3. Evidence has been discussed indicating that the configuration of the side-chain in sarsasapogenin and isosarsasapogenin differs at C-22.

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Sterols. CXVII. Sapogenins. XLVI. The Structure of Pseudosapogenins

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When the steroidal sapogenins are heated with acetic anhydride at 200° they are converted into pseudosapogenins[1,2,3] which are important intermediates in the preparation of the steroidal hormones.[4,5,6] In previous papers we have presented a discussion of various formulas[7,8,9] which may be assigned to the pseudosapogenins. The experimental evidence available at that time suggested formula I in preference to formula II for these compounds. Points have been raised by Drs. Crooks, Wittle and Whitmore which convince us that II may be a peculiar tautomeric form of I. We have continued our study of the chemical structure of these compounds and have obtained evidence to this effect.

It had been observed that in the oxidation of the pseudosapogenins or their diacetates, it was only after alkaline hydrolysis of the crude oxidation product that crystalline Δ^{16}-pregnenedione-3,20 compounds or Δ^{16}-pregnenol-3-one-20 compounds could be isolated. This suggested that the conversion to the pregnenolone was a secondary reaction brought about by the action of alkali.

Pseudotigogenin diacetate, pseudodiosgenin diacetate and dihydro-pseudotigogenin (tetrahydropseudodiosgenin) diacetate have now been oxidized with chromic acid and the intermediate oxidation products have been obtained in crystalline form. The products from pseudotigogenin diacetate and dihydro-pseudotigogenin diacetate are identical and have the composition $C_{31}H_{48}O_7$. The oxidation product from pseudodiosgenin diacetate has the Δ^5-double bond and was obtained in good yield without protecting the bond with bromine before oxidation. Catalytic reduction of this in neutral solution gave the same product obtained from pseudotigogenin diacetate and dihydro-pseudotigogenin diacetate.

Hydrolysis of the oxidation product of pseudotigogenin diacetate with ethanolic potash or by boiling with alcohol containing hydrochloric acid gave Δ^{16}-*allo*-pregnenol-3(β)-one-20, while similar hydrolysis of the oxidation product from the diacetate of pseudodiosgenin gave $\Delta^{5,16}$-pregnadienol-3(β)-one-20. In both cases the yield was practically quantitative. The reduction of the oxidation product from pseudotigogenin diacetate using the method of Meerwein–Ponndorff or by catalytic hydrogenation with Adams catalyst followed by hydrolysis gave in both cases the same product. This is apparently an *allo*-pregnanetriol, differing from that recently obtained from tigogenin by persulfuric acid oxidation.[10] The reduction of the oxidation product from pseudodiosgenin diacetate using the Meerwein reaction gave a similar unsaturated triol which was reduced catalytically to the triol obtained from the oxidation product of pseudotigogenin diacetate. These products cannot be obtained in alkaline solution which hydrolyzes the oxidation products. The reduction of the oxidation product of pseudotigogenin diacetate with sodium in dry alcohol gave the expected *allo*-pregnanediol-3(β),20(α).

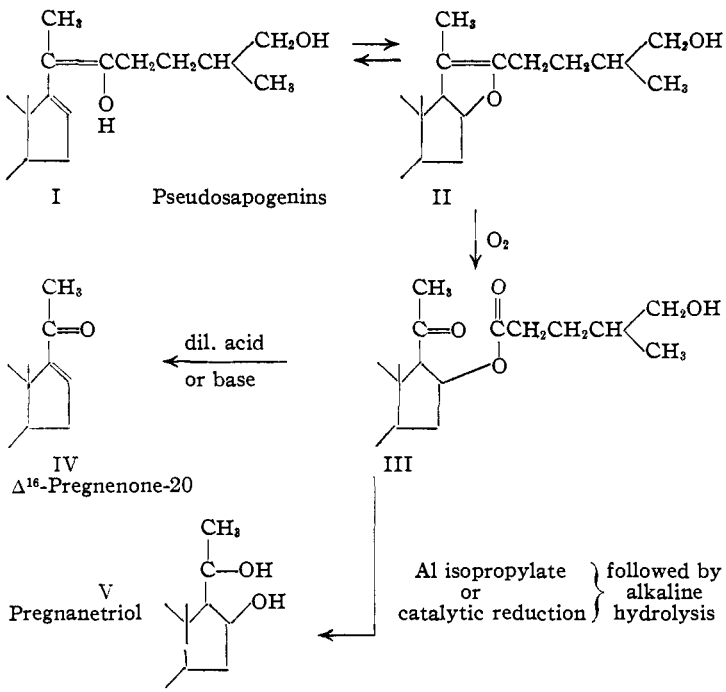
The oxidation product of dihydro-pseudotigogenin diacetate was oxidized at room temperature with chromic acid to 3-hydroxy-*etio*-*allo*-bilianic acid identical with the acid previously described.[11] There were no neutral products in this oxidation.

The intermediate oxidation products of the pseudosapogenins can best be explained by formula III corresponding to formula II for the pseudosapogenins. It is impossible to explain the diketo acid[7,9] formed as an intermediate

(1) Marker and Rohrmann, THIS JOURNAL, **62**, 518 (1940).
(2) Marker, Rohrmann and Jones, *ibid.*, **62**, 648 (1940).
(3) Marker and Rohrmann, *ibid.*, **62**, 898 (1940).
(4) Marker, Tsukamoto and Turner, *ibid.*, **62**, 2525 (1940).
(5) Marker, *ibid.*, **62**, 2543 (1940).
(6) Marker, *ibid.*, **62**, 2621 (1940).
(7) Marker and Rohrmann, *ibid.*, **62**, 521 (1940).
(8) Marker and Rohrmann, *ibid.*, **62**, 896 (1940).
(9) Marker, Jones and Krueger, *ibid.*, **62**, 2532 (1940).
(10) Marker, Turner, Wagner and Ulshafer, *ibid.*, **63**, 772 (1941).
(11) Marker, Turner and Ulshafer, *ibid.*, **63**, 763 (1941).

oxidation product by the low temperature oxidation of the unacetylated dihydro-pseudosarsasapogenin on the basis of this formula. It is also difficult to explain the behavior of dihydro-pseudosarsasapogenin toward oxidizing agents in terms of this structure,[9] and the great difference in the reactions of dihydropseudosarsasapogenin and dihydrosarsasapogenin, which should have identical formulas if II were used for the structure of the pseudosapogenins. In view of this we suggest that the pseudosapogenins may exist in tautomeric forms as both I and II.

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



Experimental Part[12]

Oxidation of Dihydro-pseudotigogenin Diacetate.—To a solution of 5 g. of dihydro-pseudotigogenin diacetate in 200 cc. of glacial acetic acid was added a solution of 4 g. of chromium anhydride in 20 cc. of 80% acetic acid, keeping the temperature below 30°. It was allowed to stand at 30° for one hundred minutes. Water was added and the product was extracted with ether. The ethereal solution was washed free of acetic acid and then the ether was removed. The residue was crystallized from dilute methanol and finally from methanol, m. p. 102–104°; yield 2.0 g. When mixed with the diacetate of dihydropseudotigogenin, m. p. 122°, it melted at 84–90°.

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.9; H, 9.1. Found: C, 69.7, 70.0; H, 9.1, 8.9.

Oxidation of Pseudotigogenin Diacetate.—To a solution of 4 g. of the diacetate of pseudotigogenin dissolved in 200 cc. of acetic acid at 15° was added a solution of 3.2 g. of chromic acid in 90% acetic acid. It was allowed to stand at 30° for forty-five minutes. Water was added and the product was extracted with ether. The ethereal solution was washed well with water and with sodium bicarbonate solution. It was then evaporated and the residue was crystallized from dilute methanol and finally from methanol, m. p. 102–104°. Mixed with the product prepared from the oxidation of dihydro-pseudotigogenin diacetate, m. p. 102–104°, it gave no depression in melting point. When mixed with the diacetate of pseudotigogenin, m. p. 97–99°, it melted at 76–82°.

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.9; H, 9.1. Found: C, 70.0; H, 9.2.

Action of Alkali and Acids on the Oxidation Product of the Diacetate of Pseudotigogenin.—A solution of 500 mg. of the oxidation product of the diacetate of pseudotigogenin in 50 cc. of 2% alcoholic potassium hydroxide was refluxed for thirty minutes. Water was added and the product was extracted with ether. The solvent was removed and the residue was crystallized from dilute methanol, m. p. 202–204°. When mixed with Δ16-*allo*-pregnenol-3(β)-one-20, m. p. 202–204°, there was no depression in melting point.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.1.

Refluxing of the oxidation product of the diacetate of pseudotigogenin with alcoholic potassium carbonate solution for one hour gave the same product. When this product was refluxed with acetic anhydride for thirty minutes it gave an acetate, m. p. 162–164°, from methanol, which gave no depression in melting point when mixed with an authentic sample of the acetate of Δ16-*allo*-pregnenol-3(β)-one-20, m. p. 162–164°.

When the oxidation product of pseudotigogenin diacetate was refluxed for two hours with 10% alcoholic hydrochloric acid the total product was Δ16-*allo*-pregnenol-3(β)-one-20, m. p. 202–204°, which gave no depression in melting point when mixed with an authentic sample.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.5; H, 10.4.

Reduction of the Oxidation Product of Pseudotigogenin Diacetate with Sodium in Dry Isopropyl Alcohol.—To a solution of 2 g. of the oxidation product of pseudotigogenin diacetate in 200 cc. of dry isopropyl alcohol was added 15 g. of sodium in small pieces. When this was dissolved, water was added and the product was extracted with ether. The solvent was removed and the residue was crystallized from acetone, m. p. 214–216°. Mixed with *allo*-pregnanediol-3(β), 20(α), m. p. 214–216°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.5; H, 11.3.

(12) Microanalyses by Dr. George H. Fleming of this Laboratory.

Oxidation of Pseudodiosgenin Diacetate.—To a solution of 10 g. of the diacetate of pseudodiosgenin, m. p. 100–101°, in 200 cc. of glacial acetic acid cooled to 15° was added a solution of 7.0 g. of chromic anhydride in 7 cc. of water and 20 cc. of acetic acid. (*The double bond in the 5 position was not protected before oxidation.*) The temperature rose to 28° where it was kept for forty-five minutes. Water was added and the product was extracted with ether. The ethereal solution was washed well with water and sodium bicarbonate solution. It was evaporated and the residue was crystallized from dilute methanol and from methanol. yield 4.1 g.; m. p. 84–86°. When mixed with pseudodiosgenin diacetate, m. p. 100–101°, it melted at 76–80°.

Anal. Calcd. for $C_{31}H_{46}O_7$: C, 70.1; H, 8.8. Found: C, 69.9; H, 8.7.

Action of Acids and Alkalies on the Oxidation Product of Pseudodiosgenin Diacetate.—A mixture of 300 mg. of the oxidation product of pseudodiosgenin diacetate was refluxed with 20 cc. of alcohol containing 300 mg. of potassium hydroxide for thirty minutes. Water was added and the product was extracted with ether. The solvent was removed and the residue was crystallized from acetone and from ethyl acetate, m. p. 213–215°. It gave no depression in melting point when mixed with $\Delta^{5,16}$-pregnadienol-3(β)-20-one.

The same product was obtained when the oxidation product was refluxed with 10% alcoholic hydrochloric acid or with alcoholic potassium carbonate solution. The yield was practically the theoretical.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.5; H, 10.1.

Reduction of the Oxidation Product of Pseudodiosgenin Diacetate with Sodium in Dry Isopropyl Alcohol.—To a solution of 2 g. of the oxidation product of the diacetate of pseudodiosgenin in 200 cc. of dry isopropyl alcohol was added 15 g. of sodium in small pieces. When this was dissolved, water was added and the product was extracted with ether. The solvent was removed and the residue was crystallized from dilute acetone and from dilute methanol. It melted unsharply at 171–176°.

A mixture of 300 mg. of the above product, 300 mg. of platinum oxide catalyst and 50 cc. of glacial acetic acid was shaken with hydrogen under a pressure of 45 pounds for one hour. The catalyst was filtered, the solvent removed and the residue was crystallized from acetone, m. p. 214–216°. When mixed with *allo*-pregnanediol-3(β),20(α), m. p. 214–216°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.9; H, 11.1.

Mild Catalytic Reduction of the Oxidation Product of Pseudodiosgenin Diacetate.—A mixture of 400 mg. of the oxidation product of pseudodiosgenin diacetate, 200 mg. of platinum oxide catalyst and 100 cc. of ether was shaken with hydrogen at 30 pounds pressure for twenty minutes. The solution was filtered and the solvent was removed. The residue was crystallized from methanol, m. p. 102–104°. It gave no depression in melting point when mixed with the oxidation product of the diacetate of pseudotigogenin, m. p. 102–104°.

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.9; H, 9.1. Found: C, 69.9; H, 9.0.

Alkaline hydrolysis gave a product which when crystallized from methanol melted at 202–204° and gave no depression in melting point when mixed with Δ^{16}-*allo*-pregnenol-3(β)-one-20.

Oxidation of the Oxidation Product of Pseudotigogenin Diacetate.—To a solution of 3 g. of the oxidation product of pseudotigogenin diacetate in 50 cc. of acetic acid was added a solution of 4.5 g. of chromic anhydride in 50 cc. of 80% acetic acid. It was allowed to stand at 25° for twenty hours. Water was added and the product was extracted with ether. The ethereal solution was shaken with sodium carbonate solution. Evaporation of the ether gave only a negligible amount of neutral material. The aqueous alkaline solution was heated on a steam-bath to complete the hydrolysis, acidified and extracted with ether. The acid product was crystallized from ether, m. p. 246–247° with decomposition if heated rapidly. When mixed with an authentic sample of 3-hydroxy-*etio*-*allo*-bilianic acid, m. p. 244–247°, there was no depression in melting point.

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.4; H, 8.9. Found: C, 67.4; H, 9.0.

Reduction of the Oxidation Product of Pseudotigogenin Diacetate with Aluminum Isopropylate.—A mixture of 10 g. of aluminum isopropylate, 4 g. of the oxidation product of the diacetate of pseudotigogenin and 300 cc. of dry isopropyl alcohol was refluxed for seven hours. The solvent was then removed over a three-hour period and the residue was refluxed with 500 cc. of a 2% methanolic potassium hydroxide solution for thirty minutes. Water was added and the precipitated product was filtered and crystallized from methanol, m. p. 285–288°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 75.1; H, 10.7.

This was an *allo*-pregnanetriol-3,16,20.

When refluxed with acetic anhydride it gave an acetate which when crystallized from pentane melted at 161–163°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.1. Found: C, 70.3; H, 9.2.

Catalytic Reduction of the Oxidation Product of Pseudotigogenin Diacetate.—A mixture of 2 g. of the oxidation product of pseudotigogenin diacetate, 3 g. of platinum oxide catalyst and 100 cc. of glacial acetic acid was shaken with hydrogen under thirty pounds pressure for two hours at room temperature. At the end of this time the temperature was raised to 70° and the hydrogenation was continued for ninety minutes. The solution was filtered and the solvent was removed *in vacuo*. The residue was refluxed for fifteen minutes with a 2% alcoholic potassium hydroxide solution. Water was added and the product was filtered and recrystallized from methanol, m. p. 285–288°. When mixed with the *allo*-pregnanetriol prepared by the aluminum isopropylate reduction of the oxidation product of pseudotigogenin diacetate there was no depression in melting point. The yield was almost quantitative.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 75.0; H, 10.8.

When refluxed in acetic anhydride for thirty minutes it gave a triacetate which was recrystallized from pentane, m. p. 161.5–163°. When mixed with the triacetate of the triol from the aluminum isopropylate reduction of the

oxidation product of pseudotigogenin diacetate, m. p. 161–163°, the m. p. was unchanged.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 69.9; H, 9.1.

Catalytic Reduction of the Oxidation Product of Pseudodiosgenin Diacetate.—A mixture of 2 g. of the oxidation product of the diacetate of pseudodiosgenin, 2 g. of platinum oxide catalyst and 100 cc. of glacial acetic acid were shaken for two hours at room temperature under 45 pounds of hydrogen. The temperature was then raised to 70° for one hour. The solution was filtered and the acetic acid was removed *in vacuo*. The residue was refluxed for fifteen minutes with a 2% alcoholic potassium hydroxide solution. Water was added and the product was filtered and recrystallized from methanol, m. p. 287–289°. When mixed with the triol from the catalytic reduction of the oxidation product of the diacetate of pseudotigogenin, m. p. 286–288°, there was no depression in melting point.

Reduction of the Oxidation Product of Pseudodiosgenin Diacetate with Aluminum Isopropylate.—A mixture of 10 g. of aluminum isopropylate, 5 g. of the oxidation product of pseudodiosgenin diacetate and 400 cc. of dry isopropyl alcohol was refluxed for seven hours. The solvent was removed over a five-hour period and the residue was refluxed with 500 cc. of 2% methanolic potassium hydroxide for thirty minutes. Water was added and the precipitated product was filtered and crystallized from methanol, m. p. 281–285°. When mixed with the saturated triol there was a depression in melting point.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.2; H, 10.1

When refluxed with acetic anhydride it gave a triacetate which was crystallized from ether–pentane, m. p. 143°.

Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.4; H, 8.8. Found: C, 70.3; H, 8.8.

Catalytic Hydrogenation of Δ^5-Pregnenetriol-3,16,20 to *allo*-Pregnanetriol-3,16,20.—A mixture of 500 mg. of the triacetate of Δ^5-pregnenetriol-3,16,20, 1 g. of platinum oxide catalyst and 200 cc. of glacial acetic acid was shaken under hydrogen at 45 pounds pressure for one hour. The solution was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in alcohol and refluxed for fifteen minutes with a 2% alcoholic potassium hydroxide solution. Water was added and the precipitated product was filtered, and recrystallized from ethanol, m. p. 285–287°. When mixed with the triol obtained by the catalytic reduction of the oxidation product of pseudotigogenin diacetate, m. p. 286–288°, there was no depression in m. p.

Summary

1. Dihydro-pseudotigogenin diacetate and pseudotigogenin diacetate give an identical oxidation product, $C_{31}H_{48}O_7$ (A).

2. Similarly pseudodiosgenin diacetate gives an oxidation product, $C_{31}H_{46}O_7$ (B). Catalytic reduction of this gives the product A. Further oxidation of A gives 3-hydroxy-*etio-allo*-bilianic acid.

3. Hydrolysis of A gives Δ^{16}-*allo*-pregnenol-3(β)-one-20. Hydrolysis of B gives $\Delta^{5,16}$-pregnadienol-3(β)-one-20.

4. Reduction of A with aluminum isopropylate or catalytically gives an *allo*-pregnanetriol-3,16,20 (C), while reduction of B with aluminum isopropylate gives a Δ^5-pregnenetriol-3,16,20, which can be catalytically reduced to C. Direct catalytic reduction of B followed by hydrolysis gives C.

5. Reduction of A with sodium in alcohol gives *allo*-pregnanediol-3(β),20(α). B gives Δ^5-pregnenediol-3(β),20(α).

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Sterols. CXVIII. The Action of Selenious Acid on Δ^5-Pregnenediol and on Δ^5-Androstenediol

BY RUSSELL E. MARKER, HARRY M. CROOKS, JR., AND EMERSON L. WITTBECKER

Two previous papers of this series have dealt with the conversion of sitosterol[1] and stigmasterol[2] to the corresponding Δ^5-3,4 and Δ^4-3,6-diols by oxidation with selenious acid in the manner of Rosenheim and Starling[3] with cholesterol. Refluxing of these unsaturated diols with alcoholic hydrogen chloride led in each case to the formation of the corresponding Δ^4-3-ketone.

Since the pregnane derivatives are readily available[4] this series of reactions has now been extended to the preparation of 20-dihydroprogesterone and testosterone, using as starting materials Δ^5-pregnenediol and Δ^5-androstenediol, respectively. In both cases the selenious acid oxidation gives apparently a great preponderance of a single isomer, presumably the Δ^5-3,4-diol, in contrast to the almost equal yields of the two isomeric diols in the case of the sterols previously reported.

(1) Marker, Kamm and Wittle, THIS JOURNAL, **60**, 1071 (1938).
(2) Marker and Rohrmann, *ibid.*, **60**, 1073 (1938).
(3) Rosenheim and Starling, *J. Chem. Soc.*, 377 (1937).
(4) Marker and Rohrmann, THIS JOURNAL, **61**, 3592 (1939), *et seq.*