EXPERIMENTAL[5]

3β-Hydroxy-19-nor-5α-androstane-17-one-p-toluenesulfonate (I). A 17-mg. sample of 3β-hydroxy-19-nor-5α-androstan-17-one (m.p. 177–179°)[6] was dissolved in 2.0 ml. dry pyridine containing 500 mg. of freshly recrystallized *p*-toluenesulfonyl chloride.[7] The solution was allowed to stand at room temperature for 24 hr. About 15 ml. of ice water was added and the resulting suspension extracted with cold chloroform. The chloroform phase was washed with cold 0.2*N* hydrochloric acid, cold 5% aqueous sodium bicarbonate and cold water till neutral, dried over sodium sulfate, and evaporated under reduced pressure to dryness. A 28.2-mg. sample of solid resulted (I); λ_{max}^{KBr} 5.78 (cyclopentyl C=O), 6.25 (phenyl C=C) 7.4, 8.5, and 14.95 μ; no hydroxyl absorption was present. A similar spectrum was obtained with the tosylate of epiandrosterone.

3α-Hydroxy-19-nor-5α-androstan-17-one (II) *from* (I). The crude tosylate (I) was dissolved in 4.0 ml. of dimethylformamide containing 180 mg. of potassium acetate in 0.5 ml. of water. The resulting solution was refluxed for 3 hr., allowed to stand overnight, and refluxed for an additional hour. Twenty milliliters of water was added to the precooled solution and the resulting suspension extracted with ether. The ether phase was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The resulting brown oil was extracted with petroleum ether (b.p. 30–60°) and the extract evaporated to dryness. A light yellow oil resulted (14.2 mg.); λ_{max}^{film} 5.75 (cyclopentyl ketone), 6.05 (C=C), 8.05 μ (acetate) and no hydroxyl present. The complex band at 8.05 μ similar to that of androsterone acetate indicated the presence of an axial acetate (3α,5α).[8] The crude oil was dissolved in 4.0 ml. methanol containing 55 mg. of potassium carbonate dissolved in 1.0 ml. of water and the mixture refluxed for 2 hr. Water was added to form a suspension which was extracted with about 100 ml. of ether, the ether phase was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The colorless oil obtained (8.5 mg.) was chromatographed on a silica gel column and eluted with benzene and benzene–ethyl acetate mixtures. The 2.7-mg. sample of white amorphous material which was eluted with benzene gave no significant ultraviolet absorption in the region of 220–360 mμ; λ_{max}^{KBr} 5.75 (cyclopentyl ketone), 6μ (isolated double bond), and no hydroxyl or acetate absorptions. Based on the infrared spectra and on reactions carried out under similar conditions with epiandrosterone[9] and allopregnane-3α-ol,11,20-dione[7] which yielded the corresponding Δ^2-elimination products, the compound is tentatively assigned the structure of Δ^2-19-norandrostan-17-one (m.p. 115–121°). Elution with benzene–ethyl acetate 9:1 and 6:1 resulted in 3.7 mg. of white amorphous material which upon crystallization from acetone-hexane yielded (II) colorless needles with the double melt 148°, 164.5–167°; $[\alpha]_D^{21.7}$ +110, (*c*, 0.765 in chloroform); λ_{max}^{KBr} 2.75 (OH), 5.75 (cyclopentyl C=O), 9.0, 9.35, 9.49, 9.65, 9.81, 10 μ (axial OH).[8]

19-Nor-5α-androstane-3α,17β-diol (III) *from* (II). A 2.1-mg. sample of II was dissolved in 1.0 ml. of methanol containing 15 mg. of sodium borohydride. The solution was stirred overnight, water was added, and the resulting suspension extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to dryness. Chromatography on silica gel yielded 1.3 mg. of white amorphous material (III). Crystallization from acetone-hexane produced colorless needles, m.p. 191–193°; $[\alpha]_D^{21.1}$ + 23.7 (*c*, 0.34 in chloroform); λ_{max}^{KBr} 2.90 (bonded OH), and 9.15, 9.40, 9.55, 9.90, 10.00 μ (axial OH).[8] Oxidation of the diol with chromic acid in acetic acid produced a dione (λ_{max}^{KBr} 5.80, 5.87 μ) identical to an oxidation product of 19-nor-5α-androstane-3β,17β diol and to an authentic sample of 5α-19-norandrostane-3,17-dione.[10,11]

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(5) All melting points are uncorrected.
(6) D. Kupfer, E. Forchielli, and R. I. Dorfman, *J. Am. Chem. Soc.*, **82**, 1257 (1960).
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(10) C. Chen, *Tetrahedron* **3**, 43 (1958).
(11) This compound was kindly supplied by Dr. Mika Hayano.

11-Oxygenated 17α-Acetoxy-9α-fluoro-6α-methyl-1,4-pregnadiene-3,20-diones

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Acylation of 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (I)[1,2] with acetic anhydride–*p*-toluenesulfonic acid[3] afforded 17α-acetoxy-9α-fluoro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (II) in 45% yield. The 11-keto analog III was obtained by the chromic acid oxidation of II.

Endocrine assays of these compounds are summarized in Table I.

TABLE I

CORTICOID AND PROGESTATIONAL ASSAYS OF COMPOUNDS I, II, AND III

Compound	Anti-Inflammatory Activity (X Hydrocortisone) Rats	Glycogen Deposition (X Hydrocortisone)	Progestational (X Progesterone)
I	131[4]	26[4]	60
II	170[5]	7[5]	60–80[5]
III	40		

Compound II is the only steroid described as effectively inhibiting both the C-3-H mammary

(1) J. A. Hogg, 6th National Medicinal Chemistry Symposium, ACS, Madison, Wis., June 23, 1958.
(2) The registered trademark of the Upjohn Company, Kalamazoo, Mich., for 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione is Oxylone.
(3) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).
(4) R. O. Stafford, A. Robert, S. C. Lyster, F. L. Schmidt, and W. E. Dulin, *Proc. Soc. Exptl. Biol. Med.*, **101**, 653 (1959).

adenocarcinoma in mice and the testosterone propionate-resistant mammary fibroadenoma in rats[5] (see Table II).

TABLE II

TUMOR INHIBITION BY COMPOUND II

Compound	Dose, mg./kg.	% Tumor Inhibition[a] TP-Resistant[b] (Rats)	% Tumor Inhibition[a] C-3-H (Mice)
Prednisolone	15	0–20	100
Testosterone propionate	5	0–15	0
Compound II	15	72	96

[a] Results derived from multiple assays, using 8–20 animals/group. The steroids were administered subcutaneously in a CMC vehicle. [b] E. M. Glenn, S. L. Richardson, and B. J. Bowman, *Endocrinology*, **64**, 379 (1959).

EXPERIMENTAL[6]

17α-Acetoxy-9α-fluoro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (II). A mixture of 5.0 g. of 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (I) in 625 ml. of glacial acetic acid, 125 ml. of acetic anhydride, and 2.0 g. of *p*-toluenesulfonic acid, monohydrate, was stirred vigorously at 26° until solution was completed (about 8 hr.). The reaction mixture was poured into a large volume of water containing 1 kg. of potassium bicarbonate. The product recovered by filtration, after drying, melted at 205–212° and constituted a quantitative yield. The crude product was recrystallized from ethyl acetate–Skellysolve B[7] to afford 2.5 g. (45.0% yield) of II, m.p. 225–228°, $[\alpha]_D$ + 49° (pyridine). The analytical sample, m.p. 230–232°, $[\alpha]_D$ + 50° (pyridine), was prepared by recrystallization from the same solvents.

Anal. Calcd. for $C_{24}H_{31}FO_5$: C, 68.89; H, 7.47; F, 4.54. Found: C, 68.90; H, 7.56; F, 4.7.

17α-Acetoxy-9α-fluoro-6α-methyl-1,4-pregnadiene-3,11,20-trione (III). To a solution of 1 g. of II in 50 ml. of acetone, 0.5 ml. of chromic acid solution[8] was added with stirring. After 5 min. the excess oxidizing agent was destroyed by the addition of a few drops of methanol. The reaction mixture was concentrated under vacuum and the product isolated by partition between methylene dichloride–water. The residue obtained from the methylene dichloride fraction when recrystallized from ethyl acetate–Skellysolve B weighed 300 mg. (30%) and melted at 273–275°. Recrystallization from the same solvents gave an analytical sample, m.p. 277–278.5°.

Anal. Calcd. for $C_{24}H_{29}FO_5$: C, 69.21; H, 7.07; F, 4.56. Found: C, 69.44; H, 7.36; F, 4.5.

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(5) Presented by E. M. Glenn, S. L. Richardson, B. J. Bowman, and S. C. Lyster at CCNSC Symposium titled, "Biologic Activities of Steroids in Relation to Cancer," Vergennes, Vt., Sept. 27–Oct. 2, 1959. (Abstracts of papers to be published.)

(6) The authors are indebted to G. E. VandenBerg of these laboratories for assistance in the preparation of these compounds.

(7) A saturated hydrocarbon fraction, b.p. 60–71°.

(8) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

The Preparation of 16-Methyl-Δ[16]-steroids Containing Ring C Substituents

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Research in this laboratory on C^{14}-substituted steroids[1] has been extended to include methyl substituents. In view of the recent publications,[2] especially that by Slates and Wendler,[2g] on C^{16}-methyl steroids we wish to report here on our work in this area. This note describes the preparation of 16-methyl-Δ[16]-steroids which contain substituents in the C-ring, in particular, on 21-acetoxy-9α-fluoro-11β-hydroxy-16-methyl-4,16-pregnadiene-3,-20-dione (VII).

Following the procedure of Wettstein[3] 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione[4] (Ia) on reaction with excess diazomethane gave 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4,9(11)-pregnadiene-3,20-dione (IIa).[5] A band attributable to —N=N—stretching[6] was observed at 1565 cm.$^{-1}$ in this and all the other pyrazolino-steroids herein prepared. Thermal decomposition of IIa readily afforded 21-acetoxy-16-methyl-4,9(11),16-pregnatriene-3,20-dione (IIIa).

N-bromoacetamide-perchloric acid treatment of 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4,9(11)-bromohydrin IV. This was converted, without further purification, in refluxing methanolic potassium acetate directly into 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-9β,11β-epoxy-4-pregnane-3,20-dione(V).

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