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

Steroids. LIV.[1] Synthesis of 19-Nor-17α-ethynyltestosterone and 19-Nor-17α-methyltestosterone[2]

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19-Nortestosterone upon oxidation with chromium trioxide followed by protection of the Δ^4-3-keto function *via* the enol ether, ethynylation with acetylene in the presence of potassium *t*-amyloxide and acid cleavage of the enol ether grouping furnished 19-nor-17α-ethynyltestosterone. This lower homolog of 17α-ethynyltestosterone proved to be a more potent, orally effective progestational hormone than any known steroid. 19-Nor-17α-methyltestosterone, differing from the orally effective androgen only in the absence of an angular methyl group, was synthesized by a modified Birch reduction of the methyl ether of 17α-methylestradiol or by reaction of 19-nor-3-ethoxy-$\Delta^{3,5}$-androstadien-17-one with methylmagnesium bromide followed by acid hydrolysis.

Recently,[4] there was recorded the preparation of 19-norprogesterone (I), which stereochemically was identical at all asymmetric centers with the natural hormone progesterone (II) but lacked the angular methyl group at C-19. Biological experiments[5] indicated that this lower homolog I exhibits between five to eight times the progestational activity of progesterone and may thus be considered to be the most active, known progestational hormone. The subsequent synthesis[6] and biological evaluation of 19-nordesoxycorticosterone (III) indicated that in the desoxycorticosterone (IV) series the removal of the angular methyl group resulted in an augmentation of the biological activity. These observations are in marked contrast to those reported for 19-nortestosterone (V)[7,8] since its androgenic activity is only about one-third[8,9] of that of the parent hormone. It seemed pertinent, therefore, to investigate the corresponding analog VIII of 17α-ethynyltestosterone (IX), a substance which, though chemically related to the androgens, is an orally effective progestational hormone and is employed clinically for such purposes.[10]

The two procedures commonly employed for the synthesis of 17α-ethynyltestosterone (IX) commence with either dehydroepiandrosterone[11] or Δ^4-androstene-3,17-dione[12] and we selected an adaptation of the latter for the preparation of the desired 19-nor-17α-ethynyltestosterone (VIII) in view of the ready availability[8] of 19-nortestosterone (V) from estrone. Chromium trioxide oxidation[13] of 19-nortestosterone to 19-nor-Δ^4-androstene-3,17-dione (VI) proceeded in good yield[14] and treatment of the latter with ethyl orthoformate in the presence of pyridine hydrochloride furnished the crystalline enol ether VII exhibiting the characteristic negative rotation[15] and ultraviolet absorption maximum at 242 mμ; the presence of the intact 17-keto group was demonstrated by the presence of a strong infrared band at 1740 cm.$^{-1}$ Reaction of a toluene solution of this enol ether VII with acetylene in the presence of potassium *t*-amyloxide,[16] followed by acid cleavage of the enol ether function, led to 19-nor-17α-ethynyltestosterone (VIII). Animal experiments by Dr. Roy Hertz, *et al.*, of the National Institutes of Health indicate[17] that this substance is several times more effective as an oral progestational hormone when compared to 17-ethynyltestosterone (IX) and the efficacy of this 19-nor analog VIII in human females has been established recently in clinical trials. The results of this extensive biological work will be reported by others in due course, but it is pertinent to emphasize that removal of the C-19 angular methyl group in both progesterone (II) and 17α-ethynyltestosterone (IX) results in a marked increase in progestational potency in spite of the fact that it has not as yet been demonstrated whether both these steroids (II, IX) exert their biological effects by the same biochemical mechanism.

In view of the availability of the enol ether VII, it seemed appropriate to prepare 19-nor-17α-methyltestosterone (X) by reaction with methylmagnesium bromide and acid hydrolysis, and this reaction sequence proceeded in the anticipated manner. Of interest is the observation that in preliminary animal experiments, 19-nor-17α-methyltestosterone (X) proved to be at least as potent an androgen as 17α-methyltestosterone (XI) in the chick comb test but was only weakly active in rats as far as increase in seminal vesicle weight is concerned. For the preparation of larger

(1) Paper LIII, G. Rosenkranz, O. Mancera and F. Sondheimer, THIS JOURNAL, **76**, 2227 (1954).

(2) Presented in part at the Milwaukee, Wisconsin, Meeting of the American Chemical Society, April, 1952; *cf.* C. Djerassi, L. Miramontes and G. Rosenkranz, Division of Medicinal Chemistry, Abstracts, p. 18J.

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(4) C. Djerassi, L. Miramontes and G. Rosenkranz, THIS JOURNAL, **75**, 4440 (1953); see also preliminary announcement by L. Miramontes, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3540 (1951).

(5) W. W. Tullner and R. Hertz, *J. Clin. Endocrinology and Metab.*, **12**, 916 (1952).

(6) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, THIS JOURNAL, **75**, 4117 (1953).

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

(8) A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5366 (1953).

(9) A. J. Birch, *Ann. Repts. Prog. Chem. (Chem. Soc. London)*, **47**, 210 (1950).

(10) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, p. 394.

(11) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); **21**, 371 (1938); H. H. Inhoffen, W. Logemann, W. Hohlweg and A. Serini, *Ber.*, **71**, 1024 (1938).

(12) H. H. Inhoffen, U. S. Patent 2,358,808 (*C. A.*, **39**, 1738 (1945)); B. Riegel and Y. C. Liu, *J. Org. Chem.*, **16**, 1610 (1951).

(13) This oxidation has since been described by Wilds and Nelson (ref. 8).

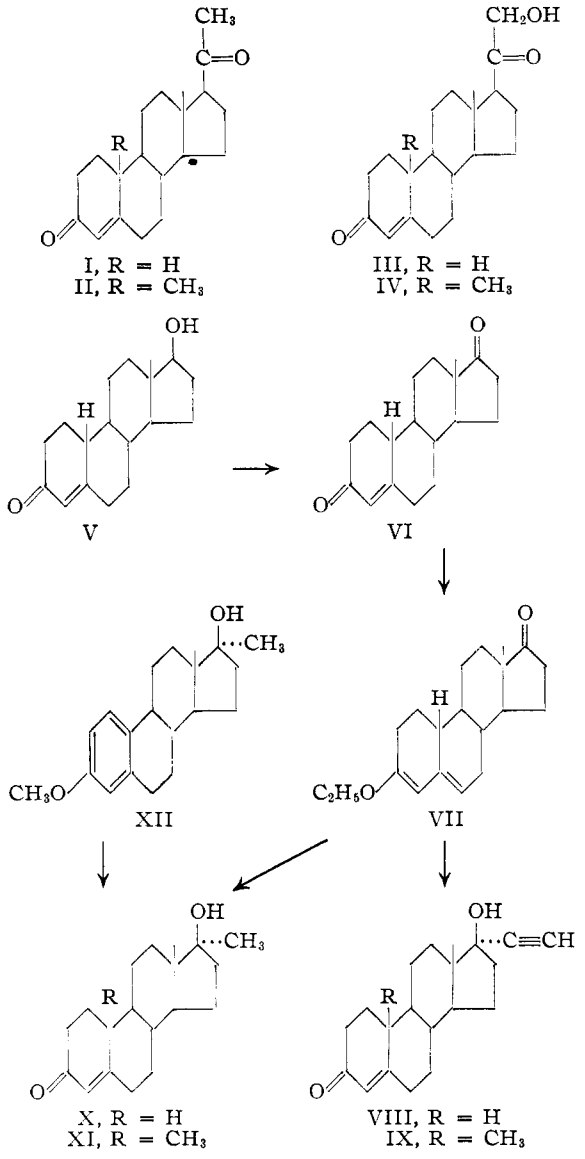
(14) From a preparative viewpoint, it was advantageous to convert estrone methyl ether directly to VI without isolation of intermediates and such a reaction sequence is given in the Experimental portion of the present paper.

(15) E. Schwenk, G. Fleischer and B. Whitman, THIS JOURNAL, **60**, 1702 (1938).

(16) *Cf.* H. Stavely, *ibid.*, **61**, 79 (1939).

(17) R. Hertz, W. Tullner and E. Raffelt, *Endocrinology*, **54**, 228 (1954).

amounts of 17α-methyl-19-nortestosterone (X) it was found preferable to subject the 3-methyl ether of 17α-methyl-estradiol (XII) to a modified Birch reduction and to hydrolyze the intermediate enol ether without purification to yield the desired 19-nor ketone X directly.



Experimental[18]

19-Nor-Δ⁴-androstene-3,17-dione (VI).—For the preparation of larger quantities of this substance, it was found preferable to carry out all steps starting with estrone methyl ether without isolation of intermediates. The isolation and characterization of the intermediates (starting with estradiol methyl ether) have already been recorded by Wilds and Nelson.[8]

To a solution of 7.5 g. of estrone methyl ether in 750 cc. of anhydrous dioxane was added 2 l. of liquid ammonia followed by the addition (15 minutes) of 15 g. of lithium wire. After stirring for one hour, 150 cc. of ethanol was added slowly and finally 500 cc. of water. The ammonia was evaporated by warming on the steam-bath, the product was extracted with ether and ethyl acetate, washed with water, dried and evaporated. The resulting solid methyl ether (7.4 g.), dissolved in 400 cc. of methanol, was refluxed for one hour with 150 cc. of 4 *N* hydrochloric acid, water was added and the crude 19-nortestosterone (V) was extracted with ethyl acetate, washed, dried and evaporated. The oil thus obtained was dissolved in 100 cc. of glacial acetic acid and was treated at 20° with stirring with a solution of 2.7 g. of chromium trioxide in 50 cc. of 70% acetic acid. After 1.5 hours at room temperature, methanol was added and the mixture was evaporated to dryness *in vacuo*. The residue was extracted with ether, washed with water until neutral, dried, evaporated and the resulting semi-solid (7.0 g.) was chromatographed on unwashed alumina. Recrystallization of the ether eluates from acetone–hexane furnished 3.2 g. (45% over-all yield) of 19-nor-Δ⁴-androstene-3,17-dione (VI) with m.p. 165–168°, which was satisfactory for the next step. The analytical sample exhibited m.p. 171–172° (Kofler), $[\alpha]_D$ +139°; λ_{max}^{EtOH} 240 mμ, log ε 4.24; $\nu_{max}^{CS_2}$ 1740 and 1674 cm.⁻¹; lit.[8] m.p. 170–171°, $[\alpha]_D$ +137°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.39; H, 8.99.

3-Ethoxy-19-nor-Δ³,⁵-androstadien-17-one (VII).—A mixture of 2 g. of the diketone VI, 50 cc. of dry, thiophene-free benzene, 0.4 g. of pyridine hydrochloride, 4 cc. of absolute ethanol and 4 cc. of ethyl orthoformate was refluxed for 3 hours, 5 cc. of distillate was collected and the solution was then refluxed for two more hours after adding an additional 4 cc. of ethyl orthoformate. The volatile components were removed *in vacuo*, the residue was extracted with ether, washed well with water, dried, evaporated and crystallized from hexane–acetone to furnish 1.0–1.4 g.[19] of the enol ether VII with m.p. 133–140° and this material was used in the subsequent transformations. The analytical sample was obtained from ether with m.p. 141–143°, $[\alpha]_D$ −87° (pyridine); λ_{max}^{EtOH} 242 mμ, log ε 4.26; $\nu_{max}^{CS_2}$ 1740 cm.⁻¹.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.75; H, 9.39. Found: C, 79.80; H, 9.15.

19-Nor-17α-ethynyl-Δ⁴-androsten-3-one-17β-ol (VIII).—A solution of 1.0 g. of the above enol ether VII in 25 cc. of dry toluene was added to 1 g. of potassium dissolved in 25 cc. of *t*-amyl alcohol and the air was displaced by bubbling nitrogen through the mixture for 15 minutes. A slow stream of dry, purified acetylene was then passed through the mixture at room temperature with stirring for 14 hours. After dilution with water and adjustment of the *p*H to 1 by addition of 50% hydrochloric acid, steam was passed through the solution until no more volatile material came over. The residue was cooled, the solid was collected and recrystallized several times from ethyl acetate; yield 64–78%, m.p. 203–204° (Kofler), $[\alpha]_D$ −25°; λ_{max}^{EtOH} 240 mμ, log ε 4.24; $\nu_{max}^{CHCl_3}$ 1668 cm.⁻¹ and free hydroxyl band.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.83; H, 8.80.

19-Nor-17α-methyltestosterone (X). (a) From 3-Ethoxy-19-nor-Δ³,⁵-androstadien-17-one (VII).—To a solution of 1 g. of the enol ether VII in 10 cc. of dry ether was added slowly 25 cc. of an ethereal solution of 10 g. of methylmagnesium bromide (Arapahoe Chemicals, Boulder, Colo.) and after refluxing for 2 hours, the reaction mixture was poured onto ice and acidified with 50% hydrochloric acid. Cleavage of the enol ether function was accomplished by allowing the acidic mixture to stand at room temperature for 1–2 hours, whereupon the product was extracted with much ether and processed in the usual manner; yield 0.95 g., m.p. 140–150°. Several recrystallizations from ether–hexane furnished the analytical sample with m.p. 156–158° (Kofler), $[\alpha]_D$ +31°; λ_{max}^{EtOH} 240 mμ, log ε 4.23; $\nu_{max}^{CS_2}$ 1680 cm.⁻¹ and free hydroxyl band.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.32; H, 9.80.

(b) By Birch Reduction of 17-Methylestradiol Methyl Ether (XII).—To a solution of 16 g. of 17-methylestradiol

(18) All melting points are uncorrected. Rotations were measured at 20° in chloroform solution, unless specified otherwise. We are grateful to Srta. Paquita Revaque for all the physical measurements and to Srta. Amparo Barba for the microanalyses. We are also indebted to Srta. Mercedes Velasco for her skillful technical assistance.

(19) This reaction was carried out several times under identical conditions with somewhat erratic results, thus accounting for the wide range in yields.

methyl ether (m.p. 99–104°, preparation described below) in 1 l. of dry ether was added 1300 cc. of liquid ammonia followed by 8 g. of lithium wire. After stirring for 30 minutes, 175 cc. of ethanol was added during 30 minutes, the solvents were evaporated, and the residue was carefully treated with water. The solid product was collected, washed well with water, dissolved in 800 cc. of methanol and refluxed with 480 cc. of 3 *N* hydrochloric acid for 15 minutes. Addition of water, isolation with ether, and crystallization from ether–hexane yielded 7.4 g. of 19-nor-17α-methyltestosterone (X), with m.p. 151–154°. A further purified specimen showed m.p. 155–157°, $[\alpha]_D$ +33°; λ_{max}^{EtOH} 240 mμ, log ε 4.24. Identity with the material prepared by method a was established through mixture m.p. and infrared comparison.

In one experiment, conducted as above, the Birch reduction product was purified prior to hydrolysis. After crystallization of the crude solid from ether, the enol ether was obtained in 62% yield, m.p. 129–131°, $[\alpha]_D$ +91°, no appreciable absorption in the ultraviolet.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.82; H, 10.34.

On acid hydrolysis, as described for the unpurified material, it yielded X in *ca.* 70% yield.

17-Methylestradiol Methyl Ether (XII).[20]—To a solution of 34 g. of estrone methyl ether in 850 cc. of dry benzene was added slowly 175 cc. of an ethereal solution of *ca.* 70 g. of methylmagnesium bromide. After being refluxed for 2 hours, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The aqueous layer was extracted with ether, and the combined organic solutions were washed with water, dried and evaporated. Crystallization from ether–pentane furnished 31.1 g. (87%) of product with m.p. 99–104°. A further purified sample exhibited constant m.p. 104–105°, $\nu_{max}^{CHCl_3}$ free hydroxyl band only; this material was chromatographically pure (reported: m.p. 95–100° (for a crude specimen)[19a]; m.p. 126.5–128°[19b]). The m.p. discrepancy may be due to polymorphism.

(20) *Cf.* (a) A. Cohen, J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 445 (1935); (b) B. C. Bocklage, H. J. Nicholas, E. A. Doisy, W. H. Elliott, S. A. Thayer and E. A. Doisy, *J. Biol. Chem.*, **202**, 27 (1953).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

Interconversion of Adrenal Cortical Side Chains. The Transformation of Cortisone and Hydrocortisone to Corticosterone

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Cortisone and hydrocortisone acetates on treatment with methanolic hydrogen chloride followed by reduction with lithium aluminum hydride and oxidation with manganese dioxide gave Δ⁴-pregnene-11β,20β-diol-3-one-21-al dimethylacetal (IV). Hydrolysis of the latter produced the corresponding aldehyde V, which could be isomerized to corticosterone (VII) by refluxing pyridine, or preferably, by methanolic sodium methoxide treatment of its sodium bisulfite addition product VI.

Corticosterone, one of the original active hormones isolated from adrenal cortical extracts,[1] has remained relatively unavailable despite its biological importance. Cortical extracts, moreover, have constituted the chief source of the very limited supply of this substance. The published chemical procedures for its preparation include only the classical synthesis from desoxycholic acid of von Euw, Lardon and Reichstein[2] and the partial synthesis from 11-dehydrocorticosterone in low yield *via* the 3,20-disemicarbazone derivative.[3] Biological formation from desoxycorticosterone by various microörganisms[4] and by the isolated adrenal gland[5] also have been described.

The present paper outlines a brief partial synthesis of corticosterone in 20–25% over-all yield from the currently readily available hormones, cortisone and hydrocortisone, by a reaction sequence capable of extension to the general conversion of the dihydroxy cortical side chain to the ketol part structure. The reverse sequence has been carried out in effect by Sarett[6] through the conversion of 20-keto-21-acetoxypregnane derivatives to their corresponding 17α-hydroxy analogs by osmylation of the Δ¹⁷⁽²⁰⁾-cyanopregnenes.

Recently Mattox[7] observed that both 17α,21-dihydroxypregnan-20-one as well as Δ¹⁶-21-hydroxypregnen-20-one derivatives[8] are transformed by methanolic hydrogen chloride to systems bearing a glyoxal 21,21-dimethyl acetal side chain; thus, cortisone acetate (I) was found to give Δ⁴-pregnene-3,11,20-trione-21-al dimethylacetal (II) in 75% yield, an observation which we have duplicated. Application of the Mattox conditions to hydrocortisone acetate (IX) was found similarly to produce the corresponding 11β-hydroxy compound X in 51% yield.[8a]

The Δ⁹⁽¹¹⁾-anhydro compound XII, prepared independently by rearrangement of Δ⁹⁽¹¹⁾-anhydro-17-hydroxycorticosterone acetate (XI), did not appear to be present to any appreciable extent, if at all. Retention of the 11β-hydroxyl group under these conditions contrasts with predominant dehydration occurring in acetic acid, chloroform or acetonitrile containing catalytic amounts of hydrogen bromide,[9] and with the acetic acid–hydrochloric

(1) (a) T. Reichstein, *Helv. Chim. Acta*, **19**, 1107 (1936); (b) T. Reichstein, *ibid.*, **20**, 953 (1937); (c) H. L. Mason, C. S. Myers and E. C. Kendall, *J. Biol. Chem.*, **114**, 613 (1936); (d) H. L. Mason, W. M. Hoehn, B. F. McKenzie and E. C. Kendall, *ibid.*, **120**, 719 (1937).

(2) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944), and earlier references cited therein.

(3) N. L. Wendler, Huang-Minlon and M. Tishler, THIS JOURNAL, **73**, 3818 (1951).

(4) (a) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (1952); (b) G. M. Shull, D. A. Kita and J. W. Davisson, U. S. Patent 2,658,023 (1953).

(5) O. Hechter, R. P. Jacobsen, R. Jeanloz, H. Levy, C. W. Marshall, G. Pincus and V. Schenker, THIS JOURNAL, **71**, 3261 (1949).

(6) L. H. Sarett, *ibid.*, **70**, 1454 (1948).

(7) V. R. Mattox, *ibid.*, **74**, 4340 (1952).

(8) E. Vischer, J. Schmidlin and A. Wettstein [*Helv. Chim. Acta*, **37**, 321 (1954)] have extended the rearrangement to 16α,21-dihydroxypregnan-20-ones.

(8a) NOTE ADDED IN PROOF.—After this manuscript was submitted the conversion of hydrocortisone acetate (IX) to the acetal X was reported by S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163 (1954).

(9) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 4722 (1953).