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SYNTHESES OF 4-FLUOROESTRADIOL AND 7α-FLUOROESTRADIOL[1a,1b]

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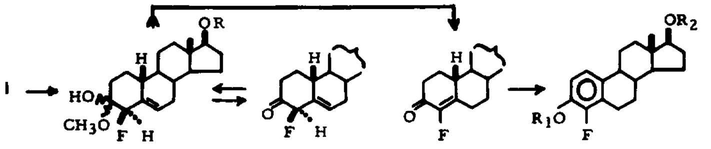
FLUORO-STEROIDS have been synthesized in the series of corticoids, gestogens, androgens, and sterol derivatives, but only a few 16-fluoro-derivatives of estrogens are known.[2]

As a part of our program aimed at the development of potentially specific inhibitors of hormone-dependent malignancies, we have undertaken the syntheses of fluoroestrogens. This communication discloses the syntheses of 4-fluoroestradiol (Va) and 7α-fluoroestradiol (XIa).



II

R = H

III

IV a, R = H

b, R = Ac

V a, R_1=R_2=H

b, R_1= H, R_2=Ac

c, R_1= R_2= Ac

The pyrrolidyl enamine of 19-nortestosterone (I)[3] was treated in methanol-water at -25° with perchloryl fluoride,affording a product showing only end absorption; λ_{max}^{KBr} 2.98μ; phase change at 120-125°, decomposition at 158°, formulated as 4β-fluoro-3ξ-methoxy-3ξ, 17β-dihydroxy-5-estrene (III).[4] Hemiketal II, on heating to 130°, or in refluxing dioxane, afforded 4β-fluoro-5-estren-17β-ol-3-one (III), decomposing at 159°, $\lambda_{max}^{Et_2O}$ 307 mμ (ε240); $\lambda_{max}^{CH_2Cl_2}$ 2.76, 5.78μ, which was reconverted to hemiketal II by recrystallization from methanol.[5,6] Hemiketal II was converted by hydrochloric acid in dimethyl formamide to 4-fluoro-19-nortestosterone (IVa), m.p. 149-150°,[3,5] λ_{max}^{EtOH} 248 mμ (ε15,900); $\lambda_{max}^{CH_2Cl_2}$ 2.75, 5.91, 6.09μ. The n.m.r. spectrum[7] of IVa showed no vinyl-H. Ketone IVa was acetylated to acetate IVb, m.p. 135-136°, λ_{max}^{EtOH} 247 mμ (ε16,200); $\lambda_{max}^{CH_2Cl_2}$ 5.79, 5.92, 6.10μ. Dehydrogenation of IVb with selenium dioxide afforded 4-fluoroestradiol 17-acetate (Vb), m.p. 238-240°, λ_{max}^{EtOH} 273 mμ (ε 1,310), $\lambda_{max}^{EtOH\text{-}KOH}$ 291 mμ (ε 2,460); and dehydrogenation of IVa gave 4-fluoroestradiol (Va), m.p. 190-191°, λ_{max}^{EtOH} 274 mμ (ε 1,210), $\lambda_{max}^{EtOH\text{-}KOH}$ 292 mμ (ε 2,340); Va-diacetate (Vc), m.p. 133.5-134.5°, λ_{max}^{EtOH} 263 mμ (ε 520), shoulder at 271 mμ (ε 440).

The n.m.r. spectrum at 60 Mc/s of III showed a doublet, centered at τ=5.34, J_{HF}=51 cps., of H-4; a partly resolved multiplet, of H-6, centered at τ =3.96, with an unusually wide[8] half-band width of 17 cps., strongly suggesting long-range spin-spin coupling of H-6 with F-4,[9] as expected for axial fluorine. The spectroscopic data for III support an axial fluorine conformation,[10] as does the 16 mμ bathochromic shift of the first extremum[11,12] of the optical rotatory dispersion curve

(O.R.D.) of III, $[\alpha]_{334}$ + 3923°, relative to that of unsubstituted 5-cholesten-3-one, $[\alpha]_{318}$ + 1268°. The applicability of our case of the α-haloketone rule [13a] and of the generalized octant rule [13b] as applied to haloketones [13c] requires that the contribution of the fluorine to the Cotton effect of III should not be overridden by effects observed in highly enhanced inherently dissymmetric chromophores [13d, e]. The fulfillment of this requirement depends on the relative geometric disposition of the 3-carbonyl group and the 5,6-double bond (Fig. 1) which does <u>not</u> correspond, in the chair-like conformation of ring A of III, to the known arrays (reference 13d, *Fig.* 3) associated with β, γ -unsaturated ketones geometrically favorable for enhancement [14]. This argument is supported by the normal absorption spectrum, $\lambda_{max}^{Et_2O}$ 293 mμ (ε 65), and O.R.D. amplitude, of the unsubstituted 5-en-3-one. Hence, the contribution of fluorine to the Cotton effect of III is evidently positive, indicating that fluorine, whose specific rotativity is negative, [13b] is positioned in a negative octant; [13c] hence, fluorine has the 4β-configuration in the chair-like [14] conformation

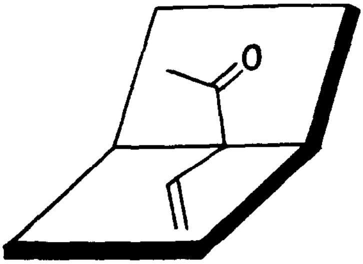
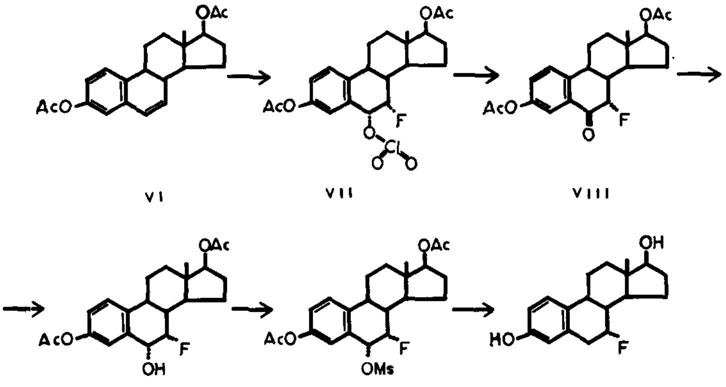


FIG. 1

of ring A of III. The n.m.r. spectrum at 100 Mc/s of 4-fluoroestradiol diacetate (Vc) showed signals for two aromatic hydrogens, forming an ABX pattern (A, H-1; B, H-2) with $J_{AB}=J_{BX}=6.8$ cps., $J_{AX}=0$ cps., $\tau_A=2.85$ and $\tau_B=3.01$, which confirms the structure of 4-fluoroestradiol.

No precendent is available for the introduction of fluorine into the 7-position of steroids. The new oxofluorination reaction[15] was applied for


VI VII VIII
IX X XIa

that purpose. The tetraene 6-dehydroestradiol diacetate VI, on oxofluorination, afforded a mixture of products, from which was isolated 6-oxo-7α-fluoroestradiol diacetate VIII,[15] m.p. 174-175°, λ_{max}^{EtOH} 211 mμ (ε 20,000), 255 mμ (ε 10,500), 305 mμ (ε 2,200); $\lambda_{max}^{CH_2Cl_2}$ 5.67, 5.79, 5.90μ. N.m.r.: $\tau=5.19$, $J_{HF}=50$ cps. (7β-H); $\tau=7.68$ (3-OAc); $\tau=7.93$ (17β-OAc). The O.R.D. of VIII showed a 16 mμ bathochromic shift, and a negative contribution of fluorine to the Cotton effect, relative to that of the parent ketone, 7-oxoestradiol diacetate. Reduction of VIII with sodium borohydride at -5° afforded the cis-fluorohydrin IX, m.p. 192-198°, λ_{max}^{EtOH} 267 mμ (ε 540), 274 mμ (ε 510); mesylate X, m.p. 206-208°, $\lambda_{max}^{CH_2Cl_2}$ 269 mμ (ε 710), 276 mμ (ε 700); NMR: τ =6.78 (6α-OMs). Reductive removal of the mesyloxyl group with lithium aluminum hydride gave 7α-fluoroestradiol XIa, m.p. 167° (dec.), λ_{max}^{EtOH} 280 mμ (ε 2,000), sh. 287 mμ (ε 1,800); $\lambda_{max}^{EtOH-KOH}$ 300 mμ (ε 2,700); λ_{max}^{KBr} 2.96, 3.20μ; diacetate XIb, m.p. 115-116°, λ_{max}^{EtOH} 267 mμ (ε 960), 274 mμ (ε 900). The structure of XIb was confirmed by n.m.r., signals at τ=5.0, J_{HF}= 50 cps. (7β-H); τ =7.72 (3-OAc); τ =7.94 (17β-OAc).

In preliminary screening tests, 4-fluoroestradiol (Va) produced inhibition of transplanted spontaneous mammary fibroadenoma in rats.

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(1) (a) Aided by Grant P-265 B from the American Cancer Society; (b) Reported in part at the XIXth International Congress of Pure and Applied Chemistry, London, July, 1963; (c) Postdoctoral Fellow.

(2) (a) G.P. Mueller and W.F. Johns, J. Org. Chem. 26, 2403, (1961); (b) C.H. Robinson, N.F. Bruce and E.P. Oliveto, J. Org. Chem. 28, 975 (1963).

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(4) All new compounds gave satisfactory elementary analyses.

(5) A product of m.p. 171°, described (reference 3) as 4-fluoro-5-estren-17β-ol-3-one containing 0.75 mole of methanol, was not identical with either our II or III. Both the 171° product, and II, afforded IVa.

(6) Electronegative groups α to carbonyl stabilize addition compounds such as hydrates and hemiketals, cf. N. L. Allinger and H. M. Blatter, J. Org. Chem. 27, 1523 (1962).

(7) N.m.r. spectra were obtained by Dr. D. P. Hollis of Varian Associates, chloroform-d being employed as the solvent.

(8) The observed spectrum of H-6 is compatible with $J_{6,7\beta}$=6 cps., $J_{6,7\alpha}$=2 cps., $J_{6,10\beta}$=2 cps., and $J_{6H,4\alpha F}$=5cps. The half-band-width of H-6 is 8 cps. in cholesterol, No. 363 in High Resolution NMR Spectra Catalog, Varian Associates, Palo Alto, (1962), and 9 cps. in 5-cholesten-3-one.

(9) Dr. G. Slomp (private communication) has observed H-F coupling in 6β-fluoroprogesterone, τ=4.13, J_{HF}=5 cps., in which the C-F bond is nearly perpendicular to the C=CH plane; and no H-F coupling (singlet, τ = 3.95) in a 6α-fluoroprogesterone.

(10) The hypsochromic shift of the carbonyl band, relative to that of 5-cholesten-3-one, $\lambda_{max}^{CH_2Cl_2}$ 5.84μ, was - 18 cm^{-1}, as in the pair of 4-*t*-butylcyclohexanone and its *trans*-2-(axial)-fluoro derivative (reference 6).

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(14) Models of the four possible boat-like conformations of ring A of III show that none has a geometry of the chromophores corresponding to those of highly enhanced β,γ -unsaturated ketones (reference 13d). In two of these conformations, only 4α-fluorines would make a contribution to the Cotton effect; however, these contributions would be *negative*, contrary to observation. The other two boat-like conformations, that with the 1β and the 4β; and that with the 2α-bond as "flagpoles", lead to the same configurational assignment for III as the preferred argument in terms of the chair-like conformation of ring A.

(15) M. Neeman and Y. Osawa, *J. Am. Chem. Soc.* **85**, 232 (1963). The arguments for the assignment of the structure and stereochemistry to VIII are analogous to those presented in this reference; the present findings are in accord with the mechanism of the oxofluorination reaction presented therein, which envisions the formation of intermediate VII by bident attack of perchloryl fluoride on the α-side of the steroid's 6,7 (styrene) bond.