This gave no depression with a sample, m. p. 228–231°, prepared by oxidizing desoxysarsasapogenin with chromic anhydride at 90–95°.

The desoxy acid (75 mg.), m. p. 230–232°, was refluxed for thirty minutes with acetic anhydride and the reaction product was sublimed in high vacuum at 120–140°. The sublimate was crystallized from ether–pentane to give white needles of the **desoxy anhydride**, m. p. 205.5–207°.

*Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 75.0; H, 9.3. Found: C, 75.0; H, 9.4.

Treatment of the desoxy anhydride with hot ethanolic potassium hydroxide gave the desoxy acid, m. p. 230–232°.


## Summary

The acetates of sarsasapogenin, tetrahydrosarsasapogenin, and sarsasapogenoic acid upon oxidation with chromic anhydride yield a $C_{19}$ dibasic acid, probably 3-hydroxy-*etio*-bilianic acid.


STATE COLLEGE, PENNA. RECEIVED JUNE 17, 1939

---

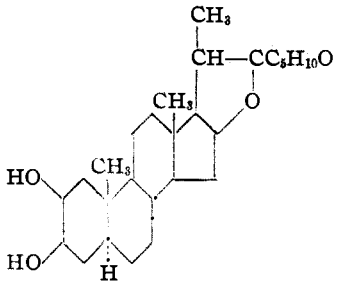
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

# Sterols. LXXIII. Reactions of Digitogenin and Gitogenin

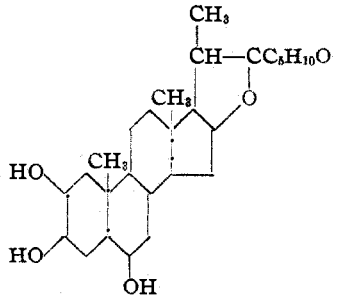
BY RUSSELL E. MARKER AND EWALD ROHRMANN

Although digitogenin (II) and gitogenin (I) were the first steroidal sapogenins to be studied,[1] the chemistry of the substances appears to be still in a somewhat confused state, particularly in regard to the nature of various oxidative degradation products. Unfortunately in all of the oxidation studies which have been reported on these substances no attempt was made to protect the reactive hydroxyl groups and therefore conclusions derived from such studies concerning the nature of the two less reactive oxygens must be regarded as of doubtful value.

The fact that tigogenin has been oxidized to gitogenic acid,[2,3] identical with that obtained by the chromic anhydride oxidation of gitogenin, shows conclusively that gitogenin is of the *allo*-configuration at C-5 and also offers strong support to the work of Tschesche and Hagedorn,[4] concerning the position of the nuclear hydroxyl groups. The evidence concerning the configuration of digitogenin at C-5 is not certain in spite of the fact that it has been degraded to gitogenic acid by the Wolff–Kishner reduction of digitogenic acid, inasmuch as inversion at C-5 may have occurred under the influence of alkali.




I. Gitogenin




II. Digitogenin

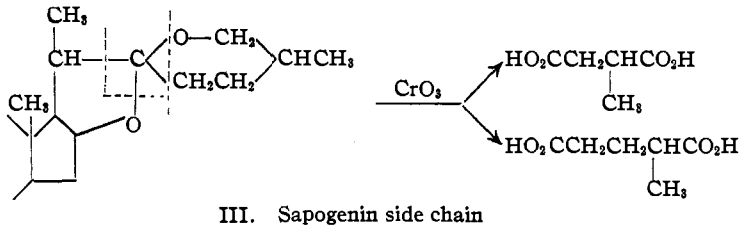
The fact that both $\alpha$-methylglutaric acid and methylsuccinic acids have been reported from the chromic anhydride oxidation of digitogenic acid[2,4] is in accordance with our recently proposed structure of the sapogenin side chain III.[5] It is no longer necessary to regard the formation of $\alpha$-methylglutaric acid as arising from the oxidation of the nucleus of the sapogenin as was necessitated by structure IV of Tschesche and Hagedorn.[4,6]

Contrary to Tschesche and Hagedorn,[7] we have found that both digitogenin and gitogenin yield insoluble digitonides, a characteristic which evidently is shown by all of the known steroidal sapogenins.

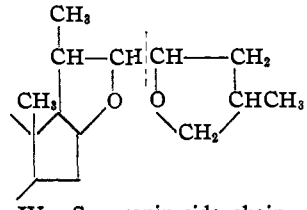
Digitogenin and gitogenin both readily yield dihydro compounds[5] upon catalytic hydrogenation in acidic medium. These dihydro compounds have not been investigated further. The acetates of digitogenin and gitogenin yield with

(1) Fieser, "Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1936.

(2) Tschesche and Hagedorn, *Ber.*, **68**, 1090 (1935).
(3) Jacobs and Simpson, *J. Biol. Chem.*, **110**, 429 (1935).
(4) Tschesche and Hagedorn, *Ber.*, **69**, 797 (1936).
(5) Marker and Rohrmann, THIS JOURNAL, **61**, 846 (1939).
(6) Tschesche and Hagedorn, *Ber.*, **68**, 1412 (1935).
(7) Tschesche and Hagedorn, *ibid.*, **68**, 2247 (1935).




III. Sapogenin side chain




IV. Sapogenin side chain (Tschesche and Hagedorn[7])

bromine characteristic monobromo derivatives. Gitogenin and digitogenin also react with selenium dioxide.

That these two sapogenins are related more closely to tigogenin[8] than to sarsasapogenin is shown further by the fact that they appear to be relatively inert to treatment with alcoholic hydrochloric acid. Attempts to reduce the substances by the Clemmensen method[3] were unsuccessful.

The acetates of the $C_{22}$ lactones of digitogenin and gitogenin were prepared by oxidizing digitogenin triacetate and gitogenin diacetate with chromic anhydride at 90–95°, the yields being comparable to those obtained by similar oxidations of sarsasapogenin and tigogenin acetates. Hydrolysis of the acetate lactones gave the corresponding hydroxy lactones.

We wish to thank Parke, Davis and Company for their generous support and assistance in the various phases of this work. We also wish to thank Mr. Paul H. Williams and Drs. Elmer J. Lawson and H. C. Benedict for their assistance in obtaining the bulbs of *Chlorogalum pomeridianum*.

## Experimental Part

**Isolation of Gitogenin from Chlorogalum Pomeridianum.**—The filtrate remaining after removal of the chlorogenin and tigogenin from *Chlorogalum pomeridianum* was evaporated to dryness and the crystalline residue acetylated by boiling for thirty minutes with a large excess of acetic anhydride. The acetic anhydride was evaporated *in vacuo* and the residue crystallized from acetone to give white needles, m. p. 241–243°. This gave no depression with a sample of gitogenin diacetate prepared from gitogenin isolated from *Digitalis purpurea*.

*Anal.* Calcd. for $C_{31}H_{48}O_6$: C, 72.1; H, 9.4. Found: C, 72.4; H, 9.5.

(8) Marker and Rohrmann, THIS JOURNAL, 61, 1516 (1939).

Hydrolysis of the acetate with ethanolic potassium hydroxide yielded a product which crystallized from 95% ethanol as fine white needles, m. p. 266–268°. This gave a 25° depression when mixed with chlorogenin. This gave no depression with a sample of gitogenin isolated from *Digitalis purpurea*.

*Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.9; H, 10.2. Found: C, 74.6; H, 10.2.

When heated with an acetic acid solution of selenium dioxide the substance readily yielded a red precipitate.

Gitogenin was recovered unchanged after treatment with amalgamated zinc and hydrochloric acid in alcohol solution for six hours.

**Digitogenin from Recovered Digitonin.**—To a hot solution of 50 g. of recovered digitonin in 400 cc. of absolute methanol was added a mixture of 100 cc. of concentrated hydrochloric acid, 100 cc. of water and 100 cc. of methanol. The resulting mixture was refluxed for eight hours. The material showed a considerable tendency to froth during the first two hours of refluxing. The mixture was then diluted with water and the white precipitate collected, washed with water and dried. The dried material was treated with Norite in 95% ethanol. Concentration of the alcoholic solution yielded white crystals which were recrystallized from dry benzene to give fine white needles, m. p. 278°.

*Anal.* Calcd. for $C_{27}H_{44}O_5$: C, 72.3; H, 9.9. Found: C, 72.6; H, 9.8.

The product reacted readily with a hot solution of selenium dioxide in acetic acid. Digitogenin was recovered essentially unchanged after treatment with amalgamated zinc and hydrochloric acid in ethanol solution for five hours.

**Dihydrogitogenin.**—A mixture of 2 g. of gitogenin diacetate, 1 g. of Adams catalyst and 100 cc. of glacial acetic acid was shaken with hydrogen (3 atmospheres) at 70° for twelve hours. The mixture was filtered and the acetic acid evaporated *in vacuo*. The residual sirup was hydrolyzed for twenty minutes in alcoholic potassium hydroxide. The resulting solution was diluted with water and the mixture extracted with ether and the product crystallized from ethyl acetate to give fine white needles, m. p. 195–197°. The substance gave a precipitate with digitonin. The substance showed no tendency to react with selenium dioxide.

*Anal.* Calcd. for $C_{27}H_{46}O_4$: C, 74.6; H, 10.7. Found: C, 74.1; H, 10.7.

**Tri-*p*-nitrobenzoate of Dihydrogitogenin.**—A solution of 100 mg. of dihydrogitogenin and 400 mg. of *p*-nitrobenzoyl chloride in 10 cc. of pyridine was heated on the steam-bath for six hours. After dilution with water the neutral material was crystallized from ether–acetone as pale yellow crystals, m. p. 189–191°.

*Anal.* Calcd. for $C_{48}H_{55}O_{13}N_3$: C, 65.35; H, 6.3. Found: C, 65.0; H, 6.3.

**Dihydrodigitogenin.**—This was prepared as described for dihydrogitogenin. The product was crystallized from acetone as white needles, m. p. 184–186°.

*Anal.* Calcd. for $C_{27}H_{46}O_5$: C, 71.9; H, 10.3; mol. wt.,

450. Found: C, 71.6, 71.9, H, 10.5, 10.3, mol. wt. (Rast), 434.

**Bromogitogenin Diacetate.**—To a solution of 300 mg. of gitogenin diacetate in 30 cc. of acetic acid acidified with 2 drops of 48% hydrobromic acid was added 0.6 cc. of 1.05 *M* bromine in acetic acid. The solution was diluted with water and the precipitate collected, washed with water and dried. The product was crystallized from acetone–methanol as white needles, m. p. 219–220° dec.

*Anal.* Calcd. for $C_{31}H_{47}O_6Br$: C, 62.5; H, 8.0. Found: C, 62.3; H, 8.0.

When reduced with sodium and absolute ethanol the bromo compound yielded gitogenin, m. p. 265–267°.

The bromo compound showed no evidence of reaction when heated with an acetic acid solution of selenium dioxide.

**Bromodigitogenin Triacetate.**—This was prepared as described for bromogitogenin diacetate. The product was crystallized from aqueous methanol as white crystals, m. p. 142° dec.

*Anal.* Calcd. for $C_{33}H_{49}O_8Br$: C, 60.6; H, 7.6. Found: C, 60.8; H, 7.6.

Its behavior toward selenium dioxide and sodium and ethanol was analogous to that of the gitogenin compound.

**Digitogenin Lactone Triacetate.**—To a solution of 3 g. of digitogenin triacetate in 100 cc. of glacial acetic acid heated at 95° was added a solution of 5 g. of chromic anhydride in 60 cc. of 80% acetic acid over a period of one hour. The resulting mixture was heated for an additional ninety minutes. The mixture was evaporated *in vacuo* to a volume of about 50 cc. The residual solution, after dilution with water, was extracted with ether and the ethereal extract washed with 3% sodium hydroxide solution to remove acidic products. The ether was evaporated and the residue crystallized from acetone as compact white crystals, m. p. 281–283°.

*Anal.* Calcd. for $C_{28}H_{40}O_8$: C, 66.6; H, 8.0. Found: C, 66.7; H, 8.1.

Hydrolysis of the lactone acetate with an excess of ethanolic potassium hydroxide gave the **trihydroxy lactone** which crystallized from acetone as small white crystals, m. p. 279–282°.

*Anal.* Calcd. for $C_{22}H_{34}O_5$: C, 69.8; H, 9.0; neut. equiv., 378. Found: C, 69.4; H, 9.0; neut. equiv., 379.5.

**Gitogenin Lactone Diacetate.**—This was prepared from gitogenin diacetate as described for digitogenin lactone triacetate. The material was crystallized from acetone–pentane as compact white crystals, m. p. 248–251°.

*Anal.* Calcd. for $C_{26}H_{38}O_6$: C, 69.9; H, 8.7. Found: C, 69.7; H, 8.6.

Hydrolysis of the resulting diacetate with ethanolic potassium hydroxide yielded the **gitogenin lactone** which crystallized from ether–acetone as white needles, m. p. 276–278°.

*Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 72.6; H, 9.4.

Treatment of the dihydroxy lactone with benzoyl chloride in pyridine at room temperature for two days gave a **dibenzoate lactone** which, after treatment with Norite, crystallized from aqueous acetone as white needles, m. p. 275–278°.

*Anal.* Calcd. for $C_{36}H_{42}O_6$: C, 75.75; H, 7.4. Found: C, 76.0; H, 7.5.

**Digitonides of Digitogenin and Gitogenin.**—To a hot solution of 250 mg. of digitogenin in 35 cc. of 95% ethanol was added a boiling solution of 1.1 g. of digitonin in 35 cc. of 80% ethanol. A precipitate started to separate after thirty minutes and after standing overnight at room temperature the precipitate was collected, washed with 95% ethanol and dried: yield of digitonide, 800 mg. This was dissolved in 10 cc. of pyridine and the resulting solution heated on the steam-bath for twenty-five minutes. The solution was then poured into a mixture of 200 cc. of ether and 15 cc. of methanol. The white precipitate was collected and washed with ether. The filtrate after shaking with dilute hydrochloric acid was evaporated and the residue crystallized from acetone–benzene to give 180 mg. of fine white needles, m. p. 276–279°. This gave no depression with a sample of digitogenin.

Similar results were obtained with gitogenin.

## Summary

Gitogenin and digitogenin resemble sarsasapogenin and tigogenin in their behavior toward catalytic hydrogenation, bromination and oxidation with selenium dioxide. They are relatively inactive toward isomerization with hydrochloric acid and Clemmensen reduction.

The $C_{22}$ lactones of digitogenin and gitogenin have been prepared.

STATE COLLEGE, PENNA. RECEIVED JUNE 17, 1939