[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Selective Reduction and Hydrogenation of Unsaturated Steroids[1]

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The selective and stepwise reductions of ethinyl androstendiol (I), ethinyl testosterone (VIII) and the products obtained by dehydration of the 17(β)-hydroxyl group (II and X) are reported. These reactions indicate that catalyst–solvent combinations may be found which will hydrogenate a double bond at C-16, C-17(20) or C-20, or a triple bond at C-20 before a C-5 double bond or a 3-keto-Δ^4 system is attacked.

Dehydroepiandrosterone is readily ethinated[2] at the 17-position and the carbinol which results is a convenient starting material for further interesting transformations. The stepwise chemical reduction and catalytic hydrogenation of this compound (I), of the enyne (II) obtained by dehydration and of the 3-keto-$\Delta^{4,5}$ analogs of both (VIII, X) are described in this paper. These catalytic hydrogenations are especially interesting in that they demonstrate that catalyst–solvent combinations may be found which will permit the selective hydrogenation of one double bond out of as many as three. In a steroid containing both A or B ring and D ring or side chain unsaturation, a double bond at the C-16, C-17(20) or C-20 position, or a triple bond at the C-20 position is more readily attacked than a double bond at C-5, or one at C-4 conjugated with a 3-ketone.

Complete hydrogenation of the ethinyl group in ethinyl androstenediol (I) and in ethinyl testosterone (VIII) by catalytic means to the ethyl compounds IV and IX, respectively, has been accomplished previously[3] only in the case of the first named compound. Apparently, this hydrogenation with Raney nickel in alcohol ceased with the absorption of two moles of hydrogen, leaving the C-5 double bond intact. The same behavior was observed in the experiments below using palladium-on-charcoal catalyst in absolute alcohol and the product was identical with authentic material prepared by the action of ethyl Grignard reagent on dehydroepiandrosterone.[4] Although the process was longer, the yield obtained over the combined ethination and reduction steps was considerably higher than that obtained by the direct Grignard reaction because of extensive reduction of the ketone in the latter case. Similarly, palladium-on-charcoal catalyst in dioxane solution accomplished a clean reduction of VIII to ethyl testosterone (IX) in 80% yield, leaving the conjugated 3-keto-Δ^4 system untouched.

The sodium–liquid ammonia reduction[5] of ethinyl androstenediol was carried out by dissolving the slightly soluble acetylenic compound in tetrahydrofuran before adding it to the solution of sodium in liquid ammonia. The crude product of the reaction could be separated into two substances by chromatography on activated magnesium silicate. Vinyl androstenediol (VII) was formed in the greater amount and was accompanied by $\Delta^{5,17(20)}$-pregnadien-3(β)-ol (V). This was identified by preparation of its monoacetate by the dehydration of IV-a with phosphorus oxychloride in pyridine.[6] A better and more direct method for the formation of V has been described by Ruzicka, Goldberg and Hardegger.[7] It seems probable that in the sodium–liquid ammonia reduction of I described in the experimental part, V is formed by the further action of the reducing agent on VII. This hypothesis is supported by our observation that a reduction in the time of reaction results in decreased formation of V, and the observation of Birch[8] that the reduction of 1-vinylcyclohexanol by sodium, ethanol and liquid ammonia leads to ethylidene cyclohexane.

It has been found that vinyl androstenediol (VII) was most readily prepared by the catalytic hydrogenation of I in pyridine solution using palladium–calcium carbonate catalyst. Previous investigators who prepared this compound with unspecified yields used a Rupe nickel catalyst[9] and a supported palladium catalyst with alcohol as a solvent.[3] No sharp break in the hydrogen absorption curves was noted. However, Ruzicka and Müller[10] found that in the reduction of the acetylene, VIII, to vinyl testosterone, XII, pyridine acted as a poison toward the palladium catalyst and contributed to the selective hydrogenation of the triple to the double bond. As might be expected, both vinyl compounds (VII and XII) are readily reduced in good yield to the corresponding ethyl compounds (IV and IX); thus the ethinyl group in ethinyl androstendiol and ethinyl testosterone may be reduced to the ethyl compounds directly, or stepwise *via* the intermediate vinyl compounds.

Since Δ^5-pregnen-3(β)-ol acetate (VI) resists further hydrogenation with palladium in neutral solvents such as alcohol or dioxane, it could be prepared with almost equal ease by the hydrogenation of $\Delta^{5,17(20)}$-pregnadien-3(β)-ol acetate (Va) or from $\Delta^{5,16}$-pregnadien-20-yne-3-ol acetate (II). Compound VI has also been prepared by the Wolff–Kishner reduction[11] of 21-acetoxypregneno-

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(1) Presented at the 119th Meeting of the American Chemical Society, Boston, Mass., April 1–6, 1951.

(2) (a) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); (b) J. Kathol, W. Logemann and A. Serini, *Naturwissenschaften*, **25**, 682 (1937).

(3) L. Ruzicka, K. Hofmann and H. Meldahl, *Helv. Chim. Acta*, **21**, 597 (1938).

(4) (a) Kindly supplied by Drs. L. F. Fieser and Huang-Minlon, Harvard University. (b) L. Ruzicka and H. Rosenberg, *Helv. Chim. Acta*, **19**, 357 (1936); (c) A. Butenandt, H. Cobler and J. Schmidt, *Ber.*, **69**, 448 (1936); (d) A. Butenandt, J. Schmidt-Thomé and H. Paul, *ibid.*, **71**, 1313 (1938).

(5) K. Campbell and L. Ely, THIS JOURNAL, **63**, 216, 2683 (1941).

(6) A. Butenandt, J. Schmidt-Thomé and H. Paul, *Ber.*, **72**, 1112 (1939).

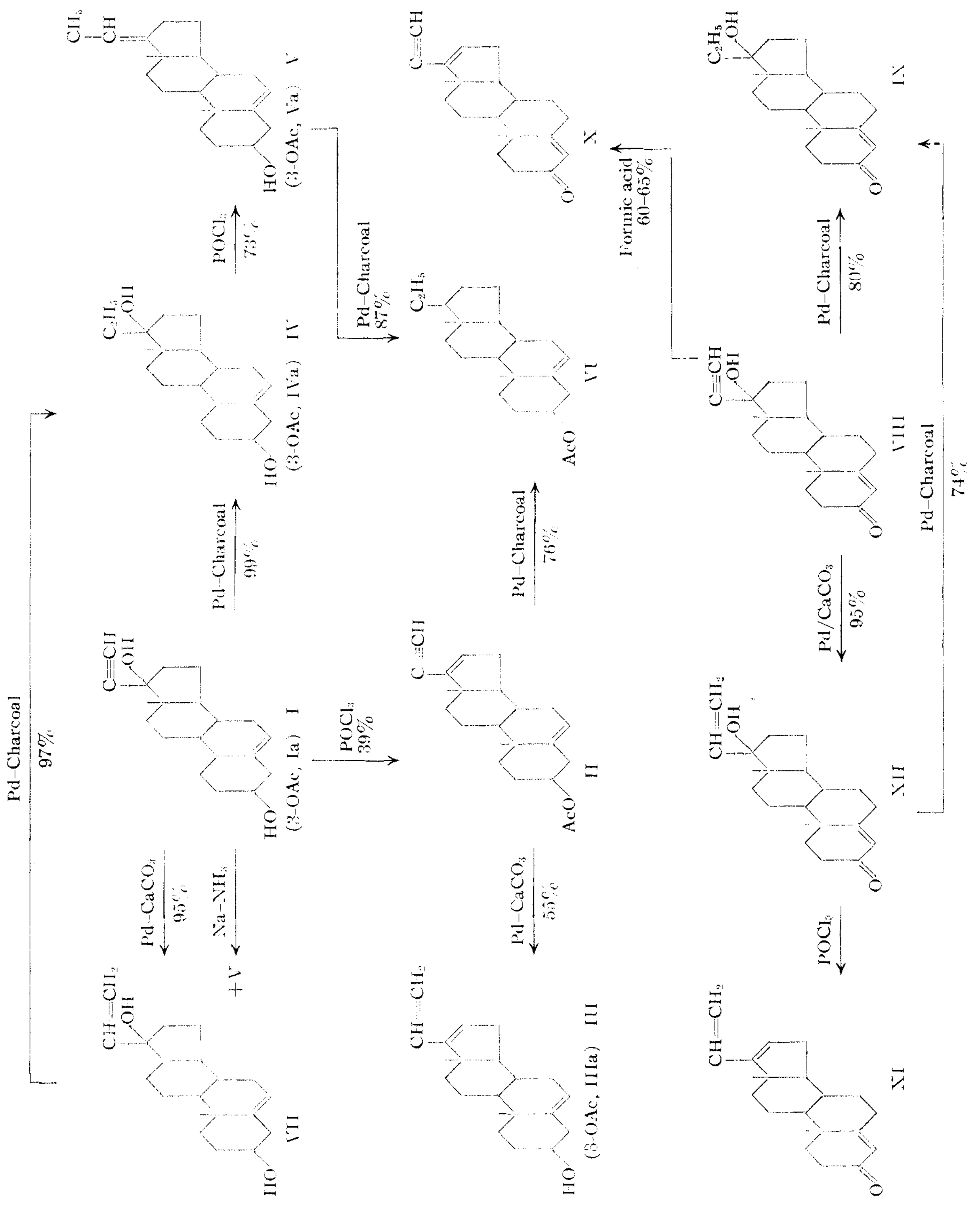
(7) (a) L. Ruzicka, M. Goldberg and E. Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939); (b) L. Ruzicka, M. Goldberg and E. Hardegger, *ibid.*, **25**, 1297 (1942).

(8) A. Birch, *J. Chem. Soc.*, 809 (1945).

(9) H. Inhoffen, W. Logemann, W. Hohlweg and A. Serini, *Ber.*, **71**, 1024 (1938).

(10) L. Ruzicka and P. Müller, *Helv. Chim. Acta*, **22**, 755 (1939).

(11) D. H. R. Barton, N. Holness and W. Klyne, *J. Chem. Soc.* 2456 (1949).



lone together with the corresponding 17-vinyl compound.

The enynes II and X required for these studies were prepared by different methods. The dehydration of 17-ethinyl androstenediol-3-acetate (I) to the enyne (II) using the procedure of Shoppee and Prins with phosphorus oxychloride in pyridine solution[12] was so improved that the yield was raised from 13% to 39%. Using formic acid, the dehydration[9] of ethinyl testosterone (VIII) was effected in even better yield to form X.

The $\Delta^{16,20}$-diene, IIIa, could be readily prepared by partial hydrogenation of the enyne, II, in pyridine solution with palladium-on-calcium carbonate catalyst. Again, the use of pyridine was specific since it limited the reduction cleanly to one double bond. An attempt to prepare 3-keto-$\Delta^{4,16,20}$-pregnatriene (XI) in an analogous manner from X was unsuccessful, for although only one mole of hydrogen was absorbed, the product did not have any appreciable ultraviolet absorption above 220 mμ. Chromatographic analysis indicated that this material was a mixture, though none of the products was identified. For comparison pur-

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[12] C. W. Shoppee and D. Prins, *Helv. Chim. Acta*, **26**, 1004 (1943).

poses, XI was prepared by the dehydration of vinyl testosterone, XII, with phosphorus oxychloride, but the yield was poor.

While ethinyl androstadienyl acetate (II) can be reduced to the 17-ethyl compound (VI) with a palladium-on-charcoal catalyst in a neutral solvent, the 3-keto-Δ^4-enyne (X) absorbed only one mole of hydrogen even under these drastic conditions, and the product was an ill-defined mixture similar to that described in the preceding paragraph.

The ultraviolet absorption spectra[13] support the chemical structures postulated. For example, the peak ϵ 19,000 for the enyne X was broad and nearly flat between 225 and 240 mμ, indicating two close peaks contributed by the 3-keto-Δ^4 unsaturated ketone and the C-16 (20) enyne systems. Of comparable intensity (ϵ 10–12,000) were the peaks for the diene, III, and the enyne, II, the former being 11 mμ nearer the visible. Chanley and Sobotka[14] adduced from their work and from that of Heilbron and co-workers[15,16,17] that the $\epsilon_{\max.}$ of the dienes in the cyclohexane series was displaced 5–7 mμ toward higher wave lengths from that of the analogous enynes and in addition had twice the absorption. However, their own data indicated that in the particular case of enynes unsubstituted in the side chain the reverse was true and ethinylcyclohexene had a somewhat greater absorption than vinylcyclohexene.

As would be expected, Compound XI showed a strong absorption at 237 mμ, ϵ 28,710. The ultraviolet maxima contributed by the unsaturated components of compounds IIIa and IX, the 3-keto-Δ^4-system and the $\Delta^{16,20}$-diene system, absorb at about the same wave length, and combine to reinforce each other in XI.

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Experimental[18]

$\Delta^{5,16}$-Pregnadien-20-yne-3(β)-ol Acetate (II).—A solution of 5.0 g. of ethinyl androstendiol 3-acetate (Ia) in 40 cc. of dry pyridine and 2.5 cc. of phosphorus oxychloride was heated at 120° for 2 hours and then poured into a mixture of 200 g. of ice and 50 cc. of concd. hydrochloric acid. The precipitated solid was collected, and upon crystallization from acetone gave two crops: 1.22 g., m.p. 172.0–174.5°, $[\alpha]_D$ −64.2° (dioxane), ϵ 10,000 at 228 mμ (methanol); and 0.65 g., m.p. 173.5–175.5° (39.4% total).

Shoppee and Prins[12] report a 13% yield of product with a melting point of 175–179°, $[\alpha]_D$ −59.9° ± 3°. They reclaimed an unspecified amount of lower melting material with a still lower rotation from the mother liquors.

$\Delta^{5,16,20}$-Pregnatrien-3(β)-ol Acetate (IIIa).—A solution of 1.0 g. of the enyne, II, in 50 cc. of dry pyridine was hydrogenated at atmospheric pressure and room temperature (24.0°) using 0.3 g. of 5% palladium-on-calcium carbonate[19] catalyst. In six minutes the absorption of hydrogen had practically ceased at one mole. After removal of the catalyst by filtration, the resulting solution was poured onto ice and hydrochloric acid and extracted with ether. The ether layer was washed in succession with 10% hydrochloric acid, water, 5% sodium carbonate, water and then dried over sodium sulfate. The solvent was distilled and the residue gave 0.56 g. (55%) of product, m.p. 107.0–109.2°, upon crystallization from methanol. A second crystallization raised the melting point to 111.0–112.4°, $[\alpha]^{24}_D$ −68.9° (dioxane); ϵ 12,680 at 239 mμ (ethanol).

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.48. Found: C, 80.83; H, 9.79.

Hydrolysis with potassium carbonate in 90% ethanol, and recrystallization from ethanol–water, gave III, m.p. 125.2–126°, $[\alpha]_D$ −74.6° (dioxane). Miescher and Scholz[20] report m.p. 125.5–126° for $\Delta^{5,16,20}$-pregnatrien-3(β)-ol, and m.p. 86.5–87° for the acetate.

17-Ethyl-Δ^5-androsten-3(β),17(β)-diol, (IV) A.—A solution of 5.0 g. of 17-ethinyl androsten-3,17-diol (I) in 170 cc. of absolute alcohol was hydrogenated at atmospheric pressure and room temperature using 0.5 g. of 5% palladium-on-charcoal[19] catalyst. Hydrogen absorption was complete in about 8 minutes with the absorption of 2 moles. After filtration of the catalyst, the solvent was evaporated under reduced pressure and the residue was crystallized from ethyl acetate. Three crops were obtained: 3.05 g., m.p. 197.0–200.0°; 1.59 g., m.p. 198.6–200.6°; and 0.34 g., m.p. 196.4–199.2° (total 5.02 g., 99%). A sample prepared for analysis by recrystallization from ethyl acetate melted at 200.6–202.4°, $[\alpha]^{24}_D$ −69.8° (dioxane) (lit.[4b] m.p. 199–200°).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.30; H, 10.76. Found: C, 78.96; H, 10.46.

Admixture with a sample, m.p. 190.4–193°, prepared by the action of ethyl Grignard reagent upon dehydroepiandrosterone[4a] showed a m.p. of 194.8–197°.

The acetate was prepared by reaction with acetic anhydride and pyridine at room temperature overnight, m.p. 165.0–166.2°, $[\alpha]_D$ −68.3° (dioxane) (lit.[6] m.p. 167–8°).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.68; H, 9.89.

B.—In the same way, 5.0 g. of vinyl androstendiol (VII) in 100 cc. absolute alcohol was hydrogenated with the aid of 0.5 g. of 5% palladium-on-charcoal. One mole of hydrogen was absorbed in 15 min., and the reaction ceased. Two crops were obtained from ethyl acetate: 4.10 g., m.p. 199.0–200.4°, $[\alpha]^{24}_D$ −70.6° (dioxane), 0.75 g., m.p. 198.6–200.0°; total 4.85 g. (97%). A mixture m.p. with a sample obtained by the hydrogenation of ethinyl androstendiol in A above showed no depression.

$\Delta^{5,17(20)}$-Pregnadien-3(β)-ol Acetate (Va).—Compound IVa was dehydrated with phosphorus oxychloride according to the method of Butenandt, Schmidt-Thomé and Paul.[6] In one experiment 50 g. of starting material gave 34.8 g. (73%) of product, m.p. 132.8–136.2°, $[\alpha]^{20}_D$ −63.7° (dioxane). One further crystallization from acetone–water raised the m.p. to 139.0–140.0° (lit.[6] m.p. 140°).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.83; H, 10.05.

Δ^5-Pregnen-3(β)-ol Acetate (VI) A.—A solution of 2.0 g. of the ethylidene compound, Va, in 50 cc. of purified dioxane[21] was hydrogenated at atmospheric pressure and room temperature, using 0.25 g. of 5% palladium-on-charcoal[19] catalyst. Hydrogen uptake ceased after the absorption of one mole. The catalyst was removed by filtration and the solution poured into water, extracted with ether and the ether layer washed twice with water, dried and evaporated. Crystallization of the residue from methanol gave 1.75 g. of product (87%), m.p. 144.0–145.5°, $[\alpha]^{20}_D$ −61.9° (dioxane) (lit.[11] m.p. 147–148°, $[\alpha]_D$ −62°).

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(13) All U. V. measurements were made with a Model DU Beckman Spectrophotometer.

(14) J. Chanley and H. Sobotka, THIS JOURNAL, **71**, 4140 (1949).

(15) I. M. Heilbron, *et al.*, *J. Chem. Soc.*, 77, 84 (1945); Heilbron, *et al.*, *ibid.*, 154 (1946).

(16) L. Haynes, I. M. Heilbron, E. R. H. Jones and F. Sondheimer, *ibid.*, 1583 (1947).

(17) E. R. H. Jones and J. McCombie, *ibid.*, 261 (1943).

(18) All melting points are corrected. All rotations were taken in a one decimeter tube at a concentration of 1%. The authors are indebted to Mr. Edwin Conner, Miss Betty Blasko, Mrs. Thomas Barrella and Mrs. Raymond MacEntire of this Laboratory for the microanalyses and optical data.

(19) The palladium catalysts are commercially standard items and were purchased from Baker and Co., Inc., Newark, New Jersey. They were prepared from highly purified palladium (at least 99.98%) without any lead, arsenic, silver, etc., comprising the remaining 0.02% of impurity. The metal was deposited either on activated wood charcoal commonly used for decolorizing purposes (−200 mesh) or on precipitated calcium carbonate powder fulfilling the requirements of USP XI.

(20) K. Miescher and C. Scholz, *Helv. Chim. Acta*, **22**, 120 (1939).

(21) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, 1941, p. 369.

A sample recrystallized from methanol for analysis melted at 145.5–146.5°.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.90; H, 10.33.

B.—A solution of 1.1 g. of the enyne, II, in 100 cc. of absolute alcohol was hydrogenated in the usual manner using 0.5 g. of 5% palladium-on-charcoal[19] catalyst. Hydrogenation ceased after the absorption of three moles of hydrogen in 8 minutes. After removal of the catalyst by filtration, the solution was concentrated to a volume of about 15 cc. and the product was allowed to crystallize. There was obtained 0.85 g. (76%), of material m.p. 146.8–148.8°, $[\alpha]$D −56.7° (dioxane). This product gave no depression in a mixed melting point with a sample obtained in A above.

17-Vinyl-Δ^{5}-androsten-3(β),17(β)-diol (VII) A.—This compound was prepared in 95% yield by the catalytic hydrogenation of ethinyl androstenediol (I) in pyridine solution using 5% palladium-on-calcium carbonate[19] catalyst; m.p. 184.5–186.0°, $[\alpha]^{21}$D −67.6° (dioxane) (lit.[3] m.p. 184–187°, $[\alpha]$D −64°).

B.—A solution of 4.0 g. of I in 75 cc. of freshly distilled tetrahydrofuran was added to a solution of 10 g. of sodium dissolved in 1 l. of liquid ammonia over a period of 10 minutes and the mixture was stirred for 1 hour. The excess of sodium was destroyed by the addition of dilute ammonium hydroxide and the solution was warmed to remove most of the ammonia and then extracted with ether. The ether layer was washed neutral, dried over sodium sulfate and evaporated to dryness. The residue, 3.61 g., melted at 179–181°, $[\alpha]$D −75.0° (dioxane). A portion of this material (1.9 g.) was dissolved in 50 cc. of benzene and chromatographed on 40 g. of activated magnesium silicate (Florosil). Elution with benzene, followed by methanol gave two fractions, 0.76 g., m.p. 125–133°, and 1.07 g., m.p. 179–191°.

The first fraction was crystallized twice from methanol and then melted at 129–131.4°, $[\alpha]^{20}$D −74.5° (dioxane). Its acetate prepared by the action of acetic anhydride and pyridine melted at 141.4–143.2°, $[\alpha]^{22}$D −66.0° (dioxane).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.57; H, 10.13.

This acetate gave no melting point depression with $\Delta^{5,17(20)}$-pregnadien-3(β)-ol acetate (Va), prepared by the dehydration of IVa.

Ruzicka, Goldberg and Hardegger[7b] report compound V with a m.p. of 132–133°, $[\alpha]$D −74.0° (chloroform), and its acetate, m.p. 143.4°, $[\alpha]$D −70.3° (chloroform).

Fraction 2, crystallized from ethyl acetate melted at 183.0–185.0°, $[\alpha]^{20}$D −74.5° (dioxane).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.88; H, 10.23.

This compound gave no melting point depression with vinyl androstendiol (VII) prepared by the catalytic reduction of ethinyl androstenediol (I).

17-Ethyl Testosterone (IX) A.—A solution of 3 g. of ethinyl testosterone (VIII) in 500 cc. of purified dioxane[21] was hydrogenated using 0.5 g. of 5% palladium-on-charcoal[19] catalyst. The uptake of hydrogen was negligible after two moles had been absorbed. The catalyst was removed by filtration and the dioxane solution was concentrated to dryness *in vacuo*. Crystallization of the residue from hexane gave two crops; 1.9 g., m.p. 136.0–137.0°, and 0.5 g., m.p. 134.6–136.0° (total 80%). The analytical sample, crystallized once again from hexane, melted at 136.4–137.4°, $[\alpha]^{23}$D +80.5° (chloroform), ϵ 15,300 at 239 mμ.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.76; H, 9.98.

Ruzicka, Hofmann and Meldahl[3] report m.p. 143–144°, $[\alpha]$D +71.2° (ethanol); Butenandt, Cobler and Schmidt[4c] report a sintering at 144° and m.p. 149° (uncor.), $[\alpha]^{20}$D −35.3° (ethanol), ϵ 14,300 at 243 mμ (chloroform), while Butenandt, Schmidt-Thomé and Paul[4d] report m.p. 139°.

B.—In an analogous fashion, 2.0 g. of vinyl testosterone (XII) in 150 cc. of purified dioxane was hydrogenated with the aid of 0.4 g. of 5% palladium-on-charcoal. After absorption of one mole of hydrogen in 30 minutes, uptake ceased. By crystallization from hexane there was obtained 1.5 g. (74%) of product, m.p. 139.0–139.8°, $[\alpha]^{21}$D +75.9° (chloroform), ϵ 15,250 at 239 mμ. A mixture m.p. with a sample of ethyl testosterone obtained in A above showed no depression.

3-Keto-$\Delta^{4,16}$-pregnadien-20-yne (X).—This compound was prepared in 60–65% yield by the dehydration[9] of VIII with formic acid, m.p. 166–169°, $[\alpha]^{20}$D −29.9° (dioxane); ϵ *ca.* 19,000 at 225–240 mμ (Inhoffen, *et al.*,[9] report m.p. 166°).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.50; H, 8.97.

The hydrogenation of 3-keto-$\Delta^{4,16}$-pregnadien-20-yne (X) using either palladium-on-calcium carbonate in pyridine, or palladium-on-charcoal in alcohol, resulted in the absorption of only one mole of hydrogen and a substance, m.p. 160.5–161.5°, $[\alpha]^{20}$D −48.6° (dioxane) was obtained in 50–75% yield. Although possessing the correct analysis for the triene, XI, this material did not show any appreciable ultraviolet absorption above 220 mμ, and chromatography over alumina indicated that it was not homogeneous.

Vinyl Testosterone (XII).—In a manner analogous to the preparation of vinyl androstendiol, ethinyl testosterone (VIII) was hydrogenated with palladium-on-calcium carbonate in pyridine and gave vinyl testosterone in 95% yield, m.p. 138–140°, $[\alpha]^{20}$D +76.1° (dioxane) (lit.[10] m.p. 140°).

3-Keto-$\Delta^{4,16,20}$-pregnatriene (XI).—Neither refluxing pyridine–phosphorus oxychloride nor refluxing formic acid gave any crystallizable product from vinyl testosterone. A small amount of XI was prepared by the following procedure. A solution of 2 g. of vinyl testosterone in 2 cc. of phosphorus oxychloride and 25 cc. of dry pyridine was allowed to stand overnight at room temperature and then poured into a mixture of ice and concentrated hydrochloric acid. After extraction with ether, the organic layer was washed with water, 10% sodium carbonate, water, and then dried over sodium sulfate. The solvent was evaporated, and the residue crystallized from hexane to give 50 mg. of material with m.p. 136.5–138.5°. One further crystallization from hexane raised the m.p. to 139.5–141.0°, $[\alpha]^{23}$D +144.8° (alcohol), ϵ 28,710 at 237 mμ.[22]

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.93; H, 9.73.

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[22] NOTE ADDED IN PROOF.—Since the submission of this article, Compound XI has been prepared independently by J. K. Norymberski, *J. Chem. Soc.*, 847 (1951). He reports m.p. 140–141°, $[\alpha]$D +147 (chloroform), ϵ 31,500 at 238 mμ (ethanol).