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

Sterols. CXLV. 21-Benzal-5-pregnen-3(β)-ol-20-one and Allied Compounds[1]

BY RUSSELL E. MARKER, EUGENE L. WITTLE, ELDON M. JONES AND HARRY M. CROOKS, JR.

We have previously reported[1a] the preparation of the 21-benzal derivatives of pregnan-3(α)-ol-20-one, *allo*-pregnan-3(β)-ol-20-one and pregnan-3(β)-ol-20-one and the conversion of the first two compounds to 3(α)-hydroxy-*etio*-cholanic acid and 3(β)-hydroxy-*etio-allo*-cholanic acid, respectively.

21-Benzal-pregnan-3(β)-ol-20-one[1] has now been converted to 3(β)-hydroxy-*etio*-cholanic acid in 70% yield and 3(α)-hydroxy-*etio-allo*-cholanic acid has been prepared in a similar manner from *allo*-pregnan-3(α)-ol-20-one. 5-Pregnen-3(β)-ol-20-one has also been converted to the 21-benzal derivative in good yield with benzaldehyde and sodium ethylate. Oxidation of the acetate of 21-benzal-5-pregnen-3(β)-ol-20-one with intermediate protection of the 5,6 double bond by bromine gave 3(β)-hydroxy-5-*etio*-cholenic acid.

Homologs of progesterone having alkyl substituents at position 21 have been reported by Wettstein and co-workers,[2] prepared through 5-*etio*-cholenic acid chloride. We have now prepared 21-benzalprogesterone by the Oppenauer oxidation of 21-benzal-5-pregnen-3(β)-ol-20-one and 21-benzyl-progesterone by a similar oxidation preceded by palladium–hydrogen reduction of 21-benzal-5-pregnen-3(β)-ol-20-one.

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Experimental Part

Oxidation of 21-Benzal-pregnan-3(β)-ol-20-one.—A solution of 1.4 g. of chromic anhydride in 25 cc. of 80% acetic acid was added to a solution of 800 mg. of 21-benzal-pregnan-3(β)-ol-20-one acetate in 50 cc. of acetic acid. The solution slowly turned green when heated to 90° on a steam-bath. The solution temperature was maintained at 60–90° for ninety minutes, then poured into water and extracted with ether. The ether extract was washed with water and potassium carbonate solution. The ether was evaporated to dryness and the residue boiled with alcoholic potassium hydroxide for fifteen minutes, cooled, acidified and the free acid extracted with ether, the ether washed free of salts and evaporated to dryness. The residue was crystallized from dilute acetone to give 3(β)-hydroxy-*etio*-cholanic acid; m. p. 229–230°; yield 400 mg.; 70%.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 75.0; H, 10.0 Found: C, 74.8; H, 10.3.

The methyl ester was prepared using diazomethane, crystallized from dilute acetone to m. p. 138–142°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.3. Found: C, 75.0; H, 10.4.

The acetate of the free acid was prepared with acetic anhydride–pyridine; m. p. 188–190°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 73.3; H, 9.6.

3(α)-Hydroxy-*etio-allo*-cholanic Acid from *epi-allo*-Pregnanolone.—A mixture of 1.2 g. of *epi-allo*-pregnanolone, 600 mg. of benzaldehyde and 30 cc. of absolute ethanol was added to the solution of 700 mg. of sodium in 15 cc. of absolute ethanol. The solution was allowed to stand for twenty-four hours and then poured into water. The mixture was extracted with ether, washed with dilute hydrochloric acid and with water and the ether was evaporated. The residue could not be obtained crystalline. The amorphous product was acetylated by boiling with acetic anhydride and a solution of half of the product in 100 cc. of acetic acid was oxidized at 100° for three hours using 2 g. of chromic anhydride in 50 cc. of 90% acetic acid. The acid fraction was isolated as before and boiled with 5% potassium hydroxide for thirty minutes. The free hydroxy acid was crystallized from dilute methanol; m. p. 282–285°.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 75.0; H, 10.0. Found: C, 74.9; H, 10.3.

The acetate was prepared by acetylation in pyridine; m. p. 208–210°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 73.2; H, 9.4.

3(β)-Hydroxy-5-*etio*-cholenic Acid from 5-Pregnen-3(β)-ol-20-one.—A solution of 3 g. of sodium in 90 cc. of absolute ethanol was added to a solution of 5 g. of 5-pregnen-3(β)-ol-20-one acetate and 2.5 g. of freshly distilled benzaldehyde in 125 cc. of absolute ethanol and the mixture was allowed to stand at room temperature for twenty-four hours. Water was added and the product was extracted with ether. The extract was washed with dilute hydrochloric acid and with water and the ether was evaporated. The residue was crystallized from aqueous acetone to m. p. 130–131° (bubbling); yield 4.8 g.

Anal. Calcd. for $C_{28}H_{36}O_2$: C, 83.1; H, 8.9. Found: C, 83.0; H, 8.9.

This compound gave an acetate (acetic anhydride and pyridine), m. p. 180–182°, from aqueous acetone.

Anal. Calcd. for $C_{30}H_{38}O_3$: C, 80.7; H, 8.6. Found: C, 80.4; H, 8.8.

A solution of 0.36 g. of bromine in 25 cc. of chloroform was added with stirring to a solution of 1 g. of 21-benzal-5-pregnen-3(β)-ol-20-one acetate in 50 cc. of chloroform which was cooled in a bath of ice–methanol. The solution was kept cold for the thirty minutes required to add the bromine solution. The chloroform was evaporated *in vacuo* and the residue was dissolved in 200 cc. of acetic acid

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(1a) Marker and Wittle, THIS JOURNAL, **61**, 1329 (1939).

(2) Wettstein, *et al.*, *Helv. Chim. Acta*, **23**, 1367, 1371 (1940).

and heated to 50°. With constant stirring, a solution of 1.5 g. of chromic acid in 75 cc. of 80% acetic acid was added during thirty minutes. The stirring was continued for five hours during which time the temperature was kept at 50°. After addition of 6 g. of zinc dust the solution was heated fifteen minutes on the steam-bath. The mixture was filtered, the filtrate evaporated *in vacuo* and the residue was taken up with ether and water, the ether layer was washed with water, evaporated and the residue boiled with 100 cc. of 2% methanolic potassium hydroxide for thirty minutes. After the addition of water and ether the alkaline layer was separated, acidified, and extracted with ether. Evaporation of the ether gave a residue; m. p. 273–274° after crystallization from dioxane.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.1; H, 9.6.

21-Benzal-progesterone.—A solution of 1 g. of 21-benzal-5-pregnen-3(β)-ol-20-one, 1.5 g. of aluminum *t*-butylate 7 cc. of dry acetone and 40 cc. of dry toluene was refluxed for five hours. The solution was poured into dilute hydrochloric acid and steam distilled vigorously to remove acetone polymers and the amorphous product was then taken up in ether, washed free of salts and the ether evaporated. The residue was crystallized from methanol to m. p. 155–158°.

Anal. Calcd. for $C_{28}H_{34}O_2$: C, 83.5; H, 8.5. Found: C, 83.1; H, 8.2.

21-Benzyl-progesterone.—A mixture of 10 g. of 21-benzal-5-pregnen-3(β)-ol-20-one acetate, 10 g. of 3% palladium-barium sulfate catalyst and 150 cc. of dioxane was shaken with hydrogen at room temperature and 3 atm. for ninety minutes. The catalyst was removed by filtering and the filtrate evaporated *in vacuo*. The residue melted at 128–129° (143–145° two forms) on crystallization from methanol.

Anal. Calcd. for $C_{30}H_{40}O_3$: C, 80.3; H, 9.0. Found: C, 80.6; H, 9.3.

A mixture of 4.5 g. of the above acetate, 4.5 g. of potassium bicarbonate and 300 cc. of 70% methanol was refluxed for three hours. Dilution with water gave a crystalline precipitate which was recrystallized from methanol to m. p. 135–136°; mixed m. p. with starting material 90–108°; 3.7 g.

Anal. Calcd. for $C_{28}H_{38}O_2$: C, 82.7; H, 9.4. Found: C, 82.3; H, 9.6.

A mixture of 1 g. of 21-benzyl-5-pregnen-3(β)-ol-20-one, 1.5 g. of aluminum *t*-butoxide, 5 cc. of dry acetone and 30 cc. of dry toluene was refluxed for five hours. The mixture was worked up in the usual manner and the residue from the ether purified by passing a ligroin solution through a short column of alumina. It was crystallized from ether–ligroin to m. p. 86–88°.

Anal. Calcd. for $C_{28}H_{36}O_2$: C, 83.1; H, 8.9. Found: C, 83.2; H, 9.4.

Summary

1. 3(β)-Hydroxy-*etio*-cholanic acid has been prepared from 21-benzal-pregnan-3(β)-ol-20-one.

2. *allo*-Pregnan-3(α)-ol-20-one has been converted to 21-benzal-*allo*-pregnan-3(α)-ol-20-one and thence to 3(α)-hydroxy-*etio-allo*-cholanic acid.

3. 5-Pregnen-3(β)-ol-20-one has been converted to 21-benzal-5-pregnen-3(β)-ol-20-one which in turn was converted to 3(β)-hydroxy-*etio*-cholenic acid, 21-benzal-progesterone and 21-benzyl-progesterone.

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Sterols. CXLVI. Sapogenins. LX. Some New Sources of Diosgenin

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In two previous papers[1,2] we have reported the isolation of diosgenin from *Trillium erectum* (L.), *Dioscorea villosa* and *Aletris formosa*. The only other source of this sapogenin was *Dioscorea tokora*.[3] The easy conversion of diosgenin to progesterone[4] made necessary the investigation of additional plant sources.

We have extracted the undried ground rhizomes of eight plants listed in the accompanying table by a procedure similar to that used in the isolation of sarsasapogenin.[5] The results and the geographical location of the plants are given in the table. The identity of the diosgenin was established by analysis of the genin and its acetate along with mixed melting point determinations on both.

	Plant	Source	Yield of diosgenin, g. per lb.
1	*Chamaelerium carolinianum*[a]	Statesville, N. C.	0.1
2	*Tofieldia gramnifolia*[a]	Hartsville, S. C.	0.5
3	*Dioscorea quartenata*[a]	Hartsville, S. C.	2.0
4	*Helonias* Root	S. B. Penick and Co.	...
5	*Trillium grandiflora*[a]	Trylon, N. C.	1.0
6	*Trillium sessile*[a]	Trylon, N. C.	1.0
7	*Clintonia borealis*	Southern New Hampshire	0.5
8	*Dioscorea hirticaulis*[a]	South Carolina	2.0

[a] We are grateful for the help of Mr. Budd E. Smith, Botany Department of the University of North Carolina, Chapel Hill, N. C., in the collection of these samples.

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

(2) Marker, *et al.*, *ibid.*, **62**, 2620 (1940).

(3) Tsukamoto, Ueno and Ohta, *J. Pharm. Soc., Japan*, **56**, 135 (1936).

(4) Marker, Tsukamoto and Turner, THIS JOURNAL, **62**, 2525 (1941).

(5) Jacobs and Simpson, *J. Biol. Chem.*, **105**, 501 (1934).