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

Steroids. LXXX.[1] 1-Methyl-19-nortestosterone and 1-Methyl-17α-ethinyl-19-nortestosterone

BY H. J. RINGOLD, G. ROSENKRANZ AND FRANZ SONDHEIMER[2]

RECEIVED NOVEMBER 15, 1955

The synthesis of 1-methyl-19-nortestosterone (Vb) and of 1-methyl-17α-ethinyl-19-nortestosterone (IXb) has been carried out. The latter substance was found to have the same order of activity as the powerful oral progestational substance-17α-ethinyl-19-nortestosterone (IXa), a new route to which is also described.

The discovery that the removal of the C-19 methyl group from steroidal hormones may lead to a considerable increase in biological activity[3] has led us to undertake an investigation aimed at making available for testing hormone analogs in which the C-19 methyl group is shifted to C-1 rather than eliminated. In the present paper we describe the synthesis of two such analogs, namely, of 1-methyl-19-nortestosterone (Vb) and of 1-methyl-17α-ethinyl-19-nortestosterone (IXb). Work of a similar nature in the pregnane series has been carried out at Wayne University, where the preparation of 1-methyl-19-norprogesterone and of 1-methyl-19-nor-17α-hydroxyprogesterone has been accomplished.[4]

1-Methylestrone (IIb), obtainable by a four-step reaction sequence from Δ^4-androstene-3,17-dione (I),[5] was converted to the methyl ether IIIb by means of methyl sulfate in the usual way. The Birch reduction of this ether with lithium in liquid ammonia[6] proceeded smoothly when propylene glycol monomethyl ether (Dowanol 33-B) rather than ethanol was used as the alcohol. The resulting 1,4-dihydro compound IVb was not purified but hydrolyzed directly with hydrochloric acid in aqueous methanol.[6] Direct crystallization then produced a 43% yield of 1-methyl-19-nortestosterone (Vb), which proved to possess less than 10% the androgenic activity of testosterone.[7]

Chromatographic purification of the mother liquors from which the solid Vb had been removed gave a product which could not be crystallized but seemed to be enriched in the C-1 isomer of Vb.[4]

For the synthesis of 1-methyl-17α-ethinyl-19-nortestosterone (IXb), the crystalline 1-methyl-19-nortestosterone (Vb) was oxidized with the chromium trioxide–pyridine complex[8] to 1-methyl-19-nor-Δ^4-androstene-3,17-dione (VIb). However, the conversion of this substance to the 17α-ethinyl compound IXb through protection at C-3 by formation of the enol ether followed by reaction with acetylene and acid hydrolysis (*cf.* the conversion of VIa to IXa in the 19-nor series[3b]) did not proceed smoothly and an alternative route was employed.

Our original synthesis[3b] of 17α-ethinyl-19-nortestosterone (IXa) proceeded from estrone methyl ether (IIIa) by successive Birch reduction to IVa, hydrolysis to 19-nortestosterone (Va), oxidation to 19-nor-Δ^4-androstene-3,17-dione (VIa), enol ether formation, acetylene reaction and acid hydrolysis. We have now found an alternate method involving the reaction of the Birch reduction product IVa with ethylene glycol in the presence of *p*-toluenesulfonic acid, whereby interchange occurs and 19-nortestosterone 3-cycloethylene ketal (VIIa)[9] was formed.[10] The structure of VIIa was confirmed by the absence of the infrared bands at *ca.* 1660 and 1690 cm.$^{-1}$ present in the 1,4-dihydroanisole IVa from which it was derived[11] and especially by the fact that oxidation with the chromium trioxide–pyridine complex[8] smoothly furnished the 17-ketone VIIIa showing no maximum at 280 mμ in the ultraviolet; under the same oxidation conditions, 1,4-dihydroestradiol methyl ether (IVa) regenerates estrone methyl ether (IIIa) in high yield.[12] Finally, the ketone VIIIa was allowed to react with acetylene and subjected to acid hydrolysis to produce 17α-ethinyl-19-nortestosterone (IXa). Although neither the intermediate VIIa nor VIIIa was crystalline, the over-all yield in the conversion of estrone methyl ether (IIIa) to the final product IXa was *ca.* 50%.

In an analogous fashion to the 19-nor series, the above mentioned Birch reduction product IVb derived from 1-methylestrone methyl ether (IIIb) was converted to the 3-cycloethylene ketal VIIb, oxidized to the 17-ketone VIIIb, allowed to react with acetylene and hydrolyzed. This procedure furnished the crystalline 1-methyl-17α-ethinyl-19-nortestosterone (IXb). In this case the final product had to be chromatographed and crystallized several

(1) Paper LXXIX, O. Mancera, G. Rosenkranz and F. Sondheimer, *Naturwiss.*, in press.

(2) Department of Organic Chemistry, The Weizmann Institute of Science, Rehovoth, Israel.

(3) *Cf.* (a) C. Djerassi, L. Miramontes and G. Rosenkranz, THIS JOURNAL, **75**, 4440 (1953); (b) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954); (c) C. Huggins, E. V. Jensen and A. S. Cleveland, *J. Exp. Med.*, **100**, 225 (1954); (d) A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **77**, 148 (1955).

(4) *Cf.* C. Djerassi, A. E. Lippman and J. Grossman, *ibid.*, **78**, 2479 (1956).

(5) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and S. Kaufmann, *ibid.*, **72**, 4540 (1950). Alternatively, 1-methylestrone (IIb) may be prepared by the rearrangement of $\Delta^{1,4}$-androstadiene-3,17-dione with mineral acids (A. S. Dreiding, W. J. Pummer and A. J. Tomasewski, *ibid.*, **75**, 3159 (1953)), but this method calls for the separation of IIb from the 1-hydroxy-4-methyl isomer also formed in the reaction.

(6) *Cf.* A. L. Wilds and N. Nelson, *ibid.*, **75**, 5366 (1953).

(7) Carried out by Dr. C. Huggins, University of Chicago, with the hypophysectomized rat[3c] and by Dr. E. G. Shipley, Endocrine Laboratories, Madison, Wisconsin, with the castrated mouse.

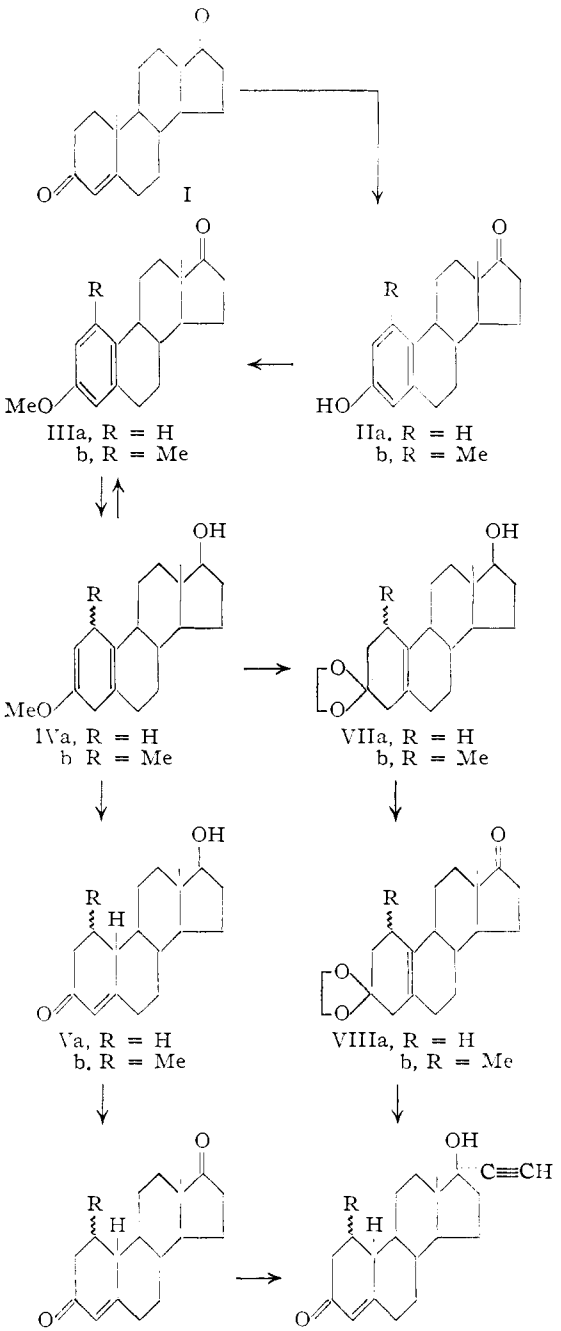
(8) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(9) For simplicity, the double bond in the formula for this substance, as well as for VIIb, VIIIa and VIIIb, has been placed at the original $\Delta^{5(10)}$-position. However, migration to the $\Delta^{5(6)}$-position is not excluded.

(10) We are indebted to Professor Gilbert Stork of Columbia University for suggesting this interchange reaction.

(11) G. Stork, THIS JOURNAL, **73**, 504 (1951).

(12) Dehydrogenation in ring A of IVa takes place also through N-bromoacetamide or Oppenauer oxidation and to some extent even by allowing IVa to be in contact with air for long periods.



times before it was obtained pure, probably due to the formation of the two isomers at C-1. Since the total Birch product had been employed for the production of the crystalline IXb, it is not possible at present to determine whether this substance has the same configuration at C-1 as the above described crystalline 1-methyl-19-nortestosterone (Vb).

Preliminary experiments carried out in rabbits indicate that 1-methyl-17α-ethinyl-19-nortestosterone (IXb) has the same order of activity as an oral progestational hormone as does 17α-ethinyl-19-nortestosterone (IXa)[3b] which up to now has been the most powerful substance known with this activity.

Experimental[13]

1-Methylestrone Methyl Ether (IIIb).—A boiling solution of 17 g. of 1-methylestrone (IIb)[5] in 250 cc. of methanol and 600 cc. of 10% aqueous sodium hydroxide was treated dropwise during 20 minutes with 85 cc. of dimethyl sulfate, with stirring. After being boiled for a further 30 minutes, the solution was diluted with 170 cc. of 40% aqueous sodium hydroxide and a further 85 cc. of dimethyl sulfate was then added dropwise during 20 minutes. Boiling was continued for 1 hour and the cooled solution was then treated with 200 cc. of water. The resulting precipitate was collected and washed well with water. This procedure yielded 15.0 g. (84%) of the methyl ether IIIb with m.p. 125–128°. Crystallization from acetone–hexane furnished the analytical sample with m.p. 129–130°, $[\alpha]_D$ +238°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.15; H, 8.59.

1-Methyl-19-nortestosterone (Vb).—Liquid ammonia (2 l.) was carefully added to a solution of 13 g. of 1-methylestrone methyl ether (IIIb) in 1 l. of dry, redistilled propylene glycol monomethyl ether (Dowanol 33-B), the reaction being carried out in a well lagged 12-l. flask. Lithium wire (25 g.) was added gradually during 20 minutes with vigorous stirring and the reaction was allowed to proceed for 2 hours, when the blue color had disappeared. The mixture was diluted with 5 l. of water and the precipitate was collected, washed with water and taken up in hot benzene. The benzene solution was washed well with water, dried and evaporated. The residual crude enol ether IVb showed no absorption maximum in the ultraviolet, whereas the infrared spectrum (in carbon disulfide) showed bands at 1660 and 1690 cm.$^{-1}$, as expected for the 1,4-dihydroanisole grouping.[11]

The crude enol ether IVb derived from 13 g. of 1-methylestrone methyl ether (IIIb) was heated at 60° for 15 minutes with 500 cc. of methanol and 400 cc. of 3 *N* hydrochloric acid. Dilution with water, followed by extraction with ethyl acetate and crystallization from acetone yielded 5.4 g. (43% from IIIb) of 1-methyl-19-nortestosterone (Vb) with m.p. 200–204°. A further purified specimen showed m.p. 205–207°, $[\alpha]_D$ +43°, λ_{max} 242 mμ, log ϵ 4.15, $\nu_{max}^{CS_2}$ 1680 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.47; H, 9.98.

The mother liquors on several successive chromatographic purifications on silica yielded an amorphous product with λ_{max} 243 mμ, log ϵ 4.09, with an infrared spectrum similar to crystalline Vb. This material resisted all attempts at crystallization and is probably enriched in the C-1 isomer of the crystalline 1-methyl-19-nortestosterone.

1-Methyl-19-nor-Δ^4-androstene-3,17-dione (VIb).—A solution of 100 mg. of the crystalline 1-methyl-19-nortestosterone (Vb) in 5 cc. of glacial acetic acid was treated with 50 mg. of chromium trioxide in 1 cc. of water and the solution was allowed to stand for 1 hour. Dilution with water, extraction with ethyl acetate and crystallization of the crude product (75 mg., m.p. 173–177°) from acetone–hexane gave 1-methyl-19-nor-Δ^4-androstene-3,17-dione (VIb) with m.p. 192–195°, $[\alpha]_D$ +132°, λ_{max} 242 mμ, log ϵ 4.16.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.29; H, 8.95.

17α-Ethinyl-19-nortestosterone (IXa) from Estrone Methyl Ether (IIIa) by the Ketal Route.—The Birch reduction of 20 g. of estrone methyl ether (IIIa) was carried out as described previously.[3b,6] The resulting crude enol ether IVa (19.8 g.) was then boiled for 20 hours with 400 cc. of benzene and 70 cc. of ethylene glycol in the presence of 4.4 g. of *p*-toluenesulfonic acid, a continuous water separator being employed. Aqueous sodium carbonate was added and the organic layer was separated, washed with water, dried and evaporated. The residual crude amorphous ketal VIIa (21.4 g.; λ_{max} 234 mμ, log ϵ 3.23) was dissolved in 200 cc. of anhydrous pyridine, the solution was cooled in ice and

(13) Melting points are uncorrected. Rotations were determined (at 20°) in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Miss M. T. Cardenas and Mrs. P. Lopez for these measurements and for the infrared spectra, which were obtained with a Perkin–Elmer model 12C spectrophotometer with sodium chloride prism. Thanks are also due to Mrs. A. Gonzalez for the microanalyses, and to Mr. Francisco Alvarez for his skillful assistance.

21.4 g. of chromium trioxide was added gradually under nitrogen with stirring and continued cooling. The mixture was then allowed to stand at room temperature for 20 hours. Dilution with ethyl acetate, followed by filtration through Celite and alumina and evaporation of the filtrate, produced 18.3 g. of the 3-cycloethylene ketal of 19-nor-Δ^4-androstene-3,17-dione (VIIIa) as an oil showing λ_{max} 232 mμ, log ϵ 3.24, but no maximum at 280 mμ. This product was dissolved in 400 cc. of dry toluene and a solution of 18.3 g. of potassium in 430 cc. of *t*-amyl alcohol was added. The air was displaced by nitrogen and a current of dry, purified acetylene was passed through the mixture at room temperature for 20 hours. Water was added and then hydrochloric acid to *p*H 1. The organic solvents were removed by steam distillation, the mixture was cooled and the precipitate was collected, washed well with water and dried. Crystallization from ethyl acetate produced 9.46 g. of 17α-ethinyl-19-nortestosterone (IXa) with m.p. 201–204°, $[\alpha]_D$ −24°, and chromatography of the mother liquors on alumina furnished another 1.07 g. with m.p. 202–205° (total yield, 50%). Identity with the previously reported compound (m.p. 203–204°, $[\alpha]_D$ −25°)[3b] was shown through mixture m.p. determination and infrared comparison.

1-Methyl-17α-ethinyl-19-nortestosterone (IXb) from 1-Methylestrone Methyl Ether (IIIb).—The Birch reduction of 7 g. of 1-methylestrone methyl ether (IIIb) was carried out as described above under the preparation of 1-methyl-19-nortestosterone (Vb). The resulting unhydrolyzed enol ether IVb was then carried through the stages of ketalization, chromium trioxide–pyridine oxidation, acetylene condensation and acid hydrolysis, exactly as described in detail in the preceding paragraph for the 1-unsubstituted series. Chromatographic purification of the final product on silica followed by several crystallizations from ether–pentane produced 1-methyl-17α-ethinyl-19-nortestosterone (IXb) with m.p. 196–197°, λ_{max} 242 mμ, log ϵ 4.16.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 81.21; H, 9.15.

Oxidation of 1,4-Dihydroestradiol Methyl Ether (IVa) to Estrone Methyl Ether (IIIa).—The methyl ether IVa[3b,6] (300 mg.) dissolved in 3 cc. of pyridine was oxidized with 300 mg. of chromium trioxide, as described above for the ketal VIIa. The total product showed m.p. 160–165°, λ_{max} 280 mμ, log ϵ 3.32 (91% aromatization) and one crystallization produced 0.21 g. (70%) of estrone methyl ether with m.p. 166–168°, λ_{max} 280 mμ, log ϵ 3.36, undepressed on admixture with an authentic sample with m.p. 168–170°.

Oxidation of IVa with N-bromoacetamide (0.5 g. of IVa, 0.5 g. of N-bromoacetamide, 5 cc. of pyridine and 0.5 cc. of water, 2 hours at 20°) gave a product with λ_{max} 280 mμ, log ϵ 3.29 showing ring A to have aromatized to the extent of 85%. Similarly Oppenauer oxidation of IVa (0.5 g. of IVa, 0.25 g. of aluminum isopropoxide, 20 cc. of toluene and 5 cc. of cyclohexanone, refluxing for 2 hours) gave material with λ_{max} 280 mμ, log ϵ 3.01, showing aromatization to be 45% complete.

MEXICO D. F., MEXICO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

1-Methyl-19-norprogesterone and 1-Methyl-19-nor-17α-hydroxyprogesterone

BY CARL DJERASSI, A. E. LIPPMAN AND J. GROSSMAN[1]

RECEIVED NOVEMBER 15, 1955

In view of the high biological activity of 19-norprogesterone, a progesterone analog was prepared in which the angular methyl group was moved to the adjacent carbon atom rather than eliminated. Of the two isomers obtained, one possessed approximately one-half the biological activity of progesterone. The synthesis of 1-methyl-19-nor-17α-hydroxyprogesterone is also described.

The removal of the C-19 angular methyl group of progesterone (I) leads to a substance, 19-norprogesterone (II),[2] which considerably surpasses the parent hormone I in its biological activity. That such a structural change, at least in the progesterone series, results in increased biological potency was confirmed by the synthesis of 19-nor-17α-ethynyltestosterone (III),[3] which proved to be the most effective oral progestational hormone known at the present time. In view of the extreme specificity of progestational action—even minor structural modifications usually resulting in loss of activity—it appeared of very considerable interest to determine what effect on biological activity the shift (rather than elimination) of the angular methyl group would produce. The present paper is concerned with the synthesis of such a compound, 1-methyl-19-norprogesterone (IX), and of some closely related steroids.[4,5]

1,4,6,16-Pregnatetraene-3,20-dione (IV), readily prepared from progesterone (I) in two steps,[6] was rearranged in improved yield by the zinc chloride procedure[7] to the known[8] 1-methyl-3-acetoxy-17β-acetyl-1,3,5,6,16-estrapentaene (Va). Catalytic hydrogenation (VIa), followed by saponification (VIb) and methylation afforded 1-methyl-3-methoxy-17β-acetyl-1,3,5-estratriene (VIc). The remaining steps were patterned after our earlier 19-norprogesterone (II) synthesis[2] and involved modified[8] Birch reduction to the intermediate enol ether VII which was not isolated but rather cleaved directly with acid. The resulting 1-methyl-19-nor-Δ^4-pregnen-3-one-20-ol (VIII) was obtained as a mixture of isomers[9] of which one could be isolated in apparently pure form by virtue of its insolubility. Chromium trioxide oxidation of this crystalline isomer VIII led to one (m.p. 152°, $[\alpha]_D$ +88°) of the possible isomers of 1-methyl-19-norprogesterone (IX). The mother liquors from the acid-cleaved Birch reduction product were oxidized separately and then chromatographed. In addition to some unreduced starting material VIc, there was isolated a second isomer (m.p. 171°, $[\alpha]_D$ +11°) of 1-methyl-19-norprogesterone (IX).

In the acid treatment of the Birch reduction products of various aromatic steroids, which are

(1) Research Corporation Predoctorate Fellow, 1954–1955.

(2) C. Djerassi, L. Miramontes and G. Rosenkranz, THIS JOURNAL, **75**, 4440 (1953).

(3) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954).

(4) The synthesis of various 1-methyl-19-nor steroids of the androstane series is described in an accompanying paper.[5]

(5) H. J. Ringold, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 2477 (1956).

(6) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, *ibid.*, **73**, 1523 (1951).

(7) A. S. Dreiding and A. Voltman, *ibid.*, **76**, 537 (1954).

(8) *Cf.* A. L. Wilds and N. Nelson, *ibid.*, **75**, 5366 (1953).

(9) If one assumes that the hydrogen atom at C-10 is β-oriented, there can be formed four isomers by virtue of the two new asymmetric centers at C-1 and C-20.