(B) In another experiment the crude reduction product was chromatographed on alumina (Merck, for chromatographic purposes) and was separated as follows: 0.1498 g. (15.3% of the total) of 3-α-cholestanol, m.p. 187–189° (lit.[8] m.p. 186–187°), 0.0893 g. (8.8% of the total) of a mixture of 3-cholestanols, m.p. 137–177° and 0.7414 g. (75.7% of the total) of 3-β-cholestanol, double m.p. 127° and 145° (lit.[8] m.p. *ca.* 125° and 141–142°) which was acetylated as above to give a crude 3-β-cholestanyl acetate, $[\alpha]_D^{24}$ + 13.9.°

Reduction with lithium aluminum hydride.[4] This was carried out in the usual way and the crude reaction product was acetylated as described above. The rotation of the acetyl derivative $[\alpha]_D^{25}$ 14.8° rose to 15.4° upon further drying, corresponding to 9.4% cholestanyl-3-α acetate. In a second experiment the crude material was chromatographed. Of the eluate (96% recovery), 91% melted at 144–145° (3-β isomer) and 9% melted at 170–172° (slightly impure 3-α-isomer).

Reduction under equilibrating conditions. To a solution of 1.0 g. (7.5 mmoles) of aluminum chloride in 30 ml. of ether was added 6.0 ml (1.68 mmoles) of a 0.28*M* solution of lithium aluminum hydride in ether, followed by 2.3 g. (7.31 mmoles) of 3-cholestanone in ether solution. After refluxing overnight, the solution was worked up in the usual way and the residue chromatographed. There was obtained 0.24 g. (9% of the eluate) of an unidentified semisolid, followed by 1.39 g. (53% of eluate) of crude 3-cholestanone, m.p. 110–111° whose infrared spectrum indicated the absence of hydroxylated material and 0.98 g. (38%) of 3-β-cholestanol, m.p. 142–143°. No 3-α-cholestanol was detected.

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Fluorinated Steroids. III. Synthesis of 16ζ-Fluorotestosterone

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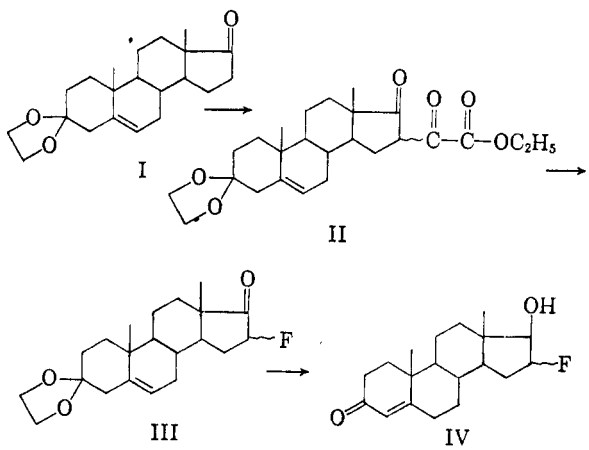
In previous papers[1] we have described a method for the introduction of fluorine into the steroid molecule which consists in the reaction of the sodio enolate of an α-alkoxalyl keto steroid with perchloryl fluoride[2] followed by removal of the alkoxalyl moiety under mildly alkaline conditions. In this note we wish to report the application of this method to the synthesis of 16ζ-fluorotestosterone (IV).[3]

A suitable starting material for the synthesis of a 16-alkoxalylandrostene derivative was 3-ethylenedioxy-5-androsten-17-one (I).[4] This compound was prepared by the chromic oxide–pyridine oxidation[5] of testosterone 3-ethylene ketal.[4d,6] Condensation of I with ethyl oxalate and sodium ethoxide in benzene afforded a white, crystalline ethoxalyl derivative II in 72% yield. Reaction of the sodio enolate of this substance with perchloryl fluoride in methanol followed by the potassium acetate-catalyzed cleavage of the ethoxalyl group gave 3-ethylenedioxy-16ζ-fluoro-5-androsten-17-one (III) in poor yield and also afforded a by-product, $C_{21}H_{29}FO_5 \cdot H_2O$, which has not been identified thus far. Compound III was converted to 16ζ-fluorotestosterone (IV)[3] by sodium borohydride reduction of the 17-keto group[7] followed by acid-catalyzed regeneration of the Δ^4-3-one system. The stereochemistry of the fluorine atom at C_{16} in III and IV is uncertain. However, the physical characteristics of the product are in good agreement with those reported in the patent literature[3] for 16α-fluorotestosterone.



(1) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **81**, 1262 (1959); H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960), (paper II of this series).

(2) We would like to thank the Pennsalt Chemicals Corporation for a generous sample of perchloryl fluoride.

(3) J. Fried and G. H. Thomas (U. S. Patent 2,857,403) prepared 16α- and 16β-fluorotestosterone in a reaction sequence which involved displacement of the mesyloxy group in 16α-mesyloxy-4-androstene-3,17-dione by fluoride ion.

(4) H. Koster and H. H. Inhoffen, U. S. Patent 2,302,-636; (b) E. Fernholz, U. S. Patents 2,356,154 and 2,378,918; (c) H. L. Herzog, M. A. Jevnik, M. E. Tully, and E. B. Herschberg, *J. Am. Chem. Soc.*, **75**, 4425 (1953); (d) H. J. Dauben, B. Loken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

(5) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(6) A more direct preparation of I has been reported[4d] through the preferential 3-ketalization of 4-androstene-3,17-dione with 2-methyl-2-ethyl-1,3-dioxolane. However, in our hands, this procedure gave a product contaminated with 3,17-bisethylenedioxy-5-androstene.[4c]

(7) Metal hydride reductions of 16-halo 17-ketones have been reported by several workers to afford the 17β-hydroxy derivatives.[8] However, in a few instances, mixtures of the 17-epimeric alcohols have been obtained.[9]

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(9)(a) C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958); (b) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958).

EXPERIMENTAL[10]

3-Ethylenedioxy-5-androsten-17-one (I). To a chilled solution of 1.64 g. (4.94 mmoles) of 3-ethylenedioxy-17β-hydroxy-5-androstene[4d] in 15 cc. of dry pyridine was added the chromic oxide–pyridine reagent[5] prepared from 2.06 g. of chromic oxide and 15 cc. of pyridine. The stirred mixture was kept at room temperature over night and was then added to 100 cc. of ice water. Chloroform was added and the mixture was filtered through diatomaceous earth. The precipitate was washed with more chloroform and the layers of the filtrate were separated. The chloroform phase was washed with water, and was dried and partially decolorized over magnesium sulfate and activated charcoal. The solution was filtered and freed from solvents by evaporation. The residue was crystallized from methanol to afford 1.18 g. (73%), m.p. 189–197° (lit. m.p. 185–192°,[4c] 197–198°[4d]).

16-Ethoxalyl-3-ethylenedioxy-5-androsten-17-one (II). Sodium (75 mg.) was dissolved with heating in a mixture of 30 cc. of benzene and 2 cc. of methanol. Solvent was distilled from the stirred mixture until the distillation temperature reached 80°. To the resulting stirred suspension, cooled to room temperature, was added 1 g. (3 mmoles) of 3-ethylenedioxy-5-androsten-17-one (I) and 1 cc. of ethyl oxalate. The mixture was stirred at room temperature for 16 hr. and was then extracted with several portions of 1% aqueous potassium hydroxide solution. The extracts were neutralized with 30% aqueous sodium dihydrogen phosphate solution and the mixture was extracted several times with chloroform. The combined chloroform extracts were washed with water, dried, and evaporated. The residue was crystallized from ether to afford 0.795 g. (72%) of white solid with m.p. 161–164°. A sample recrystallized from ether showed m.p. 161–163; $[\alpha]_D^{25}$ −103° (*c*, 0.793 in chloroform); λ_{max} 5.76 μ (ester), 5.94 μ, and 6.17 μ (enolized β-diketone system); positive enol test.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.98; H, 8.20.

3-Ethylenedioxy-16ζ-fluoro-5-androsten-17-one (III). To a suspension of 860 mg. (2 mmoles) of 16-ethoxalyl-3-ethylenedioxy-5-androsten-17-one (II) in 20 cc. of methanol, cooled to −15°, was added 3 cc. of a 1*N* methanolic sodium methoxide solution and the stirred, cooled solution was saturated with a rapid stream of perchloryl fluoride gas.[11] Nitrogen was then blown through the solution to remove excess perchloryl fluoride and the reaction mixture (neutral, negative enol test) was evaporated *in vacuo* at room temperature. The residue was dissolved in chloroform and water, and the layers were separated. The organic phase was dried and evaporated and the residue was redissolved in 20 cc. of methanol. Potassium acetate (1.5 g.) was added and the stirred mixture was heated under reflux for 1 hr. The solvent was evaporated and the residue was dissolved in chloroform and water. The chloroform layer was washed with a little water and was dried and evaporated to afford 913 mg. of a glass. This was crystallized from 10 cc. of ether and the solid was collected and washed twice with 5-cc. portions of ether. There was obtained 170 mg. (24%) with m.p. 227–230°. The analytical sample was recrystallized twice from methylene chloride–ether; m.p. 240–243°; $[\alpha]_D^{25}$ + 26.8° (*c*, 1.64 in chloroform); λ_{max} 5.70 μ (17-one), 9.08 μ (3-ketal).

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.37; H, 8.39; F, 5.45. Found: C, 72.01; H, 8.73; F, 5.82.

Total evaporation of the ether mother liquors and trituration with a small amount of fresh ether afford 360 mg. of a solid with m.p. 100–105°. This was recrystallized from acetone-hexane and from ether; m.p. 109–111°; $[\alpha]_D^{25}$ −63.5° (*c*, 0.38 in chloroform); λ_{max} 2.83 μ (OH), 5.70 μ (shoulder, α-fluoroketone), 5.78 μ (ester?), 7.90–8.02 μ (ester?), 9.08 μ (3-ketal).

Anal. Calcd. for $C_{21}H_{29}FO_5 \cdot H_2O$: C, 63.29; H, 7.84; F, 4.77; H_2O, 4.52. Found: C, 62.86; H, 7.87; F, 4.53; H_2O, 4.84.

16ζ-Fluoro-4-androstene-3,17-dione (*16ζ-Fluorotestosterone*, IV). A solution of 348 mg. (1 mmole) of 3-ethylenedioxy-16ζ-fluoro-5-androsten-17-one (III), in 10 cc. of methanol and 0.5 cc. of water was reduced with 175 mg. of sodium borohydride at the reflux point for 3 hr. The mixture was cooled and poured into 25 cc. of water to give a suspension which was extracted with four 10-cc. portions of chloroform. The combined extracts were washed with water, dried and evaporated. The residue was crystallized once from methanol to afford 0.3 g. (86%) with m.p. 189–195°; λ_{max} 2.80 μ (OH region), no absorption in the C=O region. The solid was redissolved in 20 cc. of methanol containing 1 cc. of 8% aqueous sulfuric acid and the mixture was allowed to reflux for 2 hr. and was then diluted with an additional 30 cc. of methanol. Duolite A-4 anion exchange resin (OH form)[12] was added with stirring until the solution was neutral. The resin was removed by filtration and was washed well with methanol. The combined filtrate and washings were evaporated and the residue was dissolved in chloroform and water. The chloroform phase was washed with a little water and was dried and evaporated to give a crystalline residue which was recrystallized from ether to afford 0.17 g. (55% over-all from III), m.p. 154–156°; $[\alpha]_D^{25}$ +117° (*c*, 0.5 in chloroform) (lit. values[3] for 16α-fluorotestosterone: m.p. 153–158°, $[\alpha]_D$ +113° in chloroform); λ_{max} 240 mμ (ε, 15,800); λ_{max} 2.94 μ (OH), 6.01 μ (Δ⁴-3-one).

Anal. Calcd. for $C_{19}H_{27}O_2F$: C, 74.47; H, 8.88; F, 6.20. Found: C, 74.46; H, 9.03; F, 6.00.

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(10) Melting points were taken on a Kofler micro hot-stage and are corrected. Ultraviolet spectra were determined in methanol on a Cary recording spectrophotometer and infrared spectra (potassium bromide disks) on a Perkin Elmer spectrophotometer (Model 21). An ethanolic solution of ferric chloride was used for the enol test. Solutions were dried over magnesium sulfate and evaporated under reduced pressure.

(11) V. Papesh, *Chem. Eng. News*, **37**, (No. 28), 60 (1959) has reported an explosion resulting from the addition of sodium methoxide to a vessel containing the mixed vapors of methanol and perchloryl fluoride.

(12) Duolite A-4 is the trademark of the Chemical Process Co., Redwood City, Calif., for a weakly basic anion exchange resin.

6β-Hydroxylation of 9α-Fluorohydrocortisone

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In a study of the hydroxylation of 9α-fluorohydrocortisone (I) by a variety of *Streptomyces* species we have found that a strain of *S. rimosus* (Lederle Laboratories Collection No. T1686B) affords as a major product a very polar reducing monohydroxylated 9α-fluorohydrocortisone II different from the previously described 1ξ- and 16α-hy-

(1) Present address: Wyeth Laboratories, Inc., Philadelphia, Pa.