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

Sterols. LXXXVIII. Pregnanediols from Sarsasapogenin

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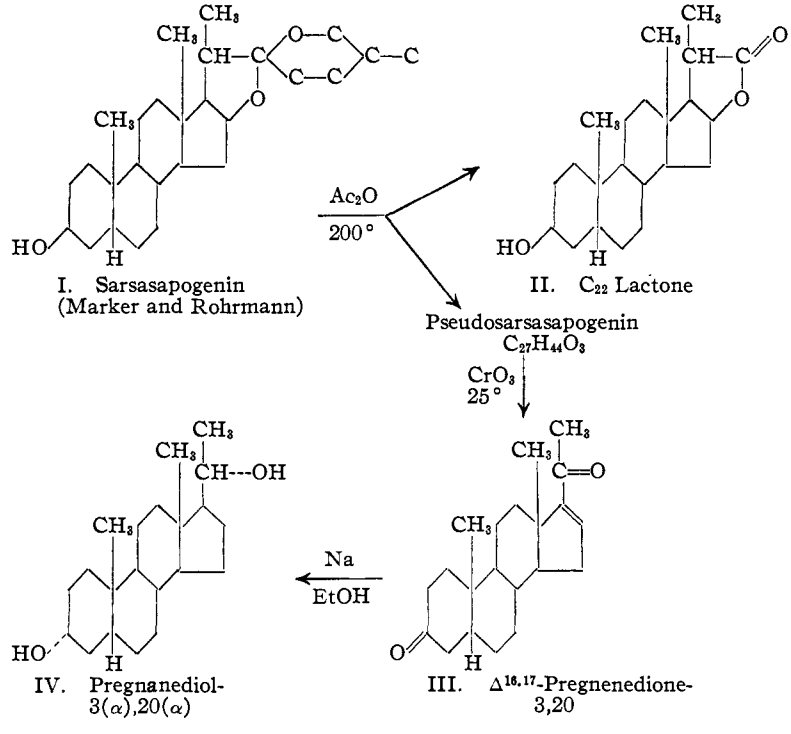
In a recent communication[1] we reported the successful conversion of sarsasapogenin to pregnanediol-3(α),20(α). The fact that this transformation can be accomplished by simple reactions in good yields makes sarsasapogenin one of the cheapest and most practical sources of pregnane derivatives from which it is possible to prepare progesterone, testosterone and desoxycorticosterone.

Sarsasapogenin (I) reacts with acetic anhydride at 200° to yield an isomeric substance, which because of its superficial resemblance to the sapogenins has been designated as pseudosarsasapogenin. While this substance undergoes many interesting reactions, the work herein reported is concerned with the preparation of the product, its oxidation to $\Delta^{16,17}$-pregnenedione-3,20 and a study of the reduction products of this latter substance.



I. Sarsasapogenin (Marker and Rohrmann)

II. C_{22} Lactone

Pseudosarsasapogenin $C_{27}H_{44}O_3$

III. $\Delta^{16,17}$-Pregnenedione-3,20

IV. Pregnanediol-3(α),20(α)

The isomerization of sarsasapogenin to pseudosarsasapogenin is also effected by acid anhydrides other than acetic anhydride. Propionic anhydride is quite effective while succinic anhydride is less effective and with phthalic anhydride no crystalline products were isolated. In the case of *n*-butyric anhydride (b. p. 198°) the isomerization was effected by simple refluxing. It is of interest that acidic products were encountered in all of these isomerization reactions. These were investigated in the acetic anhydride reaction and found to consist largely of the C_{22} hydroxy lactone (II) of sarsasapogenin.[2,3] Pseudosarsasapogenin forms a di-*p*-nitrobenzoate, indicating the presence of two hydroxyl groups.

In attempting to convert pseudosarsasapogenin to pseudosarsasapogenone by mild oxidation with chromic anhydride, an unsaturated diketone of the composition $C_{21}H_{30}O_2$, m. p. 202°, was obtained in good yields. This substance is unquestionably $\Delta^{16,17}$-pregnenedione-3,20 (III), a substance first reported by Masch[4] and referred to briefly by Butenandt, *et al.*,[5] in a recent publication concerning $\Delta^{16,17}$-*allo*-pregnenedione-3,20. The product was reported to melt at 196° and was obtained in a study of 17-bromopregnanol-3-one-20.

That our product is $\Delta^{16,17}$-pregnenedione-3,20 is shown by the fact that on reduction with sodium and ethanol it yields pregnanediol-3(α),20-(α) (IV) identical with that isolated from various urines. This reduction indicates that the ethylenic bond is conjugated with a carbonyl group. Reduction of $\Delta^{16,17}$-pregnenedione-3,20 with palladium catalyst gave pregnanedione-3,20 as would be anticipated. Catalytic hydrogenation of the unsaturated diketone with Adams catalyst in neutral medium gave pregnanediol-3(β),20(β),[6]

(1) Marker and Rohrmann, THIS JOURNAL, **61**, 3592 (1939).

(2) Askew, Farmer and Kon, *J. Chem. Soc.*, 1399 (1936).

(3) Marker and Rohrmann, THIS JOURNAL, **62**, 76 (1940).

(4) Masch, Dissertation, Danzig, 1938.

(5) Butenandt, Mamoli and Heusner, *Ber.*, **72**, 1614 (1939).

(6) Marker, Kamm and Jones, THIS JOURNAL, **59**, 1595 (1937).

pregnanediol-3(β),20(α)[7] and pregnanediol-3(α),20(β). There appear to be appreciable amounts of other products formed in these reductions but we have not yet succeeded in isolating any product other than those of the regular pregnane series. One might expect to obtain some isopregnane compounds (*i. e.*, isomerized at C-17)[8] in these reactions.

The transformation of sarsasapogenin to $\Delta^{16,17}$-pregnenedione-3,20 definitely clears up several important points regarding the nuclear structure of sarsasapogenin, namely, the presence of a C-21 methyl group and the presence of an hydroxyl group at C-3. Inasmuch as the sarsasapogenin lactone (II) has been converted into tigogenin lactone,[9] it follows that the nuclear structure of tigogenin differs only in the configuration at C-5.

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

Experimental Part[10]

Reaction of Sarsasapogenin Acetate with Acid Anhydrides. (a) Acetic and Propionic Anhydrides.—A mixture of 8 g. of sarsasapogenin acetate and 30 cc. of acetic anhydride was heated in a bomb tube at 195–200° for ten hours. The acetic anhydride was evaporated *in vacuo* and the residual sirup hydrolyzed with ethanolic potassium hydroxide. The alkaline solution was diluted with water and the precipitated solid taken up in ether. The ether was evaporated to a small volume and the white crystals collected, washed with ether and recrystallized from ethyl acetate to give white needles, m. p. 171–173°; yield 70%.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6; mol. wt., 416. Found: C, 77.8, 77.9; H, 10.6, 10.5; mol. wt. (Rast), 440.

The product gave a **di-*p*-nitrobenzoate** which crystallized rather poorly from acetone as pale yellow crystals, m. p. 156.5–159°.

Anal. Calcd. for $C_{41}H_{50}O_8N_2$: C, 68.9; H, 7.1. Found: C, 68.7, 68.9; H, 6.9, 7.0.

Attempts to prepare a crystalline acetate with boiling acetic anhydride were unsuccessful.

The aqueous alkaline layer from the above hydrolysis was acidified with hydrochloric acid and the mixture extracted with ether. The ethereal extract was washed with water, the ether evaporated and the residual material sublimed in high vacuum at 150–200°. The sublimate was crystallized from ether–pentane to give white needles, m. p. 199–201°. This gave no depression in melting point with an authentic sample of sarsasapogenin lactone, m. p. 199–200°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.9. Found: C, 76.4; H, 9.9.

With boiling acetic anhydride this yielded an **acetate** which was crystallized from ether–pentane as white needles, m. p. 184–185°. This gave no depression in melting point with an authentic sample of sarsasapogenin lactone acetate, m. p. 184.5–185.5°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.15; H, 9.3. Found: C, 74.3; H, 9.4.

When sarsasapogenin acetate was treated with propionic anhydride as described for acetic anhydride, a good yield of pseudosarsasapogenin, m. p. 169–171°, was obtained.

When sarsasapogenin acetate (2 g.) was heated in a bomb tube with glacial acetic acid (20 cc.) at 210° for seven hours the only product which could be isolated crystalline was a small amount of sarsasapogenin (after hydrolysis).

(b) Succinic Anhydride.—A mixture of 2 g. of sarsasapogenin acetate and 12 g. of succinic anhydride was heated in a bomb tube at 195–200° for ten hours. The brown colored solid reaction mixture was refluxed for thirty minutes with an excess of ethanolic potassium hydroxide. The mixture was diluted with water and the precipitated solid taken up in ether. The ether was evaporated and the residual crystalline solid was treated with Norite and crystallized from ethyl acetate–acetone to give white needles, m. p. 169–172°. This gave no depression with the product obtained above, m. p. 171–173° obtained with acetic anhydride. A similar reaction using phthalic anhydride gave only non-crystalline products.

(c) With *n*-Butyric Anhydride.—A solution of 4 g. of sarsasapogenin acetate and 30 cc. of *n*-butyric anhydride was refluxed for eight hours. The *n*-butyric anhydride was evaporated *in vacuo* and the residual sirup hydrolyzed with ethanolic potassium hydroxide. The product was crystallized from ether–acetone as white needles, m. p. 170–173°. This gave no depression with a sample of pseudosarsasapogenin prepared above, m. p. 171–173°.

$\Delta^{16,17}$-Pregnenedione-3,20 from Pseudosarsasapogenin.—To a solution of 1 g. of pseudosarsasapogenin in 30 cc. of acetic acid was added a solution of 1.0 g. of chromic anhydride in 10 cc. of 80% acetic acid. After standing at room temperature for one hour the solution was diluted with water and the precipitate taken up in ether. The ethereal solution was washed with water and 3% sodium hydroxide solution. Evaporation of the ether gave a solid which was crystallized from acetone as large white plates, m. p. 200–202°. This substance is $\Delta^{16,17}$-pregnenedione-3,20. The yield varied from 50 to 70% in different preparations.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.0, 80.1; H, 9.4, 9.6.

With semicarbazide acetate this gave a **semicarbazone** which crystallized from ethanol as white crystals, m. p. 310° dec.

Anal. Calcd. for $C_{23}H_{36}O_2N_6$: C, 64.4; H, 8.5. Found: C, 64.2; H, 8.6.

The acidic fraction from the oxidation gave a product which crystallized from ether–pentane as small white crystals, m. p. 234–237°. This gave no depression with a sample of 3-keto-*etio*-bilianic acid, m. p. 235–238°.

(7) Marker, Kamm, Wittle, Oakwood, Lawson and Laucius, THIS JOURNAL, **59**, 2291 (1937).

(8) Butenandt and Mamoli, *Ber.*, **68**, 1847 (1935).

(9) Marker and Rohrmann, THIS JOURNAL, **61**, 1291 (1939).

(10) Microanalyses by Dr. John R. Adams, Jr., of this Laboratory.

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.8; H, 8.4. Found: C, 67.5; H, 8.5.

Reduction of $\Delta^{16,17}$-Pregnenedione-3,20. (a) **With Sodium and Ethanol.**—To a boiling solution of 300 mg. of $\Delta^{16,17}$-pregnenedione-3,20 in 100 cc. of absolute ethanol was added 7 g. of sodium over a period of seventy-five minutes. The solution was diluted with water and the precipitated solid taken up with ether. The ethereal extract was washed well with water and the ether evaporated until crystals began to separate. These were collected, washed with ether and crystallized from acetone as small white crystals, m. p. 236–239°. This gave no depression with an authentic sample of pregnanediol-3(α),20(α), m. p. 237–239°. The yield was 250 mg.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.7; H, 11.3.

With boiling acetic anhydride this gave a **diacetate** which crystallized from methanol as small white plates, m. p. 177–179°. This gave no depression with a sample of the diacetate of pregnanediol-3(α),20(α), m. p. 177–179°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.2; H, 10.0.

(b) **With Adams Catalyst.**—A mixture of 700 mg. of $\Delta^{16,17}$-pregnenedione-3,20, 120 cc. of absolute ethanol and 400 mg. of Adams catalyst was shaken with hydrogen at 3 atm. pressure at room temperature for fifteen hours. The catalyst was removed and the filtrate evaporated to a volume of about 20 cc. To this hot solution was added a hot solution of 1 g. of digitonin in 50 cc. of 90% ethanol. After standing for two hours at room temperature the digitonide was filtered, washed and dried.

The filtrate containing the *epi*-fraction was evaporated *in vacuo* to a volume of about 10 cc. After the addition of 150 cc. of ether the mixture was filtered and the filtrate evaporated. The residue was crystallized from ethanol to give small, compact, white crystals, m. p. 232–234°. The mixture with a sample of pregnanediol-3(α),20(β), m. p. 231°, melted at 231–234°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.7; H, 11.3.

With hot acetic anhydride the product yielded a diacetate which crystallized from aqueous ethanol as white needles, m. p. 108–109.5°. This gave no depression with a sample of the diacetate of pregnanediol-3(α),20(β), m. p. 109–110°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 75.4; H, 9.9.

The digitonide (750 mg.) was dissolved in 10 cc. of pyridine and heated at 90° for one hour. The solution was diluted with ether and the turbid mixture filtered. The pyridine was removed from the filtrate with dilute hydrochloric acid and the ether evaporated. After treatment with Norite the product was crystallized from aqueous ethanol as compact white crystals, m. p. 173–175°. This gave no depression with an authentic sample of pregnanediol-3(β),20(β), m. p. 174–176°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.5; H, 11.2.

The first mother liquor from the beta-sterol fraction was freed from solvent and acetylated with boiling acetic anhydride. After repeated crystallization from aqueous ethanol a product was obtained as white needles, m. p 138–140°. This gave no depression with a sample of the diacetate of pregnanediol-3(β),20(α), m. p. 141°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.4; H, 9.9.

(c) **With Palladium.**—A mixture of 250 mg. of $\Delta^{16,17}$-pregnenedione-3,20, 120 cc. of absolute ethanol and 1 g. of palladium–barium sulfate catalyst was shaken with hydrogen at 1 atm. pressure at room temperature for ninety minutes. The catalyst was removed and the solvent distilled *in vacuo*. The residue was crystallized from aqueous ethanol to give compact white crystals, m. p. 117–119°. This gave no depression with an authentic sample of pregnanedione-3,20, m. p. 117.5–119°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.5; H, 10.1.

With semicarbazide acetate in the usual manner the substance gave a **di-semicarbazone** which crystallized from aqueous ethanol as white crystals, m. p. 244° dec.

Anal. Calcd. for $C_{23}H_{40}O_2N_6$: C, 63.8; H, 9.3. Found: C, 63.6; H, 9.2.

Summary

The isomerization of sarsasapogenin to pseudosarsasapogenin with acid anhydrides is described.

Pseudosarsasapogenin on mild oxidation with chromic anhydride is converted into $\Delta^{16,17}$-pregnenedione-3,20.

The reduction products of $\Delta^{16,17}$-pregnenedione-3,20 have been studied.

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