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.

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

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

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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-

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methyl ether IIa, m.p. 130–131°. Pyridine hydrochloride fusion of the methyl ether IIa gave the estradiol isomer 1,3,5(10)-estratriene-2,17β-diol (IIb), m.p. 218–221°. The corresponding estrone isomer was obtained by oxidation of the methyl ether IIa with the Jones reagent[12] to give the 17-keto methyl ether IIc, m.p. 113–115°, which in turn was cleaved with pyridine hydrochloride to yield 2-hydroxy - 1,3,5(10) - estratriene - 17 - one, IId, m.p. 202–204°.

A modified Birch reduction[13] of the 2-methyl ether IIa proceeded as expected and gave the enol ether intermediate III, m.p. 148–152°. Mild mineral acid hydrolysis of III shifted the double bond into conjugation and yielded the new α,β-unsaturated ketone IVa, m.p. 146–148°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ (ε 16,000). Although a new asymmetric center is created at C-5 during the hydrolysis only one product was isolated. Examination of the mother liquors failed to reveal any isomeric substance. It is clear that a preference for one configuration at C-5 results in the exclusive formation of one isomer. In the case of the analogous formation of Δ4-3-keto-19-nor compounds a similar preference is exhibited and the stereochemistry at C-10 was assigned as β, since this would give the preferred anti relationship with the hydrogen at C-9. This orientation was later confirmed by optical rotatory dispersion.[14] Although there is no similar syn or anti relationship possible for the C-5 hydrogen, molecular models indicate that the 5α compound permits ring B to exist in the preferred chair form, while the 5β stereochemistry would require a boat or half-chair form for ring B. That the stereochemistry of the C-5 hydrogen is indeed α in compound IV was confirmed by reducing the α,β-unsaturated ketone IVa with lithium and ammonia in the absence of ethanol to give the saturated ketone VIa, m.p. 150–152° with the 10β configuration.[15] Wolff-Kishner reduction of VIa led to 19-norandrostane-17β-ol VIc, m.p. 126–129° identical in all respects with that obtained by Wolff-Kishner reduction of 19-nordihydrotestosterone.[7a] The optical rotatory dispersion curves of the two ketones IVa and VIa were in agreement with the stereochemical deduction.[16] The curve of the unsaturated ketone IVa was comparable with that of 19-nortestosterone[14] since the two compounds have the same bicyclic environment when IVa is rotated 180°.[17] The curve for the saturated ketone V was similar to that of the 2-keto A/B *trans* steroids.[18] In accordance with the A/B *trans* stereochemistry the ketone V was reduced to the same diol VIb by both sodium borohydride and lithium in liquid ammonia. The equatorial 2α orientation is suggested for the new diol with m.p. 209–211° since a *cis* A/B structure would have been expected to lead to the axial 2α-ol with sodium borohydride, and to the epimeric 2β-ol with metal and ammonia.

The biological activities of the unsaturated ketone IVa and 2-hydroxy isomer of estradiol IIb were investigated.[19] The 19-nor compound IVa showed only minimal androgenic and anabolic activity by the seminal vesicle, levator ani, and ventral prostate weight gain assay. It exhibited slight estrogenic action but no anti-estrogen activity in the uterine assay. The estradiol analog IIc was a very weak estrogen, but did show a 34% estrogen inhibition which was, however, independent of the dosage. The general physiological inertness of these compounds may be a further indication of the necessity of an oxygen function at C-3 in steroid hormones.

The new 19-nor compounds are of particular interest in that they permit chemical approach to the hitherto difficultly accessible C-10 position. Work with these $\Delta^{1(10)}$ compounds is being continued in these laboratories.

EXPERIMENTAL[20]

1,3,5(10)-Estratriene-2,3,17β-triol-2-methyl ether 3-diethylphosphate-17-acetate (Ib). Five grams of 2-methoxyestradiol-17β-acetate Ia was dissolved in 100 cc. of carbon tetrachloride and 50 cc. of purified tetrahydrofuran. To the solution was added 2.7 g. of diethyl phosphite and 3 cc. of triethylamine. The mixture was allowed to stand for 3 days at room temperature. The precipitated triethylamine hydrochloride was then filtered off and the filtrate was diluted with 200 cc. chloroform. The solution was washed with 5% sulfuric acid, 5% sodium hydroxide, and then water. After drying and evaporation the oily residue crystallized from a large amount of petroleum ether to give 5 g. of Ib as needles, m.p. 104–106°. An additional crop of 0.3 g., m.p. 100–104° was obtained.

The analytical sample was obtained from petroleum ether and melted at 106–108°; $[\alpha]_D^{25}$ +41°.

Anal. Calcd. for $C_{25}H_{37}O_7P$: C, 62.49; H, 7.76. Found: C, 62.10; H, 7.66.

1,3,5(10)-Estratriene-2,17β-diol-2-methyl ether (IIa). To a solution of 5 g. of the diethylphosphate Ib in 320 ml. of tetrahydrofuran in a three neck flask equipped with a stirrer was added 800 ml. of liquid ammonia. Stirring was started and sufficient sodium (4 g.) was added slowly until the dark blue color persisted. After 5 minutes stirring, ethanol was

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added carefully until the blue color was discharged. The ammonia was evaporated, the residue was diluted with 400 ml. of water, and the mixture was extracted with chloroform. After drying and evaporation, the crystalline residue weighed 2.9 g. and melted at 120–132°. Recrystallization from petroleum ether afforded 2.6 g. of pure IIa, m.p. 130–133°.

The analytical sample melted at 131–133°; $[\alpha]_D^{25}$ +90°, $\lambda_{max}^{C_2H_5OH}$ 280, ϵ 4000.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.72; H, 9.15. Found: C, 79.64; H, 9.31.

1,3,5(10)-Estratriene-2,17β-diol (IIb). Five grams of freshly distilled pyridine hydrochloride was preheated to 190° and 250 mg. of 2-methoxy 3-desoxyestradiol IIa was introduced. The solution was kept at 190–200° for 15 min., and was then poured into excess 5% hydrochloric acid. After cooling, the mixture was filtered, and the precipitate was recrystallized from benzene to give 150 mg. of IIb as plates, m.p. 218–222°.

The analytical sample was obtained also from benzene and melted at 222–224°; $[\alpha]_D^{27}$ +101° (ethanol).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.40; H, 8.88. Found: C, 79.29; H, 8.93.

2-Hydroxy-1,3,5(10)-estratriene-17-one 2-methyl ether (IIc). A solution of 100 mg. of 2-methoxy-3-desoxyestradiol IIa in 20 cc. acetone was treated dropwise with 8*N* chromic acid until the orange color persisted. After 5 min. at room temperature the solution was poured into water and extracted with ether. The ether was washed with 5% sodium bicarbonate and water. After drying and evaporation the residue was crystallized from a small amount of methanol as long needles, m.p. 110–112°.

The analytical sample was obtained from the same solvent and melted at 113–116°; $[\alpha]_D$ +157°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.88; H, 8.75.

2-Hydroxy-1,3,5(10)-estratriene-17-one (IId). Pyridine hydrochloride fusion of IIc was accomplished as described above. The product was recrystallized from ether as prisms, m.p. 202–204°.

The analytical sample was obtained from acetone–petroleum ether and showed no change in melting point.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.23; H, 8.46.

2,5(10)-Estradiene-2,17β-diol 2-methyl ether (III). A three neck flask was fitted with a Dry Ice condenser and a stirrer and was charged with a solution of 2 g. of 2-methoxy-3-desoxyestradiol IIa in 350 ml. of tetrahydrofuran and 500 ml. of liquid ammonia. Four grams of lithium ribbon was added in small pieces over 15 min. and the blue solution was stirred for an additional 20 min. Ethyl alcohol was then added carefully until the blue color was discharged. The ammonia was evaporated and the residue was diluted with 1 l. of water. The aqueous mixture was extracted with benzene, and the combined organic layers were well washed with water. After drying and evaporation of the solvent the residual oil was crystallized from petroleum ether to give 760 mg. of III as prisms, m.p. 145–152°. The analytical sample was obtained from petroleum ether and had a melting point 148–152°; $[\alpha]_D^{24}$ +117°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.55; H, 9.61.

17β-Hydroxy-1(10)-estrene-2-one (IVa). A solution of 1 g. of the enol ether III in 50 ml. of methanol and 35 ml. of 3*N* hydrochloric acid was kept at 70° for 1 hr. The solution was then poured into 300 cc. of water and extracted three times with benzene. The organic layers were washed with 5% sodium bicarbonate solution and water. Drying and evaporation of solvent resulted in an oil which was crystallized from petroleum ether–ether to give 720 mg. of product IVa, m.p. 145–148° (needles).

Two additional crystallizations from ether afforded the analytical sample, m.p. 148–151°; $[\alpha]_D^{26}$ −58°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, ϵ 16,000.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.96; H, 9.56.

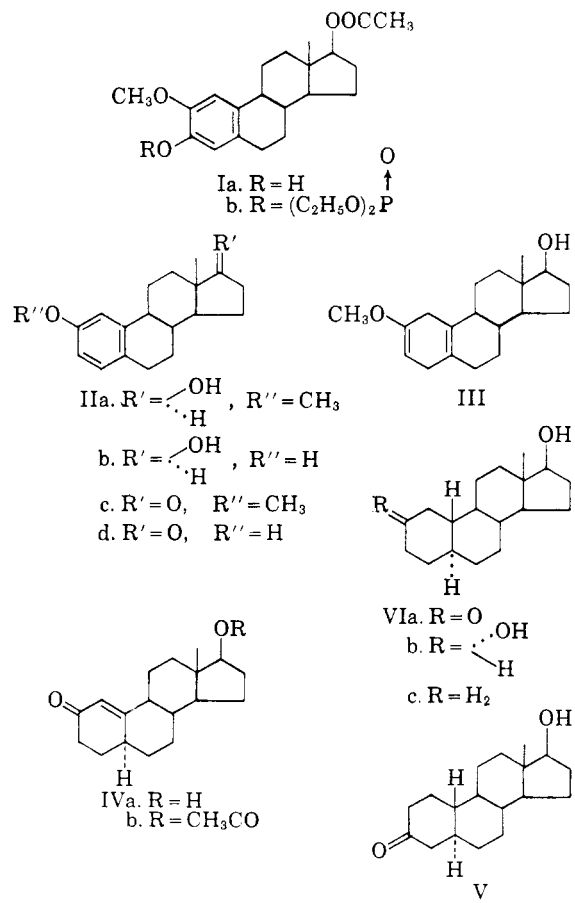
Paper chromatography of the product and its mother liquors in several systems failed to disclose the presence of any other α,β-unsaturated keto compound.

The acetate IVb was prepared in the usual manner and recrystallized from acetone petroleum ether to give the 17β-hydroxy-1(10)-estrene-2-one 17 acetate (IVb), m.p. 159–163°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.04; H, 9.15.

17β-Hydroxyestrane-2-one (VIa). A solution of 100 mg. of the α,β unsaturated ketone IVa in 10 cc. of dry tetrahydrofuran and 5 cc. of dry ether was added to a stirred solution of 30 mg. of lithium in 20 cc. of liquid ammonia. This was immediately followed by the addition of 5 cc. of acetone which discharged the blue color. After evaporation of the ammonia, water was added and the mixture was extracted with chloroform. The organic layer was washed with 5% hydrochloric acid, 5% sodium bicarbonate, and water. The crude material obtained after removal of solvent weighed 104 mg. and contained 6% of starting material as determined by U.V. measurements. The crude product was chromatographed on 10 g. of alumina and was resolved into two main fractions. Elution with benzene afforded 61 mg. of crystals which were recrystallized from petroleum ether to give 52 mg. of 17β hydroxyestrane-2-one (VIa), m.p. 151–153° (needles). The analytical sample had an unchanged melting point, $[\alpha]_D$ +59°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.66; H, 10.21.



Elution with chloroform afforded 22 mg. which on recrystallization from benzene–petroleum ether gave 15 mg. of estrane-2α,17β-diol (VIb) as prisms, m.p. 209–211°, $[\alpha]_D$ +37°.

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.63; H, 10.82. Found: C, 78.04; H, 10.88.

Reduction of a small sample of 17β-hydroxyestrane-2-one (VIa) with sodium borohydride in ethanol water for 2 hr. afforded from benzene–petroleum ether hexagonal *prisms*, m.p. 208–210°, identical with the estrane 2α,17β-diol (VIb) obtained above by mixed melting point and infrared spectra comparison.

Estrane-17β-ol (VIc). (a) *By Huang-Minlon reduction of 17β-hydroxyestrane-3-one* (V). To a solution of 50 mg. of 17β-hydroxyestrane-3-one (V) in 7 cc. of ethanol and 7 cc. of diethylene glycol 5 cc. of hydrazine hydrate was added. After refluxing for 30 min., 0.3 g. of solid potassium hydroxide was added and refluxing was continued for another 15 min. The condenser was then removed and the temperature of the solution was allowed to rise to 190°. Refluxing was then continued for 2.5 hr., at which point water was added and the mixture was extracted with ether. After washing with 5% hydrochloric acid, 5% sodium bicarbonate, and water, the ether was dried and evaporated. The residue weighing 28 mg. was purified by sublimation at 90°, and subsequent crystallization from dilute ethanol. The estrane-17β-ol (VIc) melted 130–133° (needles); $[\alpha]_D$ −8°.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.39; H, 11.52. Found: C, 81.99; H, 11.51.

(b) *By Huang-Minlon reduction of 17β-hydroxyestrane-2-one* (VIa). Reduction of 17β-hydroxyestrane-2-one (VIa) by the same procedure as above, gave crystals, m.p. 128–130°, identical by mixed melting point and infrared spectra comparison with estrane-17β-ol (VIc).

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16α-Methylated Adrenal Hormones. 17α-Hydroxylation by the Glyoxylate Process

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The glyoxylate process has been utilized for the introduction of a C-17 hydroxyl group in the 16-alkyl-20-ketopregnane series. Thus, the 3α-hydroxy-16α-methyl-11,20-dioxo-21-pregnaneglyoxylic acid (III) has been converted in good yield to 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione[1] (VI).

One of the difficult problems encountered in the synthesis of 16-alkylated cortical steroids was the introduction of the C-17 hydroxy group. Apparently an alkyl substituent in the 16- position exerts a steric effect which renders the enol-acetylation procedure of Gallagher[2] very impractical.[3] It has been found that the utilization of the 20-keto-21-glyoxylate (III) offers an excellent route for the introduction of the 17α-hydroxy group. This method was based on the procedure of Hogg and Nathan.[4]

This glyoxylate procedure was admirably suited for the synthesis of 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione (VI),[5] a key intermediate for the preparation of Decadron® (16α-methyl-9α-fluoroprednisolone).

The condensation of diethyl oxylate in ether with 3α-hydroxy-16α-methyl-11,20-dione using sodium methylate was very facile. The resulting sodium salt of the glyoxylate II was hydrolyzed in aqueous methanol without purification to give the 21-glyoxylic acid (III), m.p. 243°, $\lambda_{max}^{CH_3OH}$ 293 (10,200).

The treatment of III with acetic anhydride and either perchloric or 2,4-dinitrobenzenesulfonic acid at 25° gave an excellent conversion to the enol lactone acetate IV as a mixture of geometrical isomers, m.p. 165–175°, $\lambda_{max}^{CH_3CN}$ 297 mμ (22,800). Epoxidation of this isomeric mixture of IV with perbenzoic acid afforded the epoxy lactone V in quantitative yield, m.p. 225–227°, $\lambda_{max}^{CH_3CN}$ 226 mμ (11,400). The hydrolysis of V under mild conditions in aqueous ethanol yielded the desired 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione (VI) in an 80% yield, m.p. 191–193°.

We cannot understand the experience of the Ciba group[3] who found that the application of this procedure to a similar series of 16α-methylated steroids did not give the desired enol lactone acetate (compare IV). These authors imply that the selective enol lactone acetate formation ($\Delta^{17,20}$) from the glyoxylic acid III is inhibited because of steric interaction of the 16-methyl substituent and the grouping at C-20. That this explanation is not completely valid, is attested to by the synthesis of VI and also by the application of this approach by Hoffsommer *et al.*[6] to the synthesis of 3α,17α-dihydroxy-16,16-dimethylpregnane-11,20-dione—a compound in which this type of steric effect should be enhanced. Perhaps the reason for the divergence is because of minor differences in procedure.

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