flask was cooled in an ice-bath. When all the ketone had been added the mixture was hydrolyzed by pouring over cracked ice and adding dilute (10%) sulfuric acid. After drying, the ether layer was rectified yielding 3-methyl-1,1,1,2,2-pentafluoro-3-pentanol and 3,3,4,4,4-pentafluoro-2-butanol.

The Reaction of Isopropyl Grignard with 3,3,4,4,4-Pentafluoro-2-butanone.—Twenty-four grams of 3,3,4,4,4-pentafluoro-2-butanone was added to an ether solution of isopropyl Grignard reagent, prepared from 0.2 mole of isopropyl iodide and 0.2 mole of magnesium. After addition was completed the hydrolysis was accomplished by pouring over cracked ice and dilute sulfuric acid (25%). The ether layer was dried and rectified. A yield of 54% of the reduction product 3,3,4,4,4-pentafluoro-2-butanol was obtained

2-Methyl-3,3,4,4,4-pentafluoro-1-butene.—Phosphorus pentoxide (15 g., 0.11 mole) was added to a three-necked 200-ml. flask with dropping funnel and a reflux condenser attached. Forty grams (0.22 mole) of 2-methyl-3,3,4,4,4-pentafluoro-2-butanol was added through the dropping funnel. Reaction was slow at first but vigorous when heating was begun. A liquid b.p. 30–70° was collected which smelled only slightly of the initial alcohol. Rectification yielded the desired olefin.

3,3,4,4,4-Pentafluoro-1-butene.—Twenty-five grams of 3,3,4,4,4-pentafluoro-2-butanol was added to 10 g. (0.07 mole) of phosphorus pentoxide in a 200-ml. flask with attached condenser and Dry Ice cooled trap.

The alcohol was added through the condenser. On addition the mixture sputtered and fumed and heat was evolved. Heating was continued for three hours and the material in the flask turned dark and viscous. Fifteen grams of material was collected in the Dry Ice cooled trap and rectified in a low temperature Podbielniak column to give the olefin.

1,2-Dibromo-2-methyl-3,3,4,4,4-pentafluorobutane.—Seventeen grams (0.10 mole) of 2-methyl-3,3,4,4,4-pentafluoro-1-butene was added slowly dropwise to 16 g. (0.10 mole) of bromine dissolved in 50 ml. of carbon tetrachloride. A three-necked flask, with dropping funnel and condenser attached, was used. At first the flask was cooled in ice, but since no decolorization of the bromine solution was apparent, the flask was allowed to warm up and illuminated by a 100-watt lamp bulb. After 24 hours the bromine color still remained. The solution was washed with sodium bisulfite solution and rectified to yield the dibromo derivative.

1,2-Dibromo-3,3,4,4,4-pentafluorobutane.—Twenty grams of 3,3,4,4,4-pentafluoro-1-butene (0.13 mole) was distilled into a cooled Carius tube containing a solution of 64 g. of bromine (0.4 mole) in 50 ml. of carbon tetrachloride. After sealing, the mixture was allowed to warm to room temperature and illuminated by a 100-watt lamp bulb for 20 days. The tube was opened and the excess bromine removed with sodium bisulfite. After drying over Drierite the solution was rectified to give the dibromo derivative.

3,3,4,4,4-Pentafluoro-2-butyl Acetate.—An excess of acetic anhydride was added to 46 g. (0.25 mole) of 3,3,4,4,4-pentafluoro-2-butanol and refluxed overnight. Water was added to separate the acetic acid and the alcohol. The mixture was warmed to destroy the excess of anhydride, and the lower organic layer was washed with water several times, dried and rectified to obtain the acetate.

Methyl Xanthate of 3,3,4,4,4-Pentafluoro-2-butanol.—Sixty-seven and one-half grams of 3,3,4,4,4-pentafluoro-2-butanol (0.4 mole) was added to 500 ml. of anhydrous diethyl ether and 50 ml. of carbon tetrachloride in a two-liter flask equipped with stirrer, dropping funnel and reflux condenser. Seventeen grams of sodium hydroxide (0.42 mole) was pulverized and added to the solution which was refluxed for three hours. Carbon disulfide (30.4 g., 0.4 mole) was then added and the mixture refluxed for four hours. Methyl iodide (56.8 g., 0.4 mole) was added dropwise and the mixture refluxed for 12 hours. The liquid was decanted from the solids, the low boiling constituents removed by distillation and the remaining liquid distilled under reduced pressure.

Preparation of Derivatives.—Known procedures were used for the preparation of the derivatives listed in Table II.

LAFAYETTE, INDIANA RECEIVED AUGUST 29, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, QUEEN'S UNIVERSITY]

2-Octadecenoic Acid. II. Preparation of the 2,3-Epoxystearic Acids and the Configurational Relationships between the 2,3-Epoxy-, Bromoacetoxy- and Dihydroxystearic Acids

BY GORDON S. MYERS[1]

The reaction scheme described by Swern, to correlate the configurations of the compounds formed in the conversion of oleic and elaidic acids (*cis*- and *trans*-9-octadecenoic acids, respectively) to the 9,10-dihydroxystearic acids, through the intermediate epoxy and chlorohydroxy compounds, has been used to correlate the stereochemical relationships involved in the conversion of *cis*- and *trans*-2-octadecenoic acids to the 2,3-dihydroxystearic acids, both by direct hydroxylation and by way of the intermediate bromoacetoxy and oxirane compounds. Positions have been assigned to the bromine and acetoxy groups in three 2,3(3,2)-bromoacetoxystearic acids, the preparations of which were recorded in a previous publication. The following new compounds have been described: 2,3-epoxystearic acid (m.p. 87.5–88°), 2,3-epoxystearic acid (m.p. 90.5–91°), 3,2-bromohydroxystearic acid (m.p. 83–83.3°) and its ethyl ester, and ethyl 3,2-bromoacetoxystearate (m.p. 40.5–41°).

The stereochemical relationships involved in the conversion of *cis*- and *trans*-9-octadecenoic acids to the 9,10-dihydroxystearic acids, by the way of the intermediate epoxy and chlorohydroxy compounds, have been studied by King[2] and also by Atherton and Hilditch.[3] More recently, Swern[4] has suggested a scheme, differing on several points with those proposed by the former, which correlates the configurational relationships involved. It was of interest to extend this mechanism scheme to correlate the stereochemical relationships of the 2,3-epoxy-, bromoacetoxy- and dihydroxystearic acid derivatives of the 2-octadecenoic acids; the latter, unlike oleic and elaidic acids, having the carbon–carbon unsaturation adjacent to the carboxyl group.

The 2,3(3,2)-bromoacetoxystearic acid melting at 57° (I), which was obtained by reaction of the high-melting 2,3-dihydroxystearic acid isomer (m.p. 126°) with hydrogen bromide in acetic acid,[5] has been converted with dilute alkali to 2,3-epoxystearic acid melting at 87.5° (II). Although this epoxide was difficult to hydrolyze in hot dilute sulfuric acid, the oxirane ring could be opened readily by acetylation with acetic acid containing a catalytic amount of sulfuric acid. The diacetoxystearic acid so obtained (not isolated) was saponified to the low-melting 2,3-dihydroxystearic acid isomer (m.p. 107°). Both the 2,3-bromoacetoxystearic acid

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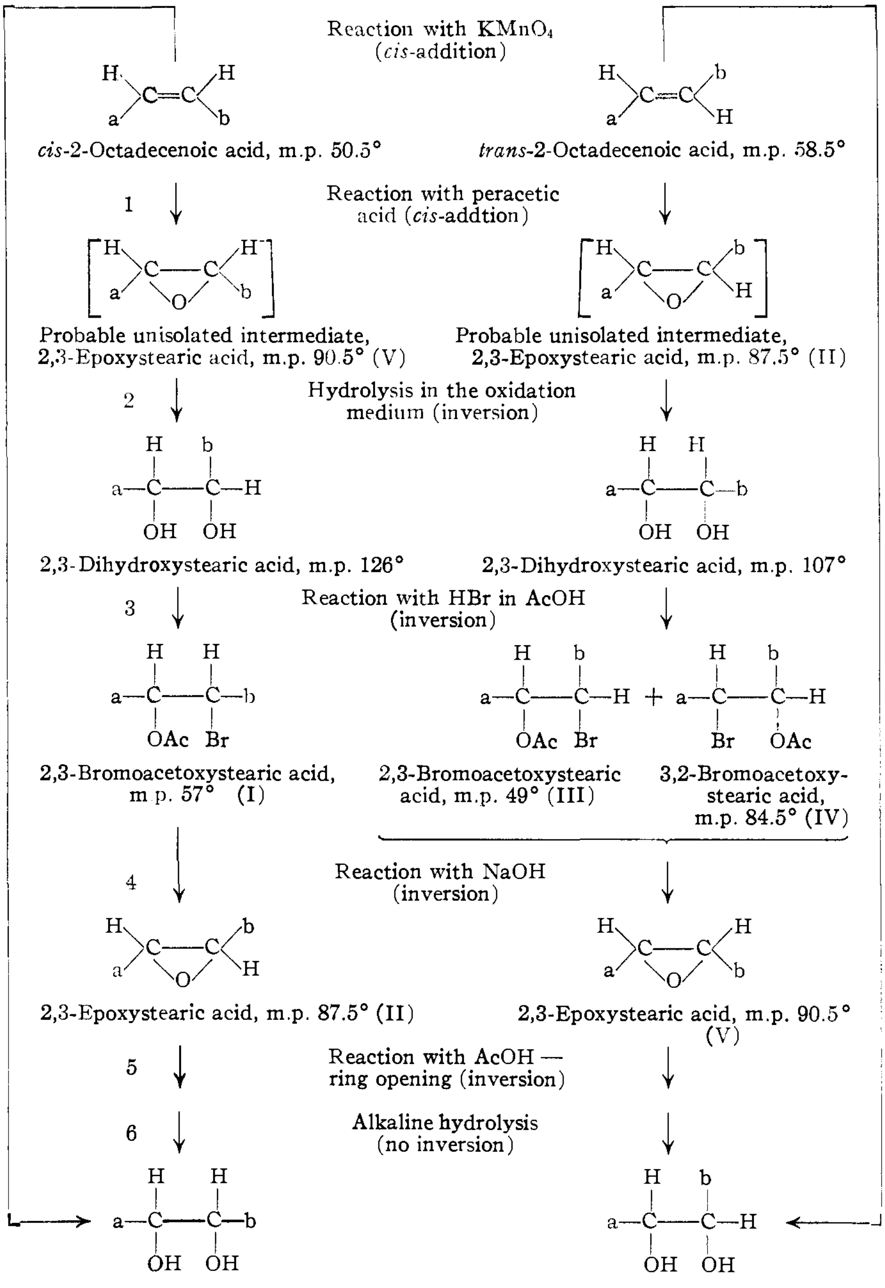
(1) Ayerst, McKenna & Harrison Ltd., Montreal.

(2) G. King, *J. Chem. Soc.*, 387 (1942).

(3) D. Atherton and T. P. Hilditch, *ibid.*, 204 (1943).

(4) D. Swern, THIS JOURNAL, **70**, 1235 (1948).

(5) G. S. Myers, *ibid.*, **73**, 2100 (1951).



a = CH_3—$(CH_2)_{14}$-; b = —CO_2H; Ac = CH_3—CO—

Fig. 1.

melting at 49° (III) and the 3,2-bromoacetoxystearic acid melting at 84.5° (IV), (obtained by treating 2,3-dihydroxystearic acid (m.p. 107°) with an acetic acid solution of hydrogen bromide[5]) on similar treatment with alkali, gave the other 2,3-epoxystearic acid isomer (V); m.p. 90.5°. Acetolysis of V, and subsequent hydrolysis of the product so obtained, gave the expected 2,3-dihydroxystearic acid melting at 126°.

When the preparations of the three bromoacetoxystearic acids (I, III, and IV) were originally described,[5] no definite positions were assigned to the bromine and acetoxy groups. Theoretically, two 2,3- and two 3,2-bromoacetoxy stereoisomers are possible. Attempts to establish the position of the acetoxy group in I and III by their catalytic hydrogenolysis to either of the known 2-acetoxy- or 3-acetoxystearic acids, were unsuccessful. Stearic acid resulted instead, in each case. However, when III was refluxed with methanol in the presence of a small amount of sulfuric acid, and the product so obtained (probably methyl 2,3-bromohydroxystearate) was debrominated by catalytic hydrogenolysis and then saponified, 3-hydroxystearic acid resulted. This would indicate III to be a 2,3-bromoacetoxystearic acid. Compound I is the other isomeric 2,3-bromoacetoxystearic acid since it was converted to 3-hydroxystearic acid on similar treatment. Since both III and IV gave the same epoxide, IV must be one of the 3,2-bromoacetoxystearic acid isomers. This was demonstrated when a solution of 2,3-epoxystearic acid (V) in ether was treated with dry hydrogen bromide and the 3,2-bromohydroxystearic acid so obtained (VI), m.p. 86–86.3° (identified as such by catalytic hydrogenolysis to 2-hydroxystearic acid) was acetylated to give a 3,2-bromoacetoxystearic acid identical to IV (see Fig. 2).

The stereochemical relationships of the compounds discussed above are outlined in Figs. 1, 2, and 3. They are in agreement with the following postulates made by Swern[4] in similar studies with oleic and elaidic acids: (1) Hydroxylation of unsaturated acids with alkaline potassium permanganate, or epoxidation with organic peracids, takes place by *cis*-addition; (2) opening and closing of an oxirane ring, as well as replacement of a hydroxyl group by halogen or a halogen by hydroxyl, are each accompanied by an inversion.

Findley, Swern and Scanlan[6] have shown that epoxy acids are formed in the peracetic acid oxidation of unsaturated acids in an organic solvent. Moreover, King[7] has isolated both 9,10-epoxystearic

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[6] T. W. Findley, D. Swern and J. T. Scanlan, THIS JOURNAL, 67, 412 (1945).

[7] G. King, *J. Chem. Soc.*, 37 (1943).

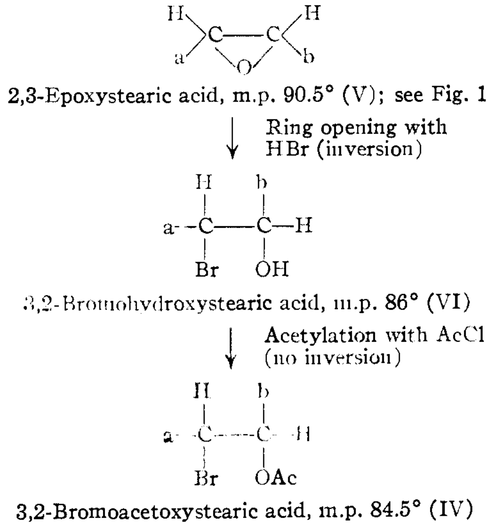

Fig. 2.

acid and 9,10(10,9)-hydroxyacetoxystearic acid when elaidic acid and oleic acid, respectively, are treated under restrained conditions of oxidation with hydrogen peroxide and acetic acid. Although no attempts were made to isolate the epoxystearic acid intermediates postulated in reaction 1 of Fig. 1, it is most probable that they were formed initially and were converted subsequently to the dihydroxy acids by a secondary hydrolysis.

Replacement of the bromine in 2,3-bromoacetoxystearic acid melting at 57° (I) with a hydroxyl group, by treatment with silver acetate followed by saponification, gave a dihydroxystearic acid with the expected inversion (see Fig. 3). The 2,3-bromoacetoxystearic acid melting at 49° (III), on similar treatment, gave what seemed to be a mixture of the two 2,3-dihydroxystearic acids—the one with the expected inversion (low-melting isomer) occurring to the smaller extent. In this connection, it is recalled that reaction of III in acetone with zinc dust gave a mixture of *cis*- and *trans*-2-octadecenoic acids, whereas I gave only the *trans*-acid.[5]

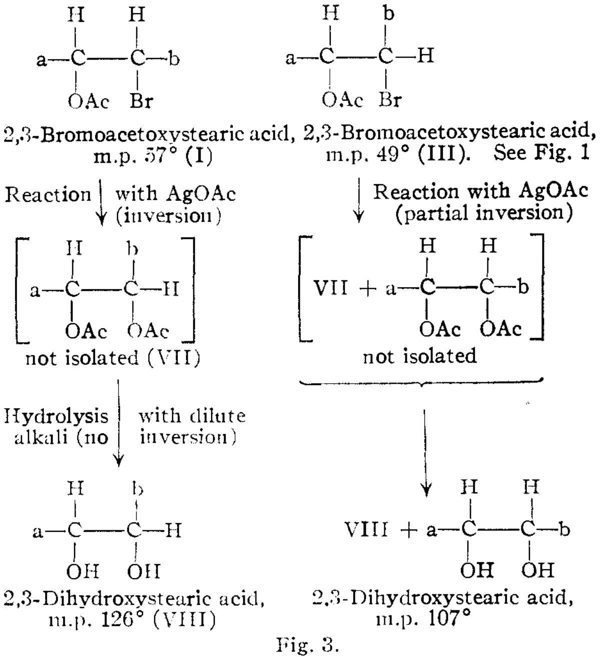

Fig. 3.

Experimental

Hydrogenolysis of the Isomeric 2,3-Bromoacetoxystearic Acids to Stearic Acid.—The high-melting 2,3-bromoacetoxystearic acid isomer (I), m.p. 57° (0.1 g.), was shaken in ethanol for 15 hours with hydrogen and Raney nickel catalyst at 3 atmospheres pressure. Removal of the catalyst, evaporation of the solvent, and crystallization of the residue (m.p. 66–67°) from acetone, gave 0.053 g. (79% yield) of stearic acid, m.p. 68.5–69°, which gave no melting point depression on admixture with an authentic sample.

The low-melting 2,3-bromoacetoxystearic acid isomer (III), m.p. 49° (0.1 g.), was hydrogenated in the same manner to give crude stearic acid (m.p. 64–66°) in quantitative yield. One crystallization from acetone gave 0.046 g. (68% yield); m.p. 67.5–68°.

Conversion of the Isomeric 2,3-Bromoacetoxystearic Acids to 3-Hydroxystearic Acid.—A solution of the low-melting 2,3-bromoacetoxystearic acid (III), m.p. 49° (0.2 g.), in 30 cc. of methanol containing 0.75 cc. of concentrated sulfuric acid, was refluxed for 24 hours. This solution was then diluted with water, extracted with ether and the ether extracts were washed with water and concentrated. The residue so obtained was dissolved in 20 cc. of ethanol containing 100 mg. of Adams platinum oxide catalyst and shaken with hydrogen, under slight pressure, for 4 days. The catalyst was then removed by filtration and the filtrate was diluted with 10 cc. of 10% aqueous sodium hydroxide and refluxed for 2 hours. This hydrolysate was acidified and then extracted with ether to give 0.136 g. of product, m.p. 60–65°. This material was suspended in 15 cc. of petroleum ether (b.p. 60–70°) and the insoluble 3-hydroxystearic acid (0.062 g.; 43% yield; m.p. 83–85°) was crystallized from acetone:hexane to a m.p. of 87–88°. This m.p. was depressed when the material was mixed with 2-hydroxystearic acid or either of the two 2,3-epoxystearic acids but was not depressed on admixture with 3-hydroxystearic acid (m.p. 90–90.2°).

The high-melting 2,3-bromoacetoxystearic acid (I), m.p. 57° (0.1 g.), on similar treatment gave a product melting at 87–88° which was identified as above as 3-hydroxystearic acid.

Preparation of the Isomeric 2,3-Epoxystearic Acids.—The low-melting isomer (II) was obtained by refluxing a solution of 0.22 g. of 2,3-bromoacetoxystearic acid (I), m.p. 57°, in 1.5 cc. of ethanol, with 3 cc. of 10% aqueous potassium hydroxide. The product was isolated by acidifying the reaction mixture and extracting it with ether. Evaporation of the ether gave 0.15 g. (97% yield) of 2,3-epoxystearic acid, m.p. 85–87°, which was recrystallized from acetone and ethanol to a constant m.p. of 87.5–88°.

Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.15; H, 11.4. Found: C, 71.2; H, 10.7.

The high-melting isomer (V) was obtained in excellent yield when 0.442 g. of 2,3-bromoacetoxystearic acid (III), m.p. 49°, in a 2 cc. of ethanol, was treated as described above with 6 cc. of 10% aqueous potassium hydroxide. The crude 2,3-epoxystearic acid was washed with petroleum ether and filtered to give 0.28 g. (90% yield), m.p. 89–90°. Further crystallizations from acetone raised the m.p. to 90.5–91°.

Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.15; H, 11.4. Found: C, 72.1; H, 11.5.

2,3-Epoxystearic acid (V) was obtained also, in almost theoretical yield, when 3,2-bromoacetoxystearic acid (IV), m.p. 84.5°, was treated in the same manner with alkali.

Hydrolysis of the 2,3-Epoxystearic Acids to the Isomeric 2,3-Dihydroxystearic Acids.—A 2% solution of sulfuric acid in acetic acid (10 cc.) and 0.298 g. of 2,3-epoxystearic acid (V) was digested at 100° for four hours. The reaction mixture was extracted with ether and the ether extract was washed with water and concentrated. The residue so obtained was saponified on a steam-bath with 10% aqueous sodium hydroxide. The crude 2,3-dihydroxystearic acid was extracted with ether from the acidified hydrolysate. Evaporation of the ether and crystallization of the residue from alcohol, gave 0.289 g. (92% yield) of 2,3-dihydroxystearic acid, m.p. 125–125.5°.

The low-melting 2,3-epoxystearic acid isomer (II)

(0.298 g.) on identical treatment gave 0.265 g. (84% yield) of purified 2,3-dihydroxystearic acid, m.p. 106–107°.

Preparation of 3,2-Bromohydroxystearic Acid (VI) and Its Ethyl Ester.—A solution of 1 g. of 2,3-epoxystearic acid (V) in 30 cc. of 0.3 *N* dry hydrogen bromide in ether, was allowed to stand for two days and then washed with water and evaporated. The residue (1.33 g., m.p. 44–56°) was separated by fractional recrystallization from petroleum ether and acetone, into 0.45 g. (36% yield) of 3,2-bromohydroxystearic acid (m.p. 83–84°), and 0.51 g. (38% yield) of ethyl 3,2-bromohydroxystearate (m.p. 53–53.5°). The bromohydroxystearic acid melted at 86–86.3° after further crystallizations from a mixture of acetone and petroleum ether.

Anal. Calcd. for $C_{18}H_{35}O_3Br$: C, 57.0; H, 9.31; Br, 21.1. Found: C, 56.4; H, 9.24; Br, 20.9.

Confirmation of the structure of the ethyl ester of VI (obtained above) was afforded by its preparation from esterification of VI (0.028 g.) with 10 cc. of absolute ethanol containing 0.2 cc. of concentrated sulfuric acid. The yield of crude ethyl ester after refluxing the reaction mixture for three hours, was 0.029 g. (96% yield), m.p. 52–53°.

Anal. Calcd. for $C_{20}H_{39}O_3Br$: C, 58.9; H, 9.65; Br, 19.6. Found: C, 59.5; H, 9.94; Br, 19.7.

Acetylation of 3,2-Bromohydroxystearic Acid (VI) and Its Ethyl Ester.—A solution of 0.05 g. of VI in 3 cc. of acetyl chloride was refluxed for one hour and then diluted with water and extracted with ether. Evaporation of the ether gave 0.055 g. of crude 3,2-bromoacetoxystearic acid, m.p. 74–78°. Further crystallizations of the crude from acetone and petroleum ether raised the m.p. to 82–83°. Mixed melting point with IV (m.p. 84.5°) gave no depression.

Treatment of 0.1 g. of the ethyl ester of 3,2-bromohydroxystearic acid (m.p. 53–53.5°) for one hour with 3 cc. of boiling acetyl chloride, gave 0.11 g. of gummy solid, which, after several crystallizations from petroleum ether (at −35°), gave small spherical crystalline clumps of ethyl 3,2-bromoacetoxystearate, m.p. 40.5–41°.

Anal. Calcd. for $C_{22}H_{41}O_4Br$: C, 58.8; H, 9.20; Br, 17.8. Found: C, 59.5; H, 9.51; Br, 17.9.

2-Hydroxystearic Acid from 3,2-Bromohydroxystearic Acid (VI).—A solution of 0.014 g. of VI in 10 cc. of alcohol was shaken for two days with hydrogen and Adams platinum oxide catalyst at 3 atmospheres pressure. The reaction mixture was then saponified at 37° with potassium hydroxide, acidified, and extracted with ether. The ether was evaporated to give 0.01 g. (90% yield) of crude 2-hydroxystearic acid, m.p. 83–84°. One crystallization from ethanol raised the m.p. to 84–85°. The m.p. of this material was depressed on admixture with 3-hydroxystearic acid (m.p. 90–90.2°) and with the isomeric 2,3-epoxystearic acids, but not with 2-hydroxystearic acid (m.p. 90–90.5°).

Conversion of the 2,3-Bromoacetoxystearic Acids to the Isomeric 2,3-Dihydroxystearic Acids.—A solution of 0.22 g. of 2,3-bromoacetoxystearic acid (I) and 0.23 g. of silver acetate in 3 cc. of acetic acid, was refluxed for 12 hours. The mixture was then treated with hydrochloric acid and extracted with ether. The ether extract was concentrated and the oily residue so obtained was saponified with aqueous potassium hydroxide and then acidified and extracted with ether. Evaporation of the ether gave a residue (m.p. 121–122°) which was washed with petroleum ether and crystallized from ethanol to give 0.132 g. (80% yield) of 2,3-dihydroxystearic acid, m.p. 125–125.5°.

A solution of 0.3 g. of 2,3-bromoacetoxystearic acid (III) and 0.3 g. of silver acetate in 3 cc. of acetic acid on similar treatment, gave 0.22 g. of solid (m.p. 116–118°), which was separated by fractional recrystallizations from acetone, petroleum ether and alcohol into 0.144 g. (64% yield), m.p. 122–124°, of the high-melting 2,3-dihydroxystearic acid isomer and 0.061 g. of material melting at 99–102°. Further crystallizations of the latter from mixtures of acetone and petroleum ether gave 0.020 g. of white solid, m.p. 100–103° which was probably the low-melting 2,3-dihydroxystearic acid isomer (since its m.p. was not depressed on admixture with an authentic sample. Its mixed melting point with the 2,3-dihydroxystearic acid of m.p. 126° was 99–109°).

Acknowledgment.—The author is indebted to the late Professor R. G. Sinclair for his interest and encouragement in this work. This study was made possible through a grant to the Department of Biochemistry, Queen's University, by the Ontario Cancer Treatment and Research Foundation.

MONTREAL, CANADA RECEIVED AUGUST 20, 1951

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Approaches to Total Synthesis of Adrenal Steroids. I. 3-Ethoxy-1,3-pentadiene

BY LEWIS H. SARETT, ROBERT M. LUKES, GEORGE I. POOS, JAMES M. ROBINSON, ROGER E. BEYLER, JOHN M. VANDEGRIFT AND GLEN E. ARTH

The preparation of 3-ethoxy-1,3-pentadiene and its Diels–Alder reactions with benzoquinone and toluquinone are described. The benzoquinone adduct may be reduced catalytically to 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione (XIII). The latter is smoothly reduced with lithium aluminum hydride to 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol (XIV).

Introduction to a Group of Papers

It is evident from consideration of formula A[1] that in any successful synthetic approach to the adrenal hormones, those reactions which generate linkages between rings will be stereospecific. The AB ring juncture does not offer a stereochemical problem, the angular methyl group at C_{10} being taken arbitrarily as above the plane of the nucleus and the double bond destroying asymmetry at C_5. Nor does any theoretical problem exist in introducing a 4,5-double bond into saturated intermediates with the AB juncture either *cis*[2] or *trans*.[3] On the other hand, the difficulties in establishing the *anti-trans* relationship between the three centers C_{10}, C_9 and C_8 are very real. Several approaches have involved the reduction of an 8,9-double bond, either as such or as part of an aromatic Ring C. That this reduction does not lead predominantly to compounds with the *anti* relationship of C_{10} and C_9 has been demonstrated by Cornforth and Robinson[4] in their fundamental investigations. In order to avoid the stereochemical uncertainties which in many ap-

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[1] A review of the data upon which this structure is based is presented by R. B. Turner in Fieser and Fieser's "Natural Products Related to Phenanthrene," Third Edition, Reinhold Publishing Corp., New York, N. Y., 1949.

[2] A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

[3] G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

[4] J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 676 (1946); *Nature*, **160**, 737 (1947).