Notes

1-Fluoro Steroids. II.[1a] 1ξ-Fluoro-5α-androst-2-en-17β-ol Acetate

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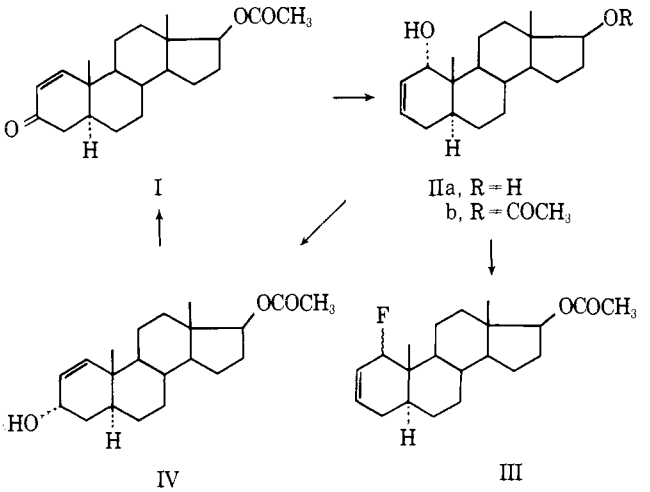
The concept of the essentiality of sp^2 hybridization in the A ring of androstanes and estranes for favorable anabolic–androgenic activity ratios as enunciated by the Syntex group[2] is supported by many sets of examples.[3] In line with these concepts and in continuation of our studies of the reaction of 2-chloro-1,1,2-trifluoroethyldiethylamine with 1α-hydroxy steroids,[1a] we have examined the action of this reagent on 17β-acetoxy-5α-androst-2-en-1α-ol (IIb).[4] As observed in our earlier work,[1a] reaction at room temperature was rapid, with complete utilization of starting material within 30 min. Thin layer chromatographic analysis indicated the presence of a major mobile product (III) and of several more polar components, one of which (IV) predominated.

The product III, formulated as 1-fluoro-5α-androst-2-en-17β-ol acetate, was isolated by direct crystallization in 72% yield. However, on attempted column chromatography of the reaction mixture from one experiment on silica gel, only the nonfluorinated IV, shown later to be 17β-acetoxy-5α-androst-1-en-3α-ol, could be recovered.

Proton nmr spectra of III showed three key features which support the assigned 1-fluoro-Δ^2 structure: (a) a C-19 methyl proton doublet (J = 1.5 cps),[5] characteristic of coupling between fluorine and angular methyl protons;[6,7,10] (b) two half-proton doublets (J = 5 cps) separated by 50 cps centered at 4.50 ppm, indicative of an HCF system, the proton of which is further coupled to an adjacent proton; and (c) two poorly resolved, overlapping proton signals, one a doublet at 5.85 ppm (J = 5 cps) showing fine splitting and the other a broad singlet at 5.90 ppm.

From the over-all similarity of the olefinic proton signals of III to those of IIa and IIb as well as to other 5α-Δ^2-steroids,[11] a Δ^2 double bond is indicated for III.



Since the product IV of an allylic rearrangement was also obtained in the synthesis, it was necessary to exclude a 3-fluoro-Δ^1 structure for III. The vinyl proton signals of III clearly serve to eliminate Δ^1 structures.[11] A 3-fluoro structure is also ruled out on the basis of the C-19 proton splitting, since neither 3α- nor 3β-fluoro steroids are known to exhibit such coupling.[6,10]

The indicated fine splitting of the olefinic proton signals (*ca.* 1 cps) may be a consequence of coupling between the vinyl protons and the 1-fluorine atom. The resonance signal of the 1-proton of III is also split by about 5 cps. The C-1, C-2, and C-3 protons probably constitute an ABX system. With the added

(1) (a) Paper I of this series: L. L. Smith, T. J. Foell, and D. M. Teller, *J. Org. Chem.*, **30**, 3781 (1965). Leading references to other reported reactions between hydroxy steroids and 2-chloro-1,1,2-trifluoroethyldiethylamine are given therein. (b) To whom inquiries should be addressed at the Department of Biochemistry, University of Texas Medical Branch, Galveston, Texas 77550.

(2) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

(3) A. D. Cross, J. A. Edwards, J. C. Orr, B. Berköz, L. Cervantes, M. C. Calzada, and A. Bowers, *ibid.*, **6**, 162 (1963); (b) J. C. Orr, O. Halpern, P. G. Holton, F. Alvarez, I. Delfin, A. de la Roz, A. M. Ruiz, and A. Bowers, *ibid.*, **6**, 166 (1963); (c) J. A. Edwards, P. G. Holton, J. C. Orr, L. C. Ibañez, E. Necoechea, A. de la Roz, E. Segovia, R. Urquiza, and A. Bowers, *ibid.*, **6**, 174 (1963); (d) J. A. Edwards, M. C. Calzada, and A. Bowers, *ibid.*, **6**, 178 (1963); (e) M. E. Wolff, W. Ho, and R. Kwok, *ibid.*, **7**, 577 (1964).

(4) C. Djerassi, D. H. Williams, and B. Berköz, *J. Org. Chem.*, **27**, 2205 (1962).

(5) The C-19 proton signal is at higher field than is the C-18 proton signal in III or IIb. The assignment of the higher field signal in III to the C-19 protons cannot be reversed, for the signal is split 1.5 cps by the adjacent fluorine atom (in both deuteriochloroform, where some instability of spectra was noted, and carbon tetrachloride). A reversal of assignments in III would require not only long-distance coupling of the fluorine and C-18 protons through a minimum of eight bonds,[6] but also shielding effects of the fluorine on the C-18 protons (−0.02 ppm) and deshielding effects on the C-19 protons (+0.04 ppm) relative to the position of the angular methyl protons of 5α-androst-2-en-17β-ol acetate where both C-18 and C-19 protons resonate at the same frequency.[7] The high-field assignment of the C-19 methyl protons in IIb follows from the known shielding influence (−0.01 to −0.05 ppm,[8] −0.12 ppm[9]) of the 1α-hydroxyl group on the C-19 protons.

(6) Long-distance coupling between 10β-fluorine and C-18 protons (through seven bonds) has not been observed: see A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 3784 (1962).

(7) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *ibid.*, **85**, 1851 (1963).

(8) L. L. Smith, *Steroids*, **4**, 395 (1964).

(9) A. I. Cohen and S. Rock, *ibid.*, **3**, 243 (1964).

(10) (a) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736 (1962); (b) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A.D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

(11) The C-2 and C-3 vinyl protons of the 5α-Δ^2-derivatives IIa and IIb do not appear to couple significantly with one another or with adjacent protons. The olefinic proton signals of IIb appear as two sharp singlets at 5.79 and 5.85 ppm whereas those of IIa appear as a broad singlet at 5.86 ppm. Additional examples of Δ^2-vinyl proton spectra have been published.[12] The Δ^2-vinyl protons are thus readily distinguished from the vinyl protons of 5α-Δ^1-androstenes, which show the general pattern; I, 7.10 (doublet, J = 10 cps), 5.82 ppm (doublet, J = 10 cps); 5α-androst-1-ene-3,17-dione, 7.21 (doublet, J = 10 cps), 5.93 ppm (doublet, J = 10 cps); 17β-acetoxy-5α-estr-1-en-3-one, 7.10 (doublet, J = 11 cps), 5.98 ppm (quartet, J = 2 and 11 cps); and IV, 6.08 (doublet, J = 10 cps), 5.60 ppm (quartet, J = 4 and 10 cps).

(12) (a) P. D. Klimstra and R. E. Counsell, *J. Med. Chem.*, **8**, 48 (1965); (b) K. D. Michael and G. A. Selter, *J. Org. Chem.*, **30**, 2549 (1965); (c) J. Fishman and M. Torigoe, *Steroids*, **5**, 599 (1965); (d) R. F. R. Church, A. S. Kende, and M. J. Weiss, *J. Am. Chem. Soc.*, **87**, 2665 (1965); (e) S. M. Kupchan, R. W. Doskotch, P. Bollinger, A. T. McPhail, G. A. Sim, and J. A. Saenz Renauld, *ibid.*, **87**, 5805 (1965); (f) D. Lavie, E. Glotter, and Y. Shvo, *J. Chem. Soc.*, 7517 (1965).

complication of coupling with fluorine, no further analysis of the spectrum was attempted. Accordingly, we are unable to assign, at this time, a configuration to the 1-fluoro substituent in III.[13]

The secondary product IV from the fluorination reaction contained no fluorine, and elemental analysis and spectra suggested a 3-hydroxy-Δ^1 structure. Chromic acid oxidation of IV gave the Δ^1-3-ketone I. Since IV differs in physical properties from the known 17β-acetoxy-5α-androst-1-en-3β-ol,[2,14] the 3α-epimeric structure is assigned. Olefinic proton spectra already mentioned[11] and the triplet signal at 4.08 ppm (J = 4 cps) of the C-3 proton support in detail the 3α-hydroxy-Δ^1 structure of IV.[15]

In bioassay by a modified Hershberger, *et al.*, procedure,[17] the fluoro olefin III exhibited approximately 2% of the androgenic and 18% of the anabolic activity of testosterone propionate. This separation of activities for III compares favorably with data published for the nonfluorinated analog 5α-androst-2-en-17β-ol,[2] and thus constitutes further support of the concepts of A-ring sp^2 hybridization necessary for high anabolic activity.

Experimental Section[18]

5α-Androst-2-ene-1α,17β-diol (IIa).—A solution of 29 g of 17β-acetoxy-5α-androst-1-en-3-one (I) in 500 ml of methanol was cooled to 15–18° and stirred while 108 ml of 4 *N* NaOH solution and 108 ml of 30% H_2O_2 were added dropwise over 30 min. The mixture was stirred for 10 min, 100 ml of water was added, the mixture was filtered, and the product was washed successively with water and methanol and dried. The 1α,2α-epoxide (11.5 g) was dissolved in 240 ml of 2-propanol, and 60 ml of hydrazine hydrate and 3 ml of acetic acid were added. The solution was heated on a steam bath for 30 min, then held at room temperature for 1 hr. Ice and water were added, and the product was extracted with ethyl acetate. Evaporation of the extract gave an oil which was chromatographed on 450 g of alumina (activity III). Elution with benzene–$CHCl_3$ (1:1) gave 3.64 g of IIb, mp 155–155.5° after recrystallization from methanol–hexane (lit.[4] mp 158–160°); δ = 0.70 (C-19 protons), 0.77 (C-18 protons), 2.02 (17β-acetoxyl protons), 3.70 (broad, half-width 7 cps, 1β-proton), 4.59 (triplet, J = 8 cps, 17α-proton), 5.79 (C-2 vinyl proton), 5.87 ppm (C-3 vinyl proton). Continued elution of the column with the same solvent pair gave 656 mg of the 1α,17β-diol, which was recrystallized from acetone–hexane, yielding 514 mg of IIa: mp 143–144°; $[\alpha]D$ +143°; λ_{max}^{KBr} 3.03 μ etc.; δ = 0.74 (C-18 and C-19 protons), 3.4–3.8 (multiplets, 1β- and 17α-protons), 5.85 ppm (broad, 2H, C-2 and C-3 vinyl protons).

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.71; H, 10.55.

1ξ-Fluoro-5α-androst-2-en-17β-ol 17β-Acetate (III).—A solution of 3.6 g of IIb in 30 ml of CH_2Cl_2 under nitrogen was treated with 3 ml of 2-chloro-1,1,2-trifluoroethyldiethylamine. The solution was stirred at room temperature for 30 min, at which time no starting material was detected on thin layer chromatograms. Solid $NaHCO_3$ was added, the mixture was washed with water until neutral, and the CH_2Cl_2 was evaporated under vacuum. The residue was crystallized from methanol, yielding 1.9 g of product, mp 150–156°. Recrystallization from methanol gave 1.46 g of pure III: mp 156–159°; $[\alpha]D$ +102°; λ_{max}^{KBr} 5.76 8.08 μ, etc.; δ = 0.73 (doublet, J = 1.5 cps, C-19 protons), 0.80 (C-18 protons), 2.03 (17β-acetoxyl protons), 4.50 (doublet of doublets, $J_{1,2}$ = 5 cps, J_{HF} = 50 cps, 1-proton), 4.60 (triplet, J = 7 cps, 17α-proton), 5.85 (doublet, J = 5 cps, C-2 vinyl proton), 5.90 ppm (C-3 vinyl proton); in carbon tetrachloride, δ = 0.72 (doublet, J = 1.5 cps, C-19 protons), 0.78 (C-18 protons), 2.00 (17β-acetoxyl protons), 4.50 (doublet of doublets, $J_{1,2}$ = 5 cps, J_{HF} = 50 cps, 1-proton), 4.65 (triplet, J = 8 cps, 17α-proton), 5.94 ppm (broad, 2 H, C-2 and C-3 vinyl protons).

Anal. Calcd for $C_{21}H_{31}FO_2$: C, 75.41; H, 9.34; F, 5.68. Found: C, 75.64; H, 9.63; F, 5.72.

17β-Acetoxy-5α-androst-1-en-3α-ol (IV).—Repetition of the fluorination reaction with 1.12 g of IIb in 40 ml of CH_2Cl_2 and 2.8 ml of 2-chloro-1,1,2-trifluoroethyldiethylamine gave a crude crystalline product, 801 mg, which consisted mainly of the desired product, III, together with some IV. Chromatography of the material on 130 g of silica gel and successive elution with hexane, hexane–ethyl acetate, and pure ethyl acetate failed to give any III, but the nonfluorinated polar component IV, 241 mg, was eluted by ethyl acetate. Recrystallization from ethyl acetate gave 190 mg of IV:[20] mp 187–190°; $[\alpha]D$ −64.9°; λ_{max}^{KBr} 2.94, 5.85, 7.87, 8.02 μ, etc.; δ = 0.80 (C-18 and C-19 protons), 2.03 (17β-acetoxyl protons), 4.08 (triplet, J = 4 cps, 3β-proton), 4.60 (triplet, J = 8 cps, 17α-proton), 5.60 (quartet, $J_{2,3}$ = 4 cps, $J_{1,2}$ = 10 cps, C-2 vinyl proton), 6.08 ppm (doublet, J = 10 cps, C-1 vinyl proton).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.58; H, 9.54.

17β-Acetoxy-5α-androst-1-en-3-one (I).—A solution of 50 mg of IV in 4 ml of acetone was oxidized with the Jones reagent (chromium trioxide) in the usual manner yielding 22.5 mg of crude I, mp 106–109°. Recrystallization from hexane gave pure I, mp 125–127°, $\lambda_{max}^{95\%EtOH}$ 230–232 mμ (ϵ 10,200), identical by infrared spectra and chromatographic behavior with an authentic sample.

(13) By assuming that no changes in conformation are involved in the Δ^2-steroids IIb and III, and by disregarding the 50-cps coupling between the 1-proton and the 1-fluoro group, then the doublet pattern of the 1-proton in III may be taken as an indication of a different configuration of the 1-proton from that in IIb. Thus a 1α-proton is suggested for III with a 1β-fluorine atom. This *cis* configuration between the 1-fluorine atom and the C-19 methyl group could account for the 1.5-cps splitting of the C-19 proton signal in III. The generalizations of Cross and Landis[6] leave open the question of coupling between 1α- and 1β-fluorine atoms and the C-19 protons. The 5α- and 9α-fluorine substituents do not split C-19 proton signals, but 12α- and 17α-fluorines do split C-18 proton signals.[6]

(14) R. E. Counsell, P. D. Klimstra, and F. B. Colton, *J. Org. Chem.*, **27**, 248 (1962). The specific rotation of the Syntex sample (−43.5°)[2] appears to be in error at least in sign and does not agree with Counsell, *et al.* (rotation +33.4°), or with a calculated $[\alpha]D$ value based on rotation data of other 3β-alcohols.

(15) The C-3 proton is coupled by 4 cps to the adjacent C-2 vinyl proton (whose signal also shows a 4-cps coupling together with a 10-cps coupling with the C-1 vinyl proton) and to the axial C-4 proton. The chemical shift of the C-3 proton is within the range recognized for saturated A-ring, axial 3α-alcohols in the 5α series (3.85–4.14 ppm *vs.* 3.08–3.70 ppm for epimeric equatorial 3β-alcohols[8]), and from this position and from the coupling pattern is equatorial. Thus, the 3α-hydroxyl group is axial. In contrast, other A-ring, epimeric, unsaturated 3-alcohols have C-3 proton spectra: a Δ^1-3α-alcohol at 4.03 ppm, a Δ^4-3β-alcohol at 4.20 ppm,[8] a $\Delta^{5(10)}$-3α-alcohol at 3.77 ppm, and a $\Delta^{5(10)}$-3β-alcohol at 4.00 ppm.[16]

(16) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, **No. 23**, 1517 (1963).

(17) (a) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953); (b) R. A. Edgren, *Acta Endocrinol.*, **44**, *Suppl.* **87**, 1 (1963).

(18) All melting points were taken on a Kofler block under microscopic magnification. Optical rotations were obtained on 1% solutions in chloroform. All reactions and purifications were monitored by thin layer chromatography using silica gel–rice starch chromatoplates[19] irrigated with hexane–ethyl acetate (4:1) and visualized with an acidified 10% alcoholic phosphomolybdic acid solution. Nmr spectra were obtained on 10% deuteriochloroform solutions using a Varian Associates Model A-60 spectrometer. Chemical shifts (δ) were measured downfield from an internal reference of tetramethylsilane.

(19) L. L. Smith and T. Foell, *J. Chromatog.*, **9**, 339 (1962).

(20) The 3α-alcohol IV is mentioned without physical constants: A. H. Cross and A. Bowers, U. S. Patent 3,127,429 (March 31, 1964).

Derivatives of 1- and 2-Tetralones

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The preparation of intermediates related to 1- and 2-tetralones for use in the total synthesis of steroids is well documented.[1] Our interest in these intermediates

(1) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 181–538.