[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. LXXI.[1] Synthesis of 1-Dehydroprogesterone and 1-Dehydro-17-ethinyltestosterone

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Syntheses of the novel $\Delta^{1,4}$-pregnadiene-3,20-dione (1-dehydroprogesterone) (I) and 17α-ethinyl-$\Delta^{1,4}$-androstadien-17β-ol-3-one (1-dehydro-17-ethinyltestosterone) (II) from allopregnan-3β-ol-20-one (III) and $\Delta^{1,4}$-androstadiene-3,17-dione (XI), respectively, are described.

The recent discovery[2] that 1-dehydrocortisone and 1-dehydrohydrocortisone possess medicinal properties superior to those of the parent hormones has focussed attention on the 1-dehydro derivatives of other steroidal hormones. 1-Dehydrotestosterone,[3] 1-dehydrodesoxycorticosterone acetate,[4] 1-dehydro-17-hydroxyprogesterone[5] and 1-dehydro-17-hydroxydesoxycorticosterone acetate[5] are all known compounds. The 1-dehydro derivatives of the potent progestational hormones progesterone and 17-ethinyltestosterone, however, have not been described previously. It is the purpose of this paper to report upon the synthesis of these compounds, namely, of 1-dehydroprogesterone (I) and of 1-dehydro-17-ethinyltestosterone (II). This work was carried out some time ago in connection with a program aimed at making available substances which could be compared with microbiological transformation products.[6]

The conventional method for preparing steroidal $\Delta^{1,4}$-dien-3-ones involves dibromination of a saturated 3-ketone of the 5α- or 5β-series, followed by dehydrobromination.[7] This sequence cannot, however, be employed directly for the synthesis of 1-dehydroprogesterone (I) since dibromination of ring A of allopregnane-3,20-dione (and also presumably of pregnane-3,20-dione) cannot be effected without bromination at C-17, the attack by bromine occurring first at C-2, then at C-17 and finally again at C-2.[8] For this reason we decided to employ allopregnan-20β-ol-3-one acetate (VIb)[8,9] for the synthesis of I; no interference by the side chain in the bromination step was now to be expected.

It was found most convenient to prepare VIb from the readily available allopregnan-3β-ol-20-one (III) through protection of the 3β-hydroxy group as the dihydropyran adduct IV,[10] followed by sodium borohydride reduction at C-20, acetylation, acid hydrolysis at C-3 to allopregnane-3β,20β-diol 20-monoacetate (VIa)[9] and chromic acid oxidation.[11] The over-all yield from III to VIb was 44%.

The dibromination of allopregnan-20β-ol-3-one acetate (VIb) in acetic acid in the presence of hydrogen bromide led to the amorphous 2,4-dibromide VII[8] which on dehydrobromination with a mixture of boiling γ-collidine and 2,4-lutidine furnished 64% (from VIb) of the required $\Delta^{1,4}$-pregnadien-20β-ol-3-one acetate (VIIIa). The structure of this substance was confirmed by the maximum at 244 mμ in the ultraviolet,[13a] by the doublet at 1620 and 1600 cm.$^{-1}$ in the double bond region of the infrared[14] and by the dienone–phenol rearrangement to 4-methyl-19-nor-$\Delta^{1,3,5(10)}$-pregnatriene-1,-20β-diol diacetate (IXa)[15] with the typical comparatively low-intensity ultraviolet maximum at 266 mμ.[13b]

Finally the acetate VIIIa was saponified with potassium hydroxide and the hydroxyl group of the resulting $\Delta^{1,4}$-pregnadien-20β-ol-3-one (VIIIb) was oxidized with the chromium trioxide–pyridine complex.[16] The resulting $\Delta^{1,4}$-pregnadiene-3,20-dione (1-dehydroprogesterone) (I), produced in 70% yield, showed a band at 1700 cm.$^{-1}$ in the infrared, indicative of the C-20 keto group (as well as bands at 1660, 1620 and 1600 cm.$^{-1}$ due to the $\Delta^{1,4}$-dien-3-one system[14]), but no longer showed a hydroxyl band. On dienone–phenol rearrangement it was converted to 4-methyl-19-nor-$\Delta^{1,3,5(10),17(20)}$-pregnatetraene-1,20-diol diacetate (IXb)[15,17] and

(1) Paper LXX, O. Mancera, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **77**, 5669 (1955).

(2) J. J. Bunim, M. M. Pechet and A. J. Bollet, *J. Am. Med. Assoc.* **157**, 311 (1955); H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(3) H. H. Inhoffen, G. Zühlsdorf and Huang-Minlon, *Ber.*, **73**, 451 (1940).

(4) R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, THIS JOURNAL, **77**, 661 (1955).

(5) G. Rosenkranz, J. Pataki, S. Kaufmann, J. Berlin and C. Djerassi, *ibid.*, **72**, 4081 (1950).

(6) *Cf.* E. Vischer and A. Wettstein, *Experientia*, **9**, 371 (1953); J. Fried, R. W. Thoma and A. Klingsberg, THIS JOURNAL, **75**, 5764 (1953). ADDED IN PROOF: E. Vischer, C. Meystre and A. Wettstein (*Helv. Chim. Acta*, **38**, 835 (1955)) have now described the obtention of 1-dehydroprogesterone with physical properties very similar to ours by the incubation of progesterone with *Calonectria decora*.

(7) H. H. Inhoffen, *Angew. Chem.*, **59**, 207 (1947), and references cited there; C. Djerassi and C. R. Scholz, THIS JOURNAL, **69**, 2404 (1947); C. Djerassi and G. Rosenkranz, *Experientia*, **7**, 93 (1951).

(8) M. Rubin, H. Wishinsky and F. Bompard, THIS JOURNAL, **73**, 2338 (1951).

(9) R. E. Marker, O. Kamm, D. M. Jones and T. S. Oakwood, *ibid.*, **59**, 614 (1937).

(10) The best yield of this substance was obtained when the reaction between III and dihydropyran was carried out in benzene solution with *p*-toluenesulfonic acid as catalyst, rather than in excess dihydropyran or in ether with concentrated hydrochloric acid.[11,12]

(11) *Cf.* A. C. Ott, M. F. Murray and R. L. Pederson, THIS JOURNAL, **74**, 1239 (1952).

(12) G. F. Woods and D. N. Kramer, *ibid.*, **69**, 2246 (1947); W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948); C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951); W. G. Dauben and H. L. Bradlow, THIS JOURNAL, **74**, 559 (1952).

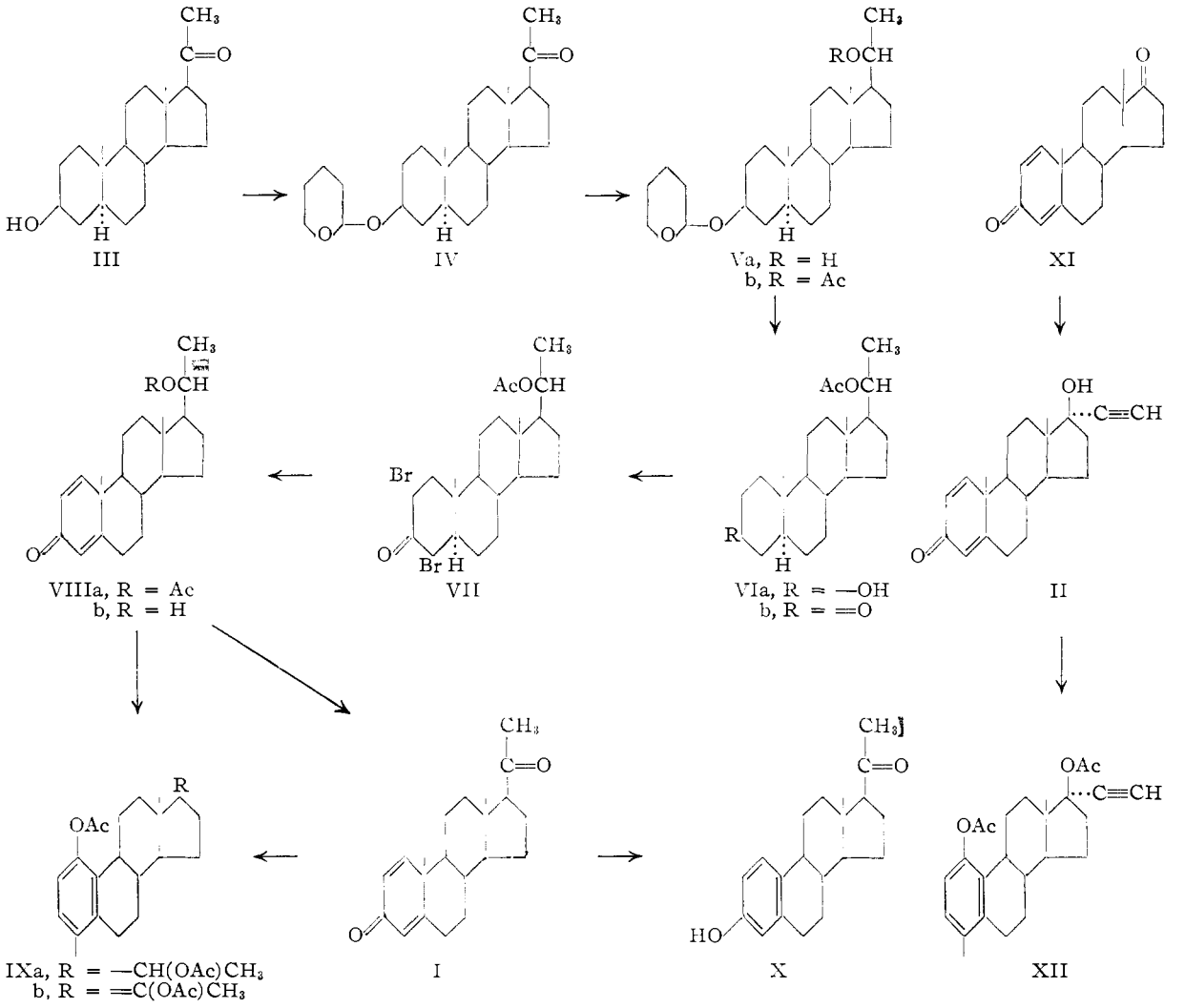
(13) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), (a) Table 9; (b) Table 19.

(14) R. N. Jones, P. Humphries, E. Packard and K. Dobriner, THIS JOURNAL, **72**, 86 (1950).

(15) *Cf.* R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950); R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. H. Menzel, *Ber.*, **86**, 594 (1953); A. S. Dreiding and A. Voltman, THIS JOURNAL, **76**, 537 (1954).

(16) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(17) Pregnan-20-ones unsubstituted at C-17 and C-21 are known to yield the 20-acetoxy-$\Delta^{17(20)}$-pregnenes on being heated with acetic anhydride and *p*-toluenesulfonic acid (C. W. Marshall, T. H. Kritchevsky, S. Lieberman and T. F. Gallagher, THIS JOURNAL, **70**, 1837 (1948); T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **73**, 184 (1951)).



on pyrolysis at 600° in mineral oil it furnished the known 19-nor-$\Delta^{1,3,5(10)}$-pregnatrien-3-ol-20-one (X).[18]

For the synthesis of 1-dehydro-17-ethinyltestosterone (II) the estrone intermediate $\Delta^{1,4}$-androstadiene-3,17-dione (XI)[3] was employed as starting material. Since it was not found possible to protect the 3-keto group of XI through ketalization, enol ether formation or reduction,[19] the direct reaction with acetylene in an inert solvent in the presence of potassium *t*-amylate[20] was investigated. The product proved to be a high melting, probably polymeric material, but the required 1-dehydro-17-ethinyltestosterone (II) could be isolated in about 12% yield when XI was allowed to react with sodium or lithium acetylide in liquid ammonia.[21]

The structure of II was confirmed by the disappearance of the infrared band at 1736 cm.$^{-1}$ due to the 17-keto group, whereas the ultraviolet maximum at 244 mμ[13a] (as well as the infrared bands at 1660, 1620 and 1600 cm.$^{-1}$ [14]) indicative of the $\Delta^{1,4}$-dien-3-one system was retained. Moreover II gave a heavy precipitate with ammoniacal silver nitrate (presence of ethinyl group with active hydrogen) and on dienone–phenol rearrangement 4-methyl-17α-ethinyl-$\Delta^{1,3,5(10)}$-estatriene-1,17-diol diacetate (XII)[15,22] was produced.

Experimental[23]

Allopregnan-3β-ol-20-one 3-(2′-Tetrahydropyranyl) Ether (IV).—Tetrahydropyran (40 cc.) was added to a solution

(18) (a) L. Velluz and G. Muller, *Compt. rend.*, **226**, 411 (1948); *Bull. soc. chim. France*, 166 (1950); (b) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, THIS JOURNAL, **73**, 1523 (1951).

(19) *Cf.* F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, *Chemistry and Industry*, 1482 (1954).

(20) H. E. Stavely, THIS JOURNAL, **61**, 79 (1939).

(21) Compare the analogous preferential ethinylation of the saturated keto group when Δ^4-9-methyloctalin-3,8-dione is treated with sodium acetylide in liquid ammonia (C. A. Friedmann and R. Robinson, *Chemistry and Industry*, 777 (1951)). In addition to compound II, a substance with λ_{max}. 328 mμ was produced, which was not isolated. We believe this ultraviolet maximum to be caused by the 3-ethinyl-$\Delta^{1,3,5}$-androstatriene chromophore, formed from the $\Delta^{1,4}$-dien-3-one by reaction with acetylene, allylic rearrangement and dehydration.

(22) It is known (*cf.* L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937)) that the 17-hydroxy group in 17α-ethinylandrostan-17β-ol derivatives is acetylated under vigorous acetylating conditions.

(23) Melting points are uncorrected. Rotations were determined at 20° in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We would like to thank Mrs. P. Lopez and Miss T. Cardenas for these measurements as well as for the infrared spectra which were determined in chloroform solution (unless otherwise stated) on a Perkin-Elmer model 12C single beam spectrophotometer with sodium chloride prism. The microanalyses were performed by Mrs. A. Gonzalez and staff.

of 20 g. of allopregnan-3β-ol-20-one (III) in 600 cc. of benzene and about 50 cc. was distilled to remove moisture. *p*-Toluenesulfonic acid (0.8 g.) was added to the cooled solution, which was then allowed to stand at room temperature for 4 days. The solution was washed with sodium carbonate and water, dried and evaporated. The residue could be crystallized directly, but it was found most efficient to chromatograph it on 600 g. of neutral alumina. Crystallization of the fractions eluted with hexane from pentane yielded 19.52 g. (77%) of the ether IV with m.p. 118–121°. The analytical sample showed m.p. 125–127°, $[\alpha]_D$ +65°, $\nu_{max.}$ 1700 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.50; H, 10.32.

When the reaction was carried out in ether with concentrated hydrochloric acid as catalyst[11] the yield of IV was 68%.

Allopregnane-3β,20β-diol 3-(2′-Tetrahydropyranyl) Ether (Va).—A solution containing 2 g. of the ether IV and 0.66 g. of sodium borohydride in 120 cc. of methanol and 12 cc. of water was allowed to stand for 16 hours at room temperature. The excess reagent was destroyed by the dropwise addition of acetic acid and the solution was then poured into water. Crystallization of the dried precipitate from chloroform–hexane furnished 1.74 g. (87%) of Va with m.p. 157–160°. A further purified sample showed m.p. 164–165°, $[\alpha]_D$ 0°, $\nu_{max.}$ free hydroxyl band.

Anal. Calcd. for $C_{26}H_{44}O_3$: C, 77.18; H, 10.96. Found: C, 77.21; H, 11.13.

The acetate Vb was prepared in over 95% yield by heating 1 g. of Va with 4 cc. of pyridine and 4 cc. of acetic anhydride for 1 hour at 90°. It was crystallized from acetone–ether and showed m.p. 132–133°, $[\alpha]_D$ +33°, $[M]_D$ +147, $\nu_{max.}$ 1718 cm.$^{-1}$, no free hydroxyl band. The compound showed the comparatively large positive shift in rotation compared with its precursor Va, as it is to be expected on passing from a 20β-ol to its acetate.[24]

Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.17; H, 10.64.

Allopregnane-3β,20β-diol 20-Monoacetate (VIa).—Three drops of concentrated hydrochloric acid were added to a solution of 1 g. of the acetate Vb in 30 cc. of methanol. After 1 hour at room temperature the solution was diluted with water, the precipitate was collected, washed well with water and dried. Crystallization from chloroform–ether produced 0.75 g. (92%) of the diol monoacetate VIa with m.p. 172–173°, $[\alpha]_D$ +34°, $\nu_{max.}$ 1718 cm.$^{-1}$ and free hydroxyl band; reported[9] m.p. 170–171°.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56. Found: C, 76.46; H, 10.40.

Allopregnan-20β-ol-3-one Acetate (VIb).—The oxidation of 1 g. of VIa was carried out with 0.26 g. of chromic acid in 40 cc. of acetic acid for 1 hour at room temperature.[9] Crystallization of the product from chloroform—methanol furnished 0.74 g. (74%) of the ketone VIb with m.p. 156–157°, $[\alpha]_D$ +55°, $\nu_{max.}$ 1718 and 1700 cm.$^{-1}$, no free hydroxyl band; reported m.p. 156°[9]; m.p. 148–149°, $[\alpha]_D$ +56°.[8]

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.84; H, 9.72.

Δ^{1,4}-Pregnadien-20β-ol-3-one Acetate (VIIIa).—A solution of 10.1 g. of bromine in 100 cc. of glacial acetic acid was added dropwise with stirring to a solution of 10 g. of allopregnan-20β-ol-3-one acetate in 300 cc. of glacial acetic acid containing a little hydrogen bromide. After 4 hours at room temperature, water was added and the crude amorphous dibromide VII[8] was collected. It could not be induced to crystallize.

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: Br, 30.84. Found: Br, 31.49.

The total bromo compound from 10 g. of VIb was refluxed for 90 minutes with 45 cc. of γ-collidine and 45 cc. of 2,4-lutidine with exclusion of moisture. The solution was cooled and the precipitated base hydrobromide(s) (11 g.) was removed. The filtrate was diluted with ether and washed with excess hydrochloric acid, sodium carbonate solution and water. The dried extract was evaporated and the residue was chromatographed on 500 g. of neutral alumina. Crystallization of the fractions eluted with benzene from acetone–ether produced 6.29 g. (64%) of the dienone VIIIa with m.p. 160–164°. The analytical specimen showed m.p. 168–169°, $[\alpha]_D$ +85°, $\lambda_{max.}$ 244 mμ, log ε 4.24, $\nu_{max.}$ 1718, 1660, 1620 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.32; H, 8.96.

4-Methyl-19-nor-Δ$^{1,3,5(10)}$-pregnatriene-1,20β-diol Diacetate (IXa).—A solution of 200 mg. of the dienone VIIIa and 60 mg. of *p*-toluenesulfonic acid in 8 cc. of acetic anhydride was heated at 90° for 4 hours. The cooled solution was poured into water, the anhydride was allowed to hydrolyze and the solid product was collected, washed well with water and dried. Crystallization from acetone–ether yielded 170 mg. (76%) of the aromatic diacetate IXa with m.p. 200–201°, $[\alpha]_D$ +183°, $\lambda_{max.}$ 266 mμ, log ε 2.50, $\nu_{max.}$ 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.70; H, 8.86.

Δ^{1,4}-Pregnadien-20β-ol-3-one (VIIIb).—A solution of 2.5 g. of potassium hydroxide in 10 cc. of water was added to 3 g. of the acetate VIIIb dissolved in 100 cc. of methanol and the solution was refluxed for 2 hours under nitrogen. Water was added and the product was isolated with ether in the usual way. Crystallization from chloroform–hexane furnished 2.29 g. (86%) of the keto alcohol VIIIb with m.p. 193–194°, $[\alpha]_D$ +15°, $\lambda_{max.}$ 244 mμ, log ε 4.24, $\nu_{max.}$ 1660, 1620 and 1600 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.93; H, 9.84.

When the reaction was carried out at room temperature with potassium hydroxide or at reflux temperature with sodium carbonate, saponification was incomplete.

Δ^{1,4}-Pregnadiene-3,20-dione (1-Dehydroprogesterone) (I).—Chromium trioxide (2 g.) was added slowly and with cooling to 40 cc. of dry pyridine (temperature kept below 20°). A solution of 2 g. of Δ^{1,4}-pregnadien-20β-ol-3-one in 40 cc. of pyridine was then added dropwise with continued ice-cooling and the mixture was allowed to stand at room temperature overnight. Water and ethyl acetate were added, the mixture was filtered through Celite and the latter was washed well with ethyl acetate. The organic layer was washed repeatedly with water, dried and evaporated. Crystallization of the residue from acetone–hexane yielded 1.39 g. (70%) of 1-dehydroprogesterone with m.p. 152–153°, $[\alpha]_D$ +120°, $\lambda_{max.}$ 244 mμ, log ε 4.25, $\nu_{max.}$ 1700, 1660, 1620 and 1600 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 81.00; H, 9.27.

4-Methyl-19-nor-Δ$^{1,3,5(10),17(20)}$-pregnatetraene-1,20-diol Diacetate (IXb).—The dienone–phenol rearrangement was carried out with 200 mg. of 1-dehydroprogesterone (I) as described above for VIIIa. The product was crystallized from acetone—ether and gave 160 mg. (63%) of the aromatic diacetate IXb with m.p. 206–208°, $[\alpha]_D$ +171°, $\lambda_{max.}$ 266 mμ, log ε 2.53, $\nu_{max.}$ 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{32}O_4$: C, 75.72; H, 8.14. Found: C, 75.98; H, 8.24.

19-Nor-Δ$^{1,3,5(10)}$-pregnatrien-3-ol-20-one (X).—Δ^{1,4}-Pregnadiene-3,20-dione (500 mg.) was pyrolyzed in mineral oil at 600° exactly as described previously for the Δ^{16}-analog, Δ^{1,4,16}-pregnatriene-3,20-dione.[18b] The resulting mixture was cooled at 0° for several days and the precipitate was collected, washed with hexane and crystallized from acetone. This procedure produced 150 mg. of the phenol X with m.p. 240–243°, whereas chromatography of the mother liquors on neutral alumina gave another 30 mg. of the same material (38% total yield). A further purified sample showed m.p. 248–250°, $\lambda_{max.}$ 280 mμ, log ε 3.36, ν_{max}^{null} 1700 cm.$^{-1}$ and free hydroxyl band. Identity with an authentic specimen[18b] with m.p. 247–249° was established through mixture m.p. determination and infrared comparison.

17α-Ethinyl-Δ^{1,4}-androstadien-17β-ol-3-one (1-Dehydro-17-ethinyltestosterone) (II).—To a solution of sodium acetylide in liquid ammonia (1500 cc.), prepared from 10 g. of sodium (using the ferric nitrate catalyst of Vaughn, *et al.*,[25] to catalyze the formation of sodamide), Δ^{1,4}-androstadiene-3,17-dione (10 g.) in 500 cc. of dry ether was added during

(24) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); W. Klyne and D. H. R. Barton, THIS JOURNAL, **71**, 1500 (1949).

(25) T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, *ibid.*, **56**, 2120 (1934).

15 minutes with stirring and cooling (alcohol–Dry Ice). The cooled mixture was stirred 4 hours more and 50 g. of ammonium chloride was then added carefully in portions. The ammonia was allowed to evaporate, ether and water were added to the residue and the organic layer was washed with hydrochloric acid, sodium bicarbonate solution and water. The dried extract was evaporated and the residue (9.3 g., $\lambda_{max.}$ 244 mμ, $E^{1\%}_{1\,cm.}$ 288 and 328 mμ, $E^{1\%}_{1\,cm.}$ 118[21]) was chromatographed on 400 g. of alumina. The fractions eluted with benzene–ether on crystallization from acetone–ether produced 1.35 g. (12%) of 1-dehydroethinyltestosterone with m.p. 227–229°, $[\alpha]_D$ −15°, $\lambda_{max.}$ 244 mμ, log ε 4.20, ν^{mull}_{max} 1660, 1620 and 1600 cm.$^{-1}$ and free hydroxyl band. A heavy precipitate was formed when an alcoholic solution of the substance was added to aqueous ammoniacal silver nitrate.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.87; H, 8.67.

When the reaction was carried out with lithium acetylide (5 g. of lithium for 10 g. of $\Delta^{1,4}$-androstadiene-3,17-dione, no ferric nitrate catalyst, other conditions identical) the yield of II was 11%. When $\Delta^{1,4}$-androstadiene-3,17-dione was allowed to react with acetylene in toluene solution in the presence of potassium *t*-amylate[20] an intractable product with m.p. *ca.* 320–325°, λ_{max} 244 mμ, $E^{1\%}_{1\,cm.}$ 62 and 328 mμ, $E^{1\%}_{1\,cm.}$ 91, was obtained and none of the required II could be isolated.

4-Methyl-17α-ethinyl-$\Delta^{1,3,5(10)}$estratriene-1,17-diol Diacetate (XII).—A solution of 300 mg. of 1-dehydroethinyltestosterone and 90 mg. of *p*-toluenesulfonic acid in 12 cc. of acetic anhydride was heated at 90° for 4 hours. The cooled solution was poured into water, the anhydride was allowed to hydrolyze and the precipitate was collected, washed with water and dried. Crystallization from acetone–hexane yielded 260 mg. (68%) of the phenol diacetate XII with m.p. 191–192°, $[\alpha]_D$ +75°, $\lambda_{max.}$ 266 mμ, log ε 2.55.

Anal. Calcd. for $C_{25}H_{30}O_4$: C, 76.11; H, 7.67. Found: C, 76.38; H, 7.97.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. LXXII.[1] 16-Methylenetestosterone

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16-Methylene-Δ^4-androsten-17β-ol-3-one (16-methylenetestosterone) (Ia) has been synthesized from 16ξ-dimethylaminomethyl-Δ^5-androsten-3β-ol-17-one (III) through successive steam distillation to IVa, Oppenauer oxidation to V, sodium borohydride reduction to VIa and VIb and finally differential manganese dioxide oxidation at C-3. In addition the known 16ξ-methyl-Δ^4-androsten-17ξ-ol-3-one (16ξ-methyltestosterone) (II) has been prepared from IVa by a variant of the methods described previously.

In this paper we describe the synthesis of 16-methylene-Δ^4-androsten-17β-ol-3-one (16-methylenetestosterone (Ia), an analog of testosterone prepared in these laboratories in connection with a program aimed at making available new anabolic agents. As part of the same program the 16ξ-methyltestosterone (II) of Julian, *et al.*,[2] has been synthesized by a variant of the routes used previously.[2]

For the preparation of Ia, 16ξ-dimethylaminomethyl-Δ^5-androsten-3β-ol-17-one (III) was employed as starting material, a substance readily obtainable in *ca.* 75% yield by the Mannich condensation of Δ^5-androsten-3β-ol-17-one with paraformaldehyde and dimethylamine.[2a] The cleavage of III by means of acetic acid and acetic anhydride to 16-methylene-Δ^5-androsten-3β-ol-17-one acetate (IVb) has been described,[2a] but the next step in our projected synthesis of Ia, the saponification of IVb to IVa, was unsuccessful. Treatment of the acetate IVb under mild basic or acidic conditions led mainly to polymeric, intractable materials, doubtless due to the unstable nature of the 16-methylene-17-keto function. The required free 16-methylene-Δ^5-androsten-3β-ol-17-one (IVa) was finally obtained in over 90% yield by carrying out the cleavage of the dimethylaminomethylene compound III by distillation with steam.[3]

The next step involved the Oppenauer oxidation of IVa, which when carried out with aluminum isopropoxide and cyclohexanone in toluene under carefully defined conditions, furnished about 20% of 16-methylene-Δ^4-androstene-3,17-dione (V) in addition to polymeric material. The structure of V follows from its ultraviolet maximum at 236 mμ, ε 23,400 (due to the superposition of the maxima at 228 mμ, ε 8000[2a] and at 241 mμ, ε 16,600[4] to be expected for the 16-methylene-17-ketone and Δ^4-3-ketone systems, respectively) and from the infrared band at 890 cm.$^{-1}$ (which however was rather weak), indicative of a methylene grouping.[5] Reduction of V with sodium borohydride yielded what we believe to be a mixture consisting of 16-methylene-Δ^4-androstene-3β,17β-diol (VIa) and the 3α,17β-diol VIb,[6] without appreciable absorption in the ultraviolet. The mixture, without purification, was subjected to oxidation with manganese dioxide[7] at room temperature. Although the diols VIa and VIb each contain two allylic alcohol functions, the 17β-hydroxy groups appear to be situated in a suf-

(1) Paper LXXI, F. Sondheimer, M. Velasco and G. Rosenkranz, THIS JOURNAL, **77**, 5673 (1955).

(2) (a) P. L. Julian, E. W. Meyer and H. C. Printy, *ibid.*, **70**, 3872 (1948); (b) M. Romero, J. Romo and J. Lepe, *Bol. inst. quim. univ. nacl. auton. Mex.*, **4**, 115 (1952).

(3) *Cf.* F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 318.

(4) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), Table 7.

(5) N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 26 (1952).

(6) For the stereochemical course of the reduction of Δ^4-3-ketones with sodium borohydride, see W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, **74**, 3852 (1952). The reduction of ring D unsubstituted 17-keto-androstanes with the metal hydride gives almost exclusively the 17β-ol; inspection of a model of a 16-methylene-17-ketone such as V shows that the methylene group does not hinder the α-side of the molecule and the 17β-ol should therefore be formed in this case as well. However, the 17α-ol configuration for VIa, VIb, VIIa and Ia, although unlikely, cannot definitely be excluded at present. Unfortunately, no conclusions can be reached from rotational data, since 17α-ols and 17β-ols show almost identical rotations.

(7) *Cf.* (a) F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953); (b) F. Sondheimer, O. Mancera, M. Urquiza and G. Rosenkranz, *ibid.*, **77**, 4145 (1955), footnote 17.