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

Steroids. CI.[1] 19-Nordihydrotestosterone Derivatives[2]

BY A. BOWERS, H. J. RINGOLD AND E. DENOT

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19-Nortestosterone (Ia) undergoes stereospecific reduction with a lithium in liquid ammonia system to the dihydroallo series (rings A/B *trans*). By appropriate choice of experimental conditions this reduction can be made to afford either the dihydroallo-3-ketone IIa or the 3β-alcohol IIIa. Sodium borohydride reduction of IIa also yields IIIa. 1α-Methyl-, 17α-methyl- and 17α-ethyl-19-nortestosterone undergo a similar series of reactions. Under completely anhydrous conditions 17α-ethynyl and 17α-vinyl-19-nortestosterone are selectively reduced with preservation of the ethynyl and vinyl groups to the dihydroallo-3-ketones VIII and IX. A series of interconversions between the 17α-ethynyl-, vinyl- and ethyl-dihydroallo-19-nortestosterone are described.

Following Birch's synthesis of 19-nortestosterone (Ia)[3] a number of 19-nor analogs of the steroid hormones and metabolites have been prepared[4a–i] and many of these compounds exhibited unusual biological activity, notably the markedly potentiated progestational activity of 17α-methyl-19-nortestosterone,[5,6] 17α-ethyl-19-nortestosterone,[5] 17α-ethynyl-19-nortestosterone,[5,7] 19-norprogesterone[8] and 17α-ethynyl-19-nor-$\Delta^{5(10)}$-androsten-17β-ol-3-one[5]; the high mineralocorticoid activity of 19-nordesoxycorticosterone[4b]; and the favorable anabolic–androgenic ratios of 19-nortestosterone,[9,10] 17α-methyl-19-nor-testosterone[10] and 17α-ethyl-19-nortestosterone.[10]

We now wish to describe the synthesis of a new series of biologically active[11] 19-nor compounds, namely, the 4,5-dihydroallo derivatives of 19-nortestosterone, and the 17α-methyl, ethyl, vinyl and ethynyl analogs as well as the corresponding diols.

Catalytic hydrogenation of 19-nortestosterone (Ia) and its 17α-methyl and 17α-ethyl derivatives led to mixtures of the rings A/B *cis* and *trans* compounds as shown by the rotatory dispersion curves of the total product; it was only possible to isolate the dihydroallo compound with difficulty. Clearly, for preparative purposes a more stereospecific approach was needed. Since it is known that reduction of α,β-unsaturated ketones in liquid ammonia with a dissolving metal such as sodium or lithium affords the thermodynamically more stable dihydro ketone,[12a,b] an investigation along these lines warranted attention. Indeed, it was found that reduction of 19-nortestosterone (Ia) in anhydrous and alcohol-free ether–dioxane solution with lithium in liquid ammonia followed by ammonium chloride decomposition furnished in excellent yield 19-nordihydroallotestosterone (IIa).[12c] The rings A/B allo configuration for IIa, which could be predicted on thermodynamic grounds[12b] was firmly established by its rotatory dispersion curve[13a] which was typical of 5α-3-ketosteroids.[13b]

Reduction of 19-norandrostane-17β-ol-3-one (IIa) with either sodium borohydride or with lithium in liquid ammonia followed by decomposition with methanol afforded only one alcohol (IIIa) in good yield, the 3β (equatorial) configuration being assigned to the newly introduced hydroxyl group. This completely reduced product (III) was also prepared directly, by the lithium-ammonia–methanol reduction of 19-nortestosterone (Ia). It is of interest to note that even in the presence of a large excess of lithium no reduction of the 3-keto group took place provided that completely anhydrous conditions were observed and ammonium chloride was used as the proton source. However, substitution of methanol for ammonium chloride led to complete reduction of the Δ^4-3-ketone moiety to the 3β-hydroxydihydroallo system.

In a like manner to 19-nortestosterone, 17α-methyl-19-nortestosterone (Ib)[4d] and 1α-methyl-19-nortestosterone (Ic)[4i] underwent reduction in liquid ammonia to the corresponding dihydroallo derivatives IIb and IIc, respectively, whence sodium borohydride reduction furnished the 3β-alcohols IIIb and IIIc. Oxidation of IIIb with 8 *N* chromic acid in acetone solution gave IIb in high

(1) Paper C, A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, THIS JOURNAL, **80**, 6110 (1958).

(2) A preliminary announcement of part of this work has been published (A. Bowers, H. J. Ringold and R. I. Dorfman, *ibid.*, **79**, 4556 (1957)).

(3) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(4) (a) L. Miramontes, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3540 (1951); **75**, 4440 (1953); (b) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4117 (1953); (c) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953); (d) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954); (e) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *ibid.*, **76**, 6210 (1954); (f) B. J. Magerlein and J. A. Hogg, *ibid.*, **79**, 1508 (1957); (g) F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *ibid.*, **79**, 1123 (1957); (h) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 2477 (1956); (i) C. Djerassi, A. E. Lippman and J. Grossman, *ibid.*, **78**, 2479 (1956).

(5) G. Pincus, M. Chang, M. X. Zarrow, E. S. E. Hafez and A. Merrill, *Science*, **124**, 891 (1956); *Endocrinol.*, **59**, 695 (1956).

(6) J. Ferin, *Acta Endocrinol.*, **22**, 303 (1956); G. A. Overbeek and J. de Visser, *ibid.*, **22**, 318 (1956).

(7) R. Hertz, W. Tullner and E. Raffelt, *Endocrinol.*, **54**, 228 (1954); E. Tyler, *J. Clin. Endocrinol. and Metab.*, **15**, 881 (1955); R. B. Greenblatt, *ibid.*, **16**, 869 (1956).

(8) W. Tullner and R. Hertz, *ibid.*, **12**, 916 (1952).

(9) L. G. Hershberger, E. G. Shipley and L. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

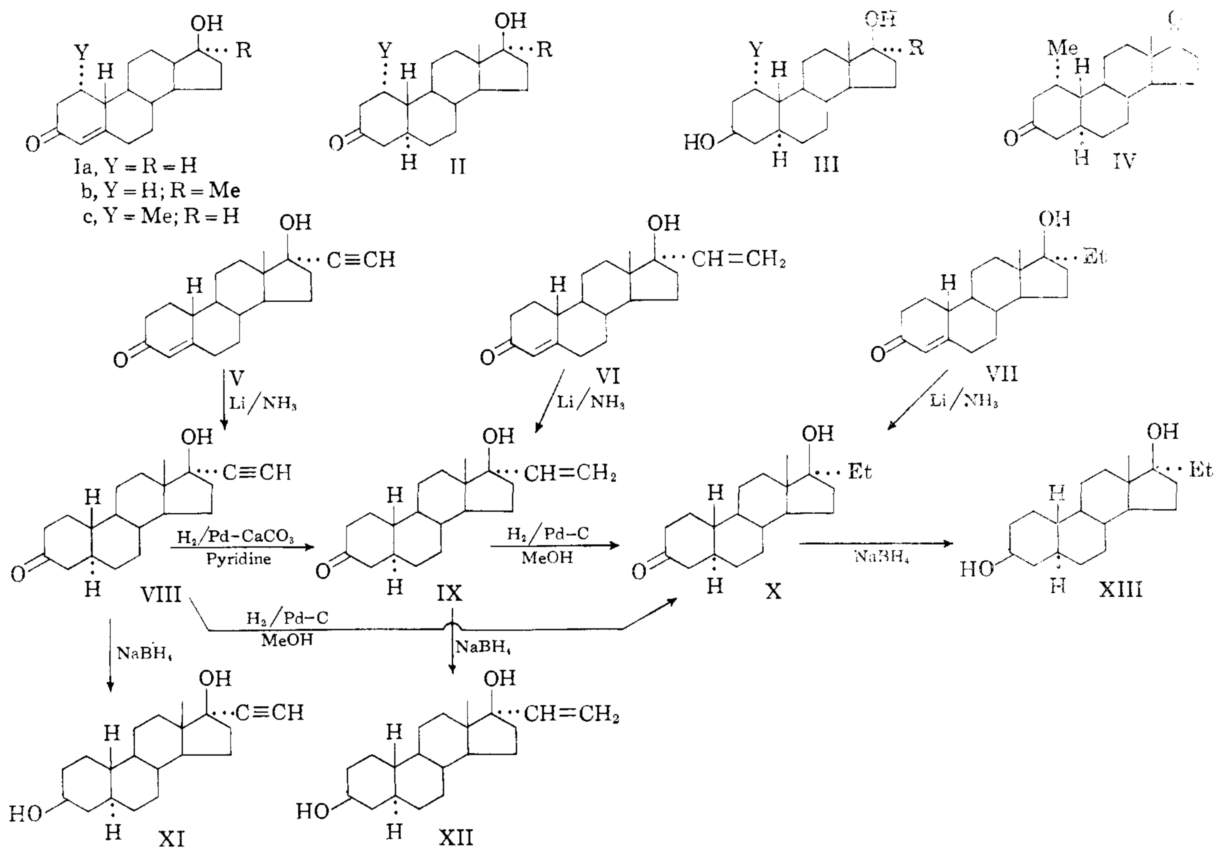
(10) F. J. Saunders and V. A. Drill, *Endocrinol.*, **58**, 567 (1956).

(11) For a preliminary report of the biological data see ref. 2. A detailed evaluation of the biological properties of the new compounds described in this paper will be reported at a later date by Dr. R. I. Dorfman and his associates.

(12) *Cf.* (a) F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2696 (1952); (b) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954), and reference cited therein.

(12c) NOTE ADDED IN PROOF.—After the submission of our manuscript, C. Chen, *Tetrahedron*, **3**, 43 (1958), described the preparation of a 19-nordihydrotestosterone with constants similar to IIa and to which the 5β-configuration was ascribed. A direct comparison of the two compounds showed that they were identical and Dr. Chen has kindly informed us that he confirms our conclusion that IIa has the dihydroallo (5α) stereochemistry.

(13) (a) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958); (b) C. Djerassi, *Bull. soc. chim. France*, 741 (1957), and references cited therein.



yield and oxidation of IIc gave the 3,17-diketone IV.

In view of Dobson and Raphael[14] having found that monosubstituted acetylenes are stable to attack by the sodium–ammonia–ammonium chloride system we extended this work to the preparation of 17α-ethynyl-19-nordihydroallotestosterone (VIII) which was formed in good yield from 17α-ethynyl-19-nortestosterone (V)[4d] providing completely anhydrous conditions prevailed. In the presence of moisture reduction of the ethynyl group to the vinyl group took place. The structure proof of the reduction product VIII, followed from elemental analysis, the observed bands in the infrared region at 3330 (hydroxyl) 2750 (acetylenic hydrogen) and 1700 cm.$^{-1}$ (saturated ketone) and its selective hydrogenation in pyridine solution over a palladium-calcium carbonate catalyst[15] to 17α-vinyl-19-nordihydroallotestosterone (IX). The latter compound also was prepared by the direct lithium–ammonia–ammonium chloride reduction of 17α-vinyl-19-nortestosterone[15] (VI). Hydrogenation of both VIII and IX in ethyl acetate solution over palladium–carbon afforded 17α-ethyl-19-nordihydroallotestosterone (X) identical to that obtained by the lithium–ammonia–ammonium chloride reduction of 17α-ethyl-19-nortestosterone (VII).[4e] The corresponding 3β-alcohols XI, XII and XIII were obtained readily by sodium borohydride reduction of the appropriate ketones VIII, IX and X, respectively.

(14) N. A. Dobson and R. A. Raphael, *J. Chem. Soc.*, 3558 (1955).

(15) L. Ruzicka and P. Muller, *Helv. Chim. Acta*, **22**, 755 (1939).

Experimental[16]

19-Norandrostane-17β-ol-3-one (IIa).—A solution of 19-nortestosterone (Ia) (1.0 g.) in dioxane–ether (1:1, 20 cc.) was added in a steady stream to a solution of lithium (100 mg.) in anhydrous liquid ammonia (100 cc.) with good stirring. At the end of the addition the blue color was discharged by the addition of ammonium chloride (5 g.) and the ammonia allowed to evaporate. The product was extracted with ether, washed with water, dried (Na_2SO_4) and the ether solution evaporated to afford a gum which was adsorbed from benzene (100 cc.) onto alumina (50 g.). Elution with benzene–ether (90:10, 500 cc.) afforded 19-norandrostane-17β-ol-3-one (IIa) (870 mg.), m.p. 124–127°, raised by several crystallizations from aqueous acetone to 130–131°, $[\alpha]_D$ + 60°, IIa exhibited no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.34; H, 9.94.

19-Norandrostane-3β,17β-diol (IIIa). (a) **By the Sodium Borohydride Reduction** of IIa.—To a solution of 19-norandrostane-17β-ol-3-one (IIa) (350 mg.) in dioxane (25 cc.) was added a solution of sodium borohydride (300 mg.) in water (1 cc.) and dioxane (5 cc.). After 1 hour at room temperature addition of water and isolation with ether gave a product which was adsorbed from benzene (300 cc.) onto alumina (35 g.). Elution with benzene–ether (70:30, 500 cc.) afforded 19-norandrostane-3β,17β-diol (IIIa) (300 mg.), m.p. 152–158°, raised by several crystallizations from acetone to 168–170°, solvated with two moles of acetone, $[\alpha]_D$ + 16°.

Anal. Calcd. for $C_{18}H_{30}O_2 \cdot 2(CH_3)_2CO$: C, 73.05, H, 10.73. Found: C, 72.88; H, 10.94.

(16) Melting points were determined in capillary tubes and are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Mr. E. Avila for these measurements and for the infrared spectra which were obtained with a Perkin-Elmer model 21 spectrophotometer with a sodium chloride prism. The elemental analyses were carried out by A. Bernhardt, Mulheim, Ruhr, Germany.

(b) **By the Li/NH$_3$/MeOH Reduction of Ia.**—A solution of 19-nortestosterone (Ia) (500 mg.) in dioxane–ether (1:1, 20 cc.) was added in a steady stream to a solution of lithium (150 mg.) in liquid ammonia (125 cc.) with good stirring. After 5 minutes methanol was added dropwise until the blue color was discharged and the ammonia then was allowed to evaporate. Isolation with ether gave a product which was adsorbed from benzene (500 cc.) onto alumina (30 g.). Elution with benzene–ether (70:30, 400 cc.) yielded 19-norandrostane-3β,17β-diol (IIIa) (320 mg.), m.p. 167–169°, undepressed on admixture with a sample prepared in method a. The infrared spectra of the two compounds were identical.

(c) **By the Li/NH$_3$/MeOH Reductions of IIa.**—Reduction of IIa by the method described in the previous experiment afforded IIIa in 65% yield identical in all respects with the product prepared by methods a and b above.

17α-Methyl-19-norandrostane-17β-ol-3-one (IIb).—Reduction of 17α-methyl-19-nortestosterone (Ib) (1.0 g.) by the method described above for the conversion (Ia → IIa) afforded, after chromatography over alumina (50 g.) and elution with benzene–ether (90:10, 500 cc.), 17α-methyl-19-norandrostane-17β-ol-3-one (IIb) (690 mg.), m.p. 142–146°, raised by several crystallizations from acetone–hexane to 145–146°, $[\alpha]_D + 35°$; IIb exhibited no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.49; H, 10.40.

17α-Methyl-19-norandrostane-3β,17β-diol (IIIb). (a) **By the Sodium Borohydride Reduction of IIb.**—Sodium borohydride reduction of 17α-methyl-19-norandrostane-17β-ol-3-one (IIb) (100 mg.) by the method a described above for the conversion of IIa → IIIa furnished 17α-methyl-19-norandrostane-3β,17β-diol (IIIb) (95 mg.), m.p. 168–173°, raised by several crystallizations from aqueous acetone to 174–176°, $[\alpha]_D \pm 0°$.

Anal. Calcd. for $C_{19}H_{32}O_2 \cdot 2(CH_3)_2CO$: C, 73.48; H, 10.85. Found: C, 73.76, H, 11.12.

(b) **By the Li/NH$_3$/MeOH Reduction of Ib.**—Using the method described above, the diol IIIb was prepared from Ib in 80% yield, identical with a sample prepared in the preceding experiment.

Oxidation of 17α-Methyl-19-norandrostane-3β,17β-diol (IIIb).—A solution of IIIb (190 mg.) in acetone (10 cc.) at 0° was treated with an excess of 8 *N* chromic acid[17] for 2–3 minutes. Addition of water gave a precipitate which was collected, dried and crystallized from acetone–hexane to afford 17α-methyl-19-norandrostane-17β-ol-3-one (IIb) (155 mg.), m.p. 142–144°, raised by crystallization to 145–146°, undepressed on admixture with a sample prepared as above (Ib → IIb).

1α-Methyl-19-norandrostane-17β-ol-3-one (IIc).—A solution of 1α-methyl-19-nortestosterone[4i,18] (Ic) (2.0 g.) in dioxane–ether (1:1, 150 cc.) was added in a steady stream to a solution of lithium (160 mg.) in liquid ammonia (175 cc.) with good stirring. Ammonium chloride (5 g.) then was added and the ammonia allowed to evaporate. Isolation with ether gave a product which was adsorbed from benzene (100 cc.) onto alumina (75 g.). Elution with benzene–ether (80:20, 500 cc.) afforded 1α-methyl-19-norandrostane-17β-ol-3-one (IIc) (1.28 g.), m.p. 184–189°, raised by several crystallizations from methanol to 186–188°, $[\alpha]_D + 46°$; IIc exhibited no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.4. Found: C, 78.78; H, 9.94.

1α-Methyl-19-norandrostane-3β,17β-diol (IIIc). Sodium borohydride reduction of IIc by the method described above afforded, in 70% yield, 1α-methyl-19-norandrostane-3β,-17β-diol (IIIc) having m.p. 204–206°, $[\alpha]_D + 51°$.

Anal. Calcd. for $C_{19}H_{32}O_2$; C, 78.03, H, 11.03. Found: C, 77.55; H, 10.84.

1α-Methyl-19-norandrostane-3,17-dione (IV).—1α-Methyl-19-norandrostane-17β-ol-3-one (IIc) (500 mg.) in acetone (40 cc.) at 0° was treated with an excess of 8 *N* chromic acid[17] for 3 minutes. Addition of water and isolation with ether gave a product which was adsorbed from benzene–hexane (1:1, 50 cc.) onto alumina (25 g.). Elution with benzane (500 cc.) afforded 1α-methyl-19-norandrostane-3,17-dione (IV) (470 mg.), m.p. 150–152°, raised by crystallizations from aqueous acetone to 154–156°, $[\alpha]_D + 115°$.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.23, H, 9.98.

17α-Ethynyl-19-norandrostane-17β-ol-3-one (VIII).—A solution of 17α-ethynyl-19-nortestosterone[4d] (15 g.) in dioxane–ether (1:1, 250 cc.) was added rapidly to a well-stirred solution of lithium (2.25 g.) in liquid ammonia (1.5 l.); ammonium chloride (30 g.) then was added and the ammonia allowed to evaporate. Isolation with methylene chloride afforded a product which was adsorbed from benzene–hexane (50:50, 500 cc.) onto alumina (700 g.). Elution with benzene (1.5 l.) afforded 17α-ethynyl-19-norandrostane-17β-ol-3-one (VIII) (10.8 g.), m.p. 195–215°, raised by crystallizations from acetone–hexane to 222–223°, $[\alpha]_D + 6°$; VIII exhibited no selective absorption in the ultraviolet λ_{max}^{KBr} 3330 (OH), 2750 (—C≡CH) and 1700 cm.$^{-1}$ (=CO).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.30; H, 9.52.

17α-Ethynyl-19-norandrostane-3β,17β-diol (XI).—Reduction of 17α-ethynyl-19-norandrostane-17β-ol-3-one (VIII) (470 mg.) with sodium borohydride using the method described above afforded 17α-ethynyl-19-norandrostane-3β,-17β-diol (XI) (370 mg.), m.p. 188–192°, raised by several crystallizations from acetone to 192–193°, $[\alpha]_D - 15°$.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.63; H, 9.84.

17α-Vinyl-19-norandrostane-17β-ol-3-one (IX). (a) **By the Li/NH$_3$/NH$_4$Cl reduction of 17α-vinyl-19-nortestosterone** (VI).[15]—This reduction was carried out as described above (V → VIII). 17α-Vinyl-19-nortestosterone (VI) (7.5 g.) yielded after chromatography the dihydroallo compound IX (4.25 g.), m.p. 186–190°, raised by several crystallizations from methanol to 192–193°, $[\alpha]_D + 47°$; IX exhibited no selective absorption in the ultraviolet λ_{max}^{KBr} 3400 (—OH), 1700 (>C=O) and 908 cm.$^{-1}$ (>C=CH$_2$).

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.18; H, 10.05.

(b) **By the Hydrogenation of 17α-Ethynyl-19-norandrostane-17β-ol-3-one** (VIII).—A suspension of 2% palladium-on-calcium carbonate (400 mg.) in pyridine (20 cc.) was hydrogenated for 36 hours. A solution of 17α-ethynyl-19-norandrostane-17β-ol-3-one (VIII) (750 mg.) in pyridine (20 cc.) then was added to the catalyst and stirred at atmospheric pressure under hydrogen. After 35 minutes the uptake of hydrogen was 1.05 moles and had virtually ceased. The catalyst was removed by filtration through Celite. Addition of water to the filtrate and extraction with methylene dichloride (pyridine was washed out with 2*N* hydrochloric acid) afforded 17α-vinyl-19-norandrostane-17β-ol-3-one (IX) (700 mg.), m.p. 191-193°, undepressed on admixture with a sample prepared as in method a; $[\alpha]_D + 49°$.

17α-Vinyl-19-norandrostane-3β,17β-diol (XII).—Reduction of 17α-vinyl-19-nor-androstane-17β-ol-3-one (IX) (1.0 g.) with sodium borohydride using the method described above afforded 17α-vinyl-19-norandrostane-3β,17β-diol (XII) (950 mg.), m.p. 155–157° raised by crystallizations from acetone–hexane to 167–169°, $[\alpha]_D + 9°$.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.63; H, 10.71.

17α-Ethyl-19-norandrostane-17β-ol-3-one (X). (a) **By the Li/NH$_3$/NH$_4$Cl Reduction of 17α-Ethyl-19-nortestosterone** (VII).[4g]—This reduction was carried out exactly as described above (V → VIII). 17α-Ethyl-19-nortestosterone (VII) (1 g.) yielded after chromatography the dihydroallo compound X (600 mg.), m.p. 196–199°, raised by several crystallizations from methanol to 212–213°, $[\alpha]_D + 33°$.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.47; H, 10.49.

(b) **By the Hydrogenation of 17α-Vinyl-19-norandrostane-17β-ol-3-one** (IX).—A suspension of 5% palladium-on-carbon (500 mg.) in methanol (50 cc.) was hydrogenated for 30 minutes. A solution of 17α-vinyl-19-norandrostane-17β-ol-3-one (IX) (1.6 g.) in methanol (200 cc.) was added to the catalyst and stirred at atmosphere pressure for 2.5 hours when the uptake of hydrogen ceased. After removal of the

(17) For details of this procedure see A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(18) For assignment of the 1α-configuration see C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6377 (1956).

catalyst by filtration the solution was evaporated to afford 17α-ethyl-19-norandrostane-17β-ol-3-one (X) (1.56 g.), m.p. 195–200°, raised by several crystallizations from acetone-hexane to 211–213°, identical in all respects with the sample prepared as in method a.

(c) **By the Hydrogenation of 17α-Ethynyl-19-norandrostane-17β-ol-3-one** (VIII).—As described in the previous experiment the 17α-ethynyl compound VII was hydrogenated to yield 17α-ethyl-19-norandrostane-17β-ol-3-one (X) (63% yield), identical in every respect with the products obtained in the two preceding experiments.

17α-Ethyl-19-norandrostane-3β,17β-diol (XIII).—Reduction of 17α-ethyl-19-norandrostane-17β-ol-3-one (X) (1.0 g.) with sodium borohydride using the method described above afforded 17α-ethyl-19-norandrostane-3β,17β-diol (XIII) (670 mg.), m.p. 174–180°, raised by crystallizations from acetone–hexane to 181–183°, $[\alpha]_D + 2°$.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38 H, 11.18. Found: C, 78.20 H, 11.03.

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

Steroids. CII.[1] Synthesis of 19-Norprogesterone from Estrone[2]

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17α-Ethinylestradiol methyl ether 17-acetate (IId), obtainable in three steps from estrone, was converted by means of hypobromous acid followed by zinc treatment into 17α-acetylestradiol 3-methyl ether 17β-acetate (IVb). Removal of the 17α-acetyl group was accomplished concurrently with Birch reduction of the aromatic ring and 19-norprogesterone (VIII) was prepared without isolation of intermediates by acid hydrolysis of the dihydroanisole and oxidation at C-20, the over-all yield from 17α-ethinylestradiol 3-methyl ether (IIc) being 30%. Alternatively, this reaction sequence could also be applied to 17α-ethinylestradiol diacetate (IIb), whereupon 3-hydroxy-17β-acetyl-1,3,5-estratriene (Va) was obtained in 62% over-all yield, all of the intermediates having been characterized. Finally, 19-nor-17α-ethinyltestosterone (XIa) also has been converted into 19-norprogesterone (VIII), the key step being calcium–ammonia reduction of the 3-enol ether XIII of 17β-acetoxy-17-iso-19-norprogesterone.

19-Norprogesterone (VIII) was the first 19-nor steroid in which removal of the angular methyl group was shown to be accompanied by a remarkable increase in biological activity.[3,4] This prompted the synthesis of a large number of 19-nor analogs of steroid hormones[5b] and the first to find clinical application has been 19-nor-17α-ethinyltestosterone (Norlutin), a substance readily obtainable[5a,6] from estrone (I). On the other hand, 19-norprogesterone (VIII) so far has been prepared[4] only by Birch reduction[7] of 3-methoxy-17β-acetyl-1,3,5-estratriene (Vb) and the latter's synthesis[8,9] is cumbersome and unattractive for large scale work. Since considerable amounts of the aromatic precursor Va as well as of 19-norprogesterone (VIII) were required for extensive biological and chemical experimentation, alternative synthetic routes were examined and the present paper deals with several successful approaches.

Salamon and Reichstein[10] were the first to observe that Faworsky bromination[11] of 17α-ethinyl-17β-acetoxy steroids followed by debromination leads to the corresponding 17α-acetoxy-20-keto-pregnane derivatives (IX). We decided to examine this reaction in the estrogen series in order to obtain a substrate suitable for Birch reduction and the first studies were conducted with the previously unknown 17α-ethinylestradiol 3,17-diacetate (IIb), prepared by acid-catalyzed acetylation of 17α-ethinylestradiol (IIa).[12] Treatment of the diacetate IIb with N-bromoacetamide in buffered aqueous acetic acid furnished in 96% yield, the dibromo ketone IIIa, which could be debrominated with zinc dust to 17α-acetylestradiol 3,17β-diacetate (IVa). The problem resolved itself now largely to developing conditions for the deacetoxylation of IVa without producing a D-homo rearrangement.[13] Rosenfeld[14] reported recently that allopregnane-3β,17β-diol-20-one diacetate (IX) could be deacetoxylated in 46% yield to allopregnan-3β-ol-20-one acetate (X) by employing a large excess of zinc in glacial acetic acid. These conditions did not appear suitable for large scale work nor applicable to a Δ^4-3-keto-19-nor steroid (XIII) and attention was directed, therefore. at the calcium–liquid ammonia reaction.[15] The Glaxo group[15] de-

(1) Paper CI, A. Bowers, H. J. Ringold and E. Denot, THIS JOURNAL, **80**, 6115 (1958).

(2) Presented at the 6th National Medicinal Chemistry Symposium, Madison, Wisc., June 25, 1958.

(3) M. Ehrenstein, *J. Org. Chem.*, **9**, 435 (1944), first prepared an amorphous 19-norprogesterone from strophanthidine and found it to be at least as active as progesterone (see W. M. Allen and M. Ehrenstein, *Science*, **100**, 251 (1944)). Subsequently, this substance was obtained in crystalline form (G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957)) and shown to possess the 14-iso-17-iso orientation with the 10β-configuration (C. Djerassi, M. Ehrenstein and G. W. Barber, *ibid.*, **612**, 93 (1958)). The crystalline isomer exhibited eight times the biological activity of progesterone.

(4) C. Djerassi, L. Miramontes and G. Rosenkranz, THIS JOURNAL, **75**, 4440 (1953), first described (for preliminary communication see *ibid.*, **73**, 3540 (1951)) 19-norprogesterone (VIII) with the correct stereochemistry at all asymmetric centers (see C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956)).

(5) (a) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4089 (1954); (b) additional biological data as well as references to the preparation of other 19-nor steroids are given by D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958).

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