[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CXXXVIII. The Conversion of Pregnan-3(β)-ol-20-one into etio-Cholan-3(β)-ol-17-one

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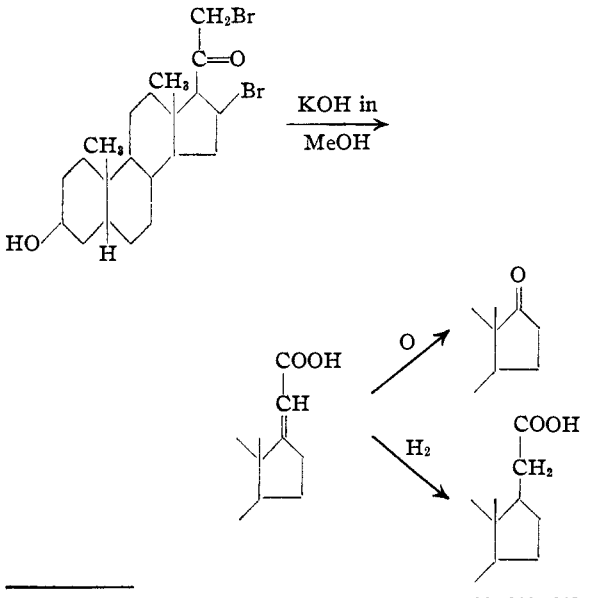
One of the possibilities sought in our present study of the halo-pregnan-3(β)-ol-20-one compounds[1] was a new method of conversion of the pregnane to the *etio*-cholane series. This end has now been attained. One of the experiments of Faworskii's[2] pioneer work on brominated ketones was the treatment of 3-methyl-1,3-dibromobutan-2-one with alcoholic potassium hydroxide to obtain β,β-dimethylacrylic acid. Analogous treatment of a 17,21-dibromopregnane compound should give a Δ^{17-20}-pregnene acid-21 capable of easy degradation to the *etio*-cholane series. This has been found to be the case with 17,21-dibromopregnan-3(β)-ol-20-one.

If 17,21-dibromo-pregnan-3(β)-ol-20-one be boiled with excess alcoholic potassium hydroxide, it is dehalogenated without rearrangement of the steroidal nucleus to give the unsaturated acid, 3(β)-hydroxy-Δ^{17-20}-pregnenoic acid-21. This unsaturated acid was reduced with hydrogen (Adams catalyst) to obtain a lower melting saturated acid. Oxidation of the acetylated unsaturated acid either by ozonolysis or with chromic acid in acetic acid gave *etio*-cholan-3(β)-ol-17-one acetate which was isolated as the semicarbazone. Hydrolysis of the semicarbazone gave the free hydroxy ketone which agreed in properties and composition with the reported values for this compound.



The reactions are summarized in the accompanying chart.

We wish to thank Parke, Davis and Company for their assistance.

Experimental

Action of Alcoholic Potassium Hydroxide on 17,21-Dibromopregnan-3(β)-ol-20-one.—To a solution of 1 g. of 17,21-dibromopregnan-3(β)-ol-20-one in 100 cc. of methanol was added a solution of 5 g. of potassium hydroxide in 5 cc. of water. The mixture was evaporated to 20 cc. on the steam-bath over a period of one hour. At the end of this time crystals had appeared. Water was added, whereby more solid precipitated. The total mixture was washed once with ether and then acidified. After warming five minutes with shaking, the mixture was cooled and extracted with ether, whereby the solid completely dissolved in the ether layer. The ether extract was washed with water and evaporated. The residue was crystallized from methanol to give white plates, m. p. 257–258° dec.; yield 0.37 g. This was 3(β)-hydroxy-Δ^{17-20}-pregnenoic acid-21.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 76.0; H, 9.7.

A solution of 0.1 g. of the unsaturated acid in 10 cc. of acetic anhydride was refluxed twenty minutes. The acetic anhydride was removed *in vacuo* and the residue was crystallized from methanol to give white crystals, m. p. 234°. Probably this compound is a mixed anhydride.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.1; H, 8.7. Found: C, 72.3; H, 8.8.

An acetate formed by the pyridine–acetic anhydride procedure crystallized from aqueous methanol as white crystals, m. p. 209–212°. This material apparently contains one molecule of water of crystallization.

Anal. Calcd. for $C_{23}H_{34}O_4 \cdot H_2O$: C, 70.4; H, 9.2. Found: C, 70.4; H, 8.9.

Catalytic Reduction of 3(β)-Hydroxy-Δ^{17-20}-pregnenoic Acid-21.—To a solution of 0.25 g. of the above acid in 100 cc. of acetic acid was added 0.25 g. of Adams catalyst, and the mixture was shaken with hydrogen at 3 atm. for two hours. The reaction mixture was filtered and the acetic acid removed *in vacuo*. The solid residue crystallized from methanol to give flat white needles, m. p. 219–221°; yield 0.2 g.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.4; H, 10.3.

Oxidation of the Acetylated 3(β)-Hydroxy-Δ^{17-20}-pregnenoic Acid-21.—With boiling acetic anhydride, 1.9 g. of

(1) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 210, 213 (1942).

(2) Faworskii, *J. Russ. Phys.-Chem. Soc.*, **44**, 1358 (1913); *J. prakt. Chem.*, [2] **88**, 658 (1913).

the above unsaturated acid was converted to the acetate. The excess acetic anhydride was evaporated *in vacuo* and the residue was dissolved in 50 cc. of acetic acid. To this solution was added a solution of 4 g. of chromic anhydride in 50 cc. of 80% acetic acid. The mixture was allowed to stand at 50–55° for four hours. The reaction mixture was cooled and poured into water. The mixture was extracted with ether and the ether extract was washed with water and 10% sodium hydroxide. The ether was evaporated and the residue was warmed with 5% alcoholic potassium hydroxide solution. The mixture was cooled, poured into water and extracted with ether. The ether was evaporated and the residue was dissolved in 50 cc. of 90% ethanol. To the hot alcoholic solution was added 2 g. of semicarbazide hydrochloride and 3 g. of sodium acetate. After refluxing for one hour, water was added and the precipitated solid was filtered. This material was crystallized from ethanol, m. p. 241–243° dec., yield 1 g. This gave no depression when mixed with an authentic sample of the semicarbazone of *etio*-cholan-3(α)-ol-17-one.

Anal. Calcd. for $C_{20}H_{33}N_3O_2$: C, 69.1; H, 9.6. Found: C, 69.3; H, 9.6.

Ozonolysis of 3(β)-Hydroxy-Δ^{17-20}-pregnenoic Acid-21.—The product obtained from the acetylation of 3.5 g. of 3(β)-hydroxy-Δ^{17-20}-pregnenoic acid-21 was dissolved in 300 cc. of dry chloroform. Oxygen containing 7% ozone was bubbled through this solution at the rate of 30 liters per hour for ten minutes. At the end of this time no more ozone was absorbed. The reaction mixture was poured into water and stirred for thirty minutes. It was then heated on the steam-bath with stirring until the chloroform had all distilled off. After cooling it was extracted with ether. The ether was evaporated and the residue was warmed with 3.5 g. of potassium hydroxide dissolved in 200 cc. of ethanol for one hour. The mixture was then treated as described above isolating the product as the semicarbazone. This latter was crystallized from ethanol, m. p. 253° dec., yield 2.0 g. It gave no depression in melting point when mixed with an authentic sample of the semicarbazone of *etio*-cholan-3(β)-ol-17-one.

Anal. Calcd. for $C_{20}H_{33}N_3O_2$: C, 69.1; H, 9.6. Found: C, 69.4; H, 9.5.

Hydrolysis of the Semicarbazone of *etio*-Cholan-3(β)-ol-17-one.—A solution of 1.3 g. of the semicarbazone of *etio*-cholan-3(β)-ol-17-one in 75 cc. of ethanol containing 7 cc. of concentrated sulfuric acid and 15 cc. of water was refluxed for one hour and then poured into water. The precipitated solid was extracted with ether. The ether extract was washed with water and the ether was evaporated. The crystalline residue was crystallized from ether–pentane to give long needles, m. p. 150–152°, which gave no depression in melting point when mixed with an authentic sample of *etio*-cholan-3(β)-ol-17-one.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.4; H, 10.3.

Summary

17,21-Dibromo-pregnan-3(β)-ol-20-one acetate has been converted to 3(β)-hydroxy-Δ^{17-20}-pregnenoic acid-21 and the latter reduced to 3(β)-hydroxy-pregnanoic acid-21.

3(β)-Hydroxy-Δ^{17-20}-pregnenoic acid-21 has been oxidized to *etio*-cholan-3(β)-ol-17-one.

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Sterols. CXXXIX. Sapogenins. LIX. The Bio-reduction of 4-Dehydrotigogenone[1,1a]

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Since coprosterol has not been obtained directly from cholesterol by chemical action, Schoenheimer believed that cholestenone was an intermediate in the formation of coprosterol in the animal intestine. He therefore fed cholestenone to a dog and examined the sterol content of the feces.[2] When the dog was on a basic meat diet an increased coprosterol excretion was observed, but with a diet of dog biscuits there was an increased cholesterol excretion. It seemed reasonable to conclude that the formation of cholestenone from cholesterol is a biologically reversible process. Additional evidence to this effect was secured by Diels[3] who found an increase in cholesterol content of the livers of guinea pigs after the administration of cholestenone. However, these experiments are subject to the objection noted by Anchel and Schoenheimer[4] that the cholesterol may not arise from the administered cholestenone but by a secondary effect of the latter on sterol metabolism, especially since it is known that the feeding of squalene and various other substances increases the excretion of cholesterol.[5] In order to make the experiments more exact, Schoenheimer and his co-workers introduced deuterium as an indicator. However, the feeding of deuterocholestenone to mice did not give information concerning the formation of cholesterol from cholestenone. Cholesterol with insignificant deuterium content was isolated from the feces but

(1) *Cf.* Marker, *et al.*, THIS JOURNAL, **63**, 1769 (1941).

(1a) Original manuscript received June 23, 1941.

(2) Schoenheimer, Rittenberg and Graff, *J. Biol. Chem.*, **111**, 183 (1935).

(3) Diels, *Z. ges. exp. Med.*, **100**, 527 (1937).

(4) Anchel and Schoenheimer, *J. Biol. Chem.*, **125**, 23 (1938).

(5) Channon and Tristram, *Biochem. J.*, **31**, 738 (1937).