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Sterols. CLII. Rearrangement of 16,17-Dibromopregnan-3(β)-ol-20-one[1]

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During the course of our recent studies of bromopregnan-20-keto compounds, we found that 17,21-dibromopregnan-3(β)-ol-20-one acetate[2] under vigorous alkali treatment yields 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid. We now find that 16,17-dibromopregnan-3(β)-ol-20-one acetate undergoes a rearrangement to give this same product and the corresponding methyl ester.

Bromination of 16-pregnen-3(β)-ol-20-one acetate (I) in acetic acid solution gives a good yield of the 16,17-dibromide (II). That the formation of the latter was not attended by any rearrangement was shown by the simple debromination of the product (II) with methanolic sodium iodide to give the original olefinic compound (I) in almost quantitative yield. The debromination was effected equally well with boiling pyridine. Since the dibromo compound (II) was easily converted to 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) under exactly the same conditions as those required for the formation of IV from 17,21-dibromopregnan-3(β)-ol-20-one acetate[2] it was necessary to show that these two dibromo compounds were really different. For this purpose, 16,17-dibromopregnan-3(β)-ol-20-one acetate (II) was refluxed with potassium acetate in acetic acid solution. The product isolated was 16-pregnen-3(β)-ol-20-one acetate (I). Similar treatment of 17,21-dibromopregnan-3(β)-ol-20-one acetate has been previously shown[3] to give 21-bromo-16-pregnen-3(β)-ol-20-one acetate. Thus the 16,17-dibromide is readily debrominated to give the olefinic compound, whereas the 17,21-dibromide loses hydrobromic acid under the same conditions to give an unsaturated monobromide. The peculiar reactivity of the 16,17-dibromide is further shown by its action with hydrogen and palladium-barium sulfate catalyst in the presence of dioxane and pyridine to give compound I.

When 16,17-dibromopregnan-3(β)-ol-20-one acetate (II) is treated with a boiling solution of methanolic potassium hydroxide, it gives a mixture of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) and the corresponding methyl ester (III). The unsaturated acid agrees in properties and composition with that obtained by similar treatment of 17,21-dibromopregnan-3(β)-ol-20-one acetate. Although the reaction of the latter with alcoholic potash is similar to a reaction reported by Faworskii,[4] who obtained β,β′-dimethylacrylic acid from 3-methyl-1,3-dibromo-2-butanone, we have been unable to find in the literature any analogous rearrangement for α,β-dibromo ketones. Whereas α,β-dibromo ketones are known to hydrolyze to α,β-diketones, it was impossible for our compound to take such a course.

The unsaturated acid (IV) is converted to the unsaturated methyl ester (III) by diazomethane in ether. This methyl ester (III) is identical with the ester isolated in the neutral fraction of this reaction. The ester was not found by us in our previously described rearrangement[2] of the 17,21-dibromo compound, and its isolation here may have an important bearing on any mechanism which might be proposed.

Catalytic hydrogenation of the acid (IV) with Adams catalyst gave a lower melting saturated acid which was identified by composition and physical properties as 3(β)-hydroxypregnan-21-oic acid, previously described by us.[2] Similar hydrogenation of the unsaturated methyl ester (III) followed by alkaline hydrolysis gave the same saturated acid. Both the saturated and the unsaturated (III) methyl esters, acetylated and unacetylated, agree in melting points and properties with the corresponding esters obtained by subsequent treatment of the acid from the rearrangement of the 17,21-dibromide acetate. The saturated methyl ester depresses the melting point of the methyl ester of 3(β)-hydroxy-17-methyl-etiocholanic acid obtained from the reaction of 17-bromopregnan-3(β)-ol-20-one with alcoholic potassium bicarbonate.[5]

In order to furnish additional proof of the identity of this unsaturated acid (IV) it was oxidized by ozonolysis in chloroform to give etio-cholan-3(β)-ol-17-one (V) which was isolated as the semicarbazone. Acid hydrolysis of the latter gives the free hydroxy-ketone (V) which was the same as the compound described before.[2]

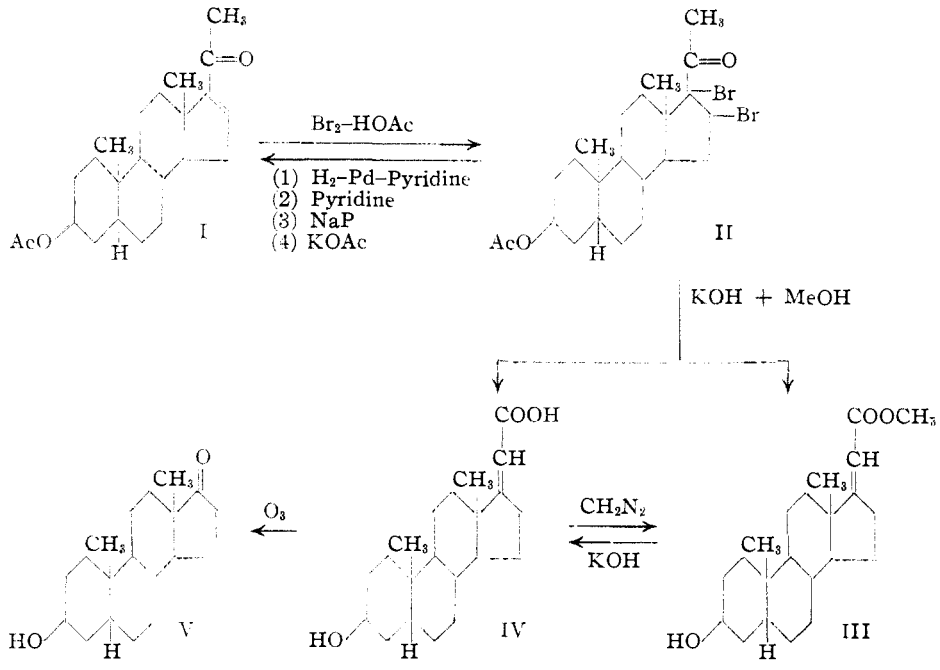
(1) Original manuscript received July 16, 1941.

(2) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 817 (1942).

(3) *Ibid.*, **64**, 213 (1942).

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

(5) Marker and Wagner, THIS JOURNAL, **64**, 216 (1942).



The reactions discussed are summarized in the chart.

The easy attainment of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid by the rearrangement of 17,-21-dibromopregnan-3(β)-ol-20-one[5] has encouraged further studies on this acid. Furthermore, it was desirable to prepare several derivatives which would ensure the identity of the rearrangement products from the 16,17-dibromo compound (II).

While we previously[5] reported the degradation of this unsaturated acid (IV) to *etio*-cholan-3(β)-ol-17-one (V) by the method of ozonolysis or chromic anhydride oxidation, we have now found a much better method for this conversion, namely, alkaline potassium permanganate oxidation. The product (V) is isolated directly in the free state and does not have to be purified in the form of the semicarbazone as previously reported. This modification results in a greater over-all yield and furnishes a good source of the hydroxy-ketone.

In order to obtain the hydroxy-ketone having the *epi*-configuration, the methyl ester of the unsaturated acid (III) was successively oxidized and reduced by the Oppenauer and Meerwein procedures. The methyl ester of 3(α)-hydroxy-Δ^{17-20}-pregnen-21-oic acid was not isolated but was ozonized to give *etio*-cholan-(3)α-ol-17-one 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. It was further identified by mixed melting point with an authentic sample of *etio*-cholan-3(α)-ol-17-one.

The fact that α,β-unsaturated acids are easily reduced by sodium and alcohol was used to advantage when the unsaturated acid (IV) was simultaneously reduced at the 17,20-position and epimerized at C-3 by sodium and amyl alcohol to give 3(α)-hydroxy-pregnan-21-oic acid. Oxidation of 3(β)-hydroxy-pregnan-21-oic acid gave the 3-keto acid which by neutral hydrogenation (Adams catalyst) gave 3(α)-hydroxypregnan-21-oic acid. The methyl esters of these acids were prepared to further characterize them and these were reduced by a Bouveault–Blanc reduction to the corresponding pregnan-3,21-diols.

Experimental Part

16,17-Dibromo-pregnan-3(β)-ol-20-one Acetate (II).—To a solution of 5 g. of 16,17-pregnen-3(β)-ol-20-one acetate (I) in 200 cc. of acetic acid was added 14 cc. of molar bromine in acetic acid solution. The mixture was poured into water and filtered. The dibromide was crystallized twice from methanol, m. p. 137–140°; yield 4.8 g.

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.3; H, 6.6. Found: C, 53.5; H, 6.7.

Debromination of 16,17-Dibromopregnan-3(β)-ol-20-one Acetate (II)—(a) With palladium hydrogen and pyridine: a solution of 1 g. of the dibromide (II) in 125 cc. of dioxane and 3 cc. of pyridine was shaken with hydrogen and 2 g. of palladium–barium sulfate catalyst for two hours at room temperature and three atmospheres. The catalyst was filtered, and the solution was evaporated *in vacuo*. An

ethereal solution of the residue was washed with dilute hydrochloric acid and water, and then evaporated. The residue was crystallized three times from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate (I), 143–144°; yield 0.5 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.1; H, 9.7.

(b) **With pyridine:** a solution of 1 g. of the dibromide (II) in 5 cc. of pyridine was refluxed for three hours. Water was added, and the mixture was extracted with ether. The ether layer was washed with water, dilute hydrochloric acid and water, and then evaporated. The residue crystallized from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate (I), 141–144°; yield 0.1 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.0; H, 9.7.

(c) **With alcoholic sodium iodide:** a solution of 2.1 g. of the dibromide (II) in 100 cc. of methanol was refluxed with 2.2 g. of sodium iodide for one hour. A solution of sodium bisulfite was added and the mixture extracted with ether. The ether layer was washed with water and evaporated. The residue was recrystallized twice from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate, 141–144°; yield 1.2 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 76.7; H, 9.5.

(d) **With potassium acetate:** a solution of 1 g. of 16,17-dibromo-pregnan-3(β)-ol-20-one acetate (II) in 15 cc. of acetic acid was refluxed with 1.5 g. of fused potassium acetate for one hour. The solution was evaporated *in vacuo* and the residue was extracted with ether. The ether layer was washed and evaporated. The residue was crystallized twice from methanol, m. p. and mixed m. p. with 16-pregnen-3(β)-ol-20-one acetate, 140–143°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 76.9; H, 9.7.

Reaction of Methanolic Potassium Hydroxide with 16,17-Dibromopregnan-3(β)-ol-20-one Acetate (II).—A solution of 5 g. of the dibromide (II) in 1 l. of methanol was refluxed with 25 g. of potassium hydroxide for one hour. Water was added and the mixture was extracted with ether.

Acid Fraction.—The alkaline water layer was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed with water and evaporated. The crystalline residue was recrystallized from methanol, m. p. and mixed m. p. with 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid, 254–256° dec.; yield 2.0 g.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 76.2; H, 9.7.

(a) **Methyl Ester** (III).—When treated with an ethereal solution of diazomethane, the above unsaturated acid formed a methyl ester, m. p. and mixed m. p. with the methyl ester of 3(β)-hydroxy-$\Delta^{17,20}$-pregnen-21-oic acid, 153–156°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.4; H, 9.8.

(b) **Acetate of** (IV).—The acetate was prepared by the action of pyridine and acetic anhydride on the above unsaturated acid. It was crystallized from dry methanol to give white crystals, m. p. 161–163°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.7; H, 9.2. Found: C, 73.7; H, 9.2.

(c) **Reduction of Unsaturated Acid** (IV).—A mixture of 200 mg. of the above unsaturated acid was hydrogenated with Adams catalyst at room temperature and three atm. for two hours. The product was crystallized from methanol, m. p. and mixed m. p. with 3(β)-hydroxypregnan-21-oic acid, 219–220°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.5; H, 10.2.

(d) **Acetate of the Saturated Acid.**—When the saturated acid from (c) was treated with pyridine–acetic anhydride mixture it gave an acetate which crystallized from methanol, m. p. and mixed m. p. with 3(β)-acetoxypregnan-21-oic acid, 219–221°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.3; H, 9.6. Found: C, 73.6; H, 9.7.

(e) **Methyl Ester of Saturated Acid.**—An ethereal solution of 200 mg. of the unacetylated saturated acid from (c) was treated with an ethereal solution of diazomethane to give the methyl ester, m. p. and mixed m. p. with the methyl ester of 3(β)-hydroxypregnan-21-oic acid, 141–143°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.8; H, 10.4. Found: C, 76.0; H, 10.4.

(f) **Acetate of Saturated Methyl Ester.**—A solution of 100 mg. of the saturated methyl ester from (e) in pyridine–acetic anhydride yielded a product which crystallized from methanol as large white plates, m. p. and mixed m. p. with the methyl ester of 3(β)-acetoxy-pregnan-21-oic acid, 105–106°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 74.2; H, 9.9.

Neutral Fraction.—The neutral fraction was obtained by evaporating the ether from the alkaline hydrolysis product and crystallizing the residue from methanol, m. p. and mixed m. p. with the methyl ester of the above unacetylated unsaturated acid from (a), 153–156°; yield 0.3 g. This also did not give any depression of melting point when mixed with the methyl ester of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.4; H, 9.8.

(g) **Acetate of the Unsaturated Methyl Ester** (III).—An acetate formed by the pyridine–acetic anhydride procedure crystallized from methanol, m. p. and mixed m. p. with the methyl ester of 3(β)-acetoxy-$\Delta^{17,20}$-pregnen-21-oic acid, 103–105°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.2; H, 9.3. Found: C, 74.1; H, 9.1.

(h) **Reduction of the Acetylated Unsaturated Methyl Ester** (III).—A solution of 150 mg. of the acetate from (g) in acetic acid was hydrogenated with Adams catalyst at room temperature and three atm. for two hours. The product was crystallized from methanol to give fine white needles, m. p. and mixed m. p. with the methyl ester of 3(β)-acetoxy-pregnan-21-oic acid and with the acetylated saturated methyl ester from (f), 102–105°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 74.1; H, 9.9.

(i) **Hydrolysis of the Saturated Methyl Ester.**—A solution of 100 mg. of the saturated methyl ester from (h) in 20% ethanolic potassium hydroxide was refluxed for sixteen hours, the mixture cooled and diluted with water. The solid suspension was washed with ether, acidified, and ether-extracted. The product crystallized from methanol to give white needles, m. p. and mixed m. p. with (3)-hydroxypregnan-21-oic acid and the saturated acid from (c), 218–220°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.3; H, 10.2.

Ozonolysis of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid (IV) Obtained by Rearrangement of the 16,17-Dibromide (II).—Through a solution of 2.1 g. of the unsaturated acid (IV) in chloroform was bubbled oxygen containing 7% ozone at the rate of 30 l. per hour for ninety minutes. The mixture was decomposed with water and the chloroform steam distilled. The product was extracted with ether and the ethereal solution was washed with 10% potassium hydroxide and evaporated. The residue with an ethanolic solution of semicarbazide acetate yielded a semicarbazone which crystallized from methanol, m. p. and mixed m. p. with the semicarbazone of *etio*-cholan-3(β)-ol-17-one (V), 251–253° dec.; yield 0.8 g.

Anal. Calcd. for $C_{26}H_{33}N_3O_3$: C, 69.1; H, 9.6. Found: C, 69.4; H, 9.6.

A solution of the semicarbazone dissolved in 50 cc. of ethanol containing 5 cc. of concd. sulfuric acid and 10 cc. of water was refluxed for one hour. The product was crystallized from ether–pentane to give long needles, m. p. and mixed m. p. with *etio*-cholan-3(β)-ol-17-one, 150–152°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.7; H, 10.3.

In the following experiments only 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid from the rearrangement of 17,21-dibromopregnan-3(β)-ol-20-one acetate[2] was used.

Conversion of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid (IV) to etio-Cholan-3(β)-ol-17-one (V).—To 0.5 g. of 3(β)-hydroxy-$^{17-20}$-pregnen-21-oic acid (IV) suspended in 20 cc. of water was added a solution of 0.5 g. of potassium hydroxide in 20 cc. of water. The mixture was stirred at 0° until all of the acid dissolved. To this solution was added 30 cc. of 2% potassium permanganate, which was the amount necessary to give a permanent pink color. The excess permanganate was destroyed with sodium bisulfite and the mixture extracted with ether. The ethereal solution was washed with water and evaporated. The solid residue was crystallized from ether–pentane to give long needles, m. p. and mixed m. p. with *etio*-cholan-3(β)-ol-17-one (V), 150–152°; yield 0.3 g.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.7; H, 10.3.

Methyl Ester of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid.—A solution of 50 mg. of 3(β)-hydroxy-$^{17-20}$ pregnen-21-oic acid (IV) in ether was treated with a cold ethereal solution of diazomethane. The ethereal solution after standing sixteen hours was evaporated and the residue was crystallized from methanol to give white flat plates, m. p. 153–155°.

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

Conversion of the Methyl Ester of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid to *etio*-Cholan-3(α)-ol-17-one.—To a solution of 4 g. of the methyl ester of 3(α)-hydroxy-$^{17-20}$-pregnen-21-oic acid in 200 cc. of dry toluene was added 25 cc. of dry acetone and 20 g. of aluminum isopropylate. The mixture was refluxed six hours, cooled, and acidified with dilute hydrochloric acid. The product was extracted with ether. After evaporation of the solvent, the residue was again treated with 200 cc. of dry isopropyl alcohol and 20 g. of aluminum isopropylate at reflux temperature for sixteen hours. The solution was slowly distilled over a period of five hours. The residue was acidified with dilute hydrochloric acid and extracted with ether. The product from the removal of the solvent was suspended in water and the volatile oils removed by steam distillation. The water was decanted and the remaining solid was dissolved in methanol and treated with digitonin in the usual manner. The non-digitonin precipitated fraction was dissolved in 200 cc. of chloroform. Through this solution was bubbled oxygen containing 7% ozone for fifteen minutes at the rate of 30 l. per hour. At the end of this time no more ozone was absorbed. The reaction mixture was decomposed with water and the chloroform removed by steam distillation. After cooling, the residue was dissolved in ether and the ethereal solution was washed well with 10% potassium hydroxide. The product from ether was converted to the semicarbazone, which crystallized from ethanol, m. p. 235° dec.; yield 0.5 g.

Anal. Calcd. for $C_{20}H_{33}N_3O_2$: C, 69.1; H, 9.6. Found: C, 68.7; H, 9.6.

The above semicarbazone was dissolved in 25 cc. of ethanol containing 2 cc. of concentrated sulfuric acid and 5 cc. of water. The mixture was refluxed for one hour and then poured into water. The product was crystallized from ether, m. p. and mixed m. p. with *etio*-cholan-3(α)-ol-17-one, 147°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.5; H, 10.3.

Epimerization and Reduction of 3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic Acid (IV). (a) With Sodium and Amyl Alcohol.—To a solution of 0.5 g. of the unsaturated acid (IV) in 200 cc. of *n*-amyl alcohol was added 10 g. of sodium. The mixture was heated under reflux for nine hours. The cooled reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The residue from the ether was warmed with 50 cc. of 10% methanolic potassium hydroxide and the alcohol removed. The remaining oily layer was removed with ether. The aqueous layer was acidified and any volatile acids were removed by steam distillation. The cooled mixture was extracted with ether and the product was crystallized from methanol, m. p. 224–226°; yield 0.2 g. This substance is 3(α)-hydroxy-pregnan-21-oic acid. It depressed the melting point of 3(β)-hydroxy-pregnan-21-oic acid and the starting material (IV).

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

The methyl ester was prepared in the usual manner with diazomethane and crystallized from 80% methanol as white needles, m. p. 118–119°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.8; H, 10.4. Found: C, 75.6; H, 10.3.

The acetate of the above methyl ester was prepared by the pyridine–acetic anhydride procedure. It was crystallized from aqueous methanol as white platelets, m. p. 85–87°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 73.7; H, 10.0.

(b) **By Catalytic Reduction Followed by Epimerization.**—A solution of 0.3 g. of the unsaturated acid in acetic acid was shaken with hydrogen and Adams catalyst for two hours at room temperature and three atm. pressure. This gave 3(β)-hydroxy-pregnan-21-oic acid, previously described.[2] The product was dissolved in 90 cc. of *n*-amyl alcohol and treated with 6 g. of sodium as described in (a). The product was crystallized from methanol, m. p. and mixed m. p. with the material from (a), 224–226°.

3-Keto-pregnan-21-oic Acid.—To a solution of 1 g. of 3(β)-hydroxy-pregnan-21-oic acid in 50 cc. of acetic acid was added a solution of 0.5 g. of chromic anhydride in 50 cc. of 90% acetic acid. After standing one hour at room temperature, the mixture was diluted with water. The precipitated solid was extracted with ether and the ethereal solution was washed thoroughly with water to remove the acetic acid. The solvent was removed and the residue was crystallized from acetone, m. p. 170–172°; yield 0.7 g.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 75.5; H, 9.7.

The methyl ester was prepared as described above and crystallized from aqueous methanol to give white crystals, m. p. 121–123°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.2; H, 10.0.

Reduction of 3-Keto-pregnan-21-oic Acid.—A solution of 200 mg. of the keto acid in dioxane was shaken with hydrogen and Adams catalyst for two hours at room temperature and 3 atm. pressure. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was crystallized from methanol, m. p. and mixed m. p. with the above 3(α)-hydroxypregnan-21-oic acid, 223–226°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.6; H, 10.3.

Methyl Ester of 3(β)-Hydroxypregnan-21-oic Acid.—A solution of 200 mg. of 3(β)-hydroxypregnan-21-oic acid in ether was added to a cold ethereal solution of diazomethane. The product was crystallized from methanol as white plates, m. p. 141–143°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.8; H, 10.4. Found: C, 75.8; H, 10.5.

The above mother liquor was evaporated to dryness and the residue was treated with pyridine and acetic anhydride. The product was crystallized from methanol as white crystals, m. p. 102–104°. This is the acetate of the methyl ester of 3(β)-hydroxypregnan-21-oic acid.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 74.2; H, 9.9.

Pregnan-3(β),21-diol.—To a solution of 0.5 g. of the methyl ester of 3(β)-hydroxypregnan-21-oic acid in 100 cc. of absolute ethanol was added 10 g. of sodium metal. After the vigorous reaction had ceased, the mixture was refluxed for thirty minutes. The excess sodium was dissolved with aqueous ethanol and the reaction mixture was acidified with hydrochloric acid. The product was extracted with ether and the ethereal solution was washed with 10% potassium hydroxide. Acidification of the latter aqueous solution gave a small acid fraction. The neutral fraction from the ether was crystallized from aqueous methanol, m. p. 164–166°; yield 0.1 g.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 7.2; H, 11.5.

The diacetate was prepared by the pyridine–acetic anhydride procedure and crystallized from aqueous methanol, m. p. 76–79°

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.4; H, 10.0. Found: C, 74.3; H, 10.0.

Pregnan-3(α),21-diol.—A solution of 0.5 g. of the methyl ester of 3(α)-hydroxypregnan-21-oic acid in 100 cc. of absolute ethanol was treated as described above. The product crystallized from methanol as white platelets, m. p. 205–206°.

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

Summary

Bromination of 16-pregnen-3(β)-ol-20-one acetate (I) yields 16,17-dibromopregnan-3(β)-ol-20-one acetate (II). Alkali treatment of the latter yields a mixture of 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) and the corresponding methyl ester (III) by a new rearrangement.

3(β)-Hydroxy-Δ^{17-20}-pregnen-21-oic acid (IV) has been converted to *etio*-cholan-3(β)-ol-17-one (V) by a new method and also to *etio*-cholan-3(α)-ol-17-one. Simultaneous reduction and epimerization of (IV) gave 3(α)-hydroxypregnan-21-oic acid. The latter was also prepared by neutral catalytic hydrogenation of 3-keto-pregnan-21-oic acid and by epimerization of 3(β)-hydroxy-pregnan-21-oic acid. Bouveault–Blanc reduction of the methyl esters of the pregnanoic acid (IV) and its epimer gave the corresponding pregnan-3,21-diols.

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