acid was distilled *in vacuo*. The residue was dissolved in ether, washed with water and with potassium hydroxide solution. The alkaline solution was acidified with hydrochloric acid and the product was extracted with ether. It was crystallized from ether and from acetone, m. p. and mixed m. p. with neoyuccagenic acid prepared from neoyuccagenin, 242–245° dec.

Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.4; H, 8.8. Found: C, 70.1; H, 9.0.

Neomanogenic Acid from Neomanogenin.—To a solution of 5 g. of neomanogenin in 500 cc. of acetic acid was added a solution of 5 g. of chromic anhydride in 10 cc. of water with stirring. It was allowed to stand at room temperature for thirty minutes, water was added and the product was extracted with ether. The ethereal solution was washed well with water and the solvent removed. The residue was crystallized from dilute acetone and from dilute acetic acid, m. p. 262–264° dec.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.0; H, 8.5. Found: C, 68.3; H, 8.7.

Neomanogenic Acid from Neohecogenin.—To a solution of 5 g. of neohecogenin in 300 cc. of glacial acetic acid was added a solution of 5 g. of chromic anhydride in 10 cc. of water with shaking. The product was then heated to 50° for two hours, extracted with ether and the ethereal solution was washed well with water and with potassium hydroxide solution. The alkaline solution was acidified with hydrochloric acid and extracted with ether. The solvent was removed and the residue was crystallized from dilute acetone and from dilute acetic acid, m. p. and mixed m. p. with neomanogenic acid prepared above from neomanogenin, 262–264° dec.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.0; H, 8.5. Found: C, 68.3; H, 8.4.

Summary

A correlation has been made between all of the known steroidal sapogenins with the neo side chain.

TEXCOCO, MEXICO RECEIVED MAY 15, 1946

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

Steroidal Sapogenins. No. 167. Pregnene Derivatives from Nologenin

BY RUSSELL E. MARKER

We have shown that the steroidal sapogenins isolated from the rhizones of the Mexican dioscoreas by the strong acid hydrolysis of the saponide mixtures consist of a mixture of diosgenin, neodiosgenin, nologenin, pennogenin, kryptogenin, bethogenin and fesogenin.[1] The first two compounds account for approximately only 40% of the steroidal sapogenins present in the rhizones of the freshly collected and dried dioscoreas. Up to the present time these are the only sapogenins utilized from the mixture for the preparation of the steroidal hormones. The latter five compounds are all derived from nolonin,[1] the saponide of nologenin, by acid or alkaline treatment and represent approximately 50–60% of the total steroidal fraction from the freshly collected dioscoreas. Strong acid hydrolysis of the saponide mixture converts the majority of the nolonin into pennogenin and kryptogenin and other products, which are of no value in hormone synthesis. By carefully controlled hydrolysis of the saponides we are now able to isolate the nologenin without any conversion of it into its degradation products, pennogenin, kryptogenin, fesogenin or bethogenin. We have now made a study of the reactions of nologenin leading to its conversion to the steroidal hormones and find that the yields of these products from the dioscoreas can be doubled by utilizing the nologenin as well as the diosgenin and neodiosgenin in their preparation.

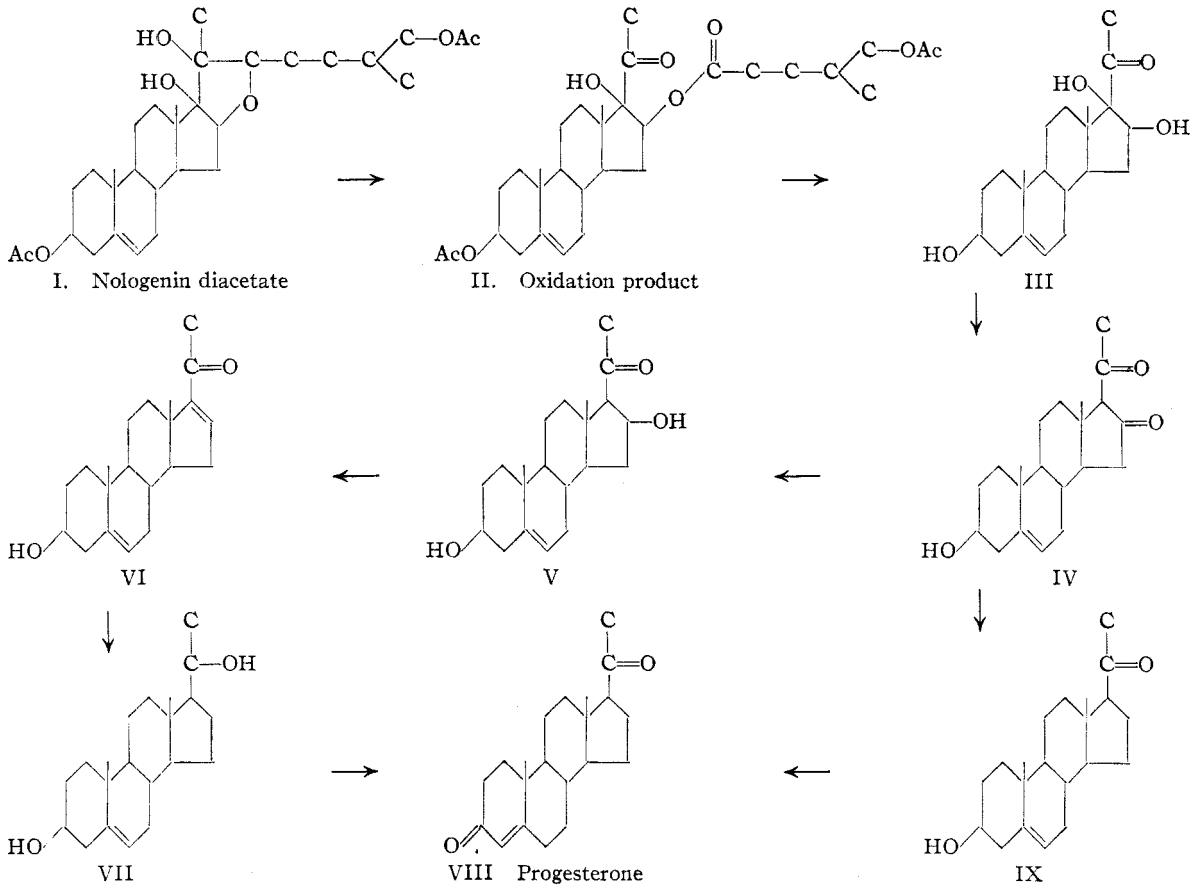
Mild oxidation of nologenin diacetate (without protection of the double bond) with chromic anhydride at 15° gives II with a cleavage between C-20 and C-22, such as is obtained in the oxidation of the pseudo sapogenins. This compound is identical with the oxidation product of pseudodiosgenin diacetate with the exception that it contains a hydroxyl group at C-17. Acid treatment of this oxidation product hydrolyzes off the ester group at C-16 which is followed by the conversion of the 16-17-dihydroxy-20-keto compound to a 16-20-diketo compound, 5-pregnenol-3(β)dione-16-20 (IV).

Mild catalytic reduction of the dione (IV) gives a compound saturated at C-5. Further reduction of this product reduces the ketone group at C-16 to a hydroxy group, which because of it being beta to the ketone group at C-20 dehydrates to the unsaturated ketone which further reduces to give allo-pregnanediol-3(β),20(β). Reduction with aluminum isopropylate follows the same route to give VI, which upon further reduction gives 5,16-pregnadienediol-3(β),20(β). Catalytic reduction of the latter compound gave allo-pregnanediol-3(β),20(β).

Sodium reduction in isopropyl alcohol follows the same route from IV to VI, which further reduces the double bond at C-16 and the conjugated ketone group at C-20 to give 5-pregnenediol-3(β),20(α), VII. Catalytic reduction of this product gave allo-pregnanediol-3(β),20(α). Oxidation of 5-pregnenediol-3(β),20(α), VII, either with chromic anhydride or with aluminum tertiary butylate gave a good yield of progesterone, VIII.

Mild Clemmensen reduction of 5-pregnenol-3(β)dione-16,20 with unamalgamated zinc strips, alcohol and hydrochloric acid removes only the ketone group at C-16 giving 5-pregnenol-3(β)-one-20 in approximately 80–85% yield. The same product is obtained when the oxidation product of nologenin II is treated directly in alcohol with unamalgamated zinc and hydrochloric acid. The latter compound is readily converted into either

(1) Marker and Lopez, THIS JOURNAL, **69**, 2389 (1947).



progesterone or dehydro-iso-androsterone with good yields.

Experimental Part

Oxidation of Nologenin.—A solution of 44.8 g. of nologenin in 100 cc. of acetic anhydride was refluxed for thirty minutes. This was then diluted with 400 cc. of acetic acid and cooled to 15°. To this was added a solution of 15 g. of chromic anhydride in 20 cc. of water and 200 cc. of acetic acid. Addition was over a period of one hour maintaining the temperature at 15°. It was stirred an additional fifteen minutes and was then diluted with water and extracted with ether. The ethereal solution was washed well with water and finally with sodium bicarbonate solution. The solvent was removed and the residue was crystallized from methanol, m. p. 98–101°. Yield was 14.2 g. of crystalline product.

Anal. Calcd. for $C_{31}H_{46}O_8$: C, 68.1; H, 8.5. Found: C, 68.4; H, 8.6.

5-Pregnenol-3(β)dione-16,20.—The solvent was removed from the above mother liquors of crystallization of the oxidation product of nologenin acetate and the total was combined and dissolved in 500 cc. of ethyl alcohol to which was added 100 cc. of concd. hydrochloric acid. The product was refluxed for two hours, water was added and it was extracted with ether. The solvent was removed and the residue was refluxed for fifteen minutes with 100 cc. of acetic anhydride. The excess acetic anhydride was removed by vacuum distillation and the residue was crystallized from methanol, m. p. 186–188°. Yield was 22.1 g.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.1; H, 8.7. Found: C, 74.3; H, 8.7.

Hydrolysis of the above acetate gave a product which was crystallized from dilute methanol, m. p. 188–190°. When mixed with the acetate it melted at 163–168°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.1; H, 9.4. Found: C, 75.9; H, 9.6.

Reduction of 5-Pregnenol-3(β)-dione-16,20.—(a) **Mild Catalytic.**—A mixture of 1 g. of 5-pregnenol-3(β)dione-16,20 acetate, 200 cc. of ethyl alcohol and 500 mg. of platinum oxide catalyst was shaken with hydrogen at 5 pounds pressure for fifteen minutes. The catalyst was filtered and the solvent removed to a small volume. Upon standing in the cold it crystallized, m. p. 185–186°. When mixed with starting material the melting point was depressed 22–28°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.7; H, 9.2. Found: C, 73.7; H, 9.4.

Hydrolysis gave a product which was crystallized from dilute methanol, m. p. 185–186°; mixture with the starting material caused a depression to 164–170°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 76.0; H, 10.0.

(b) **Strong Catalytic.**—A mixture of 1 g. of 5-pregnenol-3(β)-dione-16,20 acetate, 200 cc. of acetic acid and 500 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. The residue was refluxed with alcoholic potassium hydroxide, extracted with ether and the solvent removed. The residue was crystallized from ethyl alcohol, m. p. and mixed m. p. with allopregnanediol-3(β),20(β) was 196°; yield 0.7 g.

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

Acetylation gave a diacetate which was crystallized from ethyl acetate, m. p. and mixed m. p. with allo-pregnanediol-3(β),20(β) diacetate, 142–144°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.0; H, 9.9.

(c) **With Sodium in Isopropyl Alcohol.**—To a solution of 2 g. of 5-pregnenol-3(β)-dione-16,20 in 200 cc. of dry isopropyl alcohol was added 10 g. of sodium in small strips at the reflux temperature. Water was added and the product was extracted with ether. It was crystallized from dilute methanol, m. p. 180–183°. This is 5-pregnenediol-3(β),20(α). Yield was 1.6 g.

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

To prove the identity of the above product it was reduced catalytically using platinum oxide catalyst, acetic acid and hydrogen. The product was crystallized from acetone, m. p. 214–216°. It gave no depression when mixed with allo-pregnanediol-3(β),20(α).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.8; H, 11.3.

To a solution of 3.2 g. of 5-pregnenediol-3(β),20(α) in 100 cc. of acetic acid was added a solution of 1.65 g. of bromine in 20 cc. of acetic acid. To this was added a solution of 1.6 g. of chromic anhydride in 5 cc. of water and 20 cc. of acetic acid, keeping the temperature at 20°. It was allowed to stand for thirty minutes and then 5 g. of zinc dust was added and the product heated on a steam-bath for fifteen minutes. It was allowed to stand for three hours at room temperature. The zinc was filtered and the solvent was removed under reduced pressure. The product was extracted with ether, washed well with water and sodium bicarbonate solution and finally crystallized from methanol, m. p. and mixed m. p. with progesterone 128.5°; yield 2.1 g. The same product was obtained when 5-pregnenediol-3(β),20(α) was oxidized with aluminum *t*-butylate in acetone and benzene.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.4; H, 9.6.

(d) **By Mild Clemmensen.**—To a solution of 10 g. of 5-pregnenol-3(β)-dione-16,20 in 500 cc. of alcohol was added 100 g. of zinc strips; 100 cc. of concentrated hydrochloric acid was slowly dropped in over a period of one and one-half hours at the reflux temperature. It was heated for an additional two hours, filtered and the solvent removed under reduced pressure. The product was extracted with ether, the solvent was removed and the residue was crystallized from alcohol, m. p. and mixed m. p. with 5-pregnenol-3(β)-one-20, 196°; yield, 8.13 g. The same product was obtained when the original oxidation product of nologenin diacetate was treated with zinc, alcohol and hydrochloric acid.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.0; H, 11.0.

Acetylization and crystallization from methanol and from ethyl acetate gave pregnenol-3(β)-one-20 acetate, m. p. and mixed m. p. 146–148°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.7; H, 10.2.

(e) **With Aluminum Isopropylate.**—A mixture of 2 g. of 5-pregnenol-3(β)-dione-16,20, 10 g. of aluminum isopropylate and 200 cc. of dry isopropyl alcohol was refluxed for seven hours. The solvent was then slowly distilled over a period of three hours. The residue was refluxed with alcoholic potassium hydroxide for fifteen minutes, extracted with ether and the solvent was removed and the residue was crystallized from ether, m. p. 170–172°. This is 5,16-pregnadienediol-3(β),20(β); yield 0.8 g.

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

Acetylation 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, 75.0; H, 9.0.

A mixture of 1 g. of the above dienediol, 100 cc. of methanol and 500 mg. of platinum oxide catalyst was shaken with hydrogen at 30 pounds pressure for thirty minutes. The solution was filtered and the solvent removed. The residue was crystallized from acetone, m. p. and mixed m. p. with allo-pregnanediol-3(β),20(β), 194°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.9; H, 11.0.

Summary

Experiments on the conversion of nologenin into pregnane derivatives have been described.

TEXCOCO, MEXICO RECEIVED MAY 24, 1946

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

Steroidal Sapogenins. No. 168. The Structural Relationship of Botogenin. A New Steroidal Sapogenin, to all Other Known Sapogenins

BY RUSSELL E. MARKER[1] AND JOSEFINA LOPEZ

A new steroidal sapogenin, botogenin, has been isolated from the acid hydrolysis mixture of sapogenins of *Dioscorea mexicana*. Removal of its ketonic group by the Wolff–Kishner reaction gave diosgenin. Hydrogenation under mild conditions reduced its double bond to give hecogenin, whereas hydrogenation under more drastic conditions reduced both its double bond and the ketone group to give rockogenin. This shows a structure of 12-keto-diosgenin for botogenin.

The correlation of the structures of the various steroidal sapogenins having the smilagenin or normal side-chain is now established as shown in the accompanying chart. This is self-explanatory from the results given in the experimental part of this paper. The relationship between the structures of mexogenin, samogenin and smilagenin had previously been established.[2]

Experimental

Botogenin.—An alcoholic extract of the saponides of freshly dried *Dioscorea mexicana* was hydrolyzed with hydrochloric acid. The crude sapogenins were extracted with ether and the ethereal solution was washed with sodium hydroxide solution to free of acids. The ether was distilled to a small volume and the crystalline sapogenins were separated by filtration. The mother liquors were concentrated and the residue was hydrolyzed with alcoholic sodium hydroxide. The product was again extracted with ether and a second crop of sapogenins was obtained which were combined with the first. Two kilograms of these crude sapogenins was refluxed for thirty minutes with five liters of acetic anhydride and the mixture was allowed to crystallize overnight at room tem-

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

(2) Marker and Lopez, THIS JOURNAL, **69**, 2373 (1947).