Isomerization of Pseudosapogenins. (a) **Pseudosarsasapogenin.**—To a solution of 500 mg. of pseudosarsasapogenin, m. p. 170–173°, in 100 cc. of 95% ethanol was added a mixture of 85 cc. of ethanol and 15 cc. of concentrated hydrochloric acid. After standing at 25° for twenty hours, water was added and the precipitated solid taken up in ether and crystallized from acetone to give 400 mg. of white needles, m. p. 199–201°. This gave no depression with a sample of sarsasapogenin, m. p. 199–201°.

With chromic anhydride at room temperature, this gave a neutral product which crystallized from acetone as white plates, m. p. 223–226°. This gave no depression with a sample of sarsasapogenone, m. p. 223–226°.

With hot acetic anhydride an acetate was formed which was crystallized repeatedly from acetone–methanol to give white plates, m. p. 125–127°. When mixed with a sample of sarsasapogenin acetate, m. p. 143–145°, the mixture melted from 126–144°. When seeded with a crystal of sarsasapogenin acetate, m. p. 143–145°, a product of m. p. 142–144° was obtained. This gave no depression with sarsasapogenin acetate.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.8; H, 10.2.

Similar results were obtained when pseudosarsasapogenin was refluxed in ethanol solution with aqueous hydrochloric acid for ninety minutes.

Dihydropseudosarsasapogenin, m. p. 169°, was recovered unchanged after refluxing for two hours in aqueous ethanolic hydrochloric acid solution.

(b) **Pseudotigogenin.**—Pseudotigogenin when refluxed for one hour with aqueous ethanolic hydrochloric acid gave a good yield of a product which crystallized from acetone as white needles, m. p. 203–205°. This gave no depression with a sample of tigogenin, m. p. 204–206°.

With boiling acetic anhydride this yielded an acetate, m. p. 202–204°, which gave no depression with an authentic sample of tigogenin acetate, m. p. 202–204°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.7; H, 10.0.

(c) **Pseudochlorogenin.**—Pseudochlorogenin when treated as described for pseudotigogenin gave a good yield of a product which crystallized from acetone as white needles, m. p. 269–272°. This gave no depression with a sample of chlorogenin, m. p. 270–273°.

With boiling acetic anhydride this yielded a diacetate, m. p. 149–151°, which gave no depression with a sample of chlorogenin diacetate, m. p. 149–151°.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.05; H, 9.4. Found: C, 72.1; H, 9.3.

Summary

Pseudosarsasapogenin, pseudotigogenin and pseudochlorogenin are isomerized by hydrochloric acid to the original sapogenins.

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

Sterols. XCVI. *allo*-Pregnanediols from Tigogenin

BY RUSSELL E. MARKER AND EWALD ROHRMANN

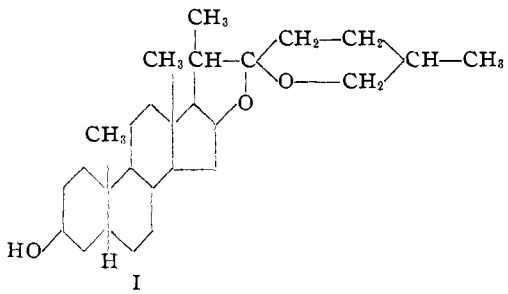
In a recent publication[1] the conversion of sarsasapogenin to $\Delta^{16,17}$-pregnenedione-3,20 and the subsequent reduction of this to various pregnane derivatives was described. In the present work we have extended some of these reactions to tigogenin (I), a substance having the *allo*-configuration at C-5.

Tigogenin upon treatment with acetic anhydride at 200° is converted to pseudotigogenin which upon mild oxidation with chromic anhydride is converted to an unsaturated diketone of the composition $C_{21}H_{30}O_2$. This substance is undoubtedly $\Delta^{16,17}$-*allo*-pregnenedione-3,20 (II) a substance first reported by Butenandt, Mamoli and Heusner.[2] Their product was prepared from androsterone by conversion to the nitrile, reaction with methyl Grignard reagent and subsequent oxidation. The product was reported to melt at 205–208°, while our product from tigogenin melts at 210–212°.

Reduction of the unsaturated diketone with sodium and ethanol yields *allo*-pregnanediol-3(β),20(α) while reduction with Adams catalyst yields *allo*-pregnanediol-3(β),20(β). The ease of reduction with sodium and ethanol indicates the presence of an α,β-unsaturated ketone grouping.

Although data have been presented indicating that the configuration of the C-3 hydroxyl group in tigogenin is *beta*, none of this evidence can be considered conclusive inasmuch as it has been derived from digitonin precipitation data[3] and from reduction experiments on $\Delta^{4,5}$ unsaturated ketones,[4] reactions which might conceivably be influenced by the presence of the complex side chain.

(1) Marker and Rohrmann, THIS JOURNAL, **62**, 518 (1940).
(2) Butenandt, Mamoli and Heusner, *Ber.*, **72**, 1614 (1939).
(3) Tschesche and Hagedorn, *ibid.*, **68**, 2247 (1935).
(4) Marker and Rohrmann, THIS JOURNAL, **61**, 1291 (1939).



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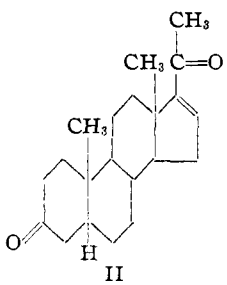

II

The conversion of tigogenin to *allo*-pregnanediol-3(β),20(β) and *allo*-pregnanol-3(β)-one-20 by reactions in which the original C-3 hydroxyl group remains intact definitely proves that the configuration of the C-3 hydroxyl group is *beta*. Pseudotigogenin was acetylated and oxidized with chromic anhydride under relatively mild conditions, giving a non-crystalline product. Reduction of this with Adams catalyst followed by mild oxidation with chromic anhydride and subsequent hydrolysis yielded *allo*-pregnanol-3-(β)-one-20, while direct hydrolysis of the reduction product yielded *allo*-pregnanediol-3(β),20(β).

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

Experimental Part

Pseudotigogenin.—A mixture of 3.6 g. of tigogenin and 25 cc. of acetic anhydride was heated at 195–200° for eight hours. The solvent was removed *in vacuo* and the residue hydrolyzed with ethanolic potassium hydroxide. The neutral material was crystallized from aqueous acetone to give white crystals, m. p. 193–196°. When mixed with tigogenin, m. p. 204°, it gave a depression in melting point to 180–186°, yield 3.1 g.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 77.5; H, 10.5.

$\Delta^{16,17}$-*allo*-Pregnenedione-3,20 from Pseudotigogenin.—To a solution of 1.5 g. of pseudotigogenin in 100 cc. of acetic acid was added a solution of 1.5 g. of chromic anhydride in 25 cc. of 90% acetic acid. It was allowed to stand at 25–28° for two hours, poured into water and extracted with ether. The ethereal solution was washed with 2% sodium hydroxide solution and the product remaining after evaporation of the ether was sublimed in a high vacuum at 120–125°. This was crystallized from ether–pentane and finally from ether to give small white crystals, m. p. 210–212°. It gave a 25° depression with *allo*-pregnanedione-3,20, m. p. 210°; yield 425 mg.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.0; H, 9.5.

The substance was unchanged by refluxing with acetic anhydride.

***allo*-Pregnanediol-3(β),20(α) from $\Delta^{16,17}$-*allo*-Pregnenedione-3,20.**—To a solution of 200 mg. of $\Delta^{16,17}$-*allo*-pregnenedione-3,20 in 50 cc. of boiling absolute ethyl alcohol was added 4 g. of sodium in small pieces. After the sodium had dissolved, water was added and the product was extracted with ether. It was recrystallized from methanol and acetone, giving white crystals, m. p. 213–214°. It gave no depression in melting point when mixed with *allo*-pregnanediol-3(β),20(α), m. p. 214–217°; yield 160 mg.

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

This product gave an acetate with hot acetic anhydride which was crystallized from methanol as white crystals, m. p. 166–168°. It gave no depression in melting point when mixed with the diacetate of *allo*-pregnanediol-3(β), 20(α), m. p. 166–168°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.0; H, 9.9.

***allo*-Pregnanediol-3(β),20(β) from $\Delta^{16,17}$-*allo*-Pregnenedione-3,20.**—A solution of 200 mg. of $\Delta^{16,17}$-*allo*-pregnenedione in 100 cc. of acetic acid was shaken with 100 mg. of Adams catalyst under a pressure of 45 pounds (3 atm.) of hydrogen for three hours. The product was crystallized from ethanol to give white crystals, m. p. 192–193°. It gave no depression in melting point when mixed with *allo*-pregnanediol-3(β),20(β), m. p. 192–194°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.6; H, 11.2.

Oxidation of Pseudotigogenin Acetate with Chromic Oxide.—A solution of 1.6 g. of pseudotigogenin in 10 cc. of acetic anhydride was refluxed for thirty minutes. The excess acetic anhydride was removed *in vacuo* and the residue was dissolved in 100 cc. of glacial acetic acid. To this was added 2 g. of chromic oxide in 10 cc. of 80% acetic acid. After standing at 28° for two hours, water was added and the precipitated solid taken up in ether. The acids were removed by washing with water and sodium carbonate solution. Upon evaporation of the ether the residue failed to crystallize from acetone or ethanol, probably due to some by-products of the oxidation. The total product was dissolved in acetic acid and shaken with hydrogen under 45 pounds (3 atm.) pressure in the presence of Adams catalyst for one hour. A portion of the reduction product was hydrolyzed by refluxing for thirty minutes with alcoholic potassium hydroxide solution. This product was crystallized from ethyl alcohol to give white crystals, m. p. 192–194°. Mixed with *allo*-pregnanediol-3-(β),20(β), m. p. 192–194°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.4; H, 11.3.

The remainder of the reduction product was dissolved

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

BY RUSSELL E. MARKER AND EWALD ROHRMANN

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).