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

Sterols. CXII. Sapogenins. XLI. The Preparation of Trillin and its Conversion to Progesterone

BY RUSSELL E. MARKER AND JOHN KRUEGER

The hydrolysis of the alcoholic extract of the root of *trillium erectum* has been shown to yield pure diosgenin.[1] We have proved the previously reported "trillarigenin" of Grove, Jenkins and Thompson[2] to be a mixture of trillin and diosgenin.[3] Trillin was characterized as a monoglucoside of diosgenin. We have now synthesized an α-tetraacetylglucoside of diosgenin which is identical with the acetate of trillin, isolated from *trillium erectum*. The free glucosides from both sources are identical, and thus trillin must be composed of a molecule of glucose joined through an α-glucosidic linkage to the 3-position of the diosgenin molecule.

We have also prepared the glucoside from sarsasapogenin. Van der Haar[4] has described a glucoside of sarsasapogenin of m. p. 230° which he obtained in less than 2% yield by condensing acetobromoglucose with sarsasapogenin in toluene–quinoline solution. The α-glucosides of diosgenin and sarsasapogenin reported in the present paper were prepared in approximately 50% yields by Zemplén's method.[5]

It has previously been shown[6] that diosgenin upon heating with acetic anhydride is readily converted into a pseudo sapogenin. This is the case of all the steroidal sapogenins studied in this Laboratory. The pseudo sapogenins upon mild oxidation are converted into Δ^{16}-pregnenone-20 derivatives in good yield. Thus it can be seen that diosgenin having a double bond at C-5 would be an ideal starting material for the synthesis of the steroidal hormones. It was thought necessary to protect the double bond in pseudodiosgenin with bromine before carrying out the oxidation. In the bromination a considerable amount of the pseudo sapogenin is attacked in its vulnerable side-chain. In an experiment now reported we find that the oxidation of the side-chain to a Δ^{16}-pregnenone-20 derivative goes so rapidly that even if there is a double bond at C-5 it is unnecessary to protect it before oxidation. Trillin acetate was heated with acetic anhydride at 200° giving a pseudo derivative of the glucoside. This was then oxidized directly with chromic anhydride, *without protecting the double bond*, giving a good yield of $\Delta^{5,16}$-pregnadienol-3-one-20 after acid hydrolysis of the glucosidal group at C-3. Catalytic hydrogenation using palladium–barium sulfate catalyst gave an almost quantitative yield of Δ^{5}-pregnenol-3-one-20, the conjugated bond at C-16 being reduced. The latter compound was readily converted into progesterone.

We wish to thank Parke, Davis and Company for their help.

Experimental Part

Trillin Tetraacetate.—A mixture of 1 g. of diosgenin, 1.3 g. of bromoacetylglucose, and 0.5 g. of mercuric acetate in 12 cc. of dry benzene was refluxed for two hours. The solution was evaporated *in vacuo* and the oily residue was dissolved in ether. The ethereal solution was concentrated to a small volume and chilled. The crystalline precipitate which appeared was filtered off, triturated with ether and crystallized from methanol, m. p. 197°. It showed no depression in melting point when mixed with the acetate of trillin, m. p. 199–200°, isolated from *trillium erectum*.

Anal. Calcd. for $C_{41}H_{60}O_{12}$: C, 66.1; H, 8.2. Found: C, 66.2; H, 8.3.

Hydrolysis with 2% methanolic potassium hydroxide yielded trillin, m. p. 270°, which gave no depression in melting point when mixed with that obtained from *trillium erectum*.

Glucoside of Sarsasapogenin.—The tetraacetate was prepared by the above procedure from sarsasapogenin and bromoacetylglucose. The product was crystallized from ether and from ethanol to a constant melting point of 227°; yield 600 mg. from 1 g. of sarsasapogenin.

Anal. Calcd. for $C_{41}H_{62}O_{12}$: C, 65.9; H, 8.4. Found: C, 66.2; H, 8.3.

The tetraacetyl glucoside was hydrolyzed with 2% methanolic potassium hydroxide to yield a glucoside of m. p. 245°.

Anal. Calcd. for $C_{33}H_{54}O_8 \cdot H_2O$: C, 66.4; H, 9.4. Found: C, 66.3; H, 9.1.

$\Delta^{5,16}$-Pregnadienol-3-one-20 from Trillin Acetate.—A mixture of 5.2 g. of trillin tetraacetate and 15 cc. of acetic anhydride was heated in a bomb tube for ten hours at 200°. Attempts were made to crystallize a portion of this product after hydrolysis with alkali, but an unsatisfactory product was obtained.

(1) Marker, Turner and Ulshafer, THIS JOURNAL, **62**, 2542 (1940).

(2) Grove, Jenkins and Thompson, *J. Am. Pharm. Assoc.*, **27**, 457 (1938).

(3) Marker and Krueger, THIS JOURNAL, **62**, 2548 (1940).

(4) A. W. Van der Haar, *Rec. trav. chim.*, **48**, 726 (1929).

(5) Zemplén, *Ber.*, **63**, 2720 (1930); *cf.* also Linstead, THIS JOURNAL, **62**, 1766 (1940).

(6) Marker, Tsukamoto and Turner, *ibid.*, **62**, 2525 (1940).

To a solution of 4 g. of the crude pseudo-trillin acetate in 200 cc. of acetic acid cooled to 15° was added a solution of 1.2 g. of chromic anhydride in 20 cc. of 90% acetic acid. After standing for one hour at 25°, water was added and the product was extracted with ether. The ethereal solution was washed well with water and 3% sodium hydroxide solution. The ether was evaporated leaving a crystalline residue. This was refluxed for ninety minutes with 50 cc. of ethanol containing 5 cc. of concentrated hydrochloric acid. The ketones were removed by Girard reagent and distilled in a high vacuum at 120–140°, and the distillate was crystallized from ether, acetone, and dilute methanol, m. p. 210–212°. When mixed with an authentic sample of $\Delta^{5,16}$-pregnanedienol-3-one-20, m. p. 212–214°, there was no depression in melting point; yield 160 mg. There was considerable material left in the mother liquors.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 79.8; H, 9.7.

Δ^5-Pregnenol-3-one-20.—To a solution of 150 mg. of $\Delta^{5,16}$-pregnadienol-3-one-20 in 50 cc. of ether was added 200 mg. of palladium–barium sulfate catalyst and the mixture was shaken under hydrogen at 15 pounds pressure for ninety minutes. The solution was filtered and the solvent was removed. The product was crystallized from dilute acetone, m. p. 188–190°. When mixed with a sample of Δ^5-pregnenol-3-one-20, m. p. 190°, it gave no depression in melting point. When mixed with *allo*-pregnanol-3-one-20, m. p. 194°, it melted at 156–170°. When mixed with $\Delta^{5,16}$-pregnadienol-3-one-20, it melted at 150–165°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.8; H, 10.2.

Progesterone.—A mixture of 100 mg. of Δ^5-pregnenol-3-one-20 and 100 mg. of platinum black was heated at 250–300° under an atmosphere of carbon dioxide for one hour. The product was then extracted with ether, sublimed in high vacuum and crystallized from dilute acetone, m. p. 120–121°. When mixed with an authentic sample of progesterone, m. p. 120°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 79.8; H, 9.6.

Summary

The glucosides of sarsasapogenin and diosgenin were prepared. The glucoside of diosgenin was identical with that obtained from *trillium erectum*, showing the latter to be a 3-α-glucoside of diosgenin. Trillin was converted to the pseudo derivative, which was oxidized directly without protecting the double bond to give $\Delta^{5,16}$-pregnadienol-3-one-20. The latter compound was reduced catalytically to Δ^5-pregnenol-3-one-20, which in turn was oxidized to progesterone.

STATE COLLEGE, PENNA. RECEIVED JULY 26, 1940

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

Sterols. CXIII. Sapogenins. XLII. The Conversion of the Sapogenins to the Pregnenolones

BY RUSSELL E. MARKER

Treatment of a steroidal sapogenin with acetic anhydride at 200° converts it into a pseudo sapogenin which can be oxidized to a Δ^{16}-pregnenone-20 derivative in good yield. By this method we have prepared Δ^{16}-pregnenol-3(β)-one-20[1] by the oxidation of the diacetate of pseudosarsasapogenin, as well as by the oxidation of the diacetate of dihydropseudosarsasapogenin. In a like manner we have prepared Δ^{16}-*allo*-pregnenol-3(β)-one-20[2] from the diacetate of pseudotigogenin and the diacetate of dihydropseudotigogenin, and have made Δ^{16}-*allo*-pregnenol-3(α)-one-20[3] from pseudo-*epi*-tigogenin and dihydropseudo-*epi*-tigogenin. Of the four possible compounds, Δ^{16}-pregnenol-3-one-20 isomeric at C-3 and C-5 there remained but Δ^{16}-pregnenol-3(α)-one-20 to be prepared. This compound has now been made by the oxidation of the diacetate of pseudo-*epi*-sarsasapogenin and the diacetate of dihydropseudo-*epi*-sarsasapogenin.

Reduction of Δ^{16}-pregnenol-3(α)-one-20 with sodium in alcohol gave pregnanediol-3(α),20(α). This is identical with the pregnanediol obtained from pregnancy urines. Reduction with palladium gave pregnanol-3(α)-one-20, identical with another pregnancy urine product, whereas reduction with platinum oxide catalyst gave pregnanediol-3(α),20(β). Oxidation of the unsaturated hydroxy ketone gave Δ^{16}-pregnenedione-3,20 which is also obtained by the oxidation of pseudosarsasapogenin or dihydropseudosarsasapogenin directly without acetylation.[1]

We had previously obtained Δ^{16}-pregnenol-3(β)-one-20 by the oxidation of acetylated pseudosar-

(1) Marker and Rohrmann, THIS JOURNAL, **62**, 518 (1940).
(2) Marker and Turner, *ibid.*, **62**, 3003 (1940).
(3) Marker, *ibid.*, **62**, 2621 (1940).