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

Sterols. CIX. Sapogenins. XXXVIII. The Preparation of Dihydro-isoandrosterone from Diosgenin

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Using procedures developed in this Laboratory,[1,2,3] involving the oxidation of 20-keto-pregnane compounds with Caro's acid, we recently[4] prepared dihydroandrosterone starting with *epi*-tigogenin.

We have now studied the oxidation of *allo*-pregnanol-3(β)-one-20 with Caro's acid. The preparation of this substance started with the diacetate of dihydropseudotigogenin. Dihydropseudotigogenin was made by the catalytic reduction of pseudodiosgenin[5] and also by the reduction of pseudotigogenone, prepared from tigogenone. Pseudotigogenone is similar to the other pseudosapogenins. Thus treatment with mineral acid converts it to tigogenone. Oxidation of pseudotigogenone at room temperature with chromic acid gave Δ^{16}-*allo*-pregnenedione-3,20. The oxidation of the diacetate of dihydropseudotigogenin gave Δ^{16}-*allo*-pregnenol-3(β)-one-20. When this was reduced catalytically *allo*-pregnanol-3(β)-one-20 was obtained.

allo-Pregnanol-3(β)-one-20 was oxidized with Caro's acid. This gave a mixture of substances from which a ketone fraction was separated with Girard's reagent. From this *allo*-pregnanediol-3,21-one-20 was isolated as its diacetate. The crude ketonic fraction was treated with alcoholic potassium hydroxide solution to give 3(β)-hydroxy-*etio*-*allo*-cholanic acid. The non-ketonic fraction from the oxidation gave dihydro-isoandrosterone, which was identified by conversion to androstanedione.

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Experimental Part

Pseudo-tigogenone (II).—A mixture of 3 g. of tigogenone (I) and 15 cc. of acetic anhydride was heated in a bomb tube at 200° for ten hours. After cooling, the excess acetic anhydride was evaporated *in vacuo* and the residue was refluxed for thirty minutes with 200 cc. of ethanol containing 5 g. of potassium hydroxide. Water was added and the product was extracted with ether. The solvent was removed and the residue was crystallized from dilute acetone and from methanol; m. p. 108–111°. It is very soluble in ordinary solvents and crystallized with difficulty. The correct melting point may be slightly higher than the value given here, but the material used in the following experiments was of this quality.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.2. Found: C, 77.8; H, 10.0.

Conversion of Pseudo-tigogenone (II) to Tigogenone (I).—To a hot solution of 100 mg. of pseudo-tigogenone in 20 cc. of ethanol was added 2 cc. of concentrated hydrochloric acid. After standing one hour, water was added and the product was filtered and crystallized from methanol and acetone; m. p. 204–206°. Mixed with tigogenone, m. p. 204–206°, it gave no depression in melting point.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.2. Found: C, 78.1; H, 10.2.

Oxidation of Pseudo-tigogenone (II) to Δ^{16}-*allo*-Pregnenedione-3,20 (III).—To a solution of 1 g. of pseudo-tigogenone in 50 cc. of glacial acetic acid was added 1 g. of chromic anhydride in 20 cc. of 90% acetic acid. It was allowed to stand at 25–28° for ninety minutes. Water was added and the product was extracted with ether. The ethereal solution was washed with water and 3% sodium hydroxide solution. After removal of the solvent the residue was crystallized from ether–pentane and from ether; m. p. 207–210°. Mixed with Δ^{16}-*allo*-pregnenedione-3,20, m. p. 208–211°, it gave no depression in m. p.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.1; H, 9.4.

Reduction of Pseudo-tigogenone (II) to Dihydro-pseudo-tigogenin (IV).—A mixture of 1 g. of pseudo-tigogenone, 500 mg. of Adams catalyst and 100 cc. of glacial acetic acid was shaken with hydrogen under a pressure of 3 atm. for four hours. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was crystallized from ether and from methanol, m. p. 202–205°. When mixed with tetrahydro-pseudo-diosgenin (dihydro-pseudo-tigogenin), m. p. 202–205°, there was no depression in melting point.

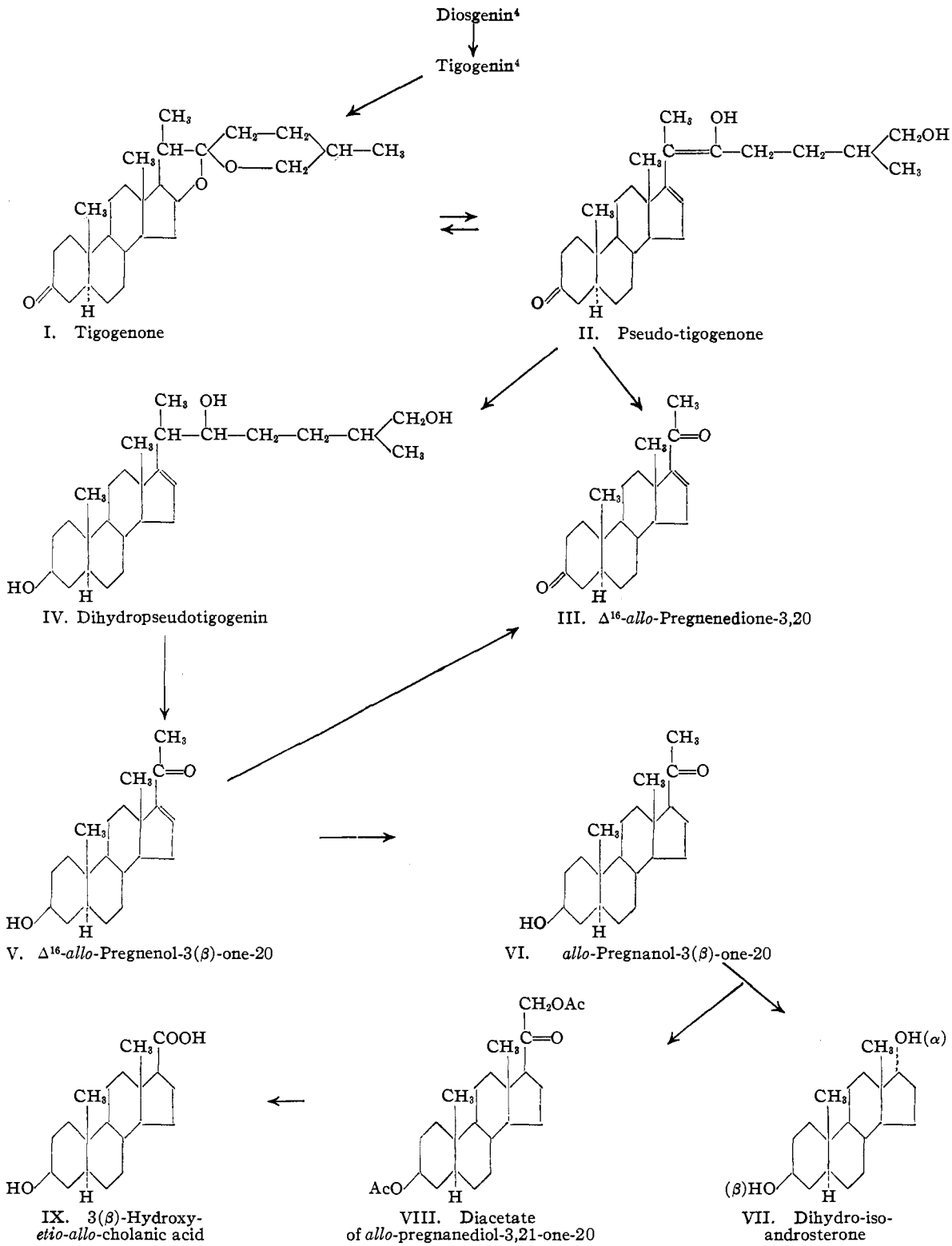
Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.4; H, 11.2. Found: C, 77.7; H, 11.2.

A solution of 100 mg. of dihydro-pseudo-tigogenin in 5 cc. of acetic anhydride was refluxed for thirty minutes. Upon cooling, the product crystallized and was filtered. It was crystallized from methanol, m. p. 122–124°. When mixed with the diacetate of dihydro-pseudo-*epi*-tigogenin,[4] m. p. 118–121°, it melted at 105–110°.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.0; H, 10.0. Found: C, 74.0; H, 10.0.

A solution of 100 mg. of pseudo-diosgenin in 10 cc. of acetic anhydride was refluxed for thirty minutes. The solvent was evaporated and the residue was crystallized from methanol to give the diacetate, m. p. 98–100°.

(1) Marker, Rohrmann, Wittle, Crooks and Jones, THIS JOURNAL, **62**, 650 (1940).
(2) Marker, *ibid.*, **62**, 2543 (1940).
(3) Marker and Rohrmann, *ibid.*, **62**, 521 (1940).
(4) Marker, *ibid.*, **62**, 2621 (1940).
(5) Marker, Tsukamoto and Turner, *ibid.*, **62**, 2525 (1940).



Anal. Calcd. for $C_{31}H_{46}O_5$: C, 74.6; H, 9.3. Found: C, 74.5; H, 9.4.

A solution of 50 mg. of the diacetate of pseudo-diosgenin in 50 cc. of acetic acid was shaken with 100 mg. of platinum oxide catalyst under hydrogen at a pressure of 3 atm. for six hours. The catalyst was filtered off and the filtrate

was evaporated *in vacuo*. The residue was crystallized from methanol, m. p. 122–124°. It gave no depression in melting point when mixed with the **diacetate of dihydro-pseudo-tigogenin** prepared above.

Δ^{16}-*allo*-Pregnenol-3(β)-one-20 (V) from the Diacetate of Dihydro-pseudo-tigogenin.—To a solution of 20 g. of the diacetate in 500 cc. of glacial acetic acid cooled to 15° was added a solution of 15 g. of chromic anhydride in 20 cc. of water and 30 cc. of glacial acetic acid. The temperature rose to 30°. It was kept there for two hours. Water was added and the product was extracted with ether and washed well with water and finally with a 3% solution of sodium hydroxide. The ether was evaporated and the residue was hydrolyzed by refluxing it with a 1% alcoholic potassium hydroxide solution for thirty minutes. The product was extracted with ether and the solvent was removed. The residue was crystallized from dilute methanol and from ether; m. p. 202–204°. The product in the mother liquors was sublimed in a high vacuum at 120° and the sublimate upon crystallization from ether gave an additional quantity of Δ^{16}-*allo*-pregnenol-3(β)-one-20; yield 7.1 g.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.0.

Upon refluxing with acetic anhydride it gave an acetate which was crystallized from methanol; m. p. 162–164°.

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

Reduction of Δ^{16}-*allo*-Pregnenol-3(β)-one-20 (V) to *allo*-Pregnanol-3(β)-one-20 (VI).—A mixture of 5 g. of unsaturated ketone, 500 cc. of ethyl alcohol and 5 g. of palladium–barium sulfate catalyst was shaken under an atmosphere of hydrogen for three hours. The catalyst was filtered and the solvent was removed. The residue was crystallized from dilute ethanol; m. p. 192–194°. Mixed with *allo*-pregnanol-3(β)-one-20, m. p. 193–195°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.0; H, 10.7.

Oxidation of Δ^{16}-*allo*-Pregnenol-3(β)-one-20 (V) to Δ^{16}-*allo*-Pregnenedione-3,20 (III).—To a solution of 100 mg. of Δ^{16}-*allo*-pregnenol-3(β)-one-20 in 10 cc. of glacial acetic acid was added a solution of 50 mg. of chromic oxide in 5 cc. of 90% acetic acid. After standing for thirty minutes, water was added and the product was extracted with ether. The solvent was removed and the residue was crystallized from ether; m. p. 210–211°. Mixed with Δ^{16}-*allo*-pregnenedione-3,20, m. p. 209–211°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.3; H, 9.6.

Conversion of *allo*-Pregnanol-3(β)-one-20 (VI) to Dihydro-iso-androsterone (VII).—A solution of 2.4 g. of *allo*-pregnanol-3(β)-one-20 acetate in 400 cc. of glacial acetic acid was treated with 80 g. of von Baeyer's dry persulfate mixture. It was allowed to stand for seven days at 25°. At the end of this time 40 g. more of persulfate mixture was added and allowed to stand for three more days. At the end of this time a slight excess of 50% potassium hydroxide solution was added to neutralize the inorganic acids. It was then slightly acidified, the salts were filtered and the filtrate was concentrated *in vacuo*. The residue was extracted repeatedly with ether and washed with water. The solvent was removed and the residue was treated with Girard reagent to remove ketones. The non-ketonic fraction, 610 mg., was hydrolyzed with alcoholic potassium hydroxide solution and the neutral fraction was sublimed in a high vacuum. The sublimate was crystallized from dilute acetone and from dilute methanol. This was dihydro-iso-androsterone (VII); m. p. 162–164°.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.0; H, 11.1. Found: C, 77.7; H, 11.0.

A solution of 50 mg. in 10 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was distilled *in vacuo* and the residue was crystallized from ethyl acetate and dilute alcohol; diacetate, m. p. 124–126°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.4; H, 9.7. Found: C, 73.7; H, 9.6.

To prove the identity of the above product, the diol (VII) was oxidized in acetic acid with chromic anhydride, giving androstanedione, m. p. 128–131°, which gave no depression in melting point when mixed with an authentic sample.

The ketonic Girard fraction was let stand for three hours with dilute hydrochloric acid and extracted with ether. The solvent was removed and the residue was dissolved in a small amount of methanol from which crystals were obtained on cooling. These were dissolved in benzene and the solution was passed through a 5-cm. height of aluminum oxide and washed with ether–benzene and finally with ether. The solvent was removed and the residue was crystallized from methanol. This was probably the diacetate of *allo*-pregnanediol-3,21-one-20 (VIII). It melted at 151–152°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.7; H, 9.2. Found: C, 71.5; H, 9.0.

A less pure sample of the diacetate (320 mg.), m. p. 125–140°, was refluxed for one hour with 50 cc. of a 5% solution of alcoholic potassium hydroxide. The solvent was removed to 10 cc. and water was added. The product was well extracted with ether and the alkaline solution was acidified and extracted with ether. The solvent was removed and the residue was crystallized from dilute methanol and dilute acetone to give 3(β)-hydroxy-*etio-allo*-cholanic acid (IX), m. p. 248–251°. When mixed with an authentic sample, m. p. 250–254°, it gave no depression in melting point.

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

Summary

Dihydro-isoandrosterone and related compounds were made from tigogenin prepared from diosgenin.

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