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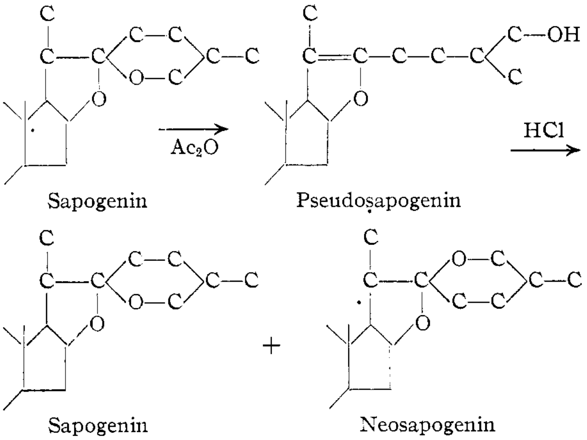
Steroidal Sapogenins. No. 160. The Conversion of Pseudosapogenins to Sapogenins and Neosapogenins

BY RUSSELL E. MARKER AND JOSEFINA LOPEZ

Previously it was assumed that only one side chain isomer was formed on the treatment of pseudosapogenins with mineral acids. A more careful examination of the products formed in this reaction shows that both possible side chain isomers are formed in the relative proportion of approximately 80 to 20%. In previous work only the predominating sapogenin was isolated and no examination of the mother liquors was made for isomers.



By utilizing this reaction a number of sapogenins were made which are side-chain isomers of the products isolated from nature. This work was carried out with the purpose of assisting in the identification of new products which we are isolating from plant sources. In this work the preparation of neokammogenin, neomanogenin, neoyuccagenin, neogitogenin, neohecogenin, neotigogenin, neodiosgenin, neochlorogenin, neomexogenin and neosamogenin are reported. It was found that neoyuccagenin was identical with lilagenin.[1]

Acid isomerization of pseudosamogenin gives a mixture of samogenin and neosamogenin (texogenin[2]). The latter was previously reported as a natural product, but its actual isolation was by acid isomerization of the crude pseudosapogenins. This probably came from the samogenin present in the plant from which it was isolated and it was not therefore isolated as a naturally occurring product.

Experimental Part

Pseudokammogenin.—A mixture of 30 g. of kammogenin diacetate and 60 cc. of acetic anhydride were heated at 200° for eight hours. The excess acetic anhydride was evaporated under reduced pressure on a steam-bath and the residue was crystallized from methanol, m. p. 148–149°; yield 25.4 g.

Anal. Calcd. for $C_{33}H_{46}O_8$: C, 69.5; H, 8.1. Found: C, 69.4; H, 8.0.

The pseudokammogenin triacetate was hydrolyzed by refluxing with an alcoholic potassium hydroxide solution for twenty minutes on a steam-bath. The product was poured into water, filtered and crystallized from acetone, m. p. 188–190°.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.9; H, 9.1. Found: C, 72.7; H, 9.0.

Neokammogenin.—To a cold solution of 20 g. of pseudokammogenin dissolved in 500 cc. of ethyl alcohol was added 20 cc. of concentrated hydrochloric acid. The product was allowed to stand in a refrigerator overnight, poured into water and filtered. The precipitate was dried and acetylated by refluxing for thirty minutes with 50 cc. of acetic anhydride. The excess acetic anhydride was distilled *in vacuo* and the residue was crystallized from ether, m. p. and mixed m. p. with kammogenin diacetate, 258–260°; yield 11.2 g.

The solvent from the above mother liquors was removed and the residue was crystallized from methanol to give a product, m. p. 203–205°; yield 4.3 g.

Anal. Calcd. for $C_{31}H_{44}O_7$: C, 70.4; H, 8.4. Found: C, 70.5; H, 8.6.

Hydrolysis of this diacetate gave neokammogenin, which was crystallized from ether, m. p. 228–230°.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.9; H, 9.1. Found: C, 72.7; H, 9.0.

When neokammogenin was refluxed for seventy-two hours with an alcoholic solution of hydrochloric acid it gave a product, m. p. and mixed m. p. with kammogenin, 242°. Acetylation of this product with acetic anhydride gave kammogenin diacetate, m. p. and mixed m. p. 258–260°.

Neomanogenin.—A solution of 200 mg. of neokammogenin diacetate in 150 cc. of ether containing a few drops of acetic acid was shaken with 200 mg. of Adams catalyst and hydrogen at 3 atm. and room temperature for fifteen minutes. The solution was filtered and the product was crystallized from methanol to give the diacetate of neomanogenin, m. p. 222°.

Anal. Calcd. for $C_{31}H_{46}O_7$: C, 70.2; H, 8.7. Found: C, 70.2; H, 8.9.

Hydrolysis of the diacetate with alcoholic potassium hydroxide gave a product which was crystallized from ether, m. p. 242–244°.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.6; H, 9.5. Found: C, 72.4; H, 9.4.

When neomanogenin was refluxed for seventy-two hours with an alcoholic solution of hydrochloric acid it gave a product, m. p. 254°, which gave no depression when mixed with manogenin. Acetylation of this product with acetic anhydride gave the diacetate of manogenin, m. p. and mixed m. p. 242°.

Neoyuccagenin (Liligenin[1]).—To a solution of 10 g. of sodium in 200 cc. of absolute ethanol was added 2 g. of neokammogenin diacetate and 10 cc. of 85% hydrazine hydrate. The product was heated for twelve hours at 200°. Water was added and the precipitated product was filtered off. The product was dried and then crystallized from ether, m. p. 245–247°. Further crystallization from alcohol did not change the melting point. This product gave no depression in melting point when mixed with liligenin, isolated from *Lilium rubrum magnificum.*

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(1) Marker and co-workers, THIS JOURNAL, **62**, 2620 (1940).

(2) Marker and co-workers, *ibid.*, **65**, 1206 (1943).

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.3; H, 9.8. Found: C, 75.2; H, 9.9.

The diacetate of neoyuccagenin (liligenin) was prepared by refluxing with acetic anhydride. The excess acetic anhydride was removed and the residue was crystallized from methanol, m. p. and mixed m. p. with liligenin diacetate, 158–159°.

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.3; H, 9.0. Found: C, 72.4; H, 8.9.

A mixture of 300 mg. of neoyuccagenin, 10 cc. of concentrated hydrochloric acid and 50 cc. of ethanol was refluxed for fifty hours. The alcohol was distilled and the residue was crystallized from ether, m. p. and mixed m. p. with yuccagenin, 248–250°. This material was acetylated and crystallized from a small amount of acetic anhydride. It gave the diacetate of yuccagenin, m. p. and mixed m. p. 176–178°.

Neogitogenin.—A mixture of 200 mg. of neoyuccagenin, 500 mg. of Adams catalyst, 300 cc. of ether and a few drops of acetic acid was shaken with hydrogen at room temperature and three atm. for one hour. The solution was filtered and the product was crystallized from ether as needles, m. p. 248°.

The same product was obtained when neomanogenin was treated with hydrazine hydrate, alcohol and sodium at 200°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 75.0; H, 10.3. Found: C, 75.2; H, 10.2.

The diacetate of neogitogenin was prepared by refluxing the above product with acetic anhydride for thirty minutes. It was crystallized from methanol, m. p. 212°.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.1; H, 9.4. Found: C, 72.1; H, 9.6.

Neodiosgenin and Neotigogenin.—The neodiosgenin was isolated as a naturally occurring product from *Dioscorea mexicana*. It melted at 201° and gave an acetate melting at 184–185°.

A mixture of 10 g. of neodiosgenin, 1 liter of ethanol and 200 cc. of concentrated hydrochloric acid was refluxed for one day on a steam-bath. The product was poured into water and the solution was filtered. The dried precipitate was refluxed for thirty minutes and 25 cc. of acetic anhydride. It was allowed to cool to room temperature and the solution was filtered and crystallized from ethanol, m. p. and mixed m. p. with diosgenin acetate, 203–204°. A mixture with neodiosgenin acetate melted at 162–170°.

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.3; H, 9.7. Found: C, 76.1; H, 9.8.

When hydrolyzed with alcoholic potassium hydroxide it gave a product after crystallization from ether, m. p. 210–212°, which gave no depression when mixed with diosgenin.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.2. Found: C, 78.4; H, 10.0.

A mixture of 500 mg. of neodiosgenin, 500 cc. of ether, 600 mg. of Adams catalyst and a few drops of acetic acid was shaken with hydrogen at 3 atm. and room temperature for three hours. The solution was filtered and the filtrate was evaporated. The product was crystallized from ether, m. p. 203–204°. This is neotigogenin.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.7. Found: C, 77.7; H, 10.7.

Acetylation of the above product with acetic anhydride gave the acetate of neotigogenin, m. p. 179–180°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.1; H, 10.3.

Pseudohecogenin.—A solution of 30 g. of hecogenin in 50 cc. of acetic anhydride was treated as described for the preparation of pseudokammogenin. The solvent was removed *in vacuo* and the residue was hydrolyzed by boiling with alcoholic potassium hydroxide for thirty minutes. The product was extracted with ether and the solvent was removed. It was crystallized from acetone, m. p. 190°; yield 21.3 g.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.3; H, 9.8. Found: C, 75.0; H, 9.6.

Neohecogenin.—To a cold solution of 20 g. of pseudohecogenin in 500 cc. of ethyl alcohol was added 20 cc. of concentrated hydrochloric acid. The product was allowed to stand in a refrigerator overnight, poured into water and filtered. The precipitate was dried and crystallized from methanol, m. p. and mixed m. p. with hecogenin, 257°; yield 12 g.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.3; H, 9.8. Found: C, 75.1; H, 9.7.

Conversion of the above product to the acetate gave a compound m. p. and mixed m. p. with hecogenin acetate, 242°.

The solvent was removed from the total mother liquors above and the residue was refluxed with acetic anhydride for twenty minutes. The excess anhydride was removed *in vacuo* and the residue was crystallized from methanol, m. p. 228°; when mixed with hecogenin acetate there was a depression to 215–223°.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.7; H, 9.4. Found: C, 73.5; H, 9.3.

Hydrolysis of the above acetate and crystallization from dilute methanol gave neohecogenin, m. p. 238°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.3; H, 9.8. Found: C, 75.1; H, 9.9.

Neotigogenin.—To a solution of 10 g. of sodium in 200 cc. of absolute ethanol was added 2 g. of neohecogenin acetate and 10 cc. of 85% hydrazine hydrate. The product was heated for ten hours at 200°. Water was added and the solution was filtered and the product dried. It was crystallized from ether to give neotigogenin, m. p. and mixed m. p. 203–204°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.7. Found: C, 77.6; H, 10.5.

Acetylation of the above product with acetic anhydride gave the acetate of neotigogenin, m. p. and mixed m. p. 180°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.0; H, 10.3.

Neochlorogenin.—To a solution of 10 g. of neodiosgenin in 500 cc. of acetic acid cooled to 15° was added 10 g. of chromic anhydride dissolved in 20 cc. of water and 150 cc. of acetic acid. The oxidizing mixture was added at such a rate that the temperature was maintained at 15–18°. It was allowed to stand at this temperature for one hour. At the end of this time 20 g. of zinc dust was added and the mixture was refluxed for two hours with stirring. The solution was filtered and the excess acetic acid was distilled *in vacuo* to about 100 cc. The product was then extracted with ether and washed well with water, followed by dilute potassium hydroxide solution to remove acidic products. Upon distillation of the ether to a small volume the product crystallized, m. p. 245–248°; yield 4.2 g. This is neochlorogenone.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.7; H, 9.4. Found: C, 75.5; H, 9.3.

To a boiling solution of 2 g. of neochlorogenone in 500 cc. of absolute ethanol was added 40 g. of sodium in small pieces. After the sodium had dissolved the solution was diluted with one liter of water and extracted with ether. The ether was distilled to a small volume and cooled. The product which precipitated was recrystallized from acetone, m. p. 264–266°. This is neochlorogenin.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 75.0; H, 10.3. Found: C, 75.1; H, 10.1.

The diacetate of neochlorogenin was prepared by refluxing with acetic anhydride for thirty minutes. It was crystallized from methanol, m. p. 198–200°.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.1; H, 9.4. Found: C, 72.4; H, 9.3.

To a boiling solution of 500 mg. of neochlorogenin in 100 cc. of ethanol was added 12 cc. of concentrated hydrochloric acid. The solution was refluxed for thirty hours.

The solvent was distilled to about 50 cc. and then extracted with ether and washed well with water. The ether was evaporated to a small volume and cooled overnight. The crystals were filtered and the product was crystallized from dilute methanol and finally from ether, m. p. and mixed m. p. with authentic chlorogenin, 274-276°.

The above product was refluxed with acetic anhydride for thirty minutes. The excess acetic anhydride was removed and the residue was crystallized from dilute methanol, m. p. and mixed m. p. with authentic chlorogenin diacetate, 154-155°.

Pseudomexogenin.—A solution of 30 g. of mexogenin in 50 cc. of acetic anhydride was treated as described for the preparation of pseudohecogenin. The product was crystallized from ether and from acetone, m. p. 145°; yield 22.8 g.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.6; H, 9.5. Found: C, 72.5; H, 9.4.

Neomexogenin.—A mixture of 20 g. of pseudomexogenin, 500 cc. of ethyl alcohol and 20 cc. of concentrated hydrochloric acid was treated as described for neokammogenin. The solvent was distilled to a small volume and allowed to stand overnight in a refrigerator. The crystals were filtered and recrystallized from ether, m. p. and mixed m. p. with mexogenin, 244-246°; yield 11.2 g. Upon acetylation with acetic anhydride a product was obtained which melted at 205-207° and gave no depression when mixed with the diacetate of mexogenin.

The ethereal mother liquors from the crystallization of mexogenin were evaporated and the residue was acetylated by refluxing with acetic anhydride for thirty minutes. The solvent was removed and the residue was crystallized from a small amount of methanol to give the diacetate of neomexogenin, m. p. 162-164°; yield 3.6 g.

Anal. Calcd. for $C_{31}H_{46}O_7$: C, 70.2; H, 8.7. Found: C, 70.4; H, 8.9.

The above product was hydrolyzed by refluxing with alcoholic potassium hydroxide for twenty minutes. It was crystallized from dilute methanol and from ether, m. p. 222°.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.6; H, 9.5. Found: C, 72.8; H, 9.2.

When neomexogenin was refluxed with alcoholic hydrochloric acid for forty hours a product was obtained melting at 246-247° which gave no depression in melting point when mixed with mexogenin.

Neosamogenin.—To a solution of 10 g. of sodium in 200 cc. of absolute ethanol was added 2 g. of neomexogenin diacetate and 10 cc. of 85% hydrazine hydrate. The product was heated at 200° for ten hours. Water was added and the precipitated product was filtered, dried and crystallized from acetone to give neosamogenin, m. p. 174-176°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 75.0; H, 10.3. Found: C, 74.8; H, 10.1.

Neosamogenin upon refluxing with acetic anhydride gave a diacetate which was crystallized from methanol as needles, m. p. 173-175°.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.1; H, 9.4. Found: C, 71.9; H, 9.5.

The above product gave no depression in melting point with that prepared from pseudosamogenin.

Pseudosamogenin.—A solution of 30 g. of samogenin in 50 cc. of acetic anhydride was treated as described for the preparation of pseudomexogenin. After hydrolysis with alcoholic potassium hydroxide the product was crystallized from methanol, m. p. 182-184°; yield 21.6 g.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 75.0; H, 10.3. Found: C, 74.9; H, 10.5.

To a cold solution of 20 g. of pseudosamogenin in 500 cc. of ethyl alcohol was added 20 cc. of concentrated hydrochloric acid. The product was allowed to stand in a refrigerator overnight. It was then extracted with ether, washed well with water and the solvent removed to a small volume. It was allowed to stand overnight in a refrigerator and was then filtered. It was crystallized from ether, m. p. and mixed m. p. with samogenin, 212°; yield 10.6 g. Upon acetylation this product gave the diacetate of samogenin, m. p. and mixed m. p. 198°.

The mother liquors from the above crystallization of samogenin were distilled and the residue was acetylated by boiling for thirty minutes with acetic anhydride. The solvent was removed *in vacuo* and the residue was crystallized from methanol, m. p. and mixed m. p. with neosamogenin acetate, 173-175°; yield 4.1 g.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.1; H, 9.4. Found: C, 72.0; H, 9.4.

Hydrolysis with alcoholic potassium hydroxide gave a product m. p. and mixed m. p. with neosamogenin, 174-176°. This is identical with the product reported above.

When neosamogenin was refluxed with alcoholic hydrochloric acid for thirty hours it gave a product which gave no depression in melting point with samogenin. Acetylation gave a diacetate, m. p. and mixed m. p. with samogenin diacetate, 197-198°.

Summary

Neokammogenin, neomanogenin, neoyuccagenin, neogitogenin, neohecogenin, neotigogenin, neodiosgenin, neochlorogenin, neomexogenin and neosamogenin were prepared.

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Steroidal Sapogenins. No. 161. The Seasonal Variation of Sapogenins in Plants

BY RUSSELL E. MARKER AND JOSEFINA LOPEZ

A study has been made of the steroidal sapogenins present in various parts of *Yucca schottii*, *Samuela carnerosana* and *Agave striata* before and after fruiting. It was shown that after fruiting the plants contained no monohydroxy steroids, but contained only the complex polyhydroxy steroids. As the flowering and fruiting season approaches these polyhydroxy steroids are changed progressively to the simpler steroids which are discarded in the fruit or flower stem of the plant. It is interesting to note that the flowers of *Yucca schottii* contained manogenin, gitogenin, tigogenin and smilagenin, yet in the course of only a few weeks until the fruit was formed these were all changed into their side-chain isomers neomanogenin, neogitogenin, neotigogenin and sarsasapogenin. The only sapogenin that could be isolated from the flowers of *Samuela carnerosana* was smilagenin, yet when the fruit was formed this contained only its side chain isomer, sarsasapogenin. *Agave striata* medium aged plants contained only neo-manogenin, but the flower stems and flowers from old plants contained a mixture of neogitogenin and neoheco-