[CONTRIBUTION FROM THE LABORATORY OF BOTANICA-MEX, S. A.[1]]

Steroidal Sapogenins. 172. Pregnen-5-ol-3-dione-12,20 from Botogenin and Neobotogenin

BY RUSSELL E. MARKER[2]

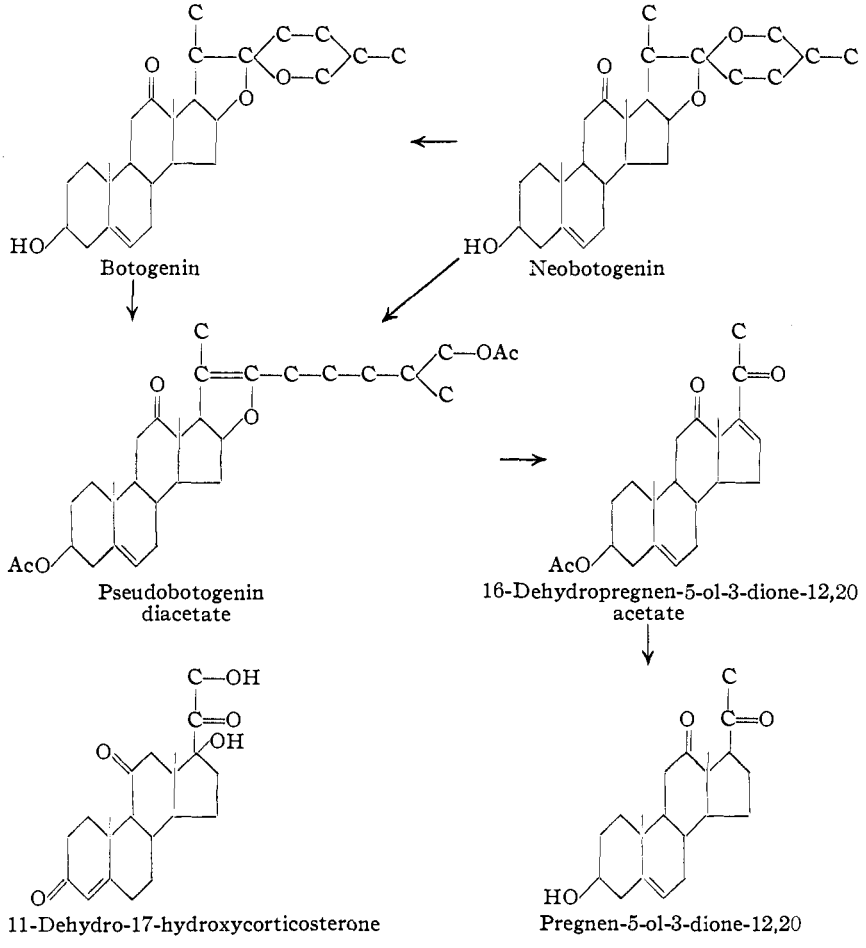
The recent discovery that 11-dehydro-17-hydroxycorticosterone is a cure for rheumatoid arthritis[3] has focused attention of many laboratories on a practical method for its synthesis.[4]

As no sterols are known to occur in nature in large quantities which have an oxygen on C-11 suitable for its synthesis, desoxycholic acid, having an oxygen atom on C-12 has been used as starting material. By using 12-dehydrodesoxycholic acid a hydroxyl group can be readily introduced on the desired C-11 position.[5] The production of 11-dehydro-17-hydroxycorticosterone from this product, because of the great number of steps involved, leads to very unsatisfactory yields. Two of the factors responsible for the low yields are the elimination of the side-chain of the acid and the introduction of a double bond in ring A.

The discovery of botogenin, a naturally occurring sapogenin, which has been proved to have the structure of 12-ketodiosgenin,[6] gives a desirable starting material for the synthesis of the cortical steroids. The side-chain of this sapogenin can be removed in high yields to form pregnen-5-ol-3-dione-12,20. This product has a double bond in the desired position and contains a ketonic group on C-12.

Because of the recent interest in the cortical steroids, a method will be given in detail for the preparation of pregnen-5-ol-3-dione-12,20 from botogenin. This involves the formation of pseudo botogenin diacetate, followed by oxidation and hydrolysis to give 16-dehydropregnen-5-ol-3-dione-12,20 acetate. It is not necessary or desirable to isolate the intermediates in the production of this product, which is then reduced catalytically to give pregnen-5-ol-3-dione-12,20 acetate, which on hydrolysis gives the unacetylated product.

Neobotogenin, which differs from botogenin only in the configuration of the side-chain, gives the latter upon prolonged treatment with alcoholic hydrochloric acid. Neobotogenin upon treatment with acetic anhydride at 195° gives pseudobotogenin diacetate, which upon oxidation and subsequent hydrolysis also gave 16-dehydropregnen-5-ol-3-dione-12,20.



Experimental Part

16-Dehydropregnen-5-ol-3-dione-12,20 Acetate from **Botogenin.**—A mixture of 50 g. of botogenin acetate and 50 cc. of acetic anhydride was heated in a bomb tube at

(1) Now with Hormosynth S. A., Cervantes Saavedra, No. 5, Mexico City.

(2) Present address: Hotel Geneve, Mexico City.

(3) Proceedings of the Staff Meeting of the Mayo Clinic: *J. Am. Med. Assoc.*, 1274 (1949).

(4) *Ibid.*, 1294 (1949).

(5) Marker and Lawson, THIS JOURNAL, **60**, 1334 (1938).

(6) Marker and Lopez, *ibid.*, **69**, 2397 (1947).

195° for ten hours. The pseudobotogenin diacetate which was formed was not isolated. The tube was cooled and its contents was dissolved in 1 liter of glacial acetic acid and cooled to 18°. To this solution was added dropwise with stirring a solution of 22 g. of chromic anhydride dissolved in 25 cc. of water and 200 cc. of acetic acid. The temperature was maintained at 18° during the addition, which took about fifteen minutes. *It should be noted that it is not necessary to protect the double bond at 5,6 during this oxidation.* The oxidation mixture was allowed to stand at 18° for twenty minutes. At the end of this time 20 g. of zinc dust was added in small portions with stirring. The temperature rose to about 40–45°. After fifteen minutes the product was filtered and the filtrate concentrated on a steam-bath with vacuum to about 500 cc. and shaken with 200 cc. of water until all solid material was in suspension. The solution was extracted with ether, washed with water and finally with sodium bicarbonate solution and the ether was distilled. The oily residue was dissolved in 200 cc. of boiling methanol and to this was added a solution of 25 g. of potassium carbonate in 100 cc. of water previously heated to 60°. The product was refluxed for twenty minutes, during which time a heavy precipitate separated. It was cooled and extracted well with ether, and the ethereal solution was washed with water and the solvent removed. The solid residue was refluxed for fifteen minutes with 100 cc. of acetic anhydride. The excess anhydride was removed *in vacuo* and the solid residue was stirred with 200 cc. of hot methanol. This was cooled in a refrigerator overnight and the product was filtered, washed with cold methanol and recrystallized from ethyl acetate; yield 24 g. of 16-dehydropregnen-5-ol-3-dione-12,20 acetate, m. p. 226–228°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.5; H, 8.2. Found: C, 74.6; H, 8.3.

Pregnen-5-ol-3-dione-12,20 Acetate.—A solution of 24 g. of 16-dehydropregnen-5-ol-3-dione-12,20 acetate in 1 l. of ethyl acetate was shaken for twenty minutes with 20 g. of 4% palladium-on-barium sulfate catalyst, under hydrogen at 40 pounds pressure, keeping the temperature at 45°. The product was filtered, the solvent was removed to about 50 cc. and cooled. It was filtered and recrystallized from ethyl acetate and from methanol, in which it is very insoluble, to give a yield of 21 g. of pregnen-5-ol-3-dione-12,20 acetate, m. p. 205–207°. When mixed with the unreduced acetate above it gave a depression in melting point of 17–22°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.2; H, 8.7. Found: C, 74.3; H, 8.5.

Hydrolysis with alcoholic potassium hydroxide followed by crystallization from ether and from methanol gave pregnen-5-ol-3-dione-12,20, m. p. 252–254°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2. Found: C, 76.2; H, 9.2.

allo-**Pregnantrione-3,12,20.**—A mixture of 500 mg. of pregnen-5-ol-3-dione-12,20, 50 cc. of acetic acid and 500 mg. of platinum oxide catalyst was shaken with hydrogen at 45 pounds pressure and room temperature for one hour. The solution was filtered and to the filtrate was added a solution of 800 mg. of chromic anhydride dissolved in 20 cc. of 80% acetic acid. It was allowed to stand for thirty minutes at room temperature, water was added and the product was extracted with ether. The ethereal solution was washed well with water and sodium bicarbonate solution and the solvent was removed by distillation. The residue was crystallized from ether to give *allo*-pregnantrione-3,12,20, m. p. 262–264°. A mixture with the same product prepared by the oxidation of pseudohecogenin, and subsequent hydrolysis and reduction with palladium catalyst as described previously,[7] gave no depression in melting point.

Neobotogenin.—The ketonic fraction of the crude sapogenins was isolated as previously described.[6] Instead of refluxing with alcoholic hydrochloric acid to convert the total neosapogenins present into those containing the normal side-chain, 100 g. of the crude keto-sapogenin fraction was refluxed with 300 cc. of acetic anhydride for thirty minutes. The product was allowed to stand at room temperature overnight and the precipitate which formed was filtered. This upon recrystallization from acetone and from methanol gave botogenin acetate, 248°; yield 38 g. Hydrolysis with alcoholic potassium hydroxide followed by crystallization from ether gave botogenin, m. p. and mixed m. p. with a known sample, 262°.

The acetic anhydride mother liquors from the above precipitation were evaporated under reduced pressure to about half-volume and allowed to stand for one month in a refrigerator. The product was filtered, the precipitate washed well with methanol, and then fractionally crystallized from ethyl acetate, acetone and methanol, giving 13 g. of neobotogenin acetate, m. p. 234°. A mixture of this product and botogenin acetate melted 5–12° lower.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.0; H, 9.0. Found: C, 74.3; H, 9.1.

Hydrolysis with alcoholic potassium hydroxide and crystallization of the product from ether gave neobotogenin, m. p. 246–248°. Mixed with botogenin a depression in melting point was obtained of 6–9°.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.7; H, 9.4. Found: C, 75.6; H, 9.2.

Botogenin from Neobotogenin.—A mixture of 2 g. of neobotogenin, 100 cc. of ethyl alcohol and 10 cc. of concd. hydrochloric acid was refluxed for sixty hours on a steam-bath. The product was extracted with ether and concentrated to a small volume. Upon standing overnight crystals appeared. These were filtered and recrystallized from ether, m. p. and mixed m. p. with botogenin, 261–263°. Acetylation with boiling acetic anhydride and crystallization of the product from methanol gave botogenin acetate, m. p. and mixed m. p. 246–248°.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.0; H, 9.0. Found: C, 74.2; H, 9.0.

16-Dehydropregnen-5-ol-3-dione-12,20 Acetate from Neobotogenin Acetate.—When neobotogenin acetate was heated with acetic anhydride, followed by oxidation and hydrolysis as described above for the similar treatment of botogenin acetate, it gave 16-dehydropregnen-5-ol-3-dione-12,20 acetate; m. p. and mixed m. p. with the product from botogenin acetate was 226–228°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.5; H, 8.2. Found: C, 74.3; H, 8.2.

Summary

A method is given for the conversion of botogenin and neobotogenin into pregnen-5-ol-3-dione-12,20, which may be desirable as a starting material for the synthesis of cortical-type hormones.

PLAZA DE SAN PABLO NO. 6
TEXCOCO, MEXICO

RECEIVED MAY 26, 1949

(7) Marker and co-workers, THIS JOURNAL, **69**, 2167 (1947).