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

Sterols. XCII. The Preparation of Neotigogenin from Sarsasapogenin

BY RUSSELL E. MARKER AND EWALD ROHRMANN

The fact that tigogenin,[1,2,3] chlorogenin,[4] gitogenin[3,5] and digitogenin[3,5] show no noticeable tendency to react with boiling aqueous ethanolic hydrochloric acid indicates that the side chains of these sapogenins differ in configuration from that of sarsasapogenin which by similar treatment is isomerized to isosarsasapogenin[6] (smilagenin[7]).

We have now obtained substantiating evidence which conclusively shows that tigogenin differs from sarsasapogenin not only in its configuration at C-5 but also in the configuration of the side chain. Sarsasapogenone upon bromination with two moles of bromine yields dibromosarsasapogenone, a substance which has a bromine in the C-4 position as well as one in the side chain.[8] Dibromosarsasapogenone upon treatment with boiling pyridine yields bromo-$\Delta^{4,5}$-dehydro-sarsasapogenone. Reduction of this product with sodium and ethanol and separation of the isomers with digitonin yields a digitonin precipitable product, m. p. 198–200°, which is different from tigogenin and sarsasapogenin but which appears to be identical with neotigogenin, a substance recently obtained by Goodson and Noller[1] from the sapogenins of *Chlorogalum pomeridianum*. Inasmuch as tigogenin, chlorogenin and diosgenin[9] have been converted to the same desoxy compound it follows that these substances all have the same side chain configuration.

These results definitely indicate that the side chain of neotigogenin is of the "sarsasapogenin configuration." It seems most probable that the side chain of tigogenin, chlorogenin and diosgenin is of the "isosarsasapogenin configuration," although it is evident that final proof of this supposition is dependent upon the conversion of isosarsasapogenin to tigogenin. The stability of gitogenin and digitogenin to aqueous ethanolic hydrochloric acid suggests that these substances likewise have the isosarsasapogenin side chain configuration.

(1) Goodson and Noller, THIS JOURNAL, **61**, 2420 (1939).
(2) Marker and Rohrmann, *ibid.*, **61**, 1516 (1939).
(3) Unpublished experiments from this Laboratory.
(4) Marker and Rohrmann, THIS JOURNAL, **61**, 3479 (1939).
(5) Marker and Rohrmann, *ibid.*, **61**, 2724 (1939).
(6) Marker and Rohrmann, *ibid.*, **61**, 846 (1939).
(7) Kon, Soper and Woolman, *J. Chem. Soc.*, 1201 (1939).
(8) Marker and Rohrmann, THIS JOURNAL, **61**, 1921 (1939).
(9) Tsukamoto, Neno and Ohta, *J. Pharm. Soc., Japan*, **57**, 9 (1937)

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Experimental Part

Treatment of Dibromosarsasapogenone with Pyridine.—A solution of 5 g. of dibromosarsasapogenone[8] in 50 cc. of dry pyridine was refluxed for eight hours. Some crystalline material had separated at the end of this time. This was filtered, washed with water and dried to give small white crystals, m. p. 235° dec. The product is probably a pyridinium salt.

Anal. Calcd. for $C_{32}H_{45}O_3NBr_2$: C, 59.0; H, 7.0. Found: C, 58.6; H, 7.3.

The filtrate from the above was diluted with aqueous sulfuric acid and the precipitated solid taken up in ether, treated with Norite and crystallized from acetone to give small compact white crystals, m. p. 185–188° dec. This is bromo-$\Delta^{4,5}$-dehydrosarsasapogenone, yield 2.2 g.

Anal. Calcd. for $C_{27}H_{39}O_3Br$: C, 66.0; H, 8.0. Found: C, 66.2; H, 8.1.

Reduction of Bromo-$\Delta^{4,5}$-dehydrosarsasapogenone with Sodium and Ethanol.—To a boiling solution of 2 g. of bromo-$\Delta^{4,5}$-dehydrosarsasapogenone in 400 cc. of absolute ethanol was added 17 g. of sodium over a period of one hour. Water was added and the precipitated solid taken up in ether, washed well with water and the ether evaporated. A precipitate formed when a solution of the residual sirup was treated with digitonin in 80% ethanol. The insoluble digitonide was decomposed with pyridine in the usual manner. The product was dissolved in methanol and treated with norite. It crystallized from methanol as small white crystals, m. p. 198–200°; yield, 600 mg. A mixture with tigogenin, m. p. 204–206°, melted at 179–192° and a mixture with a sarsasapogenin, m. p. 199–201°, melted at 160–170°. It gave no depression with a sample of neotigogenin, m. p. 199–201°, isolated from *Chlorogalum pomeridianum*.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 77.7; H, 10.6.

With boiling acetic anhydride the product gave an **acetate** which crystallized from methanol as white plates, m. p. 173–175°. This gave no depression with a sample of neotigogenin acetate, m. p. 173–175°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.9; H, 10.0.

Neotigogenone.—When oxidized with chromic anhydride at room temperature in acetic acid solution for thirty minutes, the neotigogenin yielded a product which crystallized from acetone as white plates, m. p. 207–210°. A mixture with tigogenone, m. p. 202–205°, melted at 198–204°. The mixture with neotigogenone, m. p. 208–211°, melted at 207–210°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.2. Found: C, 78.5; H, 10.2.

Summary

The preparation of $\Delta^{4,5}$-bromosarsasapogenone is described.

$\Delta^{4,5}$-Bromosarsasapogenone upon reduction with sodium and ethanol yields neotigogenin, indicating that tigogenin, chlorogenin and diosgenin differ from sarsasapogenin in the side chain configurations.

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Sterols. XCIII. *epi*-Pseudosarsasapogenin, Pseudosarsasapogenone and Pseudochlorogenin

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In continuation of our study of the pseudosapogenins[1,2,3,4] we have extended the acetic anhydride isomerization to *epi*-sarsasapogenin, sarsasapogenone, isosarsasapogenin and chlorogenin. All of these substances are thus isomerized to give pseudo compounds.

As in the case with pseudosarsasapogenin[3] both *epi*-pseudosarsasapogenin and pseudochlorogenin take up a mole of hydrogen in the presence of Adams catalyst to yield dihydropseudosapogenins. Dihydropseudochlorogenin forms a triacetate and *epi*-dihydropseudosarsasapogenin a di-*p*-nitrobenzoate. Pseudosarsasapogenone forms a monosemicarbazone.

As would be expected from the previous results with pseudosarsasapogenin[1,2,3] both *epi*-pseudosarsasapogenin and pseudosarsasapogenone yield $\Delta^{16,17}$-pregnenedione-3,20 on mild oxidation with chromic anhydride.

From the suggested structures of sarsasapogenin[5] and isosarsasapogenin[5] one might expect these substances to yield the same pseudo compound, which was found to be the case. It is a significant fact that dihydrosarsasapogenin[5] was unaffected by treatment with acetic anhydride.

We wish to thank Parke, Davis and Company for their generous help and assistance in the various phases of this work.

Experimental Part[6]

Reduction of Sarsasapogenone with Sodium and Ethanol.—To a boiling solution of 6 g. of sarsasapogenone in 800 cc. of absolute ethanol was added 25 g. of sodium over a period of two hours. Water was added and the precipitated solid taken up in ether, washed with water and crystallized from acetone as white needles, m. p. 205–207°, yield 5.1 g. This gave no depression with a sample of *epi*-sarsasapogenin, m. p. 205–207°.

With hot acetic anhydride the product gave an **acetate** which crystallized from acetone as white plates, m. p. 191–193°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.8; H, 10.0.

***epi*-Pseudosarsasapogenin.**—A mixture of 2 g. of *epi*-sarsasapogenin acetate and 20 cc. of acetic anhydride was heated at 200° for ten hours in a sealed tube. The acetic anhydride was evaporated *in vacuo* and the residue hydrolyzed with hot ethanolic potassium hydroxide. The neutral fraction was crystallized from acetone as white needles, m. p. 211–213°. This gave a large depression with both *epi*-sarsasapogenin, m. p. 205–207°, and sarsasapogenin, m. p. 199–201°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 77.6; H, 10.6.

***epi*-Dihydropseudosarsasapogenin.**—A mixture of 1.5 g. of *epi*-pseudosarsasapogenin, 1 g. of Adams catalyst and 150 cc. of acetic acid was shaken with hydrogen at 3 atm. pressure at room temperature for seventeen hours. After removal of the catalyst, concentration *in vacuo* gave a residue which was saponified for five minutes with ethanolic potassium hydroxide. The product was crystallized from acetone to give white needles, m. p. 135–137°.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.4; H, 11.1. Found: C, 77.3; H, 11.0.

With *p*-nitrobenzoyl chloride in pyridine at 60° the product gave a **di-*p*-nitrobenzoate** which crystallized from acetone as white needles, m. p. 207–209°.

Anal. Calcd. for $C_{41}H_{52}O_9N_2$: C, 68.7; H, 7.3. Found: C, 68.6; H, 7.3.

$\Delta^{16,17}$-Pregnenedione-3,20 from *epi*-Pseudosarsasapogenin.—To a solution of 100 mg. of *epi*-pseudosarsasapogenin in 10 cc. of acetic acid was added a solution of 300 mg. of chromic anhydride in 8 cc. of 80% acetic acid. After standing at room temperature for one hour, water was added and the precipitate taken up in ether and washed free from acids with a solution of sodium hydroxide. The neutral fraction crystallized from acetone as white

(1) Marker and Rohrmann, THIS JOURNAL, **61**, 3592 (1939).
(2) Marker and Rohrmann, *ibid.*, **62**, 518 (1940).
(3) Marker and Rohrmann, *ibid.*, **62**, 521 (1940).
(4) Marker and Rohrmann, *ibid.*, **62**, 647 940).
(5) Marker and Rohrmann, *ibid.*, **61**, 846 (1939).
(6) Microanalyses by Dr. John R. Adam., Jr., of this Laboratory.