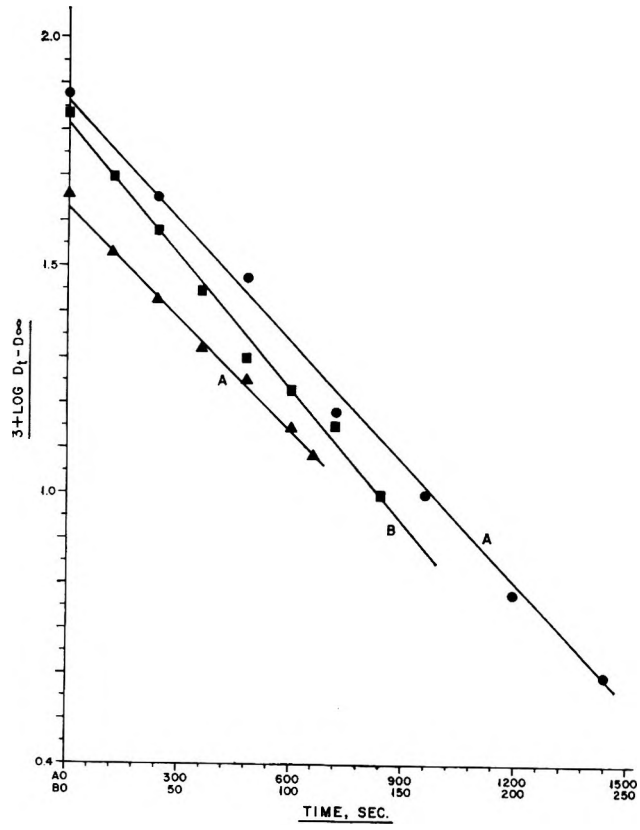


Fig. 3.—The dark reactions of 3,3′-dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene: □, *aci*-nitro–nitro tautomerization in ethanol at −75.5°; O, *cis–trans* isomerization in ethanol at 39.1°; and Δ, in cyclohexane at 27.6°.

TABLE I

THERMODYNAMIC PROPERTIES OF THE *cis–trans* ISOMERIZATION OF 3,3′-DINITRO-4,4′-DI(2-PYRIDYLMETHYL)AZOXYBENZENE

Solvent	E_{exp}, kcal./mole	ΔS^*, e.u.	A, sec.$^{-1}$
Ethanol	23.1 ± 0.1	0.79	2.6×10^{13}
Cyclohexane	23.6 ± 0.1	6.7	4.9×10^{14}

The values of E_{exp} agree closely with those found by Luner and Winkler[12] for the isomerization of pure *cis*-azoxybenzene and *cis-p,p′*-azoxytoluene in the same solvents. For azoxybenzene in ethanol, the energy of activation was found to be 22.9 kcal./mole, the same value as that reported by the above workers.

The rate of isomerization of I in cyclohexane is almost ten times as fast as in ethanol. At 34.5°, for example, the values of k in cyclohexane and ethanol were found to be 8.04×10^{-3} and 9.83×10^{-4} sec.$^{-1}$, respectively. This rate change arises from the almost tenfold difference in entropies of activation. The smaller value of ΔS^* observed for ethanol solutions probably signifies that, due to solvation, there is in this solvent more restriction to rotation about the nitrogen–nitrogen single bond in the activated state.

Experimental

Materials.—3,3′-Dinitro-4,4′-di(2-pyridylmethyl)azoxybenzene[1,13] was purified by recrystallization from 2:1 ethanol–water,

(12) P. Luner and C. A. Winkler, *Can. J. Chem.*, **30**, 679 (1952).

(13) The n.m.r. spectrum, measured in deuteriochloroform, was consistent with the assigned structure.

and melted at 135–136°. Azoxybenzene (Eimer and Amend) was recrystallized from methanol and melted at 36°, lit.[14] m.p. 36°. Spectro Grade cyclohexane and absolute alcohol were used as solvents in the kinetic measurements.

aci-Nitro–Nitro Tautomerism.—Rate studies at low temperatures in the range −106.4 to −64.8° were carried out in a 2.5-cm. cell maintained at the required temperature in a specially constructed cryostat.[15] Ethanol solutions (10^{-3} *M*) cooled in the cryostat were exposed for 30 sec. to the unfiltered radiation from a General Electric H3FE 85-watt mercury lamp with a Pyrex glass envelope. Uniform coloring of the solutions was observed. The cryostat was quickly transferred to the sample cell compartment of a Cary Model 14 spectrophotometer, and the decrease in absorbance of the visible absorption band at 610 mμ was followed with respect to time. A matched cell containing pure solvent was in the reference beam.[15] In all cases, the absorbance of the system ultimately fell to zero. In order to obtain all the kinetic data reported in this paper, at least three runs were made at each temperature.

Room temperature measurements were carried out by flash photolysis techniques previously described.[4]

Geometrical Isomerization.—Rate measurements in the temperature range 11 to 50° were carried out in a 2.5-cm. cell on solutions ($\sim 10^{-5}$ *M*) in ethanol and cyclohexane. Required temperatures were maintained by circulating water from a Haake temperature-regulating bath through a thermostatable cell jacket.[16] Solutions were exposed for 30 sec. to the radiation from the lamp described above, and the cell was quickly transferred to the sample compartment of the spectrophotometer. For both compound I and azoxybenzene, the increase in absorbance of the ultraviolet absorption band at 330 mμ was followed with respect to time. A matched cell containing pure solvent was in the reference beam. In all cases, the absorbance at 330 mμ ultimately returned to its value before irradiation.

Temperature Measurement.—Measurements of temperatures were made by a glass encased copper-constantan thermocouple which dipped into the solutions at the cell neck.

Calculations.—Values of the first-order specific rate constant, k, were calculated from the slope of the straight line obtained in plots of $\log D_t - D_\infty$ *vs.* time, where D_t is the optical density at a given time interval and D_∞ is the optical density after complete isomerization. In the case of the *aci*-nitro–nitro isomerization, D_∞ was equal to zero. The reactions were followed for at least three half-lives. Illustrative plots are given in Fig. 3. The Arrhenius activation energy, E_{exp}, the entropy of activation, ΔS^*, and the frequency factor, A, were calculated by procedures given previously.[4,6]

Ultraviolet and Visible Absorption Measurements.—A Cary Model 14 spectrophotometer was used. Solutions were measured in a 2.5-cm. cell against a reference of pure solvent in a matched cell.

Acknowledgment.—We wish to thank Dr. G. Wettermark for the flash photolysis experiments.

(14) G. M. Badger, R. G. Buttery, and G. E. Lewis, *J. Chem. Soc.*, 2143 (1953).

(15) J. A. Sousa and J. Weinstein, *Rev. Sci. Instr.*, **34**, 150 (1963).

(16) W. R. Brode, J. H. Gould, and G. M. Wyman, *J. Am. Chem. Soc.*, **75**, 1856 (1953).

Thermal Reactions of Trifluoroiodomethane with Halobenzenes

EARL S. HUYSER AND ERNEST BEDARD[1]

Department of Chemistry, University of Kansas, Lawrence, Kansas

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Trifluoroiodomethane reacts with chloro-, bromo-, and iodobenzene at 198° yielding the *o*-, *m*-, and *p*-halobenzotrifluorides, fluoroform, and molecular iodine. A mechanism involving addition of trifluoroiodomethane to the aromatic ring in a free-radical chain reaction followed by elimination of hydrogen iodide which reacts with trifluoroiodomethane to form fluoroform and iodine is proposed for these reactions.

Previous work by others has shown that trifluoromethyl radicals add readily to various aromatic systems. The gas phase reactions of benzene with trifluoromethyl radicals produced by the photolysis of hexafluoroacetone are reported to yield fluoroform, benzotrifluoride, and polymeric oils.[2] The formation of fluoroform and benzotrifluoride was observed to occur at low benzene pressures (less than 10 mm.), but no fluoroform was noted at higher benzene pressures (greater than 40 mm.). The following mechanism which is consistent with these observations is proposed (eq. 1–5).

$$CF_3COCF_3 \xrightarrow{h\nu} 2\cdot CF_3 + CO \quad (1)$$

$$\cdot CF_3 + \bigcirc \rightarrow \text{A}\cdot \quad (2)$$

$$\text{A}\cdot + \cdot CF_3 \rightarrow HCF_3 + \bigcirc\!-\!CF_3 \quad (3)$$

$$\text{A}\cdot + \bigcirc \rightarrow \text{B}\cdot \quad (4)$$

$$\text{B}\cdot + \bigcirc \rightarrow \text{trimeric radical} \quad (5)$$

The cyclohexadienyl radical A· apparently is formed readily as shown in reaction 2, and at higher benzene pressures essentially all of the trifluoromethyl radicals formed by the photolysis react with benzene in this manner. Apparently, only at lower pressures is the concentration of trifluoromethyl radicals great enough for reaction 3, which produces the fluoroform, to occur. Szwarc and his co-workers point out that, in the liquid phase, where the concentration of the aromatic compound is about 3000 times that at 40-mm. pressure, no fluoroform would be expected from a reaction of an adduct radical such as A· with trifluoromethyl radicals.[3] This assumption formed the basis of the method used by Szwarc and his co-workers for determining the relative reactivities of various unsaturates and aromatics toward reaction with trifluoro-

(1) Taken from the thesis submitted by E. Bedard in partial fulfillment of the requirements for the M.S. degree from the University of Kansas, 1963.

(2) S. W. Charles and E. Whittle, *Trans. Faraday Soc.*, **56**, 794 (1960); S. W. Charles, J. T. Pearson, and E. Whittle, *ibid.*, **57**, 1356 (1961); J. L. Holmes and K. O. Kutsche, *ibid.*, **58**, 333 (1962).

(3) I. M. Whittemore, A. P. Stefani, and M. Szwarc, *J. Am. Chem. Soc.*, **84**, 3799 (1962).

TABLE I

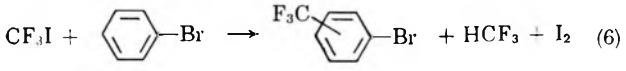
REACTIONS OF TRIFLUOROIODOMETHANE WITH HALOBENZENES AT 198°

Halobenzene (mmoles)	CF_3I, mmoles	Halobenzotrifluoride, mmole[a]			Isomer ratio	Yield, %[b]
		ortho	*meta*	*para*	*ortho–meta–para*	
Bromobenzene (94.4)	11.4	1.21	0.65	0.78	1.86:1.00:1.20	23
Bromobenzene (94.4)	10.7	1.31	0.63	0.82	2.1:1.00:1.30	26
Chlorobenzene (97.8)	3.84	0.96	0.44	0.53	2.17:1.00:1.20	50
Iodobenzene (88.1)	7.55	1.55	1.34	1.38	1.16:1.00:1.02	56

[a] Determined by infrared spectrometric analysis of the reaction mixtures. Experimental certainty of the values shown is of the order of about ±5% for each isomer. [b] Based on trifluoroiodomethane originally present.

methyl radicals generated in the liquid phase by the photolysis of hexafluoroazomethane.[3,4] Somewhat earlier, Haszeldine and Emeleus reported that a photochemical reaction occurred between benzene and trifluoroiodomethane, presumably in the liquid phase, in which fluoroform was a reaction product.[5] Dimeric and polymeric products were reported to be formed in these reactions as well.

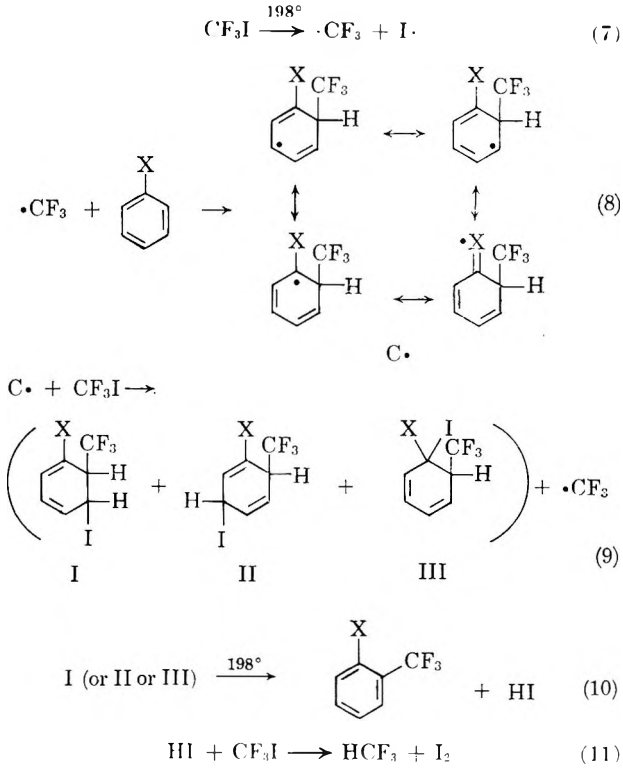
The present study is concerned with the reaction of the halobenzenes with trifluoroiodomethane. Attempts to induce a reaction between trifluoroiodomethane and bromobenzene at 40° by the use of light failed to yield any reaction products involving the aromatic halide (see Experimental). Similarly, benzoyl peroxide failed to induce any reaction between trifluoroiodomethane and bromobenzene. However, at 198°, a reaction between trifluoroiodomethane and bromobenzene did occur which produced a mixture of the *o*-, *m*-, and *p*-bromobenzotrifluorides, and molecular iodine and fluoroform. The halobenzotrifluorides were identified both by gas chromatography and in-



frared analysis of the reaction mixtures. Similar reactions occurred with chlorobenzene and iodobenzene. The quantitative determinations of the relative amounts of the isomeric halobenzotrifluorides formed in the thermal reactions of trifluoroiodomethane with bromo-, chloro- and iodobenzene shown in Table I were accomplished by infrared analysis.

Fluoroform was identified as a reaction product by infrared analysis of the gaseous materials remaining at the end of the reactions. Although unchanged trifluoroiodomethane could be detected in the gaseous products, no hexafluoroethane was found. Distillation of the reaction mixtures left no higher boiling residues indicating the absence of polymeric material, and gas chromatographic analysis indicated the absence of any benzotrifluoride in the reaction mixtures.

Any mechanism that might be suggested for these thermal reactions of trifluoroiodomethane with the halobenzenes in the liquid phase must account for the fact that no polymeric materials are formed and that fluoroform, a product not expected in a liquid phase reaction, is produced. The following mechanism (shown for formation of the *ortho* isomer) involving the thermally induced free-radical addition of trifluoroiodomethane to the aromatic compound satisfactorily accounts for these observations.



The thermal decomposition of trifluoroiodomethane at elevated temperatures is evident from the observation that radical chain reactions involving this material can be induced thermally.[6] Reactions 8 and 9 comprise a radical chain sequence involving addition of trifluoroiodomethane to the halobenzene. The high reactivity of the trifluoroiodomethane toward radical attack could account for the fact that the cyclohexadienyl radical C· reacts exclusively with this reagent producing the addition product (or possibly products) rather than with another molecule of the aromatic compound leading to polymeric materials as in the case with the other sources of the trifluoromethyl radical cited previously. The loss of hydrogen iodide from the addition product (or products) as shown in eq. 10 at these elevated temperatures producing the aromatic nucleus and hydrogen iodide is not unexpected. If the addition product III is produced in the case of chloro- and bromobenzene, the elimination of hydrogen iodide is still more probable than the elimination of either of the other hydrogen halides. The reaction of the hydrogen iodide with trifluoroiodomethane then could produce the observed molecular iodine and fluoroform. This is not an unexpected

(4) A. P. Stefani and M. Szwarc, *J. Am. Chem. Soc.*, **84**, 3661 (1962); A. P. Stefani, L. Herk, and M. Szwarc, *ibid.*, **83**, 4732 (1961).

(5) T. N. Haszeldine and H. J. Emeleus, *Research* (London), **1**, 715 (1948).

(6) R. N. Haszeldine, *J. Chem. Soc.*, 2856 (1949); 3037 (1950); 3761 (1953); J. Banus, H. J. Emeleus, and R. N. Haszeldine, *ibid.*, 3011 (1950); T. N. Bell, *ibid.*, 4973 (1961).

$$\overset{\delta-}{F_3C}—\overset{\delta+}{I}$$

reaction[7] in view of the positive character of the iodine in the highly polarizable trifluoroiodomethane.[8]

The orientation of the entering trifluoromethyl group is consistent with a mechanism involving the formation of a cyclohexadienyl-adduct radical in the same manner proposed for other free-radical aromatic substitution reactions.[9] Resonance contributions from the aromatically bonded halogen atom become important if the entering radical bonds at the positions *ortho* and *para* to the halogen atom. The reason more of the *ortho* isomer than the *para* isomer is formed is probably the statistical factor, namely that there are two *ortho* positions and only one *para* position. The apparent decrease in the reactivity of the *ortho* position in the case of iodobenzene may possibly be due to steric effects. Phenylation studies of the halobenzenes by Hey and his co-workers show a similar, although not so marked, decrease in the relative amount to the *ortho* isomer in the iodobenzene reactions compared to that of the other halobenzenes.[10]

Experimental

Materials.—The halobenzenes were obtained from Matheson Coleman and Bell and were redistilled before using. Trifluoroiodomethane (Research Chemicals Co.) was used without further purification. Authentic samples of the *o*-, *m*-, and *p*-bromo-, chloro-, and iodobenzotrifluorides used as standards for the infrared and gas chromatographic analyses were obtained from Pierce Chemical Co.

Attempted Photoinduced Reaction of Trifluoroiodomethane with Bromobenzene.—A reaction mixture consisting of 14.95 g. (0.095 mole) of bromobenzene and 4.45 g. (0.023 mole) of trifluoroiodomethane was illuminated in a sealed Pyrex tube at 40° for 2.5 hr. with a 275-watt sunlamp. The formation of molecular iodine was noted immediately. The gaseous materials were allowed to escape from the reaction mixture, the iodine was removed with a 10% sodium hydroxide solution, and the remaining material was distilled. Essentially all of the material distilled at 153° and proved to be unreacted bromobenzene. A qualitative test for fluoride ion in the sodium fusion mixture of the distillate performed by addition of cerous nitrate in acetic acid to the fusion mixture previously neutralized with acetic acid was negative.[11]

Attempted Benzoyl Peroxide-Induced Reactions of Bromobenzene with Trifluoroiodomethane.—A mixture of bromobenzene (18.7 g., 0.12 mole), trifluoroiodomethane (4.45 g., 0.011 mole), and benzoyl peroxide (0.10 g., 0.0004 mole) was heated in a sealed Pyrex tube at 80° for 19 hr. The reaction mixture was distilled and yielded a single fraction (17.9 g., b.p. 152–154°) which gave a negative test for fluorine.

Reaction of the Halobenzenes with Trifluoroiodomethane.—The halobenzenes and trifluoroiodomethane in the amounts shown in Table I were sealed in Pyrex tubes. The tubes were heated for a period of 72 hr. in a refluxing ethylene glycol vapor bath (198–200°). At the end of this period the reaction mixture assumed a deep purple color due to the free iodine produced. After cooling, the tubes were opened and any unchanged CF_3I and the fluoroform produced were allowed to escape (see below for identification of fluoroform). A weighed aliquot of the reaction mixture was diluted with carbon disulfide for infrared analysis. Infrared absorptions in the region 1400–1000 cm.$^{-1}$, absorptions not present in the parent halobenzene, were present and due to carbon–fluorine stretching.[12] Absorptions at 760.5, 790.5, and 833 cm.$^{-1}$ were assigned to the *ortho*, *meta*, and *para* halo-substituted benzotrifluorides, respectively. Quantitative determination of the isomers was made by comparison of the absorbance at these frequencies with those of several standard mixtures composed of authentic materials.

Gas chromatographic analysis of the bromobenzene reaction mixtures on a 16 ft. × 1/8 in. column packed with 10% dimenthyl sebacate (column temperature, 150°) showed four distinct peaks. These peaks corresponded exactly in retention time to the peaks of authentic samples of bromobenzene and the *o*-, *m*-, and *p*-bromotrifluorides. No peak corresponding in retention time with that of an authentic sample of benzotrifluoride was observed. Gas chromatographic analyses of the chlorobenzene reaction mixture gave only one broad peak on this column. No attempt was made to chromatograph the iodobenzene reaction mixture.

Attempts to separate the reaction mixture into its components by distillation were unsuccessful, largely because of the similarity of the boiling points of both the products and the starting material and to the small amounts of material involved.

Identification of Fluoroform.—The gaseous products from a reaction of chlorobenzene with trifluoroiodomethane at 198° were obtained by opening the tube after solidifying the reaction mixture in a liquid nitrogen bath and fitting the opened tube with a gas delivery tube leading to an evacuated trap immersed in liquid nitrogen. The contents of the reaction mixture tube were warmed to room temperature and the evolved gases were condensed in the liquid nitrogen trap. These gases were allowed to vaporize into an evacuated, 10-cm. infrared gas cell. The infrared spectrum of the gas showed absorptions at 3031, 1372, 1150, and 700 cm.$^{-1}$, the reported fundamental frequencies for fluoroform.[13] Absorption at 1183, 1076, and 746 cm.$^{-1}$, the fundamental frequencies reported for trifluoroiodomethane,[14] were also present. No absorptions at 1250, 1117, and 714 cm.$^{-1}$, fundamental frequencies reported for hexafluoroethane,[15] were observed.

(7) Preliminary studies indicate that hydrogen iodide and trifluoroiodomethane react at room temperature to yield molecular iodine. No attempt was made to detect fluoroform. Hydrogen bromide and bromotrichloromethane, however, do react to produce molecular bromine and chloroform.

$$CCl_3Br + HBr \longrightarrow HCCl_3 + Br_2$$

(8) J. Banus, H. J. Emeleus, and R. N. Haszeldine, *J. Chem. Soc.*, 60 (1951).

(9) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 482–485.

(10) D. H. Hey and G. W. Williams, *Discussions Faraday Soc.*, **14**, 216 (1953).

(11) In a positive test for fluoride ion, cerous fluoride, a white precipitate which is insoluble in acetic acid, is formed [J. H. Simons and E. O. Ramler, *J. Am. Chem. Soc.*, **65**, 389 (1943)]. A positive test was obtained in the case of the thermal reactions of the halobenzenes with trifluoroiodomethane.

(12) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 70.

(13) H. D. Rix, *J. Chem. Phys.*, **21**, 1077 (1953); E. K. Phyler and W. S. Benedict, *J. Res. Natl. Bur. Std.*, **47**, 202 (1951).

(14) S. R. Polo and M. K. Wilson, *J. Chem. Phys.*, **20**, 1183 (1952); P. R. McGee, F. F. Cleveland, A. G. Meister, C. E. Decher, and S. I. Miller, *ibid.*, **21**, 242 (1953).

(15) J. R. Neilson, C. M. Richards, and H. L. McMurry, *ibid.*, **16**, 67 (1948); D. G. Williams, W. B. Person, and B. Crawford, Jr., *ibid.*, **23**, 179 (1955).

The Addition of Fluorine to Halogenated Olefins[1]

EUGENE R. BISSELL AND DOUGLAS B. FIELDS

Lawrence Radiation Laboratory, University of California, Livermore, California

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The use of a mixture of lead dioxide and sulfur tetrafluoride as a reagent for the selective addition of fluorine to the double bond of halogenated olefins has been studied. This reagent generally affords higher yields under somewhat milder conditions than have been reported previously. Iodine-containing olefins have been fluorinated for the first time. Four new halocarbons, namely 1,1-dichloro-1,2-difluoroethane, *dl*-1,2-dichloro-1,2-difluoroethane, *meso*-1,2-dichloro-1,2-difluoroethane, and 1-bromo-1,2-difluoroethane, have been synthesized and characterized.

The selective addition of fluorine to the double bond of a halogen-containing olefin was first reported by Henne and Waalkes[2] in 1945. They employed lead tetrafluoride general *in situ* from lead dioxide and hydrogen fluoride. Seven examples were cited with yields ranging from 17–59%. Antimony pentafluoride,[3] cobalt trifluoride generated *in situ* from cobaltic oxide and hydrogen fluoride,[4] preformed cobaltic fluoride,[5-8] mercuric fluoride generated *in situ* from mercuric oxide and hydrogen fluoride,[9] chlorine trifluoride,[10] preformed manganese trifluoride,[6,8] preformed silver difluoride,[8] and preformed ceric fluoride[8] all have been used for fluorination of double bonds. In general these methods have not found widespread synthetic application even though the yields in some cases were quite good. The procedures involving the *in situ* formation of lead tetrafluoride, cobalt trifluoride, or mercuric fluoride from the oxides and hydrogen fluoride require handling of large excesses of hydrogen fluoride if satisfactory yields are to be obtained; those employing preformed metal fluorides usually involve elemental fluorine or chlorine trifluoride which require special handling techniques. The olefins studied include a variety of two-, three-, and four-carbon olefins substituted by various combinations of fluorine, chlorine, and bromine, but perfluoro olefins and those containing iodine have not been investigated. The reaction conditions usually employed would be expected to result in extensive replacement of iodine.

The recently reported preparation of metal fluorides by the reaction of the corresponding oxides with sulfur tetrafluoride[11] suggested the possibility of employing this reagent for the *in situ* preparation of the metal fluoride used in the fluorination of double bonds. The anticipated advantage lay in the fact that water would not be one of the products, thus eliminating the need for a large excess of the fluorinating agent to drive the formation of the metal fluoride to completion. The results obtained on treating nineteen halogenated olefins, including four perfluoro olefins and two containing iodine, with a mixture of lead dioxide and sulfur tetrafluoride are summarized in Table I. In most cases the yields were significantly higher than those from any of the previously reported methods. The advantage of the sulfur tetrafluoride method particularly was pronounced in the case of reactive olefins and those containing iodine. Since the examples cited in Table I were all run under the same reaction conditions, the yield and conversion data provide an estimation of the relative reactivity of the various olefins.

No effort was made to maximize the yield from each olefin, but the reaction was studied in some detail with trichloroethylene. Optimum reaction temperature ranged from about 40–100° with reaction times of 2–8 hr. Increasing the reaction temperature above about 120° resulted in extensive side reactions including replacement of chlorine and carbon–carbon bond scission. The optimum ratio of lead dioxide to trichlorethylene was about 1:1.5. The particle size of the lead dioxide had a slight but measurable effect on yield, the optimum being about 40–60 mesh. Lead tetrafluoride is presumably an intermediate in the fluorination process; however, if the olefin was added to preformed lead tetrafluoride under conditions which afforded a maximum yield in the one-step process, the yields and conversions were very low. The optimum ratio of sulfur tetrafluoride to trichloroethylene was about 5:1. The function of excess sulfur tetrafluoride is most likely that of a solvent in which the olefin double bond can be easily polarized.

Fluorination of either *cis*- or *trans*-1,2-dichloroethylene yielded both *dl*- and *meso*-1,2-dichloro-1,2-difluoroethane, although in slightly different ratios. It was shown in separate experiments that the olefins were thermally stable and were not isomerized, at the reaction temperature employed, by either lead dioxide or by sulfur tetrafluoride alone. It would appear, therefore, that the two fluorines being added cannot add simultaneously, and that a cyclic intermediate cannot be involved.

The possibility that the reaction proceeds *via* addition of sulfur tetrafluoride to the double bond is not thought to be likely. The haloalkyl sulfur trifluorides that would be formed by such an addition appear to be stable at temperatures considerably above those employed here.[12] For example, heptafluoropropyl sulfur trifluoride has been prepared[12] by addition of sulfur tetrafluoride to hexafluoropropene in the presence of cesium fluoride at 150°, whereas we found that sulfur tetrafluoride and hexafluoropropene in the presence of lead dioxide at 100° gave octafluoropropane in 63%

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) A. L. Henne and T. P. Waalkes, *J. Am. Chem. Soc.*, **67**, 1639 (1945).

(3) A. L. Henne and W. J. Zimmerschied, *ibid.*, **67**, 1235 (1945).

(4) A. F. Benning and J. D. Park, U. S. Patent 2,437,993 (March 16, 1948).

(5) C. I. Gochenour, U. S. Patent 2,554,857 (May 29, 1951).

(6) G. Fuller, M. Stacey, J. C. Tatlow, and C. R. Thomas, *Tetrahedron*, **18**, 123 (1962).

(7) A. L. Dittman and J. M. Wrightson, U. S. Patent 2,690,459 (Sept. 28, 1954).

(8) D. A. Rausch, R. A. Davis, and D. W. Osborne, *J. Org. Chem.*, **28**, 494 (1963).

(9) A. L. Henne and K. A. Latif, *J. Am. Chem. Soc.*, **76**, 610 (1954).

(10) J. Muray, British Patent 878,585 (Oct. 4, 1961).

(11) A. L. Oppegard, W. C. Smith, E. L. Muetterties, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 3835 (1960).

(12) R. M. Rosenberg and E. I. Muetterties, *Inorg. Chem.*, **1**, 756 (1962).

TABLE I

LEAD DIOXIDE–SULFUR TETRAFLUORIDE FLUORINATION OF HALOGENATED OLEFINS

Olefin	Product(s)	% yield	% conversion	Chromatography: Column[a]	Chromatography: Temp., °C.
$CF_2=CF_2$	C_2F_6	2.1	2.0	A	100
	C_3F_8	5.8	5.6		
	C_4F_{10}[b]	6.7	6.4		
$CF_3CF=CF_2$	C_3F_8	63.0	42.4	A	100
$CF_3CF=CFCF_3$	C_4F_{10}		<1	A	100
cyclo-C_4F_6	cyclo-C_4F_8	23.0	3.2	A	100
$CF_2=CFCl$	CF_3CF_2Cl	60.0	60.1	A	100
$CF_2=CFBr$	CF_3CF_2Br	57.1	45.1	B	20
$CF_2=CFI$	CF_3CF_2I	65.2	62.7	B	20
$CF_2=CCl_2$	CF_3CFCl_2	87.8	74.1	B	20
$CF_2CF_2CF_2CCl=CCl$	$CF_2CF_2CF_2CFClCFCl$[c]	46.6	8.9	C	50
$CCl_2=CCl_2$	$CFCl_2CFCl_2$	77.0	77.0	C	100
$CCl_2=CFCl$	$CFCl_2CF_2Cl$	77.4	77.4	C	70
$CF_2=CHF$	CF_3CHF_2	40.8	40.8	A	100
$CCl_2=CHCl$	$CFCl_2CHFCl$	85.1	85.1	C	50
$CHF=CFCl$	CHF_2CF_2Cl	95.8	89.2	A	100
$CF_2=CHI$	CF_3CHFI	53.4	53.4	C	70
$CF_2=CH_2$	CF_3CH_2F	27.6	21.5	A	100
$CCl_2=CH_2$	$CFCl_2CH_2F$	58.8	58.8	C	50
cis-CHCl=CHCl	*dl*-CHFClCHFCl	68.5	46.0	C, D, E	50
	meso-CHFClCHFCl	21.1	14.2		
trans-CHCl=CHCl	*dl*-CHFClCHFCl	54.3	43.2	C, D, E	50
	meso-CHFClCHFCl	26.1	20.8		
$CH_2=CHBr$	$CH_2FCHFBr$	19.8	19.8	C, D, E	50

[a] See under Chromatography in the Experimental section. [b] Plus large amounts of polymer. [c] Presumably a mixture of *cis* and *trans* isomers.

TABLE II

PHYSICAL PROPERTIES AND N.M.R. DATA

	$CFCl_2CH_2F$	$CHFClCHFCl$ *dl*	$CHFClCHFCl$ *meso*	$CH_2FCHFBr$
A[a]	7.74437	7.83872	7.81781	7.80861
B[a]	1564.2	1649.2	1644.4	1633.6
B.p. °C. (at 760 mm.)	48.4	59.4	59.9	58.3
ΔH_{vap}[b]	6807	7187	7167	7167
Trouton ratio	21.2	21.6	21.5	21.6
Mol. wt.				
Obsd.	131.2[c]	134.9[d]	138.3[d]	145.6[d]
Theor.	135.0	135.0	135.0	145.0
CH[e]		−1.34[f]	−1.34[f]	−1.83
CH_2	+0.21			+0.09
CF	−11.0[g]	+68.4[f]	+89.9[f]	+70.2[g]
	+132.2[h]			+135.9[h]
$J_{CH,CF}$[i]		48.8[j]	49.1[j]	51.6[j]
		7.0[k]	7.2[k]	11.9[k]
J_{CH,CH_2}				3.5, 5.4
$J_{CH,CH}$		3.77	3.83	
$J_{CF,CF}$	22.4	26.5	20.6	22.1
J_{CF,CH_2}	13.6[k]			20.4, 22.5[k]
	46.5[j]			46.5[j]

[a] A and B are the constants for the vapor pressure equation $\log P_{mm\ of\ Hg} = A - B/T°_K$ in the range 300–800 mm. The vapor pressure curves and constants derived therefrom were obtained as previously described by E. R. Bissell, *J. Org. Chem.*, **26**, 5100 (1961). [b] Calories/mole at the normal boiling point. [c] Determined by means of a gas density balance [A. Liberti, L. Conti, and V. Crescenzi, *Nature*, **178**, 1067 (1956)] using nitrogen and chlorodifluoromethane as carrier gases and 1,1-dichloroethylene as an internal standard. [d] Determined by PVT measurements. [e] N.m.r. chemical shifts are reported in p.p.m. relative to water for hydrogen and to hexafluoroacetone for fluorine. See ref. 19. [f] Typical ten-line spectrum for an A_2X_2 grouping. [g] For the fluorine adjacent to the chlorine or bromine substituent. [h] For the fluorine of the CH_2F group. [i] Coupling constants are given in cycles per second. [j] For the hydrogen with the fluorine on the same carbon. [k] For the hydrogen with the fluorine on the adjacent carbon.

yield. It could be argued that lead dioxide or one of the various possible lead fluorides or oxyfluorides could be more efficient than cesium fluoride as a catalyst for the decomposition of heptafluoropropyl sulfur trifluoride to octafluoropropane, but there is no evidence for such a supposition.

In the course of these experiments four previously unreported halocarbons were prepared. Physical properties and nuclear magnetic resonance data (n.m.r.) are tabulated in Table II; infrared spectral data are given in the Experimental section.

The structure of the adduct from vinyl bromide was confirmed by infrared and n.m.r. spectra, molecular weight, and dehydrobromination to *cis*-1,2-difluoroethylene. The structures of the three dichloro compounds were readily and unequivocally established from

their infrared and n.m.r. spectra, their molecular weights, and the fact that each was readily dehydrochlorinated by treatment with bases to 1-chloro-1,2-difluoroethylene. The 1,1-dichloro and *meso*-1,2-dichloro isomers yielded exclusively *cis* olefin, while *dl*-1,2-dichloro-1,2-difluoroethane gave only *trans* olefin. The assignment of *dl* and *meso* configurations was made on this basis. The assignment of *cis* and *trans* configurations to the two isomers of 1-chloro-1,2-difluoroethylene was made on the following bases: (1) the CF absorption in the infrared spectrum of the *trans* isomer appears at a higher frequency than that of the *cis* isomer[13,14]; (2) the intensity of the C=C stretching frequency is lower for the *trans* isomer than for the *cis* isomer[15]; (3) the total number of absorption bands is smaller for the *trans* isomer[15]; and (4) we have observed that for halogenated ethylenes the vapor–liquid phase chromatography (v.p.c.) retention time for the *trans* isomer is generally less than that for the *cis* isomer.

Experimental[16]

Materials.—Tetrafluoroethylene was prepared by the thermal depolymerization of polytetrafluoroethylene. 1-Chloro-1,2-difluoroethylene was prepared by zinc dechlorination of 1,2-difluoro-1,1,2-trichloroethane, and 1,1-difluoro-2-iodoethylene was made by dehydrochlorination of 1-chloro-1,1-difluoro-2-iodoethane.[17] The remainder of the olefins, the lead dioxide, and the sulfur tetrafluoride were commercial products used without further purification.

Fluorination Procedure.—A 25-ml. stainless steel pressure vessel[18] was charged with 3.59 g. (0.015 mole) of lead dioxide, 0.010 mole of the olefin, and 0.05 mole of sulfur tetrafluoride. Lead dioxide and liquid olefins were weighed directly into the vessel before closing; sulfur tetrafluoride and olefins which were gaseous at room temperature were measured gasometrically and were condensed into the pressure vessel which previously had been cooled in liquid nitrogen and evacuated. The reaction vessel was allowed to warm to room temperature and then rocked at 100° for 2 hr. After cooling to room temperature, the volatile portion of the contents of the reaction vessel was vaporized through a wash tower containing 300 ml. of 30% aqueous sodium hydroxide cooled to 0°. Material passing the hydroxide wash was passed through a trap cooled in 1,2-dichloroethane slush (−36°) and condensed at liquid nitrogen temperature. The total amount of material thus obtained was measured either gasometrically or by transferring to a suitable container and weighing (after further drying, if necessary). High boiling products were recovered from the −36° trap by separating from the bulk of the water and drying with anhydrous magnesium sulfate or calcium chloride. Vapor–liquid phase chromatography (v.p.c.) was employed to analyze the products and to isolate samples for identification. For those products which had been reported previously, identification was made by comparison of infrared spectra with spectra of authentic samples or with published spectra.

Chromatography.—The analytical columns were 1/4-in.-o.d. copper or stainless steel tubing packed with 20 wt. % partitioning liquid on 42–60-mesh GC-22 firebrick (except for column A, which was a silica gel adsorption column). The lengths and partitioning agents were the following: (A) 7.5 ft., none; (B) 20 ft., di-*n*-decyl phthalate; (C) 3 m., di-*n*-decyl phthalate; (D) 3 m., nonylphenoxy(polyethoxy)ethanol; and (E) 3 m., Zonyl E-91.[19] The carrier gas was helium at a flow rate of 100 ml./min. The detector was a thermal conductivity cell operated at 150°. Where the amounts of materials required were too large to be handled conveniently on a 1/4-in. column, a Model A-700 Autoprep[20] employing a 3/8-in.-o.d. aluminum column was used for the initial separations. The samples used for measurement of the n.m.r. and physical constants reported in Table II were rechromatographed until all three columns (C, D, and E) showed less than 0.1% total impurities.

Infrared Spectra. 1,1-Dichloro-1,2-difluoroethane.—3.41 (w) (CH stretch), 6.94 (w) (CH_2 deformation), 7.30 (w), 8.00 (m), 8.60 (s) (CF), 9.14 (s) (CF), 9.40 (s) (CF), 10.25 (vw), 10.67 (vs) (CF), 11.50 (vs) (probably CF), and 13.00 (m) μ.

***dl*-1,2-Dichloro-1,2-difluoroethane.**—3.35 (w) (CH stretch), 7.63 (w) (CH deformation), 7.90–7.96 (vw doublet), 8.23 (m), 8.70 (m), 8.98 (s) (CF), 9.03 (s) (CF), 9.45 (s) (CF), 11.00 (vw), 12.05 (s), 12.83 (m), and 13.6 (w) μ.

***meso*-1,2-Dichloro-1,2-difluoroethane.**—3.40 (w) (CH stretch), 7.30 (w), 7.45 (w) (CH deformation), 7.80 (w), 8.30 (m), 8.63 (w), 8.82 (s) (CF), 9.10 (vs) (CF), 9.47 (s) (CF), 10.30 (m), 12.10 (s), and 12.75 (vs) μ.

1-Bromo-1,2-difluoroethane.—3.35 (m) (CH stretch), 6.90 (w) (CH_2 deformation), 7.23 (m), 7.45 (w) (CH deformation), 7.90 (w), 8.35 (w), 8.95–9.02 (vs doublet) (CF) 9.20 (s, sh) (CF), 9.60 (vs) (CF), 11.00 (m), 11.12 (m), and 13.50 (vs) μ.

(13) A. Demiel, *J. Org. Chem.*, **27**, 3500 (1962).

(14) H. G. Viehe, *Chem. Ber.*, **93**, 1697 (1960).

(15) H. J. Bernstein and J. Prowling, *J. Am. Chem. Soc.*, **73**, 1843 (1951).

(16) Infrared absorption spectra were obtained in the vapor state on a Perkin-Elmer Model 137 Infracord spectrometer and are reported in μ. The n.m.r. spectra were obtained on a 40-Mc. Varian n.m.r. spectrometer; the authors are indebted to James A. Happe for these measurements.

(17) J. D. Parks, J. Abramo, M. Hein, D. N. Gray, and J. R. Lacher, *J. Org. Chem.*, **23**, 1661 (1958).

(18) E. R. Bissell and R. E. Spenger, *ibid.*, **24**, 1147 (1959).

(19) E. I. du Pont de Nemours and Co., Inc., Organic Chemicals Department, Dyes and Chemicals Division, Wilmington 98, Del.

(20) Wilkins Instrument and Research, Inc., Walnut Creek, Calif.

Synthesis and Configurational Significance of 3-(O-Methyl)neoepipicropodophyllin[1,2]

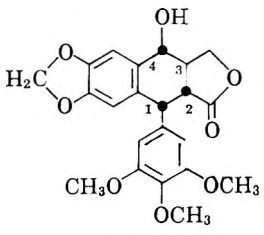
WALTER J. GENSLER, MERVYN V. LEEDING, AND A. SOMASEKAR RAO

Chemistry Department, Boston University, Boston 15, Massachusetts

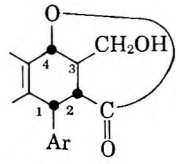
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The methyl ether of neoepipicropodophyllin has been prepared in two ways. Dimethyl sulfate with alkali methylates picropodophyllic acid as well as epipicropodophyllic acid selectively on the primary alcohol group. The resulting methylated compounds lactonize on warming to give the same lactone, 3-(O-methyl)neoepipicropodophyllin. Proof that the ring closures involve the 4-position was obtained by hydrogenating the lactone to 3-(O-methyl)-4-desoxypicropodophyllic acid, with the hydroxyl group missing but with methoxyl retained. Mild saponification of the lactone furnishes 3-(O-methyl)epipicropodophyllic acid. Since the lactone can exist only in a rigid well-defined form, the configuration of the derived 3-(O-methyl)epipicropodophyllic acid is unambiguously fixed. This information allows the configuration of hydroxyl in podophyllotoxin and picropodophyllin to be determined unequivocally. The new results support the original assignment.

An early proposal[3] for the structure of podophyllotoxin (I) had the lactone ring 2,4 as in II instead of 2,3 as in I. This proposal was incorrect,[4a] and compound II, which may be called neopodophyllotoxin, has in fact never been obtained.[4b] The present paper describes



podophyllotoxin
I



neopodophyllotoxin
II

the methyl ether VII of a stereoisomer of neopodophyllotoxin and shows how this compound provides evidence confirming the original configurational assignment[5,6] for the secondary hydroxyl group of podophyllotoxin (I).

Picropodophyllin (IV), which is epimeric with podophyllotoxin (III = I) at the 2-position, saponifies readily to picropodophyllic acid (V).[7] The saponification does not affect the stereochemistry at any of the four centers of asymmetry, since picropodophyllic acid (V) can be shown to be stable to alkali and is known to relactonize readily to picropodophyllin (IV). No sign of lactonization involving the secondary instead of the primary hydroxyl group of acid V (*i.e.*, 2,4-lactonization) has been observed. To realize this mode of lactonization, we tried to block reaction at the preferred primary hydroxyl group by selective methylation. Treatment of picropodophyllic acid (V) with dimethyl sulfate and alkali gave product VI, which contained one hydroxyl group and one new methoxyl group and which lost water on heating to give lactone VII.

Proof that methylation had occurred as expected on the primary and not on the secondary hydroxyl group was obtained by hydrogenolysis of the monomethyl compound VI. Evidence for lactonization to VII during the course of the hydrogenolysis was obtained, but the relative importance of hydrogenolysis *via* VI or *via* VII was not determined. Under the conditions used, the only bond susceptible to reductive cleavage was the benzylic carbon-to-oxygen bond at the 4-position. The hydrogenolysis product VIII, which proved to be the same as 3-(O-methyl)desoxypicropodophyllic acid (VIII)[8] prepared from desoxypodophyllotoxin, retained the new methoxyl group. Accordingly, acid VI, with hydroxyl and not methoxyl at the 4-position, is 3-(O-methyl)picropodophyllic acid, and the derived lactone VII must be a 2,4-lactone.

Mild alkaline hydrolysis of lactone VII did not regenerate acid VI, but instead gave acid XII isomeric with VI. The new acid XII, on warming, was smoothly recyclized to lactone VII; in fact, ring closure occurred more readily with XII than with VI. No configurational changes could have occurred in the hydrolysis of lactone VII to acid XII because, first, no change can occur before ring opening, since there is no reason to expect action with alkali at the 1- or 3-positions and no possibility of change in the bridged cyclic system at the 2- and 4-positions (*cf.* XIII). Note, in this connection, that by Bredt's rule enolization at the 2-position of the lactone is precluded. Second, experiment shows that after ring opening product XII is not changed by alkali. Third, the possibility that alkyl-to-oxygen instead of the more familiar carbonyl-to-oxygen bond cleavage occurs in the lactone hydrolysis[9] was considered but dismissed. In a methanol-rich solvent, alkyl-to-oxygen cleavage, whether by monomolecular ionization or by bimolecular displacement, could be expected to produce appreciable amounts of open product carrying methoxy at the 4-position. The fact that no such product could be detected rules out the alkyl-to-oxygen bond breaking. Accordingly, the stereochemistry of lactone VII and acid XII must be the same. Both are epipicropodophyllin derivatives, in which the orienta-

(1) This is paper XV in the series entitled "Compounds Related to Podophyllotoxin." The preceding paper is by W. J. Gensler and F. Johnson, *J. Am. Chem. Soc.*, **85**, 3670 (1963).

(2) The work was supported by a grant from National Cancer Institute, U. S. Public Health Service (CA-02891).

(3) W. Borsche and J. Niemann, *Ann.*, **499**, 59 (1932); *Ber.*, **66**, 1633 (1932); E. F. Späth, F. Wessely, and E. Nadler, *ibid.*, **66**, 1773 (1932).

(4) (a) J. L. Hartwell and A. W. Schrecker, *J. Am. Chem. Soc.*, **73**, 2909 (1951). (b) This is no longer true; *cf.* M. Kuhn and A. von Wartburg, *Experientia*, **19**, 391 (1963). The neo designation used by Kuhn and von Wartburg for the 2,4-lactones has been adopted here.

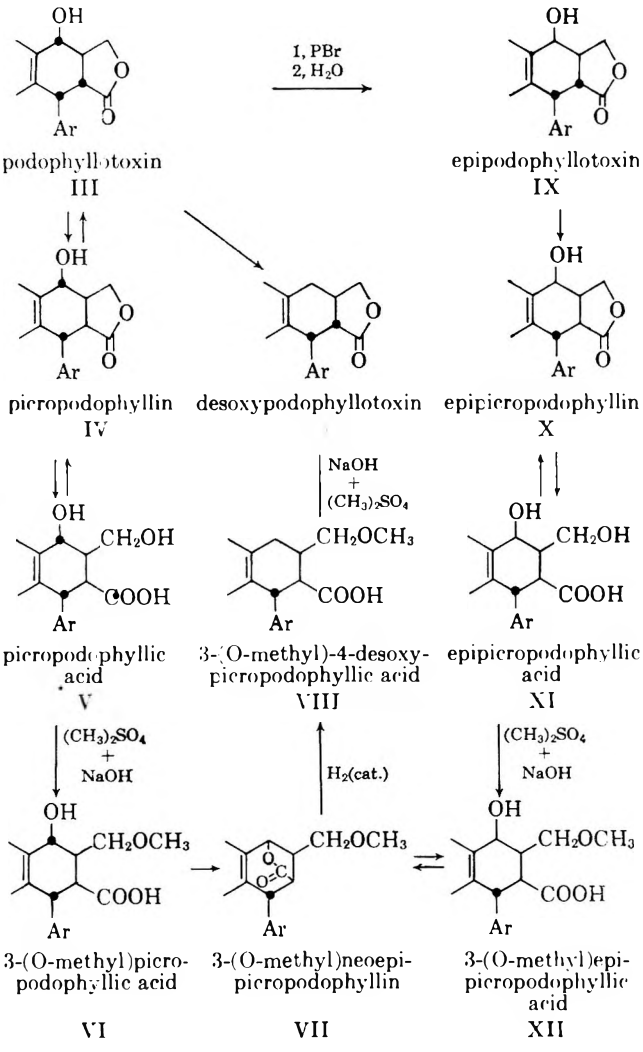
(5) N. L. Drake and E. H. Price, *J. Am. Chem. Soc.*, **73**, 201 (1951).

(6) A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5916 (1953).

(7) A comprehensive review of the chemistry of these compounds has been presented by J. L. Hartwell and A. W. Schrecker, *Progr. Chem. Org. Nat. Prod.*, **15**, 83 (1958).

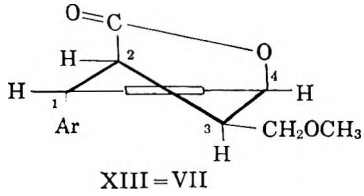
(8) A. W. Schrecker and M. M. Trail [*J. Org. Chem.*, **23**, 767 (1958)] reported m.p. 180–184° (foaming) for 3-(O-methyl)desoxypicropodophyllic acid (VIII), but this value must be low. L. Marion [*Can. J. Research*, **20B**, 157 (1942)] described the same compound with m.p. 194–195°; K. Noguchi and M. Kawanami, [*J. Pharm. Soc. Japan*, **60**, 629 (1940); *Chem. Abstr.*, **47**, 6386 (1953)] found 205°.

(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 342; A. G. Davies, *Quart. Rev.* (London), **9**, 203 (1955); *cf.* J. Kenyon and P. R. Sharan, *J. Chem. Soc.*, 4084 (1963).



tion at the 4-position is opposite that in the picro series. Clearly, inversion occurs at the 4-position when 3-(O-methyl)picropodophyllic acid (VI) lactonizes to VII. Support for these assignments was obtained when epipicropodophyllic acid (XI),[4a] derived from podophyllotoxin (III) by way of epipodophyllotoxin (IX) and epipicropodophyllin (X), gave the same monomethylated acid XII on treatment with dimethyl sulfate and alkali.

The relative orientation of the groups at the 1-, 2-, and 3-positions of picropodophyllin (IV) and epipicropodophyllin (X) is well established as *trans*-1,2–*cis*-2,3[6] and, consequently, neolactone VII is constrained to the rigid ring system as in XIII. Here the groups at positions 2 and 4 must both be axial, or in other words, the arrangement must be *cis*-2,4. Since the epi acid XII is the one that is configurationally related to the neolactone, this acid XII also has *cis*-2,4 groups. The stereo chemistry is conveniently traced back by means of the 1 and 4 groups, which are seen to be *trans*-1,4 in 3-(O-methyl)epipicropodophyllic acid (XII), epipicropodophyllic acid (XI), and epipodophyllotoxin (IX), but *cis*-1,4 in podophyllotoxin (III). Corresponding results are obtained through the picro compounds. Since 3-(O-methyl)picropodophyllic acid (VI) lactonizes to VII with inversion at the 4-position, derivative VI must have *trans*-2,4 and, therefore, the *cis*-1,4 arrangement. The *cis*-1,4 relation may now be traced back through picropodophyllic acid (V), picropodophyllin (IV), and finally podophyllotoxin (III). The original stereochemical assignment for the 4-hydroxyl group, based on comparisons of the ease of elimination of 4-acyloxy derivatives,[5,6] is thus substantiated.[10]



XIII = VII

Experimental

General.—Melting points were determined in capillary tubes and were not corrected. Infrared absorption curves were taken with Perkin-Elmer spectrophotometers; ultraviolet absorption curves were obtained with a Bausch and Lomb instrument. Elementary analysis were furnished by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Thin layer chromatograms were run on plates coated with 0.3-mm. layers of silica gel containing 5% calcium sulfate (Camag, Merck). The two solvent mixtures used in this work are: system A, methylene chloride–acetone, 4:1; and system B, methylene chloride–ethyl acetate–acetic acid, 5:2:1. Spots were developed by spraying the plate with a 1:1 mixture of ethanol–concentrated sulfuric acid and warming the treated plate for about 10 min. at 120°. The observed R_f values were found to vary somewhat from plate to plate and with the age of the solvent mixtures, but the separation of spots was always reproducible and reliable.

3-(O-Methyl)picropodophyllic Acid (VI) from Podophyllotoxin (III).—Heating a mixture of podophyllotoxin (2.5 g., 6.0 mmoles), potassium hydroxide (180 g. of 85% material, 2.7 moles), and water (500 ml.) on the steam bath for 25 min. gave a clear solution. An atmosphere of nitrogen was maintained over this solution throughout the reaction. To the stirred mixture at 0° freshly distilled dimethyl sulfate (115 ml., 1.20 moles) was added by drops over a period of 4 hr. After standing at room temperature for a day, the mixture was brought to 0°, and more dimethyl sulfate (80 ml., 0.84 mole) was added over 1 hr. The reaction mixture was then allowed to stand for 2 days. In some of the reactions, the total reaction period was 2 days.

Trace amounts of alkali-insoluble material were removed by extraction with two 100-ml. portions of chloroform. The extracted aqueous solution, cooled to 0°, was acidified with ice-cold 4 *N* hydrochloric acid to pH 3. The chloroform extract (four 100-ml. portions) of the acidified mixture was washed with water, dried with sodium sulfate, and distilled under reduced pressure to remove solvent.

Two crops were taken from the residual material (2.5 g.), the first (0.6 g.) from chloroform and the second (0.3 g.) from methylene chloride–cyclohexane. The combined solids were crystallized from aqueous acetone, two crops again being taken (0.6 g.). Finally, pure 3-(O-methyl)picropodophyllic acid (VI), m.p. 159–160° (foaming), was obtained (0.52 g., 19%) by crystallization from ethyl acetate–hexane.

The same compound VI, m.p. 159.5–160.5° and m.m.p. 159–160°, was obtained in about the same yield by methylating picropodophyllin (IV) essentially according to the above procedure.

Anal. Calcd. for $C_{23}H_{26}O_9$: C, 61.89; H, 5.87; 4(CH_3O), 27.80. Found: C, 61.73; H, 5.85; CH_3O, 27.38.

A 2×10^{-4} *M* solution of 3-(O-methyl)picropodophyllic acid (VI) in 95% alcohol showed an absorption maximum at 292–293 mμ (log ε 3.65). The compound as a mull with mineral oil showed infrared absorption peaks at 3250, 1710, and 1585 cm.$^{-1}$; and as a solution in chloroform, at 3440 (m), 1740 (m), 1705 (s), and 1588 (s) cm.$^{-1}$. The optical rotation was determined as $[\alpha]^{25}D$ −91° (*c* 4.0, acetone) or −95° (*c* 0.62, absolute alcohol). Thin layer chromatography with system B gave a single spot with R_f 0.34.

(10) Recent n.m.r. work has provided further confirmation for the *cis*-1,4 orientation in podophyllotoxin (III) and the *trans*-1,4 orientation in epipodophyllotoxin (IX) [E. Schreier, *Helv. Chim. Acta*, **46**, 75 (1963)].

When the material remaining in the mother liquors from the original two crops was examined by thin layer chromatography, three spots appeared corresponding to picropodophyllic acid (V), picropodophyllin (IV), and 3-(O-methyl)picropodophyllic acid (VI). The infrared absorption spectrum determined with the material in chloroform showed peaks at 3500 (hydroxyl), 1775 (lactone carbonyl), 1750, and 1710 cm.$^{-1}$ (carboxylic acid). Approximately half of the mixture consisted of picropodophyllin (IV).

Recovery of Picropodophyllic Acid (V) after Its Exposure to Concentrated Alkali.—A mixture of picropodophyllin (0.50 g., 1.2 mmoles) and 100 ml. of 7.1 *N* aqueous potassium hydroxide solution was heated on the steam bath for 20 min. under nitrogen. The homogeneous solution, still under nitrogen, was set aside at room temperature for 2 days.

Acidification at −5° with ice-cold 4 *N* hydrochloric acid brought the solution to pH 3. After addition of a few milliliters of chloroform to the cold solution, it was stirred vigorously for 10 min. The white crystalline precipitate was collected, washed quickly on the funnel with small portions of cold water to remove hydrochloric acid, and dried in a vacuum desiccator over calcium sulfate (Drierite) for 2 days. This material (471 mg.) showed m.p. 151.5–152° (foaming) by itself or admixed with authentic picropodophyllic acid (V). Drying the product over phosphorus pentoxide for 30 hr. at 100° and a pressure of 0.005 mm. gave 460 mg. (88%) of solvent-free picropodophyllic acid (V), m.p. 210–213°, on increasing the temperature *ca.* 2°/min. from 140°. Further drying for 48 hr. at 100° resulted in no loss of weight. The solid, as a mineral oil mull, showed the expected infrared absorption peaks at 3450 (hydroxyl) and 1704 cm.$^{-1}$ (carboxylic acid). A weak absorption at 1763 cm.$^{-1}$ (lactone) suggested the presence of a trace of picropodophyllin (IV). In agreement, while the product before drying at 100° gave only one spot on thin layer chromatography with system B, the final material showed the same spot plus a second minor spot corresponding to picropodophyllin.

Methoxy Lactone VII from 3-(O-Methyl)picropodophyllic Acid (VI).—A 165-mg. sample of 3-(O-methyl)picropodophyllic acid was sublimed under 0.01-mm. pressure in a test tube (27-mm. diameter). A cold finger cooled with acetone–Dry Ice served as condenser. The bath temperature was raised from 130 to 185° over a period of 0.5 hr. and was kept at this temperature for 45 min. The solid sublimate (113 mg.) became oily on standing overnight in a desiccator. This material plus the product (49 mg.) from an 83-mg. sublimation was combined, and 150 mg. of the sublimate in 10 ml. of benzene was added to a chromatography tube containing 15 g. of acid-washed alumina (Merck). Three 50-ml. portions of benzene were passed through the column followed by two 50-ml. portions of benzene–chloroform (9:1). The solvent-free fractions were examined with the help of thin layer chromatography (system B). The materials in the last three fractions (102 mg.) were combined and were crystalized twice from benzene–hexane to give 77 mg. (35% yield from acid VI) of methoxy lactone VII. The melting point, determined after heating the product at 60° (0.005 mm.) over phosphorus pentoxide for 2 hr., depended on the procedure. A capillary sample immersed at 68° and heated at 1°/min. softened at 80° and melted at 90–100°. Under the same conditions but in an evacuated sealed capillary, the product softened at 86° and liquified at 93–99°. Further exposure of this lactone product VII to temperatures around 65° (0.005 mm.) for 38 hr. brought the melting point in a sealed evacuated capillary to 93–96° with very little preliminary softening.

Anal. Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; $4CH_3O$, 28.97. Found: C, 64.26; H, 5.46; CH_3O, 28.47.

Note that a carefully purified sample of podophyllotoxone showed about a 0.5% discrepancy in the methoxyl analysis.

Anal. Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89; $3CH_3O$, 22.58. Found: C, 64.23; H, 4.98; CH_3O, 22.07.

Methoxy lactone VII as a mull with mineral oil showed an absorption peak at 1767 cm.$^{-1}$, corresponding to lactone, but none in the hydroxyl region. The lactone in chloroform solution showed this peak at 1765 cm.$^{-1}$. The optical rotation in chloroform was $[\alpha]_D$ +50° (*c* 0.22) and +81° (*c* 0.12, absolute alcohol). Thin layer chromatography (system B) gave only a single spot with R_f 0.63; 3-(O-methyl)picropodophyllic acid under same conditions showed R_f 0.32 and could be detected at levels corresponding to 1% of the lactone. The ultraviolet absorption curve for a 2×10^{-4} *M* absolute ethanol solution of lactone VII gave a maximum at 293 mμ (log ε 3.58).

3-(O-Methyl)epipicropodophyllic Acid (XII) by Saponification of Methoxy Lactone VII.—A sample of 3-(O-methyl)picropodophyllic acid (VI) was sublimed as before at 180–185° (0.005 mm.) to give lactone VII in 78% yield. The sublimate (lactone carbonyl peak at 1767 cm.$^{-1}$) was hydrolyzed with hot 6% methanolic potassium hydroxide. The hydrolysis product (51%) gave a single spot on a thin layer chromatogram with the proper R_f value for 3-(O-methyl)epipicropodophyllic acid (XII). The melting point was 179.5–181° (softening at 178°) either with or without admixture of 3-(O-methyl)epipicropodophyllic acid (XII) from epipicropodophyllin (X). This acid in chloroform showed absorption peaks at 3480 (m), 1737 (s), 1704 (s), and 1590 (s) cm.$^{-1}$.

No sign of any product other than 3-(O-methyl)epipicropodophyllic acid (XII) was obtained when sodium methoxide in methanol containing trace amounts of water was used for the hydrolysis. Thus, a solution of 4 mg. of lactone VII in 3 ml. of absolute methanol containing 80 mg. of sodium was boiled for 2 hr. under nitrogen. Aliquots removed at various times were examined by thin layer chromatography (solvent system B). At no time was more than two spots—corresponding to lactone VII (R_f 0.83) and acid XII (R_f 0.60)—observed. The identifications were made by comparing the movement of authentic material spotted on the same plate. The intensity of the lactone spot rapidly decreased until, at the end of 0.5 hr., it became and remained very faint. The spot corresponding to acid XII was dark minutes after the start of the reflux period. After the 2-hr. period, several drops of water were added, and the mixture was allowed to stand overnight at room temperature. Aliquots of the solution as it was at the end of the 2-hr. period and after treatment with water were examined with the use of solvent system A. Both aliquots showed only two spots corresponding to the lactone (R_f 0.87, very faint) and the acid (R_f 0.02, dark).

3-(O-Methyl)epipicropodophyllic Acid (XII) from Epipicropodophyllin (X).—Epipicopodophyllin (X) was hydrolyzed with aqueous alkali and then was methylated with dimethyl sulfate in a manner completely analogous to that described above for the conversion of podophyllotoxin (III) or picropodophyllin (IV) to 3-(O-methyl)picropodophyllic acid (VI). The chloroform extract of the acidified aqueous solution (pH 3) contained 1.78 g. of crude product when 2.07 g. (5.0 mmoles) of epipicropodophyllin (X) was taken as starting material. The crude solvent-free product consisted of a gum mixed with crystals. Addition of benzene dissolved the gum and allowed the crystals to be collected and rinsed with benzene.

The crystals weighed 90 mg. and showed m.p. 175–179°. The infrared absorption curve of this material dissolved in chloroform was identical with that of the 3-(O-methyl)epipicropodophyllic acid (XII) obtained by hydrolysis of lactone VII. Thin layer chromatography (system B) produced a dark spot with R_f 0.43, the same as that obtained from material derived from the lactone; a very faint spot remaining at the origin was probably epipicropodophyllic acid (XI). On the same plate, 3-(O-methyl)picropodophyllic acid (VI) showed R_f 0.38, 3-(O-methyl)epipicropodophyllic acid (XII) showed R_f 0.48, and a mixture produced two spots with R_f 0.41 and 0.50.

Crystallization from ethyl acetate–hexane afforded 68 mg. of 3-(O-methyl)epipicropodophyllic acid (XII), m.p. 179–180° and $[\alpha]_D$ −41 ± 3° (*c* 0.07, chloroform) and −45° (*c* 0.17, absolute alcohol). A mixture of methylated acids VI (m.p. 159.7–160.5° with shrinking at 158°) and XII melted at 157.5–160.5° with shrinking at 155°; the capillary sample here was placed in the bath at 145° and the temperature was raised 2°/min.

Anal. Calcd. for $C_{23}H_{26}O_9$: C, 61.89; H, 5.87; $4CH_3O$, 27.80. Found: C, 61.67; H, 6.06; CH_3O, 27.51.

The infrared absorption curves of acids VI and XII in chloroform solutions showed considerable differences especially in the 1500–800-cm.$^{-1}$ region. The ultraviolet absorption spectrum of 3-(O-methyl)epipicropodophyllic acid (XII) in 2×10^{-4} *M* alcohol solution showed λ_{max} 292 mμ (log ε 3.64).

When the benzene solution of the gummy product was checked by thin layer chromatography (system B), the major spot (R_f 0.72) fell close to the spot for lactone VII (R_f 0.71). The infrared absorption spectrum of the solute in chloroform solution was very similar to that of the lactone. The benzene solution was passed through a 60-g. column of Merck acid-washed alumina, and the following eluent fractions were collected: 700 ml. of benzene, 200 ml. of 9:1 benzene–chloroform, 200 ml. of 4:1 benzene–chloroform, two 100-ml. portions of chloroform,

and one 100-ml. portion of 9:1 chloroform–ethanol. The last two portions contained 1.37 g. of lactone VII giving a single spot on thin layer chromatography (R_f 0.68). A portion of this material (0.52 g.) was exposed for 1.5 hr. to a boiling solution of potassium hydroxide (4.25 g.) in 85% aqueous methanol (100 ml.). Two crystallizations of the resulting organic acids from ethyl acetate–hexane gave 0.34 g. (44%) of 3-(O-methyl)-epipicropodophyllic acid (XII), m.p. 178–180°. The melting point did not change when this material was mixed with the crystals described above.

Stability of Methylated Acids VI and XII to Alkali.—A solution of 0.7 mg. of 3-(O-methyl)picropodophyllic acid (VI) in 0.16 ml. of 35% aqueous potassium hydroxide was heated on the steam bath under nitrogen for 20 min. and then allowed to stand under nitrogen for 50 hr. A solution of 0.6 mg. of 3-(O-methyl)epipicropodophyllic acid (XII) in 0.14 ml. of alkali was treated the same way. For thin layer chromatography, a 0.01-ml. aliquot was mixed with 0.1 ml. of acetic acid and 0.1 ml. of acetone, and half of this solution was spotted on a plate and run with system B. Each solution gave only one spot whose R_f value corresponded to the respective starting material. A mixture of the two solutions showed the expected two spots. Tripling the amount of methoxy acid spotted brought out some very faint spots but none that corresponded to interconversion of the two materials.

Lactone VII from 3-(O-Methyl)epipicropodophyllic Acid (XII).—A sample (46 mg.) of 3-(O-methyl)epipicropodophyllic acid (XII) was sublimed at 0.005 mm. in the apparatus used for the lactonization of 3-(O-methyl)picropodophyllic acid (VI). The temperature was held at 155° for 20 min. (no sublimate) and then at 183–185° for 50 min. The white sublimate (40 mg.) gave an infrared absorption spectrum identical with that obtained with the lactone VII from 3-(O-methyl)picropodophyllic acid (VI), and a thin layer chromatogram (system A) showing spots with R_f 0.71 (intense; lactone VII has R_f 0.73), 0.41 (very weak; unidentified), and 0.03 (very weak; 3-(O-methyl)epipicropodophyllic acid has R_f 0.02).

The product in 5 ml. of benzene was placed on a column of Merck acid-washed alumina (5 g.) and was eluted with 300 ml. of benzene, 200 ml. of benzene–chloroform (9:1), and 100 ml. of benzene–chloroform (4:1). Since all fractions showed only a single spot at the lactone position on thin layer chromatograms, they were combined. The eluted material (34 mg.) after two crystallizations from benzene–hexane gave a product (24 mg., 55%) that melted at 93–95.5° either with or without admixture of lactone VII from 3-(O-methyl)picropodophyllic acid (VI).

Ease of Lactonization of 3-(O-Methyl)picropodophyllic Acid (VI) and 3-(O-Methyl)epipicropodophyllic Acid (XII).—Separate solutions of the two acids VI and XII were boiled under a reflux condenser. From time to time aliquots were removed and examined by thin layer chromatography (system B). The pure compounds involved here showed the following R_f values: 3-(O-methyl)picropodophyllic acid (VI), 0.26; 3-(O-methyl)-epipicropodophyllic acid (XII), 0.33; and lactone VII, 0.62. No other spots were noted on any of the plates.

Boiling acid VI or acid XII in benzene for 5 hr. resulted in no lactonization whatever.

Better results were obtained with boiling solutions of the acids (1.5 mg.) in toluene (2 ml.). Thin layer chromatographic examination of the toluene reaction mixtures showed a more rapid lactonization of acid XII than of acid VI. Thus, after 3.75 hr., the lactone spot from VI was just discernable, while the lactone spot from acid XII was intense; and after 9.25 hr., the spot corresponding to unchanged XII was barely detectable, while the spot for unchanged VI remained darker than the lactone spot.

After 9.25 hours, all the solvent was removed, and the weighed residues were dissolved in ethanol to give solutions of *ca.* 1 mg./ml. From the observed specific rotations of the residues from acid VI and acid XII ($[\alpha]^{23}D$ −48 and +81°, respectively) and from the optical rotations of pure compounds (−95° for VI, −45° for XII, and +81° for lactone VII), the approximate composition of the residues could be calculated. The yield of lactone VII from 3-(O-methyl)picropodophyllic acid (VI) was 27 ± 5%; the yield from 3-(O-methyl)epipicropodophyllic acid (XII) was 100 ± 5%.

Hydrogenolysis of 3-(O-Methyl)picropodophyllic Acid (VI) to 3-(O-Methyl)-4-desoxypicropodophyllic Acid (VIII).—Hydrogen was slowly bubbled through a mixture of 3-(O-methyl)picropodophyllic acid (VI, 113 mg., 0.25 mmole), 10% palladium on charcoal (127 mg., American Platinum Co.), and pure toluene (3 ml.) on the steam bath. After 1.5 hr., thin layer chromatography with system B showed that the starting material (R_f 0.25) was absent and that methoxy lactone VII and hydrogenolysis product VIII were both present (R_f 0.58 and 0.53, respectively). After 5 hr., the spot corresponding to the product was more intense while that corresponding to the lactone was less intense.

The hot solution was filtered, and the catalyst was rinsed with hot toluene. Cooling the combined filtrate and washings deposited white needles, m.p. 197–199° dec., which were homogeneous by thin layer chromatography. Crystallization from toluene–pentane gave 55 mg. (51%) of 3-(O-methyl)-4-desoxypicropodophyllic acid (VIII), m.p. 196–198.5°, and $[\alpha]^{22}D$ −68° (*c* 0.11, chloroform). A chloroform solution showed infrared absorption peaks at 3500, 1740, and 1707 (s) cm.$^{-1}$. An absolute alcohol solution (2×10^{-4} *M*) showed λ_{max} 295.5 mμ (log ε 3.69).

Anal. Calcd. for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09; $4CH_3O$, 28.84. Found: C, 64.34; H, 6.06; CH_3O, 29.68.

No complications attributable to the solvent or catalyst were likely, since the only change that occurred on exposing acid VI to acetic acid containing catalyst was lactonization to VII. Thus, glacial acetic acid (0.1 ml.) containing 5 mg. of 3-(O-methyl)picropodophyllic acid (VI) and 6 mg. of 10% palladium on carbon was heated on the steam bath under nitrogen for 5 hr. Aliquots removed at hourly intervals and examined by thin layer chromatography (system B) showed only one spot whose R_f value (0.58) corresponded to that of lactone VII (0.59) but was far removed from that of the starting material VI (0.25). The ultraviolet absorption spectra of other aliquots dissolved in alcohol showed no sign of the 311-mμ maximum expected for an "α-apo" dehydration product but only the 293-mμ peak associated with the nonconjugated systems.

Storing the reaction mixture overnight in a vacuum desiccator over potassium hydroxide pellets removed all the acetic acid. The residual solids were warmed with chloroform and filtered. The infrared absorption curve of the clear filtrate showed no hydroxyl peak in the 3500-cm.$^{-1}$ region and proved to be identical with that of methoxy lactone VII.

3-(O-Methyl)desoxypicropodophyllic Acid (VIII) from Desoxypodophyllotoxin.—A 1.62-g. sample of desoxypodophyllotoxin (from podophyllotoxin, III[11]) was saponified and methylated essentially as described above for the conversion of podophyllotoxin (III) to 3-(O-methyl)picropodophyllic acid (VI). The acidic products, desoxypicropodophyllic acid plus 3-(O-methyl)-desoxypicropodophyllic acid (VIII), were dissolved in methylene chloride (*ca.* 100 ml.) and chromatographed on a column of silica gel (60 g.). The following solvents were passed through the column: 400 ml. of methylene chloride, 200 ml. of ethyl acetate–methylene chloride (1:9), 200 ml. of ethyl acetate–methylene chloride (1:4), and finally 300 ml. of ethyl acetate–methylene chloride (1:1). Removal of solvent from the last 300 ml. of eluate left a residue, which on recrystallization from methylene chloride–pentane afforded 0.43 g. of 3-(O-methyl)-desoxypicropodophyllic acid (VIII), m.p. 205.5–206.5°.

The mixture melting point with the same material from 3-(O-methyl)picropodophyllic acid (VI) was 202–204°. The two samples of VIII showed identical infrared absorption curves, and by thin layer chromatography with either solvent system were both homogeneous and indistinguishable.

Acknowledgment.—We are grateful to Dr. J. Renz and Dr. J. Rutschmann of Sandoz, Ltd., for a generous gift of podophyllotoxin.

(11) A. W. Schrecker, M. M. Trail, and J. L. Hartwell, *J. Org. Chem.*, **21**, 292 (1956).

Irradiation-Induced De-esterification

A. MacLachlan

Radiation Physics Laboratory, Engineering Department, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware

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Solutions of benzyl esters in various solvents are efficiently de-esterified by high-energy electron irradiation. Dose rate and intensity effects are examined and a schematic mechanism proposed. In addition to synthetic applications, the efficient generation of acid can be used as an organic radiation dosimeter.

In connection with a study of solute effects on electron irradiation of cyclohexane and other solvents,[1] a novel and synthetically useful method of de-esterification has been discovered. Previous work on solute reaction in solvents subjected to irradiation led to the discovery that benzyl-type compounds ($C_6H_5CH_2X$, where X = Cl, Br, OH, $OCOCH_3$) had a high reactivity in proportion to their concentration. Furthermore, it was shown previously by iodine-scavenging methods that normal free-radical attack on the solute, thus accounting for its loss, could not explain the high G obtained.[1]

Additional insight into this reaction was desired, and, for this reason, a search for the reaction products containing the substituent X was initiated. Benzyl acetate was chosen as the solute to be examined, and acetic acid was considered likely as one of the products of the reaction of the fragment X, if it became dissociated from the parent molecule. The unexpectedly high yield of acetic acid found, indicating a high proportion of C–X cleavage, prompted the detailed investigation reported in this paper. The possibility that the reaction is general for benzyl esters is investigated. Some of the parameters that affect the efficiency and extent of this reaction also are examined.

Results

Benzyl acetate converts with a variable efficiency to acetic acid, as shown in Table I and Fig. 1 and 2. Solvents have a strong effect, and, for benzyl acetate, ethanol yields an almost quantitative amount of acetic acid. Radiation intensity was varied by a factor of ten and had no effect on the G (acid), as shown in Table II.

Figure 1 demonstrates that the concentration of ester definitely has an effect on the efficiency of acid production. However, excellent linearity of acid production is obtained when conversions of ester are less than 50% and when the initial concentration is 0.2 M (Fig. 2).

Dibenzyl succinate was investigated in some detail. If the irradiation is carried out in cyclohexane, succinic acid precipitates, owing to its lack of solubility. There exists the possibility that both benzyl groups come off simultaneously. The data given in Table III demonstrate that the G is low and is a strong function of starting ester concentration. This behavior is consistent with a two-step de-esterification.

Table IV lists the G (acid) yields for a series of benzyl or benzyl-type esters, and, by comparison with Table V, it is obvious that the benzyl structure is necessary for the efficient acid production.

Benzyl ethyl succinate presents an interesting example of the specificity of the reaction. Only β-carbethoxy propionic acid is formed, showing that only the benzylated ester is affected.

Discussion

The results given in Tables I–V demonstrate that benzyl esters cleave to acids under the influence of high-energy radiation. The reaction appears quite general and offers a method of de-esterification under conditions of environment that are not possible with other methods. Recent publications have appeared where photolytic methods have been used to convert esters to acids.[2,3] Interestingly, the esters that appear to photo de-esterify most efficiently are those which form stable free radicals.

Some deductions pertaining to the mechanism may be made from the data. If direct photolysis were involved, it would seem reasonable to propose a photodissociation either leading directly to acid, as shown in reaction 2, or to acid through the intermediate carboxyl radical (reactions 3 and 4).

$$\mathrm{RCOOBz} + h\nu \longrightarrow \mathrm{RCOOBz}^* \quad (1)$$

$$\mathrm{RCOOBz}^* + \mathrm{R'H} \longrightarrow \mathrm{RCOOH} + \text{products} \quad (2)$$

$$\mathrm{RCOOBz}^* \longrightarrow \mathrm{RCOO}\cdot + \mathrm{Bz}\cdot \quad (3)$$

$$\mathrm{RCOO}\cdot + \mathrm{R'H} \longrightarrow \mathrm{RCOOH} + \mathrm{R'}\cdot \quad (4)$$

In this work, high-energy radiation introduces a further set of reactions that have to be considered. Most of the energy is initially absorbed by the solvent, and yet the high G for ester disappearance calls for a mechanism of transferring the energy to the ester.[1] Two general types of reactions suggest themselves: one an energy transfer process (reaction 6), and the other a free radical derived from the solvent attacking the ester to produce acid as the major product (reactions 7 and 8).

$$\mathrm{R'H\ (solvent)} + \epsilon \longrightarrow \mathrm{R'H}^* \quad (5)$$

$$\mathrm{R'H}^* + \mathrm{RCOOBz} \longrightarrow \mathrm{R'H} + \mathrm{RCOOBz}^* \quad (6)$$

$$\mathrm{R'H}^* \longrightarrow \mathrm{H}\cdot + \mathrm{R'}\cdot \quad (7)$$

$$\mathrm{R'}\cdot \text{ and/or } \mathrm{H}\cdot + \mathrm{RCOOBz} \longrightarrow \mathrm{RCOOH} + \text{products} \quad (8)$$

A possible means of separating the parts of the debenzylation reaction is by adding free-radical scavengers. If free-radical attack on the ester is the major source of its reaction, then scavengers should prevent the reaction of the ester, and no acid will be produced. Irradiation of 0.1 M benzyl acetate in cyclohexane saturated with iodine (0.05 M) yielded $-G$ (ester) = 2.3, and G (acetic acid) = 1.4, as compared to the values

(1) A. MacLachlan, *J. Am. Chem. Soc.*, **82**, 3309 (1960).

(2) (a) D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *Tetrahedron Letters*, 1055 (1962); (b) J. A. Barltrop and P. Schofield, *ibid.*, 697 (1962).

(3) (a) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **83**, 4486 (1961); (b) H. E. Zimmerman and V. R. Sandel, *ibid.*, **85**, 915 (1963).

TABLE I

Ester	Concn., M	Solvent	Dose, e.v./ml. $\times 10^{-21}$	$-G$ (ester)	G (acid)	% yield, acid
Benzyl acetate	0.1	Cyclohexane	1.08	2.7	1.8	67
Benzyl acetate	0.1	Ethanol[a]	1.00	1.6	1.6	100
Benzyl acetate	0.1	Methanol	0.98	1.6	0.85	53
Benzyl butyrate	0.1	Cyclohexane	0.98	2.8	1.4	50
Benzyl butyrate	0.1	Ethanol	0.98	1.8	1.3	72
Benzyl isobutyrate	0.1	Cyclohexane	0.53	2.5	1.7	68

[a] Ethanol was irradiated in the absence of benzyl acetate, and no acetic acid was detected.

TABLE II

RADIATION INTENSITY EFFECT ON G (ACID) FOR BENZYL ACETATE IN CYCLOHEXANE

Beam current,[a] ma.	G (acid)
0.5	2.25
1.0	2.05
2.0	2.05
3.0	2.15
5.0	2.25

[a] Conversions were all adjusted for about 30% reaction of the benzyl acetate.

TABLE III

Initial concn. of dibenzyl succinate, M	G (succinic acid)[a]
0.10	0.047
0.067	0.055
0.020	0.14
0.005	0.10

[a] Same total amount of energy into each sample. Solvent is cyclohexane.

TABLE IV

ACID YIELDS FOR BENZYL-TYPE ESTERS[a]

Ester	Dose, megarads	G (acid)	Acid formed
Benzyl benzoate	11.5	1.08	Benzoic
Benzyl cholate	9.5	1.8	Cholic
α-(Naphthyl)methyl acetate	12.5	1.3	Acetic
Benzyl ethyl succinate	17.2	2.4	β-Carbethoxy propionic

[a] All esters were 0.1 M in cyclohexene except benzyl cholate which was 0.1 M in cyclohexene.

TABLE V

ACID YIELDS FOR NONBENZYL ESTERS[a]

Ester	Dose, e.v./ml. $\times 10^{-20}$	G (acid)
β-Phenylethyl acetate	6.9	0.084
γ-Phenylpropyl acetate	6.7	0.16
Cyclohexyl acetate	6.9	0.23
Cyclohexylmethyl acetate	5.8	0.19
Phenyl acetate	5.7	0.37
Phenyl benzoate	6.2	0.87
Ethyl benzoate	1.6	0.02[b]

[a] All esters 0.1 M in cyclohexane. [b] G.l.c. analysis for loss of ethyl benzoate indicated no detectable reaction.

of 2.7 and 1.8 in the absence of scavengers. While both yields are reduced slightly, it would seem most reasonable to eliminate the free-radical attack mechanism.

If acetoxy radicals are produced by dissociation of excited ester, then one would expect either decarboxylation or a capture by the iodine.[4-6]

(4) A. Rembaum and M. Szwarc, *J. Am. Chem. Soc.*, **77**, 3486 (1955).
(5) C. Walling and R. B. Hodgdon, *ibid.*, **80**, 228 (1958).
(6) H. J. Shine and D. M. Hoffman, *ibid.*, **83**, 2782 (1961).

Ethyl benzoate yielded negligible amounts of acid (Table V) and at the same time was not detectably reacted at a dose that would have destroyed 50% of the benzyl acetate (0.1 M). This lack of reactivity demonstrates that the aromatic ring is not the major point of attack for any solvent-derived free radicals. Again, this supports a nonradical path for the acid formation.

Zimmerman and co-workers[3] have found photo-induced heterolysis reactions of substituted benzyl compounds in polar solvents. The heterolysis mechanism would not appear to be applicable in this work since de-esterification to form acid occurs with unsubstituted benzyl compounds even in cyclohexane. However, if heterolysis in nonpolar solvents of simple benzyl esters requires higher excited states than that obtained by photolysis or perhaps even ionized molecules, ionizing radiation certainly has this capability.

In summary, the data obtained indicate that some type of energy transfer process other than a free-radical reaction is responsible for the efficient excitation of the ester by electron irradiation. Furthermore, a direct dissociation of excited ester into carboxyl radicals and benzyl radicals does not seem reasonable because of the high acid yields obtainable.[4-6] It is suggested that the reaction sequence for excited ester decomposition (reactions 9 and 10) best fits the experimental facts.

$$\mathrm{RCOOBz^{*}} + \mathrm{R'H} \longrightarrow \left[\mathrm{RC(OH)-O-Bz}\right] + \mathrm{R'\cdot} \qquad (9)$$

$$\left[\mathrm{RC(OH)-O\text{-}Bz}\right] \longrightarrow \mathrm{RC(=O)-OH} + \mathrm{Bz\cdot} \qquad (10)$$

Iodine might effect the reaction by reacting directly with the excited ester, but this could be much less efficient than its reaction with radicals.

A similar intermediate has been suggested as contributing to the photodecomposition of alkyl esters.[7] Excited carbonyl-abstracting hydrogen atoms are, of course, well known in ketone photolysis.[8-13]

In addition to the obvious synthetic applications of this reaction as an additional means of de-esterification, it has the possibility of being a simple and convenient organic dosimeter. The dose rate and total dose effects investigated, in Fig. 1 and 2 and Table II, indicate that there are large regions of linearity of acid production; and, therefore, its use as a dosimeter seems ideal. A discussion of the needs for a chemical dosimeter that

(7) P. Ausloos, *ibid.*, **80**, 1310 (1958).
(8) J. A. Bell and H. Linschitz, *ibid.*, **85**, 528 (1963).
(9) W. M. Moore, G. S. Hammond, and R. P. Foss, *ibid.*, **83**, 2789 (1961).
(10) G. S. Hammond, W. P. Baker, and W. M. Moore, *ibid.*, **83**, 2795 (1961).
(11) G. Porter and F. Wilkinson, *Trans. Faraday Soc.*, **57**, 1686 (1961).
(12) D. McClure and P. Hanst, *J. Chem. Phys.*, **23**, 1772 (1955).
(13) G. S. Hammond and P. A. Leermakers, *J. Am. Chem. Soc.*, **84**, 207 (1962).

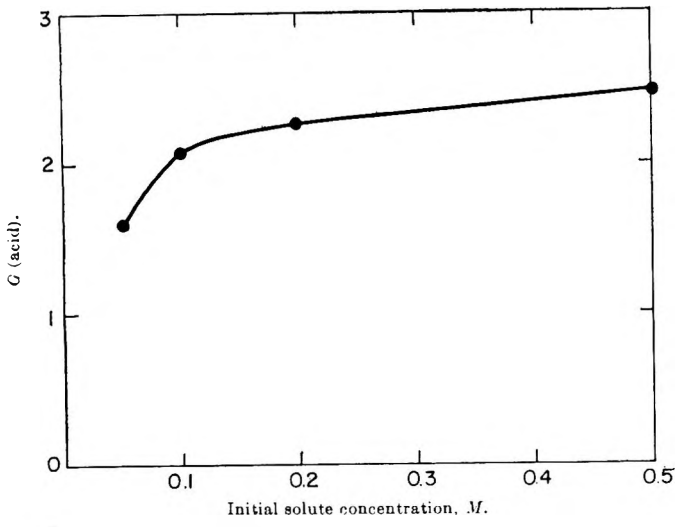


Fig. 1.—Effect of benzyl acetate concentration on G (acid) in cyclohexane. Dose for each irradiation was 5×10^{20} e.v./ml.

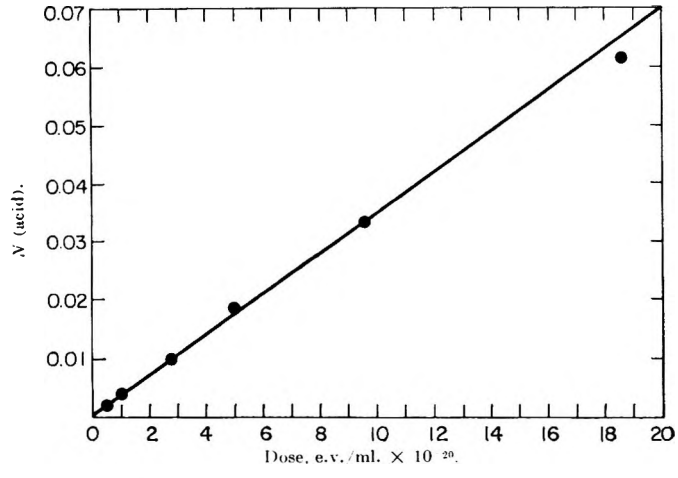


Fig. 2.—N (acid) *vs.* total irradiation dose for 0.2 M benzyl acetate in cyclohexane.

can be used in metallic vessels as well as glass vessels is given by Hardwick and Guenther.[14]

Experimental

Irradiation Procedure.—The radiation source used in this work was a General Electric resonant transformer supplying 2-m.e.v. electrons, at beam currents up to 5 ma. Samples were irradiated in the multiple cell sample holder previously described[15] or on a larger scale in a deoxygenating flask. This flask is a flat-bottom beaker, with a ground glass rim. The total volume is 250 ml. with an inside diameter of 9 cm. After placing the solution to be irradiated and a magnetic stirring bar in the vessel, the top is sealed with a sheet of aluminum foil held in place with a clamped aluminum ring. Deoxygenating is accomplished by purging with argon through a side arm for 20 min. before and continuing the flow at a lower rate during irradiation. Temperature is controlled by immersing the entire lower two-thirds of the vessel in a constant temperature bath. Evaporation losses were prevented by presaturation of the argon with the appropriate solvent.

Iodine-scavenging experiments were carried out by maintaining excess solid iodine in the stirred irradiation cell.

Analytical Procedures.—Acid and ester yields were analyzed by g.l.c. analysis whenever possible. Benzyl acetate, butyrate, ethyl benzoate, acetic acid, and butyric acid conveniently were analyzed on a 5-ft. column of 15% stearic acid–15% silicone grease on Chromosorb at 108–150°.

Acid yields also were determined by titration with 0.02 M aqueous sodium hydroxide to the phenolphthalein end point. Aliquots of the irradiated solution were added to an equal volume of distilled water, flushed with argon to remove the carbon dioxide, and then titrated.

β-Carbethoxy propionic acid and cholic acid were isolated from the irradiation of their respective benzyl esters. The irradiated solutions were extracted with 10% aqueous sodium bicarbonate; the extracts were neutralized with dilute hydrochloric acid and extracted with ether. After drying the ether solution over Drierite, the acids were isolated by removing the solvent. Infrared spectral analyses and comparison with authentic samples of the acids served to prove the structures. Blanks were carried through the isolation procedure to be certain no ester hydrolysis occurred.

Materials.—Cyclohexane was Eastman Spectro Grade, ethanol was Pharmco absolute, and methanol was Baker Analyzed reagent.

β-Carbethoxy benzyl propionate was prepared from β-carbethoxy propionyl chloride by the method of Hauser.[16] β-Carbethoxy propionyl chloride was prepared by the method of Riegel and Lillienfield.[17]

Benzyl cholate was synthesized by placing 100 g. (0.24 mole) of cholic acid in 50 ml. of water and neutralizing to the phenolphthalein end point with 20% aqueous sodium hydroxide. Benzyl chloride (45 g., 0.35 mole) was added and the mixture refluxed for 2 hr. After cooling, the mixture was extracted with ether and the ether layer washed with 10% aqueous sodium bicarbonate and dried over Drierite. After evaporation of the ether, the oil was extracted eight times with cyclohexane to remove the residual benzyl chloride. No success was obtained with crystallizing the benzyl cholate, and therefore, it was used directly. After a time, the viscous oil crystallized spontaneously. Infrared spectroscopy was used to verify the ester structure.

α-(1-Naphthyl)methyl acetate (I) was prepared by refluxing 40 g. (0.28 mole) of α-chloromethylnaphthalene with 0.3 M sodium acetate in 250 ml. of glacial acetic acid for 3 hr. The acetic acid was removed by evaporation, and the residue extracted with ether. After evaporating the ether, the oil was distilled to yield I, b.p. 80° (0.5 mm.).

α-Cyclohexylmethyl acetate was prepared from 25 g. (0.18 mole) of cyclohexylcarbinol by reaction with 14.5 g. (0.19 mole) of acetyl chloride in 23 g. (0.2 mole) of dimethylaniline and 50 ml. of ether. The acetyl chloride was added dropwise at a rate necessary to maintain reflux. The residue was extracted with ether. The ether layer was extracted with 10% aqueous hydrochloric acid, then washed with 10% sodium bicarbonate, water, and then dried over Drierite. The ether was removed and the ester was distilled under vacuum, b.p. 105° (56 mm.).

Acknowledgment.—Thanks are due to J. M. White for his assistance in carrying out the experiments.

(14) T. J. Hardwick and W. S. Guenther, *J. Phys. Chem.*, **63**, 896 (1959).
(15) A. MacLachlan, *Rev. Sci. Instr.*, **29**, 790 (1958).
(16) C. R. Hauser, *et al.*, *Org. Syn.*, **24**, 19 (1944).
(17) B. Riegel and W. M. Lillienfield *J. Am. Chem. Soc.*, **67**, 1273 (1945).

The Preparation of Cyclic Siliconmethylene Compounds

WILLIAM A. KRINER[1]

The Rohm and Haas Company, Philadelphia, Pennsylvania

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A novel method has been found for the preparation of cyclic siliconmethylene compounds such as $[(CH_3)_2SiCH_2]_2$, $[(CH_3)_2SiCH_2]_3$, $[Cl(CH_3)SiCH_2]_2$, $[C_2H_5O(CH_3)SiCH_2]_2$, $[C_2H_5O(CH_3)SiCH_2]_3$, and others. The above cyclic compounds containing Cl^- or $C_2H_5O^-$ groups bonded to silicon were converted to various derivatives such as $[H(CH_3)SiCH_2]_2$, $[H(CH_3)SiCH_2]_3$, $[C_6H_5(CH_3)SiCH_2]_2$, $[C_6H_5(CH_3)SiCH_2]_3$, etc.

The common method for preparing compounds containing the Si–C–Si linkage utilizes the coupling reaction of halomethylsilanes with halo or alkoxy silanes by means of lithium, sodium, or magnesium. These reactions have been reviewed elsewhere.[2] Cyclic siliconmethylene compounds of the general formula $[(CH_3)_2SiCH_2]_n$ have been prepared in this manner, but in small yields.[2] A six-membered ring compound, $[Cl_2SiCH_2]_3$, has been isolated from the products of the reaction of CH_2Cl_2 with Si–Cu alloys. This has been converted to $[H_2SiCH_2]_3$ by reaction with lithium aluminum hydride, and to various alkyl derivatives.[2] Fritz and co-workers have shown that cyclic siliconmethylenes can be obtained in small quantities from the pyrolysis of $(CH_3)_4Si$, $(CH_3)_3SiCl$, $(CH_3)_2SiCl_2$, and $(CH_3)SiCl_3$.[2]

The smallest cyclic siliconmethylene ring, 1,3-disilacyclobutane, has been synthesized as the 1,1,3,3-tetramethyl derivative[3] by a multistep process culminating in the ring closure dehalogenation reaction as shown by the following equation.

$$F(CH_3)_2SiCH_2Si(CH_3)_2CH_2Cl + Mg \longrightarrow [(CH_3)_2SiCH_2]_2 - MgCl(F) \quad (1)$$

A similar preparation was carried out using $Cl(CH_3)_2SiCH_2Si(CH_3)_2CH_2Cl$ in the final step.[4] Recently, 1,1,3,3-tetramethyl-1,3-disilacyclobutane was identified as one of the products from the pyrolysis of $(CH_3)_4Si$.[5] The four-membered ring compound has also been isolated from the products of the reaction of chloromethyldimethylchlorosilane and magnesium in ether in yields around 4%.[6]

None of the above described methods provides a quick, versatile means for preparing cyclic siliconmethylene compounds in substantial yields. The purpose of this investigation was to perfect a method for preparing these compounds and particularly to introduce some silicon functionality into the rings. The method chosen was similar to that of Müller, *et al.*[6]

Results and Discussion

Direct Preparation of Cyclic Siliconmethylenes.—The interaction of chloromethyldimethylchlorosilane with magnesium in diethyl ether proceeded as in eq. 2. The yield of small ring compounds (n = 2, 3, and 4) was small, in agreement with Müller, *et al.*,[6] most of the product being a viscous residue. The reaction proceeded more readily in tetrahydrofuran; however, the yield of simple compounds was again small, the major product being a siliconmethylene polymer having an average molecular weight of 930 ± 10. A most successful procedure, resulting in yields up to 50% for 1,1,3,3-tetramethyl-1,3-disilacyclobutane (I) and around 19% for 1,1,3,3,5,5-hexamethyl-1,3,5-trisilacyclohexane (II) and 1,1,3,3,5,5,7,7-octamethyl-1,3,5,7-tetrasilacyclooctane (III) in small quantities, was perfected by utilizing the reverse addition of magnesium to the silane in tetrahydrofuran (reaction 1D in Experimental). High molecular weight cyclic silmethylenes and possibly some linear compounds probably linked with Si–O–Si bonds, due to hydrolysis of residual Si–Cl end groups, were also produced.

$$n ClCH_2Si(CH_3)_2Cl + nMg \longrightarrow [(CH_3)_2SiCH_2]_n + nMgCl_2 \quad (2)$$
$$n = 2 \text{ and greater}$$

The most likely steps for this reaction are shown in Scheme I, eq. 3–10.

This reaction path involves multiple steps, which are consistent with the literature. However, it is oversimplified in that all the Grignard intermediates formed, such as shown in eq. 6 and 8, can react with any active Si–Cl available, not just starting material. It can be seen, according to Scheme I, that linear siliconmethylenes terminated by unreacted $\equiv SiCH_2Cl$ and $\equiv SiCl$ groups can also be produced in addition to cyclic compounds.

One can postulate that the reason for the success of the inverse addition process is that this procedure favors the production of $ClCH_2(CH_3)_2SiCH_2Si(CH_3)_2Cl$ according to eq. 4, since only small amounts of $ClMgCH_2Si(CH_3)_2Cl$ will be formed in an environment rich in $ClCH_2Si(CH_3)_2Cl$. This advantage holds until the concentration of $ClCH_2(CH_3)_2SiCH_2Si(CH_3)_2Cl$ becomes appreciable. The normal addition method, in contrast, will produce a relatively high concentration of $ClMgCH_2Si(CH_3)_2Cl$ resulting in a preponderance of chain lengthening reactions.

One of the major objects of this research was to produce cyclic siliconmethylenes having silicon functionality, *i.e.*, compounds containing Si–halogen, Si–H, and Si–alkoxy bonds. The direct preparation of 1,3-dichloro-1,3-dimethyl-1,3-disilacyclobutane (IV), according to eq. 11, gave low yields as a result of the many side reactions which can occur as evidenced by the large yield of the isotropic mixture, $C_6H_{15}Cl_3Si_3$. This mixture could be separated into two components: a liquid, $Cl_2(CH_3)SiCH_2Si(CH_3)CH_2Si(CH_3)(Cl)CH_2$ (V), and a solid, $[Cl(CH_3)SiCH_2]_3$ (VI), the major portion being V. According to the reaction path proposed, the possible expected intermediate, $Cl_2(CH_3)SiCH_2Si(CH_3)(Cl)CH_2Si(CH_3)(Cl)CH_2MgCl$, could couple with itself

(1) University of Pennsylvania, Philadelphia, Pa.

(2) R. K. Ingham and H. Gilman, "Inorganic Polymers," F. G. A. Stone and W. A. G. Graham, Ed., Academic Press, New York, N. Y., 1962, p. 321.

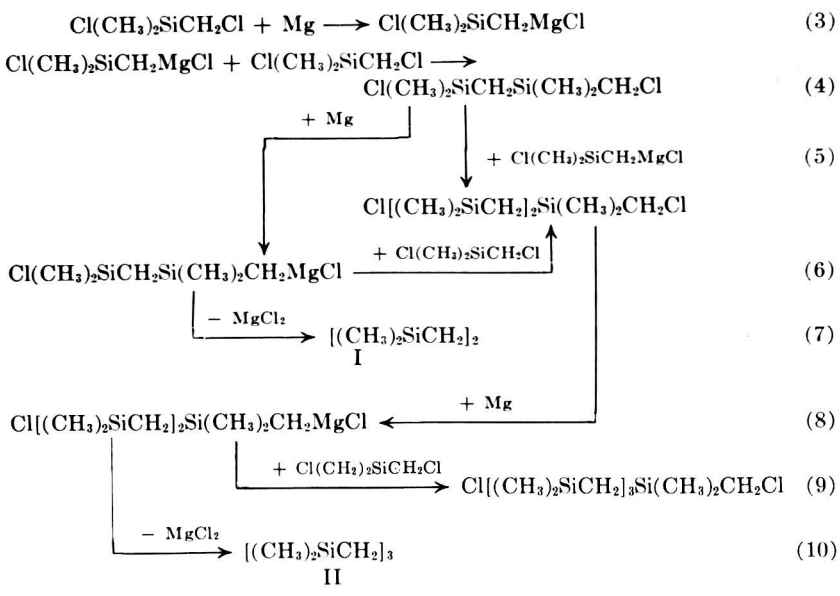
(3) W. H. Knoth, Jr. and R. V. Lindsey, Jr., *J. Org. Chem.*, **23**, 1392 (1958); W. H. Knoth, Jr., U. S. Patent 2,850,514 (1958).

(4) G. Greber and G. Degler, *Makromol. Chem.*, **52**, 174 (1962).

(5) G. Fritz and J. Grobe, *Z. anorg. allgem. Chem.*, **315**, 157 (1962); G. Fritz, W. Kemmerling, G. Sonntag, H. J. Becker, E. H. V. Ebsworth, and J. Grobe, *ibid.*, **321** 10 (1963). The latter paper includes a correction of a previous work [G. Fritz and J. Grobe, *ibid.*, **311**, 325 (1961)] in which the structure $(CH_3)_2Si{=}CHSi(CH_3)_3$ was assigned to $Si_2C_6H_{16}$.

(6) R. Müller, R. Köhne, and H. Beyer, *Ber.*, **95**, 3030 (1962).

SCHEME I



$$2ClCH_2Si(CH_3)Cl_2 + 2Mg \longrightarrow [Cl(CH_3)SiCH_2]_2 + 2MgCl_2 \quad (11)$$

by interaction of the Grignard end with the silicon halogen bond in either the 4- or the 6-position leading to V or VI, respectively. An alternate course to V would be the reaction of the intermediate, $Cl_2(CH_3)SiCH_2MgCl$ with IV. Proof of the structures IV, V, and VI is discussed later.

To eliminate the side reactions discussed above the starting silane was modified by substituting the less active ethoxy group for one of the chlorines on silicon, *i.e.*, $ClCH_2Si(CH_3)(OC_2H_5)Cl$. This resulted in a moderate (35.3%) yield of 1,3-diethoxy-1,3-dimethyl-1,3-disilacyclobutane (VII), along with a small quantity of 1,3,5-triethoxy-1,3,5-trimethyl-1,3,5-trisilacyclohexane (VIII). When the starting silane had both active chlorines replaced by ethoxy groups, *i.e.*, $ClCH_2Si(CH_3)(OC_2H_5)_2$, the reaction with magnesium gave 12.4% VII and a moderate (40.4%) yield of VIII. These results are consistent with the proposed scheme in that the intermediate $Cl(C_2H_5O)(CH_3)SiCH_2Si(CH_3)(OC_2H_5)CH_2MgCl$ would be more likely to undergo a ring closure reaction than the intermediate of the second case, $(C_2H_5O)_2(CH_3)SiCH_2Si(CH_3)(OC_2H_5)CH_2MgCl$, due to the steric hindrance of the ethoxy groups. The latter would more readily proceed similarly to eq. 5, resulting eventually in the formation of $(C_2H_5O)_2(CH_3)SiCH_2Si(CH_3)(OC_2H_5)CH_2Si(CH_3)(OC_2H_5)CH_2MgCl$ which can undergo a less hindered ring closure reaction to give the six-membered ring, VIII.

Derivatives and Conversions.—Compounds I through XVI and some of their physical properties are summarized in Table I. The ethoxy derivatives VII and VIII were converted to the corresponding chloro derivatives IV and VI, respectively, by conventional means. The latter chloro derivatives gave high yields of the hydride derivatives IX and X with lithium aluminum hydride. Complete methylation of IV, VI, VII, and VIII with methyl Grignard gave the known methyl derivatives I and II. Partial methylation of IV and VII gave the monofunctional derivatives XI and XII, respectively. Compound V was methylated to give XIII. An alternate preparation of XIII was accomplished by the reaction of XI with $(CH_3)_3SiCH_2Li$. Compounds IV and VI were readily converted to phenyl derivatives using phenyl Grignard. The novel siloxane XVI resulted from the hydrolysis of XII.

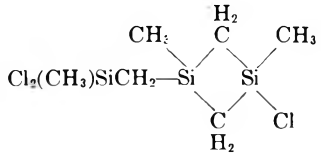
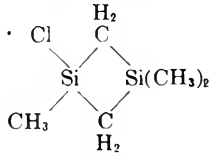
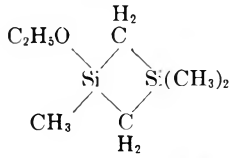
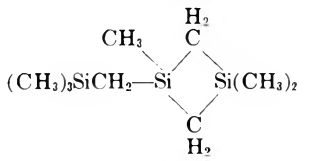
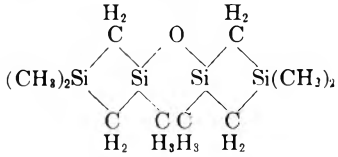
Some of the derivatives (IV–X, XIV, and XV) of 1,3-disilacyclobutane and 1,3,5-trisilacyclohexane obviously can have isomeric forms. However, none as yet have been resolved into one form or the other and must be assumed to be mixtures.

Spectroscopic Data.—The infrared spectra of compounds I through XVI were recorded on a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics. Their absorption frequencies are recorded in Table II. Assignments were made wherever possible. All compounds, except VI (which was dissolved in carbon tetrachloride), were examined as thin films between sodium chloride plates. Of particular interest in these spectra is the position of the $Si–CH_2–Si$ band which in linear siliconmethylenes is found in the 1050-cm.$^{-1}$ region.[7] This band is usually much narrower than the broad Si–O–Si absorption frequency also found around 1050 cm.$^{-1}$. The 1,3,5-trisilacyclohexane derivatives gave an absorption band in the 1040–1065-cm.$^{-1}$ region, but the 1,3-disilacyclobutane derivatives absorbed between 935–955 cm.$^{-1}$. This shift may be attributed to the strained ring structure of the latter compounds and may be compared to the similar shifts of the Si–O–Si frequency which occur in several cyclic siloxanes as the ring size is decreased.[8,9] In the compounds $Cl_2(CH_3)SiCH_2Si(CH_3)CH_2Si(CH_3)(Cl)CH_2$ and $(CH_3)_3SiCH_2Si(CH_3)CH_2Si(CH_3)_2CH_2$ which contain both a linear and cyclic $Si–CH_2–Si$ structure, two bands are indeed found, one in the 1050-cm.$^{-1}$ region and one in the 950-cm.$^{-1}$ region.

(7) H. Kriegsmann, *Z. Electrochem.*, **61**, 1088 (1957).
(8) W. A. Piccoli, G. G. Haberland, and R. L. Merker, *J. Am. Chem. Soc.*, **82**, 1883 (1960).
(9) A. W. P. Jarvie, H. J. S. Winkler, and H. Gilman, *J. Org. Chem.*, **27**, 614 (1962).

TABLE I

PHYSICAL PROPERTIES OF CYCLIC SILICONMETHYLENES

	Compound	B.p., °C. (mm.) [m.p., °C.]	$n^{25}D$
I	$[(CH_3)_2SiCH_2]_2$	119.5 60 (100) [−9 to −8.5]	1.4401
II	$[(CH_3)_2SiCH_2]_3$	112 (50)	1.4601
III	$[(CH_3)_2SiCH_2]_4$	104 (2) [79–80.5]	
IIV	$[C_2(CH_3)SiCH_2]_2$	59 (20) [−7 to −6.5]	1.4725
V		131 (20)	1.4901
VI	$[Cl(CH_3)SiCH_2]_3$	117–118 (5) 93–94 (2) [59]	
VII	$[(C_2H_5O)(CH_3)SiCH_2]_2$	78–79 (16)	1.4336
VIII	$[(C_2H_5O)(CH_3)SiCH_2]_3$	68–69 (0.20–0.25) 97 (1.7)	1.4478
IX	$[H(CH_3)SiCH_2]_2$	96	1.4546
X	$[H(CH_3)SiCH_2]_3$	68–71 (19)	1.4705
XI		67.5–68 (59)	1.4568
XII		71 (40)	1.4364
XIII		112.5–113 (50) 75 (10)	1.4556
XIV	$[C_3H_5(CH_3)SiCH_2]_2$	99 (1.1)	1.5727
XV	$[C_3H_5(CH_3)SiCH_2]_3$		1.5873
XVI			1.4525

Experimental

Materials.—Anhydrous ether was used without further treatment. Tetrahydrofuran was distilled as needed from lithium aluminum hydride. Magnesium turnings were ground to 2-mm. mesh and stored under nitrogen. Grignard reagents were standardized commercial products unless otherwise indicated. Commercially available chloromethyldimethylchlorosilane and chloromethylmethyldichlorosilane were redistilled on a 36-in. spinning band column. Ethoxy derivatives of the latter were prepared as described below.

Chloromethylmethylethoxychlorosilane was prepared by the partial ethanolysis of $(CH_3)(CH_2Cl)SiCl_2$. To a vigorously stirred solution of 655.0 g. (4.005 moles) of $(CH_3)(CH_2Cl)SiCl_2$ and 316.4 g. (4.000 moles) of pyridine in 500 ml. of benzene was slowly added 184.2 g. (3.998 moles) of ethanol over a period of 4 hr. After an additional 16 hr. of stirring, the pyridine hydrochloride was filtered off and washed with benzene. The benzene was removed from the filtrate by distillation. Fractional distillation of the residue gave 435.7 g. (2.517 moles, 62.9% yield) of $(CH_3)(CH_2Cl)Si(OC_2H_5)Cl$, b.p. 64° (40 mm.), $n^{25}D$ 1.4256.

Anal. Calcd. for $C_4H_{10}Cl_2OSi$: C, 27.75; H, 5.82; Cl, 40.96; mol. wt., 173. Found: C, 28.07; H, 5.83; Cl, 41.13; mol. wt., 175. All molecular weights were determined cryoscopically in benzene unless otherwise indicated.

Chloromethylmethyldiethoxysilane was prepared in a similar manner. $(CH_3)(CH_2Cl)SiCl_2$ (327 g., 2.00 moles) reacted with excess ethanol (240 ml., 4.09 moles) in the presence of pyridine (320 ml., 3.97 moles) in 300 ml. of benzene. Distillation yielded 239 g. (1.43 moles, 71.5% yield) of $(CH_3)(CH_2Cl)Si(OC_2H_5)_2$, b.p. 67° (20 mm.), lit.[10] b.p. 162–165°, $n^{25}D$ 1.4120, lit.[10] $n^{20}D$ 1.4145.

Reaction Procedure.—The reactions were carried out under nitrogen in conventional standard tapered glassware unless otherwise indicated. A conventional vacuum line was used for the manipulation of small quantities.

Reaction 1. Chloromethyldimethylchlorosilane and Magnesium. A. No Solvent.—No reaction occurred when 2.62 g. (0.0183 mole) of $(CH_3)_2(CH_2Cl)SiCl$ and 0.50 g. (0.021 g.-atom) of magnesium were heated to reflux in a sealed evacuated Carius tube.

B. In Diethyl Ether.—To a mixture of 6.1 g. (0.25 g.-atom) of magnesium in 100 ml. of ether, plus a few iodine crystals to activate the magnesium, was slowly added, over a period of 3.5 hr., a 50% solution of 35.5 g. (0.248 mole) of $(CH_3)_2(CH_2Cl)SiCl$ in ether while heating to reflux. The reaction mixture became cloudy and upon an additional 16 hr. of stirring a thick white sludge was produced. The product was hydrolyzed, extracted with ether, and distilled to give 1.79 g. (0.0124 mole, 10.0% yield) of 1,1,3,3-tetramethyl-1,3-disilacyclobutane (I); mol. wt. found, 145 (vapor density), and calcd., 144; b.p. 119.5°, lit.[3] b.p. 117–119°. A viscous yellow clear residue was the major product.

C. In Tetrahydrofuran.—To a mixture of 20 g. (0.82 g.-atom) of magnesium in 50 ml. of tetrahydrofuran was added a small amount of iodine and 4 drops of methyl iodide. To this stirred mixture was slowly added over a period of 2.5 hr., 71 g. (0.50 mole) of $(CH_3)_2(CH_2Cl)SiCl$ in sufficient tetrahydrofuran to make a 33% solution. The exothermic reaction was cooled occasionally. After the reduction had subsided, the viscous slurry, due to the large amount of magnesium chloride formed, was heated to reflux for 2 hr. and then cooled. A slow addition of 250 ml. of water produced two layers which were separated. The water layer was extracted with ether and the extract was added to the organic layer and distilled to give 2.4 g. (0.017 mole, 6.7% yield) of I, b.p. 60° (100 mm.), identified also by infrared; 0.50 g. (0.0023 mole, 1.4% yield) of 1,1,3,3,5,5-hexamethyl-1,3,5-trisilacyclohexane (II), b.p. 120° (50 mm.); and 21 g. (58% yield based on $[(CH_3)_2SiCH_2]_n$) of a viscous opaque residue, mol. wt. 930 ± 10, the infrared spectrum of which indicated a siliconmethylene polymer.

D. Reverse Addition in Tetrahydrofuran.—To a small mixture of magnesium turnings covered by tetrahydrofuran was added 4 drops of methyl iodide followed by the addition of a small portion of 284 g. (1.98 moles) of $(CH_3)_2(CH_2Cl)SiCl$ to start the reaction which was evidenced by a sharp exotherm. The remainder of the silane, in sufficient tetrahydrofuran to bring the final silane concentration to 33%, was added rapidly with continuous stirring. The remainder of 80 g. (3.3 g.-atoms) of magnesium turnings was slowly added to maintain a reaction temperature of 30–50° over a period of 2 hr. Occasional cooling was necessary. After an additional 1.5 hr. of stirring with heating to 50°, the reaction was cooled and 500 ml. of water was added slowly. The organic layer was separated, washed with water, and distilled to give 71.3 g. (0.494 mole, 49.9% yield) of I, m.p. −9 to −8.5° (by magnetic plunger technique[11]), b.p. 60.5–61.0° (100 mm.), $n^{25}D$ 1.4401, lit.[3] $n^{27}D$ 1.4380, d_{25} 0.793.

Anal. Calcd. for $C_6H_{16}Si_2$: C, 49.91; H, 11.17; mol. wt., 144. Found: C, 50.03; H, 11.37; mol. wt., 145 (vapor density).

In addition there was obtained 26.7 g. (0.123 mole, 18.6% yield) of II, b.p. 112° (50 mm.), lit.[12] b.p. 96–97° (26 mm.), $n^{25}D$ 1.4601, lit.[13] $n^{25}D$ 1.4606.

Anal. Calcd. for $C_9H_{24}Si_3$: C, 49.91; H, 11.17; mol. wt., 217. Found: C, 49.94; H, 11.00; mol. wt., 215.

(10) K. A. Andrianov and L. M. Volkova, *Zh. Obshch. Khim.*, **30**, 2393 (1960).

(11) A. Stock, "Hydrides of Boron and Silicon," Cornell University Press, Ithaca, N. Y., 1933, p. 184.

(12) N. S. Nametkin, A. V. Topchiev, and V. I. Zetkin, *Dokl. Akad. Nauk SSSR*, **93**, 1045 (1953).

(13) J. T. Goodwin, U. S. Patent 2,607,791 (1952).

TABLE II

INFRARED ABSORPTION FREQUENCIES OF CYCLIC SILICONMETHYLENES[a]

Compound																
I	II	III	IV	V	VI[b]	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	Assignments
													3090 ms	3070 m		C–H stretch (C_6H_5Si)
													3040 ms	3020 m		
2995 s	2960 m	2970 ms	2980 m	3009 m	2970 m	2985 s	2975 ms	2975 ms	2960 s	2970 ms	2970 s	2960 s	2975 ms	2960 m	2965 s	C–H stretch
2930 m	2910 m	2910 ms	2920 w	2970 w	2920 w	2900 m	2890 m	2920 w	2915 m	2910 m	2905 m	2910 ms	2920 ms	2910 m	2910 ms	(CH_3Si) and/or (C_2H_5—O—Si)
							2750vw	2140 vs	2120 vs		2735 vw					Si–H stretch
													1965 w	1955 w		
													1885 w	1875 w		
													1815 w	1810 w		
													1765 w			
													1645 vw			
													1590 w	1593 m		C=C stretch (C_6H_5Si)
													1490 ms	1488 m		
						1485 w	1485 w				1482 w					CH_2 deformation (C_2H_5OSi)
						1447 w	1447 w				1445 w					CH_3–C deformation (C_2H_5OSi)
													1434 vs	1430 vs		C=C stretch (C_6H_5Si)
1410 w	1410 w	1420 w	1405 m	1415 ms	1405 m	1393 m	1395 m	1415 w	1415 w	1402 m	1393 m	1405 m	1407 w	1407 vw	1403 m	CH_2 deformation (antisym.)
		1398 w														
1365 m	1355 w	1374 m	1345 s	1352 s	1350 m	1342 m	1353 m	1357 m	1360 m	1350 s	1350 m	1355 ms	1345 m	1355 m	1342 s	CH_2 deformation ($SiCH_2Si$)
1340 m																
													1302 w	1298 w		C–H deformation (C_6H_5Si)
						1293 w	1295 w				1290 w					C_2H_5OSi characteristic
1255 vs	1250 vs	1255 vs	1256 vs	1262 s	1258 s	1253 s	1256 s	1258 ms	1252 vs	1250 vs	1251 vs	1250 vs	1251 vs	1253 s	1252 vs	CH_3–Si sym. deformation
	1184 vw															
													1190 w	1190 w		
						1165 ms	1166 ms				1165 m					C_2H_5OSi rocking
													1157 w	1153 w		
													1115 vs	1108 vs		C_6H_5–Si
						1105 vs	1110 vs				1107 vs					Si–O–C stretch
						1075 vs	1083 vs				1080 vs					
													1090 w			
													1067 w			
	1045 vs	1048 vs		1065 vs	1050 vs		1040 vs		1040 vs			1045 vs		1040 vs		CH_2 wag ($SiCH_2Si$)
															1050 vs	Si–O–Si
														1025 vs	1025 vs	
													1010 m			
													1000 m	996 w		
													987 w			

| | | |

Anal. Calcd. for $C_6H_{15}Cl_3Si_3$: C, 25.94; H, 5.44; Cl, 38.29; mol. wt., 278. Found: C, 26.02; H, 5.61; Cl, 38.13; mol. wt., 277.

Reaction 7. 1,3-Dichloro-1,3-dimethyl-1,3-disilacyclobutane and Lithium Aluminum Hydride.—To a stirred slurry of 1.20 g. (0.0316 mole) of lithium aluminum hydride in 50 ml. of diethylene glycol dimethyl ether was slowly added 10.19 g. (0.0550 mole) of IV over a period of 30 min. After stirring for an additional 30 min., the product was fractionated in the vacuum line by trap to trap distillation to give 6.11 g. (0.0525 mole, 95.5% yield) of 1,3-dimethyl-1,3-disilacyclobutane (IX), b.p. 96°, $n^{25}D$ 1.4546.

Anal. Calcd. for $C_4H_{12}Si_2$: C, 41.30; H, 10.40; mol. wt., 116. Found: C, 41.20; H, 10.34; mol. wt., 114 (vapor density).

Reaction 8. 1,3,5-Trichloro-1,3,5-trimethyl-1,3,5-trisilacyclohexane and Lithium Aluminum Hydride.—Utilizing the procedure of reaction 7, 6.70 g. (0.0241 mole) of VI dissolved in 25 ml. of ether and 2.0 g. (0.053 mole) of lithium aluminum hydride in 25 ml. of ether were treated to give on distillation 3.26 g. (0.0187 mole, 77.6% yield) of 1,3,5-trimethyl-1,3,5-trisilacyclohexane (X), b.p. 68–71° (19 mm.), $n^{25}D$ 1.4705.

Anal. Calcd. for $C_6H_{18}Si_3$: C, 41.30; H, 10.40; mol. wt., 174. Found: C, 41.75; H, 10.32; mol. wt., 173.

Reaction 9. 1,3-Dichloro-1,3-dimethyl-1,3-disilacyclobutane and Methylmagnesium Iodide in Excess.—To 0.0347 mole of freshly prepared $(CH_3)MgI$ in 25 ml. of diethyl ether was slowly added 3.15 g. (0.0170 mole) of IV over a period of 30 min. followed by an additional 30 min. of stirring. The product was filtered and distilled to give 2.08 g. (0.0144 mole, 84.7% yield) of I; mol. wt. found, 145 (vapor density), and calcd., 144; confirmed by infrared spectrum.

Reaction 10. 1,3-Diethoxy-1,3-dimethyl-1,3-disilacyclobutane and Methylmagnesium Bromide in Excess.—A 1.94-g. (0.00949 mole) sample of VII was added to a solution of 0.024 mole of $(CH_3)MgBr$ in ether, heated to reflux for 6 hr., and stirred for 16 hr. The product was fractionated to give 1.17 g. (0.00810 mole, 85.4% yield) of I, confirmed by infrared spectrum.

Reaction 11. 1,3,5-Trichloro-1,3,5-trimethyl-1,3,5-trisilacyclohexane and Methylmagnesium Bromide in Excess.—A 3.91-g. (0.0141 mole) sample of VI was treated with 0.045 mole of $(CH_3)MgBr$ in the manner described in reaction 10. Fractionation gave 2.92 g. (0.0135 mole, 95.7% yield) of II, $n^{25}D$ 1.4605, confirmed by infrared spectrum.

Reaction 12. 1,3-Dichloro-1,3-dimethyl-1,3-disilacyclobutane and Methylmagnesium Bromide in Equimolar Quantities.—To an ether solution of 7.70 g. (0.0416 mole) of IV was slowly added 0.042 mole of $(CH_3)MgBr$ over a period of 30 min. The reaction was stirred 16 hr., filtered, and distilled to give 0.20 g. of I and 3.40 g. (0.0206 mole, 49.5% yield) of 1-chloro-1,3,3-trimethyl-1,3-disilacyclobutane (XI), b.p. 67.5–68° (59 mm.), $n^{25}D$ 1.4568.

Anal. Calcd. for $C_5H_{13}ClSi_2$: C, 36.44; H, 7.95; Cl, 21.52. Found: C, 37.24; H, 8.21; Cl, 19.84.

Reaction 13. 1,3-Diethoxy-1,3-dimethyl-1,3-disilacyclobutane and Methylmagnesium Bromide in Equimolar Quantities.—A 15.9-g. (0.0778 mole) sample of VII and 0.078 mole of $(CH_3)MgBr$ were treated as described in reaction 12. Distillation of the product gave 4.40 g. (0.0252 mole, 32.4% yield) of 1-ethoxy-1,3,3-trimethyl-1,3-disilacyclobutane (XII), b.p. 71° (40 mm.), $n^{24}D$ 1.4364.

Anal. Calcd. for $C_7H_{18}OSi_2$: C, 48.21; H, 10.40; mol. wt., 174. Found: C, 48.31; H, 10.30; mol. wt., 175.

Reaction 14. 1-Methyldichlorosiliconmethylene-3-chloro-1,3-dimethyl-1,3-disilacyclobutane and Methylmagnesium Iodide.—To 0.0555 mole of freshly prepared $(CH_3)MgI$ was slowly added 5.00 g. (0.0180 mole) of V over a 30-min. period. The product was hydrolyzed, extracted with ether, and distilled to give 2.90 g. (0.0134 mole, 74.5% yield) of 1-trimethylsilmethyl-1,3,3-trimethyl-1,3-disilacyclobutane (XIII), b.p. 112.5–113° (50 mm.), $n^{25}D$ 1.4578.

Reaction 15. 1-Chloro-1,3,3-trimethyl-1,3-disilacyclobutane and Trimethylsiliconmethylene Lithium.—A 4.50-g. (0.0273 mole) sample of XI was added to $(CH_3)_3SiCH_2Li$ prepared from 5.49 g. (0.0447 mole) of $(CH_3)_3SiCH_2Cl$ and excess lithium dispersion (0.26 mole) in hexane. The reaction was heated to reflux for 40 hr., cooled and filtered, and fractionated *in vacuo* to give 4.20 g. (0.0194 mole, 71.0% yield) of XIII, b.p. 75° (10 mm.), $n^{25}D$ 1.4556. The infrared spectrum was identical with XIII prepared in reaction 14.

Anal. Calcd. for $C_9H_{24}Si_3$: C, 49.91; H, 11.17; mol. wt., 217. Found: C, 51.64; H, 11.19; mol. wt., 219.

Reaction 16. 1,3-Dichloro-1,3-dimethyl-1,3-disilacyclobutane and Phenylmagnesium Bromide in Excess.—To a solution of 0.0699 mole of $(C_6H_5)MgBr$ in 35 ml. of ether was slowly added 5.93 g. (0.0320 mole) of IV over a period of 30 min. The reaction was refluxed for 6 hr., stirred for 16 hr. more, and hydrolyzed; and the product was extracted with ether. Upon evaporation of all high volatiles, 8.00 g. (0.0298 mole, 93.1% yield) of crude 1,3-dimethyl-1,3-diphenyl-1,3-disilacyclobutane (XIV) was obtained. The product was difficult to distil conventionally and was best purified by molecular distillation. The physical properties were b.p. 99° (1.1 mm.), $n^{25}D$ 1.5727.

Anal. Calcd. for $C_{16}H_{20}Si_2$: C, 71.57; H, 7.51; mol. wt., 269. Found: C, 71.89; H, 7.41; mol. wt., 263.

Reaction 17. 1,3,5-Trichloro-1,3,5-trimethyl-1,3,5-trisilacyclohexane and Phenylmagnesium Bromide in Excess.—Following the procedure of reaction 16, the interaction of 0.054 mole of $(C_6H_5)MgBr$ and 4.19 g. (0.0151 mole) of VI gave on work-up 4.01 g. (0.00996 mole, 66.0% yield) of crude 1,3,5-trimethyl-1,3,5-triphenyl-1,3,5-trisilacyclohexane (XV). Biphenyl which was formed as a by-product was sublimed *in vacuo*, and the residue was purified by molecular distillation. The purified XI was a slightly yellow viscous liquid, $n^{25}D$ 1.5873.

Anal. Calcd. for $C_{24}H_{30}Si_3$: C, 71.57; H, 7.51; mol. wt., 403. Found: C, 69.85; H, 7.44; mol. wt., 402.

Reaction 18. Hydrolysis of 1-Ethoxy-1,3,3-trimethyl-1,3-disilacyclobutane.—A 8.10-g. (0.0464 mole) sample of XII was combined with 10.0 g. (0.555 mole) of water in 10 ml. of ethanol and refluxed for 16 hr. Ether extraction of the resulting mixture gave 5.20 g. (0.0189 mole, 81.8% yield) of bis(1,3,3-trimethyl-1,3-disilacyclobutyl)-1-siloxane (XVI), $n^{25}D$ 1.4525.

Anal. Calcd. for $C_{10}H_{26}OSi_4$: C, 43.73; H, 9.54; mol. wt., 275. Found: C, 43.49; H, 9.54; mol. wt., 272.

Silicon Heterocyclic Compounds. I. Synthesis of the 3-Sila-1-heterocyclohexanes[1]

RALPH J. FESSENDEN AND MARVIN D. COON

Department of Chemistry, San Jose State College, San Jose, California

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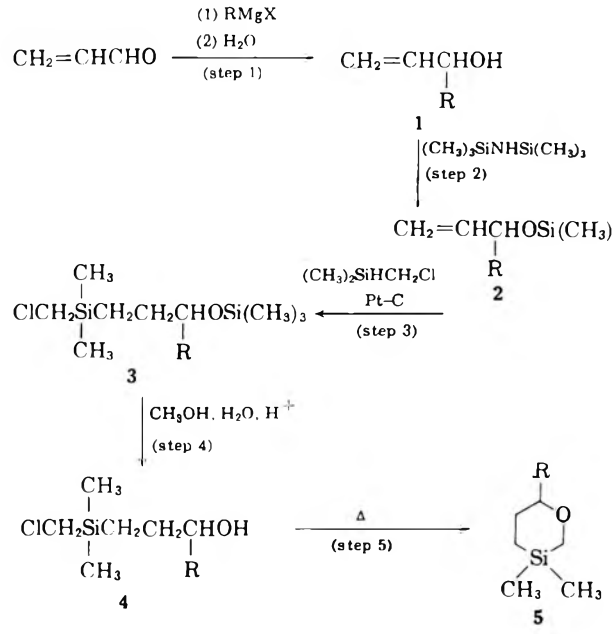
A series of 1-sila-3-heterocyclohexanes of the general formula $(CH_3)_2SiCH_2CH_2CH(R)ZCH_2$ where R is H and Z is O (**5**), $SiCl_2$ (**7**), S (**8**), and n-$C_4H_9N{\cdot}HBr$ (**9**) have been synthesized. The 6-alkyl derivatives (R = CH_3, C_2H_5, and C_3H_7) were prepared in the case where Z = O. Compound **5** (R = H) was prepared by the following sequence, starting with allyl alcohol (**1**). Reaction of **1** and $[(CH_3)_3Si_2]NH$ gave $CH_2{=}CHCH(R)OSi(CH_3)_3$ (**2**). Condensation of **2** with $(CH_3)_2SiH(CH_2Cl)$ using platinum on carbon as catalyst gave $ClCH_2Si(CH_3)_2CH_2CH_2$-$CH(R)OSi(CH_3)_3$ (**3**). Cleavage of **3** to $ClCH_2Si(CH_3)_2CH_2CH_2CH(R)OH$ (**4**) was carried out by refluxing with acid and methanol. Atmospheric distillation of **4** yielded **5**. In the cases of R = CH_3, C_2H_5, and C_3H_7, the starting alcohol, $CH_2{=}CHCH(R)OH$ (**1**), was prepared from acrolein and the corresponding Grignard reagent. The other members of the series were prepared from $XCH_2Si(CH_3)_2CH_2CH_2CH_2X$ (**6**). Reaction of **4** with $SOCl_2$ gave **6a**, X = Cl, and cleavage of **5** with hydrobromic and sulfuric acids gave **6b**, X = Br. Treatment of the di-Grignard reagent of **6a** with $SiCl_4$ gave **7**. Reaction of **6b** with Na_2S gave **8** and with n-butylamine gave **9**.

There has been an expanding interest in silicon heterocyclic chemistry. In general, the reports have concerned themselves with the syntheses and properties of the silacyclohexanes and related silacycloalkanes.[2] Silaheterocycles which contain another heteroatom in the ring are well known.[3] With the exception of systems such as phenoxsilins,[4] these dihetero ring systems generally are of the type which contain the silicon adjacent to the other heteroatom.[5] As a consequence, these silaheterocyclic compounds exhibit a chemistry similar to that of their open-chain analogs. Simple heterocyclic systems in which a silicon atom and another heteroatom are separated by at least one methylene group have not been reported.[6] Extrapolating from the chemistry of carbon-functional organosilicon compounds,[7] one would expect that this type of heterocyclic compound would exhibit interesting chemical properties.

This report is concerned with the synthesis of a series of 1-sila-3-heterocyclohexanes. Subsequent reports will deal with the preparation of the corresponding silaheterocycloheptanes, the limitations of the synthetic method, as well as the chemistry, spectra, and physical properties of these new heterocyclic compounds.

The synthetic route used for the preparation of 3,3-dimethyl-3-sila-1-oxacyclohexane (**5**, R = H) and the 6-alkyl silaoxacyclohexanes (**5**) is shown in Chart I.

CHART I



The synthesis of the parent member of this series, 3,3-dimethyl-3-sila-1-oxacyclohexane (**5**, R = H), was carried out with isolation and characterization of each intermediate. In the preparations of the 6-alkyl derivatives (**5**, R = CH_3, C_2H_5, C_3H_7), only the ring-closed products were characterized.

In the synthesis of **5**, R = H, the starting material was allyl alcohol. Because a silicon hydride reacts with an alcohol in the presence of a catalyst,[8] it was necessary to protect the hydroxyl group prior to step 3. The trimethylsiloxyl group was chosen as blocking group on the basis of its ease of formation by treatment of the alcohol with hexamethyldisilazane,[9] its ease of removal,[10] and its inertness to a silicon hydride in the presence of platinum on carbon.[11] In the reaction with allyl alcohol, the hexamethyldisilazane was freshly prepared from trimethylchlorosilane and ammonia in petroleum ether (b.p. 30–60°).[12] After filtration of the ammonium chloride, this solution was used directly. For the other alcohols (**1**), freshly distilled hexamethyl-

(1) This work was supported by a grant (GP-315) from the National Science Foundation.

(2) (a) R. West, *J. Am. Chem. Soc.*, **76**, 6012 (1954); (b) **76**, 6015 (1954); (c) R. A. Benkeser and E. W. Bennett, *ibid.*, **80**, 5414 (1958); (d) G. D. Oshesky and F. F. Bentley, *ibid.*, **79**, 2047 (1957).

(3) (a) J. W. Curry, *ibid.*, **78**, 1686 (1956); (b) L. H. Sommer and O. F. Bennett, *ibid.*, **79**, 1009 (1957); (c) R. W. West, *ibid.*, **77**, 2339 (1955); (d) L. H. Sommer and G. A. Baum, *ibid.*, **76**, 5002 (1954); (e) W. H. Knoth and R. V. Lindsey, *J. Org. Chem.*, **23**, 1392 (1958); (f) W. H. Knoth and R. V. Lindsey, *J. Am. Chem. Soc.*, **80**, 4106 (1958); (g) K. A. Andrianov and S. E. Yakushkina, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 1396 (1962); *Chem. Abstr.*, **58**, 2466 (1963); (h) G. Fritz and G. Teichmann, *Ber.*, **95**, 2361 (1962); (i) N. S. Nametkin and A. V. Topchiev, *Issled. v Obl. Kremniiorgan. Soedin. Sinez i Fiz.-Khim. Svoistva Akad. Nauk SSSR Inst. Neftekhim. Sinteza Sb. Statei*, 190 (1962); *Chem. Abstr.*, **58**, 6852 (1963); (j) K. A. Andrianov, V. I. Pakhomov, and N. E. Lapteva, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 2039 (1962); *Chem. Abstr.*, **58**, 9112 (1963); (k) N. Wieber and N. Schmidt, *Ber.*, **96**, 1019 (1963); (l) H. Niederpruem and W. Simmler, *ibid.*, **96**, 965 (1963).

(4) D. Wittenberg, H. A. McNinch, and H. Gilman, *J. Am. Chem. Soc.*, **80**, 5418 (1958).

(5) Ref. 3e and f.

(6) The syntheses of disilacycloalkanes have been reported; see ref. 3e, h, i, and l.

(7) (a) C. Eaborn, "Organosilicon Compounds," Academic Press, Inc., New York, N. Y., 1960, Chapter 14; (b) P. D. George, M. Prober, and J. R. Elliott, *Chem. Rev.*, **56**, 1065 (1956).

(8) Ref. 7a, p. 200 and 294, and the references therein.

(9) R. J. Fessenden and J. S. Fessenden, *Chem. Rev.*, **61**, 361 (1961).

(10) H. Gilman and G. N. R. Smart, *J. Org. Chem.*, **19**, 441 (1954).

(11) Unpublished research, R. J. Fessenden.

(12) R. C. Osthoff and S. W. Kantor, *Inorg. Syn.*, **5**, 55 (1957).

disilazane was used. Hexamethyldisiloxane, the hydrolysis product of the disilazane,[13] was a contaminant in the lower boiling alkoxenylsilanes (**2**), but did not interfere with the condensation (step 3).

Step 3, the condensation of (chloromethyl)dimethylsilane with silyl-blocked alkenyl alcohols (**3**),[14] proceeded with substantial evolution of heat. With the lower boiling reactants and, in particular, with allyloxytrimethylsilane, the reaction proceeded with almost explosive violence. The procedure outlined in the Experimental has been used with safety in runs varying from 0.1 to 6.0 moles. In some runs, the catalyst failed, due to the presence of free alcohol in **2**, allowing a buildup of reactants, but addition of a new portion of catalyst (caution) resulted in continuation of the reaction.

The removal of the siloxyl-blocking group from **3** (step 4) was carried out in high yields (79–81%) by the "transesterification" reaction characteristic of alkoxy silanes.[15] A large excess of aqueous methanol with a trace of acid was used. The resulting methoxytrimethylsilane and hexamethyldisiloxane, as well as the excess methanol and water, were removed by distillation prior to water work-up and fractional distillation. The combination of steps 3 and 4, with filtration to remove the Pt–C prior to distillation, resulted in overall yields of 63 to 74%.

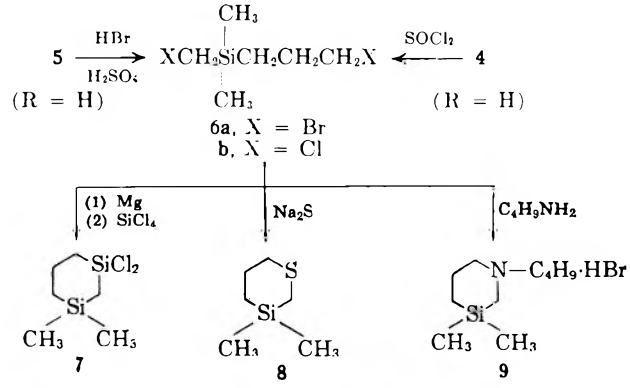
Substantial difficulty was encountered in obtaining an analytical sample of **4** (R = H) because of the tendency of this compound to undergo ring closure to **5**. The desired sample was obtained only after repeated vacuum distillation.

The ring **5** (R = H) was obtained in 54 to 58% yields by slow atmospheric distillation of **4**. The distillate was collected in a flask containing solid sodium carbonate to minimize the contact time of **5** with hydrogen chloride. With the 6-alkyl compounds, higher yields of the cyclic product were obtained: R = CH_3, 73%; R = C_2H_5, 81%; R = C_3H_7, 68%.

The syntheses of other 1-sila-3-heterocyclohexanes by extension of the synthetic scheme are summarized in Chart II. The preparation of the 6-alkyl derivatives of these rings was not attempted.

The key intermediate for the synthesis of 1,1-dichloro-3,3-dimethyl-1,3-disilacyclohexane (**7**), 3,3-dimethyl-3-sila-1-thiacyclohexane (**8**), and 3,3-dimethyl-3-sila-1-butyl-1-azacyclohexane hydrobromide (**9**) was the dihalogen compound, **6a** or **6b**. Compound **6a**, α-bromopropyl(bromomethyl)dimethylsilane, was obtained from **5**, R = H, in 73 to 83% yields using 48% hydrobromic acid and concentrated sulfuric acid. The procedure employed was developed for the conversion of tetrahydropyran to 1,5-dibromopentane[16] (80–82% yield). This reaction is indicative that **5** should show a chemistry similar to that of tetrahydropyran.

CHART II



Compound **6b** was obtained in yields of 63 to 80% by treatment of **4**, R = H, with thionyl chloride, followed by distillation of the crude reaction mixture at atmospheric pressure. The classical procedures[17] gave substantially lower yields (32–40%).

A Grignard ring-closure reaction was used to obtain compound **7**. The di-Grignard reagent of **6a** was prepared in the usual manner,[18] and the ring closure was carried out using inverse addition. The work-up procedure described in the Experimental is a modification of that employed by West for the synthesis of 1,1-dichlorosilacyclohexane (51% yield).[19] Compound **7** was obtained from this reaction in 42 to 50% yields.

The silathiacyclohexane **8** was prepared in 69% yield from **6a** and in 47% yield from **6b**. The procedure used was that of Tarbell,[20] which was developed for the synthesis of tetramethylene sulfide (64% yield).

The reaction of **6a** with *n*-butylamine, spontaneous and exothermic, gave the ring **9** in 51% yield. No attempt has yet been made to prepare other 1-alkyl derivatives of **9**. All attempts to synthesize the parent 3-sila-1-azacyclohexane have met with failure.

Experimental[21]

Silaoxacyclohexanes. (Chloromethyl)dimethylsilane.—To 37.9 g. (1.0 mole) of lithium aluminum hydride in 1 l. of anhydrous ether was added dropwise with cooling, over a period of 1 hr., 429 g. (3.0 moles) of (chloromethyl)dimethylchlorosilane (b.p. 115–117°). After the addition had been completed, the reaction mixture was heated at reflux for 1 hr., then cooled and filtered, using suction and Filter-Cel, to remove the insoluble inorganic salts. The clear filtrate was returned to the reaction flask and water was added (vigorous reaction). After the reaction had subsided, the resulting white salts were decomposed using dilute hydrochloric acid, and finally the reaction mixture was made neutral using sodium bicarbonate solution. The ethereal layer was separated, the aqueous layer was extracted with two 200-ml. portions of ether. The ethereal extracts were combined and dried with magnesium sulfate. Distillation

(13) R. O. Sauer and R. H. Hasek, *J. Am. Chem. Soc.*, **68**, 241 (1946).

(14) That the direction of addition of the silicon hydride to the double bond is as indicated is shown by the stability of the resulting alcohol to refluxing acid. If the addition had occurred in the reverse direction, the product of step 5 would have been a β-hydroxyalkyl silane [*i.e.*, $Cl-CH_2Si(CH_3)_2CH(CH_3)CH_2OH$] which would be expected to be acid unstable [F. C. Whitmore, L. H. Sommer, J. R. Gold, and R. E. Van Strein, *ibid.*, **69**, 1551 (1947)]. Further evidence for the structure assignment is found in the n.m.r. spectrum of **4**, R = H, which shows an ill-defined pentuplet at δ 1.65 ($-CH_2-CH_2-CH_2-$) and a triplet at 0.20 ($Si-CH_2-CH_2-$). The areas under these two peaks were in the ratio of 2:2, in agreement with structure **4**.

(15) Ref. 10.

(16) D. W. Andrus, *Org. Syn.*, **23**, 67 (1943).

(17) E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1954, p. 269, and the references cited therein.

(18) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice Hall, Englewood Cliffs, N. J., 1962, p. 449.

(19) Ref. 2a.

(20) D. S. Tarbell and C. Weaver, *J. Am. Chem. Soc.*, **63**, 2939 (1941).

(21) All boiling points are uncorrected. Distillations, unless otherwise noted, were made at atmospheric pressure using a 3-ft. modified Podbielniak column (*cf.* ref. 18, p. 237). The infrared spectra were recorded using a Beckman IR-4 spectrophotometer. The n.m.r. data were obtained using a Varian A-60 instrument, carbon tetrachloride solution with TMS as internal reference. The carbon, hydrogen, chlorine, and nitrogen analyses were performed by the Berkeley Microanalytical Laboratory. Silicon analyses were performed in this laboratory.

yielded 223 g. (69%) of (chloromethyl)dimethylsilane, b.p. 80–82°, $n^{25}D$ 1.4182; lit.[22] b.p. 81°, $n^{25}D$ 1.4165. The yields varied from 60 to 73%.

Allyloxytrimethylsilane.—Ammonia gas was passed through a solution of 364 g. (8.4 moles) of trimethylchlorosilane dissolved in 2.4 l. of petroleum ether (b.p. 30–60°) until the reaction vessel became cool to the hand. The addition of the ammonia required approximately 5 hr. The mixture was then filtered to remove the ammonium chloride, and the filter cake was washed thoroughly with petroleum ether to remove any hexamethyldisilazane. To the filtrate, containing crude hexamethyldisilazane and petroleum ether, was added 370 g. (6.4 moles) of allyl alcohol. The mixture was heated at reflux for 24 hr. and then distilled without further work-up to yield 568 g. of allyloxytrimethylsilane, b.p. 100°, $n^{24}D$ 1.3950; lit.[23] b.p. 100°, $n^{30}D$ 1.3905. The yields varied from 61 to 86%. Gas phase chromatography of the alloxytrimethylsilane indicated that it contained approximately 3% hexamethyldisiloxane (b.p. 100°). No attempt was made to further purify the alloxytrimethylsilane.

γ-(Trimethylsiloxy)propyl(chloromethyl)dimethylsilane.—To a 1-l. flask containing 0.1 g. of Pt–C (5%) was added 50 g. of a mixture of 202.3 g. (1.89 moles) of (chloromethyl)dimethylsilane and 245.3 g. (1.89 moles) of allyloxytrimethylsilane. The mixture was heated to about 80°, at which point a very vigorous reaction ensued (caution). After the reaction had subsided, the remaining mixture of reactants was added dropwise while the temperature of the reaction mixture was maintained at greater than 120°. In some runs, the addition of another 0.1 g. of Pt–C (caution) was required to maintain the temperature of the reaction. The addition of the reactants required about 1 hr. After the addition had been completed, the mixture was heated at reflux for 1.5 hr. During the reflux period, the reflux temperature rose from 130° to about 175°. The mixture was then cooled, filtered, and distilled. There was obtained 366 g. (81%) of γ-(trimethylsiloxy)propyl(chloromethyl)dimethylsilane, b.p. 222–225°, $n^{25}D$ 1.4386.

Anal. Calcd. for $C_9H_{23}ClOSi_2$: C, 45.28; H, 9.64; Cl, 14.88. Found: C, 45.51; H, 9.66; Cl, 14.86.

Yields varied from 74 to 84%. The infrared spectrum showed the characteristic absorption bands at 8.0 (Si–CH_3) and 9.1 μ (Si–O–C).

γ-Hydroxypropyl(chloromethyl)dimethylsilane.—A mixture of 307 g. (1.29 moles) of γ-(trimethylsiloxy)propyl(chloromethyl)-dimethylsilane, 400 ml. of methanol, 80 ml. of water, and 4 ml. of 6 *N* sulfuric acid was heated at reflux for 15 min. The mixture then was distilled without further work-up, and material boiling up to 70° was discarded. The residue was diluted with 500 ml. of water and extracted with ether. Fractional distillation of the ethereal extracts resulted in 172 g. (81%) of γ-hydroxypropyl-(chloromethyl)dimethylsilane, b.p. 125° (30 mm.), $n^{22}D$ 1.4662. The yields varied from 78 to 81%.

Gas phase chromatography indicated that the hydroxy compound was contaminated with a lower boiling material, shown later to be 3,3-dimethyl-3-sila-1-oxacyclohexane (**5**). An analytical sample was finally obtained after repeated distillation with b.p. 80° (3.0 mm.).

Anal. Calcd. for $C_6H_{15}ClOSi$: C, 43.24; H, 9.00; Cl, 21.40; Si, 16.8. Found: C, 43.12; H, 8.96; Cl, 21.52; Si, 16.7.

The infrared spectrum of the hydroxy compound was in agreement with the assigned structure, showing the expected bands at 3.0 (OH) and 8.0 μ ($SiCH_3$).

In other runs, the aqueous methanol and sulfuric acid were added directly to the crude γ-(trimethylsiloxy)propyl(chloromethyl)dimethylsilane reaction flask, the mixture was heated at reflux for 15 min., filtered to remove the Pt–C, and then distilled. The over-all yields based on allyloxytrimethylsilane and (chloromethyl)dimethylsilane ranged from 63 to 77%.

3,3-Dimethyl-3-sila-1-oxacyclohexane.—In a 1-l. round-bottomed flask was placed 500 g. (3.0 moles) of γ-hydroxypropyl-(chloromethyl)dimethylsilane, and the material was distilled at atmospheric pressure while the distillate was collected on solid sodium carbonate. The distillation was carried out over a period of 12 hr. The boiling point of the distillate was maintained between 120 and 135°. There remained after the distillation 165 g. of residue which was not characterized, but which was used for the preparation of compound **6b**. The distillate was washed with three 100-ml. portions of saturated sodium carbonate solution, dried with anhydrous sodium carbonate, then fractionally distilled to yield 215 g. (54%) of 3,3-dimethyl-3-sila-1-oxacyclohexane, b.p. 135–138°, $n^{22}D$ 1.4444. The yields using this procedure varied from 46 to 57%.

Anal. Calcd. for $C_6H_{14}OSi$: C, 55.38; H, 10.77; Si, 21.54. Found: C, 55.65; H, 10.70; Si, 21.50.

6-Alkyl Silaoxacyclohexanes.—The following procedure was used to prepare the 6-alkyl 3,3-dimethyl-3-sila-1-oxacyclohexanes. In all cases, only the final silaoxacyclohexane was completely characterized.

Preparation of Alcohols.—To the alkyl Grignard reagent was added acrolein, and the reaction mixture was worked up in the standard fashion. Runs were carried out on a 4.0-mole basis. The yields and physical constants of the crude alcohols were 3-hydroxy-1-butene, 58%, b.p. 96–97°, lit.[24] b.p. 96–97°; 3-hydroxy-1-pentene, 43%, b.p. 112–114°, $n^{25}D$ 1.4242, lit.[25] b.p. 114–114.5°; 3-hydroxy-1-hexene, 46%, b.p. 70–75° (150 mm.), $n^{21}D$ 1.4295, lit.[26] b.p. 79–82° (100 mm.).

Preparation of Silyl-Blocked Alcohols.—Purified hexamethyldisilazane (b.p. 124–126°) was heated to reflux in a 1-l. round-bottomed flask, and the alcohol was added in small portions through the condenser. The addition for a 2.0-mole run required about 1 hr. After the mixture was heated at reflux for an additional 15 to 24 hr., the reaction mixture was distilled. The yields and physical constants of the crude siloxy derivatives were 3-trimethylsiloxy-1-butene, 91%, b.p. 107°, $n^{27}D$ 1.3934; 3-trimethylsiloxy-1-pentene, 91%, b.p. 130°, $n^{24}D$ 1.4047; 3-trimethylsiloxy-1-hexene, 63%, b.p. 151°, $n^{24}D$ 1.4101.

Condensation with (Chloromethyl)dimethylsilane.—A mixture of the silyl-blocked alcohol and the (chloromethyl)dimethylsilane (0.5 to 1.0-mole runs) was made, and the procedure described for the preparation of γ-(trimethylsiloxy)propyl(chloromethyl)dimethylsilane was followed. After the reflux period, the reaction mixture was filtered, then an equal volume of aqueous methanol (15% water by volume) with a trace of hydrochloric acid was added. The mixture was heated at reflux for 0.5 hr., distilled at atmospheric pressure until distillation became difficult, then distilled at reduced pressure. The yields and physical constants of the crude hydroxy compounds were γ-hydroxybutyl(chloromethyl)dimethylsilane, 86%, b.p. 87° (2.8 mm.), $n^{25}D$ 1.4618; γ-hydroxypentyl(chloromethyl)dimethylsilane, 82%, b.p. 92° (2.7 mm.), $n^{25.5}D$ 1.4620; γ-hydroxyhexyl(chloromethyl)-dimethylsilane, 71%, b.p. 109–110°, $n^{25}D$ 1.4620.

Ring Closure.—The ring-closure reactions of the γ-hydroxyalkyl (chloromethyl)silanes were carried out using the procedure as described for 3,3-dimethyl-3-sila-1-oxacyclohexane. The yields and physical properties are summarized in Table I.

TABLE I

YIELDS AND PHYSICAL PROPERTIES OF THE 6-ALKYL 3,3-DIMETHYL-3-SILA-1-OXACYCLOHEXANES

Compound	Yield, %	B.p., °C.	$n^{25}D$
6-Methyl-[a]	73	147–148	1.4394
6-Ethyl-[b]	81	163–169	1.4418
6-Propyl-[c]	68	190–191	1.4440

[a] *Anal.* Calcd. for $C_7H_{16}OSi$: C, 58.32; H, 11.10; Si, 19.50. Found: C, 58.12; H, 11.04; Si, 19.24. [b] *Anal.* Calcd. for $C_8H_{18}OSi$: C, 60.75; H, 11.38; Si, 17.76. Found: C, 60.73; H, 11.49; Si, 17.64. [c] *Anal.* Calcd. for $C_9H_{20}SiO$: C, 62.79; H, 11.63; Si, 16.29. Found: C, 62.89; H, 11.43; Si, 16.13.

Other Silaheterocyclohexanes. γ-Bromopropyl(bromomethyl)dimethylsilane.—A mixture of 32.5 g. (0.25 mole) of 3,3-dimethyl-3-sila-1-oxacyclohexane, 74 g. of concentrated sulfuric acid, and 253 g. of 48% hydrobromic acid was heated under reflux for 3 hr. and then cooled to room temperature. The reaction mixture was diluted with 100 ml. of water, and the organic material was extracted with 100 ml. of ether. The ethereal material was washed with two 50-ml. portions of saturated sodium bicarbonate solution and dried with magnesium sulfate. Fractional distillation yielded 52.7 g. (78%) of γ-bromopropyl-(bromomethyl)dimethylsilane, b.p. 103° (8.5 mm.), $n^{24}D$ 1.5066.

(22) (a) L. H. Sommer, W. P. Burie, and D. R. Wegenberg, *J. Am. Chem. Soc.*, **81**, 251 (1959); (b) R. Merker and M. J. Scott, *ibid.*, **81**, 975 (1959).

(23) E. Masuhara, K. Kojima, and N. Tarumi, *Skika Zairo Kenkyu-jo Hokoku*, **2**, 18 (1954); *Chem. Abstr.*, **52**, 1671 (1958).

(24) S. A. Morell and A. H. Auernheimer, *J. Am. Chem. Soc.*, **66**, 795 (1944).

(25) K. Rosenmund and H. Bach, *Ber.*, **94**, 2394 (1961).

(26) H. Normant, *Compt. rend.*, **240**, 314 (1955); *Chem. Abstr.*, **50**, 229 (1950).

Anal. Calcd. for $C_6H_{14}Br_2Si$: C, 26.28; H, 5.11; Br, 58.39. Found: C, 26.31; H, 5.31; Br, 58.28.

γ-Chloropropyl(chloromethyl)dimethylsilane. A.—To 29.7 g. (0.25 mole) of thionyl chloride was added in small portions (caution) 41.7 g. (0.25 mole) of γ-hydroxypropyl(chloromethyl)-silane. After the evolution of gases had subsided, the mixture was heated at reflux for 1 hr. and distilled without further work-up to yield 28.9 g. (63%) of the dichloro derivative, b.p. 212°, $n^{23}D$ 1.4656. Yields using this procedure varied from 63 to 80%. Reactions using pyridine as solvent gave yields ranging from 32 to 40%.

Anal. Calcd. for $C_6H_{14}ClSi$: C, 38.92; H, 7.56; Cl, 38.37. Found: C, 38.90; H, 7.54; Cl, 38.18.

B.—A mixture of 81.3 g. (0.685 mole) of thionyl chloride and 114 g. of the residue from the preparation of 3,3-dimethyl-3-sila-1-oxacyclohexane yielded, after a 3-hr. reflux and distillation, 100.8 g. of the dichloro derivative.

1,1-Dichloro-3,3-dimethyl-1,3-disilacyclohexane.—Using the general procedure as outlined by Cason and Rapoport,[18] the di-Grignard reagent of γ-bromopropyl(bromomethyl)dimethylsilane (54.2 g., 0.19 mole) was prepared using 9.2 g. (0.38 g.-atom) of magnesium turnings and 200 ml. of ether. The Grignard reagent was then transferred to a dropping funnel and added dropwise to a solution of 32.4 g. (0.19 mole) of silicon tetrachloride in 500 ml. of ether. The mixture was heated under reflux for 19 hr., then filtered with suction using Filter-Cel. The filtrate was distilled to yield 25.4 g. (62%) of the disilacyclohexane, b.p. 97° (20 mm.), $n^{23}D$ 1.4798. An analytical sample was obtained using a gas phase preparative column.

Anal. Calcd. for $C_6H_{14}Cl_2Si_2$: C, 33.80; H, 6.57. Found: C, 34.04; H, 6.55.

3,3-Dimethyl-3-sila-1-thiacyclohexane.—A mixture of 29.7 g. (0.104 mole) of γ-bromopropyl(bromomethyl)dimethylsilane, 26.2 g. (0.109 mole) of sodium sulfide, 50 ml. of water, and 200 ml. of ethanol was heated under reflux for 16 hr. The reaction mixture then was distilled to dryness. The first 75 ml. of the distillate, b.p. 79–81°, was diluted with water, and the oil which separated was extracted with 50 ml. of petroleum ether (b.p. 30–60°). A saturated solution of mercuric chloride was added to the remainder of the distillate until solid material ceased to form (*ca.* 1 l. was required). The solid mercuric salt was collected, washed with ethanol and water, then steam distilled. About 500 ml. of distillate was collected. The organic material was extracted from the distillate with petroleum ether (b.p. 30–60°). Combination of the extracts followed by drying over magnesium sulfate and distillation yielded 10.9 g. (69%) of the silathiacyclohexane, b.p. 181°, $n^{26}D$ 1.4978.

Anal. Calcd. for $C_6H_{14}SSi$: C, 49.31; H, 9.59; S, 21.91; Si, 19.17. Found: C, 49.53; H, 9.65; S, 21.62; Si, 19.19.

In a run using the same conditions except that γ-chloropropyl-(chloromethyl)dimethylsilane was used in place of the dibromo derivative, there was obtained a 47% yield of the silathiacyclohexane.

3,3-Dimethyl-3-sila-1-butyl-1-azacyclohexane Hydrobromide.—To 30.0 g. (0.11 mole) of γ-bromopropyl(bromomethyl)dimethylsilane was added 16.1 g. (0.22 mole) of *n*-butylamine. A spontaneous exothermic reaction occurred almost immediately, the temperature rising to 170°. After the reaction had subsided, the mixture was heated to 260°. Upon cooling, the mixture solidified. The solid was dissolved in boiling water, clarified with activated carbon, and crystallized, yielding 15.1 g. (52%) of the crude product. Recrystallization from ethanol (95%) gave an analytical sample, m.p. 210–211°.

Anal. Calcd. for $C_{10}H_{24}BrNSi$: C, 45.11; H, 9.02; N, 5.26; Si, 10.54. Found: C, 45.37; H, 8.88; N, 5.11; Si, 10.61.

Some Reactions of Carbomethoxymercuric Salts

GEORGE F. FANTA[1]

Research Laboratories, Ethyl Corporation, Ferndale 20, Detroit, Michigan

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Carbomethoxymercuric acetate (I) yielded benzyl acetate and methyl benzyl ether when treated with excess benzyl bromide. Carbomethoxymercuric bromide (II, X = Br), mercurous bromide, and mercuric bromide were also isolated. On reaction with benzyl bromide, carbomethoxymercuric bromide yielded methyl benzyl ether, carbon monoxide, and mercuric bromide. Photochemical decomposition of carbomethoxymercuric iodide (II, X = I) in benzene solution afforded methyl benzoate and a compound tentatively identified as toluene. Reaction of a methanolic solution of I with ethylene yielded β-methoxyethylmercuric acetate.

A methanolic solution of mercuric acetate will react readily with carbon monoxide to form carbomethoxymercuric acetate (I) (eq. 1). Furthermore, the acetate group of I may be easily replaced by halide (eq. 2) to form compounds of structure II[2] (X = Cl, Br, or I). Although the structures for these compounds

$$Hg(OCOCH_3)_2 + CO + CH_3OH \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OHg\overset{O}{\overset{\|}{C}}OCH_3 + CH_3CO_2H \quad (1)$$

(I)

$$I + NaX \longrightarrow XHg\overset{O}{\overset{\|}{C}}OCH_3 + CH_3CO_2Na \quad (2)$$

(II)

caused some controversy in the early literature,[2–5] a recent investigation by Halpern and Kettle[6] has proven structures I and II to be correct.

Since the chemistry of this class of organomercury compounds appears to have been little studied, the reactions of I and II (X = Br) with benzyl bromide, the photochemical decomposition of II (X = I), and the reaction of I with ethylene were investigated. The results of these studies are herein reported.

Reaction with Benzyl Bromide.—In 1920, Manchot reported the reactions of methyl iodide with carbomethoxymercuric acetate (I) and *n*-propyl iodide with carbethoxymercuric chloride (III), although the structures he proposed for I and III were incorrect.[4] The former reaction was reported to yield carbon monoxide, mercuric iodide, and mercuric acetate, whereas carbon monoxide and mercury halides were isolated from the latter. Equation 3 was suggested to account for the latter reaction, although the ethyl ether apparently was not isolated.

$$ClHg\overset{O}{\overset{\|}{C}}OC_2H_5 + RI \longrightarrow CO + HgClI + ROC_2H_5 \quad (3)$$

(III)

Since Manchot identified no organic compounds from his reactions, the reaction of compound I with an ex-

(1) Northern Regional Research Laboratory, Peoria, Ill.
(2) W. Schoeller, W. Schrauth, and W. Essers, *Ber.*, **46**, 2864 (1913).
(3) W. Schoeller, *ibid.*, **53**, 2144 (1920).
(4) W. Manchot, *ibid.*, **53**, 984 (1920).
(5) W. Manchot, *ibid.*, **54**, 571 (1921).
(6) J. Halpern and S. F. A. Kettle, *Chem. Ind.* (London), 668 (1961).

cess of benzyl bromide was run in chloroform solution. Analysis of the volatile products by vapor phase chromatography (v.p.c.) showed two major components which were separated by preparative scale v.p.c. and identified as methyl benzyl ether and benzyl acetate by their infrared spectra. The yield of benzyl acetate, calculated from the vapor chromatogram, appeared quantitative, and the calculated yield of methyl benzyl ether was 20%, based on I. Mercurous bromide, mercuric bromide, and carbomethoxymercuric bromide were isolated from the solid portion of the reaction mixture in yields of 22.7, 20.5, and 36.7%, respectively, based on I.

When carbomethoxymercuric bromide (II, X = Br) was allowed to react with benzyl bromide, carbon monoxide and methyl benzyl ether were obtained along with a 92% crude yield of mercuric bromide. The yield of methyl benzyl ether, calculated from the vapor chromatogram, appeared quantitative.

The above data suggest that the first reaction to occur when compound I is treated with benzyl bromide is that represented by eq. 4. The excess benzyl bromide present in the system then reacts with II to form methyl benzyl ether, carbon monoxide, and mercuric bromide according to eq. 5, which is essentially the same as that proposed by Manchot.[4] The path by which mercurous bromide is formed is unknown.

$$I + C_6H_5CH_2Br \longrightarrow C_6H_5CH_2OAc + II\ (X = Br) \quad (4)$$

$$II\ (X = Br) + C_6H_5CH_2Br \longrightarrow C_6H_5CH_2OCH_3 + CO + HgBr_2 \quad (5)$$

The reaction of I with benzyl bromide to form benzyl acetate and II (X = Br) is analogous to the known reactions of mercuric acetate with acetyl chloride[7] and alkyl halides.[8] Equation 5 is analogous to the reaction path formulated by Dessy and Paulik[9] for the decomposition of II (X = Cl) with acids.

Photochemical Decomposition of Carbomethoxymercuric Iodide.—Corbett and Williams[10] have studied the photochemical decomposition of methylmercuric iodide in benzene solution and have isolated toluene from the reaction mixture. The suggested mechanism involved the cleavage of methyl mercuric iodide to mercurous iodide and methyl radical followed by reaction of methyl radical with the aromatic ring. On the basis of these results, it was of interest to see if the carbomethoxy radical (IV) could be generated from II (X = I) in the presence of ultraviolet light and similarly trapped by reaction with benzene.

Photolysis of a benzene solution of II (X = I) for 6 hr. at 6–10° gave a 56% yield of crude mercurous iodide. Concentration of the benzene solution afforded methyl benzoate and a compound with the retention time of toluene in yields of 21 and 12%, respectively, as calculated from the vapor chromatogram. Owing to the small scale of the reaction, the latter compound could not be isolated in an amount sufficient to afford positive identification by infrared. On the basis of the mechanism suggested below, the above yields were calculated assuming 0.5 mole of substituted benzene per mole of carbomethoxymercuric iodide. One unknown compound was also present in the mixture. The peak area on the vapor chromatogram corresponding to this material was slightly larger than that of toluene.

Methyl benzoate was probably formed by a route analogous to that proposed for the methylmercuric iodide decomposition[10] (eq. 6 and 8). The decomposition of radical IV to carbon dioxide and methyl (eq. 7) has been observed[11] and would account for the formation of toluene.

$$II\ (X = I) \xrightarrow{h\nu} HgI + \cdot\overset{O}{\overset{\|}{C}}OCH_3 \quad (6)$$
(IV)

$$IV \longrightarrow CO_2 + \cdot CH_3 \quad (7)$$

$$ArH + IV \longrightarrow \left[\begin{array}{c} H \\ Ar \\ CO_2CH_3 \end{array}\right]\cdot \xrightarrow{R\cdot} ArCO_2CH_3 + RH \quad (8)$$
(R = ·CH₃ or IV)

Reaction of Carbomethoxymercuric Acetate with Ethylene.—When a methanolic solution of carbomethoxymercuric acetate (I) was allowed to react with ethylene, a crystalline solid was obtained. Both melting point and elemental analysis suggested that this material was β-methoxyethylmercuric acetate (V). The proposed structure was confirmed by both mixture melting point and comparison of the infrared spectrum with that of a sample of V prepared by the known reaction of ethylene with mercuric acetate in methanol.[1,12]

Two explanations for the formation of V from I may be suggested. Perhaps the most obvious route is the reaction of I with ethylene with loss of the carbomethoxy group to yield V directly. Mercuric methoxyacetate ($CH_3CO_2HgOCH_3$) could possibly be formed from I through loss of carbon monoxide prior to reaction with ethylene.[13] Another possibility is shown in eq. 9. Here, reaction of ethylene with I

$$I + CH_2{=}CH_2 + CH_3OH \longrightarrow CH_3OCH_2CH_2HgC(=O)CH_3 + CH_3CO_2H$$
(VI)

$$VI + CH_3CO_2H \longrightarrow CH_3OH + CO + CH_3OCH_2CH_2HgOCOCH_3 \quad (9)$$
(V)

in a manner analogous to that with mercuric acetate could occur to yield VI and acetic acid followed by reaction of acetic acid with VI to yield V and carbon monoxide. The data at hand, however, do not permit a choice between the various alternatives.

Experimental[14]

Preparation of Carbomethoxymercuric Acetate (I).—Carbon monoxide was passed through a methanolic solution of 100 g. (0.314 mole) of mercuric acetate according to the method of Schoeller.[2] The crude material was dissolved in warm chloroform (below 45°), filtered, and precipitated with petroleum ether to yield 88.8 g. (88.8%) of material, m.p. 103.5–107° dec. (lit.[2] m.p. 109° dec.). The n.m.r. spectrum (40 Mc.) of a sample

(7) R. C. Paul, D. Singh, and S. S. Sandhu, *J. Chem. Soc.*, 319 (1959).
(8) M. M. Koton, T. M. Zorina, and E. G. Osberg, *J. Gen. Chem. USSR*, **17**, 59 (1947); *Chem. Abstr.*, **42**, 141d (1948).
(9) R. E. Dessy and F. E. Paulik, *J. Am. Chem. Soc.*, **85**, 1812 (1963).
(10) G. E. Corbett and G. H. Williams, *Proc. Chem. Soc.*, 240 (1961).
(11) J. C. J. Thynne and P. Gray, *ibid.*, 141 (1962), and references quoted therein.
(12) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).
(13) Suggested by a referee.
(14) Melting points are uncorrected and were determined in capillary tubes unless otherwise specified.

further purified by recrystallization from chloroform–petroleum ether was in agreement with the published spectrum.[6] Sharp singlets were observed at τ 7.95 and 6.25, and the areas under these two signals were in the ratio of 1.0:0.8, respectively.

Preparation of Carbomethoxymercuric Bromide (II, X = Br).—To a solution of 20.04 g. (0.0629 mole) of carbomethoxymercuric acetate in 100 ml. of absolute methanol was added a solution of 8.39 g. (0.0815 mole) of sodium bromide in 50 ml. of water. The addition was carried out at room temperature. After addition was complete, the reaction mixture was stirred for a few minutes at room temperature, cooled, and filtered to yield 17.96 g. of crude carbomethoxymercuric bromide. This material was crystallized from diethyl ether to afford 11.97 g. (56.2% yield) of purified material, m.p. 125–128° dec. (lit.[2] m.p. 127–128° dec.).

Preparation of Carbomethoxymercuric Iodide (II, X = I).—To a cold stirred solution of 50 g. (0.157 mole) of carbomethoxymercuric acetate in 250 ml. of absolute methanol was added a solution of 32.3 g. (0.215 mole) of sodium iodide in 125 ml. of water. Addition was made over a 10–15-min. period, while the reaction mixture was cooled in ice. The gray crystalline solid was removed by filtration, dried under vacuum (wt. 36.5 g.), and recrystallized from ether to yield 23.43 g. of purified material (38.6% yield).

β-Methoxyethylmercuric acetate (V) was prepared by passing ethylene through a methanolic solution of 20.0 g. (0.0627 mole) of mercuric acetate according to the method of Schoeller.[2] The crude solid was extracted with hot pentane. On cooling, the pentane extracts deposited 14.4 g. (72%) of crystalline β-methoxyethylmercuric acetate. A small portion of this material was recrystallized a second time from pentane. The melting point (hot stage) of this purified material was 41.5–42.5° (lit.[2] m.p. 42°).

Reaction of Carbomethoxymercuric Acetate (I) with Benzyl Bromide.—A mixture of 10.12 g. (0.0318 mole) of carbomethoxymercuric acetate, 5 ml. (0.0421 mole) of benzyl bromide and 10 ml. of chloroform was heated under reflux (internal temperature of 78°) for a total of 22.7 hr. and cooled to room temperature. The reaction mass was then filtered; the gray precipitate was washed with *n*-pentane. The weight of dry solid was 9.71 g. The final filtrate, after decantation from 0.40 g. of gummy solid, was concentrated to a volume of about 50 ml. by distillation at atmospheric pressure. This material was then stirred vigorously for 1 hr. at room temperature with a solution of 7.30 g. (0.0430 mole) of silver nitrate in 50 ml. of water. The mixture was filtered; the precipitate was washed with bothpen tane and diethyl ether. The two-phase filtrate was separated and the aqueous phase was washed with ether. The combinedo rganic phase was washed with water, dried over magnesium sulfate, and concentrated by distillation at atmospheric pressure to a weight of 9.35 g. Vapor chromatographic analysis of this material showed two major components and two minor components in addition to solvent and some low-boiling minor components which came off the column quite close to solvent. The two major components were separated by preparative scale v.p.c. and were identified as methyl benzyl ether and benzyl acetate by comparison of their infrared spectra with those of authentic samples. Only traces of benzyl alcohol were detected, and no methyl phenylacetate was found. Approximate yields were calculated from the vapor chromatogram using the method of Eastman[15] (the molecular weights of the unknown minor components were estimated from their retention times). The calculated yield of benzyl acetate was quantitative (calculated yield figure was over 100%), and that of methyl benzyl ether was 20% (based on carbomethoxymercuric acetate charged). The two higher boiling minor components taken together amounted to about 10% by weight of the 9.35 g. of material originally analyzed. These components were not identified.

Fractional crystallization of the 9.71 g. of gray solid obtained earlier afforded 2.02 g. (22.7%) of crude mercurous bromide, 2.35 g. (20.5%) of mercuric bromide, and 3.94 g. (36.7%) of carbomethoxymercuric bromide. Mercurous bromide was isolated owing to its insolubility in diethyl ether. The latter two compounds were separated by fractional crystallization from chloroform. The per cent yields given are based on carbomethoxymercuric acetate charged. Mercuric bromide and the bromo compound II were identified by the melting points of purified samples and also by comparison of their infrared spectra with those of authentic samples. The observed melting point of mercuric bromide was 229–233.5° (sample appeared to start subliming about 200°), and that of bromo compound II was 124–128.5° dec. Mercurous bromide was identified by a positive ammonium hydroxide test for mercurous ion[16] and elemental analysis of a partially purified sample obtained by submitting the crude material to a single sublimation.

Anal. Calcd. for HgBr: Hg, 71.51; Br, 28.49. Found: Hg, 71.1; Br, 27.6.

Reaction of Carbomethoxymercuric Bromide (II, X = Br) with Benzyl Bromide.—A mixture of 10.10 g. (0.0298 mole) of carbomethoxymercuric bromide, 5 ml. (0.0421 mole) of benzyl bromide, and 10 ml. of chloroform was heated under reflux for 17.5 hr. and allowed to cool to room temperature. The volume of gas given off was 800 ml. (theoretical yield of carbon monoxide, assuming an ideal gas, was 733 ml.). In another experiment, this gas was collected and identified as carbon monoxide by its mass spectrum. The reaction mixture was filtered and the crude mercuric bromide was washed with *n*-pentane. The weight of this material was 9.88 g. (92% crude yield). The crude mercuric bromide was readily purified by sublimation and was identified by its melting point of 229–233.5° (sample appeared to start subliming around 200°) and also by comparison of its infrared spectrum with that of an authentic sample.

The filtrate obtained from the removal of crude mercuric bromide was diluted with *n*-pentane to a volume of about 200 ml., decanted from a very small amount of gummy solid, and concentrated to a volume of about 50 ml. by distillation at atmospheric pressure. This material was added to a solution of 7.24 g. (0.0426 mole) of silver nitrate in 50 ml. of water and the resulting mixture was stirred vigorously at room temperature for 1 hr. The mixture was then filtered from silver bromide. The two-phase filtrate was separated; the aqueous layer was extracted with ether. The combined organic phase was dried over magnesium sulfate and concentrated to a weight of 9.66 g. by distillation at atmospheric pressure. Vapor chromatographic analysis of this material showed two major components and two minor components in addition to the solvent peaks. The major components were separated by preparative scale v.p.c. and identified as methyl benzyl ether and benzyl alcohol by comparison of their infrared spectra with those of authentic samples. Methyl phenylacetate was not detected. Approximate yields were calculated from the vapor chromatogram using the method of Eastman.[15] The yield of methyl benzyl ether was quantitative, based on carbomethoxymercuric bromide charged (calculated yield figure was over 100%). A 23% recovery of benzyl bromide (as benzyl alcohol) was obtained. The two minor components taken together amounted to about 3% by weight of the 9.66 g. of material originally analyzed. These components were not identified.

The Photochemical Decomposition of Carbomethoxymercuric Iodide (II, X = I) in Benzene.—A clear solution of 3.00 g. (0.00777 mole) of carbomethoxymercuric iodide in 250 ml. of benzene was cooled to 6°. The stirred solution was then irradiated in a nitrogen atmosphere with a 70-watt Hanau PL 313 immersion-type ultraviolet source for 6 hr. During this time, the internal temperature remained between 6 and 10°, and a grayish yellow precipitate formed. Filtration of the reaction mixture afforded 1.43 g. of solid. Elemental analysis of this material indicated that it was crude mercurous iodide. The crude yield was 56.3%.

Anal. Calcd. for HgI: Hg, 61.25; I, 38.75. Found: Hg, 58.7; I, 37.8.

The clear filtrate was distilled at atmospheric pressure. After removal of excess benzene, the distillation residue was separated, by decantation into a liquid phase, plus 0.40 g. of orange solid (probably thermal decomposition products of unchanged II). After removal of more benzene from the liquid phase by atmospheric distillation, the higher boiling residue was subjected to a one-plate distillation at reduced pressure to yield 2.74 g. of distillate. Sublimation of the solid residue from the one plate distillation yielded 0.09 g. of a light yellow solid (m.p. 83–135°) whose infrared spectrum was similar to that of dimethyl terephthalate. Purification of this material, however, could not be achieved. Vapor chromatography of the above 2.74 g. of distillate indicated methyl benzoate, a compound with the reten-

(15) R. H. Eastman, *J. Am. Chem. Soc.*, **79**, 4243 (1957).

(16) C. J. Engelder, T. H. Dunkelberger, and W. J. Schiller, "Semi-Micro Qualitative Analysis," John Wiley and Sons, Inc., New York, N. Y., 1936, p. 109.

tion time of toluene, and one unknown component to be present in addition to benzene. The area under the unknown peak was slightly larger than that corresponding to toluene. Dimethyl oxalate was not detected. Calculations from vapor chromatograms, using *p*-xylene as an internal standard, showed the yields of methyl benzoate and toluene to be 21 and 12%, respectively [based on the amount of II (X = I) charged, assuming 0.5 mole of substituted benzene per mole of II]. Both methyl benzoate and toluene were separated by preparative scale vapor chromatography. Methyl benzoate was identified by comparison of its infrared spectrum with that of an authentic sample. A poor spectrum was obtained for the compound thought to be toluene since only a very small amount of material was isolated. An unequivocal assignment of structure could therefore not be made; however, bands at 727 and 692 cm.$^{-1}$ were indicative of toluene.

Reaction of Carbomethoxymercuric Acetate (I) with Ethylene.—A 2-l. stirred autoclave was charged with a mixture of 100 g. (0.314 mole) of carbomethoxymercuric acetate and 500 ml. of absolute methanol. The autoclave was pressurized with ethylene (800 p.s.i.g. at 12°) and heated to 60° (1340 p.s.i.g.) over a period of 5 hr. The reaction mixture was then stirred at 60–66° under ethylene pressure for a total of 18.5 hr. There was no noticeable pressure drop. The autoclave was cooled and discharged and the blue-green reaction mixture was filtered from a small amount of gray sediment. The filtrate was evaporated to dryness under vacuum to yield 88.1 g. of blue-green crystals. Recrystallization of 19.74 g. of this material from *n*-pentane yielded 14.94 g. of pale blue needles, m.p. 39–42.5°. The yield of partially purified β-methoxyethylmercuric acetate was calculated at 66.8%. An analytical sample (m.p. 42–43.5°, hot stage) was prepared by further recrystallization from *n*-pentane. The infrared spectrum of this material (chloroform solution) was identical with that of the β-methoxyethylmercuric acetate prepared from ethylene and methanolic mercuric acetate. The mixture melting point of these two compounds was 42–43° (hot stage).

Anal. Calcd. for $C_5H_{10}HgO_3$: C, 18.84; H, 3.16. Found: C, 19.0; H, 3.26.

Acknowledgment.—The author thanks Dr. R. D. Closson for helpful suggestions.

Carbonimidoyl Dihalides as Organic Intermediates.[1] I. The Preparation of 2-Aryl Aminobenzimidazoles[2]

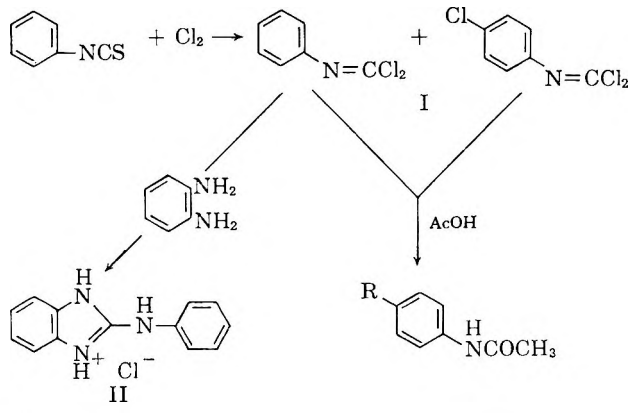
DANIEL B. MURPHY

Hunter College of the City University of New York, New York 21, New York

Received December 2, 1963

Phenyl- and *p*-chlorophenylcarbonimidoyl dichlorides, prepared by chlorination of phenyl isothiocyanate, react with *o*-phenylenediamines in a suitable solvent to form the corresponding 2-aryl aminobenzimidazoles. Moderate to almost quantitative yields are obtained, and the procedure affords a convenient route to this class of compounds.

The carbonimidoyl dichlorides I are reactive compounds which offer obvious promise as organic intermediates. They nevertheless have received little attention since the preparation of phenylcarbonimidoyl dichloride was reported in 1874.[3] These compounds may be prepared by addition of chlorine to isocyanides,[4] or more conveniently by direct chlorination of the isothiocyanates in an appropriate solvent at 0–5°.[3,4a,5]



The odor of these compounds is similar to, although not quite so obnoxious as, that of the isocyanides. The vapors are extremely irritating to the eyes. Prolonged exposure to phenylcarbonimidoyl dichloride is reported to cause corneal ulceration and temporary loss of vision, leading to its limited use as "blinding gas" during the first World War.[5a]

Nef[4a] claimed that under the conditions employed by Sell and Zierold for phenyl isothiocyanate, namely chlorination at 0° in chloroform solution, appreciable ring chlorination took place, the actual product being a mixture of phenylcarbonimidoyl dichloride and the *p*-chloro derivative. Bly, Perkins, and Lewis[5a] used carbon tetrachloride or phenylcarbonimidoyl dichloride itself as the solvent, and found no evidence of ring chlorination. In the present study it has been found that the solvent plays an important part in determining whether halogenation will occur on the ring. When chlorination was carried out in chloroform solution and the solution was then allowed to stand overnight or longer at room temperature without first removing the excess dissolved chlorine, the major product was *p*-chlorophenylcarbonimidoyl dichloride, identified by its acetolysis to *p*-chloroacetanilide.[5b] A small amount of the unsubstituted compound was also recovered, together with a little yellow oil believed to be largely 2,4-dichlorophenylcarbonimidoyl dichloride.[5a] No ring chlorination took place when the excess chlorine was aspirated from the solution *in vacuo* at room tempera-

(1) These compounds, which may be considered as derivatives of the hypothetical carbonimidic acid, $HN{=}C(OH)_2$, have been known variously as isocyanide dihalides, carbylamine halides, and carbonimidyl halides, and are currently indexed by *Chemical Abstracts* as imidocarbonyl halides. The author is indebted to Dr. Leonard T. Capell, Nomenclature Director of the Chemical Abstracts Service, for suggesting the name "carbonimidoyl dihalides" as conforming with I.U.P.A.C. practice.

(2) Presented before the Division of Organic Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

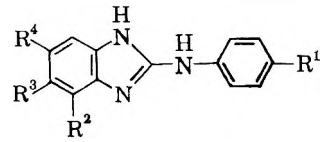
(3) E. Sell and G. Zierold, *Ber.*, **7**, 1228 (1874).

(4) (a) J. U. Nef, *Ann.*, **270**, 267 (1892); (b) P. A. S. Smith and N. W. Kalenda, *J. Org. Chem.*, **23**, 1599 (1958).

(5) (a) R. Bly, G. Perkins, and W. Lewis, *J. Am. Chem. Soc.*, **44**, 2896 (1922); (b) G. M. Dyson and T. Harrington, *J. Chem. Soc.*, 191 (1940); 150 (1942); (c) K. A. Petrov and A. A. Neimysheva, *Zh. Obshch. Khim.*, **29**, 2165 (1959).

TABLE I

2-ARYL AMINOBENZIMIDAZOLES



R¹	R²	R³	R⁴	Solvent[a]	Diamine[b]	Reflux, hr.	Yield, % HCl salt	Yield, % Base	M.p., °C., base	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
H	H	H	H	A	C	3	81	50	195–199	74.61	5.31	20.08	74.69	5.58	19.91
Cl	H	H	H	A	C	3	68	25	193–195	64.06	4.14	17.25	64.26	4.36	17.50
H	H	CH_3	H	A	D	3	...	44	167–169[c]	75.30	5.88	...	75.03	5.88	...
Cl	H	CH_3	H	A	D	7	83	...	205–207	65.24	4.70	...	64.95	4.84	...
H	H	Cl	H	A	E	3	42	19	215–217	64.06	4.14	...	64.06	4.21	...
Cl	H	Cl	H	A	E	48	66	...	169–173[d]	49.63	3.21	13.36	49.35	3.42	13.20[e]
H	H	NO_2	H	B	F	1.5	98	37	276–279	61.40	3.96	...	61.79	4.00	...
H	NO_2	H	Cl	B	G	1	...[f]	95	247–252	54.08	3.14	...[g]	53.44	3.13	...[g]
Cl	NO_2	H	Cl	B	G	0.5	...[f]	90	280–283	48.32	2.49	17.34	48.26	2.84	17.25

[a] A, 1,2-dichloroethane; B, nitrobenzene. [b] C, *o*-phenylenediamine; D, 3,4-toluenediamine; E, 4-chloro-*o*-phenylenediamine; F, 4-nitro-*o*-phenylenediamine; G, 5-chloro-3-nitro-*o*-phenylenediamine. [c] A. Keller [*Ber.*, **24**, 2498 (1891)] reported m.p. 166–167°. [d] Melting point of hydrochloride was 277–282°. [e] As hydrochloride. [f] Free base separated directly during reflux period. [g] Calcd.: Cl, 12.28. Found: Cl, 11.94.

ture immediately after the initial chlorination was complete, nor did it occur when carbon tetrachloride was used as the solvent. In carbon tetrachloride, a 90% yield of phenylcarbonimidoyl dichloride was obtained even when the solution, saturated with chlorine, was allowed to stand for 5 days at room temperature. These results suggest that the polar chloroform is acting as halogen carrier for ring substitution through solvation of the chlorine molecule. The solid intermediate which forms from the isothiocyanate during chlorination in chloroform[5b,6] did not precipitate when carbon tetrachloride was used as the solvent.

Since phenylcarbonimidoyl dichloride reacts with aniline to form 1,2,3-triphenylguanidine,[3,5a] it was reasonable to expect it to react in similar fashion with *o*-phenylenediamine to give 2-anilinobenzimidazole (II). When *o*-phenylenediamine and phenylcarbonimidoyl dichloride were mixed without a solvent, no reaction took place until the temperature was raised to 83°, at which point a violent reaction ensued with the formation of a green melt, not further identified. Reaction proceeded to only a small extent in boiling chloroform at 61°, but in 1,2-dichloroethane (b.p. 83°), an 85% yield of crude 2-anilinobenzimidazole hydrochloride precipitated over a 3-hr. period. Conversion to the base yielded a product melting at 195–199°, whose infrared spectrum was identical with that of 2-anilinobenzimidazole prepared by heating N,N′-diphenyl-S-methylisothiourea and *o*-phenylenediamine in a sealed tube at 140°.[7,8] A mixture melting point showed no depression.

The preparation is quite general, and both phenyl- and *p*-chlorophenylcarbonimidoyl dichloride reacted smoothly with *o*-phenylenediamines when heated under reflux in a suitable solvent (Table I). Although 1,2-dichloroethane was generally satisfactory, nitrobenzene gave better results with *o*-phenylenediamines containing nitro groups. Benzene and toluene were unsuitable solvents for the reaction, producing poor yields of tarry product. In nearly every case, a purple or red color appeared immediately upon mixing the reagents. After a few minutes of reflux, the color faded and crystals of the benzimidazole hydrochloride began to separate. No color was observed when *o*-phenylenediamine and phenylcarbonimidoyl dichloride were mixed in 1,2-dichloroethane, but in chloroform a violet color appeared which soon faded, although very little over-all reaction took place.

The reaction was usually complete within 1 to 3 hr. *p*-Chlorophenylcarbonimidoyl dichloride was less reactive than the unsubstituted compound, and the reaction was further retarded by the presence of a nitro group in the diamine. No product was obtained from *p*-chlorophenylcarbonimidoyl dichloride and 4-nitro-*o*-phenylenediamine, the amine being recovered unchanged. Both 2-anilino-4-nitro-6-chlorobenzimidazole and 2-(*p*-chloro)anilino-4-nitro-6-chlorobenzimidazole precipitated as the free bases in 90–95% yield after 10 min. of reflux in nitrobenzene.

Experimental[9]

Phenylcarbonimidoyl Dichloride.—Chlorine gas was bubbled through a solution of 60 ml. (67.5 g., 0.5 mole) of phenyl isothiocyanate in 200 ml. of carbon tetrachloride with stirring and ice cooling, and at such a rate that the temperature did not rise above 3°. The reaction was complete after 3–4 hr., at which time chlorine was no longer rapidly absorbed, and the solution had turned a deep red. The solvent and the sulfur dichloride produced in the reaction were removed by distillation and the residue was fractionated through a 30-cm. column packed with glass helices. The product (74–78 g., 85–90% yield) distilled at 103–106° (31 mm.), lit.[5a] b.p. 107–109° (30 mm.), as a colorless oil, $n^{25}D$ 1.5713.

The infrared spectrum (Fig. 1) shows an intense C=N stretching absorption at 1650 cm.$^{-1}$, bands at 3311, 3067, 1754, 1587, 1481, 1447, 1205, 1072, 1026, 1002, 757.6, and 692 cm.$^{-1}$, and

(6) O. Helmers, *Ber.*, **20**, 786 (1887).

(7) J. F. Deck and F. B. Dains, *J. Am. Chem. Soc.*, **55**, 4986 (1933).

(8) The first time that this procedure was followed, a product was obtained which gave the proper elemental analysis and exhibited the same infrared spectrum, but which melted at 151–152° after recrystallization from benzene, rather than at 188° as reported by Deck and Dains, and which seemed appreciably more soluble in benzene. After these crystals had stood for several months at room temperature, they were found to melt at 193–195°, suggesting that the low- and high-melting crystals were polymorphs. The products of subsequent sealed-tube preparations all melted between 195–200° after recrystallization.

(9) Melting points were determined in a calibrated Thomas–Hoover capillary melting point apparatus and are corrected. Analyses were by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

broad absorption at about 913 and 845 cm.$^{-1}$. After several months, a band, absent in the spectrum of the freshly distilled product, appeared at 2262 cm.$^{-1}$. This is attributed to the isocyanate group[10] and indicates that some hydrolysis took place on exposure to the atmosphere.

p-Chlorophenylcarbonimidoyl Dichloride.—Sixty milliliters of phenyl isothiocyanate dissolved in 200 ml. of chloroform was chlorinated in the same manner as above. After a short while a solid intermediate separated, gradually redissolving as the reaction progressed. Chlorination was complete after 5 hr., and the clear red solution, saturated with chlorine, was allowed to stand overnight or longer at room temperature. After removal of solvent and sulfur dichloride, fractionation afforded 63.5 g. (61% yield) of a faintly yellow oil, b.p. 135–141° (31 mm.), lit.[5a] b.p. 135–137° (30 mm.), n^{25}D 1.5862; together with 12 g. (14% yield) of phenylcarbonimidoyl dichloride; and about 5 g. of a yellow oil, n^{25}D 1.5904, distilling between 141–165° (31 mm.), which was probably largely 2,4-dichlorophenylcarbonimidoyl chloride.[5n]

In addition to C=N absorption at 1653 cm.$^{-1}$, the infrared spectrum (Fig. 2) shows bands at 3279, 3030, 1653, 1587, 1481, 1205, 1087, 1062, 1014, 942.5, 826.4, 754.7, 708.2, and 686.3 cm.$^{-1}$ with broad absorption centered at 900 cm.$^{-1}$. The isocyanate band again appeared at 2262 cm.$^{-1}$ upon exposure to the atmosphere.

o-Phenylenediamines.—*o*-Phenylenediamine, 3,4-toluenediamine, 4-chloro-*o*-phenylenediamine, 4-nitro-*o*-phenylenediamine, and 5-chloro-3-nitro-*o*-phenylenediamine were purchased from Eastman Kodak Co. and recrystallized from water or alcohol.

Acetolysis of Phenylcarbonimidoyl Dichloride.[5a]—One milliliter of *p*-chlorophenylcarbonimidoyl dichloride was heated under reflux with 3 ml. of glacial acetic acid until evolution of hydrogen chloride ceased. The mixture was poured into cold water, and the precipitate, after recrystallization from water, was identified by its infrared spectrum as *p*-chloroacetanilide, m.p. 178–180°. In similar fashion, phenylcarbonimidoyl dichloride formed acetanilide, m.p. 114°.

2-Aryl Aminobenzimidazoles (Table I).—Equimolar amounts of phenyl- or *p*-chlorophenylcarbonimidoyl dichloride and the *o*-phenylenediamine were heated under reflux in about 10–20 ml. of 1,2-dichloroethane or nitrobenzene per gram of amine. Both 2-anilino- and 2-(*p*-chloro)anilino-4-nitro-6-chlorobenzimidazole precipitated as the free bases which were filtered, washed with a little ether, and recrystallized from dilute alcohol. The other benzimidazoles prepared separated as the hydrochlorides. Allowing the mixture to stand for 24–48 hr. after reflux afforded a more crystalline product. The crystals were filtered, washed with a little fresh solvent, and recrystallized at least twice from 6 *N* hydrochloric acid. The purified salt was then dissolved in water and converted to the base by addition of 6 *N* sodium hydroxide. The base occasionally precipitated as a gum which crystallized very slowly. This could usually be avoided by adding the sodium hydroxide solution to a hot, well-stirred solution of the hydrochloride until the mixture was strongly basic. The base was then recrystallized from dilute alcohol or benzene.

(10) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p. 28; H. W. Johnson, Jr., and P. H. Daughhetee, Jr., *J. Org. Chem.*, **29**, 246 (1964).

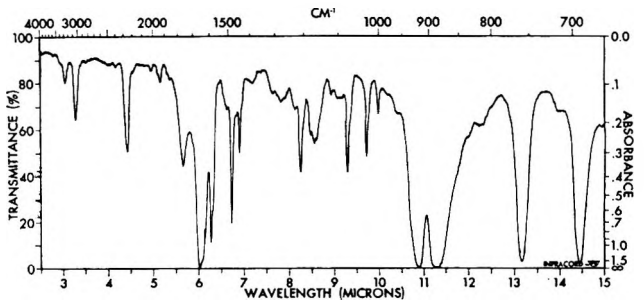


Fig. 1.—The infrared absorption spectrum of phenylcarbonimidoyl dichloride (as a liquid film). The band which appears at 2262 cm.$^{-1}$ after storage in air is attributed to the isocyanate group (see Experimental).

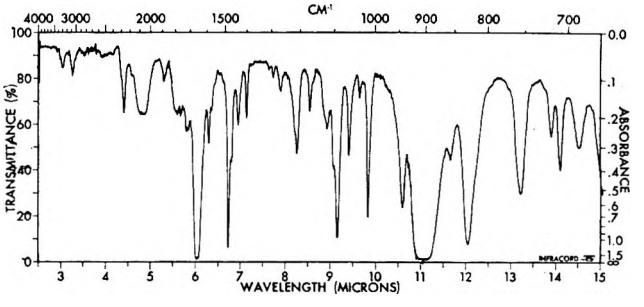


Fig. 2.—The infrared spectrum of *p*-chlorophenylcarbonimidoyl dichloride (as a liquid film). The band which appears at 2262 cm.$^{-1}$ after storage in air is attributed to the isocyanate group (see Experimental).

Acknowledgment.—Sincere appreciation is extended to Miss Jeannette Musco and Mr. Arthur Schwartz, graduate students at Hunter College, for technical assistance.

Relative Rates of Bromination of α-Substituted Toluenes by N-Bromosuccinimide

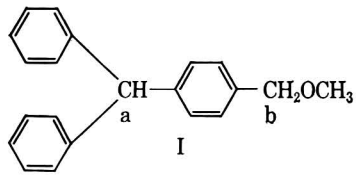
R. E. LOVINS, L. J. ANDREWS, AND R. M. KEEFER

Department of Chemistry, University of California, Davis, California

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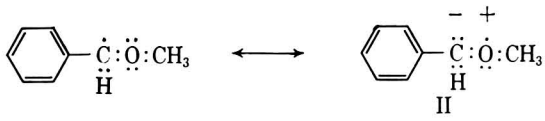
The relative rates of reaction of a series of α-substituted toluenes ($C_6H_5CH_2R$) with N-bromosuccinimide in carbon tetrachloride have been determined. A reactivity series somewhat like that reported previously for bromination of nuclear-substituted toluenes ($RC_6H_4CH_3$) has been obtained. The logarithms of the rates of benzylic bromination for the compounds of formula $C_6H_5CH_2R$, have been correlated with the substituent constant differences, $\sigma_p - \sigma_m$, for the groups R. The substituent effects are explained in terms of the relative capacities of the R groups to contribute to stabilization of the transition states of the reactions by electron release, primarily by resonance.

It has been demonstrated previously[1] that benzyl methyl ether undergoes benzylic bromination by N-bromosuccinimide much more rapidly than does toluene. In fact the methoxyl group enhances the reactivity of the methylene to which it is attached so strongly that the triphenylmethane derivative (I) is considerably more susceptible to attack by N-bromosuccimide at position b than at position a.



I

The rate effect of this substituent has been ascribed to its contribution to resonance stabilization of the radical-like transition state (II) of the reaction step in which one of the benzylic hydrogen atoms is extracted, probably by a bromine atom.[2-4]



II

In connection with projected synthetic work in which substituted benzenes offering more than one benzylic reaction site are to be selectively brominated, it has been of interest to determine the influence of various substituents (R) other than methoxyl on the relative reactivities of substituted toluenes ($C_6H_5CH_2R$). Experimental methods similar to those described in the earlier report[1] have now been used to compare the effects of a number of groups, R, which differ widely in their capacities to exert electronic influences on reaction at nearby centers.

Experimental

Materials.—Commercial samples of ethylbenzene, toluene, benzyl acetate, diphenylmethane, benzyl methyl ether, α-chlorotoluene, benzyl cyanide, and cumene (Eastman Organic Chemicals); benzyl bromide, benzyl phenyl sulfide, and α-nitrotoluene (K and K Laboratories, Inc.); and N-bromosuccinimide (Arapahoe Chemicals, Inc.) were used without further purification. Methyl phenylacetate, b.p. 218–219°, was prepared by the sulfuric acid-catalyzed reaction of phenylacetic acid and methanol. Benzyl phenyl ether, b.p. 125–127° (5 mm.), was prepared from α-chlorotoluene.[5] Eastman Organic Chemicals Spectro Grade carbon tetrachloride was used as the medium in the bromination studies.

Relative Bromination Rates of Substituted Toluenes.—Procedures similar to those described previously[1] were used in determining the rate of reaction of each substituted toluene (relative to that of toluene) with N-bromosuccinimide. For each determination a carbon tetrachloride solution of known volume which contained weighed quantities of the substituted toluene and a reference compound (toluene, ethylbenzene, cumene, or benzyl methyl ether) was prepared. The solution was treated with a limited quantity of N-bromosuccinimide and a small amount of benzoyl peroxide. The mixture was then heated under reflux until all of the N-bromosuccinimide which was accumulated at the bottom of the reaction flask had disappeared. The mixture then was analyzed by vapor phase chromatography to determine its content of unchanged substituted toluene and reference compound. The chromatograph columns were packed either with Carbowax 20 M or cyanosilicone fluid XF-1150 impregnated firebrick (60–80 mesh) and operated at temperatures ranging from 100 to 180°. Mixtures containing the nonvolatile substituted toluenes, benzyl phenyl ether, benzyl phenyl sulfide, and α-nitrotoluene, were analyzed only for the unchanged reference compound; in these cases the final concentrations [A] of substituted toluene were calculated from the starting quantity of N-bromosuccinimide and the amount of reference substance which was consumed. The reported relative reactivities of these nonvolatile compounds are based on several sets of measurements in which the reference compounds and starting concentrations of reactants were varied. In Table I a list is given of typical values of k_A/k_B (the ratio of rate constants for bromination of the substituted toluene and the reference material) for the various compounds which were investigated. These ratios were calculated from the initial ($[A_0]$ and $[B_0]$) and final ([A] and [B]) concentrations of the substituted toluenes (A) and the reference compounds (B) using eq. 1. Values of r which are reported

$$\frac{k_A}{k_B} = \frac{\log [A_0]/[A]}{\log [B_0]/[B]} \qquad (1)$$

later in Table II are k_A/k_B values in which the reference compound is toluene. The values of $r_{cor.}$ which are listed are the relative reactivities of the substituted toluenes per α-hydrogen atom, where $r_{cor.}$ for toluene itself is arbitrarily chosen as unity. When a reference compound B other than toluene was used in the experimental work, the value of $r(k_A/k_{toluene})$ was calculated from the k_A/k_B and $k_A/k_{toluene}$ values which are recorded in Table I. Each r value is an average based on the results of at least two separate experiments with different initial concentrations, $[A_0]$ and $[B_0]$, of the substituted toluene and reference compound. In some cases the reactivity of the substituted toluene was checked against two different reference compounds.

An unsuccessful attempt was made to determine a value of r for benzyl bromide. With ethylbenzene and also with cumene as the reference hydrocarbon, the experimentally determined ratio, k_A/k_B, varied widely and erratically as the quantity of N-bromosuccinimide in the reaction mixture was changed. There was some indication that the difficulty might have been associated with the selective adsorption of unchanged benzyl bromide on the solid succinimide formed as a reaction product. It was demonstrated by separate experiment that the unchanged hydrocarbon was not adsorbed to a significant extent on the succinimide which

(1) R. E. Lovins, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **28**, 2847 (1963).

(2) R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 354, 3142 (1963).

(3) (a) G. A. Russell, C. DeBoer, and K. M. Desmond, *ibid.*, **85**, 365 (1963); (b) G. A. Russell and K. M. Desmond, *ibid.*, **85**, 3139 (1963).

(4) C. Walling, A. L. Rieger, and D. D. Tanner, *ibid.*, **85**, 3129 (1963).

(5) E. M. Van Duzee and H. Adkins, *ibid.*, **57**, 148 (1935).

TABLE I

COMPETITIVE RATES OF BENZYLIC BROMINATION BY N-BROMOSUCCINIMIDE[a]

Compound A[b]	Compound B[b]	[A₀], moles	[A], moles	[B₀], moles	[B], moles	k_A/k_B
$C_6H_5CH_2CH_3$	$C_6H_5CH_3$	0.047	0.015	0.047	0.042	9.8
$C_6H_5CH_2CH_3$	$C_6H_5CH_3$	0.033	0.010	0.0545	0.048	9.3
$C_6H_5CH_2CH_3$	$C_6H_5CH_2OCH_3$	0.041	0.0335	0.041	0.018	0.26
$C_6H_5CH_2CH_3$	$C_6H_5CH_2OCH_3$	0.047	0.039	0.030	0.011	0.20
$C_6H_5CH(CH_3)_2$	$C_6H_5CH_2OCH_3$	0.031	0.025	0.031	0.016	0.31
$C_6H_5CH_2COOCH_3$	$C_6H_5CH_3$	0.033	0.027	0.033	0.022	0.50
$C_6H_5CH_2CN$	$C_6H_5CH_3$	0.043	0.036	0.043	0.025	0.35
$C_6H_5CH_2C_6H_5$	$C_6H_5CH_2CH_3$	0.0295	0.022	0.031	0.025	1.3
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH_3$	0.040	0.031	0.040	0.019	0.33
$C_6H_5CH_2OC_6H_5$	$C_6H_5CH_2CH_3$	0.038	0.021	0.038	0.027	1.7
$C_6H_5CH_2OC_6H_5$	$C_6H_5CH(CH_3)_2$	0.027	0.016	0.027	0.018	1.3
$C_6H_5CH_2OC_6H_5$	$C_6H_5CH(CH_3)_2$	0.021	0.015	0.042	0.031	1.2
$C_6H_5CH_2NO_2$	$C_6H_5CH_3$	0.036	0.023	0.042	0.030	1.3
$C_6H_5CH_2NO_2$	$C_6H_5CH_2CH_3$	0.029	0.025	0.029	0.013	0.18
$C_6H_5CH_2SC_6H_5$	$C_6H_5CH_2OCH_3$	0.025	0.018	0.025	0.012	0.43
$C_6H_5CH_2SC_6H_5$	$C_6H_5CH(CH_3)_2$	0.025	0.013	0.025	0.017	1.7
$C_6H_5CH_2SC_6H_5$	$C_6H_5CH(CH_3)_2$	0.020	0.014	0.042	0.031	1.3
$C_6H_5CH_2OCOCH_3$	$C_6H_5CH(CH_3)_2$	0.033	0.026	0.032	0.009	0.18

[a] In carbon tetrachloride at 77°. [b] Total volume of A, B, and carbon tetrachloride was initially 50 ml. at room temperature.

TABLE II

RELATIVE REACTIVITIES, r,[a] OF α-SUBSTITUTED TOLUENES IN FREE-RADICAL BROMINATION WITH N-BROMOSUCCINIMIDE

Compound	r	$r_{corr.}$[b]	σ_m[c]	σ_p[c]
$C_6H_5CH_2CN$	0.43 ± 0.08(2)[d]	0.64	0.56	0.66
$C_6H_5CH_2COOCH_3$	0.58 ± 0.08(2)	0.87	0.32	0.39
$C_6H_5CH_3$	1.00	1.00	0.00	0.00
$C_6H_5CH_2OCOCH_3$	1.6 ± 0.3 (4)	2.4	0.39	0.31
$C_6H_5CH_2NO_2$	1.9 ± 0.3 (4)	2.8	0.71	0.78
$C_6H_5CH_2Cl$	2.8 ± 0.3 (2)	4.2	0.37	0.22
$C_6H_5CH_2CH_3$[e]	9.5 ± 0.3 (2)	14	−0.07	−0.17
$C_6H_5CH_2C_6H_5$	11.8 ± 0.3 (2)	18	0.06	−0.01
$C_6H_5CH(CH_3)_2$[e]	12.1 ± 0.5 (1)	36	2(−0.07)[f]	2(−0.17)[f]
$C_6H_5CH_2OC_6H_5$	15 ± 1 (4)	22	0.25	−0.32
$C_6H_5CH_2SC_6H_5$	16 ± 2 (4)	24		
$C_6H_5CH_2OCH_3$[e]	39 ± 3 (3)	59	0.11	−0.27

[a] The term r is defined by eq. 1, with toluene as the reference compound B. All values in carbon tetrachloride at 77°. [b] The value of the relative reactivity per α-hydrogen atom (based on $r_{corr.}$ for toluene = 1.00). [c] Values taken from J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 87. [d] The numbers in parenthesis are the number of determinations from which the reported average values were obtained. [e] The authors have previously reported $k_A/k_{toluene}$ values for ethylbenzene (8.7), cumene (10), and benzyl methyl ether (32). The r values reported above for these compounds are based on new sets of experimental results. [f] It is assumed that the cumulative σ-values for the two methyl groups are twice those for a single methyl substituent.

precipitated during the course of bromination of a sample of toluene in carbon tetrachloride. A solution which originally contained 0.054 mole of toluene was found to contain 0.035 mole of the alkyl benzene after reaction with 0.020 mole of N-bromosuccinimide.

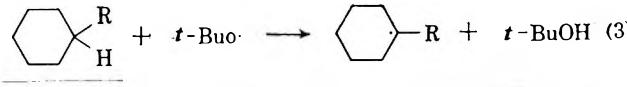
Results

The susceptibilities of a series of nuclear-substituted toluenes ($RC_6H_4CH_3$) to radical attack at the α-position decrease with changes in R in this order[3,6-9]: *p*-OCH_3 > *p*-CH_3 > *m*-CH_3 > H > *p*-Br > *p*-Cl > *m*-OCH_3 > *m*-COOH > *p*-COOH > *m*-Br > *p*-CN > *m*-CN > *m*-NO_2. These substituent effects can generally be correlated in the usual way with the Hammett σ-values or with the σ^+-values for the R groups, depending on the identity of the hydrogen abstracting radical which is taking part in the reaction.[6a,9,10] The observed order presumably is a reflection of the relative capacities of the substituents to release electrons to the reaction centers by a combination of resonance and inductive effects.

In the radical-induced copolymerization of substituted ethylenes, in which radicals are considered to form from monomers[11] as shown in eq. 2, the R groups

$$RCH{=}CH_2 + X\cdot \longrightarrow RCHCH_2X \qquad (2)$$

have more or less the reverse of the reactivity effect reported above (C_6H_5— > —CH=CH_2 > —$COCH_3$ > —CN > —COOR > —Cl > —$OCOCH_3$ > —CH_3 > —OCH_3). It has also been found that electron-withdrawing R groups enhance slightly the susceptibilities of unsaturates of the type $RCH{=}CH_2$ to reaction with methyl radicals.[12] On the other hand, the relative susceptibilities of substituted cyclohexanes to attack by *t*-butoxy radicals (eq. 3) increase as the R groups be-



(3)

(6) (a) C. Walling and B. Miller, *J. Am. Chem. Soc.*, **79**, 4181 (1957); (b) C. Walling and B. B. Jackanow, *ibid.*, **82**, 6113 (1960).
(7) R. van Helden and E. C. Kooymans, *Rec. trav. chim.*, **78**, 269 (1954).
(8) E. S. Huyser, *J. Am. Chem. Soc.*, **82**, 394 (1960).
(9) K. M. Johnston and G. H. Williams, *J. Chem. Soc.*, 1446 (1960).
(10) G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958).
(11) (a) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 121; (b) F. R. Mayo and C. Walling, *Chem. Rev.*, **46**, 191 (1950).
(12) L. Heck, A. Stefani, and M. Szwarc, *J. Am. Chem. Soc.*, **83**, 3008 (1961).

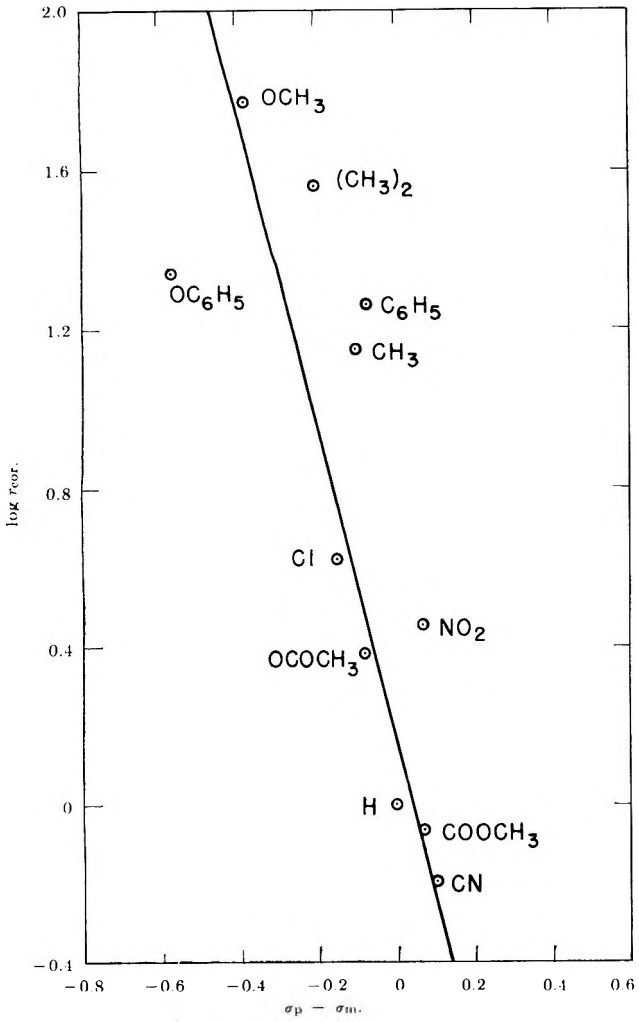


Fig. 1.—Correlation of log r_{cor} values for the reaction of N-bromosuccinimide and $C_6H_5CH_2R$ (or $C_6H_5CHR_2$) with $\sigma_p - \sigma_m$ values for R.

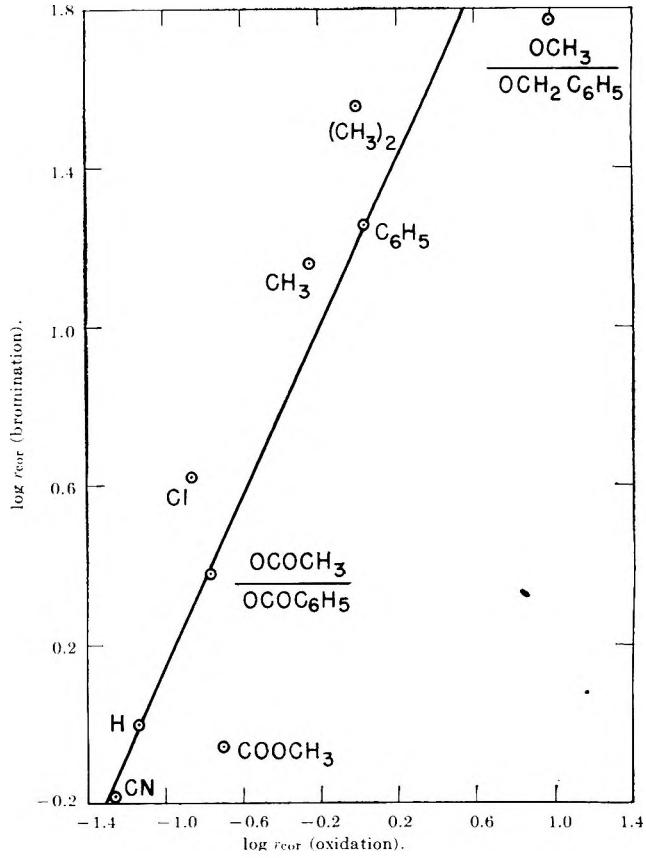


Fig. 2.—Correlation of the log r_{cor} values for reaction of $C_6H_5CH_2R$ (or $C_6H_5CHR_2$) with N-bromosuccinimide (see Table II) and for reaction of the substituted toluenes with peroxy radicals.[21] Where two substituents are listed beside a point, the ordinate value applies to the upper substituent and the abscissa value to the lower substituent; it is assumed in these cases that the two different substituents have identical electronic effects. The r_{cor} values for the oxidation reactions which were used in making these plots are based on cumene as the reference substance (r_{cor} for cumene = 1.00).

come increasingly electron releasing in an inductive sense.[13]

In the present investigation of α-substituted toluenes ($C_6H_5CH_2R$), the relative reactivities have been found to vary with R (see Table II) in this order: —OCH_3 > —SC_6H_5 > —OC_6H_5 > C_6H_5— > —CH_3 > —Cl > —NO_2 > —$OCOCH_3$ > —H > —$COOCH_3$ > —CN. This series does not closely parallel the electron releasing capacities of the substituents as measured by Hammett σ- or σ^+-values or by related constants which measure purely inductive effects. Neither are the reactivities of all of the substituted toluenes related in any obvious way to the electron-withdrawing capacities of the R groups. The best correlation of the observed reactivities with substituent constants which has so far been discovered is shown in Fig. 1, in which log r_{cor} values for the reactions with N-bromosuccinimide are plotted *vs.* Hammett $\sigma_p - \sigma_m$ values. Since σ_m is primarily an inductive parameter and σ_p is a measure of the composite resonance and inductive effects of a substituent, the quantity $\sigma_p - \sigma_m$ may serve as a crude measure of the resonance effect of a substituent.[14] A similar plot can be made of log r_{cor} *vs.* the Taft constant, σ_r, a substituent resonance parameter derived in another way.[15,16] The points thus obtained do not conform as well to a straight line as do the points of Fig. 1, although the ρ-values (slopes of the best straight lines which can be drawn) are not much affected by the choice of parameters. A figure of $\rho = -0.4$ has been obtained from the line of Fig. 1.

It appears that the relative reactivities of the various substituted toluenes, $C_6H_5CH_2R$, with respect to attack by N-bromosuccinimide are governed predominantly by the relative abilities of the R groups to participate, through electron release, in resonance stabilization of the transition states of the reactions. The inductive influences of the substituents cannot, however, be totally disregarded, as, for example, in comparing the relative reactivities of toluene, ethylbenzene, and cumene. The cyano and carbomethoxy groups are substituents which can be expected, if anything, to contribute to resonance stabilization by electron withdrawal rather than by electron release. The fact that benzyl cyanide and methyl phenylacetate are slightly less reactive than toluene may, therefore, reflect an unfavorable inductive effect of the R groups, —CN and —$COOCH_3$, on the case of formation of the radical $C_6H_5\dot{C}HR$.

(13) E. L. Patmore and R. J. Gritter, *J. Org. Chem.*, **27**, 4196 (1962).

(14) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 92, 93.

(15) R. W. Taft, Jr. and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958); **81**, 5343 (1959); *Tetrahedron*, **5**, 210 (1959).

(16) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

In this same regard the fact that α-nitrotoluene is somewhat more reactive than toluene is enigmatic. It should be recalled, however, that the ready formation of tris(*p*-nitrophenyl)methyl, $(p\text{-}NO_2C_6H_4)_3C\cdot$, has been explained on the assumption that the nitro group is involved in resonance stabilization of the radical.[17,18]

The fact that the rates of radical halogenations are subject to inductive and resonance influences of polar substituents which can interact electronically with the reaction centers is sometimes explained on the assumption that polar structures contribute to stabilization of the transition state.[19] On this basis, the transition state for a reaction in which a bromine atom derived from N-bromosuccinimide[2,3] abstracts a hydrogen atom from $C_6H_5CH_2R$ might be represented by III. Although the transition state for radical bromination of a ring substituted toluene may be subject to this kind of

$$C_6H_5\overset{H}{\underset{R}{C}}:H\cdot Br \longleftrightarrow C_6H_5\overset{H}{\underset{R}{C}}\cdot H:Br \longleftrightarrow C_6H_5\overset{H}{\underset{R}{C^+}}H:Br^-$$

III

polarization, it seems unlikely that the transition state for bromination of an α-substituted toluene under the conditions used in the present series of experiments is significantly carbonium ion-like in nature. If this were the case, strongly electron-withdrawing R groups such as nitro and cyano should have a pronounced deactivating effect, which they do not.[20]

It is interesting to note that the relative reactivities of a series of α-substituted toluenes with respect to attack by peroxy radicals[21] at 90° change with changes in substituents in much the same way as do the relative benzylic bromination rates of the substituted toluenes. In fact the log r_{cor} values for bromination of these toluenes with N-bromosuccinimide vary in approximately linear fashion with the corresponding log r_{cor} values for the oxidation reactions (Fig. 2).

It appears that, in general, hydrogen abstraction reactions which proceed by way of intermediates of the type, $RC_6H_4CH_2\cdot$, $C_6H_4\dot{C}HR$, or $>\dot{C}R$, are subject to rate enhancement as the substituents (R) become increasingly electron releasing. The relative importance of inductive and resonance effects of the substituents in controlling rates appears to vary widely from reaction to reaction. There is no sound basis for formulating a detailed explanation of these variations at the present time. Neither can a satisfactory explanation be proposed to account for the fact that substituent effects in copolymerizations of substituted ethylenes (eq. 2) are much different from those observed for hydrogen abstraction processes.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

(17) F. L. Allen and S. Sugden, *J. Chem. Soc.*, 440 (1936).

(18) Ref. 14, p. 405, 406.

(19) See ref. 11, Chapter 8.

(20) This does not rule out the possibility that in certain cases, notably where R = —OCH_3, —OC_6H_5, and —Cl, polar resonance forms (such as II $C_6H_5\overset{H}{\underset{\cdot\cdot}{C}}—\ddot{Cl}:$) contribute to radical stabilization. In fact in such cases the alternate nonpolar structures with more than an octet of electrons about oxygen and chlorine atoms, probably should not be written. It is presumed

$$(C_6H_5\overset{H}{C}::\dot{\underset{\cdot\cdot}{O}}:CH_3 \text{ and } C_6H_5\overset{H}{C}::\dot{\underset{\cdot\cdot}{Cl}}:)$$

that the resonance contribution of an α-methyl group to radical stabilization is by way of hyperconjugation.[15]

$$(C_6H_5\overset{H}{\underset{\cdot}{C}}CH_3 \longleftrightarrow C_6H_5C{=}CH_2\cdot H)$$

(21) G. A. Russell, *J. Am. Chem. Soc.*, **78**, 1047 (1956).

Notes

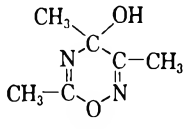
The Reaction between 2,3-Butanedione Monoxime and Aldehyde Oximes. The Preparation of 1-Hydroxyimidazoles 3-Oxides

JOHN B. WRIGHT

Department of Chemistry, The Upjohn Company, Kalamazoo, Michigan

Received November 19, 1963

In 1905 Diels and Van der Leeden[1] treated 2,3-butanedione monoxime with aldehyde oximes and obtained products which they postulated as substituted 1,2,5-oxadiazines.[2] For example, 2,3-butanedione monoxime reacted with acetaldoxime to give a product possessing the empirical formula $C_6H_{10}N_2O_2$, to which they assigned



I

the structure of 4-hydroxy-3,4,6-trimethyl-1,2,5-oxadiazine (I). The product was stated to dissolve readily in alkali, a fact that is difficult to rationalize on the basis of the structure assigned.

The product also formed a hydrochloride salt readily. It was stated by these authors[1] that the hydrochloride II could be prepared also by the action of hydrogen chloride on 2,3-butanedione monoxime directly. In this case it was suggested that the first molecule of 2,3-butanedione monoxime was cleaved with hydrogen chloride to acetyl chloride and acetaldoxime. The latter compound then reacted with a second molecule of 2,3-butanedione monoxime in the presence of hydrogen chloride to form the *hydrochloride* II.

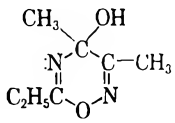
We have repeated both of the reactions indicated above for the preparation of I and its hydrochloride, II.

The product, obtained as a free base, showed a λ_{max}^{EtOH} at 225 mμ (ϵ 5800) in its ultraviolet spectrum. Its infrared absorption spectrum significantly showed no appreciable -OH absorption. An adsorption peak was present at 1235 cm.$^{-1}$, assignable to an N-oxide grouping. The most significant clue to its structure was afforded by its n.m.r. spectrum which showed a sharp singlet at 123 c.p.s. ($CDCl_3$ solvent, A-60) having an area of six protons, assignable to two *identical* methyl groups and a second sharp singlet at 137 c.p.s. having an area of three protons, assignable to the third methyl group.

The hydrochloride salt of the product obtained possessed a similar n.m.r. spectrum with a sharp singlet at 133 c.p.s. with an area of six protons, and a second sharp singlet at 154 c.p.s. with an area of three protons. Its infrared spectrum showed absorptions at 2640 and 2540 cm.$^{-1}$ assignable to a hydrochloride salt, bands at 1645, 1580, and 1495 cm.$^{-1}$ assignable to C=N, and bands at 1210 and 1085 cm.$^{-1}$ assignable to C-O or C-N. The pK_{a1} and pK_{a2} determined[3] were 4.05 and 6.3.

In order to determine whether the two identical methyl groups found as a singlet in the n.m.r. spectra were both derived from the 2,3-butanedione monoxime or whether one was derived from the starting acetaldoxime, the reaction was repeated using propionaldoxime.

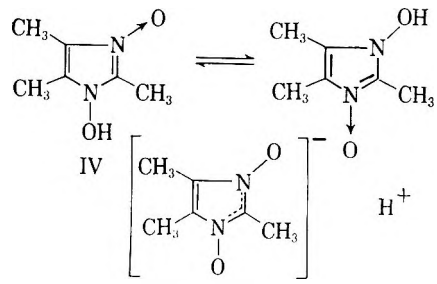
According to the general reaction as postulated by Diels and Van der Leeden,[1] this product should have the structure III.



III

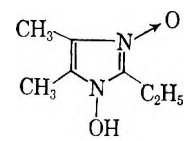
The n.m.r. spectrum of this compound showed the same singlet at 123 c.p.s. with an area of six protons and no methyl absorption in the region of 137 c.p.s. Also present were a triplet centered at 68 c.p.s. attributable to the methyl present in the ethyl group, and a quartet centered at 163 c.p.s. attributable to the methylene group. These data would indicate that the two identical methyl groups must be derived from the methyls of the 2,3-butanedione monoxime.

The structure that would appear to fit best all of these facts is 1-hydroxy-2,4,5-trimethylimidazole 3-oxide (IV). The two methyl groups in the 4- and 5-positions would be identical owing to tautomerism.



IV

The correct structure of the product derived from propionaldoxime would then be 1-hydroxy-2-ethyl-4,5-dimethylimidazole 3-oxide (V).



V

The structure of IV was proved by reduction to 2,4,5-trimethylimidazole with sodium hydrosulfite. The

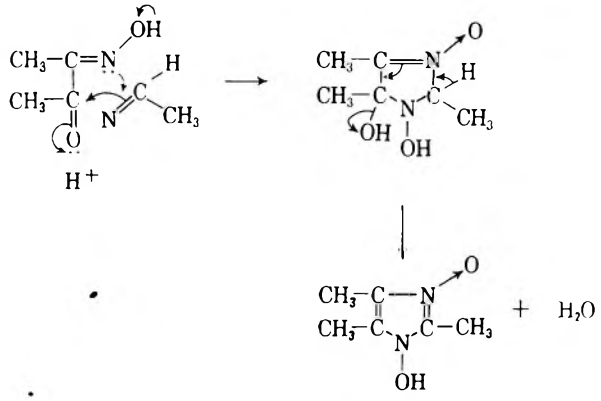
(1) O. Diels and R. Van der Leeden, *Chem. Ber.*, **38**, 3363 (1905).

(2) For a short review of this work, *cf.* Richard H. Wiley, "The Chemistry of Heterocyclic Compounds," Vol. 17, Interscience Publishers, Inc., New York, N. Y., 1962, p. 448.

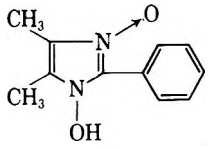
(3) These were determined by titration with potassium hydroxide in dimethylformamide (DMF) and 1:1 DMF-water solutions. Estimation of the pK_a values in water from these data was determined by the method of D. J. Weber (Meeting of the American Pharmaceutical Association, Miami, Fla., May, 1963).

reduction product showed no depression in melting point when mixed with an authentic sample of 2,4,5-trimethylimidazole and the infrared spectra of the two were identical. The melting point of the hydrochloride of the reduction product showed no depression when mixed with 2,4,5-trimethylimidazole hydrochloride and their infrared spectra were also identical.

A possible mechanism for the formation of these compounds is as follows.



The only examples of 1-hydroxyimidazole 3-oxides in the literature appear in a publication by LaParola.[4] This author investigated the reaction between dimethylglyoxime and benzaldehyde, as well as other aromatic aldehydes, and obtained a substance possessing the formula $C_{11}H_{12}N_2O_2$. To this product he assigned the structure VI. The assignment of structure was based upon the fact that upon reduction with zinc and hydrochloric acid there was obtained 2-phenyl-4,5-dimethylimidazole.[5]



VI

Thus it would appear that 1-hydroxyimidazole 3-oxides can be prepared either by reaction of 2,3-butanedione monoxime with aldehyde oximes or by the reaction of dimethylglyoxime with aldehydes. The first step in these reactions may well be exchange of the oxime grouping between the aldehyde and the α-diketone.

Experimental[6,7]

1-Hydroxy-2,4,5-trimethylimidazole 3-Oxide.—A mixture of 20.0 g. (0.34 mole) of acetaldoxime and 34.2 g. (0.34 mole) of 2,3-butanedione monoxime was warmed to obtain a homogeneous solution. After standing at room temperature for 2 days, the mixture was refluxed 1 hr. and then diluted with 500 ml. of ether. The tar solid removed by filtration weighed 30.42 g. (63%), m.p. 194° dec. Two recrystallizations from 95% ethanol gave material melting constantly at 198° dec.

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.81; H, 6.87; N, 19.56.

Two grams of the product obtained above was dissolved in chloroform and the hydrochloride precipitated by the addition of an ethereal hydrochloric acid solution. There was obtained 2.14 g. of a tan solid melting at 131.5–133° and showing no depression when mixed with the material prepared by the action of hydrochloric acid on 2,3-butanedione monoxime. The infrared spectra of the two samples were also identical.

1-Hydroxy-2,4,5-trimethylimidazole 3-oxide hydrochloride was prepared in 38% yield by treated 2,3-butanedione monoxime with dry hydrogen chloride according to the procedure for Diels and Van der Leeden.[4] Recrystallization from butanone-2 gave prisms melting at 129.5–131.5°.

Anal. Calcd. for $C_6H_{10}N_2O_2$·HCl: Cl, 19.85; N, 15.69. Found: Cl, 20.06; N, 15.80.

Reduction of 1-Hydroxy-2,4,5-trimethylimidazole 3-Oxide with Sodium Hydrosulfite.—To 2.84 g. (0.02 mole) of 1-hydroxy-2,4,5-trimethylimidazole 3-oxide in 50 ml. of water was added 17.413 g. (0.1 mole) of sodium hydrosulfite. The mixture was heated under reflux for 3.5 hr. The solution was allowed to cool and was saturated with potassium carbonate and extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, and the ether was removed. There was obtained 0.76 g. of a white solid melting at 131.5–134.5°. Recrystallization from ether gave material melting at 133.5–133.5°. A mixture melting point with authentic 2,4,5-trimethylimidazole[8] (m.p. 134.5–135.5°) showed no depression. Addition of an ethereal hydrogen chloride solution to a solution of the reaction product in ether gave the hydrochloride, melting at 315° and showing no depression when mixed with an authentic sample of 2,4,5-trimethylimidazole hydrochloride (m.p. 314°).

1-Hydroxy-2-ethyl-4,5-dimethylimidazole 3-Oxide.—A mixture of 7.3 g. (0.1 mole) of propionaldoxime and 10.11 g. (0.1 mole) of 2,3-butanedione monoxime was warmed to 40° to obtain a homogeneous solution. After standing overnight, the mixture was refluxed for 3 hr. The viscous oil was triturated with ether and the resulting solid was removed by filtration. There was obtained 10.10 g. (65%) of a cream-colored solid melting at 190.5° dec. Recrystallization from 95% ethanol gave 8.20 g. of colorless prisms melting at 195° dec.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.92; H, 7.46; N, 17.82.

(4) G. LaParola, *Gazz. chim. ital.*, **75**, 216 (1945).

(5) Very recently F. Minisci, *et al.* [*Tetrahedron Letters*, 785 (1963)], described the preparation of 1-hydroxybenzimidazole 3-oxides by the reaction between nitrile oxides and aromatic nitroso derivatives. The properties of these compounds appear to be quite similar to those of 1-hydroxyimidazole 3-oxides; that is, they form a monohydrochloride salt readily, dissolve in aqueous alkali, and are reduced readily to benzimidazoles.

(6) Melting points are corrected.

(7) The author is indebted to Dr. George Slomp and Mr. Forest MacKellar for the n.m.r. spectral studies, to Dr. Gerald Umbreit and his coworkers for the pK_a data and for the microanalytic data, and to Miss Lorraine Pschigoda for infrared spectral studies. He is indebted also to Mr. Albert Lallinger for technical assistance.

(8) R. W. Cowgill and W. M. Clark, *J. Biol. Chem.*, **198**, 36 (1952).

Quinazolines and 1,4-Benzodiazepines. XX.[1] The Formation of 3-Phenylindole-2-carboxaldehydes from 2,3-Dihydro-1*H*-1,4-benzodiazepine 4-Oxides

WERNER METLESICS, GLADYS SILVERMAN, AND LEO H. STERNBACH

Department of Chemical Research, Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey

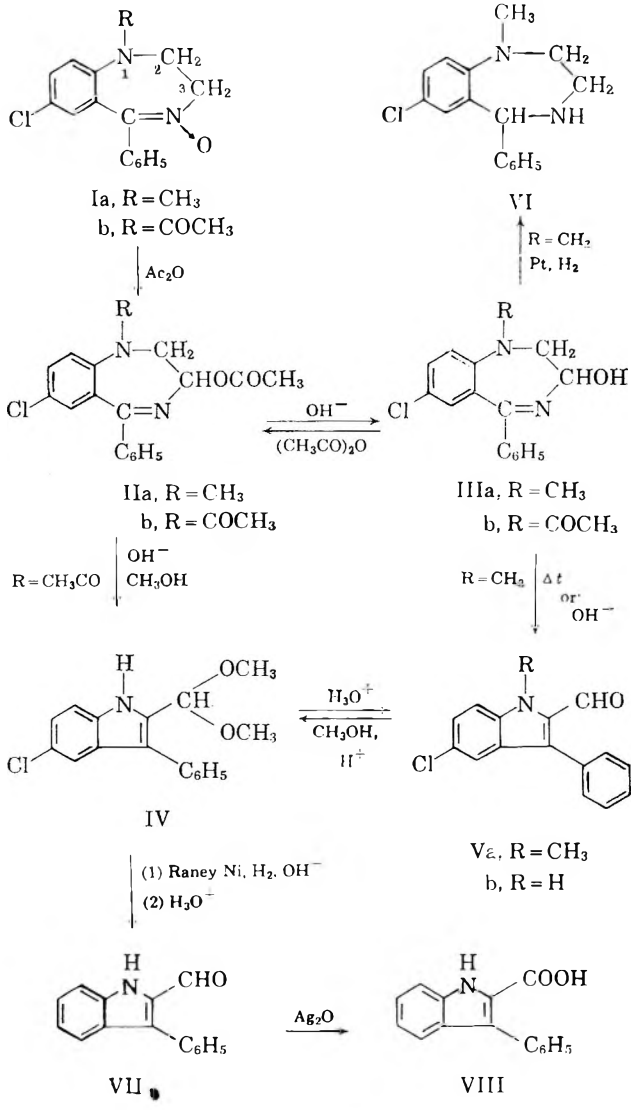
Received December 17, 1963

Recent interest in nitrones of type I[2] led us to investigate the rearrangement of these compounds with acetic anhydride. The products isolated contained an oxygen function in position 3 of the 1,4-benzodiazepine system. Their structure is in accordance with that postulated for intermediates in the Polonovski reac-

(1) Paper XVIII: L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964); paper XIX: R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).

(2) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963); W. Metlesics, G. Silverman, and Leo H. Sternbach, *ibid.*, **28**, 2459 (1963).

SCHEME I



tion.[3] As in previously reported cases,[1,4] these rearrangement products could be isolated and their reactions are shown in Scheme I.

Alkaline hydrolysis of the rearrangement product IIb under mild conditions gave IIIb which could be reacetylated to IIb. The methyl derivative IIa could not be crystallized, and in a purification attempt on a basic alumina column the hydroxy derivative IIIa was isolated. The seven-membered ring structure of compound IIIa was proved by catalytic hydrogenation to VI.[5]

In an attempt to dehydrate IIIa by distillation *in vacuo* an almost quantitative yield of Va was obtained. This ring contraction showed that the hydroxy group in IIIa was in position 3.

The ring contraction of benzodiazepines of type II or III to indolecarboxaldehydes was also observed under a variety of hydrolytic conditions. These reactions led to the indolecarboxaldehyde derivatives IV, Va, and Vb. Alkaline hydrolysis of IIb in methanol gave a 70% yield of IV and a small amount of the corresponding aldehyde Vb. These ring contractions involve the loss of ammonia and the condensation of the methylene group (C-2) with the carbon bearing the phenyl group (C-5 in II or III). Since the acetal IV could not be obtained from V under the same conditions, it must be a product of direct solvolysis.

The structure of IV was proved by dehalogenation to VII which was oxidized with silver oxide to give the corresponding carboxylic acid VIII. This was identical with a sample prepared as reported in the literature.[6]

Experimental

All melting points are corrected. The infrared and ultraviolet absorption spectra of the compounds described were determined to establish structural changes. Identity was proved by mixture melting point and comparison of infrared spectra. The ultraviolet spectra were determined in isopropyl alcohol using a Cary Model 14 spectrophotometer.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine 4-Oxide (Ia).—A solution of 5.4 g. (0.02 mole) of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine 4-oxide[2] in 100 ml. of dimethylformamide was prepared under dry nitrogen. To this solution 3.18 g. (0.066 mole) of a 50% suspension of sodium hydride in mineral oil was added with stirring and the bath temperature was raised to about 50°. After 1 hr. the mixture was cooled in an ice bath and 6 ml. (about 0.1 mole) of methyl iodide was added. The solution was kept at 25° for 18 hr. and poured into ice–water. After extraction with dichloromethane, an oil was obtained which crystallized on addition of a mixture of ether and petroleum ether (b.p. 30–60°) to give 3.9 g. of crystals melting at 133–139°.

Recrystallization from a mixture of methylene chloride and petroleum ether yielded 3 g. (53%) of yellow prisms melting at 140–143°. The product was also obtained in a second crystalline form melting at 169–172°, which showed identical spectral properties: λ_{max} 241 mμ (ε 23,000), 268 (16,000), and 306 (11,000).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27; N, 9.77. Found: C, 66.79; H, 5.40; N, 9.61.

3-Acetoxy-1-acetyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (IIb). A. **From Ib.**—A solution of 7.0 g. (0.022 mole) of Ib[2] in 60 ml. of acetic anhydride was refluxed for 7 hr. After evaporation of the acetic anhydride *in vacuo* the residue on addition of ether gave crystals which, after recrystallization from a mixture of methylene chloride and hexane, yielded 4.7 g. (59%) of white prisms melting at 177–179°, λ_{infl} 223 mμ (ε 30,000), λ_{max} 254 mμ (ε 13,000).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; Cl, 9.94; N, 7.85. Found: C, 63.70; H, 4.75; Cl, 10.00; N, 7.99.

B. **From IIIb.**—A solution of 0.05 g. of IIIb in 2 ml. of acetic anhydride was kept at 25° for 17 hr. The acetic anhydride was evaporated *in vacuo* and the residue crystallized from ether to give white prisms melting at 170–175° which were identified with IIb.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-3-ol (IIIa).—A solution of 3.5 g. (0.012 mole) of Ia in 12.5 ml. of acetic anhydride was heated for 110 min. at a bath temperature of *ca.* 115°. The acetic anhydride was removed *in vacuo*, and the residue was dissolved in a mixture of 15 ml. of 2 *N* sodium hydroxide and 100 ml. of acetone. After 10-min. standing at 25° the acetone was removed *in vacuo* (bath temp. *ca.* 50°), and the aqueous phase was extracted with methylene chloride. The methylene chloride solution was dried with sodium sulfate and evaporated to give a crystalline residue which, after recrystallization from a mixture of methylene chloride and petroleum ether, melted at 155–157° dec. The yield was 1.2 g. (34%), λ_{max} 228 mμ (ε 19,000) and 249 (17,000).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27; N, 9.77. Found: C, 67.16; H, 5.66; N, 9.73.

1-Acetyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-3-ol (IIIb).—To a solution of 1.78 g. (0.005 mole) of IIb in 50 ml. of methanol 10 ml. of 1 *N* aqueous sodium hydroxide was added dropwise over a period of 10 min. The solution was concentrated *in vacuo* without heating and extracted with dichloromethane. On concentration of the methylene chloride and addition of ether,

(3) R. Huisgen, F. Bayerlein, and W. Heydkamp, *Chem. Ber.*, **92**, 3223 (1959).

(4) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(5) For the preparation of this compound see L. H. Sternbach, E. Reeder, and G. A. Archer, *ibid.*, **28**, 2456 (1963).

(6) R. Manske, W. Perkin, and R. Robinson, *J. Chem. Soc.*, 1 (1927).

1.0 g. (63%) of white prisms was obtained which melted at 170–171° dec., λ_{infl} 220 mμ (ε 38,000), λ_{max} 253 mμ (ε 13,000).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 65.44; H, 5.22; N, 8.87.

5-Chloro-3-phenylindole-2-carboxaldehyde Dimethylacetal (IV).—A solution of 4.5 g. (0.13 mole) of IIb in 150 ml. of methanol and 50 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 3 hr. The solution was concentrated *in vacuo* and extracted with methylene chloride. The methylene chloride was removed and on addition of petroleum ether 3.1 g. of crystals were obtained which, on recrystallization from a mixture of ether and petroleum ether gave 0.1 g. of yellow needles melting at 231–237° (see Vb below).

From the mother liquor, 2.6 g. (69%) of white prisms was obtained which melted at 134–137°, λ_{max} 229 mμ (ε 35,000) and 267 (11,000).

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64; CH_3O, 20.6. Found: C, 68.11; H, 5.80; N, 4.68; CH_3O, 20.9.

This compound was also obtained from Vb by heating in methanol with *p*-toluenesulfonic acid as catalyst.

5-Chloro-1-methyl-3-phenylindole-2-carboxaldehyde (Va). A. From Vb.—To a solution of 0.5 g. (0.002 mole) of Vb in 10 ml. of dimethylformamide was added 0.2 g. (0.004 mole) of a 50% suspension of sodium hydride in mineral oil. The mixture was kept for 15 min. at 36–40°, cooled to 25°, and 0.28 ml. of methyl iodide was added. After 15 min. the solution was poured into water and filtered from the precipitate, which was recrystallized from a mixture of methylene chloride and petroleum ether to give 0.23 g. (43%) of yellow needles melting at 156–159°, λ_{max} 252 mμ (ε 30,000) and 318 (22,500).

Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.42; H, 4.72; N, 5.04.

B. From IIIa.—Hydrolysis of IIIa under basic conditions gave Va in moderate yield. However, an almost quantitative yield of Va was obtained in an attempt to distil IIIa in a bulb tube (0.1 mm., bath temp. *ca.* 150°).

5-Chloro-3-phenylindole-2-carboxaldehyde (Vb). A. From IIIb.—A solution of 0.5 g. (0.0016 mole) of IIIb in 10 ml. of methanol, 1 ml. of water, and 2 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 2.5 hr., and evaporated. The residue was taken up in methanol, and hydrochloric acid was added. A yellow precipitate which formed was collected on a filter and recrystallized from methylene chloride to give 0.2 g. of yellow needles (Vb) melting at 237–240°, λ_{max} 251 mμ (ε 31,000) and 320 (24,000).

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.56; H, 3.96; N, 5.49.

B. From IV.—A solution of 0.5 g. of IV in 15 ml. of methanol and 15 ml. of 1 *N* hydrochloric acid was heated to reflux for 5 min. Yellow crystals precipitated which melted at 235–240° and were identified with Vb.

7-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-1,4-benzodiazepine (VI).—A solution of 1.7 g. (0.006 mole) of IIIa in 50 ml. of acetic acid was hydrogenated at 25° and 1 atm. using 0.2 g. of platinum oxide as catalyst. After an uptake of 335 ml. (*ca.* 0.014 mole) the hydrogen absorption had slowed down to a rate of *ca.* 20 ml. per hr. The solution was poured on ice, made basic with aqueous sodium hydroxide, and extracted with ether. The ether solution was evaporated, and the residue was extracted with boiling heptane. Addition of hydrogen chloride in ether precipitated crystals which, after recrystallization from a mixture of ethanol and ether, melted at 240–250° (VI).[5]

3-Phenylindole-2-carboxaldehyde (VII).—A solution containing 2.4 g. (0.008 mole) of IV and 8 ml. of 1 *N* sodium hydroxide in 100 ml. of ethanol was hydrogenated at atmospheric pressure and 25° using *ca.* 5 g. of Raney nickel as catalyst. The uptake stopped after the consumption of 170 ml. (*ca.* 0.007 mole) of hydrogen. The solution was filtered from the catalyst and evaporated *in vacuo*. The residue was shaken with dilute hydrochloric acid and extracted with ether. The ether solution on evaporation gave a crystalline residue which, after recrystallization from a mixture of methylene chloride and methanol, gave pale yellow needles melting at 195–197°. The yield was 1 g. (56%); λ_{max} 230 mμ (ε 16,500), 250 (22,500), and 320 (21,000).

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01. Found: C, 81.51; H, 4.95.

3-Phenylindole-2-carboxylic Acid (VIII).—To a solution of 0.11 g. of VII in a mixture of 30 ml. of ethanol and 20 ml. of acetone was added 0.17 g. of silver nitrate and 15 ml. of 0.1 *N* aqueous sodium hydroxide. The solution was stirred at 25° for 17 hr. and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in dilute sodium hydroxide, and the solution was extracted with ether. On acidification of the aqueous layer a precipitate formed which was collected on a filter, dried, and recrystallized from a mixture of ether and petroleum ether. White prisms melting at 188–190° were obtained in *ca.* 34% yield (*ca.* 0.04 g.) and found to be identical with an authentic specimen.[6]

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and to Dr. V. Toome and Mr. S. Traiman for the determination of ultraviolet and infrared spectra.

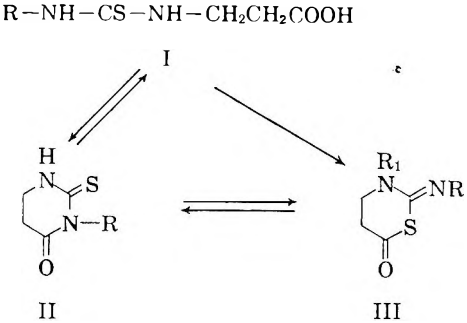
Formation of 3-Substituted 2-Thio-4-oxohexahydro-1,3-diazines and 2-Substituted Imino-6-oxo-1,3-thiazanes from 1-Substituted 3-Carboxyethylthioureas and Interconversion of Both Cyclic Systems

A. PROSEN, B. STANOVNIK, AND M. TIŠLER

Department of Chemistry, University of Ljubljana, Ljubljana, Yugoslavia

Received October 7, 1963

Recently we have described the cyclization of 3-carboxyethylthioureas (I),[1] and as a part of a continuing study we wish to report some further details and the interconversion of both cyclic systems, *e.g.*, 3-substituted 2-thio-4-oxo-hexahydro-1,3-diazines (II) to 2-substituted imino-6-oxo-1,3-thiazanes (III, $R_1 = H$) and *vice versa*.



II III

When the cyclization is carried out in acetic anhydride at 90–95°, the preponderant product is the thiazine derivative. From the mother liquor it is possible to isolate the diazine. Presented in Table I

TABLE I

SIMULTANEOUS FORMATION OF THIAZINE AND DIAZINE DERIVATIVES

R	Thiazines (III), yield, % $R_1 = H$	$R_1 = CH_2CO$	Diazines (II), yield, %	Ratio of III–II, mole
o-Tolyl	70		17	1:0.24
p-Methoxyphenyl		72.5	3.9	1:0.06
p-Ethoxyphenyl	68		7.6	1:0.11
o-Chlorophenyl	89.5		~1	1:0.01
m-Chlorophenyl		54.5	12.8	1:0.28
p-Chlorophenyl	90		8	1:0.10

(1) M. Derzaj-Bizjak, S. Oblak, and M. Tišler, *J. Org. Chem.*, **27**, 1343 (1962).

TABLE II

THIAZINES AND DIAZINES

Compound	R	R_1	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
II	*o*-Tolyl		172	$C_{11}H_{12}N_2OS$	59.99	59.47	5.49	5.49	12.76	12.89
III	*p*-Tolyl	CH_3CO	156	$C_{13}H_{14}N_2O_2S$	59.52	59.40	5.38	5.74	10.68	10.75
III	*p*-Methoxyphenyl[a]	CH_3CO	167	$C_{13}H_{14}N_2O_3S$	56.09	56.22	5.07	5.41	10.07	10.07
III	*o*-Chlorophenyl[b]	H	136	$C_{10}H_9ClN_2OS$	49.83	49.98	3.76	3.91	11.63	11.50
III	*m*-Chlorophenyl	CH_3CO	143	$C_{12}H_{11}ClN_2O_2S$	50.97	51.18	3.92	4.20	9.91	9.73
II	*p*-Chlorophenyl		204	$C_{10}H_9ClN_2OS$	49.83	49.60	3.76	4.01	11.63	11.60
III	*p*-Chlorophenyl	H	182	$C_{10}H_9ClN_2OS$	49.83	50.01	3.76	4.04	11.63	11.39

[a] Ultraviolet spectrum: λ_{max}^{EtOH} 2410 Å. (ε 16,700) and 2950 Å. (ε 11,500). [b] Ultraviolet spectrum: λ_{max}^{EtOH} 2450 Å. (ε 11,850) and 2950 Å. (ε 9860).

is the corresponding ratio for each pair of cyclic compounds. Besides reaction temperature,[1] we have also observed that the reaction time greatly influences the yield of the two products II and III. Thus yields of III in the 25–30% range were observed at 90° and a 30-min. reaction time and they are raised to 90% at the same temperature but prolonging the reaction time to 90 min. However, such conditions have led in some cases to acetylated products (III, R_1 = CH_3CO), which are readily distinguished from the unacetylated thiazines by means of their infrared spectra, exhibiting an additional peak in the 8.10-μ region and lacking NH stretching absorption.[2]

The passage from one cyclic system into the other is possible by different means. Acetic anhydride transforms the diazines into thiazines under conditions similar to those of the direct cyclization. On the other hand, diazines can be obtained from thiazines by treatment with dilute acetic acid or with pyridine; with the acetylated compounds the same conversion takes place. Although the diazines are readily hydrolyzed with aqueous alkali or acid, giving rise to the starting carboxyethylthioureas,[1] we were unable to isolate such compounds during the above-mentioned mutual conversions of both ring systems.

The interconversion of both ring systems can be followed spectrophotometrically as both heterocyclic systems are readily distinguished on the basis of their ultraviolet spectra. 1,3-Diazine derivatives have absorption characteristics almost identical with those of 2-thiouracil, whereas derivatives of 1,3-thiazine exhibit two maxima, one at about 2450 Å. and the second one at about 2950 Å. The first one apparently corresponds to the thiolactone group for maxima in this region (2350 Å.) have been registered with simple γ-thiolactones.[3] Thus we have followed spectrophotometrically the formation of a diazine (II, R = *o*-tolyl) from the corresponding thiazine with 10% acetic acid at 60° and the optimum conversion (88%) is achieved after 80 min. On the other hand the diazine (II, R = *o*-tolyl) is transformed into the thiazine by means of acetic anhydride at 60° after 120 min. (83% conversion). These results, representing optimum conversion, are most probably due to an equilibrium-controlled process.

(2) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1960, p. 249.

(3) C. M. Stevens and D. S. Tarbell, *J. Org. Chem.*, **19**, 1998 (1954).

Experimental[4]

General Remarks.—1-Substituted 3-carbethoxyethylthioureas were prepared as described previously,[1] but saponification of these esters was performed by an improved procedure: 0.05 m. of the corresponding ester was refluxed with an equivalent of 2 *N* sodium hydroxide until complete dissolution (about 15 min.). On acidification with hydrochloric acid (1:1) to pH 1–2 and standing on ice the crystals were collected. If necessary the product was crystallized from ethanol, but in this case the compounds were found to be sufficiently pure for further cyclization. By this procedure 1-(2′,4′-dimethylphenyl)-3-carboxyethylthiourea was prepared, m.p. 145°, yield 90%.

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: C, 57.13; H, 6.39; H, 11.11. Found: C, 57.37; H, 6.45; N, 10.99.

1-(*o*-Chlorophenyl)-3-carboxyethylthiourea was prepared without isolating the intermediate ester which was submitted to saponification as a crude reaction product; yield 65%, m.p. 139°.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_2S$: C, 46.42; H, 4.28; N, 10.83. Found: C, 46.89; H, 4.75; N, 10.67.

Cyclization of 1-Substituted 3-Carboxyethylthioureas.—A 0.02-mole sample of the corresponding acid I, 100 ml. of acetic anhydride, and few drops of concentrated sulfuric acid were heated 1.5 hr. at 90–95° on a water bath. On cooling, the reaction mixture was poured into about 300 ml. of water, stirred, and left aside for 15 min.; the upper liquid was decanted from the oily residue or filtered if the compound crystallized immediately. The crude product was left overnight for crystallization, and purification from ethanol yielded the pure thiazine derivative. The residual mother liquor was evaporated almost to dryness and the remaining crystals of the diazine were crystallized from ethanol. The cyclized products are presented in Table II. The acetylated thiazines are stable compounds and the acetyl group is not removed in the course of their isolation, but is removed during their conversion into the diazines.

Interconversions of Diazines and Thiazines. A.—A 1.2-g. sample of III (R = *o*-Cl-C_6H_4, R_1 = H) was heated with 10% acetic acid (30 ml.) on a water bath; the solution was evaporated almost to dryness. The residue was filtered and crystallized from ethanol to yield 1 g. (83%) of the diazine (II, R = *o*-Cl-C_6H_4), m.p. 189°. The ultraviolet spectrum showed λ_{max} 2800 Å. (ε 12,800).

Anal. Calcd. for $C_{10}H_9ClN_2OS$: C, 49.83; H, 3.76; N, 11.63. Found: C, 50.22; H, 3.27; N, 11.59.

B.—III (R = *p*-CH_3O-C_6H_4, R_1 = CH_3CO; 1.6 g.) was converted similarly to the diazine (II, R = *p*-CH_3O-C_6H_4), yield 1.5 g. (94%), m.p. 236°.[1]

C.—II (R = C_6H_5, 1.15 g.), acetic anhydride (57.5 ml.), and a few drops of concentrated sulfuric acid were heated on a water bath at 75° for 2 hr. The solvent was evaporated *in vacuo*; the residue was poured into 20 ml. of water. The crystals which separated were purified from ethanol to yield 0.9 g. (78.5%) of the thiazine (III, R = C_6H_5, R_1 = H), m.p. 142°.[1]

D.—III (R = C_6H_5, R_1 = H; 1.0 g.) and 20 ml. of pyridine were heated on a water bath for 15 min., the solvent was evaporated *in vacuo* to dryness, and the residue was triturated with water. The product obtained was crystallized repeatedly from ethanol, giving the diazine (II, R = C_6H_5), m.p. and m.m.p. 228°

(4) All melting points were determined on a Kofler hot stage and are corrected.

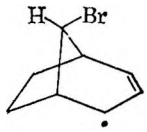
The Synthesis of *syn*-8-Bromobicyclo[3.2.1]-2-octene

L. H. ZALKOW AND A. C. OEHLSCHLAGER[1]

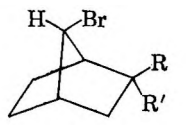
Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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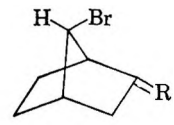
Bicyclo[2.2.2]-2-octene has been recently shown to react with N-bromosuccinimide in the presence of benzoyl peroxide in carbon tetrachloride to yield the rearranged product *syn*-8-bromobicyclo[3.2.1]-2-octene (I).[2] The skeleton of I was readily arrived at by chemical



I



III, R = OH; R′ = H
Va, R = OH; R′ = CH_3
b, R = CH_3; R′ = OH
VIIa, R = H; R′ = CH_2OH
b, R = CH_2OH; R′ = H



IV, R = O
VI, R = CH_2

means, but the position of the bromine atom in I was determined indirectly by n.m.r. and dipole moment studies.[2] We now wish to record the synthesis of I.

Treatment of norbornylene (II) with hypobromous acid gave *syn*-7-bromobicyclo[2.2.1]heptan-2-*exo*-ol (III) as the major product. Roberts, Johnson, and Carboni[3] had previously shown that hypochlorous acids adds to norbornylene to give the corresponding chloro isomer of III. Jones[4] oxidation of III gave ketone IV which on treatment with methylmagnesium iodide gave a mixture of *syn*-7-bromo-2-*endo*-methylbicyclo[2.2.1]heptan-2-*exo*-ol (Va) and its C-2 isomer Vb. The C-2 methyl group in Va gave a signal at δ 1.23 whereas the C-2 methyl group in Vb gave a signal at δ 1.55 in their n.m.r. spectra. The mixture of alcohols V was distilled in the presence of iodine to give the bromo olefin VI which on hydroboration[5] gave a mixture of 7-*syn*-bromobicyclo[2.2.1]heptane-2-methanols (VII). Heating of mixture VII in the presence of phosphorous acid gave I, identical in all respects with that previously reported.[2]

Experimental[6]

Preparation of *syn*-7-Bromobicyclo[2.2.1]heptan-2-*exo*-ol. III.—N-Bromosuccinimide (140 g.) was added to norbornylene (60 g.) dissolved in 1.2 l. of 1 *N* sulfuric acid and 800 ml. of *t*-butyl alcohol. After stirring at room temperature overnight, the solution was diluted with 5 l. of water and exhaustively extracted with petroleum ether (b.p. 35–40°). The extract was washed with sodium carbonate solution, dried over magnesium sulfate, and concentrated. Fractionation of the residue gave 18.1 g. of nortricyclene bromide (b.p. 55° at 0.70 mm.) and 55.8 g. of the bromonorborneol fraction which solidified on standing. Gas chromatographic analysis of the latter fraction (10 ft. × 0.25 in. 10% silicone 550-on-firebrick column at 190° with a flow rate of 55 cc./min.) showed that it contained two components in a ratio of 3:1. The component in larger amount was identified as *syn*-7-bromobicyclo[2.2.1]heptan-2-*exo*-ol, and the minor component was identified as 3-bromobicyclo[2.2.1]heptan-2-ol by n.m.r. The bromonorborneol fraction gave m.p. 40–43° after two sublimations and was used without further separation for the next step.

Preparation of *syn*-7-Bromobicyclo[2.2.1]heptan-2-one (IV).[7]—The above-mentioned bromonorborneol fraction was oxidized in dry acetone using a molar equivalent of Jones reagent.[4] The reaction mixture was diluted with water, then extracted with *n*-hexane. The hexane extract, after washing with sodium carbonate solution, was dried and concentrated. The residue was fractionally distilled to yield *syn*-7-bromobicyclo[2.2.1]heptan-2-one (72%), b.p. 68–70° at 0.4 mm., ν_{max}^{film} 1750 cm.$^{-1}$, n.m.r. (CS_2) δ 4.4 (C-7 proton, quartet, J = 1 c.p.s.). The gas chromatogram (same conditions as above) showed <5% impurities. The 2,4-dinitrophenylhydrazone was prepared by the addition of an acidic, methanolic 2,4-dinitrophenylhydrazine solution and, after chromatography on alumina and recrystallization from petroleum ether (b.p. 50–70°), gave m.p. 201.5–202.5°.

Anal. Calcd. for $C_{13}H_{13}BrN_4O_4$: C, 42.29; H, 3.55. Found: C, 42.36; H, 3.80.

Preparation of *syn*-7-Bromo-2-methylbicyclo[2.2.1]heptan-2-ol (V).—A solution of ketone IV (0.185 mole) in ether was slowly added to 0.190 mole of methylmagnesium iodide in 250 ml. of dry ether. After stirring for 3 hr., aqueous ammonium sulfate was added, and the solution was extracted with ether. The ether extract was dried and evaporated to yield a residue (37 g.) whose n.m.r. spectrum indicated the presence of ~30% of unreacted IV, ~50% of *syn*-7-bromo-2-*endo*-methylbicyclo[2.2.1]-heptan-2-*exo*-ol (Va), and ~20% of *syn*-7-bromo-2-*exo*-methylbicyclo[2.2.1]heptan-2-*endo*-ol (Vb). A pure sample of Vb was obtained after chromatography on Merck acid-washed alumina and had m.p. 74–75° after three recrystallizations from petroleum ether (b.p. 40–45°); ν_{max}^{KBr} 3320, 1188, and 930 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{13}BrO$: C, 46.85; H, 6.39. Found: C, 47.07; H, 6.62.

Preparation of 7-*syn*-Bromo-2-methylenebicyclo[2.2.1]heptane (VI).—The crude product (24 g.) from the above-mentioned Grignard reaction was slowly distilled at 85–110° (20–55 mm.) in the presence of a few crystals of iodine. The distillate was fractionally distilled to give 11.4 g. of 7-*syn*-bromo-2-methylenebicyclo[2.2.1]heptane (VI), slightly contaminated (<15%) with 7-*syn*-bromo-2-methylbicyclo[2.2.1]hept-2-ene (detected by n.m.r.), and 9.23 g. of a fraction containing ketone IV (unchanged from Grignard reaction) and olefin VI. The latter fraction was separated into 2.8 g. of VI and 4.8 g. of IV by use of Girard T reagent. The analytical sample of VI was obtained by preparative gas chromatography on a 20 ft. × 1/8 in. silicone nitrile column; ν_{max}^{film} 3090, 1630, and 882 cm.$^{-1}$; n.m.r. (CS_2) δ 3.87 (doublet, J = 1.5 c.p.s., C-7 proton) and 4.85 (doublet, J = 10 c.p.s., vinylic protons).

Anal. Calcd. for $C_8H_{11}Br$: C, 51.36; H, 5.93. Found: C, 51.29; H, 5.96.

Conversion of VI into *syn*-8-Bromobicyclo[3.2.1]oct-2-ene (VIII).—A solution of sodium borohydride (0.37 g.) and boron trifluoride etherate (2.5 ml.) in 10 ml. of tetrahydrofuran was added to 2.3 g. of VI in 20 ml. of dry tetrahydrofuran and the solution was stirred at 60° for 3.5 hr.[5] After destroying the excess borohydride, 1.3 ml. of 3 *N* sodium hydroxide and 1.3 ml. of 30% hydrogen peroxide were cautiously added and after stirring at 50° for 1 hr. the solution was diluted with 150 ml. of water. Extraction with ether and removal of the ether gave an oily residue which on distillation gave 1.3 g. of the isomeric *syn*-7-bromobicyclo[2.2.1]heptane-2-methanols in a ratio of 3:1 (g.l.c. on silicone 550 column). The isomeric mixture (1.3 g.) was heated at 160° with 85% phosphoric acid[8] (0.5 g.) for 30 min. at 50 mm. during which period water and a dark-colored organic liquid distilled from the reaction mixture. The residue and distillate were combined, diluted with water, and extracted with petroleum ether (b.p. 40–45°). After washing and drying, the extract was concentrated to give 352 mg. of residue. Gas chromatographic

(1) National Defense Education Act Fellow, 1962–1965.

(2) N. A. LeBel, J. E. Huber, and L. H. Zalkow, *J. Am. Chem. Soc.*, **84**, 2226 (1962).

(3) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *ibid.*, **76**, 5692 (1954).

(4) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(5) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).

(6) Melting points are uncorrected. Infrared spectra were recorded with a Beckman IR-5 spectrophotometer; n.m.r. spectra were obtained with a Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard (δ 0). Carbon and hydrogen analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

(7) The synthesis of IV was reported by Sauers and Beisler [*J. Org. Chem.*, **29**, 210 (1964)] after the submission of this paper.

(8) K. Alder, H. Krieger, and H. Weiss, *Chem. Ber.*, **88**, 144 (1955).

analysis (silicone 550 column) indicated that this residue contained ~25% of the desired bromo olefin VIII. A sample of VIII was obtained by preparative gas chromatography (silicone 550 column) and the sample so obtained was identical in infrared and nuclear magnetic resonance spectra with a sample of VIII prepared as previously described.[2]

New Butadiene Dimers

SANAE TANAKA, KIYOSHI MABUCHI, AND NOBORU SHIMAZAKI

Mizonokuchi Research Laboratory, Mitsubishi Petrochemical Company, Ltd. Kawasaki, Japan

Received July 12, 1963

It is known that treatment of butadiene with a Ziegler type catalyst (combination catalyst of organoaluminum compounds and transition metal compounds) has given stereospecific polybutadiene.[1]

During our examination of the effect of various Ziegler catalysts on butadiene, a new reaction was found which produced linear dimers in good yield.

Treatment of butadiene in a hydrocarbon solution with the combined catalyst of trialkyl aluminum and cobalt(II) chloride resulted in a good yield of the butadiene dimer. These results are summarized in Table I.

TABLE I
DIMERIZATION OF BUTADIENE

Catalyst[a]	AlR_3–$CoCl_2$ molar ratio	Solvent	Product yield (%) Dimer	Higher polymer
$Al(C_2H_5)_3$–$CoCl_2$	3.5	Benzene	90	Trace
$Al(C_2H_5)_3$–$CoCl_2$	3.5	Pentane	85	Trace
$Al(C_2H_5)_3$–$CoCl_2$	3.6	Hexane	82	Trace
$Al(C_2H_5)_3$–$CoCl_2$	3.6	Nonane	Trace	Trace
$Al(iso\text{-}C_4H_9)_3$–$CoCl_2$	3.5	Benzene	80	Trace

[a] The aluminum compound that produced the dimer was limited to trialkyl aluminum.

In comparing alkyl groups, ethyl had a higher rate of reaction than isobutyl. The dimers were not formed when nickel or iron was used as the transition metal in place of cobalt.

The product, a colorless liquid of b.p. 117–118°, slowly polymerized when left standing for a long time. Hydrogenation and bromination indicated that this product was a dimer of butadiene which had the formula C_8H_{12} with three double bonds.

Gas chromatography indicated that this dimer was a mixture of about 85% of A and about 15% of B, both of which were found to have the formula C_8H_{12}. It was assumed that the two components A and B were different, not only in the position of the double bonds but also in the skeleton, because the hydrogenated product was also composed of two components, the per cents of which were the same as the mixture dimers.

The basic skeletons of A and B were established by the fact that the hydrogenated product of A was identified as 3-methylheptane (III), and B as octane (IV).

(1) G. Natta, *Makromol. Chem.*, **16**, 213 (1955); G. Natta and P. Corradini, *J. Polymer. Sci.*, **20**, 251 (1956); G. Natta, *Rubber Plastics Age*, **38**, 493 (1959); N. G. Gaylord, T.-K. Kwei, and H. F. Mark, *J. Polymer. Sci.*, **42**, 417 (1960).

The position of the double bonds in A and B was indicated by ultraviolet, infrared, and nuclear magnetic resonance spectra.

These spectra showed that only two of the three double bonds were conjugated, since A and B, respectively, had ultraviolet absorption at 226 and 225 mμ.

Infrared spectra of A and B showed the presence of a terminal double bond (900, 1000 cm.$^{-1}$), a conjugated double bond (1605, 1636, 1650 cm.$^{-1}$), and a methyl group (1372 cm.$^{-1}$). Further, strong absorptions at 900 and 915 cm.$^{-1}$ (CH_2 out-of-plane deformation) in A showed the presence of two terminal double bonds, one of which was conjugated.

The n.m.r. spectrum showed that compound A had a secondary methyl group from the presence of a symmetrical doublet at τ = 8.88 p.p.m. and also had the following partial structure, $=CH-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH=$, because of the presence of six lines at τ = 7.12 p.p.m.

Further proof for the formula (III) was obtained by the fact that the n.m.r. spectrum showed that the hydrogenated product of A had three methyl groups.

The n.m.r. spectrum of B confirmed the presence of one methyl and methylene group, both of which were not coupled since there was a symmetrical doublet at τ = 8.38 p.p.m. and a symmetrical triplet at τ = 7.19 p.p.m.

Among the possible structures for A and B, only I and II could be proposed for dimers A and B, respectively, since the structures completely satisfied all the observations. (See Scheme I.)

It is evident that dimers like I and II are produced by 1,2-addition and 1,4-addition of butadiene monomers, respectively.

It is well-known that in the case of butadiene polymerization by Ziegler catalysts, fine differences of combined components have a great effect on the structure of the product.

Experimental

Materials.—1,3-Butadiene monomer was dried over sodium hydroxide and activated alumina. Triethylaluminum and triisobutylaluminum (Ethyl Corp., U. S. A.) were vacuum distilled. Cobalt(II) chloride (Wako Pure Chemical Industries, Ltd., Japan) was dried over thionyl chloride. All the solvents were purified or dried from commercial products by conventional procedures.

Dimerization of Butadiene by Triethylaluminum–Cobalt(II) Chloride.—Experiments were carried out in 500-ml. autoclave equipped with an inlet tube and thermometer. Additions of solvents and catalyst were performed in a dry nitrogen atmosphere. The autoclave was first purged with nitrogen, then evacuated. Liquid butadiene (200 ml.) was added to the autoclave which had been charged with 60 ml. of a benzene solution containing 3.6 ml. of triethylaluminum and 1 g. of cobalt(II) chloride. The autoclave was heated at 60° and stirred for 2 hr. After addition of 100 ml. of methanol, the reaction mixture was washed with dilute sulfuric acid and then filtered. The filtrate, dried over calcium chloride and distilled, yielded 40 g. of dimer, b.p. 117–118° (760 mm.). Chromatographic analysis showed the composition of the distillate to be 83% I and 11% II.

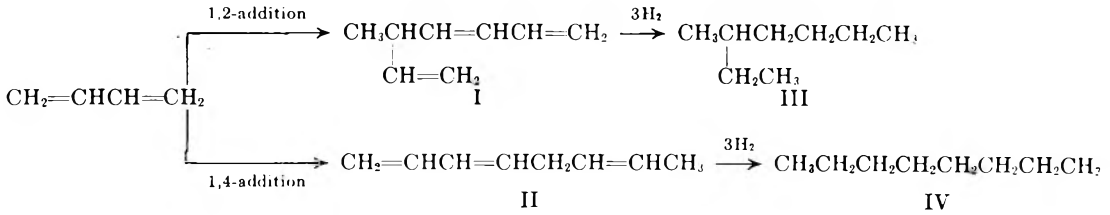
Dimer I had b.p. 117–118° (760 mm.), $n^{20}D$ 1.4670, d^{18}_4 0.7724.

Anal. Calcd. for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.78; H, 11.20.

(For the mixture of I and II: *Anal.* Found: C, 88.54; H, 11.29.)

Isolation of I and II.—Dimers I and II were isolated by gas–liquid chromatography by using a 4-m. Apiezon-M column. The conditions were column temperature, 110°; column pressure,

SCHEME I



10 p.s.i.; carrier gas, helium; and flash evaporator temperature, 200°. The first and second chromatographic peaks corresponded to I and II. The amount of II isolated was so small that analytical data, refractive index, and specific gravity of II could not be obtained; only spectroscopic data was obtained.

Hydrogenation of I and a Mixture of I and II.—Hydrogenation at atmospheric pressure of I (2.16 g.) using 100 mg. of platinum black resulted in absorption at 1520 ml. (3 equivalents) of hydrogen. After filtration, saturated hydrocarbon III (2.1 g.) was obtained. The infrared spectrum of this hydrocarbon (III) was identical with that of 3-methylheptane. Similarly on hydrogenation, a mixture of I and II absorbed 3 equiv. of hydrogen, and resulted in a mixture of 3-methylheptane (83%) and *n*-octane (11%). Octane was determined by gas chromatography.

Anal. Calcd. for C_8H_{18}: C, 84.22; H, 15.78. Found: C, 84.15; H, 15.80 (hydrogenated product III).

Anal. Found: C, 84.10; H, 15.75 (hydrogenated product of I and II).

Bromination of a Mixture of I and II.—On bromination, a mixture (10.1 g.) of I and II absorbed 3 equiv. of bromine in carbon tetrachloride (50 ml.). After filtration and evaporation, a white solid (50 g.) was obtained. It was purified by recrystallization from chloroform. The analytical sample melted at 129–130°.

Anal. Calcd. for $C_8H_{12}Br_6$: C, 16.35; H, 2.06; Br, 81.59. Found: C, 16.50; H, 2.20; Br, 81.26.

Acknowledgment.—The authors are indebted to Dr. S. Ito and Dr. K. Takase of Tohoku University, Japan, for the determination and interpretation of the n.m.r. spectra reported in this work.

4-Cholesten-3-one Ethylene Ketal

QUENTIN R. PETERSEN AND EDWARD E. SOWERS

Wabash College, Crawfordsville, Indiana

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In a study designed to extend our work of comparing the behavior of the cholesteryl and pseudo-cholesteryl systems,[1] the reaction of ethylene glycol and 5-cholesten-7-one (I) was undertaken to resolve the question of whether the pseudocholesteryl system (as I) would exhibit the unusual rearrangement of the double bond reported[2] from the preparation of the ethylene ketal III from 4-cholesten-3-one (II).

5-Cholesten-7-one (I) provided a ketal (IV), the optical rotation of which, in contrast to many other cholestane derivatives, was ambiguous[3] with respect to its use in the prediction of structure (see Table I).

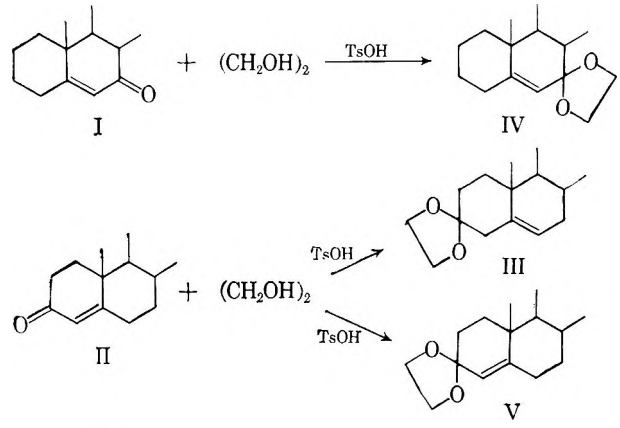
TABLE I

CHOLESTANE DERIVATIVES

Functional group	Hydroxyl position	Reported [α]D	Calculated, $\frac{[\alpha]_D\ \alpha + [\alpha]_D\ \beta}{2}$	Reported [α]D ethylene ketal
None	3α	+23[a]	+23.5	+21.6[b]
	3β	+24[a]		
5α,6α-Oxido	3α	−44[c,d]	−44.5	−33[f]
	3β	−43[e]		
5β,6β-Oxido	3α	−0.6[c]	+6	+9[f]
	3β	+12[e]		
Δ⁴	3α	+121[g]	+83	+75[g]
	3β	+45[h]		
Δ⁵	3α	−47[i]	−43.5	−28[k]
	3β	−40[j]		
Δ⁴	7α	+45[l]	+67	
	7β	+90[m]		−2.4[g]
Δ⁵	7α	−112[n]	−56	
	7β	±0[n]		

[a] L. F. Fieser and W. Huang, *J. Am. Chem. Soc.*, **75**, 4837 (1953). [b] H. Dauben, Jr., B. Löken, and H. Ringold, *ibid.*, **76**, 1360 (1954). [c] P. Plattner, A. Fürst, F. Koller, and H. Kuhn, *Helv. Chim. Acta*, **37**, 258 (1954). [d] A. Fudge, C. Shoppee, and G. Summers, *J. Chem. Soc.*, 958 (1954). [e] R. Baxter and F. Spring, *ibid.*, 613 (1943). [f] See ref. 8. [g] H. McKennis, Jr. and G. Gaffney, *J. Biol. Chem.*, **175**, 217 (1948). [h] P. Plattner, H. Heusser, and A. Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949). [i] P. Plattner and W. Lang, *ibid.*, **27**, 1872 (1944). [j] L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953). [k] See ref. 2a. [l] G. Kent and E. Wallis, *J. Org. Chem.*, **24**, 1235 (1959). [m] See ref. 1b. [n] A. Nickon and J. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961). [o] Details in this paper.

In order to compare the infrared spectrum of this possible α,β-unsaturated ethylene ketal with that of a known β,γ-unsaturated ethylene ketal, the pro-



(1) Q. R. Petersen, *J. Am. Chem. Soc.*, **82**, 3677 (1960); Q. R. Petersen and C. T. Chen, *ibid.*, **77**, 2557 (1955); Q. R. Petersen, *Proc. Indiana Acad. Sci.*, **68**, 118 (1959).

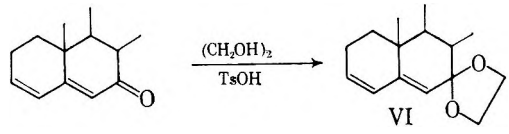
(2) (a) E. Fernholtz, U. S. Patent 2,378,918 (1945); *Chem. Abstr.*, **39**, 5052[3] (1345); (b) H. Koster and H. Inhoffen, German Patent 892,450 (1953); *Chem. Abstr.*, **52**, P18,534*g*, (1958); (c) C. Grob, W. Jundt, and H. Wicki, *Helv. Chim. Acta*, **32**, 2427 (1949); (d) R. Antonucci, S. Bernstein, R. Littell, K. Sax, and J. Williams, *J. Org. Chem.*, **17**, 1341 (1952); (e) H. Koster and H. Inhoffen, U. S. Patent 2,302,636 (1942); *Chem. Abstr.*, **37**, 2388[6] (1943).

(3) For another example of anomalous rotational contribution by the 7-oxygen function, see R. Cremlyn, R. Rees, and C. Shoppee, *J. Chem. Soc.*, 3790 (1954). Compound IV is tentatively assigned the Δ⁵-structure on the basis of its resemblance (in its mode of formation and in its instability toward hydrolysis) to the unrearranged ketals in the cholesteryl system.

cedure of Fernholtz[2a] was applied to the synthesis of the well-described 5-cholesten-3-one ethylene ketal (III). Several attempts to prepare this compound provided, reproducibly, a substance melting at 96° instead of 132° as reported for III. The identity and purity of all starting materials were checked without detection of error. Subsequent synthetic attempts following the procedure of Inhoffen[2b] led to the same result. Extensive chromatography of the crude material from these preparations provided only a little starting material and an apparently homogeneous substance (V), m.p. 96–97°, $[\alpha]D$ +75°. *None* of the expected product III with the reported[2a] constants, m.p. 132°, $[\alpha]D$ −28°, was observed.

The optical rotation (see Table I), the infrared spectrum, the elemental analysis, and the ready hydrolysis to 4-cholesten-3-one (II) led to the conclusion that V was, in fact, 4-cholesten-3-one ethylene ketal.

On the basis of the same kinds of evidence plus ultraviolet spectroscopy it was apparent that the ethylene ketal (VI) made from 3,5-cholestadien-7-one (or 5-cholesten-7-on-3β-ol acetate) also had suffered no double bond shift.[4]



VI

The recent paper of Dean and Christiansen[5] reporting the isolation of a Δ^4-ethylene ketal of testosterone[6] and an excellent and thorough examination of the properties of this and related compounds prompts us to terminate our work short of a complete study and present our remarkably similar findings in the cholestane series, reached independently and prior to the publication of their work.

During our study of the nature of V, a successful synthesis of III was achieved following the procedure of Grob.[2c] A re-examination of the experimental descriptions in the procedures used in the preparation of V showed, in common, a curiously inexact instruction in specifying the amount of *p*-toluenesulfonic acid monohydrate catalyst as "a few crystals".[2a,b] Workers[7,8] not supplying specific descriptions have generally referred to their use of the Fernholtz procedure and thus sustained the inexactness. Still other descriptions of the procedure for the formation of these derivatives define the catalyst necessary as "a trace"[9] or "a crystal".[2a]

The quantity "a few crystals" was found to be, in the hands of one of the present authors, 0.004 g. to 0.009 g. and, in the hands of the other, 0.008 g. to 0.015 g. The largest of these amounts was not sufficient to provide, on the scale of our experiments, the Δ^5-ethylene ketal III. On the scale with which we were working, approximately 0.05 g. of catalyst was required for conversion of II to III, and thus our interpretation of the term "a few crystals" was responsible for the anomalous result.

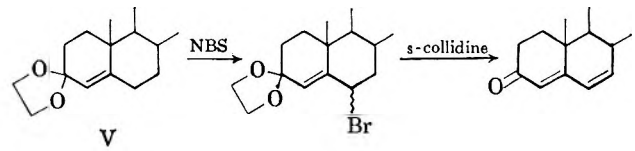
In addition to the similarity of the effect of catalyst concentration on our cholestenone system and on Dean and Christiansen's testosterone system, several other quite parallel observations were made.

(1) The infrared spectra of the Δ^4- and Δ^5-ethylene ketals (V and III) were very similar, the most notable differences being the presence of bands at 1663 (weak), 1175, and 993 cm.$^{-1}$ in the spectrum of the Δ^4-compound which were absent in the Δ^5-isomer. Bands at 1095 and 942 cm.$^{-1}$ were present in the spectra of both compounds.

(2) In our hands the Δ^4-ethylene ketal could not be epoxidized with *m*-chloroperbenzoic acid.

(3) The ethylene ketals prepared without isomerization of the double bonds (IV–VII) were extremely sensitive to hydrolysis and had to be stored over pyridine to remain uncontaminated by the parent ketone for more than a few hours. The ethylene ketals in which the double bond had shifted to the 5-position (III and VIII) proved quite stable and retained their purity over long periods of time without special protection.

(4) The bromination of the Δ^4-ethylene ketal with N-bromsuccinimide (NBS) went readily to give a unique product (VII) which, however, could not be hydrolyzed to an identifiable bromo ketone by any of the experiments carried out prior to the termination of this work. By analogy with the work of Dean and Christiansen, VII would be expected to be the 6α-bromo compound. Treatment of VII with *s*-collidine



V VII

gave an interactable oil; however, its infrared spectrum clearly showed the presence of 4,6-cholestadien-3-one.

In contrast to the testosterone system, preparative isomerization of the Δ^4- to the Δ^5-ethylene ketal was not realized when the former was refluxed in benzene with an excess of catalyst. The reaction was followed by chemical work-up and by periodic infrared spectra over 26 hr. to show an increasingly complex mixture in which only the unsaturated ketone could be positively identified.

6β-Bromo-4-cholesten-3-one provided a Δ^5-ethylene ketal (VIII) with a low catalyst concentration which would have been expected, in the nonhalogenated system, to produce a Δ^4-ketal. Under a still lower catalyst concentration there appeared to be produced a different substance which proved too unstable for purification and analysis. The structure of VIII was shown to be 6-bromo-5-cholesten-3-one ethylene ketal by optical rotation, elemental analysis, and sodium and alcohol reduction to the known ethylene ketal III.

(4) G. Fonken [*J. Org. Chem.*, **26**, 2549 (1961)] has demonstrated the nonrearrangement in the isomeric 4,6-cholestadien-3-one which we have verified.

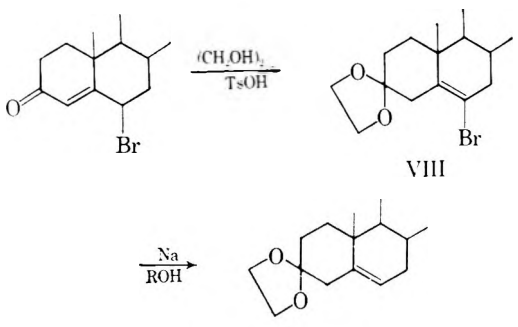
(5) J. W. Dean and R. G. Christiansen, *ibid.*, **28**, 2110 (1963).

(6) This compound was previously reported by J. Brown, R. Lenhand, and S. Bernstein [*Experientia*, **18**, 310 (1962)], but no physical constants or experimental details were given.

(7) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(8) G. Cooley, B. Ellis, D. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

(9) E. P. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 486 (1953).



III

Experimental[10]

5(4?)-Cholesten-7-one Ethylene Ketal (IV).—A solution of 1.0 g. of 5-cholesten-7-one in 100 ml. of benzene was mixed with 2.0 ml. of ethylene glycol and refluxed with a Dean–Stark water take-off in place. After 5 min., a "few crystals" of *p*-toluenesulfonic acid monohydrate were added, and the mixture refluxed for 24 hr. The benzene layer was decanted from the excess ethylene glycol and, after the addition of a drop of pyridine, evaporated under an air stream to provide a solid residue. Crystallization from methanol (pyridine) gave a fibrous, gel-like solid, m.p. 90°. Chromatography on alumina provided 0.97 g. of crystalline fractions melting variously from 100.5–102.5° to 93–101°. This substance was extremely unstable, decomposing to a significant extent if exposed to the atmosphere for 1 hr. The analytical sample showed m.p. 95–102°, $[\alpha]_D$ −2.4°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.3; H, 11.3. Found: C, 81.18; H, 11.52

The infrared spectrum showed no carbonyl adsorption and several peaks in the 900–1200-cm.$^{-1}$ region.

An acetone solution of IV when treated with a drop of concentrated hydrochloric acid and permitted to stand overnight gave, upon evaporation, pure 5-cholesten-7-one.

4-Cholesten-3-one Ethylene Ketal (V).—A solution of 1.02 g. of 4-cholesten-3-one in 100 ml. of benzene was mixed with 2.0 ml. of ethylene glycol and refluxed for 40 min. with a Dean–Stark water take-off in place. At the end of this time 0.0052 g. of *p*-toluenesulfonic monohydrate acid was added; the reflux was continued for 7 hr. The resulting mixture was washed three times with 2 *N* potassium bicarbonate and once with water. The benzene solution was filtered through anhydrous sodium sulfate and, after addition of a drop of pyridine, evaporated to a yellow oil which crystallized. The sample was recrystallized from 30 ml. of ethanol (pyridine) to provide 0.89 g. of powdery white solid, m.p. 103–104°, with some individual crystals melting between 92 and 96°. When the same was recrystallized from methanol (pyridine), it gave chunky needles, m.p. 95–97°, $[\alpha]_D$ +75°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.3; H, 11.3. Found: C, 81.05; H, 11.55.

Eight separate preparations of this compound were carried out, in each case the catalyst–steroid ratio ranging between that described above and three times that ratio. In every case the same product was obtained and none of the Δ^5-isomer was observed either by chromatographic separation or spectroscopic examination.

The ketal V apparently held some solvent under normal conditions. Fresh chromatographic fractions occasionally had a m.p. of 102° which declined to 95–97° on short standing in air, in a pyridine–air atmosphere, or upon crystallization from methanol (pyridine). The compound showed adsorption in the infrared as described in the discussion portion of this contribution.

When an acetone solution of V was treated with a few drops of 3 *N* hydrochloric acid and permitted to stand overnight it reverted completely to 4-cholesten-3-one.

(10) Melting points were determined on the hot stage of a polarizing microscope and are corrected to ±1°. Rotations were taken in pyridine at room temperature. Infrared spectra were determined in carbon tetrachloride with a Perkin-Elmer 21 instrument. Ultraviolet spectra were determined in methanol with a Beckman DU instrument. Recrystallizations from solvents containing a drop of pyridine are indicated as "methanol (pyridine)." Microanalyses were by Midwest Microlab Inc., Indianapolis, Ind.

Oxidation of the ketal according to the procedure of Poos, *et al.*,[7] provided, after work-up of the product, only unchanged ketal starting material and its hydrolysis product II.

The ketal also proved to be refractory to catalytic hydrogenation. In two attempts, 1.0 g. of the ketal was shaken with 0.093 g. of 12% palladium on charcoal in a 1% solution of potassium hydroxide in absolute ethanol under positive hydrogen pressure to give no reaction after 12 hr. The starting material was recovered quantitatively from the reaction mixture.

3,5-Cholestadien-7-one Ethylene Ketal (VI).—Using the same general techniques described for the previous experiments, 2.0 g. of 3,5-cholestadien-7-one provided 2.0 g. of an oily product which, upon chromatography on alumina, gave several crystalline fractions which could be recrystallized from methanol (pyridine) as long colorless needles, m.p. 102.5–103.5°, $[\alpha]_D$ −100°, λ_{max} 236 mμ.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.8; H, 10.8. Found: C, 81.34; H, 10.95.

This compound was also obtained each time the preparation of the ethylene ketal of 5-cholesten-7-on-3-ol acetate was attempted using the procedures described above.

6β-Bromo-4-cholesten-3-one Ethylene Ketal (VII).—A dry mixture of 0.27 g. of V and 0.13 g. of N-bromsuccinimide was added to 20 ml. of dry carbon tetrachloride, and the mixture refluxed under a spotlight for 2 min. The mixture was filtered and evaporated under an air stream to a semisolid which was crystallized from acetone to give rosettes, m.p. 120–122°. The mixture melting point with 4,6-cholestadien-3-one ethylene ketal[11] was depressed to 100°; the analysis of VII was not satisfactory.

Anal. Calcd. for $C_{29}H_{47}BrO_2$: C, 68.6; H, 9.3. Found: C, 67.47; H, 8.98.

6-Bromo-5-cholesten-3-one Ethylene Ketal (VIII).—Following the same procedure described for the preparation of V above, 2.0 g. of freshly recrystallized 6β-bromo-4-cholesten-3-one provided 1.7 g. of white needles, m.p. 136°. Samples of this material turned pasty on standing in a pyridine atmosphere, but either the paste or the crude crystals readily recrystallized from acetone to long needles, m.p. 145–146°, $[\alpha]_D$ −35.5°.

Anal. Calcd. for $C_{29}H_{47}BrO_2$: C, 68.6; H, 9.3. Found: C, 69.44; H, 9.21.

A sample of 0.15 g. of VIII was treated with 30 ml. of hot isopropyl alcohol and 2.0 g. of sodium metal was added. After the reaction was complete (15 min.), the mixture was worked up to produce 0.11 g. of III, m.p. 129–132°, shown to be authentic by mixture melting point and infrared spectrum.

When ketalization of 1.0 g. of the bromo ketone was attempted using 0.005 g. of catalyst, a portion of opaque rosettes, m.p. 105 dec., was obtained. This material showed an infrared spectrum different from either VII or VIII, but all purification attempts led to decomposition of the product.

Acknowledgment.—The authors express their appreciation for a grant from the Wolcott Gibbs Fund of the National Academy of Sciences and for a generous gift of 4-cholesten-3-one from the Schering Corporation.

(11) We find this compound (see ref. 4) to show m.p. 122°, $[\alpha]_D$ +63°.

The Synthesis of O-Acetylhydroxy-α-amino Acids

MEIR WILCHEK AND ABRAHAM PATCHORNIK

The Department of Biophysics, The Weizmann Institute of Science, Rehovoth, Israel

Received November 1, 1963

O-Acetylhydroxy-α-amino acids are conveniently used as starting materials for the synthesis of peptides and polyhydroxy-α-amino acids.[1] A number of

(1) J. Kurtz, G. D. Fasman, A. Berger, and E. Katchalski, *J. Am. Chem. Soc.*, **80**, 393 (1958).

TABLE I

O-ACETYLHYDROXY-α-AMINO ACID HYDROCHLORIDES

O-Acetyl hydrochloride of	Yield, %	M.p.,[e] °C.	Formula	% calcd. C	H	N	Cl	Neut. equiv.	% found C	H	N	Cl	Neut.[a] equiv.
Hydroxy-L-proline	91	179	$C_7H_{12}ClNO_4$	40.20	5.74	6.70	16.71	104.5	40.20	5.75	6.73	16.54	104
L-Serine	95	167[b]	$C_5H_{10}ClNO_4$	32.78	5.46	7.65	19.10	91.5	32.84	5.55	7.74	19.00	92
DL-Serine	93	158[c]	$C_5H_{10}ClNO_4$	32.78	5.46	7.65	19.10	91.5	32.75	5.40	7.60	19.00	91
L-Threonine	93	153[d]	$C_6H_{12}ClNO_4$	36.46	6.07	7.08	17.90	98.5	36.63	6.16	6.90	17.80	99

[a] The neutralization equivalent was determined by titration in ethanol with 0.1 *M* sodium methoxide using thymol blue as indicator [A. Patchornik and S. Ehrlich-Rogozinski, *Anal. Chem.*, **31**, 985 (1959)]. [b] $[\alpha]^{25}D$ +11.5° (*c* 2.2, ethyl alcohol; *c* 2, water); lit.[4] m.p. 160°, $[\alpha]^{27}D$ −7.4° (*c* 2.2, ethyl alcohol). [c] Lit.[2] m.p. 158–162°. [d] $[\alpha]^{25}D$ +15.3° (*c*, 2 water). [e] All melting points are uncorrected.

methods are known for the synthesis of O-acetylhydroxy-α-amino acids,[2-5] but these methods are relatively time consuming and laborious. We wish to report a simple, rapid, and general procedure for the synthesis of O-acetyl derivatives of hydroxyamino acids.

The amino acid is dissolved in a mixture of hydrochloric acid and glacial acetic acid and acetylated by the slow addition of acetyl chloride at 0°. The pure O-acetylhydroxyamino acid hydrochloride precipitates from the reaction mixture in a crystalline form. By this method we were able to prepare the O-acetyl derivatives of several hydroxyamino acids in 90% yield.

Experimental

The general experimental procedure is as follows. The amino acid (0.1 mole) is dissolved in 6 *N* hydrochloric acid (20 ml.). Glacial acetic acid (20 ml.) is added, and the solution is cooled to 0° in an ice bath. Acetyl chloride (200 ml.) is then added slowly to the beaker (caution, this reaction should be carried out in the hood as rapid evolution of hydrogen chloride takes place). The o-acetylhydroxyamino acid hydrochloride precipitates within a few minutes and quantitative precipitation may be brought about by adding two to three volumes of ether. The compound is filtered off, washed with ether, and dried *in vacuo*. The compounds obtained have been found to be chromatographically pure and the yields are all above 90% (Table I). The free O-acetylhydroxyamino acids can be obtained as usual[4] by dissolving the hydrochloride in solute ethanol and adding an equivalent amount of triethylamine.

O-Acetyl-N-carboxy-L-threonine Anhydride.—O-Acetyl-L-threonine hydrochloride (10.0 g.) was suspended in 100 ml. of absolute dioxane. Phosgene was passed through the suspension for 40 min. at room temperature, and a clear solution was obtained. The excess phosgene was removed by passing a stream of dry nitrogen through the solution. The dioxane was evaporated *in vacuo* at 50°. The oily residue that was obtained was shaken with petroleum ether three to four times, the petroleum ether being removed each time by decantation. The oil was then dissolved in a minumum amount of ethyl acetate, and a semicrystalline precipitate was obtained on addition of petroleum ether. The material was recrystallized twice from ethyl acetate–petroleum ether. The yield was 8.0 g. (85%), m.p. 94–95°.

Anal. Calcd. for $C_7H_9NO_5$: C, 44.92; H, 4.81; N, 7.48. Found: C, 44.85; H, 5.00; N, 7.72.

Acknowledgment.—This investigation was supported by Research Grant No. AM-5098 from the National Institutes of Health, U. S. Public Health Service.

(2) G. D. Fasman, E. R. Blout, *J. Am. Chem. Soc.*, **82**, 2262 (1960).
(3) W. Sakami and G. Toennies, *Biochem. J.*, **144**, 203 (1944).
(4) J. C. Sheehan, M. Goodman, and G. Hess, *J. Am. Chem. Soc.*, **78**, 1367 (1956).
(5) S. Fujiwara, S. Morinaga, and K. Norita, *Bull. Chem. Soc. Japan*, **35**, 438 (1962).

A Convenient Synthesis of Branched Unsymmetrical Sulfides

ERNEST L. ELIEL AND RONALD A. DAIGNAULT

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana

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It was discovered by Pettit and Kasturi[1] that the combination of lithium aluminum hydride ($LiAlH_4$) and a large excess of boron trifluoride etherate is a reagent for the reduction of esters and lactones to ethers and cyclic ethers. It has now been found that sulfides can also be conveniently prepared from the corresponding thiol esters by means of the same reagent.

Thus cyclohexyl thiolacetate gave cyclohexyl ethyl sulfide in 80% yield; cyclohexyl thiolisobutyrate gave cyclohexyl isobutyl sulfide in 73% yield, and cyclohexyl thiolpivalate gave cyclohexyl neopentyl sulfide in 37% yield. The low yield in the latter reduction may have been due to steric hindrance by the *t*-butyl group neighboring the carbonyl carbon, which apparently causes arrest of the reaction at an intermediate stage.

The reduction products were characterized by their elemental analyses and nuclear magnetic resonance spectra. Cyclohexyl ethyl sulfide is a known compound; cyclohexyl isobutyl sulfide was prepared independently and compared to the material obtained by reduction.

The starting thiol esters are readily available through well-known procedures.

Experimental

All boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord instrument. Nuclear magnetic resonance spectra were recorded with a Varian Associates high resolution instrument at 60 Mc. Elementary analyses were performed by Midwest Microlab, Indianapolis, Ind.

Cyclohexyl Thiolacetate.—This was prepared by the method of Weibull[2] involving the reaction of cyclohexene and thiolacetic acid in the presence of a few drops of di-*t*-butyl peroxide. Distillation gave cyclohexyl thiolacetate in 74% yield, b.p. 96–97° (15 mm.), lit.[2] b.p. 94–96° (15 mm.).

Cyclohexyl Thiolisobutyrate.—The thiol ester was prepared by adding 11.6 g. (0.1 mole) of cyclohexyl mercaptan to a solution containing 15.8 g. (0.1 mole) of isobutyric anhydride in 100 ml. of dry pyridine in an ice bath. The solution was shaken oc-

(1) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **25**, 875 (1960); **26**, 986, 4553, 4557 (1961); G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *ibid.*, **26**, 1685 (1961); G. R. Pettit, T. R. Kasturi, B. Green, and J. C. Knight, *ibid.*, **26**, 4773 (1961).
(2) B. Weibull, *Arkiv Kemi Mineral Geol.*, **23A**, 1 (1946).

casionally and allowed to stand at room temperature for 24 hr. After the usual work-up, the ethereal solution was concentrated and the residue was distilled to give cyclohexyl thiolisobutyrate, 7.9 g. (43%), b.p. 70–72° at 1.5 mm. Its infrared spectrum showed carbonyl absorption at 5.9 μ.

Anal. Calcd. for $C_{10}H_{18}OS$: C, 64.47; H, 9.74; S, 17.21. Found: C, 64.62; H, 9.87; S, 17.29.

Cyclohexyl Thiolpivalate.—This thiol ester was prepared by adding 11.6 g. (0.1 mole) of cyclohexyl mercaptan to a solution containing 12.1 g. (0.1 mole) of pivaloyl chloride in 100 ml. of dry pyridine at ice-bath temperature. The solution was then allowed to stand with occasional shaking at room temperature for 24 hr. After the usual work-up, distillation gave cyclohexyl thiolpivalate in 84% yield, b.p. 68° (0.6 mm.). Its infrared spectrum showed carbonyl absorption at 5.93 μ and the characteristic *t*-butyl bands at 7.19 and 7.34 μ.

Anal. Calcd. for $C_{11}H_{20}OS$: C, 65.95; H, 10.66; S, 16.00. Found: C, 66.23; H, 10.24; S, 16.29.

General Procedure For Lithium Aluminum Hydride–Boron Trifluoride Reductions.—The procedure used in the reductions of the thiol esters was identical with that of Pettit[1] using a 2:1 mole ratio of $LiAlH_4$ to thiol ester and a 15:1 mole ratio of $BF_3{\cdot}Et_2O$ to thiol ester. A solution containing both the thiol ester and $BF_3{\cdot}Et_2O$ (no diluent) was placed in a three-necked, round-bottomed flask fitted with condenser, drying tube, stirrer, and dropping funnel at ice-bath temperatures. A standard solution (*ca.* 1 *M*) of $LiAlH_4$ was then added dropwise. The mixture was allowed to stir for 45 min. The ice bath was removed and the reaction mixture was refluxed for 2 hr. Upon cooling, the mixture was hydrolyzed with 10% hydrochloric acid till two layers formed. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, saturated sodium bicarbonate solution, and saturated salt solution and then were dried over anhydrous potassium carbonate. Concentration of the ether and distillation of the residue gave the sulfide.

Cyclohexyl Ethyl Sulfide.—Cyclohexyl thiolacetate, 8 g. (0.05 mole), was reduced with $LiAlH_4$–boron trifluoride to give 5.8 g. (80%) of cyclohexyl ethyl sulfide, b.p. 74–76° (10 mm.), lit.[3] b.p. 68–70° (10 mm.), lit.[4] b.p. 72–74° (12 mm.); $n^{20}D$ 1.4885, lit.[3] 1.4908, lit.[4] 1.4890. Its infrared spectrum was identical with that of an authentic sample.[4]

Cyclohexyl Isobutyl Sulfide. A. From Cyclohexyl Thiolisobutyrate.—Cyclohexyl thiolisobutyrate, 4.65 g. (0.025 mole) was reduced with $LiAlH_4$–boron trifluoride to give 3.15 g. (73%) of cyclohexyl isobutyl sulfide, b.p. 74–76° (2.5 mm.). Its infrared spectrum was identical with an authentic sample (*vide infra*). Its nuclear magnetic resonance spectrum gave a doublet at τ 9.01 corresponding to $(CH_3)_2C$– and doublet at τ 7.67 corresponding to the methylene hydrogens neighboring the sulfur atom, *i.e.*, $-S-CH_2-C{=}$.

Anal. Calcd. for $C_{10}H_{20}S$: C, 69.70; H, 11.70. Found: C, 69.69; H, 11.85.

B. From Cyclohexene and Isobutyl Mercaptan.—To a 100-ml., three-necked, round-bottomed flask equipped with condenser, dropping funnel, immersion thermometer, and magnetic stirrer was added 9.8 g. (0.12 mole) of cyclohexene and a few crystals of benzoyl peroxide. Isobutyl mercaptan, 9.0 g. (0.10 mole), was then added dropwise at room temperature. The reaction mixture was heated to 90° for 12 hr. Distillation of the solution gave 12 g. (70%) of cyclohexyl isobutyl sulfide, b.p. 74–76° (2.5 mm.). Its infrared spectrum was identical with that of the product obtained in the $LiAlH_4$–boron trifluoride reduction of cyclohexyl thiolisobutyrate.

Cyclohexyl Neopentyl Sulfide.—Cyclohexyl thiolpivalate, 5 g. (0.025 mole), was reduced with $LiAlH_4$–boron trifluoride. The crude material obtained before distillation showed B–H bands at 4.07 and 4.10 μ and a broad OH band at 3.13 μ indicating a boron complex. Hydrolysis of the crude material, 4.25 g., was completed by boiling at reflux for 17 hr. in 50 ml. of 10% alcoholic potassium hydroxide. The mixture was neutralized and extracted with five 50-ml. portions of ether. The combined ethereal extracts were washed with water, saturated sodium bicarbonate solution, and saturated salt solution and then were dried over anhydrous potassium carbonate. Concentration of the ether and distillation of the residue gave, in addition to a considerable still-pot residue, 1.7 g. (37%) of cyclohexyl neopentyl sulfide, b.p. 76° (0.8 mm.). Its infrared spectrum showed the usual *t*-butyl bands at 7.1 and 7.3 μ. Its nuclear magnetic resonance spectrum showed a singlet at τ 9.01 corresponding to $(CH_3)_3C$ and a singlet at τ 7.6 corresponding to the methylene hydrogens neighboring the sulfur atom, *i.e.*, $S-CH_2-C{=}$.

Anal. Calcd. for $C_{11}H_{22}S$: C, 70.89; H, 11.90. Found: C, 71.20; H, 12.09.

Acknowledgment.—We gratefully acknowledge support of this research by a grant from the National Institutes of Health (GM-08848).

(3) W. E. Bacon and W. M. LeSuer, *J. Am. Chem. Soc.*, **76**, 670 (1954).
(4) E. L. Eliel, L. A. Pilato, and V. G. Badding, *ibid.*, **84**, 2377 (1962).

Novel Solvolytic Reactions in Dimethyl Sulfoxide

IRVING LILLIEN

Department of Chemistry, University of Miami, Coral Gables, Florida

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The versatility of dimethyl sulfoxide (DMSO) as a solvent medium in organic reactions has received very widespread attention in recent years. In some cases, the ability of dimethyl sulfoxide to act as an oxidant in the course of reaction has been recognized. Kornblum and co-workers[1,2] first reported the base-catalyzed oxidation of primary tosylates and halides to aldehydes[3]; this method was extended to secondary tosylates.[4] The oxidation of ethyl bromoacetate to ethyl glyoxalate by dimethyl sulfoxide has been reported.[5] More recently, the boron fluoride-catalyzed oxidation of epoxides to α-hydroxy ketones by dimethyl sulfoxide has been described.[6]

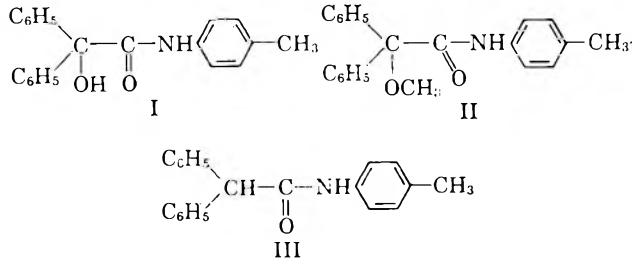
We wish herein to report the novel oxidative solvolysis of a keteneimine and a ketene in dimethyl sulfoxide under acidic conditions.

If a few drops of aqueous acid were added to a solution of diphenylketene-N-*p*-tolylimine in dimethyl sulfoxide, a high yield of N-(*p*-tolyl)-α-hydroxydiphenylacetamide (I) was obtained. Likewise, addition of diphenylketene to a dilute dimethyl sulfoxide solution of aqueous acid produced an equally high yield of benzilic acid.

If the solution of keteneimine were diluted with an excess of methanol prior to the addition of acid, N-(*p*-tolyl)-α-methoxydiphenylacetamide (II) was produced in 70% yield. This product was verified by synthesis from N-(*p*-tolyl)-α-chlorodiphenylacetamide, methanol, and triethylamine. That this product did not arise *via* etherification of the α-hydroxyamide was evident from the failure of the latter to react with methanolic hydrogen chloride. With either ketene or keteneimine, dimethyl sulfoxide, and a poor nucleophile, *i.e.*, benzoic acid, in the presence of aqueous acid, only α-hydroxy acid or α-hydroxyamide was obtained. The formation of dimethyl sulfide in this reaction was proved by converting the gas to its trimethylsulfonium salt.

(1) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. W. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).
(2) N. Kornblum, W. J. Jones, and G. Anderson, *ibid.*, **81**, 4113 (1959).
(3) See also H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).
(4) M. M. Baizer, *ibid.*, **25**, 670 (1960).
(5) I. M. Hunsberger and J. M. Tien, *Chem. Ind.* (London), 88 (1959).
(6) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961).

When the reaction with keteneimine was carried out under rigorously anhydrous conditions, *e.g.*, dry hydrogen chloride in ether–dimethyl sulfoxide, the only product isolated was simple N-(*p*-tolyl)diphenylacetamide (III) in 66% yield. Presumably the hydrogen chloride–ketenimine adduct was formed and hydrolyzed to amide during the work-up.

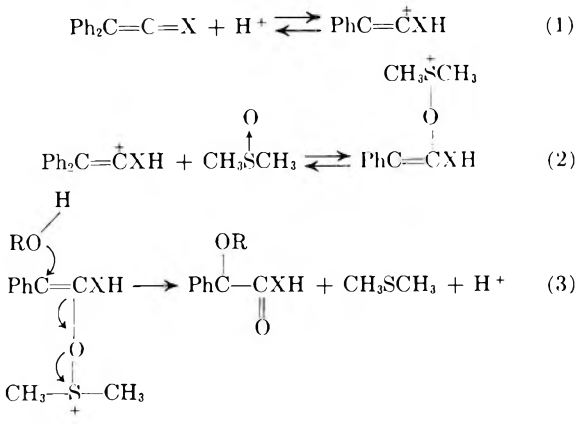


I II

III

The keteneimine was unaffected by prolonged solution in dry or slightly moist dimethyl sulfoxide alone, being recovered on dilution with water.

These results implicate dimethyl sulfoxide participation in a rapid oxidative solvolysis which appears best accomodated by the following mechanism, where =X is either =N–C$_6$H$_4$–CH$_3$ or =O.



(1)

(2)

(3)

Winstein and Smith[7] have discussed the general reactivity of dimethyl sulfoxide as a nucleophile in terms of its ability to form a sulfonium salt intermediate, R–O–$\overset{+}{S}$(CH$_3$)$_2$. The sulfonium intermediate formed in eq. 2 is entirely analogous.

The possibility of *in situ* conversion of α-diazo ketones to α-alkoxy acids as a modification of the Arndt–Eistert synthesis *via* this procedure appears attractive and is being investigated.

Experimental[8]

N-(*p*-Tolyl)-α-hydroxydiphenylacetamide.[9]—To a solution of 0.56 g. (2 mmoles) of diphenylketene-N-*p*-tolylimine[10] in 30 ml. of commercial (undried) dimethyl sulfoxide was added several drops of concentrated hydrochloric acid, and the solution was swirled. The yellow color of the keteneimine disappeared immediately; infrared inspection of petroleum ether (b.p. 30–60°) extracts showed no trace of the characteristic keteneimine band at 5 μ after admixture. After a few moments, the solution was poured into ice–water, and the resulting mixture was extracted with ether which was washed with dilute sodium bicarbonate and water, then dried, and evaporated. The solid residue was recrystallized from ethanol to yield 0.58 g. (1.8 mmoles, 91.5%) of N-(*p*-tolyl)-α-hydroxydiphenylacetamide, m.p. 189–190°, lit.[9] m.p. 189–190°; mixture melting point with authentic material was undepressed.

In one instance, the reaction was run in a flask being swept by nitrogen, and the exit gas was collected in a chilled ether trap containing an excess of methyl iodide. The ether solution was refluxed 4 hr., and the crystalline precipitate was removed. Its infrared spectrum was identical with that of authentic trimethylsulfonium iodide.

Benzilic Acid.—To a solution of several drops of concentrated hydrochloric or perchloric acid in 50 ml. of dimethyl sulfoxide was added dropwise with swirling 1.9 g. (0.01 mole) of diphenylketene. The orange ketene color was immediately discharged on contact. The solution was poured into ice–water, and the resulting precipitate was recrystallized from ethanol to yield 2.1 g. (0.0088 mole, 88%) of benzilic acid, m.p. 149–150°.

N-(*p*-Tolyl)-α-methoxydiphenylacetamide. A.—To a solution of 0.56 g. (2 mmoles) of diphenylketene-N-*p*-tolylimine in a mixture of 15 ml. of dimethyl sulfoxide and 15 ml. of methanol was added several drops of concentrated hydrochloric acid. The solution was, after a few minutes, poured into ice–water, and this was extracted with ether. The ether was washed with dilute sodium bicarbonate and water, then dried, and evaporated. The solid residue was recrystallized from ethanol to give 0.47 g. (1.4 mmoles, 71%) of N-(*p*-tolyl)-α-methoxydiphenylacetamide, m.p. 163–164°; mixture melting point with authentic material (see below) was undepressed.

N-(*p*-Tolyl)-α-methoxydiphenylacetamide. B.—To 50 ml. of dry methanol containing 5 ml. of triethylamine was added 3.3 g. (0.01 mole) of N-(*p*-tolyl)-α-chlorodiphenylacetamide,[11] and the mixture refluxed for 2 hr. The solution was diluted with ice water, and the precipitate was recrystallized from ethanol to yield 2.8 g. (0.0085 mole, 85%) of product, m.p. 163–164°. The infrared spectrum was consistent with the title structure.

Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.75; H, 6.50. Found: C, 79.55; H, 6.40.

Reaction of Diphenylketene-N-*p*-tolylimine with Dry Hydrogen Chloride in Dimethyl Sulfoxide–Ether.—In a three-necked flask equipped with a stirrer, gas inlet, and reflux condenser and protected from moisture by a drying tube was dissolved 2.8 g. (0.01 mole) of keteneimine in a mixture of 50 ml. of dry (vacuum distilled from calcium hydride) dimethyl sulfoxide and 100 ml. of dry ether. Dry hydrogen chloride was bubbled in, while the mixture was stirred, until shortly after precipitation of dimethylsulfoxonium chloride was complete. The mixture was stirred under reflux for an additional 15 hr. The ether was decanted, washed with water, dilute sodium bicarbonate, and water, then dried, and evaporated. The residue was recrystallized from ethanol to yield 2.0 g. (0.0066 mole, 66%) of N-*p*-tolyldiphenylacetamide, m.p. 180–181°.

(7) S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).

(8) All melting points are uncorrected.

(9) H. Klinger, *Ann.*, **389**, 261 (1912).

(10) C. L. Stevens and E. J. Gasser, *J. Am. Chem. Soc.*, **79**, 6057 (1957).

(11) C. L. Stevens and J. C. French, *ibid.*, **75**, 657 (1953).

Organic Disulfides and Related Substances. VIII. Preparation and Oxidation of Some Unsymmetrical Dialkyl and Alkyl Pyridinium Disulfides[1]

LAMAR FIELD, HORST HÄRLE, TERENCE C. OWEN, AND ALDO FERRETTI

Department of Chemistry, Vanderbilt University, Nashville, Tennessee

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Oxidation of 2-aminoethyl disulfide dihydrochloride (1) with hydrogen peroxide afforded an excellent syn-

(1) Reported in part at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, Abstracts, p. 31N. This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-193-MD-2030; we are indebted to Dr. T. R. Sweeney and Dr. D. P. Jacobus of the Walter Reed Army Institute of Research for helpful discussion and for evaluation of several products as antiradiation drugs. Paper VII: L. Field, J. M. Locke, C. B. Hoelzel, and J. E. Lawson, *J. Org. Chem.*, **27**, 3313 (1962).

thesis of the thiolsulfonate 2,[2] although the product originally was thought to be a disulfoxide.[3] Unsymmetrical disulfides (RSSR′) could give two isomeric thiolsulfonates, as shown by the equations, and their oxidation, therefore, became of considerable interest.

$$\underset{\mathbf{5,\ 9}}{RSSO_2R'} \underset{R'SH}{\overset{H_2O_2}{\rightleftharpoons}} \underset{\mathbf{1,\ 3,\ 7,\ 10,\ 11}}{RSSR'} \underset{RSH}{\overset{H_2O_2}{\rightleftharpoons}} \underset{\mathbf{2,\ 4,\ 8}}{RSO_2SR'}$$

5, R = $(CH_3)_3C$
9, R = $CH_3(CH_2)_2C(CH_3)_2$

1, R = $Cl^-H_3N^+(CH_2)_2$
3, R = $(CH_3)_3C$
7, R = $CH_3(CH_2)_2C(CH_3)_2$
10, R = $CH_3O_2CCH(NH_3^+Cl^-)C(CH_3)_2$
11, R = $2\text{-}C_5H_4N^+Cl^-$

2, R = $Cl^-H_3N^+(CH_2)_2$
4, R = $(CH_3)_3C$
8, R = $CH_3(CH_2)_2C(CH_3)_2$

R′ = $(CH_2)_2NH_3^+Cl^-$ in all instances

Oxidation of unsymmetrical aryl disulfides (ArSSAr′) usually occurs preferentially on the sulfur atom farthest from electron-withdrawing substituents.[4] Oxidation of unsymmetrical disulfides containing at least one aliphatic group to thiolsulfonates seems to be unreported and offers interesting prospects for examining inductive, field, and steric effects in terms of preferential oxidation. Furthermore, new preparations for unsymmetrical thiolsulfonates open up many synthetic possibilities because thiolsulfonates react with thiols to give disulfides,[2] as shown by the equations.

Introductory studies of disulfides containing at least one aliphatic moiety are reported in this paper, the second moiety being a substituted alkyl or 2-pyridinium group.

Procedures of oxidation resembled those used for preparing **2** and its N,N′-diacetyl derivative.[2] Oxidation of the *t*-butyl aminoethyl disulfide salt (**3**) gave only one isolable unsymmetrical thiolsulfonate (33% yield). The likelihood of electron supply by the *t*-butyl group to the adjoining sulfur atom suggested that the product was more likely to have the oxygen atoms on the sulfur nearer the *t*-butyl group and thus was more likely to be **4** than **5** (the field effect exerted across space by the ammonium ion also might have an important influence, although this influence is unpredictable at present). The product was in fact shown to contain the moiety $-S(CH_2)_2NH_3^+Cl^-$ and, therefore, to be **4** rather than **5**, by the following reactions which produced known disulfides.

$$\mathbf{1} + (CH_3)_3CSO_2H \underset{\mathbf{4}}{\overset{Cl^-NH_3^+(CH_2)_2SH}{\rightleftharpoons}} (CH_3)_3CSO_2S(CH_2)_2NH_3^+Cl^- \xrightarrow{(CH_3)_3CSH} \mathbf{3} + (CH_3)_3CSO_2H$$

Along with the thiolsulfonate **4**, a little taurine (2-aminoethanesulfonic acid) was isolated. Despite careful efforts to separate all products, the other possible thiolsulfonate (**5**) could not be found. The apparent absence of **5** may be a consequence of its instability rather than of selective oxidation of **3** to **4**, however.

Two other products were isolated. One was the symmetrical thiolsulfonate salt (**2**) (28%); the other, **6**, may have been *t*-butyl disulfone. Symmetrical thiolsulfonates also were isolated in the work of Leandri and Tundo.[4] The symmetrical product **2** (and **6**) could have resulted from disproportionation of the *t*-butyl aminoethyl disulfide (**3**) *before* oxidation, or of unsymmetrical thiolsulfonates **4** or **5** *after* oxidation. Formation *during* oxidation is probable however, since in analogous work[5] isolation of symmetrical thiolsulfonates after oxidation of unsymmetrical thiolsulfinates was best attributed to cleavage of the sulfur–sulfur bonds and recombination during oxidation.

2-Methyl-2-pentyl 2′-aminoethyl disulfide hydrochloride (**7**) was oxidized similarly. Isolation of the symmetrical thiolsulfonate **2** as the major product (48% yield) once more pointed to considerable "scrambling" of alkylthio groups during oxidation. Again also, the only unsymmetrical thiolsulfonate isolated (19% yield) resembled **4** in having both oxygens on the sulfur atom nearest the *t*-alkyl group (**8** rather than **9**). Structure **8** was established as with **4**.

Presence of an alkoxycarbonyl function β to the disulfide moiety had an adverse effect. Thus oxidation of the unsymmetrical β-alkoxycarbonyl disulfide (**10**) (obtained in 84% yield by reaction of penicillamine methyl ester hydrochloride with **2**) gave on oxidation only a little taurine, along with amorphous material which did not show a positive thiolsulfonate test.[6] β-Carboxy- and β-alkoxycarbonyl-β-aminothiols and disulfides also failed to give symmetrical thiolsulfonates with aqueous hydrogen peroxide; thus failures resulted with penicillamine methyl ester, penicillamine disulfide (acid and methyl ester), cysteine ethyl ester, and cystine (acid), all as hydrochlorides or in dilute hydrochloric acid.[7]

Oxidation as usual[2] of 2-pyridyl disulfide with hydrogen peroxide in dilute hydrochloric acid gave about 25% of pyridine-2-sulfonic acid.[7] Recovery of most of the disulfide indicated that the positively charged pyridine ring might have reduced the ease of oxidation of the adjoining sulfur atom and, therefore, that oxidation of 2-pyridyl 2′-aminoethyl disulfide dihydrochloride (**11**) might occur selectively on the sulfur atom adjacent to the aminoethyl moiety. Evidently the thiolsulfonate itself did not survive oxidation, because the only material isolated was unchanged **11** (39%).

2-Aminoethyl disulfide dihydrochloride (**1**) reduces lethal effects of ionizing radiation,[8] as does its thiolsulfonate (**2**).[9] Nevertheless, the *t*-butyl aminoethyl disulfide (**3**), the corresponding thiolsulfonate (**4**), and the pyridyl aminoethyl disulfide (**11**) were inactive.[9]

(2) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

(3) W. G. Christiansen and M. A. Dolliver, U. S. Patent 2,242,236 (1941); *Chem. Abstr.*, **35**, 5647 (1941).

(4) G. Leandri and A. Tundo, *Ann. chim.* (Rome), **44**, 74 (1954); *Chem. Abstr.*, **49**, 4563 (1955).

(5) D. Barnard and E. J. Percy, *Chem. Ind.* (London), 1332 (1960); *cf.* also U. Marangelli, G. Modena, and P. E. Todesco, *Gazz. chim. ital.*, **90**, 681 (1960); *Chem. Abstr.*, **55**, 16510 (1961).

(6) *I.e.*, development of an acidic reaction owing to formation of a sulfinic acid, upon treatment of a thiolsulfonate with a thiol; *cf.* D. Barnard and E. R. Cole, *Anal. Chim. Acta*, **20**, 540 (1959). Increased acidity was obvious with other thiolsulfonates which were amine hydrochlorides, even though these already were slightly acidic in solution.

(7) Unpublished results.

(8) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, pp. 33, 34, 55, 65.

(9) Private communication from Dr. T. R. Sweeney and Dr. D. P. Jacobus, Walter Reed Army Institute of Research, Washington, D. C.

Experimental[10]

Oxidation of *t*-Butyl 2-Aminoethyl Disulfide Hydrochloride (3). A. Oxidation.— To the disulfide **3** (10.09 g.)[2] in 30 ml. of water, there was added dropwise with stirring and ice cooling during about 15 min. a mixture of 9.4 ml. (100 mmoles) of 30% aqueous hydrogen peroxide and 10 ml. of water. The mixture was allowed to stand at room temperature overnight and then was evaporated below 50° in a rotary evaporator to a sirup containing crystals. After being dried under reduced pressure in a desiccator containing potassium hydroxide, the product was treated with hot chloroform (*ca.* 200 ml.).

The crystals, which did not dissolve, were removed by filtration and proved to be the symmetrical thiolsulfonate (**2**), 1.82 g. (28%), unsharp melting point beginning *ca.* 110°. For purification of **2**, at first unrecognized, it was dissolved in cold methanol; insoluble material was taurine, m.p. and m.m.p. 328–330°, infrared spectrum identical with that of authentic taurine. Addition of ether to the filtered methanol solution precipitated **2**, m.p. and m.m.p. 166–167°, infrared spectrum identical with that of authentic **2**; in a similar experiment, **2** also was characterized by conversion to **3** upon reaction with *t*-butyl mercaptan.

The chloroform filtrate upon slow cooling to room temperature and standing gave crystalline solid. This solid, removed by filtration and dried, was shown (*vide infra*) to be 2-aminoethyl 2′-methyl-2′-propanethiolsulfonate hydrochloride (**4**), 3.06 g. (26%), m.p. 160–165° dec. (foaming). **4** was soluble in water, methanol, and acetic acid. In an earlier experiment, purification seemed best effected by dissolution in cold methanol, filtration, and precipitation with ether. By this means, 2.24 g. of **4** (m.p. 160–162°) and 0.13 g. of taurine eventually were obtained from the crude **4**. Three repetitions of the methanol–ether treatment gave pure **4**, m.p. 161–162°.

Anal. Calcd. for $C_6H_{16}ClNO_2S_2$: C, 30.83; H, 6.90; N, 5.99. Found: C, 31.03; H, 7.01; N, 6.35.

After removal of **4**, the chloroform filtrate was evaporated below 50° to an oil. Partial crystallization occurred in the cold, and filtration separated 0.76 g. of solid. Dissolution in pentane, filtration, and evaporation gave a material (**6**) with m.p. 56–60°, which contained sulfur but not nitrogen. **6** gave an acidic solution when treated with a thiol in water, as expected of a thiolsulfonate,[6] and had strong infrared bands at 1115, 1165, and 1315 cm.$^{-1}$; however, no **3** could be isolated after treatment with 2-mercaptoethylamine hydrochloride, suggesting that **6** was neither the *t*-butyl thiolsulfonate, $(CH_3)_3CSO_2SC(CH_3)_3$, nor **5**. Sublimation gave **6** with m.p. 59–61°. Analysis suggested that **6** may have been *t*-butyl disulfone; insufficient **6** remained for further characterization.

Anal. Calcd. for $C_8H_{18}O_4S_2$: C, 39.65; H, 7.49. Found: C, 39.73; H, 7.95.

The remainder of the oil crystallized when well dried. The crude solid (2.04 g.) pressed on clay plate gave 0.76 g. more of **4**, m.p. 154–157°, making a total yield of crude **4** amounting to 3.82 g. (33%), infrared spectrum identical with that of authentic **4**.

B. Structural Evidence for Thiolsulfonate 4.—For reaction of **4** with *t*-butyl mercaptan, 1.17 g. of **4** in 8 ml. of water was mixed with 0.45 g. of *t*-butyl mercaptan. After 2 days of standing, the unsymmetrical disulfide (**3**) was isolated as described previously.[2] Evaporation of the hydrochloric acid extract gave 0.67 g. (67%) of **3**, which after recrystallization from ethyl acetate had melting and infrared absorption characteristics identical with those of authentic **3**.[2]

A similar reaction with 2-mereaptoethylamine hydrochloride at first failed to give the disulfide **1**. Accordingly, the method of isolation was changed. A mixture of 0.47 g. of **4** and 0.23 g. of 2-mercaptoethylamine hydrochloride in 8 ml. of water was allowed to stand overnight. Water then was removed by evaporation. Recrystallization of the residue from acetic acid gave 0.35 g. (78%) of pure 2-aminoethyl disulfide dihydrochloride (**1**), m.p. and m.m.p. 214–215°, infrared spectrum identical with that of authentic **1**.

Gas formed at the decomposition point (170°) of the **4** proved to be sulfur dioxide, as shown by the characteristic odor, decolorization of dilute aqueous permanganate and bromine vapor, and an acidic reaction with moist litmus paper.

(10) Melting points are corrected. Analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Evaporation of solvent for isolation of products was effected under reduced pressure.

2-Methyl-2-pentyl 2′-Aminoethyl Disulfide Hydrochloride (7).— 2-Methyl-2-pentanethiol (11.8 g.)[11] was added to the thiolsulfonate **2** (25.7 g.)[2] in water (50 ml.). Addition of ethanol (150 ml.) gave a homogeneous solution from which crystals quickly separated. After 16 hr., the crystals were removed by filtration (taurine, 4.0 g.). Removal of ethanol (35°, 25 mm.) left a clear aqueous solution, which was shaken with chloroform while potassium hydroxide (22 g.) in water was added. The solution was extracted six times more with chloroform, and the combined chloroform extracts then were filtered into 12 ml. of concentrated hydrochloric acid in 50 ml. of methanol. Evaporation of the chloroform–methanol solution below 35° gave a crystalline mass. This mass was dissolved in 2-propanol and separated from 0.5 g. of insoluble **1**. The solution was evaporated and the residue was crystallized from acetone to give 15.7 g. (68%) of the disulfide **7** as plates having m.p. 103.5–104°.

Anal. Calcd. for $C_8H_{20}ClNS_2$: C, 41.80; H, 8.77; Cl, 15.43; N, 6.10; S, 27.90. Found: C, 41.76; H, 8.60; Cl, 15.51; N, 6.17; S, 27.87.

Oxidation of the Disulfide 7. A. Oxidation.—Hydrogen peroxide (2.6 ml., 25.3 mmoles, of 30% aqueous solution) and water (2.5 ml.) were added to a solution of 3.00 g. of **7** and a trace of iodine in 10 ml. of ice-cold water. The solution was kept at 0° for 2 hr. and then at 30° for 20 hr. The solution was separated by filtration from a little gummy precipitate and was evaporated below 30° to an oil. The oil after being scratched and kept under vacuum (1 mm.) for 20 hr. gave a partly crystalline mass, which was taken up in cold chloroform. Filtration separated crystals which were washed with chloroform and found to be nearly pure **2**, 0.8 g. (48%), m.p. 168–170° (unchanged by recrystallization and undepressed by authentic **2**),[2] infrared spectrum identical with that of **2**.

The filtrate was again evaporated to an oil. The oil was suspended in ether, and the mixture was made homogeneous with a minimum of chloroform and then clouded slightly by addition of ether. After 3 days at 5°, soft crystals of the thiolsulfonate **8** separated (0.33 g., 10%, m.p. 112–117°). Two further crops were obtained by evaporating the mother liquors and repeating the process. The combined crops of **8** were dissolved in a little ethanol and considerable ether was added. Refrigeration and filtration separated a little precipitate. The filtrate was evaporated and the residue taken up in acetone–ether. Upon refrigeration, 2-aminoethyl 2′-methyl-2′-pentanethiolsulfonate hydrochloride (**8**) slowly separated (0.66 g., 19%), m.p. 120–123°, soluble in water, positive thiolsulfonate test,[6] infrared spectrum with strong absorption at 1110 and 1320 cm.$^{-1}$ but otherwise similar to that of **7**.

Anal. Calcd. for $C_8H_{20}ClNO_2S_2$: C, 36.69; H, 7.70; Cl, 13.54; N, 5.35; S, 24.49. Found: C, 36.64; H, 7.60; Cl, 13.85; N, 5.52; S, 24.49.

B. Structural Evidence for Thiolsulfonate 8.—Solutions of **8** (52 mg.) and of 2-aminoethanethiol hydrochloride (24.5 mg.) in water (1-ml. each) were mixed; the acidity increased. After 40 min., the solution was washed twice with ether and the aqueous layer was evaporated below 30°. The residue was recrystallized from ethanol to give **1**, 35 mg. (78%), identical with authentic **1** (as shown by m.p. 214–216°, the mixture melting point, and the infrared spectrum).

In the reaction with *t*-butyl mercaptan, the thiol (30 mg.) was added to a suspension of 50.4 mg. of **8** in 1 ml. of ethanol, followed by water (2 ml.). After 25 hr., excess thiol was removed by extraction with pentane, and chloroform (2 ml.) and aqueous potassium hydroxide (5 ml., 0.1 *N*) were added. Three extractions with chloroform, immediate extraction of the chloroform layers with dilute hydrochloric acid, and evaporation of the acid extract gave gummy crystals. Dissolution in 2-propanol, filtration from a little residue, dilution with cyclohexane, and storage at 5° overnight gave the disulfide **3**, 25 mg. (64%), identical in melting behavior[2] and infrared spectrum with authentic **3**.[2]

2-Methyl-1-amino-1-methoxycarbonyl-2-propyl 2′-Aminoethyl Disulfide Dihydrochloride (10).—The thiolsulfonate **2** (3.90 g.) was added to a stirred solution of DL-penicillamine methyl ester hydrochloride (3.00 g.)[12] in water (30 ml.). The solution, which rapidly became strongly acidic, was let stand for 30 min. Chloro-

(11) Containing 1% or less of a higher boiling isomer. Kindly furnished by J. C. Morris, Laramie Petroleum Research Center, U. S. Department of the Interior, Bureau of Mines, Laramie, Wyo.

(12) Prepared from DL-penicillamine as reported by H. M. Crooks, Jr., "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 470; 73% yield, m.p. 174–176° (reported 173–175°).

form then was added, the aqueous layer was saturated with salt, and the mixture was shaken during addition of potassium hydroxide (4.5 g.) in water. The aqueous layer was extracted six times with chloroform, the extracts being filtered directly into concentrated hydrochloric acid (4.5 ml.) in methanol (55 ml.). Evaporation of the chloroform–methanol–acid mixture below 30° gave an oil, which was dissolved in 2-propanol; the solution was diluted with cyclohexane and scratched. The disulfide **10** separated as hard crystals, 3.9 g. (84%), m.p. 171–172°.

Anal. Calcd. for $C_8H_{20}Cl_2N_2O_2S_2$: C, 30.86; H, 6.48; Cl, 22.78; N, 9.00; S, 20.60; neut. equiv., 311. Found: C, 31.01; H, 6.66; Cl, 22.54; N, 8.82; S, 20.63; neut. equiv., 313 (potentiometric titration of the **10** with alkali showed two distinct end points corresponding to consumption of 1 and then 2 moles of alkali per mole of **10**).

2-Pyridyl 2′-Aminoethyl Disulfide Dihydrochloride (11).—2-Pyridinethiol (11.1 g.)[13] in 40 ml. of alcohol was added to 25.7 g. of the thiolsulfonate **2** in water (30 ml.) and concentrated hydrochloric acid (*ca.* 0.12 mole) with stirring. A small amount of precipitate which separated was dissolved by adding a little more water. After 20 hr. of stirring, the solvent was evaporated, and the residue was dissolved in water. Extraction with chloroform removed 4.4 g. of 2-pyridyl disulfide (infrared spectrum identical with that of authentic 2-pyridyl disulfide). The aqueous solution then was shaken with chloroform while an iced aqueous solution of potassium hydroxide (28 g.) was added. The water layer was extracted twice more with chloroform. Each chloroform layer was immediately extracted with hydrochloric acid (the total amount was 60 ml. of 12 *N*, of which half was used for the first extraction). The combined acid extracts were evaporated to a thick oil, which crystallized completely upon addition of anhydrous ethanol and scratching. After an overnight period at 5°, 15.5 g. of crude **11** was collected. Repeated recrystallizations from absolute alcohol, with use of decolorizing carbon, gave 2-pyridyl 2′-aminoethyl disulfide dihydrochloride (**11**) as colorless prisms, 12.8 g. (82% conversion, 49%), m.p. 144–145° (sealed capillary); **11** was deliquescent at high relative humidity.

Anal. Calcd. for $C_7H_{12}Cl_2N_2S_2$: C, 32.42; H, 4.66; N, 10.81; S, 24.74. Found: C, 32.27; H, 4.46; N, 10.90; S, 24.74.

(13) M. A. Phillips and H. Shapiro, *J. Chem. Soc.*, 584 (1942).

Some Anomalous Results in the Bimolecular Displacement Reaction

A. JOSEPH SISTI AND SEYMOUR LOWELL

Department of Chemistry, Adelphi University, Garden City, Long Island, New York

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Recently[1] a new factor affecting reactivity in the bimolecular nucleophilic displacement reactions was observed by Bunnett.[2,3] Bunnett tentatively identifies this new factor as London interactions between nucleophile and polarizable substituent at or near the reaction site. He concludes that due to London forces there is a lowering of the transition state energy when the transition state structure is such as to bring highly polarizable atoms close to one another with a resultant increase in reaction rate. After allowances for steric and electrical effects, a change to a substituent of higher polarizability will cause more acceleration, or less deceleration, the greater the effective polarizability of the nucleophile.

The *ortho*- and *para*-methyl- and *ortho*- and *para*-bromo-substituted benzyl halides afford an excellent opportunity to observe indications of London forces in rate ratios with minimum considerations for electrical effects. The total polar effects will be nearly identical for the corresponding *para* and *ortho* substituents and will cancel in the ratios, $o\text{-}CH_3/p\text{-}CH_3$ and $o\text{-}Br/p\text{-}Br$, if the susceptibility constants ρ and ρ^* are nearly identical.[4] This has been observed to be generally true.[5] Similar reasoning for minimization of the total polar effects in the benzyl system has been offered by Bunnett.[3] Table II, composed from the kinetic data given in Table I, presents the values for the ratio $k_{o\text{-R}}/k_{p\text{-R}}$ (R = Me and Br) for each of the three nucleophiles. It is apparent that the aforementioned ratio nearly cancels the total polar effects of the substituents (ref. 4).

Table II also presents values for the adjusted rate ratios given by the expression

$$\frac{\left(\frac{k_{o\text{-R}}}{k_{p\text{-R}}}\right)_y}{\left(\frac{k_{o\text{-R}}}{k_{p\text{-R}}}\right)_{MeO^-}} = \frac{\left(\frac{k_y}{k_{MeO^-}}\right)_{o\text{-R}}}{\left(\frac{k_y}{k_{MeO^-}}\right)_{p\text{-R}}} \qquad (1)$$

y = MeO^-, $C_6H_5S^-$, and I^-
R = H, Me, and Br

In which differences in nucleophilicities are cancelled. This expression also cancels conformational differences, since the conformational changes accompanying a change of site, $p \rightarrow o$, for a given substituent should be constant and independent of the attacking reagent. Solvent effects would obviously cancel in the adjusted rate ratios if all the data were available in the same solvent. Since this is not the case, one must consider what change would occur in the value of the ratio

$$\left[\frac{\frac{k_{o\text{-R}}}{k_H}}{\frac{k_{p\text{-R}}}{k_H}}\right]_{I^-}$$

with a change of solvent (acetone to methanol). The changes in a given absolute reaction rate which accompany a change in the dipole moment of the solvent are known to be small for this charge type (charged nucleophile with neutral substrate).[6] Since the resultant small changes in absolute reaction rates are incorporated in numerator and denominator of the preceding ratio, the value of the ratio should remain unchanged. The adjusted rate ratios only should indicate interactions arising between the nucleophile and the *ortho* substituent (London, steric, or other may be significant).

The polarizabilities for the three nucleophiles employed are suggested by the ions OH^-, 1.89; SH^-, 5.28; and I^-, 7.10 (all units $cm.^3 \times 10^{-24}$); the polarizabilities of the *ortho* substituents are H, 0.42; CH_3, 2.19; and Br, 3.34 (units the same as above).[7]

(1) The work herein was taken in part from the Ph.D. thesis of S. Lowell, Adelphi University, 1963.

(2) J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5969 (1957).

(3) J. F. Bunnett and J. D. Reinheimer, *ibid.*, **84**, 3284 (1962).

(4) A plot of log (k/k_0) *vs.* σ for *p*-substituted benzyl chlorides and a plot of log (k/k_0) *vs.* σ^* for *o*-substituted benzyl chlorides for I^- in acetone at 20° produces parallel lines for substituents -F, -Cl, -Br, -I, $-NO_2$, and $-CH_3$. The ρ- and ρ^*-values are, therefore, nearly identical. It is interesting to note only the *o*-methyl falls well off the line.

(5) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 649.

(6) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 347–9.

(7) Values taken from, Landolt-Bornstein and J. A. A. Ketelaar, "Chemical Constitution," 2nd Ed., Elsevier Publishing Co., New York, N. Y., 1958, p. 91.

TABLE I

REACTION RATES[a] FOR BENZYL AND SUBSTITUTED BENZYL HALIDES

Reagent and leaving group (X)	Solvent	$C_6H_5CH_2$-X, k	p-$CH_3C_6H_4CH_2$-X, k	p-$BrC_6H_4CH_2$-X, k	o-$CH_3C_6H_4CH_2$-X, k	o-$BrC_6H_4CH_2$-X, k
MeO^-, X = Cl[b]	Methanol	1.31×10^{-5}			3.76×10^{-5}	1.37×10^{-5}
MeO^-, X = Br[c]	Methanol	5.54×10^{-4}	7.33×10^{-4}	7.83×10^{-4}		
$C_6H_5S^-$, X = Cl[b]	Methanol	14.1×10^{-3}			74.2×10^{-3}	40.1×10^{-3}
$C_6H_5S^-$, X = Br[c]	Methanol	1.08	1.62	2.57		
I^-, X = Cl	Acetone	3.35×10^{-4}[d]	5.00×10^{-4}[e]	8.66×10^{-4}[f]	3.37×10^{-3}[c]	1.46×10^{-3}[f]

[a] Rate coefficients in l. mole^{-1} sec.$^{-1}$ at 20°. [b] J. F. Bunnett and J. D. Reinheimer, *J. Am. Chem. Soc.*, **84**, 3284 (1962). [c] G. K. Klopman and R. F. Hudson, *Helv. Chim. Acta*, **44**, 1914 (1961). [d] Average of three constants given by G. M. Bennett and B. Jones [*J. Chem. Soc.*, 1815 (1935)], A. G. Evans and S. D. Hamman [*Trans. Faraday Soc.*, **47**, 25 (1951)], and P. J. C. Fierens, *et al.* [*Helv. Chim. Acta*, **38**, 2009 (1955)]. [e] A. G. Evans and S. D. Hamman, *Trans. Faraday Soc.*, **47**, 25 (1951). [f] G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935).

TABLE II

RATE RATIOS OF BENZYL HALIDES WITH VARIOUS NUCLEOPHILES[a,b]

Nucleophile	Solvent	$\frac{k_{o\text{-Br}}}{k_H}$	$\frac{k_{o\text{-Me}}}{k_H}$	$\frac{k_{p\text{-Br}}}{k_H}$	$\frac{k_{p\text{-Me}}}{k_H}$	$\frac{k_{o\text{-Br}}}{k_{p\text{-Br}}}$[c]	$\frac{k_{o\text{-Me}}}{k_{p\text{-Me}}}$[c]	$\left(\frac{k_{o\text{-R}}}{k_{p\text{-R}}}\right)_y / \left(\frac{k_{o\text{-R}}}{k_{p\text{-R}}}\right)_{MeO^-}$ -H	-Me	-Br
MeO^-	Methanol	1.05	2.87	1.41	1.32	0.74	2.17	1.00	1.00	1.00
$C_6H_5S^-$	Methanol	2.84	5.26	2.38	1.50	1.19	3.50	1.00	1.60	1.61
I^-	Acetone	4.35	10.00	2.58	1.49	1.68	6.70[d]	1.00	3.11	2.30

[a] Ratios at 20°. [b] It is assumed that the ratio $\frac{p\text{-X-}C_6H_4\text{-}CH_2\text{-Cl}}{C_6H_5CH_2\text{-Cl}}$ is equal to $\frac{p\text{-X-}C_6H_4\text{-}CH_2\text{-Br}}{C_6H_5\text{-}CH_2\text{-Br}}$ for MeO^- and $C_6H_5\text{-}S^-$; the following data is offered as justification: EtO$^-$ at 25° $\frac{p\text{-}CH_3C_6H_4\text{-}CH_2\text{-Cl}/C_6H_5\text{-}CH_2\text{-Cl}}{p\text{-}CH_3\text{-}C_6H_4CH_2\text{-Br}/C_6H_5CH_2\text{-Br}} = \frac{1.57}{1.48}$; the same ratio for I^- at 0° $\frac{1.55}{1.46}$ [data from C. Bevin, E. Hughes, and C. Ingold, *Nature*, **171**, 301 (1953); G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935); A. G. Evans and S. D. Hamman, *Trans. Faraday Soc.*, **47**, 25 (1951); J. C. Charlton and E. D. Hughes, *J. Chem. Soc.*, 855 (1956)]. [c] Numerators and denominators are relative to benzyl halide. [d] The value of 7.30 was obtained at 0° by J. C. Charlton and E. D. Hughes [*J. Chem. Soc.*, 855 (1956)].

Inspection of the adjusted rate ratios (Table II) show that the thiophenoxide and iodide entries, relative to methoxide, present the trends expected from London interactions when considering only a *given substituent.*[8] However, examination of the hydrogen, methyl, and bromine adjusted rate ratios with a *given nucleophile* does not show the trends expected from London interactions; *i.e.*, nucleophiles of relatively high polarizabilities do not give higher values for the most polarizable substituent (bromo group).

Since the latter observation differs sharply from the expected trends evident in the adjusted rate ratios presented by Bunnett,[3] the following discussion is offered as an explanation for this difference. Bunnett[2] employed the expression

$$\frac{\left(\frac{k_{o\text{-R}}}{k_H}\right)_y}{\left(\frac{k_{o\text{-R}}}{k_H}\right)_{MeO^-}} \equiv \frac{\left(\frac{k_y}{k_{MeO^-}}\right)_{o\text{-R}}}{\left(\frac{k_y}{k_{MeO^-}}\right)_H} \qquad (2)$$

R = H, Me, and Br
y = MeO^-, $C_6H_5S^-$, and I^-

for the cancellation of nucleophilicity differences. Although inherent nucleophilic differences are reflected in the ratio $(k_y/k_{MeO^-})_H$, Bunnett assumed that these differences are the same in the ratio $(k_y/k_{MeO^-})_{o\text{-R}}$; in other words, the susceptibility of methoxide to the polar changes H → *o*-R is the same as the susceptibility of iodide and thiophenoxide given the same polar changes. The apparent justification is that the ρ for the reaction is small ($\rho = +0.78$, I^- in acetone at 20°),[9] and it should not change with different nucleophiles and different solvents (I^- in acetone, $C_6H_5S^-$ and MeO^- in methanol). These assumptions are highly suspect.[10] However, the treatment presented herein more nearly cancels nucleophilicity differences. Inherent nucleophilic differences reflected in $(k_y/k_{MeO^-})_{p\text{-R}}$ are the same in $(k_y/k_{MeO^-})_{o\text{-R}}$ since $\rho \cong \rho^*$ (see ref. 4); in other words, it is the difference in response or susceptibility of methoxide, iodide, and thiophenoxide to a much smaller electrical difference, *p*-R → *o*-R. Therefore, the division (eq. 1) should more nearly cancel nucleophilicity differences.

The treatment presented and that of Bunnett[3] yield the expected trends *only* when considering a *given substituent* with nucleophiles of increasing polarizabilities, $MeO^- \rightarrow C_6H_5S^- \rightarrow I^-$ (Table II). These trends are still manifest in view of a possible increasing adverse steric effect with the three nucleophiles (see ref. 8). However, the results for a given nucleophile with *ortho* substituents of increasing polarizabilities (H → Me → Br) are anomalous. It is, therefore, apparent that, if dispersion forces are obtained in the anomalous results, some offsetting or adverse factor(s) must be considered. Possible steric dissimilarities (Me and Br), variation of distance between a given nucleophile and the *ortho* substituents,[11] conformational differences, or a combination of the three may account for the anomalous behavior. Unpublished results from this laboratory indicate that the different inductive field

(8) These trends are also consistent with a decreasing steric interaction between the nucleophiles, MeO^-, $C_6H_5S^-$, and I^-, and the given *ortho* substituent, since highly polarizable nucleophiles can easily distort their bonding electrons without bringing the rest of the molecule close enough to cause excessive repulsive forces [see R. G. Pearson, *et al.*, *J. Am. Chem. Soc.*, **74**, 5131 (1953); R. G. Pearson and J. O. Edwards, *ibid.*, **84**, 16 (1962)].

(9) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 190.

(10) Ref. 5, p. 571, 572; H. H. Jaffe, *Chem. Rev.*, **53**, 217 (1953).

(11) The benzene carbon to methyl carbon bond distance is 1.51 Å.; the benzene carbon to bromine bond distance 1.85 Å. Since dispersion forces vary inversely with the sixth power of the distance, this may be an important consideration.

effects of various substituents may be an important additional factor. A kinetic investigation is presently being undertaken with a variety of *ortho* substituents and various nucleophiles in an attempt to verify the above considerations.

Acknowledgment.—We wish to express our sincere appreciation to Dr. S. Windwer and Dr. S. Moon for their fruitful suggestions.

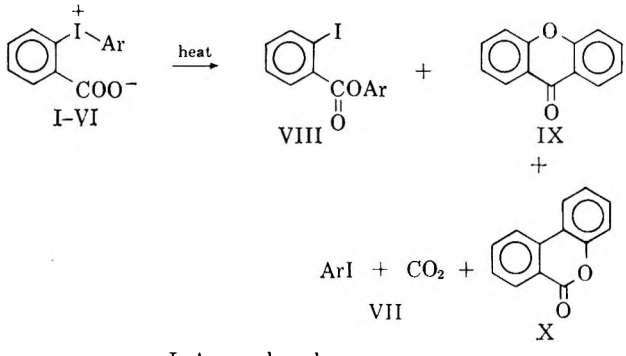
Effects of Substituents on the Rearrangement of 2-Aryl Iodoniobenzoates and Their Cleavage to Benzyne[1,2]

F. MARSHALL BERINGER AND SAMUEL J. HUANG

Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn 1, New York

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A previous article[3] reported that, on heating, 2-aryl iodoniobenzoates I–III rearrange in part to aryl 2-iodobenzoates (VIII). A competitive reaction, favored at higher temperatures, is cleavage to aryl iodides (VII), carbon dioxide, benzyne,[3,4] and perhaps other reactive intermediates.[3] In the absence of benzyne-trapping reagents, these intermediates react to give xanthone[3] (IX) and 3,4-benzocoumarin[3] (X). As the rearrangement of betaines to esters may involve intramolecular nucleophilic displacement, the effects of substituents on the rearrangement and cleavage reactions of 2-aryl iodoniobenzoates I–VI have now been studied, and the results are listed in Table I.



I, Ar = phenyl
II, Ar = mesityl
III, Ar = *p*-cyclohexylphenyl
IV, Ar = 2,4-dimethoxyphenyl
V, Ar = *m*-nitrophenyl
VI, Ar = 2-methyl-5-nitrophenyl

As expected, introduction of the electron-withdrawing nitro group facilitated the formation of ester *via* intramolecular nucleophilic substitution. A similar effect on intermolecular nucleophilic substitution reactions of diaryliodonium salts has been reported.[5,6]

TABLE I

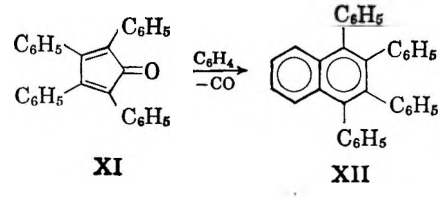
PRODUCTS FROM 2-ARYL IODONIOBENZOATES ON HEATING IN THE ABSENCE OF BENZYNE-TRAPPING REAGENTS[a]

Betaine	Solvent	Temp., °C.	Time, hr.	% yield VII	VIII	IX	X
I	C_6H_5I	100	150	*b*	100[c]		
		130	20	*b*	54	10	*b*
		150	4	*b*	30	12	15
	Diglyme	162	2	42	20	13	16
	Lactone[d]	204	2	44	6	30	6
II	Triglyme	175	2	72	5	4	*b*
III	Xylene	138	2	33	25	4	*b*
	C_6H_5Br	155	2	29	20	10	*b*
IV	C_6H_5Cl	132	15	63		20	51
	Triglyme	222	0.5	57		30	40
V	C_6H_5Cl	132	15	13	77		
VI	C_6H_5Cl	132	15	17	75		
	Triglyme	222	0.5	34	40	Trace	Trace

[a] Data on betaines I–III from ref. 3. [b] Not determined. [c] In 5% conversion. [d] γ-Butyrolactone.

In contrast, the fact that no 2′,4′-dimethoxyphenyl 2-iodobenzoate was found in the thermal reaction of 2-(2′,4′-dimethoxyphenyl) iodoniobenzoate (IV) indicates that intramolecular nucleophilic substitution was depressed by the electron-donating methoxyl groups.[5,6] The low yield of mesityl 2-iodobenzoate may be due to both steric and electronic effects. Introduction of a cyclohexyl group at the *para* position has little effect on ester formation as compared to the unsubstituted betaine.

Decomposition of betaines I–VI in the presence of 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone, XI)[3,4] gave 1,2,3,4-tetraphenylnaphthalene (XII) in yields of 23–60% (Table II). The formation of



XI XII

benzyne was not repressed by electron-donating substituents on the phenyl group of the betaines, as was shown by the fact that reactions of betaines I–IV with tetracyclone gave comparable yields of 1,2,3,4-tetraphenylnaphthalene. The yield of benzyne from betaines bearing the electron-withdrawing nitro group (V and VI) was lowered by competitive formation of ester.

TABLE II

1,2,3,4-TETRAPHENYLNAPHTHALENE FROM THE REACTIONS OF 2-ARYL IODONIOBENZOATES WITH TETRACYCLONE[a]

Betaine	I	II	III	IV	V	VI
% yield	56	55	57	60	23	25

[a] Reactions were run with equivalent amounts of reagent and betaine in γ-butyrolactone at 204° for 15 min.

In summary, it is concluded that the thermal rearrangement of 2-aryl iodoniobenzoates to aryl 2-iodobenzoates proceeds by intramolecular nucleophilic aromatic substitution. The formation of benzyne is af-

(1) This article is taken from the dissertation of S. J. Huang submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (chemistry), 1964. It is publication XXIII in the series on diaryliodonium salts.

(2) Preceding article in this series: F. M. Beringer and S. A. Galton, *J. Org. Chem.*, **28**, 3417 (1963).

(3) F. M. Beringer and S. J. Huang, *ibid.*, **29**, 445 (1964).

(4) E. LeGoff, *J. Am. Chem. Soc.*, **84**, 3786 (1962).

(5) F. M. Beringer, A. Brierly, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *ibid.*, **75**, 2708 (1953); F. M. Beringer and M. Mausner, *ibid.*, **80**, 4535 (1958).

(6) F. M. Beringer and R. A. Falk, *J. Chem. Soc.*, in press; R. A. Falk, Ph.D. dissertation, Polytechnic Institute of Brooklyn, 1961.

TABLE III
SUBSTITUTED PHENYL 2-IODOBENZOATES

From betaine	Substituents[a]	M.p., °C. Ester	M.p., °C. Phenol[b] (lit.)	Analyses of esters, % Calcd. C	Calcd. H	Found C	Found H
V	3-NO_2	136–138	95 (95[b])	40.25	2.18	40.50	2.35
VI	2-CH_3-5-NO_2	173–174	116–117 (117[d])	43.86	2.61	43.67	2.90

[a] Substituents in phenyl group of ester and in the phenol derived from it. [b] Ref. 8. [c] Ref. 5. [d] Ref. 11.

fected indirectly as ester formation provides a competitive mode of reaction of the betaines.

Experimental[7]

2-Phenyl Iodoniobenzoate (I), 2-Mesityl Iodoniobenzoate (II), and 2-(*p*-Cyclohexylphenyl) Iodoniobenzoate (III).—Betaines I, II, and III were prepared as described in ref. 3.

2-(2′,4′-Dimethoxyphenyl) Iodoniobenzoate (IV).—To a solution held at 0–5° of 26.4 g. (0.1 mole) of 2-iodosobenzoic acid[3] and 20.7 g. (0.15 mole) of *m*-dimethoxybenzene in 100 ml. of acetic anhydride, there was added slowly 10 ml. of trifluoroacetic acid. After the dark green solution had been stirred at room temperature for 24 hr., there was added with stirring 600 ml. of ether. The iodonium salt was collected as tan crystals and stirred vigorously with 200 ml. of 5 *N* sodium hydroxide solution to give a tan precipitate. This was collected, washed with water, and dried to give 31 g. (81 mmoles, 81%) of **2-(2′,4′-dimethoxyphenyl) iodoniobenzoate (IV)**. Recrystallization from methanol gave colorless crystals, m.p. 234–235° dec. The infrared spectrum showed a carboxylate group absorption band at 1620 cm.$^{-1}$. The nuclear magnetic resonance spectrum showed ring hydrogen absorption bands at τ 1.30 to 3.31 and methoxyl hydrogen absorption bands at τ 6.09 and 6.18.

Anal. Calcd. for $C_{15}H_{13}IO_4$: C, 46.89; H, 3.38; I, 33.03. Found: C, 46.87; H, 3.33; I, 33.16.

The structure of IV was proved by thermal decomposition, which gave as one product 2,4-dimethoxyiodobenzene,[8] m.p. 40° (from hexane), lit.[9] m.p. 40°.

2-(*m*-Nitrophenyl) Iodoniobenzoate (V).—To a solution of 74.4 g. (0.3 mole) of 2-iodobenzoic acid in 300 ml. of concentrated sulfuric acid at 0–5°, there was added over 1 hr. 81 g. (0.3 mole) of potassium persulfate. After the mixture had been stirred at 0–5° for 1 hr., 49.2 g. (0.4 mole) of nitrobenzene was added, and the mixture was stirred at 100° for 3 hr. The cooled mixture was poured into ice–water, and the unchanged nitrobenzene was removed by extraction with benzene. Addition to the aqueous layer of 100 ml. of saturated potassium iodide solution gave pale yellow crystals of crude 2-carboxy-3′-nitrodiphenyliodonium iodide, which were collected. The iodonium salt was stirred vigorously with 200 ml. of 5 *N* sodium hydroxide solution to give a yellow precipitate. This was collected, washed with water, and dried to give 31 g. (80 mmoles, 28%) of **2-(*m*-nitrophenyl) iodoniobenzoate (V)**, m.p. 222–224° dec. Two recrystallizations from ethanol followed by two recrystallizations from chloroform gave colorless crystals, m.p. 229° dec. The infrared spectrum showed a carboxylate group absorption band at 1600 cm.$^{-1}$ and nitro group absorption bands at 1520 and 1340 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_8INO_4$: C, 40.25; H, 2.18; I, 34.42; N, 3.79. Found: C, 40.59; H, 2.24; I, 34.31; N, 3.83.

The structure of V was proved by thermal decomposition, which gave as one product ***m*-nitroiodobenzene**,[8] m.p. 36–38° (from hexane), lit.[10] m.p. 38–39°.

2-(2′-Methyl-5′-nitrophenyl) Iodoniobenzoate (VI).—A mixture of 52.8 g. (0.2 mole) of 2-iodosobenzoic acid,[3] 27.4 g. (0.2 mole) of *p*-nitrotoluene, and 300 ml. of concentrated sulfuric acid was stirred at 100° for 2 hr. After cooling, the mixture was poured into ice–water, and the unchanged *p*-nitrotoluene was removed by extraction with benzene. Addition of 100 ml. of saturated potassium iodide solution to the aqueous layer gave pale yellow crystals of 2-carboxy-2′-methyl-5′-nitrodiphenyliodonium iodide, which were collected. The iodonium salt was stirred vigorously with 200 ml. of 5 *N* sodium hydroxide solution to give a yellow precipitate. This was collected, washed with water, and dried to give 30 g. (78 mmoles, 39%) of **2-(2′-methyl-5′-nitrophenyl) iodoniobenzoate (VI)**, m.p. 207–209° dec. The infrared spectrum showed a carboxylate group absorption band at 1600 cm.$^{-1}$ and nitro group absorption bands at 1520 and 1340 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{10}INO_4$: C, 43.86; H, 2.61; I, 33.19; N, 3.66. Found: C, 43.53; H, 2.64; I, 33.30; N, 3.38.

The structure of VI was proved by thermal decomposition, which gave as one product **2-iodo-4-nitrotoluene**,[8] m.p. 53–54° (from hexane), lit.[11] m.p. 54°.

Reactions of 2-Aryl Iodoniobenzoates.—Thermal reactions of 2-aryl iodoniobenzoates and the reactions of 2-aryl iodoniobenzoates with tetracyclone were run and worked up according to the procedures described in ref. 3. The results are listed in Tables I and II. Esters were hydrolyzed with acid or base to the corresponding known phenols and 2-iodobenzoic acid (Table III).

(7) Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were taken on a Perkin-Elmer double beam recording spectrophotometer, Model 21, and a Perkin-Elmer Infracord spectrophotometer, Model 137. Ultraviolet spectra were taken on a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectrum was taken on a Varian A-60 high resolution n.m.r. spectrometer. Melting points were taken in capillary tubes and are corrected. Solvents were purified by passage through alumina column and distillation. Reagent grade chemicals were redistilled or recrystallized before used.

(8) The infrared spectrum was identical with that of an authentic sample.

(9) H. Kauffmann and F. Kieser, *Ber.*, **45**, 2333 (1912).

(10) I. R. L. Barker and W. A. Waters, *J. Chem. Soc.*, 150 (1951).

(11) I. Keimatsu and E. Yamazuchi, *J. Pharm. Soc. Japan*, **57**, 992 (1937); *Chem. Abstr.*, **32**, 2519 (1938).

The Infrared Spectra of 1,1-Dinitrocarbanion Salts

LLOYD A. KAPLAN

Organic Chemistry Division, U. S. Naval Ordnance Laboratory, Silver Spring, Maryland 20910

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Brown[1] has given assignments to the principal infrared absorption bands for the nitro group in various classes of nitro compounds. However, with the exception of the bands at 1151 and 1241 cm.$^{-1}$ reported for the symmetrical and asymmetrical stretching modes, respectively, of the nitro groups in the potassium salt of 1,1-dinitroethane[1] and a report[2] that the anions $H(CH_2)_nC(NO_2)_2^-$, where n = 0 to 5 and 9, absorb in the range 1090 to 1157 cm.$^{-1}$ and 1201 to 1251 cm.$^{-1}$ for the symmetrical and asymmetrical stretching modes of the nitro group, there are no assignments given to this functionality in more highly substituted compounds.[3]

(1) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **77**, 6341 (1955).

(2) V. I. Slovetski, S. A. Shevelev, V. I. Erashko, A. A. Fainzil'berg, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1126 (1962); 57 (1963).

(3) In one other isolated case [L. W. Kissinger and H. E. Ungnade, *J. Org. Chem.*, **25**, 1471 (1960)], the hydrazine salts of ethyl dinitroacetate and dinitroacetohydrazide are reported to absorb at 1133 and 1269 cm.$^{-1}$ and 1124 and 1259 cm.$^{-1}$, respectively.

From the results of various studies carried out in these laboratories,[4] a number of 2- and 3-substituted 1,1-dinitroalkanes and 3-substituted 1,1-dinitro-2-alkene salts were obtained. During the course of these investigations, the infrared spectra of some of these salts were determined and used in characterization. These results, as well as the spectra of a number of previously unreported substituted 1,1-dinitrocarbanion salts, are summarized in Table I.

TABLE I

NITRO GROUP ABSORPTION OF 1,1-DINITROCARBANION SALTS

	Infrared bands	
$^-C(NO_2)_2Y$, Y =	1100–1200 cm.$^{-1}$[a]	1200–1300 cm.$^{-1}$
$-CH_2CHOHCO_2CH_3$	1165 (1130)	1262
$-CH{=}CHCO_2CH_3$	1182	1268
$-CH_2CH_2CO_2CH_3$	1165 (1120)	1245
$-CH_2CHOHCONH_2$	1175 (1132)	1273
$-CH{=}CHCONH_2$	1165	1267
$-CH_2CH_2CONH_2$	1165 (1115)	1260
$-CH_2CHOHCOO^-$	1165 (1115)	1270
$-CH_2CH_2COO^-$	1180 (1112)	1255
$-CH{=}CHNO_2$	1185	1255
$-CH_2CH_2NO_2$	1182 (1140)	1272
$-CH{=}CHCN$	1176	1268
$-CH_2CN$	1190 (1112)	1268
$-CH_2CHOHCOCH_3$	1160 (1120)	1268
$-CH_3$	1150	1240
$-(CH_2)_3CH_3$	1187 (1120)	1248

[a] Values in parentheses represent a second band of about equal or lower intensity.

From the data in Table I, the empirical assignments given to the two bands for the nitro group in substituted 1,1-dinitrocarbanion salts are 1173 ± 10 and 1269 ± 9 cm.$^{-1}$, with maximum deviations of 23 and 22 cm.$^{-1}$, respectively. In most of the saturated derivatives, a second band of about equal or somewhat lower intensity appears in the 1100–1200-cm.$^{-1}$ region. This value is given in parentheses. These bands were not used in the average since they are generally absent in the unsaturated derivatives.

By analogy with the covalent nitro compounds,[1] the 1173-cm.$^{-1}$ band would be due to the symmetrical stretching mode and the 1262-cm.$^{-1}$ band would be due to the asymmetrical stretching mode of the nitro group. This shift in the value of ν_{max} to lower frequencies as compared to the covalent nitro compounds[1] would be expected due to the resonance interaction of the carbanion with the nitro groups.

Experimental

The potassium salts were prepared as described previously.[4] *Extreme caution was exercised in grinding the samples for mull preparation as all of these salts are extremely sensitive to impact and/or friction and may explode during this operation.* Infrared spectra were determined on mulls in Nujol using a Beckman IR-4 spectrophotometer. Individual values of ν_{max} in Table I have an average deviation of 5 cm.$^{-1}$.

Acknowledgment.—This work was supported by the Foundational Research Fund of the U. S. Naval Ordnance Laboratory, Task FR-44.

(4) M. J. Kamlet and J. C. Dacons, *J. Org. Chem.*, **26**, 3005 (1961); M. J. Kamlet, J. C. Dacons, and J. C. Hoffsommer, *ibid.*, **26**, 4881 (1961); L. A. Kaplan and M. J. Kamlet, *ibid.*, **27**, 780 (1962); M. J. Kamlet and L. A. Kaplan, *ibid.*, **28**, 2128 (1963); L. A. Kaplan, unpublished results.

Solvolytic Deoxymercuration Catalyzed by Iodide Ion[1]

MAURICE M. KREEVOY AND MARGARET A. TURNER

School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

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In a previous publication[2] 2-acetoxyethylmercuric iodide has been shown to undergo a solvolytic deoxymercuration, shown in eq. 1 and 2. Acid-catalyzed

$$CH_3COOCH_2CH_2HgI \xrightarrow[\text{solvent}]{\text{rate determining}} CH_3COO^- + CH_2{-}CH_2^+ \quad (1)$$
(HgI)

$$CH_2{-}CH_2^+ + CH_3COOCH_2CH_2HgI \xrightarrow{\text{fast}} HgI_2 + CH_2{=}CH_2 + CH_3COOCH_2CH_2Hg^+ \quad (2)$$
(HgI)

deoxymercuration has been shown[3] to be subject to cocatalysis by one or two iodide ions,[3] and similar cocatalysis might be expected for solvolytic deoxymercuration. It has now been found in dilute, aqueous solution, for the reaction whose over-all course is shown in eq. 3. This completes the H^+–I^- deoxy-

$$CH_3COOCH(CH_2CN)CH_2HgI + I^- \longrightarrow HgI_2 + CH_3COO^- + CH_2{=}CHCH_2CN \quad (3)$$

mercuration system, in the sense that catalysis by zero or one proton; zero, one, or two iodide ions; and all combinations thereof, has now been observed in dilute, aqueous solution. Acid catalysis of the reaction shown in eq. 3 has also been found, but is shown to be insignificant at the pH of the iodide-catalyzed solvolysis.

Results

Reactions were carried out at 25°, in aqueous solution containing <2% of methanol. (The substrate was handled as a stock solution in methanol.) Potassium iodide was the source of iodide ion and the acid, where used, was perchloric acid.

The progress of the reaction was followed by following the buildup of the ultraviolet absorption spectrum of HgI_2 and or its iodide ion complexes, as previously described.[2-4] Substrate concentrations were in the range 10^{-4}–10^{-5} *M* and the iodide ion, when added, was always in at least tenfold excess, so that a first-order rate law was obeyed within each experiment. The integrated form of the first-order rate law, eq. 4, was

$$k_1' = \frac{2.303}{(\bar{t} - t_0)} \log \frac{(D_\infty - D_0)}{(D_\infty - \bar{D}_1)} \quad (4)$$

(1) This work was supported by the Air Force Office of Scientific Research through Grant AF-AFOSR-16-63. Reproduction is permitted for any purpose of the U. S. government.

(2) M. M. Kreevoy and G. B. Bodem, *J. Org. Chem.*, **27**, 4539 (1962).

(3) M. M. Kreevoy, R. A. Kretchmer, G. E. Stokker, and A. K. Ahmed, *ibid.*, **28**, 3184 (1963).

(4) M. M. Kreevoy, *J. Am. Chem. Soc.*, **81**, 1099 (1959).

used, except for experiments in which no iodide ion was added. In those, an additional factor of 2 appears, in the denominator, on the right hand side of eq. 4.[4] The pseudo-first-order rate constant is k_1'; the optical density is D; time is t; the time at which an optical density was measured is subscripted.

The first-order rate law was very closely obeyed for the 2–3 half-lives that were observed in most experiments, and no systematic deviations were observed. Rate constants were evaluated graphically from plots of log $(D_t - D_\infty)$ *vs.* t. Previous experience[2-4] has shown that such rate constants have a reproducibility of $\sim \pm 5\%$, and this was confirmed by repeating most of the experiments here reported. Values of k_1' are shown, as a function of iodide concentration, in Table I.

TABLE I

RATE CONSTANTS AS A FUNCTION OF $[I^-]$

$10^4[I^-]$, M	$10^4\ k_1'$ sec.$^{-1}$	$10^4\ k_1'$ sec.$^{-1}$, calcd.[b]
0.00[a]	0.50	
2.03	1.73	2.05
4.06	4.07	3.66
12.2	12.1	10.6
20.3	19.3	18.5
40.6	36.1	42.1
40.6[a]	36.1	42.1
81.2	90.4	105.6
81.2[a]	89.6	105.6
101	144	144
122	218	192

[a] Run in the presence of 6.4×10^{-3} M acetic acid and 1.37×10^{-3} M sodium acetate. [b] Calculated from eq. 5.

To test the hypothesis that these rate constants are pH independent in near neutral solutions, several were measured in acetic acid–acetate buffer solutions of pH ~4. These should differ by about 2 pH units from those in which no buffer was added. These values of k_1' are also shown in Table I. Within experimental error no change in k_1' could be observed.

The data in Table I were fitted to eq. 5. The value

$$k_1' = k_1 + k_2[I^-] + k_3[I^-]^2 \quad (5)$$

$$k_1 = 5.0 \times 10^{-5} \text{ sec.}^{-1}$$
$$k_2 = 0.75 \text{ l. mole}^{-1} \text{ sec.}^{-1}$$
$$k_3 = 67 \text{ l.}^2 \text{ mole}^{-2} \text{ sec.}^{-1}$$

of k_1 was obtained directly from k_1' measured in the absence of iodide ion. Values of k_2 and k_3 were obtained by the iterative process previously described.[3] The values of k_1' calculated from eq. 5 are shown, for comparison, along with the experimental values, in Table I. In several cases, the difference between the two is somewhat larger than the expected experimental error, but it is not systematic and does not seem to call eq. 5 seriously into question. The derived values of k_2 and k_3 are probably uncertain by about 10–15%, k_2 being somewhat more reliable than k_3. There is no question about the reality of k_3, however. At the highest iodide concentration, k_1' is larger than would be predicted by any reasonable values of k_1 and k_2 alone by about a factor of two, and is increasing, roughly, as the square of the iodide concentration.

For comparison the rate coefficient for acid catalysis, k_2^H, was also obtained, by applying eq. 6 to the k_1 values obtained in the absence of iodide ion. (The k_1 of eq. 6 is the same as that cited above.) The value of

$$k_1' = k_1 + k_2^H \quad (6)$$

1.72×10^{-3} l. mole^{-1} sec.$^{-1}$ was obtained for k_2^H from four determinations of k_1' with perchloric acid concentrations ranging up to 0.6430 M. The average deviation from the mean was 0.05×10^{-3} l. mole^{-1} sec.$^{-1}$.

Discussion

Deoxymercuration induced by halide ions alone has been previously suggested,[5-7] but the details of the kinetics do not seem to have been worked out. The present work fills in the last gaps in the H^+–I^- deoxymercuration scheme, demonstrating catalysis of the neutral solvolysis by one or two iodide ions.

As before,[3] the ratios k_2/k_1 and k_3/k_2 have the form and the significance of the first and second complexing constants of the transition state for the uncatalyzed reaction with iodide ion, as shown in eq. 7 and 8.

$$\frac{k_2}{k_1} = \frac{(*_2)}{(*_1)[I^-]} \quad (7)$$

$$\frac{k_3}{k_2} = \frac{(*_3)}{(*_2)[I^-]} \quad (8)$$

(The subscript indicates the number of iodide ions contained by the particular transition state, $*_n$.)

The ratio k_2/k_1 is 1.5×10^4 l. mole^{-1} and k_3/k_2 is 90 l. mole^{-1}. In order of magnitude these are similar to the ratios (3.2×10^3 l. mole^{-1} and 34 l. mole^{-1}) previously reported[3] (with a somewhat different substrate structure) for acid deoxymercuration. This suggests that the immediate environment of the mercury atom is similar in the two reactions, as these complexing constants are sensitive to this environment. (The formation constants of HgI_2, HgI_3^-, and HgI_4^{-2} from HgI^+, HgI_2, and HgI_3^-, respectively, are 10^{11}, 10^4, and 10^2 l. mole^{-1}.[8]) This similarity is in accord with the similar transition states that have been suggested for the two reactions.[2,9]

Both k_1 and k_2^H here reported are about an order of magnitude smaller than the similar quantities for (2-iodomercuriethyl) acetate.[2,10] This is in qualitative accord with the effect expected of the electron-withdrawing cyanomethylene group.[11]

Experimental

2-Acetoxy-3-cyanopropylmercuric Iodide.—This compound was prepared by exchange from 2-acetoxy-3-cyanopropylmercuric chloride. The latter was made from 3-cyanopropene, (Matheson Coleman and Bell, practical) by the general method of Ichikawa, Onchi, and Araki.[12] It was not isolated. Its chloroform solution was washed repeatedly with dilute aqueous potassium iodide and then with water, and dried over calcium sulfate; the solvent was evaporated under vacuum for 15 hr. The product was a light yellow, uncrystallizable, undistillable oil, but had a suitable infrared spectrum.

Anal. Calcd. for $C_6H_8HgINO_2$: C, 15.88; H, 1.76. Found: C, 16.08; H, 1.86.

(5) T. G. Traylor and S. Winstein, Abstracts, 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959, p. 81-O.
(6) G. F. Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935).
(7) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).
(8) J. Bjerrum, G. Schwartzenbach, and L. G. Sillen, "Stability Constants," The Chemical Society, London, 1958, p. 121.
(9) M. M. Kreevoy and F. R. Kowitt, *J. Am. Chem. Soc.*, **82**, 739 (1960).
(10) M. M. Kreevoy and M. A. Turner, unpublished work.
(11) L. L. Schaleger, M. A. Turner, T. C. Chamberlin, and Maurice M. Kreevoy, *J. Org. Chem.*, **27**, 3421 (1962).
(12) K. Ichikawa, H. Onchi, and S. Araki, *J. Am. Chem. Soc.*, **82**, 3880 (1960).

The Effect of Structure on Mercaptan Dissociation Constants[1]

MAURICE M. KREEVOY, BRUCE E. EICHINGER, FRANCIS L. STARY, EUGENE A. KATZ, AND JOHN H. SELLSTEDT

School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

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In a previous paper[2] the acid dissociation constants, K_A, of a number of mercaptans in water were reported and a linear relation was noted between log K_A and the Taft inductive parameters,[3] σ^*, for most of the compounds studied. Thiophenol, however, deviated from this correlation by 1.6 log units. The deviation was attributed to resonance stabilization of the anion. No Baker–Nathan effect was noted in the two alkyl mercaptans studied having other than two α-hydrogen atoms.

While that paper was in press another value for the K_A of thiophenol appeared[4] differing by over a power of ten from ours and fitting the correlation moderately well.[4] The present note reports a redetermination of the K_A for thiophenol and also a number of other K_A values, some of which are new and some redetermined. Four of these bear on the question of a Baker–Nathan effect. It is concluded that there is no Baker–Nathan effect but that there is a resonance exaltation of mercaptan dissociation constants of ~1.3 log units for conjugated mercaptans.

Results

Dissociation constants were measured by pH titration, by a spectrophotometric method, and a gas solubility method, all of which have been previously described.[2] Dissociation constants were evaluated from eq. 1, in which the mean ion activity coefficient, $f_\pm$, was evaluated from the Debeye–Hückel limiting law, eq. 2.[5] (The symbols are those of our earlier paper[2] and of Harned and Owen.[5]) In no case did the total electrolyte concentration exceed 0.1 *M*. For the pH titrations and the spectrophotometric determinations, the solutions also contained 1% ethanol, which was used as a solvent for stock solutions of the mercaptans, but this is not thought to change the dissociation constants by more than a few per cent.[2] The resulting acid dissociation constants are shown in Table I. They are not thought to differ from their thermodynamic values in pure water by more than their experimental uncertainty, ~10%. The K_A values reported here are the average of at least four determinations and the uncertainty given is the average deviation from the mean value. Better precision is precluded by the unavoidable presence of traces of oxygen, which results in the oxidation of a small, irreproducible, fraction of the mercaptide ions.

$$K_A = \frac{(H^+)(RS^-)f_\pm^2}{(RSH)} \quad (1)$$

$$\log f_\pm = -\frac{S_f\sqrt{\Gamma}}{1 + A\sqrt{\Gamma}} \quad (2)$$

TABLE I

ACID DISSOCIATION CONSTANTS OF MERCAPTANS, RSH

R	K_A	Method[g]
CH_3CO	$3.85 \pm 0.32 \times 10^{-4}$	pH tit.
	4.69×10^{-4} [a]	
C_6H_5	$2.97 \pm 0.33 \times 10^{-7}$	pH tit.
	3.0×10^{-7} [b]	
	1.66×10^{-8} [c]	
	3.2×10^{-7} [d]	
	2.0×10^{-7} [e]	
(2-Pyridyl)CH_2	$1.52 \pm 0.16 \times 10^{-9}$	pH tit.
$C_2H_5OCOCH_2CH_2$	$3.25 \pm 0.39 \times 10^{-10}$	pH tit.
$HOCH_2C(CH_3)_2$	$1.42 \pm 0.13 \times 10^{-10}$	pH tit.
CH_3	$4.7 \pm 0.8 \times 10^{-11}$	Gas sol.
t-C_4H_9	$9.0 \pm 0.6 \times 10^{-12}$	Spec.
	8.9×10^{-12} [f]	
t-C_5H_{11}	$4.5 \pm 0.6 \times 10^{-12}$	Spec.
	6.2×10^{-12} [f]	

[a] Ref. 9. [b] Ref. 2. [c] Ref. 4. [d] Ref. 6. [e] Ref. 7. [f] Ref. 10. [g] pH tit. = pH titration, gas sol. = gas solubility, spec. = spectrophotometric.

Discussion

The redetermined value of K_A for thiophenol is in excellent agreement with our previous value, which had been determined by an entirely different method (spectrophotometric) so that similar, systematic errors are quite unlikely. In addition, our values are in substantial agreement with those reported by DeDeken and co-workers[6] and by Albert and Barlin.[7] The Calvin value,[8] cited by Danehy and Noel[4] as similar to their own, was actually obtained in partially alcoholic solution, and so is not directly comparable with values in aqueous solutions. Accordingly, a value around 3×10^{-7} must be considered correct.

The agreement between the present K_A of thiolacetic acid and a very old value determined conductimetrically by Ostwald[9] is surprisingly good. For t-butyl and t-amyl mercaptans the present values are in good agreement with those of Yabroff,[10] obtained by a solvent extraction method.

In order to test more rigorously the possibility of a Baker–Nathan effect,[11] the parameters of eq. 3,[3] ρ^* and α, were redetermined using only K_A values for compounds, XCH_2SH. (Equation 3 appears in ref. 2 with a sign error but the value of α later given pertains to the correct equation.) Using the nine such K_A values previously available[2] and also that for ethyl β-mercaptopropionate, a value of 3.50 is obtained for

$$\log K_A = \sigma^*\rho^* + \alpha \quad (3)$$

(1) This work was supported by the U. S. Army, Surgeon General's Office, through Contract DA-49-193-MD-2027.

(2) M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, III, and L. T. Ditsch, *J. Am. Chem. Soc.*, **82**, 4899 (1960).

(3) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y. Chapter 13.

(4) J. P. Danehy and C. F. Noel, *J. Am. Chem. Soc.*, **82**, 2511 (1960).

(5) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1958, pp. 34–37.

(6) R. H. DeDeken, J. Broekhuysen, J. Bechet, and A. Mortier, *Biochim. Biophys. Acta*, **19**, 45 (1956).

(7) A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959).

(8) M. Calvin, "Glutathione," S. Colowick, *et al.*, Ed., Academic Press, Inc., New York, N. Y., 1954, Chapter 1.

(9) W. Ostwald, *Z. physik. Chem.* (Leipzig), **3**, 170 (1889).

(10) D. L. Yabroff, *Ind. Eng. Chem.*, **32**, 257 (1940).

(11) M. M. Kreevoy, *Tetrahedron*, **5**, 233 (1959).

ρ^* and -10.22 for α by the method of least squares.[12] (A σ^* was estimated for $C_2H_5OCOCH_2CH_2-$ by dividing that for CH_3OCO- by 2.8.)[3] As the 50% confidence limits[12] on ρ^* are about ± 0.15 in each case, these are not appreciably different from the values of 3.40 and -10.17 obtained using all the data previously available.[2] These parameters were then used in eq. 3 to calculate K_A for mercaptans having other than two α-hydrogen atoms. If there is a significant Baker–Nathan effect, K_A for methyl mercaptan should be higher than calculated and K_A values for mercaptans having less than two α-hydrogen atoms should be systematically lower.[11] It is plain from Table II that

TABLE II

DEVIATIONS FROM EQUATION 3 WITH OTHER THAN TWO α-HYDROGEN ATOMS

Compound	$\log K_A^{obsd} - \log K_A^{calcd\ a}$	$\log K_A^{obsd} - \log K_A^{calcd\ b}$
H_2S[c]	+1.49	+1.48
$HOCH_2C(CH_3)_2SH$	+0.35	+0.17
CH_3SH	0.00	−0.05
t-C_4H_9SH	+0.22	+0.13
	+0.12	+0.03

[a] Calculated using the parameters obtained with groups having two α-hydrogen atoms. [b] Calculated using the parameters of ref. 2. [c] Corrected by a symmetry factor of two.

this is not so. The large deviation for hydrogen sulfide has been discussed previously.[2] It is in the wrong direction for a Baker–Nathan effect. The other deviations, averaging 0.17 log units, are not much larger than those of values used to obtain the correlation and are also in the wrong direction for a Baker–Nathan effect. It seems likely, therefore, that the Baker–Nathan effect is not larger than 0.05 log units per α-hydrogen atom. Steric effects would also appear to be small, apart from the possibility that the H_2S anomaly is to be explained in that way.[2] In fact, as also shown in Table II, the new data seem to be excellently correlated by eq. 3 using the old parameters.

As previously noted[2] thiophenol deviates from eq. 3 by ~1.6 log units. This deviation has been attributed to enhanced resonance stabilization in the anion, and designated $\Delta pK\psi$. For thiolacetic acid $\Delta pK\psi$ is ~1.1 log units. Unfortunately this value is not so reliable as it might be, as the correlation with σ^* is being used well outside of the range in which it was experimentally verified. Nevertheless, these results tend to support the idea[13] that resonance stabilization due to a neighboring unsaturated group is roughly independent of the nature of that group.

The absence of a Baker–Nathan effect, in spite of the presence of a resonance effect due to conjugation, is interesting, since, at least in Hückel approximation, the former is usually predicted to be proportional to the latter.[11] The proportionality constant has been variously estimated as $\sim 1/10^{13}$ and $1/13$.[11] The only model which avoids this prediction is one in which *both* the carbon sp^3-orbital holding the α-hydrogen atom *and* the α-hydrogen 1s-orbital have nonzero resonance integrals with a neighboring p-orbital. This model predicts a much larger magnitude for Baker–Nathan effects in electron-deficient systems than in electron-surplus systems, such as the mercaptide ions. Although more data would be very desirable before reaching a final conclusion, this model should probably receive more attention than it has in the past.

(12) C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 36–40.

(13) M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4016 (1957).

Experimental

Dissociation Constants.—The pH titration, spectrophotometric, and gas solubility methods for determining dissociation constants have been previously described.[2] In determining the dissociation constant of methyl mercaptan it was found desirable to have more basic buffer solutions than those previously used. These were provided by phenol–phenoxide ion buffers. The hydrogen ion concentration of these was estimated using 1.00×10^{-10} as the acid dissociation constant of phenol.[14] In a simple buffer system of this sort the activity coefficients cancel, to a first approximation, and the dissociation constant of the mercaptan is given by eq. 5.

$$K_A^{CH_3SH} = K_A^{C_6H_5OH} \frac{(C_6H_6OH)(CH_3S^-)}{(C_6H_5O^-)(CH_3SH)} \qquad (5)$$

Materials.[15]—Thiolacetic acid (Eastman Kodak Co., practical grade) was redistilled and the center cut, b.p. 84–85°, was used. Thiophenol (Mathieson Co., reagent grade) was redistilled under vacuum to give b.p. 55–56° at 10 mm. (2-Pyridyl)methyl mercaptan was a gift of the Walter Reed Army Institute of Research through Dr. T. R. Sweeney and was used as supplied. Ethyl β-mercaptopropionate was prepared by the method of Karrer and Schmid[16] from β-mercaptopropionic acid (gift of Evans Chemetics, Inc.) and purified by vacuum distillation to give b.p. 54° at 6 mm. 2-Mercapto-2-methyl-1-propanol was prepared from isobutylene oxide by the method of Davies and Savige[17] and had b.p. 68° at 29 mm. Methyl mercaptan was purchased from Eastman Kodak Co. and was not further purified except that it was distilled into the gas solubility apparatus. t-Amyl mercaptan was prepared from t-amyl bromide by the method of Backer[18] and had b.p. 104°. t-Butyl mercaptan was prepared in essentially the same way from t-butyl chloride and had b.p. 63°.

(14) A. J. Biggs, *Trans. Faraday Soc.*, **52**, 32 (1956).

(15) All boiling points are uncorrected.

(16) V. P. Karrer and H. Schmid, *Helv. Chim. Acta*, **27**, 125 (1944).

(17) W. Davies and W. E. Savige, *J. Chem. Soc.*, 774 (1951).

(18) H. J. Backer, *Rec. trav. chim.*, **54**, 216 (1935).

Nucleophilic Heteroaromatic Substitution. I. Pyridazines

JOHN H. M. HILL AND JOSEF G. KRAUSE[1]

Department of Chemistry, Hobart and William Smith Colleges, Geneva, New York

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In contrast to the numerous studies of nucleophilic homoaromatic substitutions,[2] kinetic studies of nucleophilic heteroaromatic substitutions have been few. Such studies have been confined mainly to pyridines[3] and pyrimidines[4] where annular nitrogen α and/or γ to the group displaced, generally halogen, facilitates reaction through electron withdrawal.

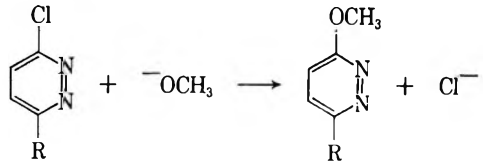
(1) Abstracted in part from the B.S. Honors thesis of J. G. K., Hobart College, 1963.

(2) W. R. Griezerstein, R. A. Bonelli, and J. A. Brieux, *J. Am. Chem. Soc.*, **84**, 1026 (1962), and references quoted therein.

(3) A. Mangini and B. F. Frenguelli, *Gazz. chim. ital.*, **69**, 86 (1939).

(4) N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1563 (1956).

We have investigated the displacement of chloride by methoxide from a series of 3-chloropyridazines variously substituted in the 6-position (compounds **1**–**9**) and have found that in most cases the reaction follows bi-



1, R = H; **2**, R = CH_3; **3**, R = OCH_3; **4**, R = SCH_3; **5**, R = SO_3^-; **6**, R = $SOCH_3$; **7**, R = CO_2^-; **8**, R = CO_2CH_3; **9**, R = Cl

molecular kinetics. In these compounds the annular nitrogens are α and β to the leaving group. Methoxide was chosen as the nucleophile to avoid the autocatalysis reported for the reaction of halopyridines with aniline,[5] where protonation of the annular nitrogen by acid liberated during reaction increases the electron-withdrawing power of the annular nitrogen. The pyridazines used are stable in dry methanol for indefinite periods with the exceptions of **1** and **6**, which undergo slow methanolysis to liberate ionic chloride. This methanolysis is sufficiently slow that good second-order plots were obtained to 65% completion of reaction when freshly prepared solutions of **1** and **6** were treated with methoxide in methanol.

Groups other than halogen can be displaced in nucleophilic aromatic substitution[6]; thus it was necessary to confirm that chloride was the only group being displaced in all of our reactions. That this was the case was indicated for compounds **4**, **8**, and **9** by the close parallel between the rate of liberation of chloride and the consumption of methoxide throughout the individual runs. Typical data are presented in Table I. No other product in addition to that expected was isolated from the reactions of compounds **3**, **4**, and **9**. The infrared spectra of the total product from reactions of **4** and **9** showed no change after two crystallizations.

TABLE I

CORRELATION BETWEEN METHOXIDE CONSUMPTION AND CHLORIDE LIBERATION FOR THE REACTION OF 3,6-DICHLOROPYRIDAZINE (20 ML., 0.2396 *M*) AND SODIUM METHOXIDE (20 ML., 0.2396 *M*)[a]

Time, sec.	$^-OCH_3$, moles/l.	Cl^-, moles/l.
40	0.1230	0.1209
300	0.0856	0.0866
600	0.0640	0.0646
900	0.0545	0.0551
1200	0.0402	0.0387
2400	0.0290	0.0284
3600	0.0226	0.0233

[a] In methanol at 40.2°.

The rates of substitution of chloride by methoxide were measured at 25.4 and 40.2° by methoxide consumption and were followed to at least 65% completion and in some cases up to 85% completion. Because of its slow reaction, compound **3** was studied only at the higher temperature and was not followed beyond 40% completion. Reactions of **5** and **7** were carried out with methoxide always present in excess to ensure that

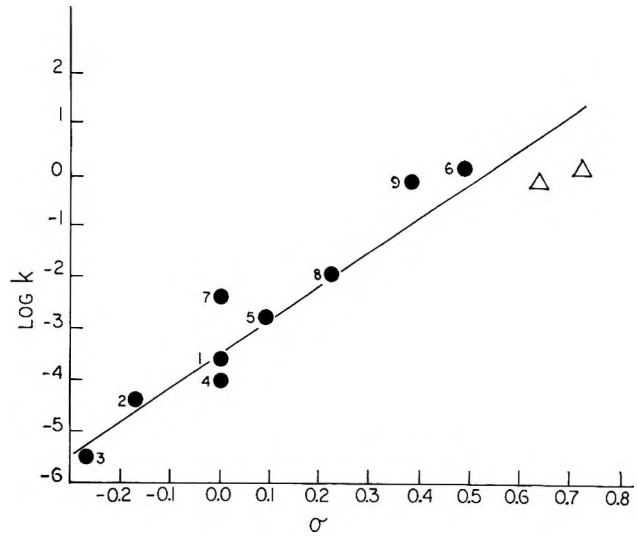


Fig. 1.—Plot of log k against σ (●) or σ^- (△) for the reaction of 3-chloro-6-R-pyridazines with methoxide.

carboxylate and sulfonate ions, instead of the corresponding free acids, were the forms present throughout reaction. Nevertheless, the rate for **7** was faster than anticipated and showed a slight increase as methoxide was consumed. Presumably the more reactive form—the free carboxylic acid—was present in equilibrium with the carboxylate ion, even initially, in sufficient quantities to affect the rate measurements. The increase in rate, then, was due to an increase in the relative amount of free acid as methoxide was consumed. Under the same conditions, the strongly acidic sulfonic acid showed no corresponding enhanced rate nor a change of rate as the reaction progressed. Kinetic data and thermodynamic parameters for the reactions studied are presented in Table II. These thermodynamic parameters are similar to those found by others for nucleophilic substitutions in homo- and heteroaromatic systems.[4,7,8]

A mechanism that may involve a cyclohexadienide intermediate has been proposed for bimolecular nucleophilic aromatic substitutions.[9] This mechanism is supported by spectroscopic, synthetic, and kinetic studies.[10] It seems probable that a similar intermediate is involved in the reaction of methoxide with 3-chloropyridazines.

A Hammett plot of the logarithms of reaction rates against σ-values (Fig. 1) shows reasonable linearity. The regression line shown in Fig. 1 was obtained from the values for compounds **1**–**5** and **9**. Compound **7** was omitted from the calculation because of the ambiguity regarding the actual nature of the substituent during reaction. Values of σ and σ^- for **6** and **8** are also shown in Fig. 1; the former lie above the regression line and the latter below it, which indicates that carbomethoxy and methylsulfinyl groups exhibit less resonance interaction with the reaction site in the cases under

(5) C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

(6) J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *ibid.*, **79**, 387 (1957).

(7) J. F. Bunnett, F. Draper, Jr., P. R. Ryason, P. Noble, Jr., R. G. Tonkyn, and R. E. Zahler, *ibid.*, **75**, 642 (1953).

(8) E. Berliner and L. C. Monack, *ibid.*, **74**, 1574 (1952). However, values of about −40 e.u. for ΔS^* are reported in ref. 2 for the reaction of piperidine with 5-R-2-nitrochlorobenzenes.

(9) J. Miller, *ibid.*, **85**, 1628 (1963).

(10) For a review of current evidence, see S. D. Ross, "Progress in Physical Organic Chemistry," Vol. 1, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 31.

TABLE II

KINETIC DATA AND THERMODYNAMIC PARAMETERS FOR THE REACTION OF METHOXIDE WITH 3-CHLORO-6-R-PYRIDAZINES

R	k at 25.4° (l./mole sec.)	k at 40.2° (l./mole sec.)	ΔH^* (kcal./mole)	ΔS^* (e.u.)
OCH_3		$2.90 \pm 0.06 \times 10^{-6}$		
CH_3	$7.42 \pm 0.20 \times 10^{-6}$	$3.85 \pm 0.04 \times 10^{-5}$	19.8	−15.6
SCH_3	$1.89 \pm 0.04 \times 10^{-5}$	$8.31 \pm 0.06 \times 10^{-5}$	19.5	−17.4
H	$5.41 \pm 0.08 \times 10^{-5}$	$2.56 \pm 0.08 \times 10^{-4}$	18.7	−15.4
SO_3^-	$3.34 \pm 0.20 \times 10^{-4}$	$1.43 \pm 0.05 \times 10^{-3}$	17.4	−16.1
CO_2^-	$9.89 \pm 0.30 \times 10^{-4}$	$3.85 \pm 0.40 \times 10^{-3}$	16.3	−17.3
Cl	$2.80 \pm 0.04 \times 10^{-3}$	$1.15 \pm 0.01 \times 10^{-2}$	16.6	−14.5
CO_2CH_3	$3.06 \pm 0.05 \times 10^{-1}$	$9.71 \pm 0.18 \times 10^{-1}$	13.7	−14.9
$SOCH_3$	$4.93 \pm 0.14 \times 10^{-1}$	1.56 ± 0.02	13.7	−13.9

discussion than has been found in most homoaromatic systems.[11]

Reported values of ρ for nucleophilic homoaromatic substitution range from +3.874 for the reaction of methoxide with 4-substituted 2-nitrochlorobenzene[12] to the unusually high value of +9.2 for the reaction of methoxide with substituted fluorobenzenes.[13] Our value of +6.82 for ρ ($r = 0.92$) indicates that electron-withdrawing substituents in the 6-position of pyridazines facilitate displacement of chloride by methoxide. This large value for ρ suggests that this reaction is very sensitive to the nature of the substituent. We tentatively ascribe this effect to resonance interaction between the annular nitrogen in the 1-position and the substituent in the 6-position, such that electron withdrawal by the substituent increases the positive character of the nitrogen in the 1-position and thus its electron demand. Although this nitrogen in the 1-position is β to the reaction site and cannot, therefore, affect it by resonance, the influence of its inductive power alone must be great. This can be deduced from comparison of the following reaction rates: 2-chloropyrimidine and ethoxide react 10^6 times as fast as do 2-chloropyridine and ethoxide, both in ethanol and at 20°,[4] and we have found that 2-chloropyridine does not react appreciably with methoxide under the same conditions required for 85% completion of the reaction of 3-chloropyridazine with methoxide.

Experimental[14]

Materials.—Dry methanol and sodium methoxide in methanol were stored in the absence of carbon dioxide and moisture and were dispensed from siphons. The concentration of sodium methoxide in solution was determined by hydrolysis of aliquots and titration with standard acid. The methoxide solution was stable throughout the duration of the experimental work.

The pyridazines were, with two exceptions, prepared by following published procedures and were crystallized from the solvents indicated: 3-chloropyridazine (**1**) from ligroin–ether, m.p. 34–35°, lit.[15] m.p. 35°; 3,6-dichloropyridazine (**9**) from cyclohexane, m.p. 66–68°, lit.[16] m.p. 68°; 3-chloro-6-methoxypyridazine (**3**) from benzene, m.p. 90–91°, lit.[17] m.p. 90.5°; 3-chloro-6-methylpyridazine (**2**) from ligroin, m.p. 61°, lit.[18] m.p. 61°; 3-chloro-6-carboxypyridazine (**7**) from ether, m.p. 145–146°, lit.[15] m.p. 146°; 3-chloro-6-methylthiopyridazine (**4**) from ligroin, m.p. 104°, lit.[19] m.p. 104°; 3-chloropyridazine-6-sulfonic acid (**5**) from ether–ligroin, m.p. 248°, lit.[20] m.p. 248–249°.

3-Chloro-6-methylsulfinylpyridazine (6).—A solution of **4** (16.0 g., 0.1 mole) in glacial acetic acid (200 ml.) was treated with 30% hydrogen peroxide (40 ml.) at room temperature and was left for 24 hr. The reaction was slightly exothermic during the first 3 hr. The solution was concentrated *in vacuo* at room temperature to a small volume and was chilled in ice. The solid that precipitated was filtered and recrystallized twice from absolute ethanol. The white crystals, 13.0 g. (74%), had m.p. 110–112°. The infrared spectrum of the product in chloroform exhibited a strong absorption at 9.58 μ, which is characteristic of the sulfoxide group.[21]

Anal. Calcd. for $C_5H_5ClN_2OS$: C, 34.00; H, 2.84; Cl, 20.11. Found: C, 33.84; H, 2.76; Cl, 19.8.

3-Chloro-6-carbomethoxypyridazine (8).—A solution of **7** (6.3 g., 0.04 mole) in ether (500 ml.) was treated with a solution of diazomethane in ether until only a slight excess of diazomethane remained. The mixture was stored overnight and the ether was distilled. The residue was crystallized from ligroin to yield fine white needles, 5.1 g. (73%), m.p. 104–105°.

Anal. Calcd. for $C_6H_5ClN_2O_2$: C, 41.8; H, 2.90; Cl, 20.57. Found: C, 41.61; H, 2.79; Cl, 20.19.

Kinetics.—For 3 at 40.2° and for 2 and 4 at 25.4°.—Solutions of known concentration of the pyridazine in dry methanol and of sodium methoxide in methanol were mixed, and 5-ml. portions of the well-shaken solution were transferred into glass ampoules which were sealed and immersed in the thermostated bath. The time of immersion was taken as zero time. Each ampoule was removed at a different time interval, opened, and its contents were flushed into about 150 ml. of ice–water. The alkali was titrated with standard acid.

For All Other Pyridazines at 25.4° and 40.2°.—Accurately measured volumes of a solution of known concentration of the pyridazine in dry methanol and of sodium methoxide solution were pipetted into separate chambers of a divided flask which was immersed in a bath thermostated at 25.4 or at 40.2°. After thermal equilibrium had been attained, the contents of the flask were mixed at zero time. Aliquots were removed with a calibrated pipet, quenched in ice–water, and titrated with standard acid. Between sample removals, the flask was tightly stoppered.

Stock solutions of the pyridazines (0.2396 M) were freshly prepared for each series of runs and the concentrations of reactants were varied by using different volumes of these solutions with or without addition of dry methanol. The ratio of concentrations of reactants was thus varied by at least a factor of four with respect to each other, and three independent runs were made inside this concentration range for each compound.

Calculations.—The rate constants were obtained graphically from a plot of $1/(a - x)$ or $[1/(b - a)] \log [a(b - x)/b(a - x)]$ against time. ΔH^* and ΔS^* were determined as described by Bunnett.[22]

Product Analyses.—The products of reaction of **2**, **3**, **4**, and **9** were obtained from the reactions of 0.01 mole of these pyridazines with an equimolar amount of sodium methoxide in refluxing methanol. The solvent was distilled, and the product

(11) H. van Bekkum, P. K. Verkade, and B. M. Wepster *Rec. trav. chim.*, **78**, 815 (1959).

(12) J. Miller, *J. Am. Chem. Soc.*, **79**, 93 (1957).

(13) J. Miller, *Australian J. Chem.*, **9**, 61 (1956).

(14) Melting points were determined on a Fisher-Johns block and are uncorrected.

(15) R. F. Homer, H. Gregory, W. G. Overend, and L. F. Wiggens, *J. Chem. Soc.*, 2195 (1948).

(16) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

(17) N. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 776 (1955).

(18) W. G. Overend and L. F. Wiggens, *J. Chem. Soc.*, 249 (1947).

(19) G. R. Duffin and J. D. Kendall, *ibid.*, 3789 (1959).

(20) N. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 1245 (1955).

(21) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen, London, 1958, p. 358.

(22) J. F. Bunnett, "Techniques of Organic Chemistry," Vol. VIII, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 199

was extracted into boiling hexane. Partial evaporation of the hexane and cooling in ice yielded the product which was crystallized from hexane. The product obtained in each case was as follows: from **3**, 3,6-dimethoxypyridazine, 74%, m.p. 107–108°, lit.[23] m.p. 108°; from **4**, 3-methoxy-6-methylthiopyridazine, 89%, m.p. 86°, lit.[24] m.p. 87°; from **9**, 3-chloro-6-methoxypyridazine (**3**), 78%, m.p. 90–91°, lit.[17] m.p. 90.5°. From **2**, 3-methoxy-6-methylpyridazine hydrochloride was obtained by addition of dry hydrogen chloride to a solution of the reaction product in hexane, m.p. 130–132°, lit.[25] m.p. 131–132°.

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(23) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).
(24) Noboru Takahayashi, *J. Pharm. Soc. Japan*, **75**, 778 (1955).
(25) W. G. Overend, L. M. Turton, and L. F. Wiggens, *J. Chem. Soc.*, 3500 (1950).

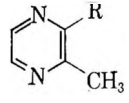
Amino Derivatives of Pyrazine N-Oxides[1]

WILSON B. LUTZ, SAM LAZARUS, SYLVESTER KLUTCHKO, AND ROBERT I. MELTZER

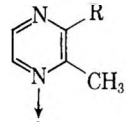
The Warner-Lambert Research Institute, Division of Basic Sciences, Morris Plains, New Jersey

Received December 26, 1963

In connection with a program of synthesis of a variety of pyrazine derivatives, we had occasion to prepare several pyrazine N-oxides. The treatment of 2-chloro-3-methylpyrazine[2] (Ia) with hydrogen peroxide afforded the N-oxide IIa,[3] melting at 74–76°, in fair yield. IIa reacted exothermically with piperidine to give a crystalline derivative (IIb) melting at 98–100°. The latter showed a very slight basicity as reflected in the low ionophoretic mobility in 5 *M* acetic acid. The



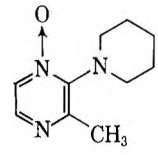
Ia, R = Cl
b, R = 1-piperidyl



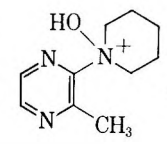
IIa, R = Cl
b, R = 1-piperidyl

piperidino derivative IIb was smoothly deoxygenated by phosphorus trichloride to give 2-piperidino-3-methylpyrazine (Ib). The properties of the free base and its hydrogen sulfate salt were found to be identical with authentic materials prepared by a different route.[4] This shows that the N-oxide obtained from commercial 2-chloro-3-methylpyrazine has structure IIa and is not derived from 2-chloro-6-methylpyrazine known to be present in significant amount in commercial Ia.[4] Similarly, reaction of the N-oxide IIa with dimethylamine resulted in dimethylamino-3-methylpyrazine N-oxide.

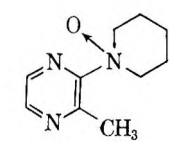
When 2-piperidino-3-methylpyrazine was treated with hydrogen peroxide in acetic or formic acid, two products were formed. One of these, obtained in very small yield, melted at 47–49° and showed an ionophoretic mobility similar to IIb. Elemental analyses were in good agreement with values calculated for an N-oxide isomeric with IIb. Since both the ultraviolet and infrared spectra differed widely from that of IIb, structure III was assigned. The bulk of the material obtained from the reaction mixture was a compound much less soluble in ligroin than III and with a high iono-



III



IV

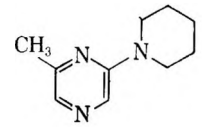


V

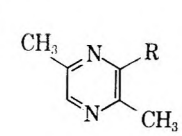
phoretic mobility. Elemental analyses were in agreement with a hydrate of a structure isomeric with IIb or III. Aqueous solutions showed a distinctly alkaline reaction. The ultraviolet spectrum was quite different from either IIb or III and was very similar to that of 2-methylpyrazine. It is well known[5,6] that, although the ultraviolet spectra of aniline and benzene differ greatly, the spectrum of the anilinium ion is very much like that of benzene. The structure of the compound in question must then be IV in which the "onium" center prevents participation of the amino nitrogen in resonance with the ring. Dehydration of IV to V by sublimation was not quite complete as the elemental analysis showed a small residual water content. The strong tendency for V to exist as the hydrate IV is characteristic of aliphatic-type N-oxides.[7]

The oxidation of 2-piperidino-6-methylpyrazine (VI) with hydrogen peroxide in formic acid gave a much more complicated reaction mixture than in the case of the isomeric Ib. However, on the basis of ionophoretic data it is clear that the compound to which structure III has been assigned did not arise from VI, conceivably present as a contaminant in starting material Ib.

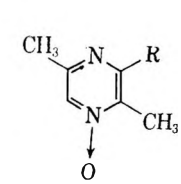
In the 2,5-dimethylpyrazine series, 2-chloro-3,6-dimethylpyrazine (VIIa) was converted to the oxide VIIIa[8] and the latter to the dimethylamino derivative VIIIb. The ultraviolet spectrum of VIIIb was very similar to that of IIb but unlike that of III. In boiling acetic anhydride, VIIIb was converted to the ester IXa which was not isolated but was saponified directly to the alcohol IXb. Structure Xc is excluded because this compound was prepared as described below and shown



VI



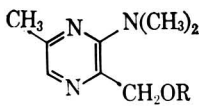
VIIa, R = Cl
b, R = $N(CH_3)_2$



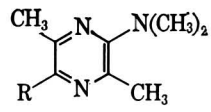
VIIIa, R = Cl
b, R = $N(CH_3)_2$

(1) Presented at the 144th Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.
(2) Wyandotte Chemicals Corp., Wyandotte, Mich.
(3) B. Klein, N. E. Hetman, and M. E. O'Donnell, *J. Org. Chem.*, **28**, 1682 (1963).
(4) W. B. Lutz, S. Lazarus, S. Klutchko, and R. I. Meltzer, *ibid.*, **29**, 415 (1964).
(5) G. W. H. Cheeseman, *J. Chem. Soc.*, 269 (1960).
(6) D. J. Brown, E. Hoerger, and S. F. Mason, *ibid.*, 4053 (1955).
(7) N. V. Sidgewick, "The Organic Chemistry of Nitrogen," New Ed., Oxford University Press, London, 1933, p. 166.
(8) R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1859 (1948).

to be quite unlike IXb. Furthermore, Klein[9] has shown that in the pyrazine series, rearrangement of an N-oxide will not occur unless a methyl group is *ortho* to the oxide function. The treatment of VIIIb with phosphorus oxychloride in benzene afforded 2-dimethylamino-5-chloro-3,6-dimethylpyrazine Xa in good yield. It was subsequently discovered that the same compound could also be obtained by the direct chlorination of VIIb in chloroform.



IXa, R = acetyl
b, R = H



Xa, R = Cl
b, R = OCH_3
c, R = OH
d, R = $N(CH_3)_2$

The chlorine atom of Xa was found to be relatively unreactive, but, under forcing conditions, nucleophilic substitution products could be obtained. With sodium methoxide, a 23% yield of the methyl ether Xb was obtained as the hydrochloride and, with dimethylamine, 2,5-bis(dimethylamino)-3,6-dimethylpyrazine (Xd) was obtained in 32% yield as the dihydrochloride. The hydrochloride of Xb lost methyl chloride at the melting point to give 2-dimethylamino-3,6-dimethyl-5-hydroxypyrazine (Xc). On a preparative scale, the demethylation could be carried out with concentrated hydrochloric acid. The ultraviolet spectrum of Xc showed a continuous shift in basic, neutral, and acidic aqueous media in accord with its expected amphoteric properties.

Experimental[10]

2-Chloro-3-methylpyrazine 4-Oxide (IIa).—A solution of partially purified commercial 2-chloro-3-methylpyrazine[4] in 300 ml. of acetic acid was treated with 400 ml. of 30% hydrogen peroxide at 65–70° for 8 hr. After standing at room temperature overnight most of the acetic acid and excess hydrogen peroxide were removed on a rotary evaporator at 25° (1 mm.). Water (200 ml.) was added to the residue and similarly removed. The residue was again dissolved in water containing ice and the pH was adjusted to 8 with potassium carbonate. The separated white solid was taken up in chloroform, and the solution was dried over potassium carbonate. The residue, after removal of chloroform, was triturated with petroleum ether (b.p. 30–60°). The resulting crystals on recrystallization from 1:9 benzene–ligroin (b.p. 65–70°) gave a 37% yield of product melting at 74–76°, lit.[3] m.p. 69–71.5°; $\lambda_{max}^{1\ N\ HCl}$ 223 mμ (log ε 4.15) and 265 (4.03).

Anal. Calcd. for $C_5H_5ClN_2O$: C, 41.54; H, 3.49; N, 19.38. Found: C, 41.58; H, 3.64; N, 19.58.

2-Piperidino-3-methylpyrazine 4-Oxide (IIb) and 2-Dimethylamino-3-methylpyrazine 4-Oxide.—A mixture of 2-chloro-3-methylpyrazine 4-oxide, 5.9 g. (0.041 mole), and 100 ml. of piperidine was kept at reflux for 8 hr. The mixture was cooled, piperidine hydrochloride was removed by filtration, and the solvent was removed on a rotary evaporator. The yellow residue was dissolved in 25 ml. of warm benzene, decolorized with charcoal, and diluted with 50 ml. of petroleum ether. White crystals separated on cooling. The product weighed 6.4 g. (81%), m.p. 98–100°. Recrystallization from ligroin afforded analytically pure material with the same melting point.

2-Dimethylamino-3-methylpyrazine 4-oxide was prepared by keeping a solution of 14.5 g. of the chloro N-oxide IIa in 50 ml. of dimethylamine in a sealed tube for 2 days at room temperature. Work-up similar to the above afforded 13.1 g. (86%) of white crystals, m.p. 87–90°. Recrystallization from ligroin gave analytically pure material melting at 89–91°; $\lambda_{max}^{1\ N\ HCl}$ 217 mμ (log ε 3.83), 256 (4.29), and 365 (3.80).

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.33; H, 8.10; N, 21.64.

Deoxygenation of 2-Piperidino-3-methylpyrazine 4-Oxide (IIb).—To 15 ml. of phosphorus trichloride was added 0.5 g. of 2-piperidino-3-methylpyrazine 4-oxide. A vigorous exothermic reaction ensued, but no attempt to control the temperature was made. After 15 min., excess phosphorus trichloride was removed *in vacuo* and the residue was treated with 15% potassium carbonate. The colorless oil which separated was extracted with 100 ml. of ether. The extract was washed with 15 ml. of water and dried over magnesium sulfate. The filtered solution was then evaporated to give 0.4 g. (89%) of a colorless oil. A Beilstein test for halogen was negative and the infrared spectrum was identical with the spectrum of 2-piperidino-3-methylpyrazine.[4]

The sulfate prepared from this base melted at 132–134°, as did a mixture with authentic sulfate.[4] The infrared spectra were also identical.

1-Hydroxy-1-(3-methyl-2-pyrazinyl)piperidinium Hydroxide (IV).—A mixture of 20.1 g. (0.11 mole) of 2-methyl-3-piperidinopyrazine, 14 ml. (0.22 mole) of 30% hydrogen peroxide, and 45 ml. of formic acid was allowed to stand at room temperature for 4 days. An additional 7 ml. of hydrogen peroxide was added on the third day. The mixture was made strongly basic with 10 *M* potassium hydroxide and extracted with chloroform. The extract was dried over potassium carbonate and concentrated on a rotating evaporator. The resulting pasty solid was treated with ligroin (b.p. 65–70°). The insoluble portion was washed with ligroin to give 18 g. (84%) of a white solid, m.p. 70–86°. After recrystallization from ethyl acetate and exposure to moist air, the product melted at 94–97°; $\lambda_{max}^{1\ N\ HCl}$ 263 mμ (log ε 3.81), 266 (3.81), and 291 (3.06).

Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 56.84; H, 8.11; N, 19.89. Found: C, 56.67; H, 8.25; N, 19.75.

2-Piperidino-3-methylpyrazine 1-Oxide (III).—Evaporation of the ligroin filtrate from the above preparation gave a white crystalline solid, m.p. 50–52°. After sublimation at 0.02 mm., the product weighed 0.2 g. (1%) and melted at 47–49°; $\lambda_{max}^{1\ N\ HCl}$ 221 mμ (log ε 3.81), 295 (3.53), and 325 (3.53); $\lambda_{min}^{1\ N\ HCl}$ 308 mμ (log ε 3.40). The material exhibited no tendency to hydrate, and had a very low ionophoretic mobility; the infrared and ultraviolet spectra were found to be quite different from that of the isomeric IIb.

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.04; H, 8.11; N, 21.69.

Preparation of 2-Dimethylamino-3-hydroxymethyl-6-methylpyrazine Hydrochloride (IXb).—A solution of 8.0 g. (0.048 mole) of 2-dimethylamino-3,6-dimethylpyrazine 4-oxide in 25 ml. acetic anhydride was maintained at reflux for 2 hr. and stripped of acetic anhydride; the crude ester was dissolved in 200 ml. of methanol. The solution was treated with 80 ml. of 10 *M* potassium hydroxide and maintained at reflux for 15 min. Water (200 ml.) was added and traces of dark, undissolved material were removed by filtration. Removal of most of the methanol gave more dark tar which was removed by decantation. Potassium carbonate, 100 g., was then added and the resulting oil was extracted with 1 l. of ether. The ether solution was treated with charcoal and anhydrous potassium carbonate and filtered. The light yellow filtrate was treated with hydrogen chloride to give a greenish, tacky salt which soon crystallized. The ether was decanted and the residue was washed several times with ether to give 3.5 g. of hygroscopic yellow solid.

Recrystallization from 25 ml. of 2-propanol afforded 1.5 g. (15%) of light yellow green solid, m.p. 135–138°.

An analytical sample was prepared by recrystallization from 2-propanol; m.p. 141–142°; λ_{max} (hydrochloride in water) 239 mμ (log ε 3.74), 260 (3.01), and 318 (3.91).

Anal. Calcd. for $C_8H_{13}N_3O \cdot HCl$: C, 47.17; H, 6.93; N, 20.63. Found: C, 47.43; H, 7.11; N, 20.70.

2-Dimethylamino-5-chloro-3,6-dimethylpyrazine Hydrochloride (Xa). Method A.—Chlorine was bubbled into a stirred solution of 15.1 g. (0.1 mole) of 2-dimethylamino-3,6-dimethyl-

(9) B. Klein, J. Berkowitz, and N. E. Hetman, *J. Org. Chem.*, **26**, 126 (1961).

(10) Infrared spectra were run on a Baird 455 spectrograph, and ultraviolet spectra were run on a Beckman DK-1. Melting points were taken in capillaries using Anschutz thermometers in a Hershberg apparatus and are therefore corrected. Ionophoreses were run in 5 *M* acetic acid on Whatman No. 1 paper at *ca.* 30 v./cm. N.m.r. spectra were run on a Varian A-60 with tetramethylsilane as standard.

pyrazine[11] in 200 ml. of chloroform. The temperature rose to near the boiling point, and the color became yellow, then yellow-brown, and finally light yellow again. The chlorine was passed in at a moderate rate for a total of 0.5 hr. Most of the chloroform was removed and 150 ml. of ether was added. The light yellow hygroscopic solid that separated was filtered and washed with ether.

Recrystallization was effected by dissolving the solid in 150 ml. of hot acetonitrile and adding ether until turbid. Crystals quickly separated and were filtered and washed with 1:1 acetonitrile–ether. The almost white crystals weighed 8.8 g., m.p. 155–157°; λ_{max} (hydrochloride in ethanol) 260 mμ (log ε 4.05) and 332 (3.76). A second crop weighed 1.5 g., m.p. 150–153°, to give a total of 10.2 g. (45.9%).[12]

Anal. Calcd. for $C_8H_{12}ClN_3 \cdot HCl$: C, 43.26; H, 5.90; N, 18.92. Found: C, 43.17; H, 6.16; N, 18.64.

In another run using prolonged reaction time and increased rate of chlorine addition, a sparingly soluble, weakly basic polychlorination reaction product was obtained in 20% yield. Two recrystallizations from 2-propanol afforded material of constant melting point (113–115°). The analysis corresponded fairly closely to a tetrachloro derivative. Only three halogens could be replaced by silver nitrate in ethanol. N.m.r. studies showed proton resonances at 2.63 and 3.08 p.p.m., with the integrated intensities being in the proportion 1:2, respectively. The above data are consistent with a compound in which three of the chlorines are located on one methyl group and one chlorine is on the ring.

Anal. Calcd. for $C_8H_9Cl_4N$: C, 33.25; H, 3.14; N, 49.08. Found: C, 33.54; H, 3.38; N, 48.60.

2-Dimethylamino-5-chloro-3,6-dimethylpyrazine Hydrochloride (Xa). Method B.—A solution of 5.1 g. (0.03 mole) af 2-dimethylamino-3,6-dimethylpyrazine 4-oxide,[13] 100 ml. of benzene, and 15 ml. of phosphorus oxychloride was maintained at reflux for 15 min. The reddish solution was freed of benzene and most of the excess phosphorous oxychloride. On the addition of 200 ml. of ether to the viscous residue, tan crystals gradually formed. The solid was filtered, washed with 20 ml. of ether, and dried in a vacuum desiccator to give 2.5 g. (37.5%) of white crystals, m.p. 149–152°.

Recrystallization from acetonitrile–ether afforded an analytical sample melting at 153–154°. The infrared spectrum was identical with that of the product obtained by direct chlorination.

2-Dimethylamino-5-methoxy-3,6-dimethylpyrazine Hydrochloride (Xb).—A solution of 0.06 mole of sodium methoxide and 5.55 g. (0.0297 mole) of 2-dimethylamino-5-chloro-3,6-dimethylpyrazine in 50 ml. of methanol was heated in a Carius tube at 125° for 18 hr. Sodium chloride was removed by filtration and the solvent was removed on a rotary evaporator. Water was added and the separated oil was extracted into ether. The dried ($MgSO_4$) yellow-green solution was treated with dry hydrogen chloride to give a yellow, partly crystalline solid. This was filtered and washed with 20 ml. of ether to give 4.4 g. of a hygroscopic solid.

Recrystallization from 25 ml. of hot ethyl acetate gave 1.5 g. (23.3%) of light yellow crystals melting at 128° with bubbling and resolidification and remelting at 232–234°. Further recrystallization from ethyl acetate gave a product which melted at 154–156° and resolidified and remelted at 232–234°.

Anal. Calcd. for $C_9H_{15}N_3O \cdot HCl$: C, 49.65; H, 7.41; N, 19.30. Found: C, 49.67; H, 7.67; N, 19.17.

2-Dimethylamino-5-hydroxy-3,6-dimethylpyrazine Hydrochloride (Xc).—A solution of 8.0 g. (0.0398 mole) of 2-dimethylamino-5-methoxy-3,6-dimethylpyrazine hydrochloride in 100 ml. of concentrated hydrochloric acid was maintained at reflux for 3 hr. and evaporated to dryness on a rotary evaporator. The remaining crude brown solid was sublimed at 140° (0.01 mm.) to give 4.5 g. (56%) of orange sublimate, m.p. 225–230°.

Recrystallization from 100 ml. of ethyl acetate gave 3.2 g. of a light orange solid, m.p. 235–240°; $\lambda_{max}^{H_2O}$ 230 mμ (log ε 3.94) and 323 (3.76). Infrared absorption of a mull showed strong bands at 1636 and 1684 cm.$^{-1}$, indicating that the material exists largely as a lactam.

Anal. Calcd. for $C_8H_{13}N_3O \cdot HCl$: C, 47.17; H, 6.93; N, 17.41. Found: C, 47.28; H, 7.01; N, 17.40.

2,5-Bis(dimethylamino)-3,6-dimethylpyrazine Dihydrochloride (Xd).—A mixture of 11.1 g. (0.05 mole) of 2-dimethylamino-5-chloro-3,6-dimethylpyrazine and 50 ml. of liquid dimethylamine was heated in a steel bomb for 18 hr. at 200°. The solvent was removed. The oily residue was treated with 50 ml. of water and 100 ml. of 50% potassium carbonate and extracted with 800 ml. of ether. The dried (K_2CO_3) solution was filtered and the ether was evaporated to give 3.4 g. of a light yellow oil. This was dissolved in 35 ml. of 2-propanol and treated with dry hydrogen chloride. The light yellow solid was filtered and washed with 2-propanol and ether to give 4.2 g. (32%) of white solid, m.p. 173–175° dec.

Recrystallization from ethanol–ether (1:1) afforded 3.9 g. of analytically pure material, m.p. 176–178°; λ_{max} (hydrochloride in ethanol) 263 mμ (log ε 4.03) and 337 (3.77).

Anal. Calcd. for $C_{10}H_{18}N_4 \cdot 2HCl$: C, 44.95; H, 7.55; N, 20.97. Found: C, 45.06; H, 7.84; N, 20.74.

Acknowledgment.—We wish to acknowledge the services of the Analytical and Physical Chemistry Section, under the supervision of Mr. Arnold D. Lewis, for physical analytical data. In particular we want to thank Mr. Thomas Wilderman, Mrs. Unni Zeek, and Miss Awilda Calenti for microanalyses; Mrs. Barbara Kane, Mr. Robert Puchalski, and Mr. Joseph Brooks for infrared and ultraviolet spectra and interpretations; and Miss Marianne Garofalo for gas–liquid chromatograms. The technical assistance of Mr. Jerry Cetenko and Mr. George Conrad is also gratefully acknowledged.

(11) H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

(12) A 70% crude yield was subsequently obtained by using a solution of chlorine (slight excess) in chloroform and maintaining the temperature at 35°.

(13) Prepared similarly to IIb, this material melted at 89–91°; $\lambda_{max}^{1 N HCl}$ 212 mμ, (log ε 3.89), 252 (4.30), and 358 (3.78). *Anal.* Calcd. for $C_7H_{11}N_3O$: C, 54.88; H, 7.24; N, 27.43. Found: C, 55.00; H, 7.53; N, 27.54.

6-Cyano-1,2,5,6-tetrahydropyridines in the Preparation of 1,2-Dihydropyridines. Tautomerism of the Dienes

E. M. FRY

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

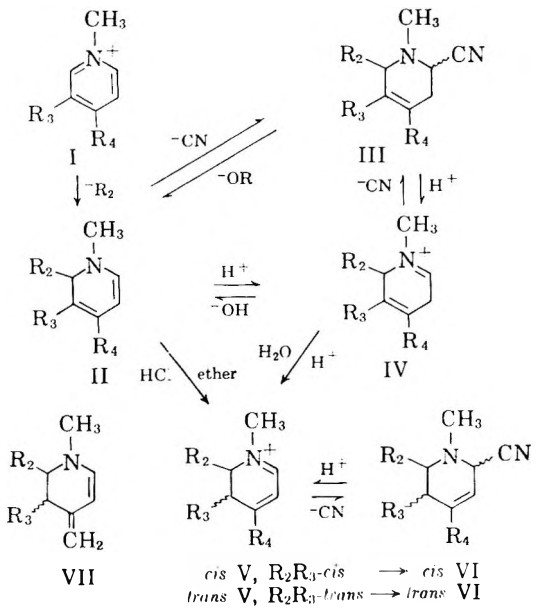
Received December 6, 1963

In the study of a 1,2-dihydropyridine for use in the synthesis of a β-benzomorphan, rearrangements leading to both a *cis*- and *trans*-2,3-dialkyldihydropyridine were encountered.[1] It was demonstrated that the *cis*-dialkylimonium salt was formed by stepwise migration of double bonds, whereas the *trans* isomer probably resulted from a concerted rearrangement of the ammonium salt. This note presents other examples of stepwise rearrangements in 1,2-dihydropyridine systems together with another example of control of the 2,3-dialkyl steric relationship. Perhaps of more general interest is a description of the use of the cyano as a protecting group in the preparation of 1,2-dihydropyridine bases by both the Grignard and borohydride reagents.

Recent work with the borohydride reagent on N-alkylpyridines suggests that, after the initial dihydro stage is reached, further reduction depends on the tautomerism of an α,β double bond to the imonium form and that unless this transformation is inhibited

(1) E. M. Fry, *J. Org. Chem.*, **28**, 1869 (1963).

CHART I



the end result is a tetrahydropyridine.[2] Substrates with N-phenyl[3] or N-glucoside[4] groups or with a substituent on the unsaturated α-[5] or β-carbon[2,6] appear to resist reduction beyond the dihydro stage and some degree of success in stopping at this point has been achieved in alkaline[4,5] solutions and by the use of other hydride reagents.[4,7]

Cyanide proved to be an effective competitor for the second active site when it was present in large excess in the alkaline sodium borohydride solution of pyridine, γ-picoline, and 3,4-lutidine N-methyl quaternary salts. Isolation of the nitriles was facilitated by means of ether and by the insolubility of these oils in the aqueous medium; small amounts of the tetrahydro products also were obtained. As is well known, nitrile groups on carbon α to tertiary nitrogen are subject to removal by hydride reagents and to what extent and under what conditions the nitriles described here might be made to survive in a homogeneous medium is not known. But as a practical matter the distribution of any imonium salt and its product cyano base between polar and nonpolar immiscible solvents should make this separation generally feasible.

The structures of the di- and tetrahydro N-methylpyridines shown in Chart I are based on spectral evidence correlated with data obtained for members of the 2-benzyl-1,3,4-trimethyl series which were uniquely identified by ultimate conversion to α- and β-benzomorphans.[1]

The tetrahydronitriles III, obtained both through the Grignard reagent and by the action of borohydride on the pyridinium salts I, are characterized by lack of a maximum in the ultraviolet above 220 mμ. Making a solution weakly alkaline caused development of a band, characteristic of II, at 330 mμ and acidification of the nitrile solution gave a developing band at 290 mμ marking the formation of V. In compounds with a 3-substituent the position of the double bond and hence the site of attack was determined by n.m.r. The bases II were usually prepared by the action of alcoholic potassium ethoxide on the nitriles III. All of the bases examined were oils and had characteristic bands at 6.05 and 6.3 μ. Acidification of alcohol solutions of the bases gave the salts IV, each characterized by lack of a maximum above 220 mμ. Solutions of the perchlorates (IV) in methylene chloride showed characteristic bands at 5.85 and 5.95 μ. Both bands lie in the absorption region reported for Δ^1-tetrahydropyridinium perchlorates.[9] Only in the case of the unsubstituted ring did the infrared absorption fail to yield this evidence. Heating the nitriles III in acid gave the dienes V except for the two examples lacking a 4-substituent. The products in these cases remain unidentified. Presumably IV is the intermediate in the rearrangement to V and it is the form usually isolated from the Grignard reaction after decomposition with acid, but one instance (R_2 = $PhCH_2$, R_3 = H, R_4 = CH_3) was encountered in which the product of acid decomposition was the conjugated diene V.

Dienes IV and V were easily distinguishable not only in the ultraviolet but by means of the derived nitriles III and VI. The latter always had a very strong band at 11.2 μ, but otherwise was like the III isomer in that it had no maxima above 220 mμ and readily lost the cyano group in acidic or basic solution. In the above case, when decomposition of the Grignard solution was carried out in aqueous sodium cyanide solution the nitrile III was obtained. The II bases were not as a rule recoverable from the V salts or the VI nitriles by the action of base. Instead oils absorbing at 6.2 μ and 300 mμ were obtained. By analogy with the 2-benzyl-1,3,4-trimethyl derivative these probably are the *exo*-methylene bases VII.[10]

The experimental conditions necessary for the preparation of *trans* V (R_2, R_3, R_4 = CH_3) were limited compared with those which gave *trans* V (R_2 = $PhCH_2$; R_3, R_4 = CH_3). The addition of ethereal hydrogen chloride to an ethereal solution of 1,2-dihydro-1,2,3,4-tetramethylpyridine (II) under conditions which provided mixing at high dilution gave an oil which rapidly crystallized to give a 48% yield of *trans* V (R_2, R_3, R_4 = CH_3). As in the case of the 2-benzyl analog, the hydrochloride of II (R_2, R_3, R_4 = CH_3) rearranged in the aprotic solvent methylene chloride, whereas the perchlorate, structure IV, proved to be stable in this solvent.

Isomers *cis* V and *trans* V were distinguished by means of the tetrahydro bases obtained by replacing the cyano groups of the respective nitriles VI with hydrogen. These gave crystalline picrates having a similar melting range which was not depressed on admixture. However, the bases gave different infrared diagrams and could be

(2) R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Letters*, (**13**), 553 (1962).

(3) M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).

(4) (a) J. J. Panouse, *Bull. soc. chim. France*, D, 60 (1953); (b) J. J. Panouse, *Thèse de Doctorat ès Sciences* (Paris) (1952).

(5) N. Kinoshita and T. Kawasaki, *J. Pharm. Soc. Japan*, **83**, 126 (1963).

(6) W. Traber and P. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958); K. Schenker and J. Druey, *ibid.*, **42**, 1960, 2571 (1959); K. Wallenfels, H. Schüly, and D. Hofmann, *Ann.*, **621**, 106 (1959); T. Tsukamoto, N. Kinoshita, and A. Ando, *J. Pharm. Soc. Japan*, **82**, 1317 (1962); N. Kinoshita, M. Hamana, and T. Kawasaki, *ibid.*, **83**, 115 (1963).

(7) E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962).

(8) The infrared and ultraviolet absorption values given in the text are only approximate. For individual compounds see Experimental.

(9) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(10) No equilibrium observations were made. For a discussion of thermodynamic stability in cisoid *vs.* transoid cyclohexadienes, see R. B. Bates, R. H. Carnighan, and C. E. Staples, *ibid.*, **85**, 3030 (1963).

separated on a vapor column. The chromatograms of each revealed traces of the other along with a trace of the Δ^3-isomer.

Experimental

Microanalyses are by the Analytical Services Section of this Laboratory, Harold McCann, director. Ultraviolet spectra are by a Cary recording spectrophotometer, Model 14, and infrared spectra are by a Perkin-Elmer Infracord, Model 137. N.m.r. spectra, 60 Mc., are with tetramethylsilane as internal reference standard. Melting points are uncorrected.

6-Cyano-1,2,5,6-tetrahydropyridines (III). A. By Sodium Borohydride Reductions in Cyanide Solutions. 6-Cyano-1,4-dimethyl-1,2,5,6-tetrahydropyridine Hydrochloride.—Fifty milliliters of 6 *N* hydrochloric acid was added slowly to a solution of 50 g. (0.77 mole) of potassium cyanide in 100 ml. of water, layered with 150 ml. of ether, and kept below 15°. Fifty grams (0.21 mole) of γ-picoline methiodide was dissolved in the cold solution and 10 g. (0.26 mole) of sodium borohydride was added. The milky, mildly effervescing solution was allowed to warm to 25° and then held at this temperature by occasional cooling. After a total of 5 hr. the ether was separated, washed with water, chilled, and treated with 2 ml. of methyl iodide which reacted over 30 min. at 5° with over-reduced material to give a precipitate of 1,1,4-trimethyl-1,2,5,6-tetrahydropyridinium iodide. The ethereal solution was decanted into a stirred solution of 33 ml. of 6.5 *N* absolute ethanolic hydrochloric acid with separation of a crystalline solid, 27.2 g. (74%), m.p. 131–133°.

Anal. Calcd. for $C_8H_{14}ClN_2$: C, 55.65; H, 7.59; N, 16.23. Found: C, 55.29; H, 7.61; N, 16.11.

6-Cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine, made as above from 3,4-lutidine methiodide, was obtained crystalline in 49% yield from a cold petroleum ether (30–60°) solution of the crude product. It melted at 43–45°. The integrated n.m.r. spectrum showed no vinylic hydrogen and an unsplit C-CH_3 band (6H). Replacement of cyano by benzyl has been reported.[1]

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65. Found: C, 71.78; H, 9.49; N, 18.41.

2-Cyano-1-methyl-1,2,3,6-tetrahydropyridine hydrochloride, prepared by the detailed procedure above from pyridine methiodide, was freed of oil with cold acetone and stored over sodium hydroxide to remove adhering hydrogen chloride. The yield of product, m.p. 115–118° (gas), was 50%.

Anal. Calcd. for $C_7H_{11}ClN_2$: C, 53.00; H, 6.99; N, 17.66; Cl, 22.35. Found: C, 53.66; H, 7.05; N, 17.06; Cl, 21.98.

B. By the Action of Cyanide on Grignard Products (Evidence bearing on low yields is given in the last experiment in this section). **6-Cyano-1,2,3-trimethyl-1,2,5,6-tetrahydropyridine Perchlorate.**—The mixture from the action of methylmagnesium iodide on 1,3-dimethylpyridinium iodide was poured with stirring into a perchloric acid–ice mixture, the ether separated, and cold sodium cyanide solution added in excess to the cold acid solution. Alternately the Grignard mixture was poured into a sodium cyanide solution with stirring. The crude oily nitrile in ether solution was converted to the crystalline perchlorate by the addition of 9 *N* perchloric acid. After purification from acetone–ether, it melted at 116–121° and was obtained in 28–31% yield. Both procedures gave the same recovery. Recrystallized from 9 *N* perchloric acid, the salt melted at 165–168° (gas). A return to the lower melting form was made in acetone. Infrared diagrams of the bases recovered from the dimorphic salts were identical.

Anal. Calcd. for $C_9H_{15}ClN_2O_4$: C, 43.12; H, 6.03; N, 11.18. Found: C, 43.23; H, 6.26; N, 10.98.

2-Benzyl-6-cyano-1,4-dimethyl-1,2,5,6-tetrahydropyridine.—A cold aqueous solution of sodium cyanide was added with stirring to the chilled suspension resulting from the action of the benzyl Grignard reagent on 1,4-dimethylpyridinium iodide. The ether was separated and distilled, the last portion being removed under reduced pressure. A solution of the oil in petroleum ether (30–60°) deposited crystals which, after trituration in cold alcohol to remove oil, were recovered in 23–29% yield. Recrystallized from petroleum ether, the material melted at 76–78°.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02. Found: C, 79.83; H, 7.98.

6-Cyano-1,2,3,4-tetramethyl-1,2,5,6-tetrahydropyridine was obtained in the same way as was described for the 1,2,3-trimethyl analog. The oily hydrobromide separated on passing hydrogen bromide into a solution in ether. It was induced to crystallize from cold acetone and was obtained in 36–41% yields. It melted at 152–153° (gas).

Anal. Calcd. for $C_{10}H_{17}BrN_2$: Br, 32.60. Found: Br, 32.55.

The **perchlorate** crystallized on addition of perchloric acid to an aqueous solution of the hydrobromide. It melted at 150–152°.

Anal. Calcd. for $C_{10}H_{17}ClN_2O_4$: C, 45.37; H, 6.48. Found: C, 45.17; H, 6.70.

2,5-Dihydropyridinium (IV) Perchlorates.—The only member of this group which has been obtained crystalline is the previously described 2-benzyl-1,3,4-trimethyl-2,5-dihydropyridinium perchlorate.[1] The others are characterized by the infrared absorption of the perchlorates, made *in situ* in methylene chloride, and by the absence of significant maxima in the ultraviolet immediately after acidification of the bases (II) (Table I).

TABLE I

R_3	R_5	R_6	Infrared,[a] μ
H	H	CH_3	5.80 (m), 5.95 (w)
H	CH_3	CH_3	5.79 (m), 5.91 (m)
CH_3	CH_3	H	5.84 (w), 5.96 (m)
CH_3	CH_3	CH_3	5.84 (m), 5.95 (m)
$PhCH_2$	H	CH_3	5.85 (m), 5.97 (m)
$PhCH_2$	CH_3	CH_3[b]	5.86 (m), 5.96 (m)

[a] m, medium; w, weak. [b] Previously reported in ref. 1.

To what extent an accompanying absorption at 6.24 μ is due to water in solvent methylene chloride is not known.

1,2-Dihydropyridines (II).—These bases are oils subject in varying degree to self-condensation (loss of volatility) and oxidation (development of color). They were most satisfactorily obtained by the action of 2.6 *N* potassium ethoxide (10 vol.) on the nitriles at room temperature. Under these conditions the condensation was minimized. The progress of the reaction was marked by precipitation of a salt, presumably potassium cyanide, over several hours, and could be followed in the ultraviolet. Finally, the alcohol solution was diluted with an equal volume of petroleum ether (30–60°), water added and mixed, the petroleum ether layer separated, and the solvent removed under reduced pressure. The recorded ultraviolet values were obtained by diluting 0.02 ml. of the preparative solution with ethanol; the infrared observations were made on the neat oils unless otherwise noted (Table II).

TABLE II

R_3	R_5	R_6	Infrared,[a] μ, all strong bands	Ultraviolet, mμ (ε)
H	H	H	6.08, 6.35 (CH_2Cl_2)	335 (2100)
H	H	CH_3	6.05, 6.33	330 (2200)
H	CH_3	CH_3	6.02, 6.26	322 (2500)
CH_3	CH_3	H	6.08, 6.32	330 (4200)
CH_3	CH_3	CH_3	6.05, 6.30	323 (4000)
$PhCH_2$	H	CH_3	6.06, 6.24 (sh), 6.35	330 (3500)
				253 (hump)
$PhCH_2$	CH_3	CH_3[b]	6.05, 6.23 (sh), 6.32	275 (4100)
				325 (3800)

[a] sh, shoulder. [b] Previously reported in ref. 1.

4-Methylene-1,2,3,4-tetrahydropyridines (VII).—The bases were obtained by the action of potassium ethoxide on the nitriles VI, or by sodium hydroxide on the salts V. All were oils and were characterized by ultraviolet and infrared bands (Table III). Contamination by the endocyclic dienes was usually evident, more so with the bases derived from the *cis* V salts than with those from the *trans*, and, in one case (R_2 = $PhCH_2$, R_3 = H, R_4 = CH_3), the presence of the exocyclic base was dubious.

2,3-Dihydropyridinium (*cis* and *trans* V) Chlorides.—The nitriles III lost hydrogen cyanide in hot 2.2 *N* hydrochloric acid to give the imonium salts *cis* V, and the reaction was readily followed by development of absorption in the ultraviolet. The infrared data are on oils obtained either by chloroform extraction of the aqueous acid solutions, or from the action of alcoholic acid on the nitriles VI (Table IV). The *trans* V sample (R_2 = R_3 = R_4 = CH_3) was formed rapidly when hydrogen chloride was passed

TABLE III

R_2	R_3	R_4		Infrared,[a] μ	Ultraviolet, mμ (ε)
H	H	CH_3		6.09 (m), 6.18 (m), 6.36 (m)	292 (2700)
H	CH_3	CH_3		6.0 (sh); 6.14 (s), 6.25 (sh)	291 (5700)
CH_3	CH_3	CH_3	*cis*	6.05 (sh), 6.18 (m), 6.3 (sh)	302 (6000)
			trans	6.16 (s)	299 (15000)
$PhCH_2$	CH_3	CH_3[b]	*cis*	6.06 (s), 6.18 (sh), 6.32 (s)	282 (4600), 300–315 (4400)
			trans	6.17 (s)	302 (14200)

[a] s, strong; m, medium; w, weak; sh, shoulder. [b] Reported in ref. 1.

TABLE IV

R_2	R_3	R_4		Infrared,[a] μ	Ultraviolet, mμ (ε)
H	H	CH_3		5.96 (m), 6.22 (s)	288 (7100)
H	CH_3	CH_3		5.99 (m), 6.26 (s)	288 (5200)
CH_3	CH_3	CH_3	*cis*	6.0 (m), 6.25 (s)	292 (5500)
			trans	6.0 (m), 6.24 (s)	290 (6800)
$PhCH_2$	H	CH_3		6.0 (m), 6.24 (s)	285 (5700)
$PhCH_2$	CH_3	CH_3[b]	*cis*	6.01 (m), 6.29 (s)	298 (4400)
			trans	6.0 (m), 6.26 (s)	282 (5800)

[a] s, strong; m, medium. [b] Reported in ref. 1.

into a methylene chloride solution of the base II; the bands characteristic of the imonium salts IV were not observed. Its preparation is given below.

trans-**1,2,3,4-Tetramethyl-2,3-dihydropyridinium** (*trans* **V**) **Chloride.**—To 30 ml. of 0.01 *N* dry ethereal hydrogen chloride, contained in a three-neck flask equipped with two graduated separatory funnels and a stirrer, was added dropwise simultaneously through each funnel 3 ml. of a solution of the base in ether and 3 ml. of an ethereal solution of an equivalent amount of hydrogen chloride. The slightly oily crystalline material which formed was filtered and washed free of oil with acetone. In this manner 0.23 g. of 1,2,3,4-tetramethyl-1,2-dihydropyridine (II) gave 0.14 g. (48%) of the hydrochloride (*trans* V). The salt was hygroscopic. It was recrystallized by adding acetone to a solution in methylene chloride, m.p. 129–135°.

Anal. Calcd. for $C_9H_{16}ClN$: C, 62.23; H, 9.29; Cl, 20.41. Found: C, 61.47; H, 9.48; Cl, 20.25.

6-Cyano-1,2,3,6-tetrahydropyridines (VI).—These were made simply by adding enough aqueous sodium or potassium cyanide to cold solutions of salts V so that the final solution was alkaline. The nitriles were recovered with ether or petroleum ether and except for the following example were oils. **6-Cyano-1,4-dimethyl-1,2,3,6-tetrahydropyridine** was obtained crystalline in 60% yield. Recrystallized from petroleum ether (30–60°) it melted at 46–49°. The infrared spectra is given in Table V.

TABLE V

R_2	R_3	R_4		Infrared, μ, all strong bands
H	H	CH_3		11.37
H	CH_3	CH_3		11.25
CH_3	CH_3	CH_3	*cis*	11.27
			trans	11.27
$PhCH_2$	H	CH_3		11.32
$PhCH_2$	CH_3	CH_3[a]	*cis*	11.23
			trans	11.31

[a] Reported in ref. 1.

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 71.06; H, 9.00; N, 19.83.

1,2,3,4-Tetramethyl-1,2,5,6-tetrahydropyridine, obtained by the action of sodium borohydride on the nitrile as previously described,[1] gave a picrate in 55% over-all yield. Recrystallized from alcohol it melted at 155–158°. The integrated n.m.r. diagram of the base showed two unsplit methyl groups at τ 8.4, and one split methyl group centered at 8.9.

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 49.23; H, 5.27.

cis-**1,2,3,4-Tetramethyl-1,2,3,6-tetrahydropyridine picrate**, obtained as above in 60% yield, melted at 167–169°, slight previous sinter. It did not depress the melting point of the Δ^3-compound. The n.m.r. diagram showed one vinylic hydrogen at τ 4.7.

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 48.85; H, 5.27.

trans-**1,2,3,4-Tetramethyl-1,2,3,6-tetrahydropyridine.**—The crude material, obtained as above from the nitrile, was distilled at about 60° (10 mm.). It was converted to the picrate in 41% over-all yield (five steps) starting from the isomeric nitrile III. The base n.m.r. diagram showed one vinylic hydrogen at τ 4.6. The picrate melted at 162–165° and the melting point was not depressed on admixture with the *cis* isomer.

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 49.10; H, 5.56.

1,2,3-Trimethyl-1,2,5,6-tetrahydropyridine was obtained in like manner from the crystalline perchlorate of the cyano derivative (III). After distillation at <100° (9 mm.), it was converted to the picrate in an over-all yield of 45%. Recrystallized from alcohol, it melted 194–195°. Its n.m.r. spectrum showed one vinylic hydrogen at τ 4.55. This picrate was obtained also from the noncrystalline portion of the preparation of the nitrile III perchlorate in an amount that signified a yield increase of 50% over that represented by crystalline material. Diastereoisomerism of the nitriles is thereby indicated.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.10. Found: C, 47.46; H, 5.11.

Rearrangements of Alkoxypyridine 1-Oxides

FRANK J. DINAN[1] AND HOWARD TIECKELMANN

Department of Chemistry, State University of New York at Buffalo, Buffalo 14, New York

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Although a number of 2-alkoxypyridine 1-oxides are known,[2,3] thermal rearrangements of these compounds are, to our knowledge, unreported.[4] It was of interest to determine whether rearrangement of 2-alkoxypyridine 1-oxide (I) would give a mixture of products such as had been obtained from 2-alkoxypyridines[5] and 4-alkoxypyrimidines,[6] or whether exclusive rearrangement to either the 3-carbon or 1-oxygen atom would occur.

For this purpose, I was prepared by treatment of 2-chloropyridine 1-oxide[7] (II) with the sodium salt of allyl alcohol under mild conditions, a procedure similar to that previously used by Gardner and Katritzky for the preparation of other 2-alkoxypyridine 1-oxides.[3] Rearrangement of I took place under very mild conditions to give 1-alloxy-2-pyridone (III) in nearly quantitative yield.

The identification of I is based on infrared and ultraviolet spectral data as well as on the method of synthesis. The infrared spectrum of I has sharp absorption bands in the 1200–1300-cm.$^{-1}$ region characteristic of

(1) Allied Chemical Corp. Fellow, 1963.

(2) E. Shaw, *J. Am. Chem. Soc.* **71**, 67 (1949).

(3) J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.*, 4375 (1957).

(4) It should be noted that Shaw[2] observed the formation of 1-benzyloxy-2-pyridone as a minor product resulting from an acid-catalyzed debenzylation of 2-benzyloxypyridine 1-oxide.

(5) F. J. Dinan and H. Tieckelmann, *J. Org. Chem.*, **29**, 892 (1964).

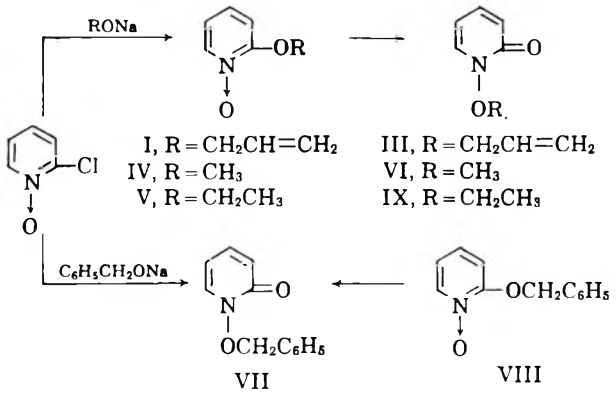
(6) F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *ibid.*, **28**, 1015 (1963).

(7) A. R. Katritzky, *J. Chem. Soc.*, 191 (1957).

pyridine 1-oxides.[8] The ultraviolet spectrum is in agreement with the data reported for 2-methoxypyridine 1-oxide (IV) and 2-ethoxypyridine 1-oxide (V).[3] The ultraviolet spectrum of the 1-alloxy isomer III is nearly identical with the spectrum reported for 1-methoxy-2-pyridone (VI).[3] In addition, a strong band at 6.01 μ in the infrared spectrum of III is consistent with the presence of a carbonyl group.

The literature pertaining to 2-alkoxypyridine 1-oxides and 1-alkoxy-2-pyridones was found to contain some anomalous and conflicting reports. It appeared that some of these data could be explained if the ease of conversion of I to III was general for 2-alkoxypyridine 1-oxide rearrangements.

Gardner and Katritzky[3] obtained 2-ethoxypyridine 1-oxide (V) and the 2-methoxy compound IV by treatment of the chloropyridine II with the sodium salts of the corresponding alcohols. However, treatment of II with the sodium salt of benzyl alcohol gave 1-benzyloxy-2-pyridone (VII) rather than the expected 2-benzyloxypyridine 1-oxide (VIII).



In our hands, treatment of II with the sodium salt of benzyl alcohol also gave VII. This reaction required more severe conditions than those used for the synthesis of the 2-alloxy compound I and, in view of the facile rearrangement of I to the isomeric pyridone III, it seems likely that the VII obtained in the former reaction results from isomerization of initially formed VIII.

The synthesis of VIII by room temperature oxidation of 2-benzyloxypyridine with perbenzoic acid was reported by Shaw.[2] Gardner and Katritzky,[3] however, reported that this procedure gave the 1-benzyloxy isomer VII rather than VIII. In our hands, VIII was formed. The ultraviolet spectrum of VIII from this reaction is in agreement with the data reported by Shaw. In addition, the infrared spectrum of VIII shows bands characteristic of the amine oxide function.[8]

The 1-benzyloxy compound VII was obtained when VIII was heated for a short time at 100°. Identification of VII is based on ultraviolet[3] and infrared spectral data. In addition, the melting point of VII prepared by rearrangement of VIII was not depressed when mixed with VII prepared by the method of Gardner and Katritzky.[3]

The conditions used to effect the rearrangement of VIII to VII are milder than those required for the attempted preparation of VII from the chloro compound II. Thus, any VIII formed in the latter reaction would be rearranged to VII under the reaction conditions. The facile rearrangement of VIII to VII may account for the different products obtained by Shaw,[2] and Gardner and Katritzky[3] from the perbenzoic acid oxidation of 2-benzyloxypyridine.

For comparison with the allyl and benzyl rearrangements, the 2-methoxy and 2-ethoxy compounds IV and V were prepared.[3] Rearrangement of IV and V gave 1-methoxy-2-pyridone (VI) and 1-ethoxy-2-pyridone (IX), respectively.

The identification of VI is based on ultraviolet spectral data,[3] and on the presence of a strong absorption band at 6.02 μ in the infrared spectrum, consistent with the presence of a carbonyl group. The ultraviolet spectrum of the 1-ethoxy compound IX is in agreement with the spectra of the 1-methoxy and 1-alloxy compounds, VI and III. Additionally, the presence of a carbonyl group is indicated by the infrared spectrum of IX.

Rearrangements of the 2-alloxy and 2-benzyloxy compounds I and VIII to the corresponding 1-alkoxy-2-pyridones were investigated at 100°. The benzyloxy rearrangement was judged complete after 2.5 hr. at this temperature, and the alloxy rearrangement after 3.5 hr. The rearrangements of the 2-methoxy isomer IV and the 2-ethoxy compound V to the 1-alkoxy compounds VI and IX were conducted at 140°. The methoxy rearrangement was complete after 1.5 hr., and the ethoxy rearrangement after 3 hr.

The mild conditions required for these rearrangements indicate that homolytic cleavage of the ether bond does not take place. The rearrangement of 2-methoxypyridine to 1-methyl-2-pyridone, a demonstrated free-radical process, requires 14 hr. at 200°.[9] Additional evidence against a radical intermediate was provided by an experiment in which the addition of 3% of a free-radical scavenger, *p*-benzoquinone, did not retard the rate of rearrangement of the 2-alkoxypyridine 1-oxides, I, VIII, or VI.

The high electron density[10] and resultant nucleophilicity of the 1-oxygen atom of pyridine 1-oxides provides an effective nucleophile. The enhanced reactivity of the 2-methoxy compound IV relative to the ethoxy isomer V is consistent with a nucleophilic substitution process and indicates that these rearrangements may take place by either intra- or intermolecular nucleophilic attack of the 1-oxygen atom on the alkyl group.

The transition state required for an intramolecular substitution reaction would, except for the 2-alloxy isomer I, involve a rather unlikely front-side displacement on the alkyl group. Both intermolecular nucleophilic substitution and rearrangement *via* ion pair formation with internal return to give product are more probable mechanisms for this transformation. The amount of ionic character may vary with the nature of the migrating group, being more important in the allylic and benzylic rearrangements and relatively unimportant in the alkyl rearrangement.

Experimental

2-Alloxypyridine 1-Oxide (I).—2-Chloropyridine 1-oxide[7] (5.2 g., 0.04 mole) was added to a solution of 0.92 g. (0.04 g.-

(8) L. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 307–308.

(9) K. B. Wiberg, T. M. Shryne, and R. R. Kintner, *J. Am. Chem. Soc.*, **79**, 3160 (1957).

(10) R. A. Barnes, *ibid.*, **81**, 1935 (1959).

atom) of sodium in 40 ml. of allyl alcohol, and the mixture was heated for 1 hr. at 50°. Excess allyl alcohol was removed at reduced pressure (50° at 0.5 mm.) and the residue was extracted with chloroform. Removal of the solvent under reduced pressure gave a crude yield of 2.8 g. (46%) of I as a light tan oil.

The product contained approximately 5% 1-alloxy-2-pyridone (III) as determined by infrared analysis. Further purification by alumina chromatography using chloroform as the eluent gave 2.3 g. (38%) of pure I.

Anal. Calcd. for $C_5H_7NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.57; H, 6.10; N, 9.40.

1-Alloxy-2-pyridone (III).—2-Alloxypyridine 1-oxide, 1.00 g. was heated at 100° for 3.5 hr. After cooling, the resulting dark brown oil was purified by chromatography on alumina. Gradient elution with benzene, chloroform, and ethyl acetate gave 0.83 g. (83%) of III as a light tan oil. This material was further purified by preparative scale gas chromatography to obtain an analytical sample. A 2-ft. 20% General Electric XF-1150 polymer on Chromosorb-W was used. The column temperature was maintained at 190° with a helium flow of 60 ml./min. The ultraviolet spectrum showed λ_{max}^{water} 296 mμ (ε 5400) and 226 mμ (ε 5500); and the infrared spectrum showed carbonyl absorption at 6.01 μ.

Anal. Calcd. for $C_5H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 61.98; H, 6.25; N, 9.47.

1-Benzyloxy-2-pyridone (VII).—2-Benzyloxypyridine 1-oxide (VIII),[2] 1.00 g., was heated for 2.5 hr. at 100°. Upon cooling, the reaction mixture solidified. Recrystallization from ethyl acetate–ligroin gave 0.92 g. (92%) of VIII, m.p. 78–79°, lit.[3] m.p. 76–78°. A mixture melting point of VIII prepared by the literature procedure and as above was not depressed. The infrared spectra of the two products are identical.

1-Methoxy-2-pyridone (VI).—2-Methoxypyridine 1-oxide (IV), 1.00 g., was heated for 1.5 hr. at 140°. The resulting dark brown oil was purified by chromatography on alumina. Gradient elution with benzene, chloroform, and ethyl acetate gave 0.89 g. (89%) of VI as a tan oil which could not be crystallized.[11] An aqueous solution of the product gave the same ultraviolet spectrum reported for authentic VI.[3] The infrared spectrum showed carbonyl absorption at 6.02 μ.

This procedure is also typical for the preparation of the following compound.

1-Ethoxy-2-pyridone (IX).—2-Ethoxypyridine 1-oxide (V) was heated for 3 hr. at 140° to give crude IX. Gradient elution chromatography as above gave 85% of IX as a light tan oil. The ultraviolet spectrum showed λ_{max}^{water} 295 mμ (ε 5900) and 225 mμ (ε 6100); the infrared spectrum showed carbonyl absorption at 6.02 μ.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.62; H, 6.90; N, 9.89.

Effect of *p*-Benzoquinone on Rate of Rearrangement.—*p*-Benzoquinone, 3% by weight, was added to the 2-alkoxypyridine 1-oxide to be investigated. Portions of this sample together with pure samples of the same 2-alkoxypyridine 1-oxide were heated together in sealed tubes in a stirred oil bath set at the desired temperature so that variations in the bath temperature could not change the rate of one rearrangement with respect to the other. Tubes containing the experimental and control samples were simultaneously withdrawn from the bath at 15-min. intervals and the infrared spectra were determined. The rate of rearrangement of the 2-alkoxypyridine 1-oxide was determined by the disappearance of the 1-oxide bands in the 7.8–8.4-μ region. Formation of product was indicated by the appearance of a carbonyl absorption band at approximately 6.0 μ.

In this manner, the rearrangements of 2-alloxypyridine 1-oxide, 2-benzyloxypyridine 1-oxide, and 2-methoxypyridine 1-oxide to the corresponding 1-alkoxy-2-pyridones were shown to proceed at the same rate in the presence and absence of added *p*-benzoquinone.

Rates of Rearrangement of 2-Alkoxypyridine 1-Oxides.—The 2-alkoxypyridine 1-oxides were heated in a stirred oil bath set at the desired temperature. Samples were withdrawn at 15-min. intervals and their ultraviolet spectra were determined on a Beckman DK-2 spectrophotometer.

(11) Gardner and Katritzky reported that this material partially solidified on standing. This has not been observed in the present case.

Rearrangements were judged complete when the maximum at approximately 250 mμ, which characterizes the spectra of 2-alkoxypyridine 1-oxides and is missing in 1-alkoxy-2-pyridones, had disappeared. At this time, the spectra corresponded to those of the corresponding 1-alkoxy-2-pyridones.

The rearrangements of 2-alloxypyridine 1-oxide (I) and 2-benzyloxypyridine 1-oxide (VIII) were found to be complete after 3.5 and 2.5 hr. at 100°, respectively. 2-Methoxypyridine 1-oxide (IV) and 2-ethoxypyridine 1-oxide (V) were rearranged at 140° and found to be complete after 1.5 and 3 hr., respectively.

Model Reactions for the Biosynthesis of Thyroxine. V. Reaction of 4-Hydroxy-3-iodophenylpyruvic Acid and of 4-Hydroxy-3,5-diiodophenylpyruvic Acid with L-Tyrosine or Its Iodinated Congeners. A Novel Synthesis of 3,3′,5′-Triiodo-L-thyronine[1,2]

TETSUO SHIBA[3] AND H. J. CAHNMANN

The National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

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DIHPPA[4] reacts with DIT[4] in the presence of oxygen to form thyroxine in over 20% yield.[5] The reaction takes place rapidly at room temperature and at or near neutrality. No racemization takes place when L-DIT is used.[6] It has been shown through experiments with labeled starting materials that the keto acid furnishes the phenolic ring of thyroxine, and the amino acid—the nonphenolic ring and the aliphatic side chain.[6] The side chain of the keto acid is eliminated in the course of the reaction.

The present investigation was undertaken in order to determine whether in this coupling reaction DIHPPA can be replaced with MIHPPA,[4] and DIT with MIT[4] or with tyrosine and to what extent the corresponding iodinated thyronines are formed in each case.

The coupling reaction was carried out essentially as described previously for the synthesis of thyroxine.[5,6] The amount of iodinated thyronine formed in each reaction was determined by isolation and weighing. A modification of the procedure of Nakano and Danowski[7] was used for the preparation of MIHPPA.

When in the coupling reaction described by Meltzer and Stanaback[5] L-DIT was replaced with L-MIT, the yield of the coupling product dropped from over 20% to 17%. When L-DIT was replaced with L-tyrosine, the yield of 3′,5′-diiodo-L-thyronine was about 0.2%. Reaction of MIHPPA with L-DIT gave 3,5,3′-triiodo-L-thyronine in about 2% yield. In view of this low

(1) For a preliminary report of this work see Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962, p. 9C.

(2) Paper IV: T. Matsuura and A. Nishinaga, *J. Org. Chem.*, **27**, 3072 (1962).

(3) Visiting Scientist from the Department of Chemistry, Faculty of Science, Osaka University, Osaka, Japan.

(4) Abbreviations: HPPA, *p*-hydroxyphenylpyruvic acid; MIHPPA, 4-hydroxy-3-iodophenylpyruvic acid; DIHPPA, 4-hydroxy-3,5-diiodophenylpyruvic acid; MIT, 3-iodotyrosine; DIT, 3,5-diiodotyrosine.

(5) R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).

(6) T. Shiba and H. J. Cahnmann, *ibid.*, **27**, 1773 (1962).

(7) N. Nakano and T. S. Danowski, *Endocrinology*, **65**, 889 (1959).

yield the reaction of MIHPPA with L-tyrosine was not investigated. The formation of only a trace of 3′-iodo-L-thyronine can be expected in that reaction. The reaction of HPPA[4] with L-MIT was not investigated because Meltzer and Stanaback[5] found that HPPA does not react with L-DIT.

The results show that iodinated thyronines can be obtained in good yield only with DIHPPA. The replacement of DIHPPA with MIHPPA results in poor yields. With DIHPPA, good yields of iodinated thyronines are obtained only when the other reaction partner is either DIT or MIT. DIHPPA reacts with tyrosine to give only traces of the corresponding iodinated thyronine.

It has been shown[6] that the coupling reaction of DIHPPA with L-DIT provides a simple method for the synthesis of a number of specifically labeled radioactive forms of L-thyroxine. Similarly, the ease with which 3,3′,5′-triiodo-L-thyronine is formed by coupling DIHPPA with L-MIT offers a convenient method for the synthesis of various specifically labeled radiosiomers of 3,3′,5′-triiodo-L-thyronine. This so-called "reverse" triiodothyronine occurs in the thyroid. Previously used procedures for its synthesis are tedious since they involve many steps.

It has been suggested[8,9] that DIHPPA may be an intermediate in the biosynthesis of L-thyroxine from L-DIT. In this connection it is of interest to compare the amounts of various iodinated thyronines present in the thyroid with the ease with which the same thyronines are formed in the nonenzymic coupling reaction. The amounts present in the thyroid decrease in this order: thyroxine > 3,5,3′-triiodothyronine > 3,3′,5′-triiodothyronine. 3′,5′-Diiodothyronine has not been detected in the thyroid. The yields in the nonenzymic coupling reaction decrease in this order: thyroxine > 3,3′,5′-triiodothyronine > 3,5,3′-triiodothyronine > 3′,5′-diiodothyronine.

All coupling reactions were carried out at about the same pH (6.7–7.7). A variation of pH within these limits does not greatly affect the yield of thyroxine from DIHPPA and DIT. It should be pointed out that, at this pH, the degree of dissociation of the phenolic groups of the various amino acids used as reaction partners differs greatly depending on the number of iodine atoms present in the *ortho* positions. The p*K* values for the phenolic groups of tyrosine, MIT, and DIT are 10.0, 8.7, and 6.5, respectively.[10] Consequently, it is possible that, at a higher pH at which the phenolic groups of MIT and of tyrosine are ionized, these two amino acids would also form the corresponding thyronines in a higher yield. It is difficult to investigate this possibility experimentally since DIHPPA is extremely unstable in alkaline medium.

Experimental[11]

4-Hydroxy-3-iodophenylpyruvic Acid.—*p*-Hydroxybenzaldehyde was iodinated with either iodine monochloride or with potassium triiodide.[12] In both cases a series of fractional crystallizations and dissolutions was required to remove starting material and the diiodinated aldehyde that was always formed together with the desired product. This purification was conveniently followed by infrared spectroscopy or by gas chromatography (1% SE 30, siliconized Gaschrom P); the pure acid had m.p. 110.5°.

A modification of the procedure of Nakano and Danowski[7] was used for the conversion of the aldehyde to 2-methyl-4-(4-acetoxy-3-iodobenzal)-5-oxazolone. The pure azlactone, m.p. 184–185°, was obtained after recrystallization from benzene–isooctane with the addition of Norit.

Anal. Calcd. for $C_{13}H_{10}INO_4$: C, 42.07; H, 2.72; I, 34.20; N, 3.78. Found: C, 42.05; H, 2.89; I, 34.31; N, 3.76.

A two-step hydrolysis[7] of the azlactone was found not to be necessary, as a single-step hydrolysis with 3 ml. of 2 *N* hydrochloric acid per mmole of azlactone (3 hr., 100°) gave the keto acid in the same yield. Recrystallization was done from water containing a few drops of 4 *N* hydrochloric acid.

3,3′,5′-Triiodo-L-thyronine.—A solution of 1.54 g. (5.0 mmoles) of 3-iodo-L-tyrosine[13] in a mixture of 100 ml. of 0.2 *M* sodium phosphate buffer (pH 6.7), 17.5 ml. of 1 *N* sodium hydroxide, and 17.5 ml. of a saturated aqueous solution of sodium sulfate was adjusted to pH 6.7 with 4 *N* hydrochloric acid. Then 50 μl. of *t*-butyl hydroperoxide[14] was added. Oxygen was bubbled through the vigorously stirred reaction mixture while 2.59 g. (6.0 mmoles) of 4-hydroxy-3,5-diiodophenylpyruvic acid[5,6,15] was added in very small portions over a period of 1.3 hr. The pH was maintained at 6.7 by adding 2 *N* sodium hydroxide slowly to the reaction mixture by means of an immersed thin polyethylene tubing. The rate of addition was automatically controlled with a pH-stat.[16] Bubbling of oxygen and stirring were continued for another 30 min. The reaction mixture was kept overnight at 2°, then filtered. The solid material was washed with a small amount of ice-cold water and dried, yielding 0.83 g. Paper chromatography revealed contamination with a small amount of 3-iodotyrosine. Dissolution in 4 *N* ammonium hydroxide and reprecipitation with 4 *N* hydrochloric acid at pH 5 gave 0.56 g. (17%) of practically pure 3,3′,5′-triiodo-L-thyronine, m.p. 191–193° dec.; R_f 0.34 (1-butanol–dioxane–2 *N* ammonium hydroxide) and 0.73 (1-butanol–acetic acid–water). For elemental analysis part of the material was reprecipitated a second time.

Anal. Calcd. for $C_{15}H_{12}I_3NO_4$: C, 27.67; H, 1.84; I, 58.48; N, 2.15. Found: C, 27.55; H, 1.79; I, 58.66; N, 2.44.

A second crop of 0.24 g. of crude 3,3′,5′-triiodo-L-thyronine was obtained from the mother liquors after concentration.

Other Coupling Reactions.—These reactions were carried out following essentially the procedure described for the synthesis of 3,3′,5′-triiodo-L-thyronine with appropriate minor modifications made necessary by the differences in the solubilities of the various starting materials and by the low coupling yields. In view of these low yields a detailed description of each coupling reaction will not be given.

The reaction of 3,5-diiodo-L-tyrosine with 4-hydroxy-3-iodophenylpyruvic acid at pH 7.0 gave chromatographically pure 3,5,3′-triiodothyronine in 2% yield. The reaction of L-tyrosine with 4-hydroxy-3,5-diiodophenylpyruvic acid at pH 7.7[17] gave 3′,5′-diiodo-L-thyronine in 0.2% yield. The identity of the coupling products was ascertained by comparison of the infrared spectra and of the chromatographic mobilities with those of authentic samples.

(8) T. Shiba and H. J. Cahnmann, *Biochim. Biophys. Acta*, **58**, 609 (1962).

(9) S. Lissitzky and C. Cheftel, *Compt. rend.*, **256**, 3898 (1963).

(10) R. Pitt-Rivers and J. R. Tata, "The Thyroid Hormones," Pergamon Press, Inc., New York, N. Y., 1959, p. 188.

(11) The microanalyses were done by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and by Mr. H. G. McCann and his associates of the analytical service laboratory of this institute. Melting points were determined in capillary tubes and are uncorrected. Paper chromatographic solvents were 1-butanol–dioxane–2 *N* ammonium hydroxide (4:1:5) and 1-butanol–acetic acid–water (78:10:12). The location of the chromatographic spots was revealed by visual inspection in short-wave ultraviolet light and by spraying with a solution of ninhydrin or of diazotized N^1,N^1-diethylsulfanilamide [T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **81**, 871 (1959)].

(12) J. H. Barnes, E. T. Borrows, J. Elks, B. A. Hems, and A. G. Long, *J. Chem. Soc.*, 2824 (1950).

(13) A commercial sample was recrystallized from water. The recrystallized material was chromatographically pure.

(14) Lucidol Davidson, Wallace and Tiernan, Buffalo, N. Y.

(15) Now commercially available from Osaka Laboratory of Synthetic Organic Chemicals, 74 Ueda Higashimachi, Nishinomiya, Japan.

(16) Radiometer, Copenhagen, Denmark.

(17) L-Tyrosine is not completely soluble at a lower pH.

The Photochemical Reactions of Ethyl Pyruvate in 2-Propanol and in Cyclohexane

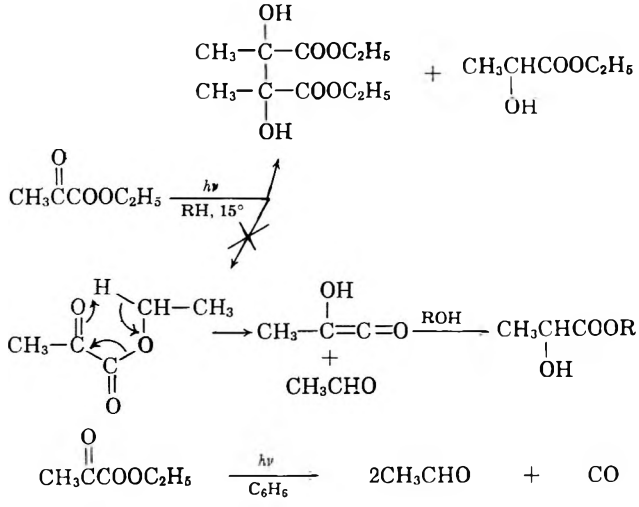
N. C. YANG[1] AND A. MORDUCHOWITZ[2]

Department of Chemistry, University of Chicago, Chicago 37, Illinois

Received January 13, 1964

Ketones with γ-hydrogen undergo Type II photochemical processes.[3] The photochemistry of ethyl pyruvate was investigated to ascertain whether it would also undergo an analogous process. The α-hydrogen of the ester function is sterically similar to the γ-hydrogen of aliphatic ketones. Photolysis of ethyl pyruvate would then yield acetaldehyde and a hydroxyketene. If the irradiation is carried out in an alcohol other than ethanol, the hydroxyketene formed would react with the alcohol to form the lactate ester.

Hammond and co-workers[4] studied the direct and sensitized photolysis of ethyl pyruvate in benzene solution. They found the principal products to be carbon monoxide and acetaldehyde. Hammond's work demonstrated the nature of the reacting species to be a triplet.



The irradiation of ethyl pyruvate in 2-propanol and in cyclohexane with a low-pressure mercury vapor lamp at 15° resulted in reductive dimerization with the formation of diethyl dimethyltartrate. A small amount of ethyl lactate also was formed, but no product which may be attributed to a process analogous to Type II was isolated. The main product may be a mixture of *meso* and racemic forms, but no separation of these components was achieved by distillation or gas chromatography. The mechanism of the reduction dimerization is believed to be analogous to that for the formation of benzpinacol from benzophenone.[5,6]

(1) Alfred P. Sloan Foundation Fellow.

(2) National Institutes of Health Predoctoral Fellow, 1959-1962.

(3) (a) R. G. W. Norrish and M. E. S. Appleyard, *J. Chem. Soc.*, 874 (1934); (b) N. C. Yang and D. H. Yang, *J. Am. Chem. Soc.*, **80**, 2913 (1958); (c) W. H. Urry and D. J. Trecker, *ibid.*, **84**, 118 (1962).

(4) G. S. Hammond, P. A. Leermakers, and N. J. Turro, *ibid.*, **83**, 2395 (1961).

(5) (a) G. S. Hammond, W. P. Baker, and W. M. Moore, *ibid.*, **83**, 2795 (1961); (b) J. N. Pitts, Jr., *et al.*, *ibid.*, **81**, 1068 (1959).

Experimental

Irradiation of Ethyl Pyruvate.—A solution of freshly distilled ethyl pyruvate (30 g., 0.25 mole) in 275 ml. of Spectro Grade 2-propanol was placed in a low pressure mercury resonance lamp.[7] The irradiation apparatus was fitted with a Freidrich condenser and immersed in a water bath which maintained the temperature of the solution between 15–20°. The outlet of the condenser was connected, in series, to a Dry Ice trap and then through a three-way stopcock to a gas buret filled with saturated potassium chloride solution. The gas buret was isolated from the system by means of the stopcock and the apparatus was flushed with high purity nitrogen for 30 min. The nitrogen flow was then discontinued and the gas buret was reopened to the system. The solution was irradiated with vigorous magnetic stirring for a period of 72 hr. Throughout the irradiation there was no gas evolution nor was there any material condensed in the Dry Ice trap. The solution then was transferred to a flask and fractionally distilled at atmospheric pressure with the aid of a Heligrid column rated at 50 theoretical plates. Acetone (9.05 g.) was collected, after which time the temperature of the distillate rose steadily until pure 2-propanol began to distil. The remaining 2-propanol was removed with the same column at reduced pressure, b.p. 54° (230 mm.).

The fractionation was next continued with the aid of a 3-ft. tantalum wire spiral column under reduced pressure to yield the following fractions: fraction I, b.p. 57–58° (15 mm.), 1.90 g.; fraction II, b.p. 54–61° (0.1 mm.), 0.73 g.; fraction III, b.p. 61–63° (0.1 mm.), 24.01 g.; residue, 1.60 g.

Fraction I was identified as mainly ethyl lactate with a small amount of ethyl pyruvate. The infrared spectrum very closely resembled that of ethyl lactate, but it gave a positive test with 2,4-dinitrophenylhydrazine reagent. The presence of ethyl pyruvate (15%) was confirmed by gas chromatography.

Fraction II was found to be mainly impure fraction III, and fraction III was identified as the diethyl ester of dimethyltartaric acid, $n^{21}D$ 1.4410.

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.30; H, 7.75. Found: C, 51.56; H, 8.10.

Identification of Diethyl Dimethyltartrate.—The compound (3 g.) was dissolved in 80 ml. of distilled water and mixed with 9.0 g. of paraperiodic acid. The reaction mixture was maintained at room temperature for 4 hr., neutralized with barium hydroxide, and filtered. The filtrate was continuously extracted with ether for 24 hr. The ethereal solution was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 1.83 g. of a material which was identified as pyruvic acid by comparison with the infrared spectrum of an authentic sample. Prior to the continuous extraction, an aliquot (5 ml.) of the filtrate was treated with 2,4-dinitrophenylhydrazine reagent and yielded a 2,4-dinitrophenylhydrazone, m.p. 214°, which was identical in all respects with an authentic sample of pyruvic acid 2,4-dinitrophenylhydrazone.

Irradiation of Ethyl Pyruvate in Cyclohexane.—A solution of ethyl pyruvate (25 g., 0.21 mole) in 275 ml. of Spectro Grade cyclohexane was irradiated as above for a period of 48 hr. There was no gas evolution throughout the irradiation and no material condensed in the trap. The cyclohexane was removed by fractionation through the Heligrid column under reduced pressure, b.p. 46° (225 mm.). The reaction mixture was then fractionated under reduced pressure through the tantalum wire column to yield: fraction I, b.p. 56.5–57.0° (20 mm.), 9.12 g.; fraction II, b.p. 61.8–63.0° (0.1 mm.), 7.14 g.; residue, 4.76 g.

Fraction I was identified as mainly unchanged ethyl pyruvate (36% recovery), and Fraction II was identified as diethyl dimethyltartrate (29% yield). The cyclohexane fraction was fractionated again at atmospheric pressure by means of the Heligrid column after the addition of acetone (75 ml.) to remove cyclohexane by azeotropic distillation. The acetone–cyclohexane azeotrope was collected at 53°. When the temperature of the distillate reached 80°, the fractionation was discontinued. The residue then was tested for unsaturation and found to decolorize bromine in carbon tetrachloride, indicating the presence of cyclohexene.

(6) NOTE ADDED IN PROOF.—After this manuscript was submitted for publication, E. S. Huyser and D. C. Neckers reported [*J. Org. Chem.*, **29**, 276 (1964)] that phenylglyoxalates, a group of α-keto esters, undergo a photochemical process analogous to Type II process of ketones at elevated temperatures.

(7) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.*, **14**, 245 (1949).

Acknowledgment.—The authors wish to thank the Petroleum Research Fund (Grant No. 726) for partial support of this work.

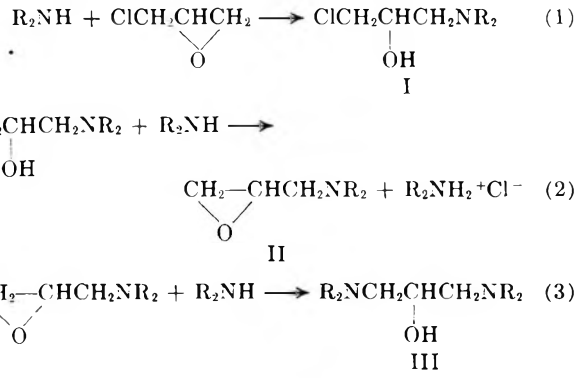
Reactions of 1-Chloro-2,3-epithiopropane

JOHN M. STEWART

Department of Chemistry, Montana State University, Missoula, Montana

Received November 26, 1963

There have been numerous investigations reported on the reaction of epichlorohydrin with amines, of which the references listed[1,2] are representative. In these reactions, with either primary or secondary amines, it has been established that the following sequence can occur, with the final product dependent mainly on the relative molar amount of amine used.



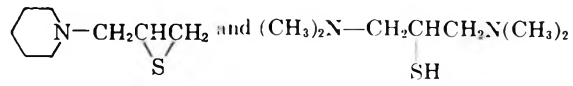
In work at this laboratory, reactions of amines with the sulfur analog of epichlorohydrin, 1-chloro-2,3-epithiopropane, have been investigated. In *no* case, regardless of the molar ratio of reactants, the manner of addition, the solvent, or the conditions of the reaction, have sulfur analog compounds corresponding to I, 1-N-substituted amino-3-chloro-2-propanethiols, been isolated.

With secondary amines, sulfur analog products corresponding to II, 1-N-disubstituted amino-2,3-epithiopropanes, and to III, 1,3-bis(N-disubstituted amino)-2-propanethiols, were formed in relative amounts dependent chiefly on the amount of amine used. Tables I and II list the physical constants, analytical data, and some derivatives for the compounds prepared. Although the course of the reactions has not been definitely established, it is believed that the same sequence occurs as in the case of epichlorohydrin, with step 2 proceeding at a much faster rate than step 1. Direct nucleophilic displacement of chlorine by amine to give products of type II in one step does not seem likely in view of the usual lower relative speed, under the conditions used, of this type of reaction as compared to the opening of the sulfide ring, nor in view of the usual close analogy of reactions of oxiirane and thiirane rings with nucleophilic reagents. Using a reactant mole ratio of 1:1, especially if the amine was added to the sulfide, with both in ether or petroleum ether (b.p. 30–60°) solution, gave predominantly the amino sulfides as products in yields varying from fair to moderately good based on the available amine. With dimethylamine, however, polymerization of the amino sulfide occurred very easily during distillation and on standing at room temperature, so that the product could not be directly analyzed. When methanol was used as solvent with dimethylamine or diethylamine, only polymers were obtained. With the three heterocyclic amines tried, methanol could be used as solvent and the amino sulfides could be isolated, but in lower yield than when ether was used as solvent, due to some polymerization. The amino sulfides, once isolated, reacted very readily with additional amine (except in the case of di-*n*-butylamine as noted subsequently) to form the 1,3-bis(N-disubstituted amino)-2-propanethiols.

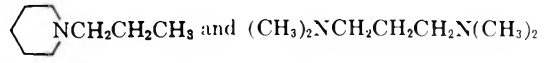
With a reactant ratio of 2 or more moles of amine to 1 of sulfide, both types of products were generally obtained. Apparently steric hindrance plays a role in determining the ratio of these products, since, for example, in the case of di-*n*-butylamine none of the 1,3-bis(dibutylamino)-2-propanethiol was ever formed regardless of the amount of amine used or conditions of the reaction.

In order to demonstrate the direction of ring opening in both steps 1 and 3, desulfurization by commercial Raney nickel catalyst of one of the amino sulfides and one of the diaminopropanethiols was employed.

The following structures were shown to be correct,

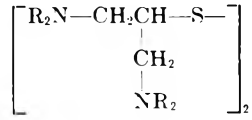


since, on treatment of each individually with Raney nickel in ethanol, these compounds were obtained.



Thus both 1-chloro-2,3-epithiopropane and the 1-N-disubstituted amino-2,3-epithiopropanes open in the so-called "normal" manner by cleavage at the primary carbon–sulfur bond when treated with amines.

In some cases the 1,3-bis(N-disubstituted amino)-2-propanethiols were oxidized with alcoholic iodine to the following corresponding disulfides.



These were either isolated and purified directly as the dihydroiodide salts or the free tetraaminodisulfide was isolated and then converted to the tetrahydrochloride salt.

In the reaction of primary amines with 1-chloro-2,3-epithiopropane, no simple compounds could be isolated and amino sulfide polymers appeared to be the only products. This was not unexpected, since the amino sulfide monomer contains a secondary amine group which can react readily with the sulfide ring in another molecule, thus leading to polymers of the following type.

(1) H. Gilman, *et al.*, *J. Am. Chem. Soc.*, **68**, 1291 (1946).
(2) D. L. Heywood and B. Phillips, *ibid.*, **80**, 1257 (1958).

TABLE I

1-N-DISUBSTITUTED AMINO-2,3-EPITHIOPROPANES

$R_2NCH_2CHCH_2$
$\quad\quad\quad

in seven times its volume of the same solvent. After the addition was complete, the mixture was allowed to stand for a period of 18–24 hr. Longer reaction times increased the amount of polymer formed. The precipitated hydrochloride was removed by filtration, the solvent and unchanged starting materials were stripped under reduced pressure, and the products were separated by vacuum distillation. Under these conditions the following yields of 1-N-disubstituted amino-2,3-epithiopropane (based on 50% of the amine used) were obtained for the indicated amine: dimethylamine, 0% (polymers only); diethylamine, 30–40%; dibutylamine, 72%; piperidine, 60–65%; and morpholine, 62.5%. Methanol as solvent appeared to give much faster reactions but also increased the amount of polymer formation. In one experiment with piperidine and a reaction time of only 5 hr., however, a yield of 75% of 1-piperidino-2,3-epithiopropane was obtained when methanol was the solvent.

B. In a Ratio of 2 Moles of Amine to 1 Mole of 1-Chloro-2,3-epithiopropane.—The same procedure was followed as described in A. The two types of products were separated by distillation. Yields of 1-N-disubstituted amino-2,3-epithiopropanes (based on the 1-chloro-2,3-epithiopropane used) varied from 30–48%, and the yields of 1,3-bis(N-disubstituted amino)-2-propanethiols (based on 25% of the amount of *amine* used) varied from 25–45%. With di-*n*-butylamine, no thiol-type product was formed, and with diethylamine the thiol-type product was formed in small per cent. The reaction with pyrrolidine appeared to be unusually fast, and, in one run in which the amine was added all at once in petroleum ether solution and the reaction period was only 5 hr., yields of 48.4% of the amino sulfide-type product and 34% of the thiol were obtained.

C. In a Ratio of 3 Moles or More of Amine to 1 Mole of 1-Chloro-2,3-epithiopropane.—In these experiments the sulfide solution was added dropwise with stirring to the excess of amine, but otherwise the procedure was the same as described in A. With dimethylamine and diethylamine both types of products were obtained, with piperidine and morpholine only the thiol. Yields were as follows: for dimethylamine, 37% amino sulfide and 33% thiol; for diethylamine, 35% amino sulfide and 50% thiol; for piperidine, 60–65% thiol; and for morpholine, 54% thiol.

Infrared Spectral Data for 1-N-Disubstituted Amino-2,3-epithiopropanes.—Infrared spectra were determined on a Beckman IR-5 spectrophotometer. Absorption bands which were *common* to all of the examples of this type of compound prepared were as follows: $\lambda_{max}^{CCl_4}$ 3.4, 3.6, 6.9, 7.2–7.3, and 9.6 μ. For comparison, 1-chloro-2,3-epithiopropane showed characteristic absorption bands at 3.35, 6.92, 7.95, 8.64, 9.18, 9.6, 13.96, and 14.9 μ.

Raney Nickel Desulfurizations in Structure Proofs.—Desulfurizations were carried out in absolute ethanol using commercial Raney nickel (No. 28 Raney Active Nickel, Raney Catalyst Co., Chattanooga, Tenn.) in an amount equal to ten times the amount of compound, and the mixtures were allowed to stand for about an hour at room temperature with frequent shaking. Evolution of heat was noticed. From the amino sulfide containing a piperidino group was obtained an amine which was immediately converted to a picrate derivative and this, after three recrystallizations from absolute ethanol, melted at 105–107°. This agrees with the m.p. 108° reported by Magnusson and Schierz[9] for N-*n*-propylpiperidine, whereas N-isopropylpiperidine picrate was reported melting at 153°.

From the diaminothiol product containing dimethylamine groups was obtained an amine which also was converted at once to the picrate and this, after one recrystallization from water, melted at 207–208°, after darkening and deformation from 205–207°. This agrees with the m.p. 207° reported by Clarke[10] for the picrate of N,N,N′,N′-tetramethyl-1,3-propanediamine, whereas N,N,N′,N′-tetramethyl-1,2-propanediamine picrate is reported[11] to melt at 190°.

Reactions of 1-Chloro-2,3-epithiopropane and Anhydrous Solutions of Chlorine and Bromine.—The general procedure described for other cyclic sulfides[3-5] was employed. Reaction with chlorine gave a 37% yield of liquid product, b.p. 157–160° (1 mm.), which, after two further distillations, crystallized in the receiver. Recrystallization from 95% ethanol gave colorless crystals, m.p. 67–69°. A mixture melting point of this product and the disulfide obtained by iodine oxidation of 2,3-dichloro-1-propanethiol prepared from reaction of 1-chloro-2,3-epithiopropane and concentrated hydrochloric acid showed no depression. The compound then is bis(2,3-dichloropropane) disulfide.

Anal. Calcd. for $C_6H_{10}Cl_4S_2$: C, 25.01; H, 3.50. Found: C, 24.89; H, 3.51.

Reaction with bromine gave a quantitative yield of slightly red solid which was recrystallized from 95% ethanol to give colorless crystals, m.p. 80–82.5°, assumed to be bis(2-bromo-3-chloropropane) disulfide.

Anal. Calcd. for $C_6H_{10}Br_2Cl_2S_2$: C, 19.11; H, 2.67. Found: C, 19.39; H, 2.64.

Reaction of 1-Chloro-2,3-epithiopropane and Aqueous Chlorine.—This reaction was carried out as described for other cyclic sulfides.[3-5] After one distillation, a yield of 47% was obtained. Redistillation gave a colorless liquid, b.p. 82.5–83.5° (1 mm.), $n^{20}D$ 1.5137, assumed to be 2,3-dichloro-1-propanesulfonyl-chloride.

Anal. Calcd. for $C_3H_5Cl_3O_2S$: C, 17.04; H, 2.38. Found: C, 17.36; H, 2.35.

Acknowledgment.—This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of this fund.

(9) H. W. Magnusson and E. R. Schierz, *Wyoming Univ., Publ.*, **7**, 1 (1940).

(10) H. T. Clarke, *J. Chem. Soc.*, **103**, 1699 (1913).

(11) R. Paul and S. Tchelitcheff, *Compt. rend.*, **238**, 2089 (1954).

Optical Resolution of (±)-1-Amino-2-propanethiol[1]

JAMES R. PIPER AND THOMAS P. JOHNSTON

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama

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The recently reported finding that (−)-2-(2-aminobutyl)-2-thiopseudourea hydrobromide is twice as effective in protecting mice against a single dose of lethal X-irradiation as the (+)-isomer[2] suggests that important differences may be found between other enantiomeric pairs of radioprotective agents previously evaluated as racemic mixtures. The optical resolution of (±)-1-amino-2-propanethiol [(±)-I] was selected for investigation because this compound has been reported to afford good radioprotection.[3]

The resolution of (±)-I was first approached *via* the crystalline salts of (±)-2-(benzylthio)propylamine with (−)-malic acid and (+)-tartaric acid, which were to be subsequently debenzylated; but optical enrichment was not attained by repeated recrystallization of these salts. The resolution was then undertaken by a method recently applied by Taguchi, *et al.*,[4] to the resolution of (±)-*trans*-2-aminocyclohexanethiol *via* the thiazolidine formed with D-glucose. The reported resolution suggests a general method, but the paucity of experimental details necessitated development of each step when applied to the resolution of (±)-I. The process that eventually evolved is outlined below.

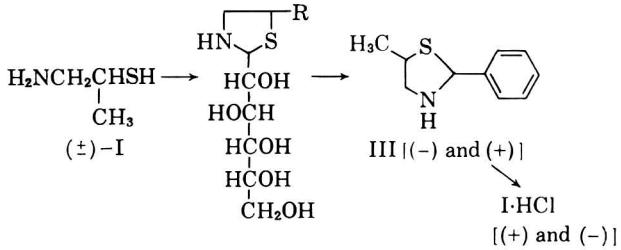
(1) This investigation was supported by the U. S. Army Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) D. G. Doherty and R. Shapira, *J. Org. Chem.*, **28**, 1339 (1963); see also Abstracts of Papers, International Congress of Radiation Research, Burlington, Vt., Aug. 10–16, 1958; *Radiation Res.*, **9**, 107 (1958).

(3) F. Yu. Rachinskii, A. S. Mozzhukhin, N. M. Slavachevskaya, and L. I. Tank, *Usp. Khim.*, **28**, 1488 (1959); J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, p. 66.

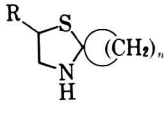
(4) T. Taguchi, T. Takatori, and M. Kojima, *Chem. Pharm. Bull.* (Tokyo), **10**, 245 (1962).

Treatment of (±)-I hydrochloride with sodium methoxide in methanol gave the free aminothiol, which was purified by sublimation. Reaction of (±)-I with D-glucose in refluxing methanol gave 1-(5-methylthiazolidinyl)-D-*gluco*-1,2,3,4,5-pentanepentol, which was isolated from the reaction mixture in two forms (levorotatory IIa and optically inactive IIb) by fractional crystallization, each being subsequently purified further by recrystallization. An exchange reaction of the less soluble, higher melting IIa with benzaldehyde in aqueous ethanol produced (−)-5-methyl-2-phenylthiazolidine [(−)-III], and the same treatment of the more soluble, lower melting IIb afforded (+)-III. Hydrolysis of (−)-III in boiling 6 *N* hydrochloric acid gave (+)-I hydrochloride; that of (+)-III, (−)-I hydrochloride. Practical yields were obtained in each step, and optical purity of the enantiomeric pairs was attested by essentially equal specific rotation of opposite sign.



II (a and b), R = CH_3
IV, R = H

The major difference between the method described above and that reported by Taguchi, *et al.*,[4] is the use of benzaldehyde in the exchange step instead of cyclohexanone. After several unsuccessful attempts to effect the exchange of the glucose moiety of IIa with cyclohexanone in boiling cyclohexanone as solvent,[4] 1-thiazolidin-2-yl-D-*gluco*-1,2,3,4,5-pentanepentol[5] (IV) was used as a model in determining the optimal conditions (1-hr. reflux) that gave a 19% yield of 1-thia-4-azaspiro[4.5]decane[6] (V) and an even lower yield of the 2-methyl derivative VI when applied to IIIa. Cyclopentanone under similar conditions gave comparably impractical yields of 1-thia-4-azaspiro[4.4]nonane (VII). Direct generation of 2-aminoethanethiol from IV by acid hydrolysis was unsatisfactory (as in the case of



V, R = H; $n = 5$
VI, R = CH_3; $n = 5$
VII, R = H; $n = 4$

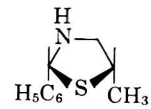
2-aminocyclohexanethiol[4]) because of the products of glucose decomposition. The action of phenylhydrazine hydrochloride on IV in hot aqueous solution resulted in the precipitation of D-glucose phenylosazone, but a practical isolation of 2-aminoethanethiol from the remaining nitroprusside-positive mixture was not devised.

(5) W. A. Bonner and W. Meyer zu Reckendorf, *Chem. Ber.*, **94**, 225 (1961).

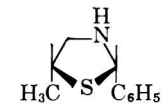
(6) A. H. Cook and I. M. Heilbron, "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p. 957.

Difficult fractionation and purification problems were encountered in an exploratory preparation of II from (±)-I hydrochloride and D-glucose in the presence of triethylamine according to the procedure described[7] for a similar reaction of 3-aminopropanethiol hydrochloride. This difficulty was overcome by the use of the free amino thiol I as in the reported[5] reaction of D-glucose with 2-aminoethanethiol. It was also found that the presence of moisture in (±)-I made the isolation of IIb exceedingly tedious.

Four diastereoisomers can theoretically result from the reaction of a racemic amino thiolsuch as (±)-I with D-glucose, but only two forms of II were isolated, each being recrystallized to a constant specific rotation and melting point. The phenylthiazolidines (−)-III and (+)-III resulting from benzaldehyde exchange of IIa and IIb, respectively, are enantiomers; yet each has two asymmetric carbon atoms, whereas the corresponding cyclohexanone exchange products would have a single asymmetric carbon atom. This means that (−)-III and (+)-III are both *cis* or both *trans*[8] as



IIIx



IIIy

illustrated by the mirror image structures IIIx and IIIy and that the benzaldehyde exchange must have taken a stereospecific course. (The formation of exactly compensating mixtures is unlikely.) In order to confirm the implication that direct formation of a thiazolidine of this type would also be stereospecific, the product from (−)-I hydrochloride and benzaldehyde was examined and found to be virtually identical with (+)-III from which (−)-I hydrochloride was derived. The alternative nonspecific reaction would have resulted in a mixture of *cis* and *trans* isomers. These observations may then explain why only two forms of the D-glucose thiazolidine II were isolated.

Experimental[9]

(±)-2-(Benzylthio)propylamine. A. Free Base.—To a stirred mixture of (±)-1-amino-2-propanethiol hydrochloride[11] (6.38 g., 0.0500 mole) and anhydrous potassium carbonate (14.5 g., 0.105 mole) in *N,N*-dimethylformamide (50 ml.) was added a solution of α-chlorotoluene (6.58 g., 0.0520 mole) in the same solvent (15 ml.). The resulting mixture was stirred under nitrogen for 1 hr. (during this period the temperature of the mixture rose spontaneously to a maximum of 51°) and then heated at 50–60° for 2.5 hr. The product was isolated essentially as the previously described 2-(benzylthio)ethylamine[12]; the yield of racemic 2-(benzylthio)propylamine as a colorless oil was 5.66 g. (62%), b.p. 86° (0.3 mm.), $n^{25}D$ 1.5623.

Anal. Calcd. for $C_{10}H_{15}NS$: C, 66.24; H, 8.34. Found: C, 66.44; H, 8.50.

(7) R. Mani, W. Meyer zu Reckendorf, and W. A. Bonner, *Chem. Ber.*, **95**, 1000 (1962).

(8) See E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 5.

(9) Unless otherwise noted, melting points were determined with a Mel-Temp apparatus and are uncorrected. Specific rotations were determined with a Standard Model D Keston polarimeter attachment to a Beckman DU spectrophotometer, calibrated with standard sucrose solutions.[10] Subsequently some of the signs of rotation were confirmed with a Rudolph Model 80 high precision polarimeter.

(10) See K. G. Poulsen, *Anal. Chem.*, **32**, 410 (1960).

(11) Generously furnished by Dr. D. P. Jacobus, Walter Reed Army Institute of Research, Washington, D. C.

(12) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **28**, 1305 (1963).

B. Salt with (−)-Malic Acid.[13]—Equimolar amounts (5.00 mmoles) of the free base and (−)-malic acid were allowed to react in boiling ethanol (4 ml.) for a few minutes. The solution was cooled and and diluted with chloroform (15 ml.). The resulting solution was placed in a refrigerator, and after 4 days the acid salt had deposited as a white crystalline powder, which was collected, washed with ether, and dried *in vacuo* at 58° over phosphorus pentoxide. The yield was essentially quantitative, m.p. 95°.[14] Recrystallization of a 1.00-g. sample from 1-propanol resulted in 85% recovery of optically inactive salt (dried *in vacuo* at 78°); melting point was unchanged.

Anal. Calcd. for $C_{14}H_{21}NO_5S$: C, 53.31, H, 6.71. Found: C, 53.26; H, 6.58.

Further recrystallizations from 1-propanol, ethanol–chloroform, or ethanol–carbon tetrachloride did not affect the melting point. This salt is very soluble in cold methanol and ethanol.

C. Salt with (+)-Tartaric Acid.—Warm (50–60°) solutions of equimolar amounts (5.00 mmoles) of the free base and (+)-tartaric acid in ethanol (4 ml.) were combined. The initially clear solution rapidly deposited a white crystalline precipitate. The mixture was diluted with ether (20 ml.), and the white solid was collected and dried *in vacuo* at 78° over phosphorus pentoxide. The yield of acid tartrate was quantitative, m.p. 146–148°.[14] Repeated recrystallizations of this salt from widely varying volumes of methanol, ethanol, aqueous 1-propanol (96%), and water did not effect optical enrichment.

Anal. Calcd. for $C_{14}H_{21}NO_6S$: C, 50.74; H, 6.39. Found: C, 50.72; H, 6.41.

(±)-1-Amino-2-propanethiol [(±)-I].—A solution of (±)-1-amino-2-propanethiol hydrochloride[11] (54.8 g., 0.430 mole) in methanol (250 ml.) was added in a thin stream with vigorous stirring to a solution of an equimolar amount of sodium methoxide (from 9.89 g., 0.430 g -atom, of sodium) in methanol (250 ml.). Precipitated sodium chloride was removed by filtration, and the filtrate was evaporated at about 25 mm. with the bath temperature not exceeding 35°. The white residual solid was purified by sublimation under reduced pressure (bath 45–70° at 20–25 mm.); the yield of (±)-I was 32.6 g. (83%).

1-(5-Methylthiazolidin-2-yl)-D-*gluco*-1,2,3,4,5-pentanepentols (IIa and IIb).—A well-stirred mixture of (±)-1-amino-2-propanethiol (32.6 g., 0.358 mole), D-glucose (64.5 g., 0.358 mole), and methanol (530 ml.) was heated under reflux for 4.5 hr. (complete solution of the D-glucose occurred within 30 min.). The solution was transferred while still hot to a beaker, and crystallization was induced by scratching. The mixture was allowed to stand securely covered at room temperature for 48 hr. The heavy precipitate of short white needles was collected without the aid of additional methanol and was pressed as dry as possible on the funnel. (The filtrate was set aside for isolation of IIb.) The crude IIa, dried *in vacuo* at room temperature, weighed 32.6 g. and melted at 124–129°. Recrystallization from methanol afforded pure IIa, yield 24.7 g. (27%), m.p. 131–132°, $[\alpha]^{25}D$ −50.9 ± 1.0° (*c* 1.48 g./dl., water). Further recrystallization did not change the melting point or the specific rotation.

Anal. Calcd. for $C_9H_{19}NO_5S$: C, 42.67; H, 7.56. Found: C, 42.54; H, 7.59.

The filtrate set aside for isolation of IIb was concentrated by distillation at atmospheric pressure until 230 ml. of distillate had been collected. The residual solution was transferred to a beaker and allowed to stand securely covered at room temperature for 72 hr. A crop of hard colorless granules gradually deposited. This first crop of crude IIb was collected and dried *in vacuo* at room temperature (11.5 g., m.p. 105–109°). The filtrate was then concentrated to about 100 ml. and seeded with a powdered sample of the first crop. Precipitation of a second crop began immediately, and after 43 hr. at room temperature the crude second crop (27.0 g., m.p. 98–107°) was collected. The two crops were separately pulverized and recrystallized twice from minimum volumes of methanol. In the first recrystallization the samples were dissolved, respectively, in 30 and 75 ml. of boiling methanol, and after 4 days at room temperature the recrystallized samples were collected: (1) 8.17 g., m.p. 109–112°; and (2) 12.9 g., m.p. 108–112°. In the second recrystallization the respective volumes of solvent were 25 and 35 ml., and after 3 days at room temperature, the recrystallized samples were collected: (1) 5.65 g. and (2) 9.76 g. having the identical m.p. 110–112° (unchanged by further recrystallization). The pure IIb obtained, 15.4 g. (17%), was optically inactive.

Anal. Calcd. for $C_9H_{12}NO_5S$: C, 42.67; H, 7.56. Found: C, 42.62; H, 7.66.

(−)- and (+)-5-Methyl-2-phenylthiazolidines [(−)-III and (+)-III].—In a typical run IIa (17.3 g., 0.0683 mole) was dissolved in warm 50% (by weight) aqueous ethanol (35 ml.), and benzaldehyde (8.90 g., 84.0 mmoles) was added. The solution was refluxed with stirring for 18 hr. The cooled reaction mixture, which deposited (−)-III as white needles, was treated with 18% sodium bisulfite solution (150 ml.), and the resulting mixture was stirred at room temperature for about 2 hr. After the mixture had been refrigerated for 2–3 hr., the crude pale yellow product was collected and dried *in vacuo* at room temperature (8.20 g., m.p. 75–77°). Recrystallization from aqueous ethanol with Norit treatment afforded 7.52 g. (61%) of (−)-III as white needles, m.p. 77–79°. For analysis a small sample was recrystallized from cyclohexane, with melting point unchanged, $[\alpha]^{25}D$ −34.9 ± 1.1° (*c* 1.30 g./dl., chloroform) and −48.1 ± 1.01° (*c* 1.40 g./dl., 0.1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}NS$: C, 66.98; H, 7.31. Found: C, 67.25; H, 7.43.

Application of the procedure described above to IIb afforded (+)-III in similar yield, m.p. 77–79°, $[\alpha]^{25}D$ +32.6 ± 1.4° (*c* 1.02 g./dl., chloroform) and +47.4 ± 1.4° (*c* 1.01 g./dl., 0.1 *N* HCl).

(+)- and (−)-1-Amino-2-propanethiol [(+)-I and (−)-I] Hydrochlorides.—A solution of (−)-III (13.62 g., 0.0760 mole) in 6 *N* hydrochloric acid (200 ml.) was heated to the boiling point in a simple distillation apparatus fitted with a Claisen head and a pressure-equalized dropping funnel, a continuously positive nitrogen pressure being maintained. The first drop of distillate contained benzaldehyde. Distillation was continued while additional 6 *N* hydrochloric acid (180 ml.) was gradually dripped into the boiling solution so as to maintain the volume at 190–200 ml. After about 200 ml. of distillate had been collected during 3 hr., the distillate had become clear. The residual solution was treated with Norit, and the filtrate was evaporated to dryness under reduced pressure. The residue, which crystallized readily, was dissolved in methanol (50 ml.); the solution was evaporated to dryness under reduced pressure. This dissolution and evaporation was repeated, the second solution being treated with Norit and filtered through a Celite mat. The resultant white crystalline solid was dissolved in boiling methanol (35 ml.). Addition of ether to the cool solution precipitated (+)-I hydrochloride as lustrous white platelets, which were collected under nitrogen and dried *in vacuo* at room temperature, yield 9.10 g. (94%), melting point not sharp (sintering at *ca.* 65°, melting completely at 80°), $[\alpha]^{25}D$ +35.3 ± 0.9° (*c* 1.46 g./dl., water).

Anal. Calcd. for $C_3H_9NS \cdot HCl$: C, 28.24; H, 7.90. Found: C, 28.44; H, 7.87.

Under the conditions described above, (−)-I was obtained from (+)-III in 95% yield and had the same melting characteristics as (+)-I, $[\alpha]^{25}D$ −36.4 ± 1.1° (*c* 1.27 g./dl., water).

Anal. Calcd. for $C_3H_9NS \cdot HCl$: C, 28.24; H, 7.90. Found: C, 28.17; H, 7.90.

(+)- and (±)-5-Methyl-2-phenylthiazolidines from (−)- and (±)-1-Amino-2-propanethiol Hydrochlorides and Benzaldehyde.—A solution of (−)-1-amino-2-propanethiol hydrochloride (1.28 g., 10.0 mmoles) and benzaldehyde (1.10 g., 10.4 mmoles) in 50% (by weight) aqueous ethanol was refluxed for 15 min., cooled, and evaporated under reduced pressure to a viscous oil. The residue was triturated in three 15-ml. portions of ether, the ethereal phase being removed by decantation. The ether-insoluble matter was then dissolved in water, and the solution was made basic by the dropwise addition of 10% sodium hydroxide solution. The white precipitate was dried *in vacuo* over phosphorus pentoxide, yield 1.42 g. (79%), m.p. 74–76°. Recrystallization from cyclohexane raised the melting point to 77–79°, which is identical with that of (+)-III made from IIb (and (−)-III made from IIa), $[\alpha]^{25}D$ +29.4 ± 2.3° (*c* 1.01 g./dl., chloroform) and +43.4 ± 2.3° (*c* 1.00 g./dl., 0.1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}NS$: C, 66.98; H, 7.31. Found: C, 67.17; H, 7.33.

The procedure described above afforded a 94% yield of crude (±)-5-methyl-2-phenylthiazolidine (7.41 g., m.p. 62–66°) when applied to (±)-1-amino-2-propanethiol hydrochloride (5.62 g.). Successive recrystallizations from aqueous ethanol and cyclohexane raised the melting point to 67–69° (unchanged by further recrystallization from cyclohexane).

(13) The salt with (+)-10-camphorsulfonic acid was a sirup, which could not be induced to crystallize.

(14) Determined with a Kofler Heizbank.

Anal. Calcd. for $C_{10}H_{13}NS$: C, 66.98; H, 7.31. Found: C, 66.98; H, 7.47.

Acknowledgment.—The authors are indebted to Dr. B. L. Appleton for pointing out the Taguchi method of resolution, to Dr. J. A. Montgomery and Dr. Y. F. Shealy for helpful discussions, and to Dr. W. J. Barrett and associates of the analytical section of this Institute for microanalyses and specific rotations.

The Cleavage of Methylenebis(diphenylphosphine) by Phenyl Azide

ADAM M. AGUIAR[1] AND JOHN BEISLER

Chemistry Department, Tulane University, New Orleans, Louisiana, and Chemistry Department, Fairleigh Dickinson University, Madison, New Jersey

Received December 12, 1963

In connection with some work on organophosphorus systems containing nitrogen, we have had occasion to study the reaction of polymethylenebis(diphenylphosphines) with phenyl azide. The isolation of *p*-phenylenebis(diphenylphosphinimine) from the reaction of 1,4-bis(diphenylphosphino)benzene with phenyl azide was reported recently.[2]

It was found that an ether–tetrahydrofuran solution of phenyl azide and 1,2-ethylenebis(diphenylphosphine) in 2:1 mole ratio evolved nitrogen to give a product which exhibited an elemental composition, molecular weight, infrared spectrum, and n.m.r. spectrum expected for 1,2-ethylenebis(diphenylphosphinimine) (I, eq. 1).

$$2PhN_3 + (Ph_2PCH_2)_2 \longrightarrow [Ph_2P(NPh)CH_2]_2\ (I) \qquad (1)$$

Hydrolysis of I produced 1,2-ethylenebis(diphenylphosphine) dioxide as expected (eq. 2).

$$[Ph_2P(NPh)CH_2]_2 + 2H_2O \longrightarrow [Ph_2P(O)CH_2]_2 + 2PhNH_2 \qquad (2)$$

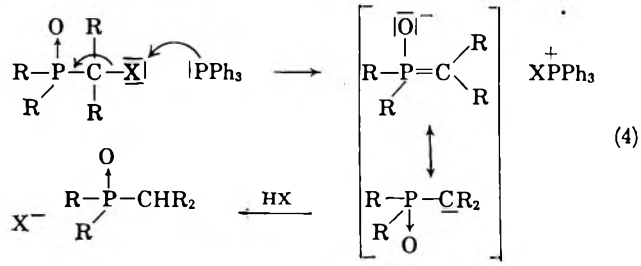
However, a 2:1 mole ratio of phenyl azide to methylenebis(diphenylphosphine) in ether did not lead to the isolation of a diphosphinimine. After a mildly exothermic slow gas evolution there occurred deposition of crystals of diphenylphosphinic acid anilide in 20.6% yield. The remaining solution gave more anilide when evaporated so that 78% was isolated. Column chromatography of the remaining sirup resulted in the isolation of methyldiphenylphosphine and its oxide in 64% yield as demonstrated by comparison with material produced from the reaction of lithium diphenylphosphide and methylchloride. Apparently the diphosphine was cleaved by phenyl azide (eq. 3).

$$(Ph_2P)_2CH_2 + PhN_3 \longrightarrow X \xrightarrow[H_2O]{air} Ph_2P(O)NHPh + Ph_2P(O)CH_3 \qquad (3)$$

The reaction was carried out under an atmosphere of prepurified nitrogen; therefore, the origin of the oxygen in the diphenylphosphinic acid anilide crystallizing out of the reaction solution poses a problem. Molecular oxygen and water were most probably present in very small amounts in the reagents and nitrogen used. Exposure to air after deposition of crystals and gas evolution had ceased did not cause any further gas evolution or precipitation. The significant fact, however, is that under similar reaction conditions essentially no cleavage of the ethylenebis compound occurred.

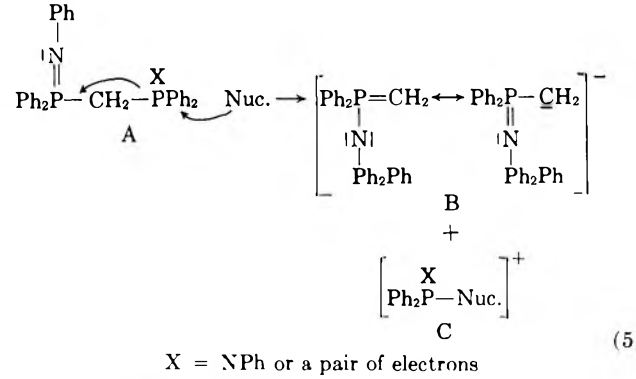
Although only 1 mole of phenyl azide appeared in the isolated products, an excess of azide helped in gaining cleavage. An equimolar solution of methylenebis(diphenylphosphine) and phenyl azide in ether evolved gas, but attempts at isolation of products resulted in the isolation of methylenebis(diphenylphosphine) dioxide (57%) and a small amount of diphenylphosphinic anilide. The presence of methyldiphenylphosphine oxide, determined by gas–liquid partition chromatography, presented further evidence that some cleavage of the diphosphine had occurred.

Horner, *et al.*, have shown that halogen atoms α to a phosphorus carrying a positive charge are not readily displaced by a nucleophile but can be replaced by a proton in the presence of triphenylphosphine.[3] Nucleophilic attack on the partially positive α-halogen with the concurrent displacement of a resonance stabilized carbanion can be proposed as an explanation (eq. 4).



(4)

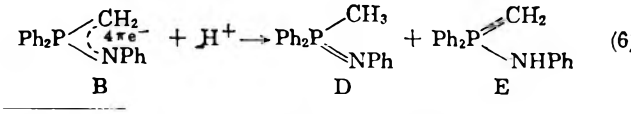
Methyldiphenylphosphine oxides are known to form anions in the presence of strong bases.[4,5] It is therefore reasonable to expect the monoimine or diimine of methylenebis(diphenylphosphine) (A) to cleave in the presence of a nucleophile (Nuc.) to give a resonance stabilized anion B (eq. 5).



X = NPh or a pair of electrons

(5)

The reaction of anion B with water (below) would result in a mixture of the N-phenylimine of methyldiphenylphosphine (D) and the tautomeric phosphinemethylene (E) (eq. 6). Further hydrolysis would be expected to lead to methyldiphenylphosphine oxide and aniline (eq. 7).



(6)

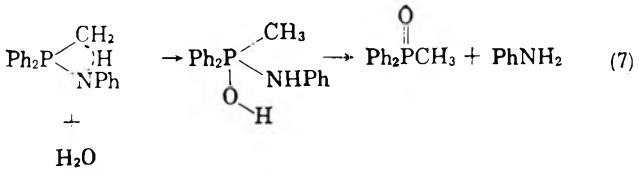
(1) To whom inquiries regarding this article should be sent at Tulane University, New Orleans 18, La.

(2) D. L. Herring, *J. Org. Chem.*, **26**, 3998 (1961).

(3) L. Horner, H. Hoffman, H. Ertel, and G. Klahre, *Tetrahedron Letters* **1**, 9 (1961).

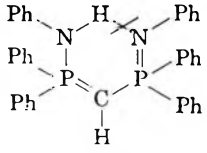
(4) J. J. Richard and C. V. Banks, *J. Org. Chem.*, **28**, 125 (1963).

(5) L. Horner, H. Hoffman, H. G. Wippel, and G. Klahre, *Chem. Ber.*, **92**, 2499 (1959).



(7)

If the cleavage is due to instability of the diimine to water, cation C would be protonated diphenylphosphinic anilide. One might expect the methylenebis(diphenylphosphinimine) to be more stable than the corresponding ethylenebis compound due to the possibility of intramolecular hydrogen bonding (structure 1).

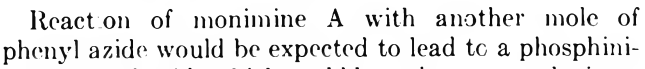


Structure 1

Staudinger reported in 1921 that phenyl azide reacted with neither phosphorus trichloride nor phenylphosphonous dichloride.[6] In view of this fact it does not seem likely that phenyl azide should exhibit sufficient nucleophilicity to displace anion B from a tertiary phosphine. Phenyl azide can be seen to behave as an electrophile toward tertiary phosphines from the order of reactivity as reported by Staudinger: triethylphosphine > diethylphenylphosphine > triphenylphosphine.[7]

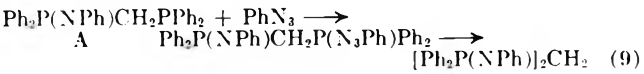
Spontaneous decomposition of monoimine A to give the products eventually seems unlikely. Support for this point of view is provided by the lesser extent of cleavage of the diphosphine in the reaction of equimolar amounts of methylenebis(diphenylphosphine) and phenyl azide.

Reaction of tertiary phosphines with phenyl azide have been reported to lead to phosphazides (in which the terminal nitrogen is bonded to the phosphorus) which then lose nitrogen producing phosphinimines[6,7] (eq. 8).



(8)

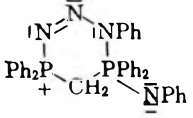
Reaction of monimine A with another mole of phenyl azide would be expected to lead to a phosphinimine phosphazide which could lose nitrogen producing a diphosphinimine (eq. 9).



(9)

The possibility of intramolecular reaction of the phosphinimine phosphazide exists when the number of bridging methylene groups is such as to allow a favorable five- or six-membered cyclical intermediate (structure 2).

Decomposition of such an intermediate might lead to cleavage of a phosphorus to carbon bond, loss of nitrogen, and, after hydrolysis, to methyldiphenylphosphine oxide and diphenylphosphinic acid anilide. Although ethylenebis(diphenylphosphine) might form a seven-membered intermediate similar to that postulated in structure 2, cleavage to form ethyldiphenylphosphine is not favored by the possibility of 3d-2p overlap in the ejected fragment. Olefinic elimination apparently involves a higher energy of activation. The reported isolation of a diphosphinimine from the reaction of *p*-phenylenebis(diphenylphosphine) and phenyl azide is not surprising, since no cyclic intermediate is possible.[2]



Structure 2

The mild conditions under which this cleavage occurs coupled with the general ease of preparation of substituted methylenebis(diphenylphosphine) make the reaction potentially useful in the synthesis of substituted tertiary phosphine oxides.

Experimental

Methylenebis(diphenylphosphine).—A solution of dichloromethane (8.5 g., 0.05 mole) in 50 ml. of tetrahydrofuran was added dropwise to a rapidly stirred, refluxing tetrahydrofuran solution of lithium diphenylphosphide prepared from 0.1 mole of triphenylphosphine.[8] The reaction mass was then refluxed in a nitrogen atmosphere for 0.5 hr. and cooled to room temperature; it was then added to 1000 ml. of water with stirring. The solid thus obtained was filtered off, water washed, and recrystallized from ethanol and water. After drying, the material weighed 17.3 g. (90% yield based on starting triphenylphosphine) and had m.p. 120–121°, lit. m.p. 122,[9] 120–121.5.[10]

The infrared spectrum was that expected for methylenebis(diphenylphosphine). The Varian A-60 n.m.r. spectrum of a deuteriochloroform solution of this material exhibited a triplet at δ = 2.8 p.p.m. and a set of aromatic peaks centering at δ = 7.25 p.p.m. in a ratio of 1:10. The coupling constant was $J_{p\text{-}CH}$ = 1.5 c.p.s. An internal standard of tetramethylsilane was used.

Oxidation of Methylenebis(diphenylphosphine).—A solution of the above compound in acetone was treated with 3% hydrogen peroxide until it became cloudy and then allowed to stand. Concentration of this acetone solution by slow evaporation at room temperature gave crystals which were filtered off and recrystallized from ethanol and water. This material exhibited phosphoryl peaks in the infrared and melted at 180–181°, lit.[11,12] m.p. 180–182°.

The Varian A-60 n.m.r. spectrum of a deuteriochloroform solution of this material showed a triplet centered at δ = 3.57 p.p.m. with a coupling constant $J_{p\text{-}CH}$ = 15 c.p.s. and phenyl hydrogens centered at 7.42 and 7.8 p.p.m. in the ratio of 1:10. An internal standard of tetramethylsilane was used.

Ethylenebis(diphenylphosphine).—Substitution of 1,2-dichloroethane for dichloromethane in the procedure described above led to ethylenebis(diphenylphosphine) in 80% yield based on starting triphenylphosphine. The material exhibited a melting point of 140–141°, lit.[10,13] m.p. 143–144°, and an infrared spectrum that fit the structure assigned. Since Issleib and Muller[9] report m.p. 159–161°, it was felt that other supporting evidence for the assigned structure was needed.

Anal. Calcd. for $C_{26}H_{24}P_2$: C, 78.4; H, 6.03; P, 15.55. Found: C, 79.9; H, 6.00; P, 15.15.

Determination of the Varian A-60 n.m.r. spectrum of a deuteriochloroform solution of this material revealed a case of "virtual coupling" in that a triplet at δ = 2.12 p.p.m. and the phenyl complex centering at 7.25 p.p.m. in the ratio of 1:5 were observed. The coupling constant was $J_{p\text{-}CH}$ = 4.2 c.p.s. All shifts are relative to an internal standard of tetramethylsilane.

Ethylenebis(diphenylphosphine) Dioxide.—The acetone–3% hydrogen peroxide oxidation of the above compound gave a new material exhibiting phosphoryl peaks in the infrared and having

(6) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
(7) H. Staudinger and E. Hauser, *ibid.*, **4**, 861 (1921).
(8) A. M. Aguiar, J. Beisler, and A. Mills, *J. Org. Chem.*, **27**, 1001 (1962).
(9) K. Issleib and D. Muller, *Chem. Ber.*, **92**, 3175 (1959); *Chem. Abstr.*, **54**, 6503*f* (1960).
(10) W. Hewertson and H. R. Watson, *J. Chem. Soc.*, 1490 (1962).
(11) J. J. Richard, K. E. Burke, J. W. O'Laughlin, and C. V. Banks, *J. Am. Chem. Soc.*, **83**, 1722 (1962).
(12) J. J. Richard and C. V. Banks, *J. Org. Chem.*, **28**, 125 (1963).
(13) J. Chatt and F. A. Hart, *J. Chem. Soc.*, 1384 (1960).

a melting point of 267–268.5°, lit. m.p. 276–278°,[14] 273–275°.[15] Issleib and Muller[9] reported m.p. 252–254°. Thus it was felt essential to obtain further support for the assigned structure.

Anal. Calcd. for $C_{26}H_{24}O_2P_2$: C, 72.56; H, 5.58; P, 14.04. Found: C, 72.64; H, 5.58; P, 13.52.

The n.m.r. Varian A-60 spectrum of a deuteriochloroform solution of this material showed the methylene hydrogens as a doublet at δ = 2.6 p.p.m. with a $J_{P\text{-}CH}$ of 2.5 c.p.s. and phenyl hydrogens centered at 7.5 and 7.8 p.p.m. in the ratio of 1:5. All shifts are relative to an internal standard of tetramethylsilane.

Reaction of Ethylenebis(diphenylphosphine) with Phenyl Azide.—A slurry of 4.0 g. (0.01 mole) of ethylenebis(diphenylphosphine) in 175 ml. of anhydrous ether was brought to complete solution with 75 ml. of anhydrous tetrahydrofuran, then placed under a nitrogen atmosphere. Dropwise addition of 2.5 g. (0.021 mole) of phenyl azide in 23 ml. of anhydrous ether to the stirred reaction solution produced a slight exothermic reaction. Immediately after completion of the addition, the reaction mass was colored an opaque yellow. In a week, 3.15 g. of cubic crystals, m.p. 194–198°, separated. The filtrate was stripped of solvent on a steam bath just short of dryness, and an air stream was directed onto the remaining sirup for 15 hr. The residue was triturated with ether–pentane (50:50) which yielded 1.2 g. of a solid, m.p. 169–187°. Repeated recrystallization from anhydrous benzene gave an analytically pure sample, m.p. 196–198°.

Anal. Calcd. for $C_{38}H_{34}N_2P_2$: C, 78.7; H, 5.87; N, 4.83; P, 10.69. Found: C, 78.21; H, 5.96; N, 4.83; P, 10.55.

An over-all yield of 75% was therefore obtained. The infrared spectrum of a chloroform solution of the material showed absorption at 3.15 (w), 6.21 (s), 6.90 (m), 7.46 (s), 7.55 (s), 8.50 (m), 8.95 (s) and 9.53 μ (m). The Varian A-60 n.m.r. spectrum of a deuteriochloroform solution of this material showed a split peak at δ = 2.7 p.p.m. and a complex set of peaks between 6.7 and 7.9 p.p.m. The relative areas were 1:7.5, respectively. All shifts are relative to an internal standard of tetramethylsilane.

The residual oil from the work-up was shown to contain ethyldiphenylphosphine oxide by comparison of the retention time (on high temperature gas chromatography) with that of an authentic sample made from lithium diphenylphosphide and ethylbromide.[16] Comparison of proton n.m.r. spectra also showed them to be identical. This compound exhibits a 1,3-coupling of the P^{31} and the methyl hydrogens in that the latter show up as a quintuplet centered at δ = 1.18 p.p.m. The methylene hydrogens show up as a complex set centered at δ = 2.31 p.p.m. while the phenyl hydrogens appear as a complex centered at about 7.65 p.p.m. Integrated areas are in the expected ratio.

The Acid Hydrolysis of Ethylenebis(phenyliminodiphenylphosphine).—A purified sample of ethylenebis(phenyliminodiphenylphosphine), m.p. 196–198° (0.52 g., 0.897 mmole), was combined with 15 ml. of 4 *N* hydrochloric acid and enough 95% ethanol to just dissolve the solid at 75°. The temperature was maintained at 75° for 40 hr. and then cooled.

Fine white crystals (0.22 g.) of ethylenebis(diphenylphosphine) dioxide, m.p. 268–269°, crystallized from the reaction. Mixture melting point with an authentic sample prepared by direct oxidation of ethylenebis(diphenylphosphine) with 3% hydrogen peroxide showed no depression. Evaporation of the ethanol solvent of the reaction mixture on a steam bath gave a second crop of solid (0.06 g.), m.p. 263–268°, bringing the total yield to 73%. The remaining aqueous solution was evaporated almost to dryness on a steam bath with the aid of an air stream. Residual water was removed azeotropically with benzene. The tan powder which remained did not melt below 270°. A small sample of this material was sublimed at atmospheric pressure and 200° to give crystals of aniline hydrochloride, m.p. 197–199°. Mixture melting point with an authentic sample produced no depression. The bulk of the powder was dissolved in 15 ml. of water (a small amount of insoluble material was filtered and discarded), made basic with concentrated sodium hydroxide solution, and ether extracted. After drying the combined ether extracts over calcium oxide, the solvent was evaporated leaving 0.087 g. (52%) of a liquid whose infrared spectrum was identical with that of aniline.

The Reaction of Methylenebis(diphenylphosphine) with 2 Moles of Phenyl Azide.—The diphosphine (2.98 g., 0.00776 mole) was dissolved in 250 ml. of anhydrous ether and to this was added 1.85 g. (0.0155 mole) of phenylazide in 30 ml. of anhydrous ether under a nitrogen atmosphere. A mildly exothermic reaction ensued, accompanied by slow gas evolution. The reaction solution was left standing for a week at room temperature. Large crystals (0.47 g.) slowly formed. The material was identified by its melting point (236–237°), infrared spectrum comparison, and mixture melting point with an authentic sample of diphenylphosphinic acid anilide.[17] The ethereal reaction solution was evaporated leaving a sirup from which 1.3 g. more of anilide, m.p. 235–237°, was obtained by ether trituration. The total yield of anilide isolated, therefore, was 78%. The triturate was stripped of solvent leaving 2.1 g. of a sirup which was chromatographed on a 1.5 × 37 cm. column of silica gel. Elution with *n*-hexane, benzene, and chloroform did not move the bands down the column. Elution with 750 ml. of chloroform saturated with water separated brown oils. When 100 ml. of chloroform–ethanol (10:1) was used as the eluent, 1.61 g. of a semicrystalline material was obtained. Recrystallization from cyclohexane yielded 1.07 g. of solid, m.p. 97–104°. Repeated recrystallization raised the melting point to 108–109°. The material showed a retention time identical with that of methyldiphenylphosphine oxide, lit.[12] m.p. 108–109°, synthesized from lithium diphenylphosphide and methyl chloride, on gas–liquid partition chromatographic analysis on silicone at 240°.[16] The Varian A-60 n.m.r. spectrum of a deuteriochloroform or carbon tetrachloride solution of this solid showed a complex signal centered around δ = 7.60 p.p.m. corresponding to the aromatic protons and a doublet centered at 1.9 p.p.m. (J = 14 c.p.s., relative to an internal tetramethylsilane standard) which could be assigned to the methyl protons. Therefore, it can be concluded that methyldiphenylphosphine oxide was produced in about 64% yield.

The Equimolecular Reaction of Methylenebis(diphenylphosphine) and Phenyl Azide.—A solution of 1.96 g. (0.00511 mole) of methylenebis(diphenylphosphine) in 250 ml. of anhydrous ether was treated with 0.61 g. (0.00512 mole) of phenyl azide in 15 ml. of anhydrous ether under nitrogen. Stirring was continued for 1 hr. after completion of the addition. The reaction mass was allowed to remain under nitrogen for 1 week. A small amount of solid material that had formed was filtered from the reaction solution and discarded. After evaporation, the ethereal solution yielded a sirup from which 0.50 g. of solid was obtained by trituration with ether–pentane (50:50). After the triturate had been stripped of solvent and allowed to stand 2 weeks, 0.55 g. of solid, m.p. 174–178°, was obtained by a similar trituration. The infrared spectra of both crops were identical with methylenebis(diphenylphosphine) dioxide, m.p. 184–185°, produced by a hydrogen peroxide oxidation of the parent biphosphine. The residual oil from the second triturate was chromatographed on a 12 mm. × 21 cm. column of silica gel eluted first with *n*-hexane and then with mixtures of *n*-hexane and benzene. The resulting fractions when combined gave 0.16 g. of methylenebis(diphenylphosphine) after one recrystallization from benzene–hexane; a total yield was 57%. Stripping the column with methanol–benzene (2:3) gave an oil which was shown to contain methyldiphenylphosphine oxide and benzene–phosphinic acid anilide by comparison of retention times with authentic samples using high temperature gas–liquid partition chromatography.[16] In addition, 0.05 g. of the anilide was isolated from the oil by recrystallization from methanol–water (m.p. 234–235°).

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(14) R. Struck, dissertation, Auburn University, 1961.

(15) P. T. Keough and M. Grayson, *J. Org. Chem.*, **27**, 1817 (1962).

(16) A. M. Aguiar, H. J. Greenberg, and K. E. Rubenstein, *ibid.*, **28**, 2091 (1963).

(17) D. C. Morrison, *J. Am. Chem. Soc.*, **73**, 5896 (1951).