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

Sterols. CXXIX. Rearrangement of 17-Bromopregnan-3(β)-ol-20-one*

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In a preceding paper[1] of this series the reaction of pregnan-3(β)-ol-20-one with an equimolecular quantity of bromine to yield the C-17 bromo derivative was described. We now wish to report that 17-bromopregnan-3(β)-ol-20-one when treated with a mild base undergoes a rearrangement which puts methyl and carbomethoxyl groups on C-17 (II).

Recently, Aston and Greenburg[2] showed that α-bromo secondary alkyl ketones reacting with sodium alcoholates readily undergo a rearrangement to give esters of tertiary acids. For example, 3-bromo-3-methyl-2-butanone treated with a suspension of sodium methylate in anhydrous ether yielded methyl trimethylacetate and 3,3-dimethoxy-2-methyl-2-butanol. By treating 17-bromo-

$$(CH_3)_2CBr\text{-}CO\text{-}CH_3 + NaOCH_3 \longrightarrow (CH_3)_3C\text{-}COOCH_3 + (CH_3)_2COHC(OCH_3)_2CH_3$$

pregnan-3(β)-ol-20-one acetate with an aqueous methanolic solution of potassium bicarbonate we have obtained the methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid (II). This substance is the main product of the reaction and represents a change entirely analogous to that obtained by Aston and Greenburg except that no second substance could be isolated.

We had hoped that the reaction would proceed by a simple replacement of the bromine to give the C-17 hydroxy derivative. Although *allo*-pregnan-3(β),17-diol-20-one is easily susceptible to oxidation at 15° and hydrogenation,[3] the acetylated compound (II) obtained by us did not lend itself to any such reactions. It was recovered unchanged from an oxidizing mixture heated at 50° for five hours and from an attempted hydrogenation with Adams catalyst. It also failed to react with semicarbazide acetate. Further, it was not affected by phosphorus oxychloride at 135°, thus showing the absence of a tertiary hydroxyl at C-17.

That our product is an ester is shown by the fact that a Bouveault reduction introduces a second hydroxy group. The product was isolated as the diacetate and as the free diol (IV). Because of its isomeric relation to the pregnanediols we have named this compound 17-methyl-21-*nor*-pregnan-3(β),20-diol (IV). The ester (II) resembles many esters of tertiary acids in that it reacts only after prolonged heating with alcoholic potash. The resulting 3(β)-hydroxy-17-methyl-*etio*-cholanic acid (V) was converted back to the original methyl ester (II) by diazomethane. The acid was oxidized with chromic anhydride to give the same keto acid (VII) as that obtained by a similar oxidation of the 17-methyl-21-*nor*-pregnan-3(β),20-diol (IV).

Because of the excellent yields of this rearrangement product the analogous compounds having the alpha configuration at C-3 were prepared to characterize it further. The non-acetylated methyl ester was oxidized at room temperature to 3-keto-17-methyl-*etio*-cholanic acid (III). Catalytic hydrogenation of the latter in a neutral medium with Adams catalyst gave as the major product the methyl ester of 3(α)-hydroxy-17-methyl-*etio*-cholanic acid (VI). A Bouveault reduction of this same keto ester gave 17-methyl-21-*nor*-pregnan-3(α),20-diol (VIII). The application of the Aston–Greenburg reaction in the steroids is being further studied.

The reactions discussed are pictured in the chart.

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Experimental Part

Reaction of 17-Bromopregnan-3(β)-ol-20-one Acetate with Methanolic Potassium Bicarbonate.—(a) To a solution of 5 g. of 17-bromopregnan-3(β)-ol-20-one acetate in 210 cc. of methanol was added a solution of 10 g. of potassium bicarbonate in 40 cc. of water. The mixture was refluxed at steam-bath temperature for three hours and then concentrated. Water was added to the concentrate and the precipitated solid was extracted with ether. An acetic anhydride solution of the residue was heated under reflux for twenty minutes. The excess solvent was removed and the residue was crystallized from methanol to give long flat needles, m. p. 136–138°; yield 2.2 g. This product is the acetate of the methyl ester of 3-(β)-hydroxy-17-methyl-*etio*-cholanic acid (II).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 73.8; H, 9.8.

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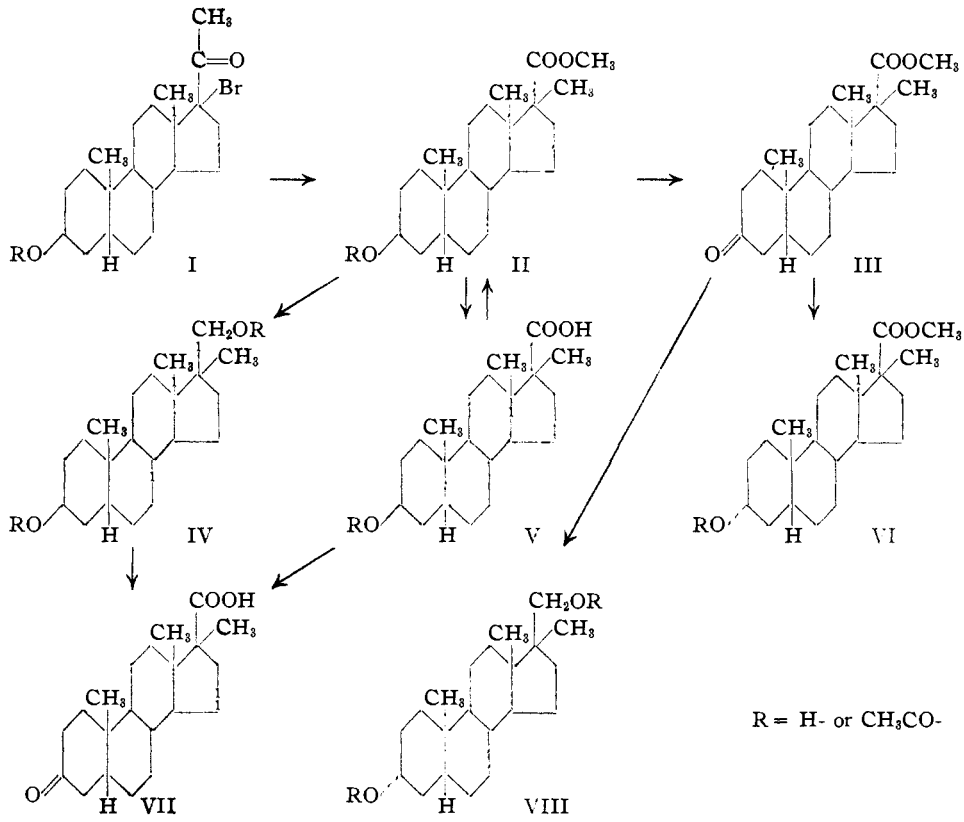
(1) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 210 (1942).

(2) Aston and Greenburg, *ibid.*, **62**, 2590 (1940).

(3) Reichstein and Gätzi, *Helv. Chim. Acta*, **21**, 1497 (1938).



(b) The same product (II) with a free 3-hydroxyl was made under the above conditions with the exception that the period of refluxing was prolonged an additional two hours and the reaction product was not acetylated. It was crystallized from aqueous methanol to give white crystals, m. p. 143–145°. This gave a depression of 60° when mixed with 16-pregnen-3(β)-ol-20-one acetate, m. p. 142–144°. It depressed the melting point of the methyl ester of 3(β)-hydroxy-*etio*-cholanic acid.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.7; H, 10.4. Found: C, 75.7; H, 9.9.

When refluxed with acetic anhydride it gave the above acetate, m. p. and mixed m. p. 136°.

The unacetylated ester was also obtained as a polymorphic form which crystallized from methanol and melted at 124–126°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.7; H, 10.4. Found: C, 75.9; H, 10.4.

The acetate (II) was recovered unchanged after refluxing at 135° for forty-five minutes with pyridine and phosphorus oxychloride. When subjected to catalytic hydrogenation in methanol–ether with Adams catalyst at 3 atm. pressure for two hours it was recovered unchanged. It did not react with semicarbazide acetate under the usual conditions. From an oxidizing mixture of chromic acid and acetic acid heated at 55° for five hours the acetate (II) was recovered unchanged.

Hydrolysis of the Methyl Ester of 3(β)-Acetoxy-17-methyl-*etio*-cholanic Acid (II).—A solution of one gram of the above methyl ester of 3(β)-acetoxy-17-methyl-*etio*-cholanic acid in 50 cc. of ethanol was heated with a solution of 10 g. of potassium hydroxide in 10 cc. of water for four days. The reaction product was precipitated with water and washed with ether. It was then acidified and extracted with ether. The ethereal solution was washed with water and evaporated. The residue was crystallized from methanol to give white crystals, m. p. 222–224°; yield 0.8 g. This depressed the melting point of 3(β)-hydroxy-*etio*-cholanic acid.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.1; H, 10.2.

When treated with an excess of diazomethane in ether it gave the original methyl ester, m. p. and mixed m. p. 142–144°.

3(β)-Acetoxy-17-methyl-*etio*-cholanic Acid.—A mixture of 100 mg. of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid, 5 cc. of dry distilled pyridine and 5 cc. of acetic anhydride was allowed to stand at room temperature for fourteen hours. It was then warmed on the steam-bath with 5 cc. of water for thirty minutes. Ether was added to the cooled mixture and the ethereal solution was washed with 10% hydrochloric acid and water. The ether was evaporated and the residue crystallized from methanol to give white crystals, m. p. 220–222°. This substance depressed the melting point of the starting material 45°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.3; H, 9.6. Found: C, 72.9; H, 9.5.

Oxidation of 3(β)-Hydroxy-17-methyl-*etio*-cholanic Acid to 3-Keto-17-methyl-*etio*-cholanic Acid.—To a solution of 100 mg. of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid in 7 cc. of acetic acid was added 60 mg. of chromic acid dissolved in 3 cc. of acetic acid. After standing for one hour

at room temperature the reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed thoroughly with water and then with 10% potassium hydroxide. The alkaline washings were combined, acidified, and extracted with ether. The ether was washed and evaporated. The residue was crystallized from methanol to give white plates, m. p. 224–226°. When mixed with the starting material there was a depression of 20° in melting point.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 75.8; H, 9.8.

Reduction of the Methyl Ester of 3(β)-Acetoxy-17-methyl-*etio*-cholanic Acid to 17-Methyl-21-*nor*-pregnan-3(β),20-diol.—To a solution of 1 g. of the methyl ester of 3(β)-acetoxy-17-methyl-*etio*-cholanic acid in 100 cc. of absolute ethanol was added 10 g. of sodium metal cut into small pieces, over a period of five minutes. After the vigorous reaction had ceased the mixture was heated under reflux for thirty minutes. Additional alcohol was added to dissolve the unreacted sodium and the mixture was diluted with water. It was acidified with dilute hydrochloric acid and the precipitated solid was extracted with ether. The ethereal solution was washed with 10% potassium hydroxide, water and 10% hydrochloric acid and evaporated. The dry residue was dissolved in 10 cc. of dry distilled pyridine and 10 cc. of acetic anhydride. The solution was allowed to stand at room temperature for fourteen hours. The reaction mixture was worked up in the usual manner and the product crystallized from methanol to give white crystals, m. p. 94–95°; yield 0.5 g.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.0; H, 9.8.

When refluxed with 2% alcoholic potassium hydroxide it gave white silky crystals from ether–pentane; m. p. 124°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.7; H, 11.3.

Oxidation of 17-Methyl-21-*nor*-pregnan-3(β),20-diol to 3-Keto-17-methyl-*etio*-cholanic Acid.—To a solution of 0.5 g. of 17-methyl-21-*nor*-pregnan-3(β),20-diol in 25 cc. of acetic acid was added a solution of 1 g. of chromic acid in 25 cc. of 90% acetic acid. It was worked up as previously described; m. p. 224–226°. A mixed melting point with the keto acid obtained by the oxidation of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid gave no depression in melting point.

A similar oxidation at room temperature for fourteen hours gave a product which crystallized from methanol as white crystals, m. p. 279°, dec. This prolonged treatment with chromic acid apparently formed a tricarboxylic acid by ring cleavage at C-3.

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.3; H, 8.5. Found: C, 66.5; H, 8.6.

Oxidation of the Methyl Ester of 3(β)-Hydroxy-17-methyl-*etio*-cholanic Acid to the Methyl Ester of 3-Keto-17-methyl-*etio*-cholanic Acid.—A solution of 1 g. of the methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid was oxidized with 0.5 g. of chromic acid in 100 cc. of acetic acid; m. p. 103–105°; yield 0.2 g.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.2; H, 9.9.

Reduction of the Methyl Ester of 3-Keto-17-methyl-*etio*-cholanic Acid to the Methyl Ester of 3(α)-Hydroxy-17-methyl-*etio*-cholanic Acid.—To a solution of 0.2 g. of the methyl ester of 3-keto-17-methyl-*etio*-cholanic acid dissolved in 35 cc. of dioxane was added 200 mg. of Adams catalyst. The mixture was shaken with hydrogen at three atm. pressure for two hours. The reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was then refluxed with acetic anhydride for twenty minutes. The solvent was removed *in vacuo* and the residue crystallized from methanol as white plates, m. p. 130–131°. When mixed with the methyl ester of 3(β)-acetoxy-17-methyl-*etio*-cholanic acid there was a 20° depression in the melting point.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 73.8; H, 9.8.

The above acetate, 100 mg., was refluxed with 2 cc. of 5% alcoholic potassium hydroxide for twenty minutes and then diluted with 5 cc. of water. The precipitated solid was filtered and washed with water. After drying it was crystallized from methanol to give white needles, m. p. 152–153°. This material gave no precipitate with digitonin.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 75.7; H, 10.2. Found: C, 75.9; H, 10.2.

Reduction of the Methyl Ester of 3-Keto-17-methyl-*etio*-cholanic Acid to the 17-Methyl-21-*nor*-pregnan-3(α),-20-diol.—The methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid, 0.4 g., was oxidized as described above. The product was reduced with sodium and ethanol in the exact manner described for the reduction of the methyl ester of 3(β)-acetoxy-17-methyl-*etio*-cholanic acid. The dry reaction product was acetylated by refluxing with acetic anhydride for twenty minutes. The solvent was removed *in vacuo* and the residue was crystallized from methanol to give white crystals, m. p. 123–125°, resolidified and melted at 156°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.5; H, 10.3.

Summary

1. 17-Bromopregnan-3(β)-ol-20-one has been shown to undergo an Aston–Greenburg rearrangement when refluxed with aqueous methanolic potassium bicarbonate to give the methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid.

2. Reduction of the methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid with sodium and ethanol gives 17-methyl-21-*nor*-pregnan-3(β),-20-diol.

3. Hydrolysis of the methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid gave the corresponding acid which upon oxidation with chromic anhydride gave the same keto acid obtained by a similar oxidation of 17-methyl-21-*nor*-pregnan-3(β),20-diol.

4. The corresponding derivatives with the alpha configuration at C-3 were prepared.

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