145–155° to 110–115°. These were combined and separated by slow crystallization from ether-hexane at room temperature to give first *2-allylestrone* (II) (4.70 g.), separating in plates, m.p. 186–187°[21] (reported[3] m.p. 186–187°), $[\alpha]_D$ +152.2° λ_{max} 284–286 mμ (ε 3020), ν_{max} 3300 (bonded OH), 3090 (CH=CH_2), 1725 (C=O), 1640 (CH=CH_2), 1618, 1592 and 1511 (aromatic C=C), 917 (CH=CH_2), 896, 877 (isolated ring H), 830 and 822 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.22; H, 8.44; O, 10.31. Found: C, 81.25; H. 8.45; O, 10.63.

The *benzoate*, prepared with benzoyl chloride in pyridine, formed colorless plates, m.p. 194–195° from methanol-acetone, $[\alpha]_D$ +119.2°, λ_{max} 226 and 270 mμ (ε 21,400 and 3390).

Anal. Calcd. for $C_{28}H_{30}O_3$: C, 81.13; H, 7.30; O, 11.58. Found: C, 81.09; H, 7.34; O, 11.70.

Further crystallization of the rearrangement product gave *4-allylestrone* (III) (14.4 g.), separating in rosettes of flat, broad needles, m.p. 130–132°, raised by further crystallization to m.p. 136–137° (reported[3] m.p. 131–132°), $[\alpha]_D$ +115.3°, λ_{max} 282 mμ (ε 2140), ν_{max} 3300 (bonded OH), 3010 (CH=CH_2), 1725 (C=O), 1641 (CH=CH_2), 1593 and 1492 (aromatic C=C), 904 (CH=CH_2), 884, 865, 820 and 814 cm.$^{-1}$ (2 adj. ring H's).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.22; H, 8.44; O, 10.31. Found: C, 81.24; H, 8.51; O, 10.50.

The *benzoate*, prepared as for that of II, formed colorless needles, m.p. 165–166°, from methanol-acetone, $[\alpha]_D$ +84.6°, λ_{max} 224 and 275 mμ (ε 20,100 and 2140).

Anal. Calcd. for $C_{28}H_{30}O_3$: C, 81.13; H, 7.30; C, 11.58. Found: C, 81.31; H, 7.24; O, 11.62.

A 3:1 mixture of the benzoates of III and II melted at 155–160°. Reported[3] m.p. 155–160°.

2-Allylestradiol (IV). A solution of sodium borohydride (500 mg.) in water (15 ml.) was added to a solution of 2-allylestrone (500 mg.) in methanol (50 ml.). The solution was allowed to stand overnight, and then neutralized with acetic acid. The crystalline product was collected, washed well with water, and dried to give 435 mg. (85.7%) of *2-allylestradiol*, m.p. 81–83°. A sample recrystallized from aqueous methanol had m.p. 82–84°, $[\alpha]_D$ +88.1°, λ_{max} 284 mμ (ε 3090), ν_{max} 3330 (bonded OH), 1640 (CH=CH_2), 1619, 1586 and 1503 (aromatic C=C), 914 (CH=CH_2), 880 (isolated ring H) and 828 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{28}O_2$: 1/2, H_2O: C, 78.45; H, 9.09; O, 12.45. Found: C, 78.51; H, 9.06; O, 11.92.

4-Allylestradiol (V). 4-Allylestrone (500 mg.) in methanol (30 ml.) was reduced with sodium borohydride (500 mg.) in water (15 ml.) as described above. The product began to separate as fine needles after 1 hr. After being allowed to stand overnight, the solution was neutralized with acetic acid, and the product was collected, washed with water and dried to give 456 mg (90.7%) of (V), m.p. 90° and 137°. The analytical sample was crystallized from aqueous methanol to m.p. 90–91° and 140° (double m.p.), $[\alpha]_D$ +44.3°, λ_{max} 282 mμ (ε 1910), ν_{max} 3340–3150 (bonded OH), 1638 (CH=CH_2), 1594 and 1479 (aromatic C=C), 905 (CH=CH_2), 859 and 812 cm.$^{-1}$ (two adjacent ring H's).

Anal. Calcd. for $C_{21}H_{28}O_2$ 1/2 H_2O: C, 78.45; H, 9.09; O, 12.45. Found: C, 78.49; H, 8.93; O, 12.33.

2-Propylestradiol (VI). A solution of 2-allylestradiol (700 mg.) in ethanol (50 ml.) was hydrogenated over Adam's catalyst (35 mg.) at room temperature and atmospheric pressure. When hydrogen uptake was complete, the solution was filtered and evaporated to give a crystalline residue which when crystallized from cyclohexane gave pure *2-propylestradiol* (590 mg.; 83.8%), m.p. 89–91°, $[\alpha]_D$ +76.6°, λ_{max} 284 mμ (ε 2820), ν_{max} 3320 (bonded OH), 1618, 1591 and 1512 (aromatic C=C) and 867 cm.$^{-1}$ (isolated ring H).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.19; H, 9.62; O, 10.18. Found: C, 80.29; H, 9.28; O, 10.25.

4-Propylestradiol (VII). A solution of 4-allylestradiol (250 mg.) in ethanol (25 ml.) was hydrogenated over Adams' catalyst (25 mg.) as described above. Hydrogen uptake was rapid and complete in 1 hour. Crystallization of the crude product from cyclohexane gave 193 mg. (76.7%) of *4-propylestradiol*, m.p. 94–94.5°, $[\alpha]_D$ +31.2°, λ_{max} 282 mμ (ε 1520), ν_{max} 3340 (bonded OH), 1593 and 1490 (aromatic C=C) and 811 cm.$^{-1}$ (2 adj. ring H's).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.19; H, 9.62; O, 10.18. Found: C, 80.34; H, 10.06; O, 9.42.

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(21) The homogeneity of all compounds was established by paper chromatograms run in hexane-benzene on formamide impregnated Whatman No. 1 paper, using iodine-potassium iodide reagent. In this system, II was more mobile than III and all other compounds had the expected mobility ratios.

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

Steroids. CLXXVII.[1] New Approaches to C-11 Oxygenated 19-Norpregnanes[2]

A. BOWERS, J. S. MILLS, C. CASAS-CAMPILLO, AND CARL DJERASSI

Received September 18, 1961

C-11 Hydroxylation of 19-norprogesterone (I) with *Rhizopus nigricans* (ATCC No. 6227b) or *Curvularia lunata* (Syntex strain 192) led to the corresponding 11α- and 11β-hydroxy analogs IIa and IIb, respectively. Microbiological dehydrogenation of the corresponding C-11 ketone (IIc) smoothly afforded the ring-A phenol (IVb). An alternate chemical synthesis of the benzoate of IVb is described which unequivocally establishes the structure assigned to the microbiological hydroxylation products.

The clinical importance of 19-nor steroids such as 19-nor-17α-methyltestosterone,[3] 19-nor-17α-ethinyltestosterone,[3] and the $\Delta^{5(10)}$-isomer[4] of the latter is now well recognized.[5] These substances are all

(1) Steroids. CLXXVI, P. G. Holton, *J. Org. Chem., in press.*

(2) A preliminary announcement of part of this work has been published; A. Bowers, C. Casas-Campillo, and C. Djerassi, *Tetrahedron*, **2**, 165 (1958).

(3) C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954); Abstracts, American Chemical Society Meeting, Milwaukee, April 1952, p. 18J.

(4) F. B. Colton, U. S. Patent **2,725,389.**

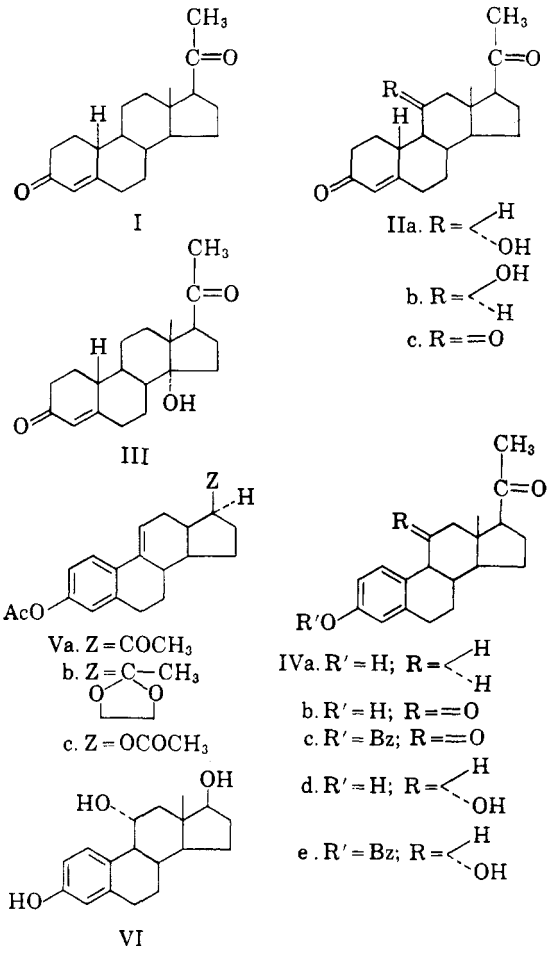
(5) For example, *c.f.*, D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958); F. J. Saunders and V. A. Drill, *Ann. N. Y. Acad. Sci.*, **71**, 516 (1958).

prepared on an industrial scale by modified Birch reductions[6] of suitable aromatic precursors. The synthesis of the more complicated 19-nor analogs of 11-oxygenated adrenal hormones[7,8] has been carried out only by adrenal incubation of 19-norpregnenes[7] or by starting with 11-oxygenated aromatic precursors[8] amenable to Birch reduction.

The much more attractive and direct route of attempting C-11 oxygenation in the 19-nor series by microbiological means has so far only been accomplished in poor yield with 19-nortestosterone[9] and is thus of no direct utility for the facile synthesis of 19-nor cortical hormones.

The direct preparation of both 11α- and 11β-hydroxy-19-norprogesterone by microbiological methods and their further conversion to their 11-keto ring-A aromatic analog is now described together with an unambiguous chemical synthesis of the latter compound.

Incubation of 19-norprogesterone[10] (I) with *Rhizopus nigricans* (ATCC No. 6227b) in a medium containing peptone and corn molasses,[11] furnished 11α - hydroxy - 19 - norprogesterone (IIa) in 70% yield.[12] Similar treatment of 19-norprogesterone (I) with *Curvularia lunata* (Syntex strain 192) led in a much lower yield to 11β-hydroxy-19-norprogesterone (IIb).[13] Oxidation of IIa and IIb with 8*N* chromic acid in acetone solution[14] afforded the same ketone, 11-keto-19-norprogesterone (IIc), thereby demonstrating that the two microbiological hydroxylation products are epimers and that oxygenation did not occur at a tertiary carbon atom. The infrared spectrum of the common oxidation product IIc requires that the newly introduced hydroxyl group forms part of a six-membered ring and the position of the ultraviolet absorption



maxima of IIa, IIb, and IIc, which remain unchanged in alkali, as well as the stability of IIa towards alkali precludes all positions except for C-11 and C-12. An independent structure proof to be described in the sequel established that C-11 and not C-12 was the site of oxygenation.[15]

Although the stereochemistry assigned to the epimeric C-11 alcohols IIa and IIb was inferred by analogy to the known stereochemical course of hydroxylation with these two microorganisms in the C-19 methyl series, it was noted that the molecular rotation changes were in full agreement with the assigned stereochemistry and incompatible with the alternate structure.[16]

Incubation of 19-norprogesterone (I) with *Rhizopus nigricans* (ATCC No. 10404) and *Rhizopus arrhizus* (ATCC No. 11145) also effected 11α-hydroxylation although in quite low yield. However, a new product was obtained in moderate yield using *Helicostylum piriforme* (ATCC No. 8992).

(6) A. J. Birch, *Quart. Rev.*, **4**, 69 (1950); *J. Chem. Soc.*, 867 (1950).

(7) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas, and C. Djerassi, *J. Am. Chem. Soc.*, **76**, 6210 (1954); **80**, 6110 (1958).

(8) B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **79**, 1508 (1957); **80**, 2226 (1958).

(9) R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke, and D. H. Peterson, *J. Am. Chem. Soc.*, **78**, 1512 (1956).

(10) C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4400 (1953); for an improved synthesis of I, *cf.* J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6118 (1958).

(11) For a detailed study of the optimum conditions for this conversion, *cf.* C. Casas-Campillo and J. Ruiz-Herrera, *Rev. Latinoamer. Microbiol.*, **3**, 213 (1960).

(12) For the analogous conversion of progesterone to 11α-hydroxyprogesterone, *cf.* D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 5933 (1952).

(13) The use of *Curvularia lunata* to effect 11β-hydroxylation was first reported by G. M. Shull and D. A. Kita, *J. Am. Chem. Soc.*, **77**, 763 (1955).

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(15) This was not an unexpected result since there are many examples of C-11 hydroxylation with both *Rhizopus nigricans* and *Curvularia lunata* (*cf.*, for example, ref. 12, 13, and 18).

(16) ΔM_D 19-Norprogesterone-11α-hydroxy-19-norprogesterone = +254 as compared to ΔM_D 19-nortestosterone-11α-hydroxy-19-nortestosterone = +284. *Cf.* ΔM_D 19-norprogesterone-11β-hydroxy-19-norprogesterone = −49.

Elemental analysis and behavior upon chromatography indicated that it was a monohydroxylated analog of 19-norprogesterone. The hydroxyl group must be tertiary, as it was recovered unchanged after treatment with an excess of 8*N* chromic acid in acetone solution. It was also found to be stable toward methanolic potassium hydroxide solution which ruled out the C-9 and C-10 positions for the newly introduced hydroxyl group. In addition, its nonidentity with 17α-hydroxy-19-norprogesterone[7] left only C-8 and C-14 for further consideration. In view of the known ability of this microorganism to hydroxylate at C-14α[17] this product is tentatively assigned the structure of 14α-hydroxy-19-norprogesterone (III).

The introduction of a double bond at positions 1 and 2 in Δ^4-3-keto steroids by microbiological means is well known[18] and application of such a reaction to a 19-nor-Δ^4-3-keto steroid should lead directly to the corresponding phenol. In fact, incubation of 19-norprogesterone with *Corynebacterium simplex* (ATCC No. 6946) for 72 hours led smoothly to $\Delta^{1,3,5(10)}$-19-norpregnatriene-3-ol-20-one (IVa) identical with an authentic sample.[19] After the completion of this work several groups reported analogous dehydrogenations in the 19-norandrostane series.[20]

Extension of this reaction to 11-keto-19-norprogesterone (IIc) then led to the hitherto inaccessible 11-keto ring-A phenol (IVb) characterized as its benzoate (IVc). However, all attempts to bring about the same transformation with 11α-hydroxy-19-norprogesterone (IIa) met with failure. Only intractable oils could be isolated.

This is an understandable result as a group at the Worcester Foundation[21] have shown that the abstraction of the 1α-hydrogen atom by the enzyme system is a necessary prerequisite for formation of the Δ^1 double bond, and it is very probable that the close proximity of the 11α-hydroxyl group to the 1α-hydrogen atom impedes the approach of such an enzyme system.

An unambiguous chemical synthesis of IVc was then carried out to establish unequivocally that the position of the oxygen atom in ring C of IVc and hence of IIa,b,c and IVb was at C-11.

Some recent work from these laboratories had established a facile route to $\Delta^{9(11)}$ ring-A phenols,[22] and it remained only to convert the $\Delta^{9(11)}$ double bond to the C-11 ketone. Pilot experiments with $\Delta^{9(11)}$-estradiol diacetate (Vc) led directly to 11α-hydroxyestradiol (VI) using Brown's hydration reaction with diborane followed by an alkaline hydrogen peroxide oxidation of the resulting trialkylborane.[23]

Prior to a similar experiment in the 20-ketopregnane series, it was necessary to protect the carbonyl group as the cycloethylene ketal. Thus $\Delta^{1,3,5(10),9(11)}$-19-norpregnatetraene-3-ol-20-one acetate (Va) was converted to the corresponding C-20 ketal (Vb) in benzene solution with ethylene glycol in the presence of *p*-toluenesulfonic acid. Brown hydration[23] of Vb followed by an acid hydrolysis of the ketal moiety led to the 11α-hydroxy ring-A phenol (IVd). Benzoylation of IVb using the Schotten-Bauman procedure led to the C-3 benzoate (IVe) which upon oxidation with 8*N* chromic acid in acetone solution[14] furnished the corresponding 11-ketone (IVc) identical in every respect with the material obtained from 19-norprogesterone by the microbiological methods outlined above.

EXPERIMENTAL[24]

11α-Hydroxy-19-norprogesterone (IIa). *Rhizopus nigricans* (ATCC 6227b) was grown in a liquid medium of the flowing composition: corn molasses (5%) and peptone (2%) in tap water.[25] 19-Norprogesterone (I) (100 mg.) in ethanol (5 cc.) was added to 200 cc. of a 24-hr. culture and incubated at 25° under shaking conditions for 22 hr. Five such incubations were combined and extracted with methylene dichloride. Removal of the solvent afforded a residue which was adsorbed from benzene onto alumina (30 g.). Elution with benzene (200 cc.) and benzene-ether (90:10, 500 cc.) afforded 11α-hydroxy-19-norprogesterone (IIa) (345 mg.), m.p. 168–173°, raised by crystallizations from acetone-hexane to 171–173°, $[\alpha]_D$ +62°, λ_{max} 242 mμ, log ϵ 4.22.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.62; H, 8.87; O, 15.21.

A solution of IIa in 2.5% methanolic potassium hydroxide was kept at room temperature for 16 hr. under nitrogen. Addition of ice water containing a little acetic acid precipitated IIa essentially unchanged.

11β-Hydroxy-19-norprogesterone (IIb). *Curvularia lunata*, (Syntex collection No. 192) was grown in a culture medium of

(17) P. D. Meister, S. H. Eppstein, D. H. Peterson, H. C. Murray, H. M. Leigh, A. Weinstraub, and L. M. Reineke, Abstracts, 123rd American Chemical Society Meeting, Los Angeles, Calif., 1953, p. 5C.

(18) *Cf.*, for example, A. Wettstein, *Experientia*, **11**, 465 (1955); G. M. Shull, *Trans N. Y. Acad. Sci.*, **19**, 147 (1956); S. H. Eppstein, P. D. Meister, H. C. Murray, and D. H. Peterson, *Vitamins and Hormones*, **14**, 359 (1956).

(19) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin, and J. Romo, *J. Am. Chem. Soc.*, **73**, 1523 (1951).

(20) (a) H. R. Levy and P. Talalay, *J. Am. Chem. Soc.*, **79**, 2658 (1957); (b) S. Kushinsky, *J. Biol. Chem.*, **230**, 31 (1958); (c) J. A. Zderic, A. Bowers, H. Carpio, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 2596 (1958).

(21) M. Hayano, H. J. Ringold, V. Stefanovic, M. Gut, and R. I. Dorfman, *Biochem. and Biophys. Res. Comm.*, **4**, 454 (1961).

(22) J. S. Mills, J. Barrera, E. Olivarez, and H. García, *J. Am. Chem. Soc.*, **82**, 5882 (1960).

(23) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956) and subsequent papers.

(24) Melting points were determined on an electrically heated hot stage and are uncorrected. Rotations were measured in chloroform and ultraviolet light absorption spectra in 95% ethanol solution. We are grateful to Dr. J. Matthews and his staff for these measurements and for the infrared spectra which were obtained with a Perkin-Elmer Model-21 spectrophotometer with a sodium chloride prism. The alumina used in this work had been suspended in ethyl acetate for 48 hr., filtered, and dried at 100°.

(25) Considerable variation in yields were obtained with tap water from different sources. Optimum yields were obtained with tap water from the home of one of the authors at Sierra Leona 735, Mexico 10, D. F. However, see ref. 11.

corn molasses (5%) and peptone (2%) in tap water. 19-Norprogesterone (I) (5 mg. in ethanol, 0.2 cc.) was added to 30 cc. of a 48-hr. culture and incubated at 25° under vigorous shaking for 24 hr. Forty such incubations were combined and extracted with methylene dichloride to afford a residue which was adsorbed from benzene-hexane (50:50) onto alumina (10 g.). Elution with benzene-ether (90:10, 400 cc.) and crystallization from acetone-hexane afforded 11β-hydroxy-19-norprogesterone (IIb) (42 mg.) m.p. 205–215°, raised by three crystallizations from acetone-hexane to 215–217°, $[\alpha]_D$ +158°, λ_{max} 242 mμ, log ϵ 4.20.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.83; H, 8.81; O, 14.86.

11-Keto-19-norprogesterone (IIc). (*a*) 11α-Hydroxy-19-norprogesterone (IIa) (140 mg.) in acetone (10 cc.) at 10° was treated with an excess of 8*N* chromic acid[14] for 2 min. Addition of ice water and isolation with ether afforded a product which was adsorbed from benzene-hexane (1:1) onto alumina (15 g.). Elution with the same solvent mixture (400 cc.) afforded 11-keto-19-norprogesterone (IIc) (131 mg.), m.p. 165–170°, raised by crystallizations from acetone-hexane to 175–176°, $[\alpha]_D$ +284°, λ_{max} 240 mμ, log ϵ 4.20. The spectrum was unchanged in ethanol containing a few drops of potassium hydroxide solution; λ_{max}^{KBr} 1700, 1655, and 1610 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; O, 15.26. Found: C, 76.32; H, 8.31; O, 15.32.

(*b*) Oxidation of 11β-hydroxy-19-norprogesterone (IIb) (30 mg.) in the same way afforded 11-keto-19-norprogesterone (IIc), m.p. 173–175°, undepressed upon admixture with a sample prepared as in method (*a*).

Incubation of I *with Helicostilium piriforme. Helicostilium piriforme* (ATCC No. 8992) was grown in a medium of corn molasses (5%) and Nutrient L-1[26] (2%) in tap water. 19-Norprogesterone (I) (100 mg.) in ethanol (5 cc.) was added to 200 cc. of a 24-hr. culture and incubated at 25° with shaking for 60 hr. Four such incubations were combined and extracted with methylene dichloride to afford a residue which was adsorbed from benzene onto alumina (20 g.). Elution with benzene-ether (95:5, 300 cc.) and three crystallizations from acetone-hexane afforded 14α-hydroxy-19-norprogesterone (III) (65 mg.), m.p. 202–204°, $[\alpha]_D$ +166°, λ_{max} 240 mμ, log ϵ 4.19, unchanged in the presence of potassium hydroxide for 24 hr. at room temperature; λ_{max}^{KBr} 3450, 1700, 1640, and 1610 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.67; H, 8.89; O, 15.29.

Treatment of III with an excess of 8*N* chromic acid in acetone solution for 5 min. at 10° followed by addition of ice water and isolation of the product with ether led only to the recovery of III in good yield.

$\Delta^{1,3,5(10)}$*-19-Norpregnatriene-3-ol-20-one* (IVa). *Corynebacterium simplex* (ATCC No. 6946) was grown in a culture medium of yeast extract (Difco) (0.1%) in tap water. 19-Norprogesterone (10 mg.) in ethanol (0.5 cc.) was added to 30 cc. of a 24-hour culture and incubated with good shaking for 24 hr. at 25°. Nineteen such cultures were combined and extracted with methylene dichloride. Removal of the solvent gave a residue which was crystallized from acetone to afford $\Delta^{1,3,5(10)}$-19-norpregnatriene-3-ol-20-one (IVa) (118 mg.), m.p. 235–239°, raised by further crystallizations from acetone to 238–240°, $[\alpha]_D$ +164°, λ_{max} 280–282 mμ, log ϵ 3.30. The m.p. was undepressed upon admixture with an authentic sample and the infrared curves were identical.

$\Delta^{1,3,5(10)}$*-19-Norpregnatriene-3-ol-11,20-dione* (IVb). *Corynebacterium simplex* (A.T.C.C. No. 6946) was grown in culture medium of yeast extract (Difco) (0.1%) in tap water. 11-Keto-19-norprogesterone (IIc) (50 mg.) was added to 200 cc. of a 24-hr. culture and incubated for 24 hr. at 25° with good shaking. Nine such experiments were combined and extracted with methylene dichloride to afford a residue which was crystallized from acetone-hexane to afford $\Delta^{1,3,5(10)}$-19-norpregnatriene-3-ol-11,20-dione (195 mg.), m.p. 220–224°, raised by crystallizations from acetone-hexane to 229–232°, $[\alpha]_D$ +324° (dioxane), λ_{max} 280 mμ, log ϵ 3.24, λ_{max}^{KBr} 3280, 1712, 1685, 1625, and 1590 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74; O, 15.37. Found: C, 76.84; H, 7.78; O, 15.30.

11α-Hydroxyestradiol (VI). $\Delta^{1,3,5(10),9,(11)}$-Estratetraene-3,17$\beta$-diol diacetate (Vc) (1 g.) in dry tetrahydrofuran (25 cc.) was treated with a rapid stream of diborane for 1 hr. The flask was then stoppered and allowed to stand for a further 2 hr. at room temperature. The excess of diborane was then destroyed by the cautious addition of water, and the cloudy solution was extracted with methylene chloride to give a resinous product. This was dissolved in ethanol (75 cc.) and sodium hydroxide (1 g.) in water (5 cc.) was added followed by the dropwise addition of 3 cc. of perhydrol (35%) with stirring during 1 hr. The precipitated material was then largely dissolved by addition of a small amount of water and the solution stirred for a further 1 hr. More water was added and the solution was neutralized with acetic acid and extracted with methylene chloride. Concentration of the dried extract and filtration gave 170 mg. of 11α-hydroxyestradiol (VI), m.p. 251–255°. Recrystallization gave a sample, m.p. 254–257°; $[\alpha]_D$ −49° (dioxane), −54° (acetone); λ_{max} 280 mμ; log ϵ 3.18. Lit.[8] reports m.p. 250–251°, $[\alpha]_D$ −63° (acetone).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.59; H, 8.32; O, 17.14.

20-Ethylenedioxy-$\Delta^{1,3,5(10),9(11)}$-19-norpregnatetraene-3-ol acetate (Vb). $\Delta^{1,3,5(10),9(11)}$-19-Norpregnatetraene-3-ol-20-one acetate (Va) (2.1 g.), benzene (100 cc.), ethylene glycol (10 cc.), and *p*-toluenesulphonic acid (60 mg.) were refluxed with stirring and with a water separator for 18 hr. Pyridine (1 cc.) was then added and the solution washed with water, the washings being back-extracted with ethyl acetate. The combined benzene–ethyl acetate mixture was dried and evaporated and the residue crystallized from methanol to yield 1.65 g. of the 20-ketal (Vb) m.p. 126–128°. An analytical sample had m.p. 130–131°, $[\alpha]_D$ +114°, λ_{max} 260 mμ, log ϵ 4.32.

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91; O, 16.73. Found: C, 75.26; H, 7.90; O, 16.90.

$\Delta^{1,3,5(10)}$*-19-Norpregnatriene-3,11α-diol-20-one* (IVd). The above ketal (Vb) (1.5 g.) in dry tetrahydrofuran (100 cc.) was treated with a rapid stream of diborane for 3 hr., and the flask was then stoppered and allowed to stand overnight at room temperature. Excess diborane was then destroyed by the cautious addition of water. Extraction with methylene chloride gave 1.4 g. of the boron complex, m.p. 283–288°, which showed weak ultraviolet absorption at 278 mμ. This material was dissolved in ethanol (70 cc.) and sodium hydroxide (1.2 g.) in water (5 cc.) was added followed by the dropwise addition of perhydrol (35%, 5 cc.) with stirring during 1 hr. Sufficient water was then added to dissolve the precipitated material and the solution stirred for a further 1 hr. The solution was then diluted with water (400 cc.) and neutralized with acetic acid and the precipitated product filtered. This product was dissolved in methanol (60 cc.) and refluxed with aqueous sulfuric acid (8%, 6 cc.) for 45 min. Precipitation with ice water and filtration gave 900 mg. of crude product which was chromatographed on 40 g. of silica. Elution with methylene chloride gave traces of the $\Delta^{9(11)}$-phenol with ultraviolet λ_{max} at 264 mμ while elution with 10% acetone–methylene chloride and crystallization from methylene chloride gave $\Delta^{1,3,5(10)}$-19-norpregnatriene-3,-11α-diol-20-one (IVd) (355 mg.), m.p. 194–196°. An analytical sample had m.p. 195–196°, $[\alpha]_D$ +42°, λ_{max} 279 mμ, log ϵ 3.25.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; O, 15.27. Found: C, 75.82; H, 8.26; O, 15.74.

The 3-benzoate (IVe) prepared by the Schotten-Bauman procedure had m.p. 173–175° (from methanol), $[\alpha]_D$ −5.5.

(26) Commercial preparation supplied by Sheffield Farms Co., Norwich, N. Y.

Anal. Calcd. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23; O, 15.29. Found: C, 77.48; H, 7.40; O, 14.9.

$\Delta^{1,3,5(10)}$-19-Norpregnatriene-3-ol-11,20-dione benzoate (IVc). (*a*) $\Delta^{1,3,5,(10)}$-19-Norpregnatriene-3-ol-11,20-dione (IVb) (200 mg.) in pyridine (3 cc.) and benzoyl chloride (Ia) was allowed to stand for 6 hr. at room temperature. Precipitation with water and crystallization from methanol gave the 3-benzoate (IVc), m.p. 206–207°, $[\alpha]_D$ +255°, λ_{max} 232 mμ, log ε 4.28.

Anal. Calcd. for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78; O, 15.37. Found: C, 77.55; H, 6.76; O, 15.62.

(*b*) $\Delta^{1,3,5(10)}$-19-Norpregnatriene-3,11α-diol-20-one benzoate (110 mg.) in acetone (6 cc.) was cooled in ice water and oxidized by the dropwise addition of 8*N* chromic acid–sulfuric acid mixture with stirring. After about 3 min. the product started to crystallize, and water containing a little sodium bisulfate was added and the product filtered. One crystallization from methanol gave the 11-ketone (IVc) (70 mg.), m.p. 203–205°, $[\alpha]_D$ +245°, undepressed with the material prepared as in (*a*). The infrared spectra of the two samples were indistinguishable.

APARTADO POSTAL 2679
MEXICO, D. F.

[CONTRIBUTION FROM DIVISION OF STEROID METABOLISM AND BIOCHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

$\Delta^{1(10)}$-19-Norsteroids[1,2]

JACK FISHMAN AND MARIA TOMASZ

Received August 23, 1961

The syntheses of 17β-hydroxy-1(10)-estrene-2-one, 1,3,5(10)-estratriene-2,17β-diol, and 2-hydroxy-1,3,5(10)-estratriene-17-one are described.

Replacement of the angular C-19 methyl group of a steroid by a β-hydrogen results frequently in compounds with valuable biological properties.[3] The 19-nor analogs of most of the steroid hormones containing the Δ^4-3-keto system have already been prepared.[4] In addition, other 19-nor compounds with variations in the ring A and B structures have also been synthesized. These include the $\Delta^{5(10)}$,[5] $\Delta^{5(6)}$,[6] and the saturated 3-keto derivatives,[7] as well as various ring A and B[8] substituted compounds. Many of these new steroids also possess interesting and useful physiological properties, which suggested that other variations on the 19-nor structure would be of interest.

The synthesis of the $\Delta^{1(10)}$ compounds represents a more fundamental variation in the 19-nor structure than any so far reported. The methyl group is replaced by a 1(10) double bond and the ketone is at carbon 2 instead of 3, giving rise to an α,β-unsaturated ketone system analogous but isomeric to the usual Δ4-3-ketone. In addition to the above compounds 1,3,5(10)-estratriene-2,17β-diol and 2-hydroxy-1,3,5(10)-estratriene-17-one isomers of estradiol and estrone were also prepared and the biological activities of the new compounds were examined.

The starting material employed in the synthesis was the readily available 2-methoxyestradiol-17β acetate Ia.[9] Removal of the free phenolic group was effected by the elegant method of Kenner and Williams.[10] The methoxy acetate I reacted with diethyl phosphite[11] in the presence of triethylamine and carbon tetrachloride to give the diethylphosphate ester Ib, m.p. 106–108°. The ester Ib was reductively cleaved with sodium in liquid ammonia under controlled conditions to give the 3-desoxy-

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Some of this work has been published in a preliminary communication. J. Fishman, *Chem. & Ind.* (London), 1556 (1958).

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