acid and oxidation of the resulting product, gave progesterone.

2. Oxidation of Δ^5-androstenediol with selenious acid, followed by dehydration with hydrochloric acid gave testosterone.

STATE COLLEGE, PENNA. RECEIVED DECEMBER 21, 1940

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

Sterols. CXIX. Sapogenins. XLVII. Pregnanetriols from Pseudosapogenins

BY RUSSELL E. MARKER, D. L. TURNER, R. B. WAGNER, PAUL R. ULSHAFER, HARRY M. CROOKS, JR., AND EUGENE L. WITTLE

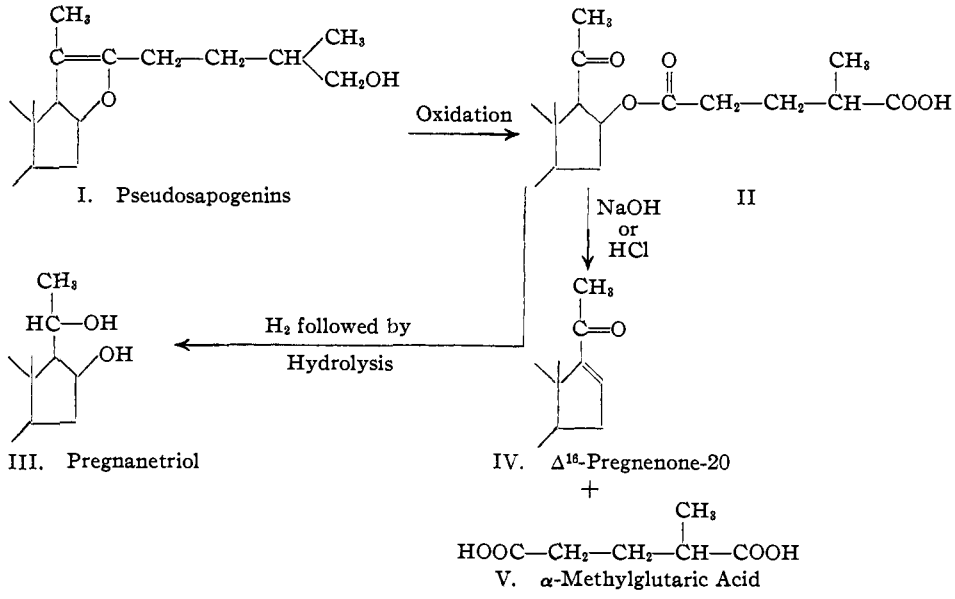
Recently we described the oxidation of the diacetates of pseudosapogenins and the conversion of the oxidation products to pregnanetriols.[1] The present work was undertaken in the hope of obtaining from *epi*-tigogenin the *allo*-pregnanetriol-3(α),16,20 which occurs in the urine of pregnant mares[2,3]; instead an isomeric triol was formed.

The diacetate of *epi*-pseudotigogenin was oxidized as described previously[1] and the crude product was reduced catalyticaly to *allo*-pregnanetriol-3(α),16,20. It differs from the *allo*-pregnanetriol-3(α),16,20 obtained from the oxidation of *epi*-tigogenin with Caro's acid[4] and neither is identical with the naturally occurring triol. Extending the same procedure to dihydro-pseudosarsasapogenin diacetate and pseudosarsasapogenin diacetate, an identical pregnanetriol-3(β),16,20 was obtained from both by catalytic reduction of the crude intermediate oxidation product. Unacetylated pseudosarsasapogenin gave the same triol. *epi*-Pseudosarsasapogenin diacetate gave a pregnanetriol-3(α),16,20(β). The preganetriols prepared by this method all differ from the corresponding triols prepared by the oxidation of sapogenins with Caro's acid.[3,4,5] On the basis of the formulas assigned to the sapogenins[6] and pseudosapogenins[6] the difference must be in configuration at C-20. The reduction of the carbonyl group at C-20 under analogous conditions has been shown in the case of the various pregnanone-20 and *allo*-pregnanone-20 compounds to give one of the isomers to which the configuration "β" has been assigned.[7,8] By analogy to these results the new triols described in this paper and in the preceding one[1] may all be assigned the β-configuration at C-20 and the triols produced by oxidation with Caro's acid would be 20(α) triols. Since the new triols can also be prepared by Meerwein reduction of the pseudosapogenin oxidation products,[1] it seemed of interest to determine the configuration of the principal product of the Meerwein reduction of the carbonyl group at C-20 in Δ^{16}-*allo*-pregnenol-3(β)-one-20 and $\Delta^{5,16}$-pregnadienol-3-(β)-one-20. The products obtained were Δ^{16}-*allo*-pregnenediol,3(β),20(β) and $\Delta^{5,16}$-pregnadienediol-3(β),20(β), respectively. This follows from the conversion of both diols to *allo*-pregnanediol-3(β),20(β). The $\Delta^{5,16}$-pregnadienediol-3(β),-20(β) has been obtained by Butenandt[9] using a considerably different method. The melting points for the substance and its acetate reported in this paper are in agreement with those recorded by Butenandt.

The hydrolysis of the oxidation product from unacetylated pseudotigogenin gave Δ^{16}-*allo*-pregnenedione while that from free pseudosarsasapogenin gave Δ^{16}-pregnenedione. The acid fraction from both of these hydrolyses gave a good yield of α-methylglutaric acid, presumably identical with the acid of Windaus and Willerding.[10] Their acid was obtained from the energetic oxidation of digitogenic acid and there is some doubt of its origin from the side-chain.[11] By analogy with the formula previously given for the oxidation products of the acetylated pseudosapogenins,[1] the unacetylated pseudosapogenins would be expected to give oxidation products with the structure II. This readily accounts for the products obtained by hydrolysis.

Finally we have oxidized the acetate of pseudodesoxysarsasapogenin. Hydrolysis of the prod-

(1) Marker, Turner, Wagner, Ulshafer, Crooks and Wittle, THIS JOURNAL, **63**, 774 (1941).
(2) Marker and Wittle, *ibid.*, **61**, 855 (1939).
(3) Marker and Turner, *ibid.*, **62**, 2540 (1940).
(4) Marker, Turner, Wagner and Ulshafer, *ibid.*, **63**, 772 (1941).
(5) Marker, *et al.*, *ibid.*, **62**, 525 (1940).
(6) Marker and Rohrmann, *ibid.*, **61**, 846 (1939).
(7) Marker, *et al.*, *ibid.*, **59**, 2291 (1937).
(8) Marker and Lawson, *ibid.*, **61**, 588 (1939).
(9) Butenandt and Schmidt-Thomé, *Ber.*, **72**, 1960 (1939).
(10) Windaus and Willerding, *Z. physiol. Chem.*, **143**, 33 (1925).
(11) Fieser, "Chemistry of Natural Products Related to Phenanthrene," 2d ed., Reinhold Publ. Corp., New York, N. Y., 1937, p. 326.



uct gave Δ^{16}-pregnenone-20, identified by conversion to pregnanone-20.[12]

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

Experimental Part

Oxidation of Pseudotigogenin.—To a solution of 10 g. of pseudotigogenin dissolved in 500 cc. of acetic acid at 20° was added a solution of 12.0 g. of chromium trioxide in 100 cc. of 80% acetic acid, keeping the temperature below 28°. It was allowed to stand at 28° for forty-five minutes, water was added and the product was extracted with ether. The acetic acid was removed by washing well with water, and the solvent was removed *in vacuo*. The residue could not be obtained crystalline.

A portion of the oxidation product corresponding to two grams of pseudotigogenin was dissolved in 50 cc. of acetic acid, containing a suspension of 2 g. of Adams platinum oxide catalyst. The mixture was shaken with hydrogen at 45 pounds pressure and 70° for two hours. The solution was filtered and the solvent was removed from the filtrate *in vacuo*. The residue was refluxed with alcoholic potassium hydroxide for thirty minutes. Water was added and the product was filtered, and recrystallized from acetone, m. p. 286–288°. A mixed melting point with *allo*-pregnanetriol-3(β),16,20(β), m. p. 286–288°, obtained from pseudotigogenin diacetate gave no depression; yield, 380 mg.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 75.2; H, 11.2.

A portion of the oxidation product was refluxed with 10% alcoholic hydrochloric acid for two hours. The resulting product was crystallized from acetone, m. p. 211–212°. It gave no depression in melting point when mixed with Δ^{16}-*allo*-pregnenedione-3,20. The same product was obtained when the oxidation product was warmed with sodium bicarbonate solution on a steam-bath.

(12) Marker and Lawson, THIS JOURNAL, **61**, 852 (1939).

The total oxidation product from 10 g. of pseudotigogenin was warmed on a steam-bath with sodium hydroxide solution for fifteen minutes. The product was extracted with ether. The neutral fraction was almost pure Δ^{16}-*allo*-pregnenedione-3,20. The alkaline solution was acidified and extracted repeatedly with ether. The ether was removed and the residue was sublimed in a high vacuum using a mercury vapor pump. A fraction subliming at 80–100° was collected. This fraction was resublimed at 90°. The sublimate was recrystallized from ether–pentane. It melted at 76–79°. Analysis and neutralization equivalent indicated that it is *α-methylglutaric acid*, yield 1.2 g.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.2; H, 6.9; neut. equiv., 73.0. Found: C, 49.6; H, 6.9; neut. equiv., 73.4.

Pregnanetriol-3(β),16,20(β) from Dihydropseudosarsasapogenin.—(a) To a solution of 19 g. of dihydropseudosarsasapogenin diacetate in 600 cc. of acetic acid at 20° was added 15.2 g. of chromium trioxide dissolved in 30 cc. of 70% acetic acid. The temperature rose to 30°. This temperature was maintained for one hour and forty-five minutes. The reaction mixture was poured into water and the precipitated solid was extracted with ether. The ethereal solution was washed with water and with sodium bicarbonate solution. The ether was removed. The residue could not be obtained crystalline. It was dissolved in acetic acid to which was added 5 g. of Adams platinum oxide catalyst and shaken with hydrogen at 35 pounds pressure for three hours. The solution was filtered and the solvent was removed *in vacuo*. The residue was dissolved in ethanol and refluxed for fifteen minutes with alcoholic potassium hydroxide. Water was added and the precipitated solid was extracted with ether. It was crystallized from acetone; m. p. 236–240°; yield, 2.6 g.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.7; H, 10.6.

When refluxed with excess acetic anhydride it gave a **triacetate** which was crystallized from pentane, m. p. 145–148°.

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

(b) Catalytic hydrogenation of the non-crystalline oxidation product of pseudosarsasapogenin diacetate followed by hydrolysis gave the same pregnanetriol obtained in (a) from dihydropseudosarsasapogenin diacetate, m. p. 236–240°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 75.0; H, 11.0.

Pregnanetriol-3(α),16,20(β) from *epi*-Sarsasapogenin.—To a solution of 10 g. of *epi*-pseudosarsasapogenin diacetate in 500 cc. of acetic acid at 15° was added a solution of 7 g. of chromium trioxide in 70 cc. of 90% acetic acid. The temperature was kept below 28° for fifty-five minutes. The oxidation product was isolated and reduced as described for the preceding experiment. The solution was filtered from the catalyst and concentrated *in vacuo*. It was hydrolyzed by refluxing with alcoholic potassium hydroxide for fifteen minutes. Water was added and the product was extracted with ether. It was crystallized from acetone, m. p. 203–206°; yield, 600 mg.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.4; H, 10.9.

When refluxed with excess acetic anhydride it gave a **triacetate** which was crystallized from ether–pentane, m. p. 175–177°.

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

***allo*-Pregnanetriol-3(α),16,20(β) from *epi*-Pseudotigogenin.**—*epi*-Pseudotigogenin diacetate was oxidized and the oxidation product was reduced catalytically, and hydrolyzed as previously described. The product was crystallized from ethyl acetate, m. p. 263–265°.

The over-all yield from 5 g. of *epi*-tigogenin was 440 mg.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 75.0; H, 10.7.

The **triacetate** was prepared by refluxing with excess acetic anhydride and was crystallized from pentane, m. p. 181°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.0; H, 9.4.

Oxidation of Pseudodesoxysarsasapogenin Acetate.—A mixture of 5 g. of pseudodesoxysarsasapogenin and 20 cc. of acetic anhydride was refluxed for thirty minutes. The product could not be obtained crystalline. It was dissolved in 100 cc. of acetic acid and a mixture of 4 g. of chromium trioxide in 25 cc. of 80% acetic acid was added, the temperature being kept at 28° for forty-five minutes. Water was added and the product was extracted with water, the ethereal solution was washed with sodium bicarbonate solution and the solvent was removed. The oxidation product would not crystallize. This was refluxed for ten minutes with 2% alcoholic potassium hydroxide solution. The product was extracted with ether, the solvent was removed and the residue was crystallized from dilute acetone; m. p. 129–131°; yield, 0.9 g. Oxidation of dihydropseudodesoxysarsasapogenin followed by hydrolysis gave the same product.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.9; H, 10.7. Found: C, 84.0; H, 10.7.

Reduction with palladium–barium sulfate catalyst in alcohol–ether gave pregnanone-20, which crystallized from dilute methyl alcohol, m. p. 116°. It was identical with that prepared from pregnanedione-3,20 of pregnancy urine.

Oxidation of Pseudosarsasapogenin.—Pseudosarsasapogenin (10 g.) was oxidized in the same manner as described for the oxidation of pseudotigogenin. The oxidation product would not crystallize. Catalytic reduction of this in acetic acid, followed by hydrolysis gave 600 mg. of pregnanetriol-3(β),16,20(β), m. p. 236–240°, which gave no depression in melting point when mixed with the samples previously prepared.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.9; H, 11.0.

Refluxing of the crude oxidation product with 10% alcoholic hydrochloric acid or with sodium carbonate solution gave Δ^{16}-pregnenedione-3,20, which crystallized from acetone, m. p. 200–201°. It gave no depression in melting point when mixed with an authentic sample.

The acidic fraction from the alcoholic hydrochloric acid treatment was sublimed in a high vacuum at 90–100°. The product was crystallized from ether–pentane, m. p. 76–79°. It gave no depression in melting point when mixed with the α-methylglutaric acid obtained from the oxidation of pseudotigogenin.

Reduction of Δ^{16}-*allo*-Pregnenol-3(β)-one-20 with Aluminum Isopropylate.—To a solution of 2 g. of Δ^{16}-*allo*-pregnenol-3(β)-one-20 in 200 cc. of dry isopropyl alcohol was added 5 g. of freshly distilled aluminum isopropylate. The mixture was refluxed for seven hours, then the solvent was slowly distilled over a period of five hours. The residue was refluxed with 100 cc. of 8% methanolic potassium hydroxide solution. Ether and water were added and the ethereal solution was washed well with water. The ether was removed to a small volume. The product was crystallized from ether and from acetone in which it is very insoluble, and finally from methanol, m. p. 188–190°; yield 800 mg. Mixed with Δ^{16}-*allo*-pregnenol-3(β)-one-20, m. p. 202–203°, it melted at 161–170°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.3; H, 10.7.

With acetic anhydride it gave a **diacetate** which was crystallized from dilute methanol, m. p. 102–104°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.6; H, 9.5. Found: C, 74.7; H, 9.5.

A solution of 200 mg. of the above product in 20 cc. of ether and 20 cc. of methanol containing a few drops of acetic acid and 200 mg. of platinum oxide catalyst was shaken with hydrogen at 45 pounds pressure for two hours. The solution was filtered and the solvent was removed. After removal of a small amount of material insoluble in cold acetone, the product was crystallized from dilute methanol, 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, 78.6; H, 11.2.

Reduction of $\Delta^{5,16}$-Pregnadienol-3(β)-one-20 with Aluminum Iso-propylate.—A mixture of 1 g. of $\Delta^{5,16}$-pregnadienol-3(β)-one-20, 5 g. of aluminum iso-propylate and 100 cc. of dry iso-propyl alcohol was refluxed for seven

hours. The solvent was then slowly distilled over a period of five hours. The residue was then refluxed with alcoholic potassium hydroxide for thirty minutes. It was extracted with ether, the solvent was removed and the residue was crystallized from ether and from dilute acetone, m. p. 169–171°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.4; H, 10.2.

On heating with acetic anhydride it gave a diacetate which was crystallized from dilute methanol, m. p. 121°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.9; H, 9.1. Found: C, 74.6; H, 9.2.

A mixture of 50 mg. of $\Delta^{5,16}$-pregnadiendiol-3,20 in 20 cc. of ether and 20 cc. of methanol containing a few drops of acetic acid was shaken with 100 mg. of platinum oxide catalyst under a pressure of 45 pounds of hydrogen for one hour. The solution was filtered and the solvent was removed. The product was crystallized from acetone 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, 78.5; H, 11.2.

Summary

1. Using methods previously developed a pregnanetriol-3(β),16,20(β), a pregnanetriol-3(α), 16,20(β) and an *allo*-pregnanetriol-3(α),16,20(β) have been prepared from the pseudosapogenins. The last was not identical with *allo*-pregnanetriol from the urine of pregnant mares.

2. Desoxypseudosarsasapogenin acetate was converted to Δ^{16}-pregnenone-20.

3. α-Methylglutaric acid has been identified as the side-chain fragment arising from the hydrolysis of the oxidation products of pseudosapogenins.

4. $\Delta^{5,16}$-Pregnadienediol-3(β),20(β) and Δ^{16}-*allo*-pregnenediol-3(β),20(β) have been prepared.

STATE COLLEGE, PENNA. RECEIVED DECEMBER 19, 1940

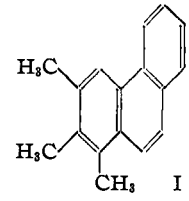
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Syntheses in the Phenanthrene and Triphenylene Series

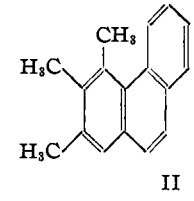
BY LOUIS F. FIESER AND WILLIAM H. DAUDT

Following Cook's observation that 5,6-dimethyl-1,2-benzanthracene and 1,2,5,6-dibenzanthracene exhibit carcinogenic activity of about the same degree when applied to the skin of mice,[1] a number of ortho and peri dimethyl derivatives of anthracene, 1,2-benzanthracene, and chrysene have been investigated as possible models of higher condensed ring compounds of established carcinogenicity having an additional aromatic ring affixed at the points of attachment of the methyl groups.[2] The only prior investigation of models in the phenanthrene series is that of Hewett,[3] who synthesized 1,2,3,4-tetramethylphenanthrene for comparison with the highly potent carcinogen 9,10-dimethyl-1,2-benzanthracene.

The present work was taken up with the idea that 1,2,3-trimethylphenanthrene (I) would be of interest for comparison with the carcinogen 10-methyl-1,2-benzanthracene and that 2,3,4-trimethylphenanthrene might constitute a model of either 9-methyl-1,2-benzanthracene or 2-methyl-3,4-benzphenanthrene, both of which are known



I



II

to be carcinogenic. Methods of synthesizing both hydrocarbons were found starting with *dl*-α,β-dimethylsuccinic anhydride, which was prepared from ethyl cyanoacetate and ethyl α-bromopropionate according to Bone and Sprankling.[4] The Friedel and Crafts reaction between this anhydride and naphthalene proceeded only poorly, but the Grignard synthesis gave very satisfactory results.

The condensation of α-naphthylmagnesium bromide and dimethylsuccinic anhydride afforded the keto acid III in yield comparable with the yields obtained in similar condensations with phthalic anhydride[5] and cyclopentane-1,2-dicarboxylic anhydride[6] and much superior to those

(1) Cook and Haslewood, *J. Chem. Soc.*, 428 (1934); Barry, Cook, Haslewood, Hewett, Hieger and Kennaway, *Proc. Roy. Soc.*, **117B**, 318 (1935).

(2) Recent papers: Fieser and Webber, THIS JOURNAL, **62**, 1360 (1940); Newman, *ibid.*, **62**, 2295 (1940).

(3) Hewett, *J. Chem. Soc.*, 293 (1940); Hewett and Martin, *ibid.*, 1396 (1940).

(4) Bone and Sprankling, *ibid.*, **75**, 839 (1899). See also Böeseken, Schweizer and van der Want, *Rec. trav. chim.*, **31**, 92 (1912); Werner and Basyrin, *Ber.*, **46**, 3229 (1913); Verkade and Hartman, *Rec. trav. chim.*, **52**, 949 (1933).

(5) Weizmann, Bergmann and Bergmann, *J. Chem. Soc.*, 1367 (1935).

(6) Bergmann and Blum-Bergmann, THIS JOURNAL, **59**, 1572 (1937).