Ozonolysis of 1,4-Diphenyl-1,3-cyclopentadiene.—The diene (1 g.) dissolved in chloroform, was allowed to react at −30° with an equivalent of ozone (2 moles) made from air. The resulting solution was treated with water and the chloroform removed by distillation. The insoluble residue was separated from the water by decantation, and dissolved in ether. After this ethereal solution had been washed several times with water, the ether was evaporated, and the residue treated with a solution of cupric acetate in absolute alcohol. A yellowish precipitate of the copper derivative of dibenzoylmethane formed immediately, was filtered off, and recrystallized from benzene; yield 45%; m. p. 296–302° with decomposition (value given in literature: 294–307° dec.). Dibenzoylmethane liberated from this copper derivative melted at 79–80°. This specimen melted at 79–80° when mixed with a pure sample of dibenzoylmethane (m. p. 79–80°) prepared synthetically.

Preparation of the *p*-Nitrophenylosazone of Glyoxal.—The ozonide of 1,4-diphenyl-1,3-cyclopentadiene prepared as above was decomposed by adding its solution (chloroform) to a solution of sodium bisulfite; the chloroform was removed by distillation. The aqueous solution was extracted with ether and then treated with 1.4 g. of *p*-nitrophenylhydrazine and 3–4 ml. of glacial acetic acid. When the mixture was warmed gently a flocculent red precipitate formed. The mixture was centrifuged, and the precipitate washed with water, and recrystallized from pyridine to constant melting range, 306–307° with decomposition.

Anal. Calcd. for $C_{14}H_{12}O_4N_6$: C, 51.20; H, 3.69. Found: C, 51.30; H, 3.71.

Summary

1. The preparation of three 1,4-diaryl-1,3-cyclopentadienes by the condensation of methyl aryl ketones and β-arylpropionates in the presence of sodium ethoxide has been described.

2. A mechanism for these syntheses has been proposed and one of the intermediates isolated.

3. Several derivatives of these dienes have been described.

4. The structure of the so-called 1,3-diphenyl-1,3-cyclopentadiene of Borsche and Menz has been shown to be that of 1,4-diphenyl-1,3-cyclopentadiene.

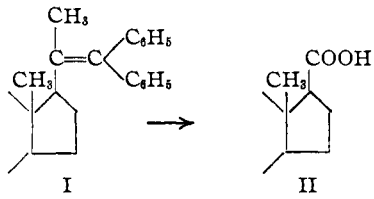
COLLEGE PARK, MD. RECEIVED MARCH 16, 1939

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

Sterols. LXII. *etio*-Cholanic Acids from the Pregnanediols

BY RUSSELL E. MARKER AND EUGENE L. WITTLE

One method of preparation of C_{21} hydroxy steroid derivatives such as occur in the recently isolated cortical hormones involves the use of *etio*-cholanic acid derivatives.[1] The *etio*-cholanic acids have been prepared previously in low yields by the oxidation of the diphenyl derivatives (I) to



I II

the corresponding acids (II),[2] or in better yield in the case of *etio*-desoxycholic acid[3] by three steps involving the condensation of 3,12-diacetoxy-*etio*-cholanyl methyl ketone with benzaldehyde followed by ozonization and oxidation with periodic acid without the isolation of intermediates. In the present work it was found that the 21-benzal derivatives of the isomeric pregnanol-3-one-20 acetates could be oxidized directly with chromic anhydride to give the correspondingly substituted *etio*-cholanic acids in good yield. Since it has been shown previously[4] that the isomeric pregnanol-3-one-20 compounds can be obtained from the pregnanediols, and since the 21-benzal derivatives are readily prepared from the former compound in good yield, this method makes the conversion of the pregnanediols to the *etio*-cholanic acid a practical one.

The condensation of benzaldehyde with pregnanol-3(α)-one-20 (III) using sodium ethylate takes place very readily at room temperature and gives an excellent yield of the 21-benzal derivative (IV). This product on acetylation formed the acetate which could be oxidized with chromic anhydride in acetic acid to give approximately 70% of the acetate of *etio*-lithocholic acid (V). Hydrolysis gave the free *etio*-lithocholic acid and oxidation of this substance yielded 3-keto-*etio*-cholanic acid. The melting points of these acids are in accord with those of the same acids prepared by Sawlewicz and Reichstein.[2]

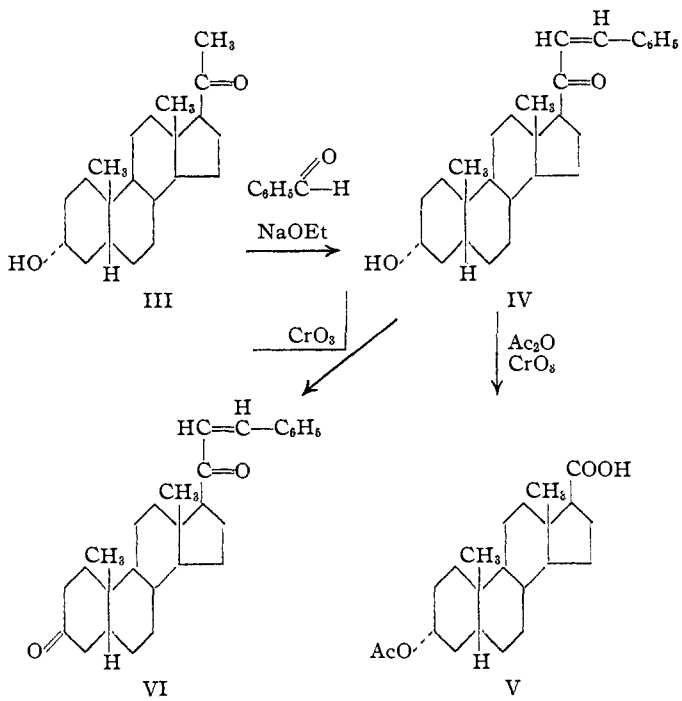
(1) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).

(2) Palmer, von Werder, Honigmann and Heyns, *Ber.*, **68**, 1814 (1935); Sawlewicz and Reichstein, *Helv. Chim. Acta*, **20**, 949 (1937); Steiger and Reichstein, *ibid.*, **20**, 1040 (1937).

(3) Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).

(4) Marker, Kamm and Jones, THIS JOURNAL, **59**, 1595 (1937); Marker, Kamm and Wittle, *ibid.*, **59**, 1841 (1937).

Treatment of pregnanol-3(β)-one-20 with benzaldehyde gave analogously the nicely crystalline 21-benzal derivative of this substance. Mild oxidation of this compound and also (IV) gave an excellent yield of the 21-benzalpregnanedione (VI), showing that these two products differ only in the configuration of the hydroxyl group at C_3. An attempt to prepare this product by the treatment of pregnanedione with one equivalent of benzaldehyde was not successful. A mixture of substances was obtained and it has not yet been possible to effect a separation. Condensation of *allo*-pregnanol-3(β)-one-20 with benzaldehyde gave the 21-benzal derivative which on acetylation and oxidation with chromic anhydride gave 3(β)-acetoxy-*etio-allo*-cholanic acid, in approximately 70% yield. Hydrolysis gave the 3(β)-hydroxy acid. The melting points of these two acids are in agreement with those of the same acids prepared indirectly from stigmasterol by Steiger and Reichstein.[2]



The authors wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous aid and assistance in various phases of this work.

Experimental

21-Benzal-pregnanol-3(α)-one-20.—To a solution of 1.0 g. of pregnanol-3(α)-one-20 and 500 mg. of benzaldehyde in 25 cc. of absolute ethyl alcohol was added at 25° and with shaking a solution of 600 mg. of sodium in 15 cc. of absolute alcohol. After standing for about twenty minutes at 25–30° crystalline material formed throughout the solution. This solution was allowed to stand for twenty-four hours and then diluted with 300 cc. of ether. The ether solution was shaken vigorously with dilute hydrochloric acid and then washed well with water and dilute potassium carbonate solution. On evaporating most of the ether the product crystallized and, after cooling, it was filtered off and washed with ether; yield 1.1 g., m. p. 228–230°. The product was crystallized readily from ethyl alcohol, m. p. 230–232°, is sparingly soluble in acetone and ether. The mother liquor gave a further small quantity of the same product, m. p. 225–228°.

Anal. Calcd. for $C_{28}H_{38}O_2$: C, 82.7; H, 9.42. Found: C, 82.6; H, 9.5.

This product was converted to the acetate by refluxing 1 g. of the substance with 12 cc. of acetic anhydride for one-half hour, evaporating the solution to dryness in vacuum and crystallizing the residue from acetone. This gave 1.0 g. of the acetate, crystallizing in thick plates from acetone, m. p. 152°.

Anal. Calcd. for $C_{30}H_{40}O_3$: C, 80.3; H, 9.0. Found: C, 80.1; H, 9.0.

21-Benzal-pregnanedione (VI).—A solution of 100 mg. of the above 21-benzal-pregnanol-3(α)-one-20, in 20 cc. of glacial acetic acid was treated with 100 mg. of chromic anhydride dissolved in 10 cc. of 90% acetic acid at 25° for one hour. The solution was diluted with water and the product was extracted with ether. The ether solution was washed well with water and then dilute potassium carbonate solution and evaporated to dryness. The product was crystallized very readily from acetone or methyl alcohol to give 70 mg. of 21-benzal-pregnanedione (VI) in heavy needles, m. p. 212–214°. This gave a marked depression in melting point with the original product.

Anal. Calcd. for $C_{28}H_{36}O_2$: C, 83.1; H, 9.0. Found: C, 83.0; H, 9.3.

etio-**Lithocholic Acid.**—To a solution of 800 mg. of 21-benzal-pregnanol-3(α)-one-20 acetate, m. p. 152°, in 100 cc. of glacial acetic acid at 50° and with stirring was added dropwise over a period of one-half hour a solution of 1.5 g. of chromic anhydride in 5 cc. of water and 50 cc. of acetic acid. The solution was stirred at 50–70° for five hours and then treated with 20 cc. of ethyl alcohol and concentrated to 25 cc. in vacuum. The remaining solution was diluted with water and the product was extracted with ether. The ether solution was washed several times with water and then extracted with excess dilute potassium carbonate solution. The potassium carbonate solution was acidified with hydrochloric acid and the acids were extracted with ether. The ether solution was washed with water and evaporated to dryness and the crystalline residue on standing in dilute methyl alcohol gave 50 mg. of crystalline acetyl-*etio*-lithocholic acid, m. p. 226–228°. The mother liquors contained benzoic acid, m. p. 120–122°. The product which was not extracted with potassium car-

bonate solution was crystallized from acetone to yield 400 mg. of the same acetyl-*etio*-lithocholic acid, m. p. 230–232°, V. This gave no depression with the above acid obtained from the potassium carbonate solution; yield approximately 70%.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 73.0; H, 9.3.

A solution of 50 mg. of the acetyl-*etio*-lithocholic acid in 30 cc. of 2% alcoholic potassium hydroxide was heated to refluxing for one-half hour. It was then poured into 200 cc. of water and this solution made acid with dilute hydrochloric acid. The white solid acid so liberated was extracted with ether, the ether solution washed with water and evaporated to approximately 5 cc. when the acid crystallized. It was crystallized from acetone to yield 30 mg. of *etio*-lithocholic acid, m. p. 275–276°.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.9; H, 10.1. Found: C, 74.9; H, 10.2.

Oxidation of this acid at 20° with excess chromic anhydride in acetic acid gave 3-keto-*etio*-cholanic acid, m. p. 246–249°.

21-Benzal-pregnanol-3(β)-one-20.—To a solution of 1.0 g. of pregnanol-3(β)-one-20 and 500 mg. of benzaldehyde in 15 cc. of absolute ethyl alcohol was added a solution of 600 mg. of sodium in 45 cc. of ethyl alcohol. In about fifteen minutes crystals formed throughout the solution. The solution was allowed to stand for twenty-four hours, then diluted with 200 cc. of ether and poured into excess dilute hydrochloric acid. After vigorous shaking the ether solution was separated, washed with water and dilute potassium carbonate solution and evaporated almost to dryness. The product crystallized at this point and after cooling the solution it was filtered and the product was washed with ether to yield 1 g. of crude product, m. p. 172–175°. Several crystallizations from acetone gave the pure product, m. p. 179°, 700 mg.

Anal. Calcd. for $C_{28}H_{38}O_2$: C, 82.7; H, 9.4. Found: C, 82.2; H, 9.3.

The acetate was prepared by refluxing 650 mg. of the product with 10 cc. of acetic anhydride for one-half hour, evaporating the solution to dryness under reduced pressure and crystallizing the product from acetone; yield of acetate 600 mg., m. p. 175°. This gave a mixed melting point with the original hydroxy product, m. p. 179°, of 150–155°.

Anal. Calcd. for $C_{30}H_{40}O_3$: C, 80.3; H, 9.0. Found: C, 80.5; H, 9.2.

Conversion to 21-Benzal-pregnanedione (VI).—A solution of 50 mg. of 21-benzal-pregnanol-3(β)-one-20, m. p. 179°, in 500 cc. of acetic acid was oxidized with 100 mg. of chromic anhydride at 25° for one hour. The product was extracted with ether after diluting the solution with water and the ether solution was washed with water. Evaporation of the ether and crystallization of the product from acetone gave 21-benzal-pregnanedione, m. p. 210°. This gave no depression in melting point with the product prepared from the 3(α) hydroxy compound.

21-Benzal-*allo*-pregnanol-3(β)-one-20.—To a solution of 750 mg. of *allo*-pregnanol-3(β)-one-20 and 350 mg. of benzaldehyde in 15 cc. of absolute ethyl alcohol was added at 25° a solution of 400 mg. of sodium in 10 cc. of absolute ethyl alcohol. The solution was allowed to stand for twenty-four hours and then poured into water. The product was extracted with ether and the ether solution was washed with dilute hydrochloric acid, water and dilute potassium carbonate and then evaporated to dryness. The residue was crystallized from methyl alcohol to yield 400 mg. of 21-benzal-*allo*-pregnanol-3(β)-one-20, m. p. 185–187°.

Anal. Calcd. for $C_{28}H_{38}O_2$: C, 82.7; H, 9.4. Found: C, 82.5; H, 9.3.

The acetate was prepared from a portion of this product by treatment with excess acetic anhydride and crystallized from methyl alcohol, m. p. 207–209°.

Anal. Calcd. for $C_{30}H_{40}O_3$: C, 80.3; H, 9.0. Found: C, 80.3; H, 9.0.

***etio-allo*-Cholanic Acid.**—To a solution of 400 mg. of 21-benzal-*allo*-pregnanol-3(β)-one-20 acetate in 100 cc. of acetic acid was added at 100° a solution of 600 mg. of chromic anhydride in 30 cc. of 90% acetic acid. The solution was kept at 100° for one hour and then diluted with water and the product was extracted with ether. The ether solution was washed well with water and then extracted with excess potassium carbonate solution. The potassium carbonate solution was acidified with hydrochloric acid and extracted with ether. The ether solution was washed with water and evaporated to dryness to leave a residue which was crystallized from dilute methyl alcohol to yield 250 mg. of 3(β)-acetoxy-*etio-allo*-cholanic acid, m. p. 240–245°. This, on recrystallization from dilute acetone, gave plates, m. p. 247–249°; yield, 70% approx.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 73.0; H, 9.2.

A solution of 50 mg. of this acetoxy acid in 10 cc. of methyl alcohol was heated for one hour with 200 mg. of potassium hydroxide in 10 cc. of 50% methyl alcohol and the solution was diluted with water, acidified and extracted with ether. The ether solution was washed with water and evaporated to dryness to leave a residue which was crystallized from dilute methyl alcohol to give 3(β)-hydroxy-*etio-allo*-cholanic acid, m. p. 250–252°. This gave a depression in melting point when mixed with the original acetoxy acid.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.9; H, 10.1. Found: C, 75.0; H, 10.0.

Treatment of Pregnanedione with Benzaldehyde.—To a solution of 1 g. of pregnanedione, m. p. 118–120°, and 350 mg. of benzaldehyde in 25 cc. of absolute ethyl alcohol at 20° was added a solution of 400 mg. of sodium in 10 cc. of absolute ethyl alcohol. The solution was allowed to stand for twenty-four hours and then diluted with 200 cc. of ether. The ether solution was shaken vigorously with dilute hydrochloric acid, washed with water and potassium carbonate solution and evaporated to dryness. The residue was an oil which could not be crystallized from acetone in which it is quite soluble or methyl alcohol in which it is difficultly soluble.

Summary

Treatment of *allo*-pregnanol-3(β)-one-20, pregnanol-3(β)-one-20 and pregnanol-3(α)-one-20 with

benzaldehyde and sodium ethylate gave the corresponding 21-benzal derivatives in excellent yield. Preparation of the acetates of these compounds and oxidation of the acetates with chromic anhydride gave the correspondingly substituted *etio*-cholanic acids in approximately 70% yields. The treatment of pregnanedione with benzaldehyde and sodium ethylate gave a mixture which could not be separated.

STATE COLLEGE, PENNA. RECEIVED MARCH 6, 1939

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

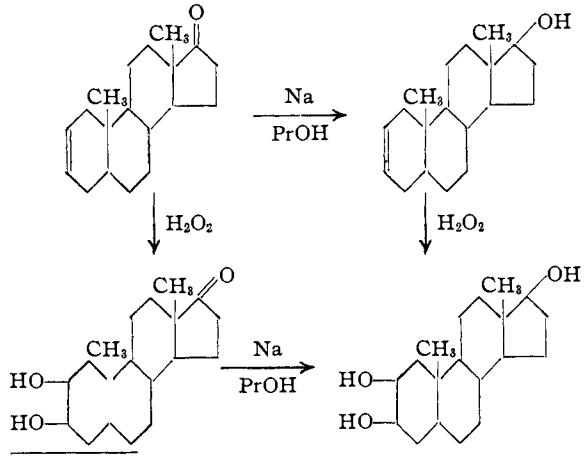
Sterols. LXIII. 2,3-Dihydroxyandrostane Derivatives

BY RUSSELL E. MARKER AND LOUIS PLAMBECK, JR.

In the course of our studies on the preparation of androstane derivatives for androgenic assay we have prepared several derivatives of androsterone which are unreported in the literature.

When Δ^2-cholestene was treated with hydrogen peroxide in acetic acid, cholestanediol-2,3 was obtained in very good yields. This upon oxidation with chromic acid gave the same dicarboxylic acid that was obtained by the vigorous oxidation of cholestanol, showing the position of the hydroxyl groups to be on C-2 and C-3.

In the same manner when Δ^2-androstenone-17[1] was treated with hydrogen peroxide we obtained 2-hydroxyandrosterone. It was very difficult to purify this product from a small amount of other isomeric products formed in the reaction. However, upon reduction with sodium in propyl alcohol it gave 2,3,17-trihydroxyandrostane which was identical with the product obtained by the action of hydrogen peroxide on androstenol-17[1]. None of these products precipitated with digitonin, suggesting that possibly the 3-hydroxyl group may be of the *epi*-configuration.



(1) Marker, Kamm, Jones and Mixon, THIS JOURNAL, **59**, 1363 (1937)

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Experimental Part

2,3-Dihydroxycholestane.—To a solution of 3.0 g. of Δ^2-cholestene dissolved in 50 cc. of acetic acid on a steam-bath was added 3.0 cc. of 30% hydrogen peroxide over a period of one hour with stirring. Water and ether were added and the acetic acid removed by shaking with sodium carbonate solution. The ether was evaporated and the residue refluxed for forty-five minutes with an excess of alcoholic potassium hydroxide solution. The product was extracted with ether and recrystallized from methanol, m. p. 195–197°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.1; H, 12.0. Found: C, 80.2; H, 12.1.

A solution of 5.3 g. of 2,3-dihydroxycholestane in 15 cc. of acetic anhydride was refluxed for one hour. Upon cooling the product crystallized and was separated by filtration. This was recrystallized from methanol to a melting point of 133–135°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.2; H, 10.7. Found: C, 76.4; H, 10.8.

Upon hydrolysis with alcoholic potassium hydroxide the diacetate gave cholestanediol-2,3, m. p. 201°; mixture with original diol gave no depression.

To a solution of 500 mg. of 2,3-dihydroxycholestane in 25 cc. of acetic acid was added a solution of 2 g. of chromic oxide in 10 cc. of 80% acetic acid. It was heated at 60° for three hours. Water was added and the solid filtered. Crystallization from acetic acid gave a product melting at 193°. This gave no depression in melting point when mixed with the acid obtained by the oxidation of cholestanol.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 75.1; H, 10.7. Found: C, 74.9; H, 10.6.

2-Hydroxyandrosterone.—To a solution of 500 mg. of androstenone-17 in 200 cc. of acetic acid at 100° was added 5 cc. of hydrogen peroxide in 1-cc. portions at ten-minute intervals with stirring. Water was added and the product was extracted with ether. After evaporation of the ether and saponification the product was crystallized from dilute acetone, m. p. 195–198°. This was very difficult to separate from a small amount of other isomeric products present. It did not precipitate with alcoholic digitonin.