254–256°; yield 0.3 g. This substance gave a 10° elevation when mixed with 3(β)-hydroxy-17,20-pregnenoic acid-21; m. p. 254–256°.

*Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.6; H, 9.5.

The methyl ester was prepared as described above. It crystallized from methanol as white plates; m. p. 150–152°. It depressed the melting point of the methyl ester of 3(β)-hydroxy-17,20-pregnenoic acid-21 (m. p. 153–155°) twenty-five degrees.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.8. Found: C, 75.8; H, 9.8.

**Catalytic Reduction of 3(β)-Hydroxy-etio-16-cholenic Acid.**—A solution of 100 mg. of the above 3(β)-hydroxy-etio-16-cholenic acid in 100 cc. of acetic acid was shaken with hydrogen and Adams catalyst for two hours at 3 atm. pressure and room temperature. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from methanol as white needles; m. p. and mixed m. p. with 3(β)-hydroxy-etio-cholanic acid, 224–227°. A mixed melting point with 3(β)-hydroxy-pregnanoic acid (m. p. 219–221°) was at 195°.

*Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.9; H, 10.1. Found: C, 75.0; H, 10.0.

**3(β)-Hydroxy-etio-5-cholenic Acid.**—From the reaction of 2 g. of 5-pregnen-3(β)-ol-20-one acetate with potassium hypoiodite as described above was isolated a product which crystallized from dioxane; m. p. and mixed m. p. with an authentic sample of 3(β)-hydroxy-etio-5-cholenic acid, 273–274°; yield 0.2 g. pure product.

*Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.3.

**3(β)-Hydroxy-etio-5,16-choladienic Acid.**—From the reaction of 2 g. of 5,16-pregnadien-3(β)-ol-20-one acetate as described above was isolated a product which crystallized from methanol as white plates; m. p. 255–257°; yield 250 mg.

*Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 76.0; H, 8.8.

## Summary

Conditions are described for the hypoiodite oxidation of 20-keto-pregnane derivatives to the corresponding 20-carboxylic acids. 3(β)-Hydroxy-etio-cholanic (II), 3(β)-hydroxy-etio-16-cholenic (III), 3(β)-hydroxy-etio-5-cholenic (IV), and 3(β)-hydroxy-etio-5,16-choladienic (V) acids have been produced by this method.

STATE COLLEGE, PENNA. RECEIVED APRIL 15, 1942

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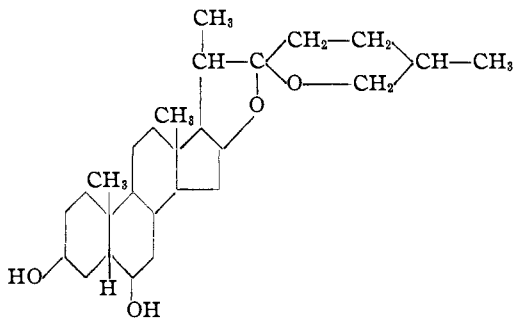
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

# Sterols. CL. Sapogenins. LXIII. The Position of the Hydroxyl Groups in Digitogenin*

BY RUSSELL E. MARKER, D. L. TURNER AND PAUL R. ULSHAFER

The position of the hydroxyl groups in chlorogenin has been established with certainty by a large number of interconversions reported from this Laboratory[1,2,3] and chlorogenin is undoubtedly 6-hydroxy-tigogenin (I). However, Noller[4]



is unable to reconcile this structure of chlorogenin with the fact that the oxidation of chlorogenin gives a keto-dibasic acid which is neither identical to digitoic acid nor to digitogenic acid. A revision of Noller's interpretation of the non-identity of the two acids is now necessary since the structure of chlorogenin is certain.

We find that oxidation of 6-keto-tigogenone[2,3] (tigogen-3,6-dione) prepared from diosgenin gives a keto-dibasic acid identical to that from natural chlorogenin and this acid differs from digitoic and digitogenic acid. The keto-dibasic acid melts with decomposition and gas evolution. Cholestane-3,6-dione was oxidized by Windaus[5] to a ketodibasic acid which melts with decomposition and gas evolution. This acid can be converted by Wolff–Kishner reduction[6] to cholestane-2,3-diacid the structure of which is certain.[6,7] We have also effected this reduction by the Clemmensen method. It, therefore, seems reasonable to suppose that the oxidation of 6-keto-tigogenone

* Original manuscript received July 2, 1941.

(1) Marker, *et al.*, THIS JOURNAL, **61**, 946 (1939); **61**, 1516 (1939); **62**, 2525 (1940); **63**, 767 (1941); **64**, 221 (1942).

(2) Marker, Jones and Turner, *ibid.*, **62**, 2537 (1940).

(3) Marker, Jones, Turner and Rohrmann, *ibid.*, **62**, 3006 (1940).

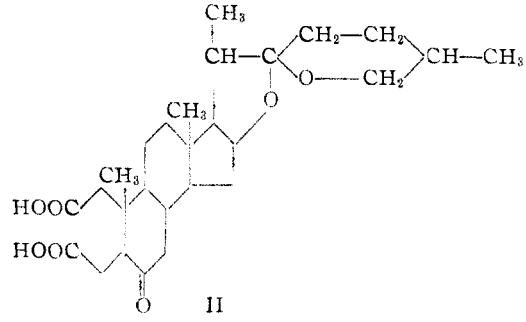
(4) Noller, *ibid.*, **59**, 1092 (1937).

(5) Windaus, *Ber.*, **36**, 3752 (1903).

(6) Windaus, Staden and Seng, *Z. physiol. Chem.*, **117**, 146 (1921).

(7) Windaus, *ibid.*, **213**, 147 (1932).

takes a similar course and gives an acid of structure II. Noller[8] found that the acid from chloro-

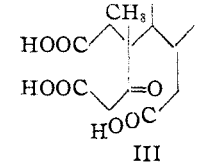


II

genin which he has named chlorogenonic acid can be reduced by the Wolff–Kishner method to gitogenic acid. Consequently, structure II is secure for chlorogenonic acid.

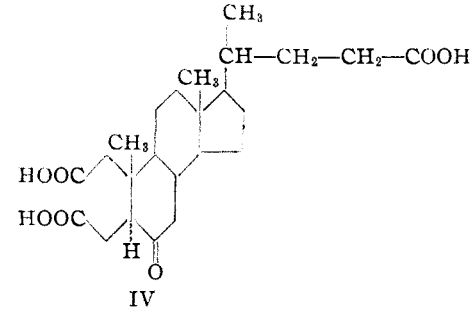
Neither digitogenic acid nor digitoic acid can have the same structure as chlorogenonic acid. Tschesche[9] has shown that digitogenic acid can be reduced to gitogenic acid and this indicates that two of the hydroxyl groups of digitogenin are at C–2 and C–3. If the third hydroxyl group of digitogenin is at C–6 as assumed by Tschesche, digitogenic acid and digitogenin would probably be of the coprostane configuration and digitoic acid of the cholestane configuration since the last acid is the stable form.[10,11,12] The side-chains of chlorogenin and digitogenic acid are the same because they have both been related to tigogenin. All three sapogenins are unaffected by treatment with hydrochloric acid in ethanol at the boiling point. This indicates that they all have the iso-configuration of the side-chain.[13]

The fact that chlorogenonic acid is not identical with digitoic acid therefore indicates that the assumption of Tschesche concerning the 6-position of the third hydroxyl group in digitogenin is incorrect.[14] Moreover the reactions of digitogenic acid and digitoic acid are completely different from those which would be expected from the known behavior of 6-keto-cholestane-2,3-diacid and similar substances of established structure. Thus 6-cholestanone was oxidized by Windaus[15] to cholestane-6,7-diacid using chromic acid or nitric acid.[16] The oxidation of digitogenic acid and digitoic acid, whether with permanganate or chromic acid, gives acids supposed by Tschesche to have structure III. These acids include oxydigitogenic acid, digitic acid[17] and acid "A" of Windaus and Willerding.[18] It would be peculiar that digitogenic and digitoic acids should not be oxidized to a 6,7-diacid if there was really a carbonyl group at C–6.



III

Much more significant is the result of catalytic reduction of digitoic and digitogenic acids. We have now found that hydrogenation in ethanol or acetic acid gives a hydroxydicarboxylic acid, the same acid being obtained from both digitoic acid and digitogenic acid. The fact that this product is not a lactone is incompatible with the supposed carbonyl group at C–6. Hyodesoxy-iso-bilianic acid (IV) was catalytically reduced by Windaus[11]



IV

and the resulting 6-hydroxy-"Staden acid" was not capable of existence as a hydroxy-acid, but immediately gave a lactone. The formation of lactones following the reduction of 6-keto-2,3-diacids of the type of IV is a general phenomenon.[19] Thus we have observed lactone formation in the reduction of 6-keto-cholestane-2,3-diacid. Only one carboxyl group of the product can be titrated in the cold.

It is interesting that the 6-keto-2,3-diacids melt with decomposition and gas evolution, *e. g.*, 6-keto-cholestane-2,3-diacid,[5] and chlorogenonic acid. This is not reported for digitogenic acid nor digitoic acid. The ester of digitoic acid can be distilled unchanged[18] *in vacuo*, and the ester of digitogenic acid is converted to that of digitoic acid. Distillation of the trimethyl ester of 6-

(8) Private communication from Professor Noller to one of us.
(9) Tschesche and Hagedorn, *Ber.*, **68**, 1090 (1935).
(10) Tschesche and Hagedorn, *ibid.*, **69**, 797 (1936).
(11) Windaus, *Ann.*, **447**, 233 (1926).
(12) Stange, *Z. physiol. Chem.*, **220**, 34 (1933).
(13) Marker and Rohrmann, THIS JOURNAL, **62**, 647 (1940).
(14) Fieser, "Chemistry of Natural Products related to Phenanthrene," 2nd. edition, New York, N. Y., 1937.
(15) Windaus and Dalmer, *Ber.*, **52**, 162 (1919).
(16) *Cf.* Windaus and Staden, *ibid.*, **54**, 1059 (1921).
(17) Windaus and Weil, *Z. physiol. Chem.*, **121**, 62 (1922).
(18) Windaus and Willerding, *ibid.*, **143**, 33 (1925).
(19) *Cf.* Windaus and Hoszfeld, *ibid.*, **146**, 177 (1925).

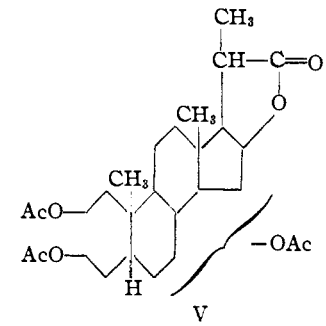
keto-Staden acid gives an unsaturated lactone with the loss of methyl alcohol.[20]

Another observation inconsistent with the C–6 position for the hydroxyl group in digitogenin is the fact that digitogenin was recovered unchanged after distillation with potassium bisulfate a method which readily dehydrates chlorogenin to 3,5-dehydrodesoxytigogenin.[21] In the case of hyodesoxycholic acid a similar dehydration occurs even more readily. Windaus[11,22] records that this acid gives hyocholadienic acid by simple distillation *in vacuo*.

Since it is impossible that digitogenin should have a hydroxyl group at C–6 it is necessary to revise all of the formulas proposed by Tschesche for the oxidation products of digitogenic acid. This is a difficult task at present because the assumption of Tschesche that oxydigitogenic acid, digitic acid, anhydrodigitic acid and their derivatives had an intact sapogenin side-chain is by no means a necessary one. Indeed, there are some indications that this may be true only of digitogenic and digitoic acids. Oxydigitogenic acid and digitic acids were prepared by treating digitogenic acid with alkaline permanganate. We have found that sarsasapogenin is oxidized to some extent by alkaline permanganate at room temperature, and this involves alteration of the side-chain.

Windaus and Weil[17] also treated oxydigitogenic acid with hydrochloric acid in acetic acid to decarboxylate it. Similar treatment of digitic acid gave anhydrodigitic acid. Heating a solution of sarsasapogenin or of gitogenin in acetic acid containing hydrochloric acid has been shown by Jacobs and Simpson[23] to remove the entire side-chain.[24] Windaus[17] records that similar treatment of oxydigitogenic acid merely caused the loss of 1 mole of carbon dioxide. The chemistry of the various acids obtained from digitogenic and digitoic acids is quite confused. It should be pointed out that the reasons given by Tschesche for considering oxydigitogenic acid a $\beta$-keto acid rather than an $\alpha$-keto acid, as preferred by Windaus and Willerding,[18] depended on the 6-position of the hydroxyl group in digitogenin. The work of Bistrzycki and Siemiradzki[25] cited by Tschesche[10] is not relevant since oxydigitogenic acid loses carbon monoxide by simple heating without treatment with sulfuric acid.

In the case of acid "A" of Windaus and Willerding there is not only a difference of opinion between Windaus and Tschesche about the structure of the acid but even about the experimental facts. Indeed, it appears that only the following facts are known with any certainty about digitogenin. Two of the nuclear hydroxyl groups are at C–2 and C–3, the side-chain is identical to that of tigogenin and chlorogenin and the third hydroxyl group is adjacent to an asymmetric carbon atom and it is not at C–6. In addition the configuration at C–5 is *allo* since digitogenic acid has been converted to gitogenic acid and the side-chain is of the iso-configuration. The fact that digitogenin triacetate has been oxidized to the triacetate of a $C_{22}$ lactone (V) by Marker and Rohrmann[26] indicates that the third hydroxyl




V

group is not in the side-chain. Consequently, only the positions 6, 7, 11 and 15 seem probable. We have eliminated the 6 position in this paper. Position 11 seems improbable because digitogenic and digitoic acids readily form semicarbazones[27] and digitogenin forms a triacetate without difficulty. The oxidation of a carbonyl group at C–7 leads to the formation of dicarboxylic acids. Thus cholestane-7-one was oxidized to cholestane-6,7-diacid[28] and 7-keto-cholanic acid to thilobilianic acid[29] (cholane-6,7,24-triacid). A hydroxyl group at C–7 is also improbable in digitogenin because it is not dehydrated by distillation over potassium bisulfate. Simple distillation of 3,7-dihydroxycholanic acid converts it to the diene acid.[30]

It would be premature to locate definitely the hydroxyl group at C–15, but there are indications that this may be the case. Digitoic acid and digi-

(20) Windaus and Bohne, *Ann.*, **442**, 7 (1925).
(21) Marker and Turner, THIS JOURNAL, **63**, 767 (1941).
(22) Windaus and Bohne, *Ann.*, **433**, 278 (1923).
(23) Jacobs and Simpson, *J. Biol. Chem.*, **105**, 501 (1934).
(24) Fieser and Jacobsen, THIS JOURNAL, **60**, 28 (1938).
(25) Bistrzycki and Siemiradzki, *Ber.*, **41**, 1665 (1908).
(26) Marker and Rohrmann, THIS JOURNAL, **61**, 2724 (1939).
(27) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 817 (1937).
(28) Stange, *Z. physiol. Chem.*, **218**, 74 (1933).
(29) Wieland and Dane, *ibid.*, **210**, 268 (1932).
(30) Wieland and Reverey, *ibid.*, **140**, 186 (1924).

togenic acid would be isomeric at C–14 or at C–16. The Wolff–Kishner reduction to gitogenic acid does not exclude this. The Wolff–Kishner reduction of 6-keto-Staden acid gives both acids isomeric at C–5 although the original acid is of the stable *allo*-configuration.[7,11] Dimroth[31] has recently shown the possibility of inversion of configuration with a carbonyl group adjacent to C–14.

There are some indications that digitogenin differs from the other sapogenins in the reactions of its side-chain. This could be conditioned by a hydroxyl group at C–15. Thus we have found that dihydro-digitogenin and bromodigitogenin are formed only with difficulty. Tetrahydrodigitogenin could not be made since digitogenin was recovered unchanged when submitted to the Clemmensen reduction for twenty-four hours. This is in contrast to the behavior of the other sapogenins which give tetrahydrosapogenins readily.[21,32] Digitogenin was also largely recovered unchanged when heated with acetic anhydride in a bomb-tube under conditions which give pseudosapogenins readily.[33]

Another fact which might indicate that the hydroxyl group may be in the neighborhood of the side-chain is that Windaus[18] oxidized pure digitogenic acid to $\alpha$-methylglutaric acid without detecting a trace of methylsuccinic acid. Using a similar vigorous oxidation method with digitogenin triacetate in which the hydroxyl groups are protected, we have obtained methylsuccinic acid as the major product of the oxidation. Methylsuccinic acid was obtained by Kiliani[34,18] by the vigorous oxidation of impure digitogenic acid, and, as Windaus has pointed out,[18] this probably arises from the gitogenic acid which was present as the impurity. If the hydroxyl group is at C–15 these facts can be explained readily.

Fieser,[35] in his defense of the Tschesche–Hagedorn formulation of the side-chain, has attempted to trace the formation of $\alpha$-methylglutaric acid in the Windaus oxidation to an extensive degradation of the nucleus. This seems most improbable and his citation of the case of Wieland's 3,12-diketo-nor-cholane-3,24-diacid[36] does not apply because the splitting of this acid is probably due to the carbonyl group at C–12.

We thank Parke, Davis and Company for their help.

## Experimental Part

**6-Keto-cholestane-2,3-diacid.**—To a solution of 50 g. of 3,6-dihydroxycholestane in 1500 cc. of acetic acid was added a solution of 50 g. of chromic anhydride in 500 cc. of 90% acetic acid during a period of ninety minutes. It was stirred for an additional hour at 70° on a steam-bath. Water was added and the product was extracted with ether. The ethereal solution was washed free of acetic acid and extracted with alkali. The alkaline extract was acidified with hydrochloric acid and the acid which precipitated was filtered and washed. It was crystallized from glacial acetic acid, m. p. 228–230° with bubbling.

*Anal.* Calcd. for $C_{27}H_{44}O_5$: C, 72.5; H, 9.9. Found: C, 72.3; H, 9.8.

**Clemmensen Reduction of 6-Keto-cholestane-2,3-diacid.**—To a refluxing solution of 2 g. of 6-keto-cholestane-2,3-diacid in 100 cc. of ethyl alcohol mixed with 50 g. of amalgamated zinc (20 mesh) was added 5 cc. of concentrated hydrochloric acid every fifteen minutes for four hours. Water was added and the product was extracted with ether. The ether was washed with water and the solvent was removed. The residue was hydrolyzed by refluxing with alcoholic potassium hydroxide, acidified with hydrochloric acid, and extracted with ether. The solvent was removed and the residue was recrystallized from glacial acetic acid, m. p. 194–195°, and gave no depression in mixed melting point with an authentic sample of cholestane-2,3-diacid.

*Anal.* Calcd. for $C_{27}H_{46}O_4$: C, 74.9; H, 10.7. Found: C, 74.8; H, 10.7.

**Catalytic Reduction of 6-Keto-cholestane-2,3-diacid.**—A mixture of 2 g. of 6-keto-cholestane-2,3-diacid, 500 mg. of platinum oxide catalyst and 100 cc. of acetic acid was shaken for two hours with hydrogen at 40 pounds pressure and room temperature. The catalyst was filtered and the solvent was removed *in vacuo*. The residue was crystallized from 70% acetic acid and then from methyl alcohol, in which it is quite insoluble, m. p. 188–190°.

*Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.7; H, 10.2; neut. equiv. (for one carboxyl), 432.4. Found: C, 74.9; H, 10.4; neut. equiv. cold, 435.8.

**Distillation of Chlorogenin over Potassium Bisulfate.**—A mixture of 1 g. of naturally occurring chlorogenin and 5.5 g. of powdered potassium bisulfate was heated in a high vacuum at 200–210° until no more product sublimed. The sublimate was crystallized from acetone as white needles, m. p. 166–168°. When mixed with 3,5-dehydrodesoxytigogenin, prepared from diosgenin, there was no depression in melting point.

*Anal.* Calcd. for $C_{27}H_{40}O_2$: C, 81.7; H, 10.2. Found: C, 81.6; H, 10.4.

**Catalytic Reduction of Digitogenic and Digitoic Acids.**—The digitogenic acid was prepared by the oxidation of 8 g. of digitogenin at room temperature with chromic anhydride in acetic acid. The digitogenin used in these experiments

(31) Dimroth and Jonsson, *Ber.*, **74**, 520 (1941).
(32) Marker and Rohrmann, THIS JOURNAL, **61**, 746 (1939).
(33) Marker and Rohrmann, *ibid.*, **62**, 518 (1940); **62**, 898 (1940).
(34) Kiliani, *Ber.*, **49**, 702 (1916).
(35) Fieser, "Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 2nd. ed., p. 326.
(36) Wieland and Vocke, *Z. physiol. Chem.*, **177**, 68 (1928).

was purified by crystallization of the triacetate. The digitogenic acid can be best purified by crystallization from ether, giving a product melting at 170–172°. The digitoic acid was prepared by isomerization of digitogenic acid with alkali and was crystallized from dilute acetic acid. It is very soluble in comparison with digitogenic acid.

A mixture of 500 mg. of digitogenic acid, 500 mg. of platinum oxide catalyst and 100 cc. of methyl alcohol was shaken with hydrogen at 40 pounds pressure and room temperature for one hour. The solution was filtered and the solvent was distilled *in vacuo*. The residue was very soluble in methanol, acetic acid and ethyl acetate. It was quite insoluble in ether and pentane. It was crystallized by dissolving in a few drops of methanol and adding ether, m. p. 285–290° dec. Reduction in acetic acid gave the same product. Reduction of digitoic acid also gave the same product.

*Anal.* Calcd. for $C_{27}H_{42}O_7$: C, 67.8; H, 8.8; neut. equiv. (2 acid groups), 239. Found: C, 67.9; H, 8.9; neut. equiv. cold, 243.

**Oxidation of 6-Keto-tigogenone.**—The 6-keto-tigogenone was prepared by the oxidation of diosgenin with chromic acid, followed by boiling the oxidation product with zinc dust and water. It melted at 239–241° when crystallized from ether and gave no depression when mixed with chlorogenone obtained by the oxidation of naturally occurring chlorogenin.

To a solution of 9 g. of 6-keto-tigogenone in 400 cc. of acetic acid at room temperature was added a solution of 5.0 g. of chromic anhydride in 5 cc. of water and 25 cc. of acetic acid, keeping the temperature below 30°. It was allowed to stand at room temperature for twenty-two hours, diluted with water and extracted with ether. The ether was washed with water, followed with alkali. The alkaline extract was acidified and extracted with ether. The solvent was removed and the residue was crystallized from aqueous acetic acid, followed by crystallization from glacial acetic acid, m. p. 230° with bubbling. When mixed with chlorogenonic acid prepared by the oxidation of natural chlorogenin there was no depression in melting point.

The acid was prepared in better yield by the oxidation of 6-keto-tigogenone with Kiliani's chromic anhydride–sulfuric acid–acetic acid mixture. This product melted at 231–234° with bubbling and gave no depression in melting point when mixed with a sample of the acid prepared from naturally occurring chlorogenin.

When crystallized from ether it gave a product melting at 232–234°, whereas when digitogenic acid is crystallized from ether it melts at 170–172°. It is stable to alkali as would be expected from the cholestane configuration at C–5. When mixed with digitoic acid (crystallized from dilute acetic acid) it shrunk at 172° and ran at 210°. The acid crystallized with one mole of acetic acid of crystallization.

*Anal.* Calcd. for $C_{27}H_{46}O_7 \cdot C_2H_4O_2$: C, 64.9; H, 8.3. Found: C, 64.7; H, 8.5.

When treated with diazomethane it gave a dimethyl ester which melted at 156–159° when crystallized from ligroin and gave no depression in melting point when mixed with a sample of the ester prepared from natural chlorogenin.

*Anal.* Calcd. for $C_{29}H_{44}O_7$: C, 69.0; H, 8.8. Found: C, 69.3; H, 8.9.

**Oxidation of Digitogenin Triacetate.**—To a solution of 10 g. of digitogenin triacetate in 300 cc. of glacial acetic acid was added a solution of 15 g. of chromic anhydride in 100 cc. of 80% acetic acid. The product was heated on a steam-bath for ninety minutes, cooled and a small amount of water was added. The product was well extracted with ether and the total solvent was removed by vacuum distillation on a steam-bath. The residue was dissolved in ether and the acid fraction was removed by shaking with a small amount of 10% alkali. The neutral fraction upon evaporation of the ether crystallized. It was very insoluble in ether and was crystallized from acetone and from ether, m. p. 282–284° and gave no depression with an authentic sample of digitogenin lactone triacetate.

The alkaline layer was acidified and extracted ten times with a liberal amount of ether. The solvent was removed and the residue was sublimed in a high vacuum at 100°. The sublimate was crystallized from ether–pentane and from chloroform, m. p. 105–109°. Mixed with α-methylglutaric acid it melted at 55–62°.

*Anal.* Calcd. for $C_5H_8O_4$: C, 45.4; H, 6.1; neut. equiv., 66. Found: C, 45.9; H, 6.3; neut. equiv., 68.

**Other Reactions of Digitogenin.**—Digitogenin is recovered unchanged after four days of boiling with strong alcoholic hydrogen chloride mixture, indicating that it has the iso-configuration.

The greater portion of digitogenin is recovered unchanged when treated with amalgamated zinc and alcoholic hydrochloric acid even for twenty-four hours of continuous addition. The other sapogenins are converted in high yields into the tetrahydrosapogenins with three to six hours of similar treatment.

The greater part of digitogenin is unchanged upon treatment with acetic anhydride in a bomb tube at 200° for ten hours. The other sapogenins are converted almost quantitatively by this treatment into the pseudosapogenins.

Sublimation of digitogenin with potassium bisulfate at 210–220° gave only recovered digitogenin and no apparent dehydration.

## Summary

Evidence has been presented indicating that there is no hydroxyl group at C–6 in digitogenin.

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