

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

Sterols. CXLIII. The Conversion of 5-Pregnen-3(β)-ol-20-one to Dehydro-iso-androsterone*

BY RUSSELL E. MARKER, HARRY M. CROOKS, JR., ELTON M. JONES AND ANTHONY C. SHABICA

It has been shown by Butenandt¹ that the pregnanones on treatment with methylmagnesium iodide and subsequent dehydration are converted to olefins which can be ozonized to the corresponding 17-keto compounds. By this method we have prepared dehydro-iso-androsterone by the ozonolysis of $\Delta^{17-5,6}$ -dibromo-20-methylpregnen-3(β)-ol acetate (IV).

Treatment of 5-pregnen-3(β)-ol-20-one acetate (I, OAc), prepared from diosgenin acetate, with methylmagnesium iodide gave the diol (II). This carbinol on treatment with acetic acid and

the acid fraction obtained from the ozonolysis of (IV).

By treating the dehydration product with bromine in chloroform at -5° , it was possible to preferentially brominate the double bond in the 5,6 position. Subsequent ozonolysis and debromination yielded dehydro-iso-androsterone (V, OH).

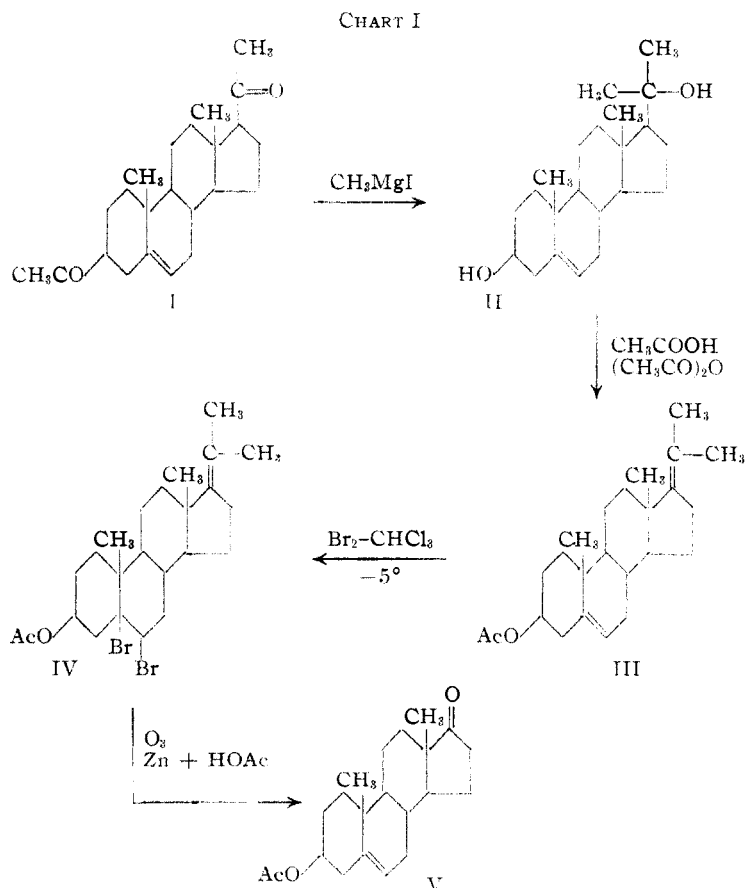
Pregnen-3(β)-ol-20-one on treatment with methylmagnesium iodide, dehydration and ozonolysis gave *etio*-cholan-3(β)-ol-17-one.

These reactions are summarized in chart I.

The work of Marker, *et al.*,² on the conversion of the halo-pregnen-3(β)-ol-20-one compounds to the *etio*-cholan series suggested still another method of converting 5-pregnen-3(β)-ol-20-one to dehydro-iso-androsterone.

If 5-pregnen-3(β)-ol-20-one or its acetate be treated with 3 moles of bromine in acetic acid solution the product in each case is the same, the acetate of 5,6,17,21-tetrabromopregnen-3(β)-ol-20-one (VIII). The esterification of the free alcohol was probably due to the high concentration of hydrogen bromide attained toward the end of the reaction since analogous results were obtained when the free hydroxy ketone was tetrabrominated in propionic acid, the tetrabromopropionate being formed in this case. Reduction of the tetrabromo acetate with iron in acetic acid gave 5-pregnen-3(β)-ol-20-one acetate (I).

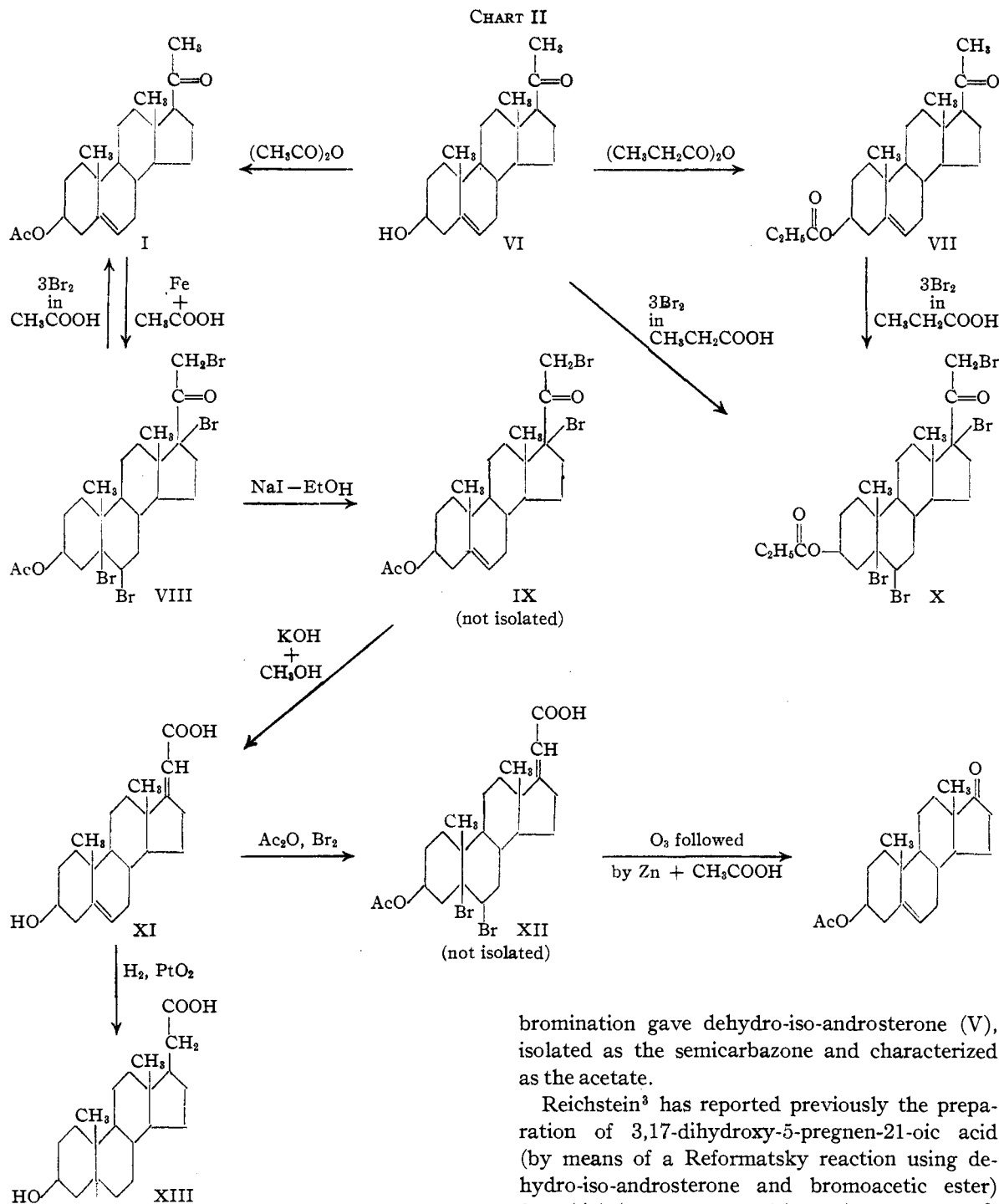
Treatment of the 5,6,17,21-tetrabromopregnen-3(β)-ol-20-one with the theoretical amount of alcoholic sodium iodide to reestablish the 5,6 double bond led to a mixture of products which on treatment with boiling alcoholic potassium hydroxide gave a good yield of a crystalline acid (XI).



acetic anhydride dehydrated, giving a mixture of isomers, from which $\Delta^{5,17}$ -20-methylpregnadien-3(β)-ol acetate (III) was isolated. Isomerization of the double bond into the ring is indicated by

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(1) Butenandt, *Ber.*, **71**, 19 (1938).(2) Marker, *et al.*, *THIS JOURNAL*, **64**, 210, 213 (1942).



This acid precipitated as an insoluble digitonide from a 1% solution of digitonin in alcohol, sublimed *in vacuo* unchanged, and absorbed hydrogen when treated in the presence of Adams catalyst in acetic acid to give compound (XIII). Cautious addition of one mol of bromine to a solution of the acid followed by ozonolysis and subsequent de-

bromination gave dehydro-iso-androsterone (V), isolated as the semicarbazone and characterized as the acetate.

Reichstein³ has reported previously the preparation of 3,17-dihydroxy-5-pregnen-21-oic acid (by means of a Reformatsky reaction using dehydro-iso-androsterone and bromoacetic ester) for which he reports a melting point of 246–247°. Dehydration of the monoacetate of this acid gave a doubly unsaturated, presumably at 5,6 and 17,20, hydroxy acid of melting point 217–218°. Since our product, m. p. 249°, gave dehydro-iso-androsterone, we feel that it actually is 3(β)-hydroxy- $\Delta^{5,17}$ -pregnadien-21-oic acid and the acid

(3) Reichstein. *Helv. Chim. Acta*, **22**, 741 (1939).

obtained by Reichstein by dehydration of the 17-hydroxy acid is possibly a ring unsaturated (16,17) isomer.

The reactions are summarized in Chart II.

We thank Parke, Davis and Company for their assistance.

Experimental Part

Reaction of 5-Pregnen-3(β)-ol-20-one Acetate with Methylmagnesium Iodide.—To a Grignard reagent prepared from 24 g. of magnesium, 150 g. of methyl iodide and 300 cc. of absolute ether was added a solution of 12 g. of 5-pregnen-3(β)-ol-20-one acetate (I) in 500 cc. of absolute ether. After stirring at room temperature for fifteen hours the ether was removed by distillation and the residue refluxed with 250 cc. of dry benzene for an additional twenty-four hours. The mixture was decomposed with ice and acidified with dilute sulfuric acid and the solid, due to its extreme insolubility in ether, was filtered, washed with water and dried. The product was crystallized from methanol-chloroform as white plates; m. p. 194–195°; yield 9.5 g. of pure product, 20-methyl-5-pregnen-3,20-diol (II).

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.5; H, 10.9. Found: C, 79.8; H, 11.0.

Dehydration of the Methyl Grignard Product (II).—A solution of 5.0 g. of the above product (II) and 100 cc. of acetic acid was refluxed for ninety minutes. The acetic acid was distilled *in vacuo* and the residue was refluxed for an additional thirty minutes with 100 cc. of acetic anhydride. The excess acetic anhydride was distilled *in vacuo* and the product was crystallized from acetone as white plates, m. p. 139–141°; yield 500 mg. of pure product. This is the acetate of 20-methyl-5,17-pregnadien-3(β)-ol (III).

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.8; H, 10.2. Found: C, 80.8; H, 10.0.

The mother liquor from the above product (III) was hydrolyzed by refluxing for thirty minutes with a 0.5 *N* methanolic potassium hydroxide solution. The reaction mixture was diluted with water and extracted with ether. The solvent was removed and the residue was crystallized from aqueous methanol as white plates; m. p. 72°. A yield of 2.87 g. of 20-methyl-5,17-pregnadien-3(β)-ol was obtained. Hydrolysis of the pure acetate gave the same product.

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.0; H, 10.9. Found: C, 83.6; H, 10.8.

Dehydro-iso-androsterone Acetate (V).—A solution of 2.87 g. of the above unsaturated compound (III) was refluxed for one hour with 100 cc. of acetic anhydride and the excess acetic anhydride evaporated *in vacuo*. The solid residue was dissolved in 100 cc. of chloroform and 1.461 g. of bromine (1 mol) in 35 cc. of chloroform added at -5° with stirring. The reaction mixture was ozonized for fifteen minutes and the chloroform distilled *in vacuo*. The oily residue was dissolved in 60 cc. of acetic acid and the solution heated for one hour with 3.0 g. of zinc dust. The ethereal extract of the reaction mixture was washed with dilute sodium carbonate solution and water. The solvent

was removed on a steam-bath and the residue treated with semicarbazide acetate. The semicarbazone which formed was crystallized from methanol as a white powder; m. p. 275° dec. A mixed melting point with an authentic sample of the semicarbazone of dehydro-iso-androsterone acetate (V) gave no depression; yield 0.6 g. of pure product.

Anal. Calcd. for $C_{22}H_{32}O_2N_2$: C, 68.2; H, 8.6. Found: C, 68.1; H, 8.6.

The semicarbazone was hydrolyzed by the previously described method and the product was refluxed for one hour with 10 cc. of acetic anhydride. The excess solvent was removed and the residue crystallized from methanol as prisms; m. p. 167°. Mixture with an authentic sample of dehydro-iso-androsterone acetate (V) gave no depression.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 76.3; H, 9.2. Found: C, 76.4; H, 9.2.

Conversion of Pregnan-3(β)-ol-20-one to etio-Cholan-3(β)-ol-17-one.—20-Methylpregnan-3,20-diol, m. p. 170–172°, was obtained by the action of methylmagnesium iodide on pregnan-3(β)-ol-20-one in 92% yield.

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 79.0; H, 11.5. Found: C, 78.6; H, 11.6.

Dehydration of this carbinol gave a 70% yield of 20-methylene-3(β)-ol which crystallized from methanol-ether as prisms; m. p. 133–135°.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.5; H, 10.6. Found: C, 80.5; H, 10.6.

Ozonolysis and hydrolysis of the dehydration product gave a semicarbazone which crystallized from aqueous methanol as a powder; m. p. 244° dec. There was no depression in m. p. when mixed with an authentic sample of the semicarbazone of etio-cholan-3(β)-ol-17-one.

Anal. Calcd. for $C_{20}H_{30}O_2N_2$: C, 69.1; H, 9.6. Found: C, 69.1; H, 9.8.

Hydrolysis of the semicarbazone gave a product which crystallized from pentane; m. p. 115–117°. This was the low melting form of etio-cholan-3(β)-ol-17-one.

5,6,17,21-Tetrabromopregnan-3(β)-ol-20-one Acetate (VIII).—To a solution of 10 g. of 5-pregnen-3(β)-ol-20-one acetate (I) in 200 cc. of acetic acid was added 28.5 cc. of a molar solution of bromine in acetic acid. After the addition of a few drops of 48% hydrobromic acid, 2 mols more, 57 cc., of the bromine solution was added. Solid material started precipitating upon addition of the last mol of bromine, and heating to 40° was necessary to cause complete reaction. The mixture was allowed to stand at room temperature for two and one-half hours, and the solid was filtered and washed with ether; m. p. 172° dec.; yield 12 g.

Anal. Calcd. for $C_{23}H_{32}O_2Br_4$: C, 40.8; H, 4.8. Found: C, 40.6; H, 4.8.

Bromination of 5-pregnen-3(β)-ol-20-one (VI) under identical conditions gave the same product.

5-Pregnen-3(β)-ol-20-one Propionate (VII).—A mixture of 1 g. of 5-pregnen-3(β)-ol-20-one (VI) and 5 cc. of propionic anhydride was refluxed for thirty minutes, and the excess anhydride was evaporated *in vacuo*. The residue was crystallized from methanol, m. p. 119–120°; yield 685 mg.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.4; H, 9.75. Found: C, 77.3; H, 9.7.

5-Pregnen-3(β)-ol-20-one propionate (VII), 665 mg., in 10 cc. of propionic acid was brominated with 3 mols of bromine, 537 cc. of a molar solution of bromine in chloroform, as described for the bromination of the acetate. The mixture was diluted with water and extracted with ether. The extract was washed with water, and the ether was evaporated. The crystalline residue was purified by boiling it with ether, filtering, and washing with ether; m. p. 175° dec.

Anal. Calcd. for $C_{24}H_{34}O_4Br_2$: C, 41.75; H, 5.0. Found: C, 41.3; H, 4.9.

Bromination of 5-pregnen-3(β)-ol-20-one (VI) in propionic acid under identical conditions gave the same product.

5-Pregnen-3(β)-ol-20-one Acetate (I) from Tetra-bromopregnanolone Acetate (VIII).—A mixture of 3 g. of 5,6,17,21-tetrabromopregnan-3(β)-ol-20-one acetate, 2 g. of 100-mesh iron, and 200 cc. of acetic acid was heated on the steam-bath for one hour. After the addition of 1 g. of 100-mesh iron, the heating continued for thirty minutes. The mixture was filtered, diluted with water, and extracted with ether. The extract was washed with dilute sodium carbonate solution and water and the ether evaporated. The residue was crystallized from methanol; m. p. 145–147°. This substance did not depress the melting point of an authentic sample of 5-pregnen-3(β)-ol-20-one acetate (I).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 76.8; H, 9.7.

3(β)-Hydroxy-pregnadien-5,17-acid-21 (XI).—A solution of 4.36 g. of sodium iodide in 100 cc. of ethanol was added to a boiling mixture of 10 g. of 5,6,17,21-tetrabromopregnan-3(β)-ol-20-one acetate (VIII) in 1500 cc. of ethanol, and the mixture was boiled for one hour. Water was added and the mixture was extracted with ether. The extract was washed with dilute sodium bisulfite solution and water, and the ether was evaporated. The residue was taken up in 1000 cc. of methanol and boiled for one hour after the addition of a solution of 50 g. of potassium hydroxide in 50 cc. of water. Water was added and the mixture was extracted with ether. The extract was washed with water and the ether was evaporated. The neutral fraction did not crystallize. The alkaline layer was acidified and extracted with ether. The extract was washed with water and the ether was evaporated. The residue melted at 210–220° after crystallization from acetone; yield 1.46 g. Further crystallization raised the melting point to 249°. It was sublimed *in vacuo* at 200° unchanged, melting at 252–253°. This acid precipitates as an insoluble digitonide from a 1% solution in 90% alcohol.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 76.3; H, 9.2. Found: C, 76.2; H, 9.0.

Reduction of 3(β)-Hydroxy-pregnadien-5,17-acid-21 (XI).—A mixture of 300 mg. of the acid (XI), 100 mg. of platinum oxide catalyst, and 80 cc. of acetic acid was shaken with hydrogen at room temperature and 3 atm. pressure for two hours. The catalyst was filtered and the solvent was evaporated *in vacuo*. The residue was crystallized from aqueous methanol; m. p. 228–230°. This is *allo*-pregnan-3(β)-ol-acid-21 (XIII).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.25. Found: C, 75.2; H, 10.3.

When warmed with acetic anhydride in pyridine the saturated acid gave an *acetate* which melted at 191–193° after crystallization from methanol.

Ozonolysis of 3(β)-Hydroxy-pregnadien-5,17-acid-21 (XI).—The acid (XI), 3 g., was refluxed with excess acetic anhydride for forty-five minutes, and the excess anhydride was evaporated *in vacuo*. The residue was dissolved in 100 cc. of chloroform and cooled in a bath of ice and hydrochloric acid. With stirring, a solution of 1.45 g. of bromine (1 mol) in 50 cc. of chloroform was added during one hour. Ozonized oxygen was passed through the cold solution until no more ozone was absorbed. The solvent was evaporated *in vacuo* at below 30° and the residue was heated on the steam-bath for one hour with 60 cc. of acetic acid and 3 g. of zinc dust. Water was added and the mixture was extracted with ether. Acidification of the alkaline wash gave only a very small amount of acidic material. The ether was evaporated and the residue was converted to the semicarbazone by refluxing with 3 g. of semicarbazide hydrochloride and 4.5 g. of sodium acetate in 100 cc. of methanol. The yield of semicarbazone was 900 mg.; m. p. 280° dec. This gave no depression in melting point when mixed with an authentic sample of the semicarbazone of dehydro-iso-androsterone acetate (V).

Anal. Calcd. for $C_{22}H_{32}O_3N_2$: C, 68.2; H, 8.6. Found: C, 68.3; H, 8.5.

A solution of 4 cc. of concentrated sulfuric acid in 12 cc. of water was added to a mixture of 820 mg. of the semicarbazone of dehydro-iso-androsterone acetate and 40 cc. of ethanol, and the resulting mixture was refluxed for one hour, diluted with water, and extracted with ether. The residue from the evaporation of the ether was boiled with 50 cc. of 3% methanolic potassium hydroxide for thirty minutes, then diluted with water and extracted with ether. The extract was washed with water and the ether was evaporated. The residue melted at 145–147° after crystallization from ether-pentane. This is dehydro-iso-androsterone.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.1; H, 9.8.

When heated with acetic anhydride in pyridine this substance gave an acetate which melted at 167–169°, after crystallization from methanol. A mixture with an authentic sample of dehydro-iso-androsterone acetate (V), m. p. 167–170°, melted at 167–170°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2. Found: C, 76.2; H, 9.1.

Summary

The methyl Grignard addition products of 5-pregnen-3(β)-ol-20-one and of pregnan-3(β)-ol-20-one were converted to dehydro-iso-androsterone acetate and *etio*-cholan-3(β)-ol-17-one, respectively.

5-Pregnen-3(β)-ol-20-one (VI) has been converted to 5,6,17,21-tetrabromopregnan-3(β)-ol-20-one acetate (VIII) and to the tetrabromopropionate (X). Iron-acetic acid reduction of the

tetrabromoacetate (VIII) gave 5-pregnen-3(β)-ol-20-one acetate (I).

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

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

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Sterols. CXLIV. Some 16-Alkyl-pregnenolones and Progesterones¹

BY RUSSELL E. MARKER AND HARRY M. CROOKS, JR.

Wettstein and co-workers^{1a} have recently prepared 5-pregnen-3(β)-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 Pedlow² in this Laboratory on the addition of various Grignard reagents to 2-cyclohexenone coupled with the ready availability of 5,16-pregnadien-3(β)-ol-20-one from diosgenin has led us to prepare some 16-alkyl homologs of 5-pregnen-3(β)-ol-20-one and of progesterone.

Treatment of 5,16-pregnadien-3(β)-ol-20-one acetate with excess methyl Grignard reagent gave an approximately 30% yield of 16-methyl-5-pregnen-3(β)-ol-20-one (isolated as the semicarbazone) as well as a non-ketonic compound, presumably 5,16-*bis-nor*-choladien-3(β),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(β)-ol-20-one gave a 60% yield of 16-methyl-progesterone.

When 5,16-pregnadien-3(β)-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(β)-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(β)-ol-20-one gave a 60% yield of 16-isopropyl-progesterone.

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

of 16-*t*-butyl-5-pregnen-3(β)-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(β)-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(β)-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(β)-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 C₂₈H₃₇O₂N₂: 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 C₂₄H₃₀O₃: 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(β)-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).