To a solution of 4 g. of the crude pseudo-trillin acetate in 200 cc. of acetic acid cooled to 15° was added a solution of 1.2 g. of chromic anhydride in 20 cc. of 90% acetic acid. After standing for one hour at 25°, water was added and the product was extracted with ether. The ethereal solution was washed well with water and 3% sodium hydroxide solution. The ether was evaporated leaving a crystalline residue. This was refluxed for ninety minutes with 50 cc. of ethanol containing 5 cc. of concentrated hydrochloric acid. The ketones were removed by Girard reagent and distilled in a high vacuum at 120–140°, and the distillate was crystallized from ether, acetone, and dilute methanol, m. p. 210–212°. When mixed with an authentic sample of $\Delta^{5,16}$-pregnanedienol-3-one-20, m. p. 212–214°, there was no depression in melting point; yield 160 mg. There was considerable material left in the mother liquors.

*Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 79.8; H, 9.7.

**$\Delta^5$-Pregnenol-3-one-20.**—To a solution of 150 mg. of $\Delta^{5,16}$-pregnadienol-3-one-20 in 50 cc. of ether was added 200 mg. of palladium–barium sulfate catalyst and the mixture was shaken under hydrogen at 15 pounds pressure for ninety minutes. The solution was filtered and the solvent was removed. The product was crystallized from dilute acetone, m. p. 188–190°. When mixed with a sample of $\Delta^5$-pregnenol-3-one-20, m. p. 190°, it gave no depression in melting point. When mixed with *allo*-pregnanol-3-one-20, m. p. 194°, it melted at 156–170°. When mixed with $\Delta^{5,16}$-pregnadienol-3-one-20, it melted at 150–165°.

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.8; H, 10.2.

**Progesterone.**—A mixture of 100 mg. of $\Delta^5$-pregnenol-3-one-20 and 100 mg. of platinum black was heated at 250–300° under an atmosphere of carbon dioxide for one hour. The product was then extracted with ether, sublimed in high vacuum and crystallized from dilute acetone, m. p. 120–121°. When mixed with an authentic sample of progesterone, m. p. 120°, it gave no depression in melting point.

*Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 79.8; H, 9.6.

## Summary

The glucosides of sarsasapogenin and diosgenin were prepared. The glucoside of diosgenin was identical with that obtained from *trillium erectum*, showing the latter to be a 3-$\alpha$-glucoside of diosgenin. Trillin was converted to the pseudo derivative, which was oxidized directly without protecting the double bond to give $\Delta^{5,16}$-pregnadienol-3-one-20. The latter compound was reduced catalytically to $\Delta^5$-pregnenol-3-one-20, which in turn was oxidized to progesterone.

STATE COLLEGE, PENNA. RECEIVED JULY 26, 1940

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

# Sterols. CXIII. Sapogenins. XLII. The Conversion of the Sapogenins to the Pregnenolones

BY RUSSELL E. MARKER

Treatment of a steroidal sapogenin with acetic anhydride at 200° converts it into a pseudo sapogenin which can be oxidized to a $\Delta^{16}$-pregnenone-20 derivative in good yield. By this method we have prepared $\Delta^{16}$-pregnenol-3($\beta$)-one-20[1] by the oxidation of the diacetate of pseudosarsasapogenin, as well as by the oxidation of the diacetate of dihydropseudosarsasapogenin. In a like manner we have prepared $\Delta^{16}$-*allo*-pregnenol-3($\beta$)-one-20[2] from the diacetate of pseudotigogenin and the diacetate of dihydropseudotigogenin, and have made $\Delta^{16}$-*allo*-pregnenol-3($\alpha$)-one-20[3] from pseudo-*epi*-tigogenin and dihydropseudo-*epi*-tigogenin. Of the four possible compounds, $\Delta^{16}$-pregnenol-3-one-20 isomeric at C-3 and C-5 there remained but $\Delta^{16}$-pregnenol-3($\alpha$)-one-20 to be prepared. This compound has now been made by the oxidation of the diacetate of pseudo-*epi*-sarsasapogenin and the diacetate of dihydropseudo-*epi*-sarsasapogenin.

Reduction of $\Delta^{16}$-pregnenol-3($\alpha$)-one-20 with sodium in alcohol gave pregnanediol-3($\alpha$),20($\alpha$). This is identical with the pregnanediol obtained from pregnancy urines. Reduction with palladium gave pregnanol-3($\alpha$)-one-20, identical with another pregnancy urine product, whereas reduction with platinum oxide catalyst gave pregnanediol-3($\alpha$),20($\beta$). Oxidation of the unsaturated hydroxy ketone gave $\Delta^{16}$-pregnenedione-3,20 which is also obtained by the oxidation of pseudosarsasapogenin or dihydropseudosarsasapogenin directly without acetylation.[1]

We had previously obtained $\Delta^{16}$-pregnenol-3($\beta$)-one-20 by the oxidation of acetylated pseudosar-

(1) Marker and Rohrmann, THIS JOURNAL, **62**, 518 (1940).
(2) Marker and Turner, *ibid.*, **62**, 3003 (1940).
(3) Marker, *ibid.*, **62**, 2621 (1940).

sasapogenin, but the product contained alcohol of crystallization. We have now prepared this compound free of solvent of crystallization.

Because of the importance of obtaining high yields of the $\Delta^{16}$-pregnenolones and $\Delta^{16}$-pregnenediones to be used as intermediates for the practical synthesis of the steroidal hormones, we have carried out a thorough investigation of the method of oxidation of the pseudosapogenins to obtain maximum yields of these compounds. We find that it is necessary to adhere very closely to the directions given if high yields of the $\Delta^{16}$-pregnenol-3-one-20 compounds are to be expected, as very slight changes in the conditions of oxidation considerably lower the yields.

We have found that the conversion of the sapogenins into the pseudosapogenins is practically a quantitative reaction and therefore it is unnecessary to isolate the pseudosapogenin before oxidation. The sapogenin acetate is merely heated to 200° with acetic anhydride for ten hours, the excess acetic anhydride evaporated and the residue oxidized directly with chromic anhydride in acetic acid. By this method we have obtained yields of 48–56% of the corresponding $\Delta^{16}$-pregnenol-3-one-20 compounds, isomeric at C-3 and C-5, based upon the amount of saturated sapogenin acetate used. On large runs the yields remain approximately the same. Under the same conditions we have prepared $\Delta^{5,16}$-pregnadienol-3($\beta$)-one-20 in 38% yield by the oxidation of diosgenin acetate which had been heated previously with acetic anhydride. This oxidation was carried out without protection of the double bond with bromine or other reagents as the oxidation of a side chain in the pseudosapogenins proceeds much more rapidly than that of the double bond at C-5. We have previously shown[4] that this is an important intermediate from which high yields of progesterone can be obtained.

Under the same conditions we have also oxidized the diacetates prepared from the purified dihydropseudosapogenins which are isomeric at C-3 and C-5, the yield varying from 47–61%.

The high yields of the pregnene compounds obtained from the sapogenins make this a superb method of preparing the steroidal hormones in comparison with the previously used procedures.

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

(4) Marker, Tsukamoto and Turner, THIS JOURNAL, 62, 2525 (1940).

## Experimental Part

**$\Delta^{16}$-Pregnenol-3($\alpha$)-one-20.**—A mixture of 9.16 g. of *epi*-sarsasapogenin acetate (prepared by the sodium reduction of sarsasapogenone) and 16 cc. of acetic anhydride was heated in a bomb tube at 200° for ten hours. The excess acetic anhydride was evaporated *in vacuo* and the residue was dissolved in 200 cc. of glacial acetic acid and cooled to 15°. It was vigorously stirred and a solution of 6 g. of chromium trioxide in 50 cc. of 85% acetic acid was added at such a rate that the temperature did not rise above 25°. It was then allowed to stand at 28° for ninety minutes. At the end of this time water was added and the product was well extracted with ether. The ethereal solution was washed well with water and with a 3% solution of sodium hydroxide. The solvent was removed and the residue was refluxed with a solution of 3 g. of potassium hydroxide in 200 cc. of ethyl alcohol for thirty minutes. The product was extracted with ether, washed well with water and the solvent was removed. The residue was then sublimed in a high vacuum at 120–130°. The sublimate was crystallized from ether, m. p. 194–196°, yield 3.3 g. or 52%.

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.5; H, 10.5.

The above product was refluxed with acetic anhydride, giving a mono-acetate of $\Delta^{16}$-pregnenol-3($\alpha$)-one-20, which was crystallized from dilute methanol and dilute acetone as needles, m. p. 96–99°.

*Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.2; H, 9.3.

Using analogous procedures for the conversion of the sapogenins to the pregnenolones as described above, 9.16 g. of tigogenin acetate gave 3.1 g. of $\Delta^{16}$-*allo*-pregnenol-3-($\beta$)-one-20, m. p. 202–204°, yield 49%.

*epi*-Tigogenin acetate (9.16 g.) gave 3.0 g. of $\Delta^{16}$-*allo*-pregnenol-3($\alpha$)-one-20, m. p. 219–222°, yield 56%.

Sarsasapogenin acetate (9.16 g.) gave 3.0 g. of $\Delta^{16}$-pregnenol-3($\beta$)-one-20, m. p. 188–190°, yield 48%. This was previously prepared[1] but the product which we then obtained contained alcohol of crystallization and melted at 207–209°. The present product was crystallized from ether–pentane.

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.8; H, 10.1.

Diosgenin acetate (9.16 g.) gave 2.4 g. of $\Delta^{5,16}$-pregnadienol-3($\beta$)-one-20, m. p. 212–214°, yield 38%. The crude pseudodiosgenin acetate was oxidized directly without protection of the double bond.

**Oxidation of the Diacetate of Dihydropseudo-*epi*-sarsasapogenin.**—A solution of 4.16 g. of dihydropseudo-*epi*-sarsasapogenin in 20 cc. of acetic anhydride was refluxed for thirty minutes. The excess solvent was removed, the residue was dissolved in 100 cc. of acetic acid and oxidized with 3.5 g. of chromic anhydride and the product was isolated as described above, m. p. 194–196°. It gave no depression in m. p. with the product prepared above. It gave an acetate, m. p. 96–98°, which gave no depression with the acetate of $\Delta^{16}$-pregnenol-3($\alpha$)-one-20, yield 1.9 g. or 61%.

In an analogous manner the diacetate prepared from 4.16 g. of pure dihydropseudosarsasapogenin upon oxida-

tion gave 1.5 g. of $\Delta^{16}$-pregnenol-3($\beta$)-one-20, m. p. 188–190°, when crystallized from ether–pentane after sublimation, yield 47%.

Dihydropseudotigogenin (4.16 g.) upon acetylation and oxidation gave 1.8 g. of $\Delta^{16}$-*allo*-pregnenol-3($\beta$)-one-20, m. p. 202–204°, yield 60%.

Dihydropseudo-*epi*-tigogenin (4.16 g.) upon acetylation and oxidation gave 1.7 g. of $\Delta^{16}$-*allo*-pregnenol-3($\alpha$)-one-20, m. p. 219–222°, yield 56%.

**Reduction of $\Delta^{16}$-Pregnenol-3($\alpha$)-one-20 with Sodium and Ethyl Alcohol.**—To a solution of 300 mg. of $\Delta^{16}$-pregnenol-3($\alpha$)-one-20 in 75 cc. of absolute alcohol was added 5 g. of sodium in small pieces. After the sodium was in solution, water was added and the product was crystallized from acetone, m. p. 242–243°. Mixed with pregnanediol-3($\alpha$),20($\alpha$), m. p. 242°, it gave no depression in melting point.

*Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 80.0; H, 11.2.

Upon refluxing with acetic anhydride it gave a diacetate which was crystallized from acetic anhydride and from methanol, m. p. 175–176°. It gave no depression in melting point when mixed with an authentic sample of the diacetate of pregnanediol-3($\alpha$),20($\alpha$), m. p. 175°.

*Anal.* Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.4; H, 10.1.

**Reduction of $\Delta^{16}$-Pregnenol-3($\alpha$)-one-20 with Palladium.**—A solution of 300 mg. of $\Delta^{16}$-pregnenol-3($\alpha$)-one-20 in 25 cc. of ether and 25 cc. of alcohol containing 1 g. of palladium–barium sulfate catalyst was shaken under an atmosphere of hydrogen for two hours. The solution was filtered and the solvent was removed. The residue was crystallized from alcohol–water, m. p. 145–147°. Mixed with pregnanol-3($\alpha$)-one-20, m. p. 145–147°, 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, 10.0.

It gave an acetate with acetic anhydride which was crystallized from aqueous alcohol, m. p. 112–114°. When mixed with an authentic sample it gave no depression in melting point.

*Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.8; H, 10.1. Found: C, 76.6; H, 10.1.

**Reduction of $\Delta^{16}$-Pregnenol-3($\alpha$)-one-20 with Platinum Oxide Catalyst.**—A solution of 300 mg. of $\Delta^{16}$-pregnenol-3-($\alpha$)-one-20 in 50 cc. of acetic acid containing 300 mg. of platinum oxide catalyst was shaken with hydrogen at 45 pounds pressure for two hours. The solution was filtered and the solvent removed *in vacuo*. The product was crystallized from alcohol, m. p. 230–232°. Mixed with an authentic sample of pregnanediol-3($\alpha$),20($\beta$), m. p. 231°, it gave no depression in melting point.

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

**Oxidation of $\Delta^{16}$-Pregnenol-3($\alpha$)-one-20 to $\Delta^{16}$-Pregnenedione-3,20.**—To a solution of 100 mg. of $\Delta^{16}$-pregnenol-3($\alpha$)-one-20 in 20 cc. of glacial acetic acid was added a solution of 60 mg. of chromic anhydride in 2 cc. of dilute acetic acid. It was allowed to stand for one hour at room temperature. Water was added and the product was extracted with ether. The ethereal solution was washed with a 2% sodium hydroxide solution and the solvent removed. The residue was crystallized from acetone, m. p. 200–202°. Mixed with $\Delta^{16}$-pregnenedione-3,20, m. p. 200–202°, it gave no depression in melting point.

*Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 79.9; H, 9.6.

## Summary

An improved method for the oxidation of the acetylated pseudosapogenins to the four compounds, $\Delta^{16}$-pregnenol-3-one-20 isomeric at C-3 and C-5 is described.

STATE COLLEGE, PENNA. RECEIVED AUGUST 17, 1940

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

# Some Alkamine Esters of 4-Acetylferulic and 3,4-Dimethoxycinnamic Acids[1]

BY L. S. FOSDICK AND A. C. STARKE, JR.

Since the preparation of procaine,[2] alkamine esters of various acids have been shown to possess local anesthetic properties.

Shriner and Keyser[3] noted that most effective anesthetics of the ester type have a carbonyl group conjugated with double bonds. The conjugation of the carbonyl group with an aromatic nucleus would not be lost by the insertion of an ethylene group and perhaps might increase the anesthetic activity in the case of cinnamate derivatives. It has been shown[4] that the alkamine esters of phenylacetic acid, which would not have the conjugated system, are almost inactive.

The use of apothesine[5] and apocaine as local anesthetics[6] has suggested that the cinnamate derivates should be further investigated. Alkamine esters of *p*-methoxycinnamic acid[7] and aminocinnamic acid[8] have local anesthetic activity.

(1) Abstract of a thesis submitted to the faculty of the Graduate School of Northwestern University by A. C. Starke in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

(2) Einhorn and Uhlfelder, *Ann.*, **371**, 131 (1909).

(3) Shriner and Keyser, THIS JOURNAL, **60**, 286 (1938).

(4) Pyman, *J. Chem. Soc.*, **111**, 167 (1917).

(5) Wildman and Thorp, U. S. Patent 1,193,649.

(6) Meeker and Frazier, *J. Pharmacol.*, **22**, 375 (1923).

(7) Brill, THIS JOURNAL, **54**, 2484 (1932).

(8) Meister, Lucius and Brüning, German Patent 187,593.