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.

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[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[6] 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]

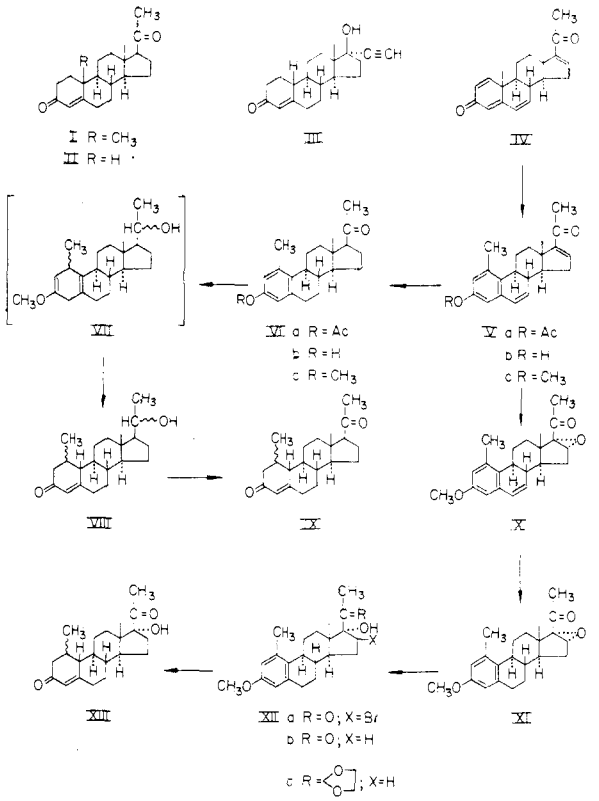
(5) H. J. Ringold, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 2477 (1956).

(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.



unsubstituted at C-1, the more stable configuration (β) at C-10 is produced invariably.[10] If the same assumption is made in this instance, then only two isomers of 1-methyl-19-norprogesterone (IX) are possible, both of which have been isolated. However, this assumption may not necessarily be valid since it is difficult to assess the effect of the 1-methyl group upon the ring juncture; inspection of models shows that in IX there is some steric interference between the 1β-methyl substituent and the methylene group at C-11. Preliminary biological tests[11] of the two 1-methyl-19-norprogesterones (IX) in rabbits indicate that while the m.p. 152° isomer possesses approximately one-half the biological activity of progesterone (I), the higher melting isomer is completely inactive in twice the effective dose of progesterone. One can conclude, therefore, that shifting the angular methyl group to C-1 is still compatible with relatively high progestational potency.

The potential synthesis of 1-methyl-19-nor analogs of cortisone and related adrenal hormones probably could be accomplished[12] *via* 1-methyl-19-nor-17α-hydroxyprogesterone (XIII) and the preparation of one of the possible isomers of XIII is now described by a reaction sequence similar to that employed in the case of 19-nor-17α-hydroxyprogesterone.[12]

(10) For molecular rotation data of various 19-nor steroids, *cf.* A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **77**, 148 (1955).

(11) Carried out by Dr. Elva G. Shipley, Endocrine Laboratories, Madison, Wis.

(12) For the synthesis of 19-norhydrocortisone and related hormones from 19-nor-17α-hydroxyprogesterone see A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, THIS JOURNAL, **76**, 6210 (1954).

Methylation of 1-methyl-3-hydroxy-17β-acetyl-1,3,5,6,16-estrapentaene (Vb)[6] followed by epoxidation with alkaline hydrogen peroxide[13] to X and catalytic hydrogenation yielded the epoxido ketone XI, which was transformed to the 17α-hydroxy-20-ketone (XIIb) by hydrogen bromide opening and catalytic debromination.[14] The 20-keto group was protected by conversion to the cycloethylene ketal XIIc, while the Birch reduction and acid cleavage were carried out as described above for the corresponding progesterone derivative IX. Only one isomer of 1-methyl-19-nor-17α-hydroxyprogesterone (XIII) could be isolated in pure form; on the basis of molecular rotation difference calculations,[15] it appears to correspond to the biologically active 1-methyl-19-norprogesterone (IX) isomer.

Experimental[16]

1-Methyl-3-methoxy-17β-acetyl-1,3,5-estratriene (VIc).—Crude 1,4,6,16-pregnatetraene-3,20-dione (IV)[6,17] (7.12 g., m.p. 231–240°) in 50 cc. of acetic anhydride was heated on the steam-bath for 3 hours with 2 cc. of a 5% solution[7] of anhydrous zinc chloride in acetic acid and then left at room temperature for 29 hours. Most of the solvent was removed *in vacuo*, the 3-acetate Va[6] was extracted with ether, washed exhaustively with dilute sodium hydroxide solution and water, dried, evaporated and crystallized from ethanol; yield 5.30 g., m.p. 127–132°.

The above material (2.01 g.) was hydrogenated for 30 minutes in ethyl acetate solution (100 cc.) with 0.4 g. of 10% palladized charcoal catalyst. The crude product (VIa),[6] obtained in quantitative yield was refluxed for 1 hour with 0.4 g. of potassium carbonate, 10 cc. of water and 80 cc. of ethanol. Concentration and dilution with water precipitated 1.72 g. of 1-methyl-3-hydroxy-17β-acetyl-1,3,5-estratriene (VIb), m.p. 232–244°, which was used directly in the next step. Recrystallization from ether raised the m.p. to 250–252° (lit.[6] m.p. 250–251.5°).

Since the phenol could not be methylated with excess diazomethane in ether solution (41 hours at room temperature), dimethyl sulfate was employed. The above crude phenol (1.72 g.), dissolved in 70 cc. of hot ethanol, was treated four times alternately with 7.2 cc. of 60% sodium hydroxide solution and 10 cc. of dimethyl sulfate, each addition of dimethyl sulfate requiring about 10 minutes. After 30 minutes at room temperature, water was added and the precipitated solid was collected; yield 1.76 g., m.p. 106–115°. Filtration in benzene solution through 30 g. of alumina furnished 1.41 g. of the methyl ether VIc, m.p. 115–122°, which was used in the Birch reduction. The analytical sample, obtained from ether, exhibited m.p. 122–124°, $[\alpha]D$ +208°, λ_{max}^{EtOH} 280–286 mμ (broad), log ϵ 3.20, λ_{min}^{EtOH} 250.5 mμ, log ϵ 2.19.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.96; H, 9.50.

1-Methyl-19-norprogesterone (IX).—A solution of 3.32 g. of 1-methyl-3-methoxy-17β-acetyl-1,3,5-estratriene (VIc) in 325 cc. of dry, redistilled propylene glycol monomethyl ether[18] was added to 1 l. of liquid ammonia cooled in a Dry Ice–acetone-bath. Lithium ribbon (20 g.) was added

(13) *Cf.* P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

(14) *Cf.* F. B. Colton, W. R. Nes, D. A. van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.*, **194**, 235 (1952).

(15) Using M_D (parent hormone) $-M_D$ (1-methyl-19-norhormone), a value of +210 is obtained in the case of XIII, as compared to +364 for the biologically active m.p. 152° isomer of IX and +605 for the m.p. 171° isomer.

(16) Melting points were determined on the Kofler block and all rotations were measured in chloroform solution. We are indebted to Mrs. Dolores Phillips for the ultraviolet and infrared spectral determinations and to Spang Microanalytical Laboratory (Plymouth, Michigan) for the microanalyses.

(17) We are greatly indebted to Syntex, S. A., Mexico City for a generous supply of this substance.

(18) The use of this solvent was suggested by Dr. Howard J. Ringold (private communication, see ref. 5).

gradually with continuous stirring and the reaction was allowed to proceed until the blue color had disappeared (4 hours). The ammonia was allowed to evaporate after the addition of 150 g. of ammonium chloride and the product was isolated by means of ether extraction. No attempt was made to purify the enol ether VII and the residue (still containing some propylene glycol monomethyl ether) was refluxed on the steam-bath for 40 minutes with 25 cc. of 10% hydrochloric acid and 50 cc. of methanol. Extraction with chloroform, thorough washing with water and evaporation furnished 2.56 g. of brownish oil, which partially crystallized on trituration with ether. Recrystallization of the solid from methanol–ethyl acetate gave 303 mg. of **1-methyl-19-nor-Δ^4-pregnen-3-one-20-ol (VIII)**, m.p. 222–233°. Several recrystallizations from chloroform–ethyl acetate led to 36 mg. of the analytical sample (m.p. 244–247°, $[\alpha]D$ +41°, λ_{max}^{EtOH} 242.5 mμ, log ε 4.14, $\lambda_{max}^{CHCl_3}$ 5.98 μ) and 244 mg. of second crop material, m.p. 215–226°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.94; H, 10.40.

The above 244 mg. in 5 cc. of acetic acid was oxidized (90 minutes, room temperature) with 50 mg. of chromium trioxide dissolved in 1.5 cc. of acetic acid and 0.3 cc. of water. The crude product (169 mg., m.p. 131–145°) was recrystallized twice from methanol to yield **1-methyl-19-norprogesterone**, m.p. 150–152°, $[\alpha]D$ +88°, $\lambda_{max}^{CHCl_3}$ 5.85, 5.98 and 6.12 μ.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.54; H, 9.80.

The oily residue, remaining after the separation of the crystalline 20-alcohol VIII, was chromatographed on 75 g. of alumina. Chromium trioxide oxidation of the benzene eluates (600 mg., no infrared carbonyl band) followed by chromatographic purification yielded 110 mg. of unreacted starting methyl ether VIc, m.p. 115–120°.

The ether eluates (1.05 g.) exhibited a strong band at 6.01 μ and were oxidized in the usual manner with chromium trioxide. Trituration with ether–pentane followed by four recrystallizations of the resulting solid from methanol gave 56 mg. of the second isomer of **1-methyl-19-norprogesterone**, m.p. 168–171°, $[\alpha]D$ +11°, λ_{max}^{EtOH} 242.5 mμ, log ε 4.11, $\lambda_{max}^{CHCl_3}$ 5.85, 5.98 and 6.12 μ.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.45; H, 9.81.

Approximately 230 mg. of crystalline material (m.p. 122–155°) obtained by chromatography of the mother liquors apparently represented a mixture of isomers of IX on the basis of the ultraviolet and infrared spectra, but the mixture could not be resolved effectively into its components.

1-Methyl-3-methoxy-17β-acetyl-1,3,5,6,16-estrapentaene (Vc).—In order to avoid reaction of the Δ^{16}-20-keto system with either diazomethane[19] or alkali[6,20] the methylation was conducted in the following manner.

A solution of 1.2 g. of 1-methyl-3-hydroxy-17β-acetyl-1,3,5,6,16-estrapentaene (Vb)[6] in 15 cc. of acetone was refluxed for 3 hours with 1.7 cc. of dimethyl sulfate and 2.5 g. of anhydrous potassium carbonate, 15 cc. of hot water was added and heating continued for 10 minutes. The product was isolated with ether and purified by filtration through alumina and recrystallization from methanol; m.p. 111–112°, $[\alpha]D$ −108°, $\lambda_{max}^{CHCl_3}$ 5.96 μ.

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.72; H, 8.25.

16α,17α-Oxido-1-methyl-3-methoxy-17β-acetyl-1,3,5,6-estratetraene (X).—The above methyl ether Vc (1.61 g.) in 20 cc. of chloroform and 150 cc. of methanol was treated simultaneously with 8 cc. of 15% sodium hydroxide solution and 11 cc. of 30% hydrogen peroxide. After 24 hours at room temperature, water was added and the product was extracted with ether. Recrystallization of the ether residue from acetone–methanol led to 1.35 g. of the epoxide X, m.p. 132–140°, suitable for the next step. The analytical sample exhibited m.p. 138–140°, $[\alpha]D$ −63°, $\lambda_{max}^{CHCl_3}$ 5.85 μ.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.29; H, 7.94.

16α,17α-Oxido-1-methyl-3-methoxy-17β-acetyl-1,3,5-estratriene (XI).—The hydrogenation of the epoxide X (3.85 g.) was carried out in the usual manner[6] in 100 cc. of ethyl acetate with 0.5 g. of 10% palladized charcoal catalyst; yield 3.58 g., m.p. 112–114°. The analytical sample was obtained from methanol–acetone, m.p. 114–115°, $[\alpha]D$ +217°.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.66; H, 8.35.

1-Methyl-3-methoxy-17α-hydroxy-17β-acetyl-1,3,5-estratriene (XIIb).—A cooled solution of 3.23 g. of the epoxide XI in 150 cc. of glacial acetic acid was treated at 15° for 15 minutes with 6.5 cc. of a 32% solution of hydrogen bromide in acetic acid. Dilution with ice-water precipitated the bromohydrin XIIb which was collected and washed well with sodium carbonate solution and water; yield 3.78 g., m.p. 70–81°.

The material was hydrogenated directly in 100 cc. of methanol with 11.5 g. of 2% palladium-on-calcium carbonate catalyst for 24 hours, the system being swept out five times with fresh hydrogen during the hydrogenation period. The solution was filtered, the catalyst was extracted with boiling chloroform and the combined organic solutions were washed with water, dried and evaporated. Chromatography of the residue on 100 g. of Merck acid-washed alumina and elution with hexane–benzene (1:1) furnished 0.54 g. of recovered oxide XI. Recrystallization of the benzene–ether (8:2) eluates from methanol gave 1.3 g. of the desired hydroxy ketone XIIb, m.p. 173–177°, which was used in the next step. The analytical sample possessed m.p. 181–183°, $[\alpha]D$ +118°, λ_{max}^{EtOH} 283 mμ (log ε 3.15), λ_{min}^{EtOH} 249 mμ, log ε 2.24, $\lambda_{max}^{CHCl_3}$ 2.90 and 5.85 μ.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.13; H, 8.93.

The ketal XIIc was prepared in the standard manner by refluxing 1.5 g. of XIIb in 120 cc. of benzene with 18 cc. of redistilled ethylene glycol and 100 mg. of *p*-toluenesulfonic acid monohydrate under a water separator for 18 hours. Once-recrystallized material (1.10 g., m.p. 160–166°) was used for the Birch reduction, while the analytical sample was recrystallized several times from methanol–acetone, m.p. 166–168°, $[\alpha]D$ +115°, no infrared carbonyl band.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.51; H, 8.94.

1-Methyl-19-nor-17α-hydroxyprogesterone (XIII).—The Birch reduction was carried out essentially as described for VIc above, except that 480 mg. of ketal XIIc, 50 cc. of propylene glycol monomethyl ether, 300 cc. of liquid ammonia and 1.5 g. of lithium were used. The crude reduction product was hydrolyzed directly with acid and chromatographed on 15 g. of Merck acid-washed alumina. Unreacted starting material (XIIb, 125 mg.) was recovered from the benzene–ether (9:1) eluates while the desired unsaturated ketone XIII was removed from the column with benzene–ether (1:1); yield 57 mg., m.p. 215–220°. The analytical sample was recrystallized from methanol, whereupon it showed m.p. 220–221°, $[\alpha]D$ +26°, λ_{max}^{EtOH} 243 mμ, log ε 4.13, $\lambda_{max}^{CHCl_3}$ 2.90, 5.84, 5.97 and 6.12 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.85; H, 9.33.

DETROIT, MICHIGAN

(19) *Cf.* A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1904); A. Sandoval, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 2383 (1951).

(20) D. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951).