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

Steroidal Sapogenins. No. 166. The Neosapogenins

BY RUSSELL E. MARKER AND JOSEFINA LOPEZ

The steroidal sapogenins with the neo side chain such as sarsasapogenin and neotigogenin differ from their isomers smilagenin and tigogenin in the configuration of the side-chain. By refluxing for approximately sixty hours with alcoholic mineral acids the sapogenins with the neo side chain are converted into the ones with the isomeric side chain.

We have now established a correlation between all of the sapogenins which we have isolated or prepared in the laboratory, thus further establishing their structures. By indirect evidence it has been established that mexogenin, neomexogenin, samogenin and neosamogenin contain the coprostane configuration at C-5. We have now proven this structure by oxidizing neosamogenin to neosamogenic acid. The same acid was prepared by the oxidation of bromosarsasapogenin which has the coprostane configuration at C-5. We had previously shown that oxidation of 3-oxygenated coprostane compounds gives rise to 2,3-dicarboxylic acids.[1] The sarsasapogenin was first brominated to prevent oxidation of the side chain to acids. After oxidation the bromine was removed with zinc and acetic acid.

Oxidation of neoyuccagenin gave neoyuccagenic acid with cleavage between C-2 and C-3. We had previously shown that the two hydroxyl groups in neoyuccagenin are at C-2 and C-3 by reduction to neogitogenin which on acid treatment gives gitogenin.[2] The same acid was obtained when diosgenin was brominated both at C-5 and in the side chain followed by oxidation, and debromination of the resulting acid. This establishes the position of the double bond in yuccagenin and neoyuccagenin at C-5,6.

Oxidation of neomanogenin results in a cleavage between C-2 and C-3 which is the position of its two hydroxyl groups, to give neomanogenic acid. The same acid was obtained when neohecogenin was oxidized. The correlation between the known steroidal sapogenins is now complete.

Neomexogenin when subjected to the Wolff–Kishner reduction loses its ketone group to give neosamogenin.[2] Neosamogenin on oxidation gave neosamogenic acid which is also obtained from the oxidation of sarsasapogenin showing that the former two compounds have the same configuration at C-5 and the same side chain as sarsasapogenin. Sarsasapogenin has been converted into neotigogenin.[3] The latter was also prepared by the reduction of neodiosgenin.[2] Neochlorogenin was prepared by the oxidation of diosgenin followed by reduction of the ene-dione with zinc and acetic acid and subsequent reduction of the dione with sodium and alcohol.[2] Elimination of the ketone group on neohecogenin gave neotigogenin.[2] Oxidation of neohecogenin gave neomanogenic acid which also was prepared by the oxidation of neomanogenin. Elimination of the ketone group on neomanogenin gave neogitogenin.[2] Catalytic reduction of neokammogenin gave neomanogenin[2] and elimination of the ketone group on neokammogenin gave neoyuccagenin.[2] Catalytic reduction of neoyuccagenin gave neogitogenin.[2]

(1) Marker and co-workers, THIS JOURNAL, **61**, 3317 (1939).
(2) Marker and Lopez, *ibid.*, **69**, 2375 (1947).
(3) Marker and Rohrmann, *ibid.*, **62**, 647 (1940).

Experimental Part

Neosamogenic Acid from Neosamogenin.—To a solution of 1 g. of neosamogenin in 100 cc. of glacial acetic acid at 25° was added a solution of 1 g. of chromic anhydride in 5 cc. of water and 20 cc. of acetic acid. It was allowed to stand for one hour. Water was added and the product was extracted with ether. The acetic acid was washed from the ethereal solution with water and then the acid was extracted with potassium hydroxide solution. The alkaline solution was well extracted with ether, then acidified with hydrochloric acid, extracted with ether and the solvent removed. The product was crystallized from acetone, m. p. 268–270° dec.

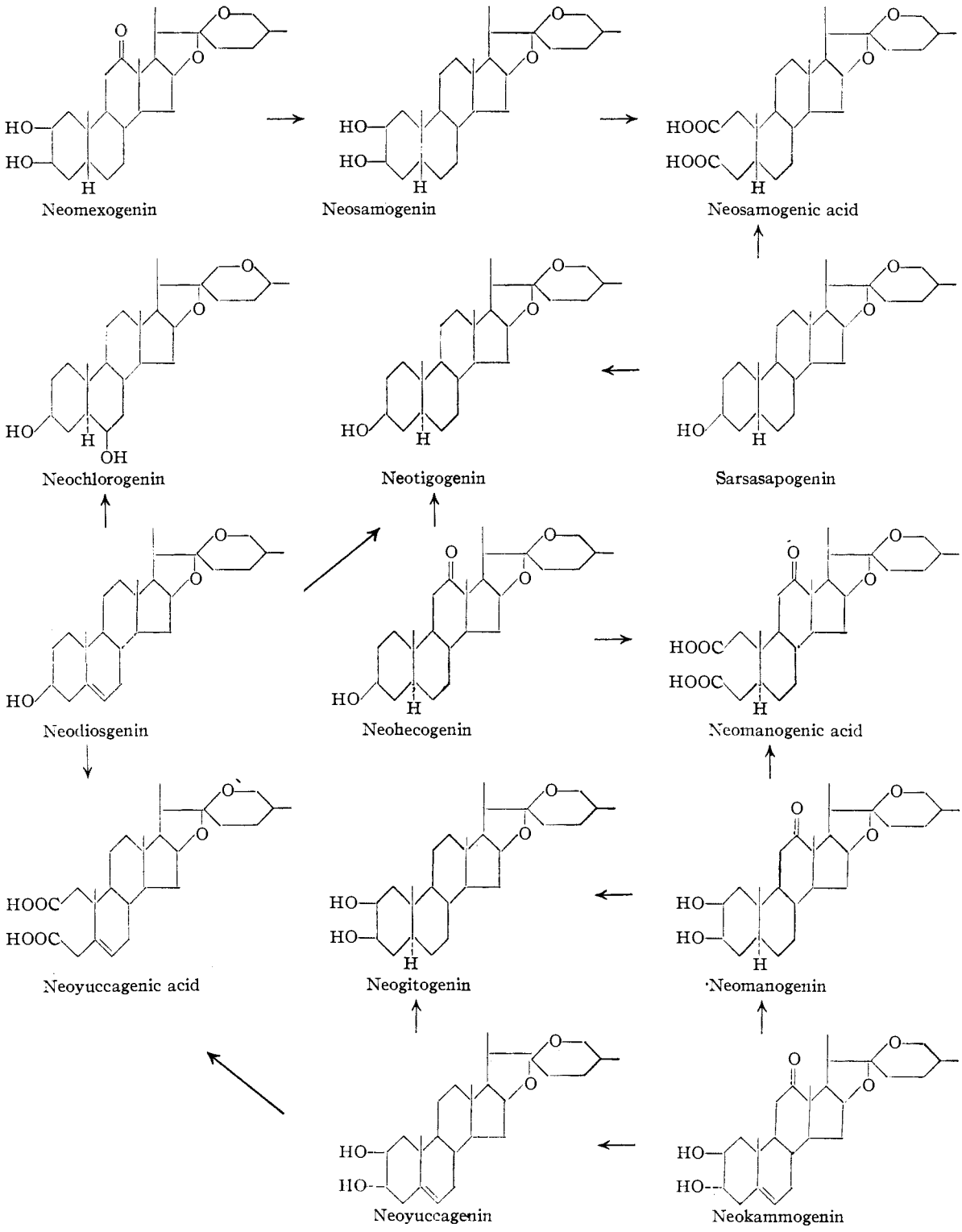
Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.3; H, 9.3.

Neosamogenic Acid from Sarsasapogenin.—To a solution of 8.3 g. of sarsasapogenin in 50 cc. of chloroform cooled at 20° was added with stirring a solution of 3.3 g. of bromine in 100 cc. of chloroform with a few drops of hydrobromic acid. When the solution was decolorized the solvent was removed under reduced pressure and the residue was dissolved in 500 cc. of glacial acetic acid. The solution was cooled to room temperature and a solution of 7 g. of chromic anhydride in 10 cc. of water and 100 cc. of acetic acid was slowly added with shaking. The product was heated at 55° for two hours. To the warm solution was added 10 g. of zinc dust and the product was heated on a steam-bath for eight hours with occasional addition of small quantities of zinc dust. The solution was filtered and the acetic acid was distilled under reduced pressure. The residue was dissolved in ether, washed well with water and extracted with potassium hydroxide solution. The alkaline solution was extracted with ether, acidified with hydrochloric acid, and again extracted with ether. The acidic fraction was crystallized from acetone, m. p. and mixed m. p. with neosamogenic acid prepared from neosamogenin, 268–270° dec.; yield 0.5 g.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.0; H, 9.0.

Neoyuccagenic Acid from Neoyuccagenin.—To a solution of 4.3 g. of neoyuccagenin in 500 cc. of acetic acid cooled to 20° was added slowly with stirring a solution of 1.6 g. of bromine in 100 cc. of acetic acid. When the solution had become decolorized a solution of 3 g. of chromic anhydride in 5 cc. of water and 50 cc. of acetic acid was added. It was allowed to stand at room temperature for thirty minutes, then 10 g. of zinc dust was added and the mixture was heated on a steam-bath for one hour with shaking. The solution was filtered and the acetic acid was distilled under reduced pressure. The residue was extracted with ether and crystallized from a small amount of ether and from acetone, m. p. 242–245° dec.

Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.4; H, 8.8. Found: C, 70.4; H, 8.7.



Neoyuccagenic Acid from Neodiosgenin.—To a solution of 8.3 g. of neodiosgenin in 500 cc. of chloroform cooled to 20° was added with stirring a solution of 6.5 g. of bromine in 100 cc. of chloroform. As soon as the solution was decolorized the solvent was distilled under reduced pressure. The residue was dissolved in 500 cc. of acetic acid and cooled to 15°. To this was added a solution of 7 g. of chromic anhydride in 10 cc. of water and 50 cc. of acetic acid. The mixture was heated to 50° for two hours, at the end of that time 20 g. of zinc dust was added and the product was heated with shaking on a steam-bath for eight hours. The solution was filtered and the acetic

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.

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[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).