in 20 cc. of acetic acid and oxidized by adding 1 g. of chromic anhydride in dilute acetic acid. The neutral fraction was refluxed for fifteen minutes with alcoholic potassium hydroxide, then crystallized from dilute ethanol to give a product melting at 192–193°. Mixed with *allo*-pregnanol-3(β)-one-20, m. p. 192–193°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.7. Found: C, 79.3; H, 10.6.

Summary

Tigogenin reacts with acetic anhydride to yield pseudotigogenin which on mild oxidation with chromic anhydride yields $\Delta^{16,17}$-*allo*-pregnenedione-3,20.

Reduction of $\Delta^{16,17}$-*allo*-pregnenedione-3,20 with sodium gives *allo*-pregnanediol-3(β),20(α) while reduction with Adams catalyst gives *allo*-pregnanediol-3(β),20(β). The configuration of the hydroxyl group in tigogenin is shown to be *beta*.

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

Sterols. XCVII. Sarsasapogenin

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We find that sarsasapogenin reacts with both ethylmagnesium bromide and methylmagnesium iodide to yield products which contain two esterifiable hydroxyl groups. Oxidation of the diacetate of the ethyl Grignard product with chromic anhydride at 90° gave 3-hydroxy-*etio*-bilianic acid.[1]

The dimethyl ester[1] of the 3-hydroxy-*etio*-bilianic acid readily was converted to a monomethyl ester by hydrolysis with one equivalent of alkali. This indicates that one of the carboxyl groups in the acid is hindered, as might be anticipated from the structure. This is also in accord with the results of Litvan and Robinson[2] concerning the analogous acid derived from *o*-methylestrone. The mono-methyl ester yielded a crystalline acetate which, upon treatment with thionyl chloride and diazomethane by the procedure of Arndt and Eistert,[3] yielded a nicely crystalline diazo ketone.

Attempts to convert the diazo ketone to a crystalline acid by treatment with silver oxide were unsuccessful. The non-crystallline acid obtained from this reaction was treated with acetic anhydride to give, after alkaline hydrolysis, a ketone of the composition $C_{19}H_{30}O_2$, m. p. 117–119°. For purposes of comparison we prepared *etio*-cholanol-3(β)-one-17 by the method used by Ruzicka and co-workers.[4] This product after purification melted at 117° when crystallized from pentane. Ruzicka reports his product to melt at 151–152°. Evidently this ketone, as in the case of many other sterol ketones, exists in several polymorphic forms with different melting points. This product did not depress in melting point when mixed with the product prepared from 3-hydroxy-*etio*-bilianic acid. Both products formed semicarbazones melting at 240–242° with decomposition.

As further proof of the identity of the above product, it was reduced by sodium in amyl alcohol and the 3-OH group epimerized to the α-form. This product was identical with *etio*-cholanediol-3(α),17(α) prepared by the reduction of *epi-etio*-cholanolone with sodium in ethanol. The *etio*-cholanediol-3(α),17(α) was converted into its diacetate and this subjected to partial hydrolysis with methanolic potassium hydroxide, followed by oxidation with chromic anhydride. The resulting product was then hydrolyzed to yield *etio*-cholanone-3-ol-20. This substance was converted readily to testosterone by bromination and subsequent removal of hydrogen bromide with pyridine.

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

Experimental Part

Reaction of Sarsasapogenin Acetate with Ethylmagnesium Bromide.—To a Grignard reagent prepared from 6.1 g. of magnesium, 27.5 g. of ethyl bromide and 100 cc. of ether was added a solution of 5 g. of sarsasapogenin acetate in 200 cc. of ether. Most of the ether was distilled off and the residual liquid was refluxed for fifteen hours with 25 cc. of benzene. The mixture was decomposed with dilute hydrochloric acid and the solid taken up in ether. The product was crystallized from ethyl acetate–pentane as flaky white needles, m. p. 159–161.5°.

(1) Marker and Rohrmann, THIS JOURNAL, **61**, 2722 (1939).
(2) Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).
(3) Arndt and Eistert, *Ber.*, **68**, 200 (1935).
(4) Ruzicka, Goldberg, Meyer, Brungger and Eichenberger, *Helv. Chim. Acta.*, **17**, 1395 (1934).

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.9; H, 11.3. Found: C, 77.9; H, 11.2.

When refluxed with an excess of acetic anhydride the product yielded a diacetate which crystallized from aqueous methanol as white needles, m. p. 87.5–89°.

Anal. Calcd. for $C_{33}H_{54}O_5$: C, 74.7; H, 10.3. Found: C, 74.8; H, 10.1.

Reaction of Sarsasapogenin Acetate with Methylmagnesium Iodide.—This reaction was carried out as described above. The product was crystallized from ethyl acetate–pentane as white plates, m. p. 179–181.5°.

Anal. Calcd. for $C_{28}H_{48}O_3$: C, 77.7; H, 11.2. Found: C, 77.7; H, 11.2.

When treated with *p*-nitrobenzoyl chloride in pyridine at 60° the substance formed a **di-*p*-nitrobenzoate**, which crystallized from ether as white crystals, m. p. 192–194°.

Anal. Calcd. for $C_{43}H_{56}O_9N_2$: C, 69.3; H, 7.6. Found: C, 69.2; H, 7.6.

Oxidation of Diacetate of Ethyl Grignard Product.—To a stirred solution of 3 g. of the diacetate of the ethyl Grignard product in 60 cc. of acetic acid heated at 90° was added a solution of 7 g. of chromic anhydride in 40 cc. of 80% acetic acid over a period of one hour. The mixture was stirred for an additional hour at 90° when ethanol was added and the mixture concentrated *in vacuo* to about one-third volume. Water was added and the solid taken up in ether and washed with water and 3% sodium hydroxide. The alkaline water layer was heated on the steam-bath for twenty minutes, cooled, acidified with hydrochloric acid and the precipitated acid taken up in ether and crystallized from chloroform as small white crystals, m. p. 220–222°. This gave no depression with a sample of 3-hydroxy-*etio*-bilianic acid, m. p. 220–222°; yield 1.1 g.

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.4; H, 8.9. Found: C, 67.2; H, 8.9.

Mono-methyl Ester of 3-Hydroxy-*etio*-bilianic Acid.—A solution of 2.68 g. of the dimethyl ester of 3-hydroxy-*etio*-bilianic acid in 25 cc. of methanol was refluxed for ninety minutes with a solution of 0.292 g. (1 mol) of sodium hydroxide in 8 cc. of water. The mixture was diluted with water, acidified with hydrochloric acid and the precipitated acid taken up in ether. The ethereal extract was washed with 0.5% potassium hydroxide solution. Evaporation of the ethereal solution gave approximately 1 g. of unchanged dimethyl ester.

The alkaline extract was acidified with hydrochloric acid and the precipitate taken up in ether and crystallized from ether–pentane as small compact white crystals, m. p. 211–213°.

Anal. Calcd. for $C_{20}H_{32}O_5$: C, 68.1; H, 9.2. Found: C, 68.3; H, 9.1.

When refluxed with an excess of acetic anhydride the monomethyl ester yielded an **acetate** which, after treatment in acetone with Norite, crystallized from aqueous acetone and aqueous methanol as compact white crystals, m. p. 181.5–183.5°.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.95; H, 8.7. Found: C, 67.0; H, 8.8.

Diazoketone from Monomethyl Ester.—A solution of 2 g. of the acetate of the monomethyl ester of 3-hydroxy-*etio*-bilianic acid in 10 cc. of dry benzene and 2 cc. of thionyl chloride (colorless) was refluxed on the steam-bath for two hours. The solvents were evaporated and the residual sirup was evaporated repeatedly *in vacuo* with dry benzene.

The acid chloride was not obtained crystalline. The product was dissolved in 60 cc. of ether and to this solution at 0° was added a cold ethereal solution of diazomethane (from 4 g. of methylnitrosourea). The solution was allowed to stand at room temperature for sixteen hours, when the solvent was evaporated. The residue was crystallized from ether–acetone–pentane as pale yellow needles, m. p. 159–160° dec. (gas); yield 1.2 g.

Anal. Calcd. for $C_{23}H_{33}O_5N_2$: C, 66.1; H, 8.0; N, 6.7. Found: C, 66.1; H, 8.1; N, 6.4.

Conversion of Diazoketone to *etio*-Cholanol-3(β)-one-17.—To a solution of 1 g. of the diazoketone in 25 cc. of absolute ethanol heated at 70–80° was added 2 g. of dry, freshly prepared silver oxide. The mixture was warmed at 70–80° for one hour, after which time the evolution of gas had ceased. The mixture was filtered and the filtrate diluted with water and the precipitated solid taken up in ether. Evaporation of the ether gave a non-crystalline sirup which was hydrolyzed with hot ethanolic potassium hydroxide. The resulting acid could not be crystallized. The sirup was refluxed with acetic anhydride for twenty-five minutes and the excess acetic anhydride was distilled off up to 250°. The residue was heated at 250° for one hour and then sublimed in high vacuum at 4 mm. pressure at 200–250°.

The sublimate was hydrolyzed with ethanolic potassium hydroxide and the neutral fraction treated with Girard reagent. The resulting ketonic material was sublimed in high vacuum and crystallized from ether–pentane as white needles, m. p. 117–119°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.5; H, 10.4. Found: C, 78.2; H, 10.7.

When treated with semicarbazide acetate the product yielded a **semicarbazone** which crystallized from aqueous ethanol as white crystals, m. p. 241–242.5° dec.

Anal. Calcd. for $C_{20}H_{33}O_2N_3$: C, 69.1; H, 9.6. Found: C, 69.0; H, 9.3.

etio-Cholanolone was prepared by the oxidation of coprostanol by the method described by Ruzicka and coworkers.[5] It was isolated as the semicarbazone, m. p. 240–242°.

Anal. Calcd. for $C_{20}H_{33}O_2N_3$: C, 69.1; H, 9.6. Found: C, 69.0; H, 9.3.

A solution of 1 g. of the above semicarbazone was refluxed with 30 cc. of ethanol and 5 cc. of concentrated sulfuric acid in 10 cc. of water for three hours. The product was extracted with ether, the solvent removed and the residue was sublimed at 120–130° in a high vacuum. It was then crystallized from pentane giving white needles, m. p. 117–118°. It gave no depression in melting point when mixed with the same product obtained from 3-hydroxy-*etio*-bilianic acid.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.5; H, 10.4. Found: C, 78.4; H, 10.7.

***etio*-Cholanediol-3(α),17(α).**—To a solution of 200 mg. of *etio*-cholanolone in 80 cc. of amyl alcohol was added 5 g.

of sodium. The solution was refluxed for ten hours to ensure epimerization of the 3 hydroxyl group. The product was sublimed in high vacuum and crystallized from ethyl acetate, m. p. 233–235°. It gave no depression in melting point with an authentic sample of *etio*-cholanediol-3(α),17(α) prepared by the reduction of *epi-etio*-cholanolone.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.0; H, 11.0. Found: C, 78.1; H, 11.1.

With boiling acetic anhydride the product gave a diacetate which was crystallized from methanol as white crystals, m. p. 124–125°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.4; H, 9.7. Found: C, 73.3; H, 9.8.

Ruzicka and co-workers[5] report a m. p. of 236–236.5° for the diol and of 124.5–125.5° for the diacetate.

Partial Hydrolysis of the Diacetate of *etio*-Cholanediol-3(α),17(α).—To a solution of 1.5 g. of the diacetate of *etio*-cholanediol-3,17 in 1 liter of absolute methanol was added 0.8 mol (titration) of potassium hydroxide in 100 cc. of methanol. After standing at room temperature for fifty hours, it was carefully neutralized with sulfuric acid and the methanol removed *in vacuo*. The residue was extracted with ether, washed well with water and the ether evaporated. The residue was dissolved in 25 cc of acetic acid, vacuum evaporated twice, and then dissolved in 25 cc. of acetic acid at room temperature. To this solution was added 700 mg. of chromic anhydride in 10 cc. of 80% acetic acid. After standing for forty-five minutes the mixture was diluted with water and extracted with ether. After washing with dilute sodium carbonate solution and water the ether was evaporated and the residue was dissolved in 50 cc. of ethyl alcohol. To this was added 2 g. of Girard reagent and the product was refluxed for twenty minutes. Water was added and the precipitated product extracted with ether. The aqueous layer was decomposed with hydrochloric acid and the solid product extracted with ether. The ether was evaporated and the residue dried with benzene. To the residue was added 1.5 g. of succinic anhydride and 5 cc. of pyridine and the mixture heated for ninety minutes. Ether was added and the pyridine removed by shaking with dilute hydrochloric acid. The ethereal extract was washed with potassium carbonate solution and the aqueous layer acidified and extracted with ether. Evaporation of the ether gave a residue which was hydrolyzed with ethanolic potassium hydroxide. The resulting product was treated with Norite in acetone and crystallized from ether–pentane (1:1). After standing overnight in a refrigerator the crystalline material was filtered. This product was not very soluble in ether, and was crystallized directly from this solvent, to give a small amount of a product melting at 145–148°, which gave no depression in melting point with *etio*-cholanone-17-ol-3(α), m. p. 149–150°.

The filtrate was evaporated and the residue crystallized from pentane to give white crystals, m. p. 139–141°. When mixed with *etio*-cholanone-17-ol-3(α) of a melting point of 148° it gave a depression of 24°. This product was *etio*-cholanone-3-ol-17.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.5; H, 10.4. Found: C, 78.2; H, 10.4.

Testosterone.—To a solution of 225 mg. of *etio*-cholanone-3-ol-17 in 20 cc. of glacial acetic acid acidified with hydrobromic acid was added 7.5 cc. of a 0.1 *M* solution of bromine in acetic acid. The solution was diluted with water and extracted with ether. The ethereal solution was shaken with dilute sodium bicarbonate solution, filtered, and the ether evaporated. The residue was crystallized from pentane–acetone. It melted over a range of 150–156°, but was not further purified.

To 100 mg. of this product was added 10 cc. of pyridine and the solution was refluxed for nine hours. Ether and water were added and the pyridine removed by shaking with dilute hydrochloric acid. The product was sublimed in a high vacuum and the sublimate crystallized from pentane to give white crystals, m. p. 149–151°, which gave no depression in melting point when mixed with an authentic sample of testosterone, m. p. 150–152°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.0; H, 9.7.

Summary

Sarsasapogenin has been converted into testosterone.

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