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

Sterols. LIX. Sarsasapogenin Derivatives. Desoxysarsasapogenin

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In a preceding paper[1] we presented evidence of the presence of a ketone spiro acetal grouping in the side chain of sarsasapogenin. We have now extended our study of the more important reactions characteristic of sarsasapogenin to desoxysarsasapogenin.

We have repeated the preparation of desoxysarsasapogenin by the sodium reduction of sarsasapogenyl chloride as described by Simpson and Jacobs,[2] and are in complete agreement both as to the properties of the compounds and the yields reported.

More recently Fieser and Jacobsen[3] reported a method of preparing the desoxy compound involving the Clemmensen reduction of sarsasapogenone in a two-phase system of benzene–alcohol and hydrochloric acid, the over-all yield from sarsasapogenin being about 45%.

We have greatly simplified the procedure of Fieser and Jacobsen[3] by carrying out the Clemmensen reduction in alcoholic solution with unamalgamated zinc. The sparingly soluble desoxy compound separates out during the reaction, thus preventing its reduction to tetrahydrodesoxysarsasapogenin. The method gives over-all yields of desoxysarsasapogenin ranging from 35 to 45%, the great insolubility of the desoxy compound allowing an easy separation from any unchanged ketone.

In order to preclude any possibility that desoxysarsasapogenin might be a desoxy isomerization product resulting from the action of acidic reagents we have prepared desoxysarsasapogenin by the Wolff–Kishner reduction of sarsasapogenone and have found it to be identical with that prepared by the other methods. The yield was about 10%, the main reaction product being sarsasapogenin.

Desoxysarsasapogenin upon reduction with amalgamated zinc in alcoholic solution yielded tetrahydrodesoxysarsasapogenin, the same product being obtained by a similar reduction of sarsasapogenone. Desoxysarsasapogenin upon catalytic hydrogenation in acetic acid yielded dihydrodesoxysarsasapogenin. Desoxysarsasapogenin formed a nicely crystalline bromo derivative. The desoxy compound was oxidized by selenium dioxide but the bromo compound was inert to this reagent.

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Experimental

Desoxysarsasapogenin from Sarsasapogenone.—A solution of 500 mg. of sarsasapogenone in 100 cc. of 95% ethanol was mixed with 20 g. of 20-mesh zinc. The mixture was refluxed for eight hours, during which time 15 cc. of concentrated hydrochloric acid was added in small portions. The mixture became milky shortly after the first addition of hydrochloric acid was made and crystalline material separated out as the reaction proceeded. The mixture was then poured into 300 cc. of water and extracted with ether. The ethereal extract was washed with water, the ether evaporated on the steam-bath. The crystalline residue was crystallized from ethyl acetate to give 250 mg. of white plates, m. p. 214–216°, which gave no depression with desoxysarsasapogenin prepared from sarsasapogenyl chloride.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.9; H, 11.1. Found: C, 80.9; H, 11.0.

When heated in benzene–acetic acid solution with selenium dioxide a red precipitate separated after a few minutes. The reaction was not studied further.

Wolff–Kishner Reduction of Sarsasapogenone.—The semicarbazone of sarsasapogenone was prepared by refluxing a solution of 2 g. of sarsasapogenone in 350 cc. of 95% ethanol with 2 g. of semicarbazide hydrochloride and 2.5 g. of sodium acetate for two hours on the steam-bath. The solution upon dilution with water gave a white solid which was recrystallized from aqueous ethanol to give an ether soluble product, m. p. 180° dec.

Anal. Calcd. for $C_{28}H_{45}O_3N_3$: C, 71.3; H, 9.6. Found: C, 70.9; H, 9.5.

To a solution of 1.2 g. of sodium in 15 cc. of absolute ethanol was added 2 g. of sarsasapogenone semicarbazone. The resulting mixture was heated in a sealed tube at 175–180° for seven hours. The material was washed out with water and extracted with ether. The ethereal extract was washed with water and the residue obtained by evaporation of the ether was crystallized from ethyl acetate to give 200 mg. of white plates, m. p. 216°. This product gave no depression with desoxysarsasapogenin.

The filtrate from the above was concentrated to give white needles of sarsasapogenin, m. p. 198°, which gave no depression with an authentic specimen.

Dihydrodesoxysarsasapogenin.—A mixture of 250 mg. of desoxysarsasapogenin, 100 cc. of glacial acetic acid, and 500 mg. of Adams catalyst was shaken with hydrogen

(1) Marker and Rohrmann, THIS JOURNAL, **61**, 846 (1939).
(2) Simpson and Jacobs, *J. Biol. Chem.*, **110**, 565 (1935).
(3) Fieser and Jacobsen, THIS JOURNAL, **60**, 2761 (1938).

(3 atm.) at 70° for eight hours. The mixture was filtered and the acetic acid was evaporated from the filtrate *in vacuo*. The residual sirup was refluxed for fifteen minutes with an excess of alcoholic potassium hydroxide and the solution poured into water. The resulting mixture was extracted with ether and the ethereal extract washed with water. The ether was evaporated on the steam-bath and the residue crystallized from aqueous acetone to give silky white needles, m. p. 109–110°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.5; H, 11.5. Found: C, 80.5; H, 11.5.

The substance gave no evidence of oxidation when heated at 90° with selenium dioxide in acetic acid–benzene solution.

Bromodesoxysarsasapogenin.—To a solution of 100 mg. of desoxysarsasapogenin in 60 cc. of glacial acetic acid acidified with 5 drops of 48% hydrobromic acid was added 0.25 cc. of 1.05 *M* bromine in glacial acetic acid. The bromine was taken up with difficulty and the solution was warmed to about 30°. The solution was poured into water and the precipitate collected and washed with water. The dried material was crystallized from acetone to give white crystals, m. p. 170°.

Anal. Calcd. for $C_{27}H_{43}O_2Br$: C, 67.6; H, 9.0. Found: C, 67.7; H, 9.1.

The substance showed no evidence of oxidation when heated for thirty minutes with selenium dioxide in benzene–acetic acid solution.

Clemmensen Reduction of Desoxysarsasapogenin to Tetrahydrodesoxysarsasapogenin.—A solution of 150 mg. of desoxysarsasapogenin in 50 cc. of 95% ethanol was mixed with 20 g. of amalgamated zinc. To this boiling mixture was added 10 cc. of concentrated hydrochloric acid over a period of nine hours. The solution was poured into water and the mixture extracted with ether. The ethereal extract was washed with water and the ether evaporated on the steam-bath. The sirupy residue was crystallized from ether–hexane to give silky white needles, m. p. 101°. The material gave a depression with dihydrosarsasapogenin.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.1; H, 12.0. Found: C, 80.0; H, 11.5.

A similar reduction of 500 mg. of sarsasapogenone in 100 cc. of 95% ethanol gave white needles, m. p. 100°. This gave no depression with that obtained from desoxysarsasapogenin.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.1; H, 12.0. Found: C, 79.8; H, 11.9.

The filtrate from this yielded 20 mg. of heavy white crystals, m. p. 118°. This gave no appreciable depression with the material, m. p. 100°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.1; H, 12.0. Found: C, 80.3; H, 11.8.

It is possible that this higher melting substance may be either a polymorphous form of the lower melting form or it may differ in configuration from the lower form.

Summary

The method of preparing desoxysarsasapogenin has been simplified and the reactions characteristic of sarsasapogenin have been extended to the desoxy compound.

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Sterols. LX. Oxidation Products of Sarsasapogenin. Structure of C_{22} Keto Acid

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In studying the chromic anhydride oxidation products of sarsasapogenin we have obtained in addition to the C_{22} lactone of Farmer and Kon[1] and the C_{27} acid and C_{27} neutral product of Fieser and Jacobsen,[2] a keto acid of the composition $C_{22}H_{34}O_4$. This substance appears to be of some importance in further elucidating the structure of the sapogenin side chain.

Sarsasapogenin acetate was oxidized at 60° with chromic anhydride as described by Fieser and Jacobsen[2] and the C_{22} acid obtained from the hydrolyzed acidic fraction after removal of most of the sarsasapogenoic acid. The yield of acid obtained under these conditions is approximately 1–2% although slightly better yields were obtained when the oxidation was carried out at 80°. The acid forms a semicarbazone readily.

The acid upon catalytic hydrogenation in neutral medium with Adams catalyst yielded largely a neutral product, m. p. 197–198°, which was identical with the C_{22} lactone (II) first obtained by Farmer and Kon[1] by the direct oxidation of sarsasapogenin acetate with chromic anhydride. In the same hydrogenation a lactone, m. p. 186–188°, was obtained which appears to be a polymorphous form of the lactone, as it gives no depression with the higher melting form. When the hydrogenation was carried out in acidic ethanol, only the lower melting form was obtained in good yield. No appreciable acidic fraction was obtained in either case.

Upon reduction with sodium and ethanol the

(1) Farmer and Kon, *J. Chem. Soc.*, 414 (1937).

(2) Fieser and Jacobsen, THIS JOURNAL, **60**, 28, 2753 (1938).