

tetrabromoacetate (VIII) gave 5-pregnen-3( $\beta$ )-ol-20-one acetate (I).

The tetrabromoacetate (VIII) on partial debromination and treatment with potassium hy-

droxide was converted to 3( $\beta$ )-hydroxy-5,17-pregnadienoic acid-21 (XI) which in turn was converted to dehydro-iso-androsterone (V).

STATE COLLEGE, PENNA. RECEIVED JANUARY 19, 1942

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

## Sterols. CXLIV. Some 16-Alkyl-pregnenolones and Progesterones<sup>1</sup>

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Wettstein and co-workers<sup>1a</sup> have recently prepared 5-pregnen-3( $\beta$ )-ol-20-one and progesterone homologs in which the 21-methyl group is replaced by a hydrogen, ethyl, propyl or isohexyl group. Recent work by Whitmore and Pedlow<sup>2</sup> in this Laboratory on the addition of various Grignard reagents to 2-cyclohexenone coupled with the ready availability of 5,16-pregnadien-3( $\beta$ )-ol-20-one from diosgenin has led us to prepare some 16-alkyl homologs of 5-pregnen-3( $\beta$ )-ol-20-one and of progesterone.

Treatment of 5,16-pregnadien-3( $\beta$ )-ol-20-one acetate with excess methyl Grignard reagent gave an approximately 30% yield of 16-methyl-5-pregnen-3( $\beta$ )-ol-20-one (isolated as the semicarbazone) as well as a non-ketonic compound, presumably 5,16-*bis-nor*-choladien-3( $\beta$ ),20-diol, in about 35% yield. Although the acetates of these two products had virtually the same melting point a mixture depressed 15°. Oppenauer oxidation of 16-methyl-5-pregnen-3( $\beta$ )-ol-20-one gave a 60% yield of 16-methyl-progesterone.

When 5,16-pregnadien-3( $\beta$ )-ol-20-one was treated with excess isopropyl Grignard reagent, the sole isolable product was an approximately 40% yield of 16-isopropyl-5-pregnen-3( $\beta$ )-ol-20-one. This compound could not be characterized by a semicarbazone (recovered unchanged from the customary treatment) but upon sodium-ethanol reduction gave a compound that was difficult to purify, melting twenty degrees below the original material and depressing the melting point of the original material below that of either component. Oppenauer oxidation of 16-isopropyl-5-pregnen-3( $\beta$ )-ol-20-one gave a 60% yield of 16-isopropyl-progesterone.

The action of excess *t*-butyl Grignard reagent on 5,16-pregnadien-3( $\beta$ )-ol-20-one gave a 50% yield

of 16-*t*-butyl-5-pregnen-3( $\beta$ )-ol-20-one as the sole isolable product. This compound again would not form a semicarbazone under ordinary conditions but upon sodium-ethanol reduction gave a new compound melting 10° lower which gave a melting point depression with the original material. Oppenauer oxidation of 16-*t*-butyl-5-pregnen-3( $\beta$ )-ol-20-one gave a 60% yield of 16-*t*-butyl-progesterone.

We thank Parke, Davis and Co. for their assistance.

### Experimental Part

**16-Methyl-5-pregnen-3( $\beta$ )-ol-20-one.**—A Grignard reagent was prepared by the standard procedure from 12 g. of magnesium and 70 g. of methyl iodide in 300 cc. of anhydrous ether. A solution of 10 g. of 5,16-pregnadien-3( $\beta$ )-ol-20-one acetate in 250 cc. of dry toluene was added in ten minutes and the resulting suspension boiled until no more ether distilled out at atmospheric pressure. The toluene suspension was allowed to heat on the steam-bath for sixteen hours. The Grignard was decomposed by pouring over ice-ammonium chloride, the toluene diluted with ether and the ether layer separated and washed free of salts. Evaporation of the solvent left a solid which was taken up in 100 cc. of methanol and refluxed for one hour with a solution of 10 g. of semicarbazide acetate in 100 cc. of methanol. The suspension was diluted to 1 liter with water, filtered, and the solid boiled with 500 cc. of ether. The ether suspension was filtered, the filter washed with ether and the powder dried; m. p. 245° (dec.); 3.3 g. 30%.

*Anal.* Calcd. for C<sub>28</sub>H<sub>37</sub>O<sub>2</sub>N<sub>2</sub>: C, 71.3; H, 9.6. Found: C, 71.4; H, 9.7.

The ethereal filtrate was concentrated and crystallized from acetone. No satisfactory crystals were obtained so the material was acetylated (acetic anhydride-pyridine) and the acetate crystallized to m. p. 173-5° from methanol; yield 3.6 g. (35%).

*Anal.* Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>3</sub>: C, 77.4; H, 9.75. Found: C, 76.75; H, 9.6.

The total semicarbazone was hydrolyzed by refluxing for ninety minutes with aqueous alcoholic sulfuric acid and the product crystallized from acetone to m. p. 191-192°; 2.6 g.; mixed m. p. with 5-pregnen-3( $\beta$ )-ol-20-one (191-192°) was 170-175°. From the analytical figures

(1) Original manuscript received June 23, 1941.

(1a) Wettstein, *et al.*, *Helv. Chim. Acta*, **23**, 1367, 1371 (1940).

(2) Whitmore and Pedlow, *THIS JOURNAL*, **63**, 758 (1941).

the substance apparently contained solvent of crystallization not removed by drying at 50°.

*Anal.* Calcd. for  $C_{22}H_{34}O_2$ : C, 80.0; H, 10.4. Found: C, 76.96; H, 9.69.

The compound was acetylated with acetic anhydride-pyridine to give crystals; m. p. 177.5–178.5° from methanol; mixed m. p. with acetate above (173–175°) was 158–165°; with starting material (176°) mixed m. p. was 160–167°.

*Anal.* Calcd. for  $C_{24}H_{36}O_2$ : C, 77.4; H, 9.75. Found: C, 77.0; H, 9.6.

**16-Methyl-progesterone.**—A mixture of 1 g. of 16-methyl-5-pregnen-3( $\beta$ )-ol-20-one, m. p. 191–192°, 1.5 g. of aluminum *t*-butylate, 5 cc. of dry acetone and 30 cc. of dry toluene was refluxed for six hours. The suspension was poured into dilute hydrochloric acid (excess), steam distilled until free of acetone condensation products and the gummy product taken up in ether. The ether was washed free of salts and evaporated to dryness. The residue crystallized from ether to give 610 mg. of m. p. 133–135°.

*Anal.* Calcd. for  $C_{22}H_{32}O_2$ : C, 80.4; H, 9.8. Found: C, 80.2; H, 9.8.

**16-Isopropyl-5-pregnen-3( $\beta$ )-ol-20-one.**—A Grignard reagent was prepared from 8 g. of magnesium and 48 g. of isopropyl bromide in 300 cc. of dry ether. To this was added, over ten minutes, a solution of 8 g. of 5,16-pregnen-3( $\beta$ )-ol-20-one in 250 cc. of dry toluene. Ether was removed by distillation on the steam-bath and the resulting suspension was allowed to heat for eighteen hours on the steam-bath. The Grignard complex was decomposed with ice-ammonium chloride and worked up as in the case of the methyl Grignard. The residue from the ether crystallized nicely from acetone to m. p. 157–158°; 3.8 g. yield.

*Anal.* Calcd. for  $C_{24}H_{38}O_2$ : C, 80.4; H, 10.7. Found: C, 80.4; H, 10.6.

The compound was recovered unchanged when refluxed for ninety minutes with an equal weight of semicarbazide acetate in methanol.

Reduction of the compound by dropping 2 g. of sodium in small pieces into a solution of 0.5 g. of compound in 35 cc. of absolute ethanol gave a difficultly crystalline compound m. p. 130–134°, which depressed to 124–132° when mixed with the starting material.

A 0.5-g. sample of the compound was acetylated with acetic anhydride-pyridine to give 400 mg. crystals; m. p. 131–132°.

*Anal.* Calcd. for  $C_{26}H_{40}O_2$ : C, 77.95; H, 10.1. Found: C, 78.0; H, 10.2.

**16-Isopropyl-progesterone.**—A mixture of 1.0 g. of 16-isopropyl-5-pregnen-3( $\beta$ )-ol-20-one, 1.5 g. of aluminum *t*-butoxide, 5 cc. of dry acetone and 30 cc. of dry toluene was refluxed for four hours. The product was worked up as

for the 16-methylprogesterone. The product crystallized from ether-pentane to give 470 mg. of compound, m. p. 106.5–108°. A further 100 mg., m. p. 98–102°, was obtained from the mother liquors.

*Anal.* Calcd. for  $C_{24}H_{36}O_2$ : C, 80.9; H, 10.2. Found: C, 80.7; H, 10.2.

**16-*t*-Butyl-5-pregnen-3( $\beta$ )-ol-20-one.**—A Grignard reagent was prepared from 12 g. of magnesium and 45 g. of *t*-butyl chloride in 300 cc. of dry ether. A solution of 5 g. of 5,16-pregnen-3( $\beta$ )-ol-20-one in 250 cc. of dry toluene was added in fifteen minutes, as much ether as possible removed by distillation from a steam-bath and the residual suspension heated eight hours on the steam-bath. The complex was decomposed and worked up as in the previous runs. The ether-soluble material crystallized from acetone to give 2.9 g., m. p. 189–192°. The compound was recovered unchanged when refluxed ninety minutes with an equal weight of semicarbazide acetate in methanol.

*Anal.* Calcd. for  $C_{26}H_{40}O_2$ : C, 80.6; H, 10.8. Found: C, 80.6; H, 10.8.

A 0.5-g. sample of the compound was acetylated with acetic anhydride-pyridine to give 350 mg., m. p. 156–158° from methanol.

*Anal.* Calcd. for  $C_{27}H_{42}O_2$ : C, 78.3; H, 10.2. Found: C, 78.0; H, 10.2.

A 0.5-g. sample was dissolved in 30 cc. of absolute ethanol and reduced by the addition of 2 g. of sodium. The product, crystallized from acetone, melted 178–180° and depressed the melting point of the starting material to 163–170°.

*Anal.* Calcd. for  $C_{28}H_{42}O_2$ : C, 80.15; H, 11.3. Found: C, 80.3; H, 11.1.

**16-*t*-Butyl-progesterone.**—A mixture of 1.0 g. of 16-*t*-butyl-5-pregnen-3( $\beta$ )-ol-20-one, 1.5 g. of aluminum *t*-butoxide, 5 cc. of dry acetone and 30 cc. of dry toluene was refluxed for seven hours. The mixture was worked up as in previous oxidations to give 625 mg. of product, m. p. 154–155°, crystallized from ether.

*Anal.* Calcd. for  $C_{28}H_{38}O_2$ : C, 81.0; H, 10.3. Found: C, 81.2; H, 10.3.

### Summary

5,16-Pregnen-3( $\beta$ )-ol-20-one has been converted to 16-methyl-, 16-isopropyl- and 16-*t*-butyl-5-pregnen-3( $\beta$ )-ol-20-one by reaction with the corresponding Grignard reagents.

16-Methyl-, 16-isopropyl- and 16-*t*-butyl-5-pregnen-3( $\beta$ )-ol-20-one have been converted by Oppenauer oxidation to the corresponding progesterone homologs.

STATE COLLEGE, PENNA. RECEIVED JANUARY 17, 1942