Steroids. CCLXXXIV.[1] Reactions of 19-Hydroxy-Δ^5-3-acetoxy Steroids with Diethyl(2-chloro-1,1,2-trifluoroethyl)amine

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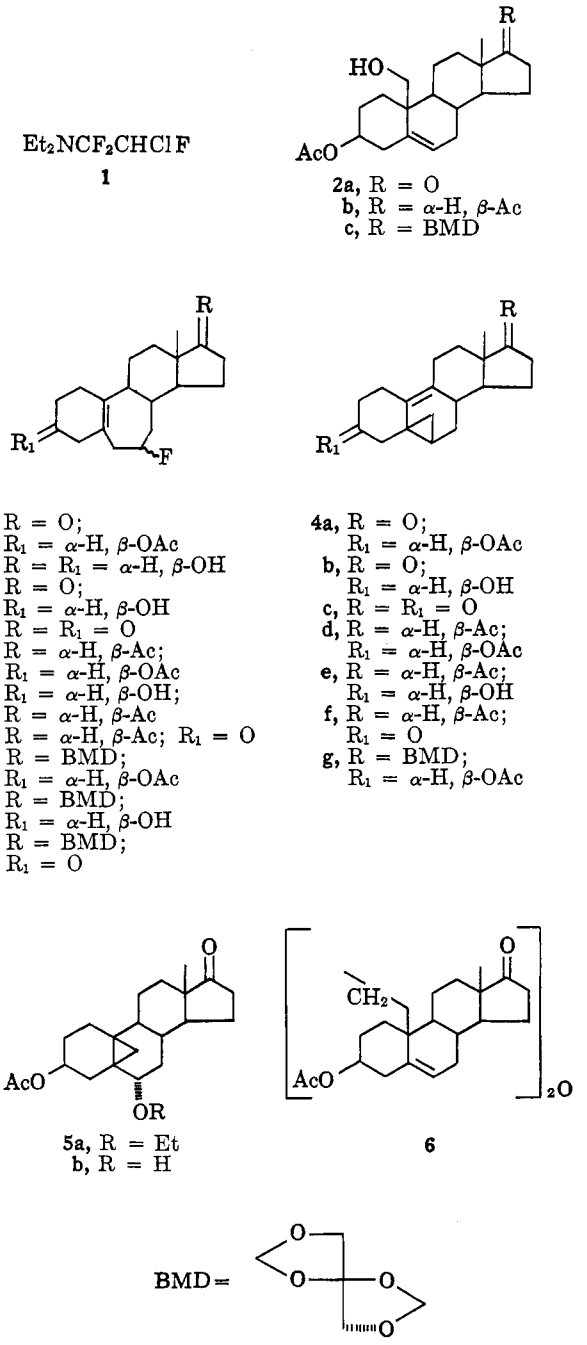
Reaction of the β,γ-unsaturated neopentyl alcohol system in 19-hydroxy-Δ^5-3-acetoxy steroids with diethyl(2-chloro-1,1,2-trifluoroethyl)amine affords predominantly B-homo-7ξ-fluoro-$\Delta^{5(10)}$, 5β,6β-methylene-$\Delta^{1(10)}$, and 5β,6β-methylene-Δ^9 derivatives. By appropriate choice of solvent, reaction temperature, and method of isolation, either the B-homo-7ξ-fluoro or the pentacyclic derivatives can be obtained in high yields. The B-homo-7ξ-fluoro-$\Delta^{5(10)}$ derivatives are readily converted to the corresponding Δ^4-3-ketones.

In an extension of our studies on the reaction of steroidal alcohols with diethyl(2-chloro-1,1,2-trifluoroethyl)amine (**1**)[2] we recently reported the reaction of this fluoramine with 19-hydroxyandrost-4-ene-3,17-dione leading to 10β-fluoro-5,10-seco-5β,19-cycloandrost-4-ene-3,17-dione and 5β,19-cycloandrost-1-ene-3,17-dione.[3] We describe now the reaction of the fluorinating reagent **1** with androstane, pregnane, and corticoid derivatives containing the related β,γ-unsaturated neopentyl alcohol system (**2**, Chart I). As previously noted,[2,4] the reaction of steroidal alcohols with the reagent **1** is both temperature and solvent dependent. In addition, the procedure of reaction work-up was also found to affect profoundly the product composition.

When 3β,19-dihydroxyandrost-5-en-17-one 3-acetate (**2a**)[5] was allowed to react with the fluoramine **1** in methylene chloride at 0° for 17 or 42 hr., and solvent was removed by distillation at steam-bath temperature, four products could be isolated by careful chromatography on Florisil. These were 3β-acetoxy-7ξ-fluoro-B-homo-estr-5(10)-en-17-one (**3a**, 31%), 3β-acetoxy-5β,6β-methylene-estr-9-en-17-one (**4a**, 5%),[6] the known 3β-acetoxy-6α-ethoxy-5β,19-cycloandrostan-17-one (**5a**, 11%),[7] and the bis steroidal ether **6** (32.4%). The structures of the products followed from a consideration of elemental composition, n.m.r., and other spectral analyses. Our colleagues have described the evidence leading to structures **3a** and **4a**.[6]

Alkaline hydrolysis of **4a** afforded the keto alcohol **4b** which was oxidized in acetone with 8 *N* chromic acid[8] to the corresponding dione **4c**. In the n.m.r. spectrum this dione showed no distinct high-field cyclopropyl proton resonance in contrast to the spectrum of the precursor **4a**. This is attributed to long-range deshielding by the carbonyl at C-3.

CHART I



Reduction of the keto ester **3a** with lithium aluminum hydride proceeded, with retention of fluorine, to give the diol **3b**, while hydrolysis of this keto ester led

(1) Steroids. CCLXXXIII: R. Ginsig and A. D. Cross, *J. Am. Chem. Soc.*, **87**, 4629 (1965).

(2) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962); *J. Org. Chem.*, **29**, 2187 (1964).

(3) L. H. Knox, E. Velarde, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 2533 (1963).

(4) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

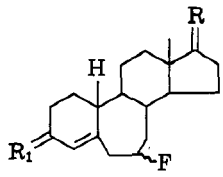
(5) O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 116 (1963).

(6) Compounds **3a** and **4a** were also obtained independently by Dr. J. A. Edwards and his collaborators, working in these laboratories, from treatment of 6α-hydroxy-5β,19-cycloandrostanes (**5b**) with hydrofluoric and other mineral acids; see H. Carpio, A. Cruz, M. G. Teran, and J. A. Edwards, *J. Org. Chem.*, in press.

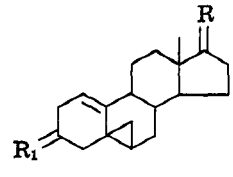
(7) O. Halpern, P. Crabbé, A. D. Cross, I. Delfín, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964). Compound **5** was formed through the inadvertent presence of ethanol in one reaction only.

(8) K. Bowden, J. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

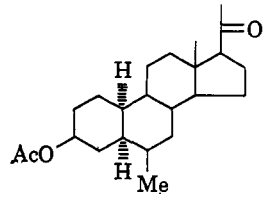
CHART II



7a, R = R$_1$ = O
b, R = α-H, β-OH; R$_1$ = H, OH
c, R = α-H, β-OH; R$_1$ = O
d, R = α-H, β-$O_2C \cdot C_2H_5$; R$_1$ = O
e, R = α-H, β-Ac; R$_1$ = O
f, R = BMD; R$_1$ = O
g, R = =O, ···OH; R$_1$ = O



8a, R = α-H, β-Ac; R$_1$ = α-H, β-OAc
b, R = α-H, β-Ac; R$_1$ = α-H, β-OH
c, R = α-H, β-Ac; R$_1$ = O
d, R = BMD; R$_1$ = α-H, β-OAc



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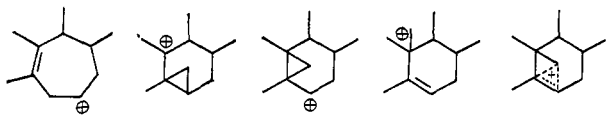
to the keto alcohol **3c**. Oxidation of the latter afforded the corresponding dione **3d** which, without purification, was isomerized under aqueous oxalic acid catalysis to furnish the conjugated enone **7a** (see Chart II). Lithium aluminum hydride reduction of this dione **7a** gave an oily mixture of diols **7b** from which 7ξ-fluoro-17β-hydroxy-B-homoestr-4-en-3-one (**7c**) was gained by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[9] The propionate ester **7d** was also prepared.

Mechanistically, the reaction of the fluoramine **1** with alcohols leads to development of positive charge at the carbon bearing hydroxyl.[2-4] Stabilization of a developing carbonium ion at C-19 through participation of the Δ^5 double bond electrons has been previously discussed.[7,10,11] Formally, the observed reaction products, **3a**, **4a**, and **5a**, may be envisaged as being derived by collapse of carbonium ion species A–C through fluoride ion intervention, proton loss, and solvent participation, respectively.



A B C D E

In the absence of further studies, the nature of and extent to which classical and nonclassical ions are involved cannot be determined.

(9) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, 14 (1960).
(10) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962).
(11) J. Tadanier and W. Cole, *Tetrahedron Letters*, 1345 (1964).

The fourth reaction product, obtained in 32.4% yield, showed resonance at 55 (18-H), 122.5 (3β-OAc), 270–302 (3α-H), and 338 (6-H, multiplet) c.p.s. and an ill-resolved pair of doublets (AB system) in the region 200–220 c.p.s. typical of the C-19 methylene protons of 19-substituted steroids. Comparison with the known 19-alcohol and 19-chloro derivatives established nonidentity with these substances. Product formation through formal collapse of carbonium ion D by interaction with a second molecule of the 19-alcohol **2a** was therefore considered, leading to the bis steroidal ether **6**.[12] This possibility found full support in the above n.m.r. data, and from elemental analysis and mass spectrometry. Although no peak was detected corresponding to the molecular ion (*m/e* 674), weak signals were recorded for *m/e* 614 and 554 ratios, the molecular ion minus one and two molecules of acetic acid, respectively. Intense *m/e* peaks were observed only for ratios below 272.

Product dependence upon reaction temperature was dramatically illustrated in two further experiments. When the alcohol **2a** and an excess of the reagent **1** in methylene chloride solution were allowed to react at $-20°$ for 48 hr. and the reaction solution was passed directly through a column of alumina before evaporation, then the 7ξ-fluoro-B-homo derivative **3a** was obtained in 63% yield, with none of the cyclopropane products **4a**.[13] Repetition of the reaction, but using acetonitrile solvent under reflux (1 hr.), led instead to the cyclopropane product **4a** in 63.5% yield.[15] Employing selective reaction conditions, 3β,19-dihydroxypregn-5-en-20-one 3-acetate[5] (**2b**) was transformed (CH_2Cl_2, $-20°$, 82% yield) into 7ξ-fluoro-3β-hydroxy-B-homo-19-norpregn-5(10)-en-20-one acetate (**3e**), alkaline hydrolysis of which furnished the free alcohol **3f**. Oxidation then gave the unconjugated 3-ketone **3g**, which was isolated and then isomerized by acid catalysis to 7ξ-fluoro-B-homo-19-norprogesterone **7e**. N.m.r. data were in agreement with the assigned structures.

The configuration of fluorine was considered in conjunction with the n.m.r. data. For the conjugated ketone **7e** the 7-proton resonates as a pair of multiplets, J_{HF} *ca.* 50 c.p.s., each multiplet being equivalent to one-half of a proton by area measurement, and having half-band width *ca.* 23 c.p.s. The last value suggests that the 7-proton maintains an axial orientation and is flanked by axially oriented protons at C-6 and C-8.[16] An unresolved resonance signal at 358 c.p.s. for the 4-proton in **7e** has half-band width *ca.* 5.5 c.p.s. which

(12) A preferred mechanism is attack of the alcohol **2a** upon the nonclassical ion E since the primary carbonium ion D is likely to be very short lived and the incoming alcohol is very bulky.
(13) It was reasoned that, since hydrogen fluoride is a probable reaction product (fluoride ion is released by the reagent), then concentration of the crude reaction solution without removal of HF would regenerate the carbonium ion A and the stable HF_2^- ion from the 7β-fluoro-B-homo product **3a**. A lower yield of the latter would therefore be expected in the absence of preventive measures.[14]
(14) In separate experiments Mr. H. Carpio (unpublished results) achieved a high yield of the fluorinated product **3a** by washing the methylene chloride reaction solution with aqueous sodium carbonate prior to evaporation.
(15) Examination of the mother liquors by n.m.r. spectroscopy disclosed the presence of some of the $\Delta^{1(10)}$ isomeric product.
(16) *Cf.* M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963). For applications of Karplus' theoretical predictions to steroid functional group configuration, see N. S. Bhacca and D. H. Willimas, "Applications of NMR Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 6.

indicates probable allylic coupling with *two* axial or near-axially oriented protons at C-6 and C-10.[17,18] Construction of models[19] leads to the conclusion that for axial protons at C-6, C-7, C-8, and C-10 ring B can maintain two conformations in which the 7-fluorine is equatorial, either α or β, and serious nonbonded interactions are minimized. However, although the 7β configuration is slightly favored, the evidence can in no way be regarded as conclusive, and the stereochemistry at C-7 requires further investigation.[20]

Reaction of the 19-hydroxypregnene derivative **2b** with the fluoramine **1** in refluxing acetonitrile gave 3β-acetoxy-5β,6β-methylene-19-norpregn-1(10)-en-20-one (**8a**, 57%, no strong ultraviolet maximum) and the isomeric norcarene analog **4d** (20%, λ_{max} 217 mμ). Alkaline hydrolysis yielded the corresponding 3β alcohols **8b** and **4e**, respectively, which were oxidized[21] to the diketones, **8c** and **4f**. In the n.m.r. spectra, dione **4f**, the ketols **4e** and **8c**, and the acetate ester **4d** all showed the expected resonances (see Experimental Section). Cyclopropyl resonance was usually partly obscured by other signals. One feature of note was the large coupling constant for the geminal protons of C-4 methylene (AB pattern at *ca.* 130 and 147, 163 and 180 c.p.s., J = 17 c.p.s.).[22] Hydrogenation of the product **8a** over 5% palladium on charcoal led to a tetrahydro derivative which showed a proton resonance doublet at 61 c.p.s., J = 7 c.p.s., for a new secondary methyl substituent. The half-band width, 12.5 c.p.s., of the resonance multiplet for the 3α-proton at 299 c.p.s. indicated an equatorial configuration[16] for this hydrogen, and the most satisfactory structure for this product is 3β-acetoxy-6β-methyl-5α,10α,19-norpregnan-20-one (**9**).

17α,20:20,21-Bismethylenedioxypregn-5-ene-3β,19-diol 3β-acetate (**2c**)[23] was treated with the fluoramine **1** (CH_2Cl_2, 0°) to furnish the 7ξ-fluoro-B-homo-19-norcorticoid precursor **3h** (76.5%). The acetate **3h** was converted, as outlined above, *via* the alcohol **3j** and the unconjugated ketone **3k** to the conjugated ketone **7f**. The bismethylenedioxy group in the latter ketone was removed by brief exposure to concentrated cold hydrochloric acid, thereby affording 17α,21-dihydroxy-7ξ-fluoro-B-homo-19-norpregn-4-ene-3,20-dione (**7g**). Preliminary attempts to introduce an 11β-hydroxyl into this "compound S" analog by means of incubation with bovine adrenals were unsuccessful.

With the fluoramine **1** in refluxing acetonitrile the 19-hydroxy derivative **2c** was transformed into the two unsaturated cyclopropane structures, **4g** (70%) and **8d** (20%). The former showed the expected ultraviolet absorption maximum at 216–218 mμ. Other spectral features for the sundry bismethylenedioxy derivatives were in complete accord with the assigned structures (see Experimental Section). No attempt was made to remove the corticoid side chain protecting group from the cyclopropanes **4g** and **8d** since pronounced lability of the A/B-ring structure to the necessary acidic hydrolytic conditions was separately determined in the pregnan-20-one series when multiple product formation was observed.

Experimental Section[24]

Reaction of 3β,19-Dihydroxyandrost-5-en-17-one 3β-Acetate (2a) with Diethyl(2-chloro-1,1,2-trifluoroethyl)amine (1). A.—A mixture of the 19-hydroxy steroid **2a** (10.4 g., 32 mmoles), the fluoramine **1** (9.12 g., 48 mmoles), and dry methylene chloride (200 ml.) was set aside at 0° for 42 hr. Solvent was removed by distillation under reduced pressure on the steam bath and the oily product was chromatographed on Florisil (300 g.). Oily fractions eluted with hexane–ether (9:1) were combined (A, 3.0 g.) and rechromatographed as described below. The crystalline fractions eluted with hexane–ether (4:1 and 1:1) consisted of 3β-acetoxy-7ξ-fluoro-B-homoestr-5(10)-en-17-one (**3a**, 3.12 g., 31.0%): m.p. 109–110° after recrystallization from methanol; $[\alpha]_D$ +54°; no strong absorption in the ultraviolet region 210–250 mμ; infrared and n.m.r. spectra as given in preceding paper.[6]

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.38; F, 5.45. Found: C, 72.37; H, 8.55; F, 5.47.

Further elution with ether yielded the bis steroidal ether **6** (3.5 g., 32.4%): m.p. 184–185°; $[\alpha]_D$ −4°; ν_{max} 1735, 1250, 1078, and 1033 cm.$^{-1}$; n.m.r. 55 (18-H, s), 122.5 (OAc, s), 200–220 (ill-resolved AB pattern for 19-protons), 270–302 (3α-H, m), and 339 c.p.s. (6-H, m); mass spectrum *m/e* peaks (among others) at 614, 554, 523, 478, 329, 271, 270, 269 (strongest of spectrum), and 268.

Anal. Calcd. for $C_{42}H_{58}O_7$: C, 74.74; H, 8.66. Found: C, 74.48; H, 8.59.

The oily fractions (A) were rechromatographed on Florisil (200 g.). The crystalline fractions eluted with hexane–ether (4:1) consisted of 3β-acetoxy-5β,6β-methyleneestr-9-en-17-one (**4a**, 0.48 g., 4.6%): m.p. 121.4–122.4° after recrystallization from methanol; $[\alpha]_D$ +69°; λ_{max} 216–218 mμ (log ϵ 3.93); infrared and n.m.r. spectra as previously described.[6]

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.91; H, 8.85.

In another experiment carried out exactly as described above, shortening the reaction time to 17 hr., there was also isolated by chromatography on Florisil the 6α-ethoxy-5β,19-cycloandrostane derivative **5a** (0.89 g., 10.9%): m.p. 150–150.5° after recrystallization from methanol, $[\alpha]_D$ +103°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.62; H, 9.07.

This product was identical in every respect with a sample prepared by an independent synthesis.[7]

B.—A solution of the 19-hydroxy steroid **2a** (4.0 g., 11 mmoles) and the fluoramine reagent **1** (3.41 g., 16.5 mmoles) in dry methylene chloride (75 ml.) was kept at −20° for 48 hr. The gross reaction mixture (without concentration) was passed through a column of alumina (200 g.) and eluted with hexane (1.2 l.) followed by methylene chloride (3.0 l.). The oils obtained were combined (6.0 g.) and chromatographed on Florisil (300 g.). The crystalline fractions eluted with hexane–ether (1:1) consisted of the 7ξ-fluoro derivative **3a** (2.53 g., 63%). A sample recrystallized from methanol had m.p. 109–110°,

(17) T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold [*J. Am. Chem. Soc.*, **85**, 1699 (1963)] and D. J. Collins, J. J. Hobbs, and S. Sternhell [*Tetrahedron Letters*, 197 (1963)] have defined the stereochemical requirements for allylic proton–proton spin–spin coupling.

(18) The element of doubt in this argument concerns the lesser possibility of a small homoallylic 4-H, 7-F coupling which would also have the effect of broadening the 4-H resonance signal.

(19) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(20) Other workers[11] suggested a 7β orientation of incoming nucleophile in the related 7-hydroxy-B-homo steroids but mainly from mechanism considerations.

(21) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(22) See Y. T. Takahashi, *Tetrahedron Letters*, 565 (1964), footnote 3.

(23) A. Bowers and J. A. Edwards, manuscript in preparation.

(24) Melting points were determined on a Mel-Temp apparatus and are corrected. Optical rotations were determined in chloroform solutions and ultraviolet absorption spectra were measured in 95% ethanol. Infrared spectra, determined in potassium bromide disks on a Perkin-Elmer Model 21 spectrometer equipped with sodium chloride optics, were recorded by Mr. Avila and his staff. N.m.r. spectra were recorded for 5–10% solutions in deuteriochloroform containing a little tetramethylsilane as an internal reference. Chemical shifts are quoted as cycles per second downfield from the reference signal (0.0 c.p.s.) for operation at 60 Mc.p.s., and are accurate to ±1 c.p.s. Coupling constants, also quoted in cycles per second, are accurate to ±0.5 c.p.s. Spectra were recorded on Varian A-60 spectrometers through the kind cooperation of Mr. E. Diaz and the Universidad Nacional Autónoma de México, and by Mr. J. Murphy (Syntex Research, Palo Alto, Calif.). In the presentation of data, s = singlet, d = doublet, and m = multiplet.

and was identical in every respect with **3a** obtained as described in part A.

C.—A mixture of **2a** (5.54 g., 16 mmoles), the reagent **1** (4.56 g., 24 mmoles), and dry acetonitrile (100 ml.) was heated under reflux for 1 hr. The mixture was cooled to room temperature and passed through a column of washed alumina (300 g.). The crystalline fractions eluted with hexane (1.2 l.) amounted to 5.27 g. Recrystallization from methanol afforded the 5β,6β-methylene-Δ^9 derivative **4a** (2.92 g.), m.p. 120–122°. The mother liquors were chromatographed on washed alumina (100 g.). The crystalline fractions eluted with hexane–ether (9:1) consisted of additional **4a** (460 mg.), m.p. 117–118°. The yield of **4a** thus amounted to 3.38 g. (63.5%). This material was identical in all respects with **4a** obtained as described above.

3β-Hydroxy-5β,6β-methyleneestr-9-en-17-one (4b).—A mixture of the keto ester **4a** (1.05 g.) in 2% methanolic potassium hydroxide (20 ml.) was warmed briefly on the steam bath to effect solution and kept overnight at room temperature. The product was isolated by dilution with cold water and filtration. Recrystallization from acetone afforded the ketol **4b** (0.85 g.): m.p. 158–160°; $[\alpha]_D$ +119°; λ_{max} 218 mμ (log ϵ 3.95); ν_{max} 3440, 1740, 1655, 1067, 1031, 1005, 918, and 820 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.96; H, 9.41.

5β,6β-Methyleneestr-9-ene-3,17-dione (4c).—A solution of the ketol **4b** (0.55 g.) in purified acetone (25 ml.) was treated with 8 *N* chromic acid[8] (0.7 ml.), and the product was isolated by dilution with water and extraction with ether. Recrystallization of the crude product from methanol gave the diketone **4c**: m.p. 149–150°; $[\alpha]_D$ −115°; λ_{max} 216–218 mμ (log ϵ 3.86); ν_{max} 1740 (shoulder), 1715, 1067, 1045, 1008, and 979 cm.$^{-1}$; n.m.r. 53 c.p.s. (18-H, s).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.43; H, 8.61.

A similar oxidation of crude ketol **4b** prepared by hydrolysis of keto acetate **4a** mother liquors afforded a sample of crude dione **4c** which showed a resonance multiplet at 334 c.p.s. in the n.m.r. spectrum due to $\Delta^{1(10)}$ isomer as impurity.

3β-Hydroxy-7ξ-fluoro-B-homoestr-5(10)-en-17-one (3c).—A solution of the keto ester **3a** (1.5 g.) in 5% methanolic potassium hydroxide (100 ml.) was set aside overnight at room temperature. The product was isolated by dilution with water and filtration. Recrystallization from aqueous methanol afforded the ketol **3c**: m.p. 72–74°; $[\alpha]_D$ +69°; ν_{max} 3460, 3300, 1738, 1082, 1058, 1040, and 903 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}FO_2 \cdot 0.5H_2O$: C, 72.36; H, 8.93; F, 6.02. Found: C, 72.53; H, 8.87; F, 6.05.

7ξ-Fluoro-B-homoestr-5(10)-ene-3β,17β-diol (3b).—A solution of the keto ester **3a** (480 mg.) in dry ether (20 ml.) was added dropwise with stirring to a suspension of lithium aluminum hydride (480 mg.) in dry ether (100 ml.). After stirring at room temperature for 30 min., the product was isolated in the normal manner and recrystallized from acetone affording pure diol **3b**: m.p. 127–128°; $[\alpha]_D$ −20°; ν_{max} 3350, 1070, 1052, 1012, 970, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}FO_2$: C, 73.98; H, 9.47; F, 6.16. Found: C, 73.90; H, 9.76; F, 5.53.

7ξ-Fluoro-B-homoestr-4-ene-3,17-dione (7a).—A solution of the ketol **3c** (4.0 g.) in purified acetone (100 ml.) was treated dropwise with stirring at 0–5° with 8 *N* chromic acid[8] (5 ml.). After 5 min. the mixture was diluted with water and extracted with ether. The organic extract was washed successively with aqueous sodium bicarbonate and water and dried over sodium sulfate. Evaporation of solvent afforded 7ξ-fluoro-B-homoestr-5(10)-ene-3,17-dione **3d** as an oil (3.45 g.). This was refluxed in ethanol solution (100 ml.) containing oxalic acid (3.5 g.) for 16 hr., and the product was isolated by dilution with water and extraction with ethyl acetate. The extract was washed with aqueous sodium bicarbonate followed by water to neutrality, dried over sodium sulfate, and evaporated to an oil (3.28 g.). Chromatography of the latter on washed alumina (200 g.) yielded crystalline fractions in the hexane–ether (1:1) eluate. Recrystallization of the combined fractions (1.82 g.) from acetone–hexane afforded pure dione **7a**: m.p. 139–140°; $[\alpha]_D$ +23°; λ_{max} 238 mμ (log ϵ 4.19); ν_{max} 1740, 1675, 1615, 1255, 1200, 1050, 1000, 883, 825, and 760 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{25}FO_2$: C, 74.97; H, 8.28; F, 6.24. Found: C, 75.35; H, 8.16; F, 6.33.

7ξ-Fluoro-17β-hydroxy-B-homoestr-4-en-3-one (7c).—To a suspension of lithium aluminum hydride (1.8 g.) in dry ether (200 ml.) there was added dropwise with stirring a solution of the dione **7a** (1.8 g.) in a mixture of tetrahydrofuran (75 ml.) and ether (10 ml.). Stirring was continued for 30 min. after addition was completed. The product diols **7b** were isolated as an oil (2.2 g.) in the usual manner and then taken up in dioxane (10 ml.), a solution of dichlorodicyanobenzoquinone (2.2 g.) in dioxane (13 ml.) was added, and the mixture was set aside at room temperature overnight. The gross reaction mixture was passed through a column of washed alumina (100 g.) eluting with methylene chloride. The oily product (1.35 g.) was then chromatographed on washed alumina (40.0 g.). The crystalline fractions eluted with hexane–ether (3:1) consisted of the B-homo-19-nortestosterone analog **7c** (1.08 g.): m.p. 134–135° after recrystallization from acetone–hexane; $[\alpha]_D$ −38°; λ_{max} 240 mμ (log ϵ 4.18); ν_{max} 3470, 1670, 1620, 1255, 1060, 1035, 1010, 975, 893, and 857 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88; F, 6.20. Found: C, 74.66; H, 9.00; F, 6.48.

Acylation of the ketol **7c** (1.8 g.) in pyridine (1.5 ml.) with propionic anhydride (3 ml.) afforded the derived propionate **7d**. Recrystallization from hexane gave the analytical sample: m.p. 163.5–164.5°; $[\alpha]_D$ −59°; λ_{max} 238 mμ (log ϵ 4.20); ν_{max} 1740, 1675, 1620, 1200, 1085, 1030, 1005, 985, 890, and 800 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}FO_3$: C, 72.90; H, 8.62; F, 5.24. Found: C, 73.08; H, 8.39; F, 4.96.

Reaction of 3β,19-Dihydroxypregn-5-en-20-one 3-Acetate (2b) with the Fluoramine 1. A.—A solution of the 19-hydroxy steroid **2b** (22.4 g., 60 mmoles) and the fluoramine reagent **1** (17.0 g., 90 mmoles) in dry methylene chloride (200 ml.) was set aside at −20° for 48 hr. The gross product was passed through a column of washed alumina (1.2 kg.) eluting with hexane. Recrystallization of the partially crystalline first three fractions (32.0 g.) afforded the 7ξ-fluoro-B-homo-$\Delta^{5(10)}$ derivative **3e** (13.92 g.), m.p. 73–75°. The mother liquors, together with the later oily fractions eluted with hexane were combined and rechromatographed on washed alumina (1.0 kg.). Crystalline fractions eluted with hexane were combined (6.55 g.) and recrystallized from hexane to yield additional **3e** (4.37 g.), m.p. 79–81°, giving a total yield of 18.29 g. (82.0%). A sample recrystallized from acetone–hexane had m.p. 85–86°; $[\alpha]_D$ −46°; ν_{max} 1738, 1710, 1245, 1085, 1037, and 985 cm.$^{-1}$; n.m.r. 42 (18-H, s), 122.5 (3-OAc, s), 127.5 (21-H, s), 280–320 (3α-H and 7ξ-H, m) c.p.s.

Anal. Calcd. for $C_{23}H_{33}FO_3$: C, 73.37; H, 8.83; F, 5.05. Found: C, 73.74; H, 9.21; F, 4.72.

B.—A solution of the 19-hydroxypregnene **2b** (11.2 g.) and the fluoramine reagent **1** (8.5 g.) in dry acetonitrile (125 ml.) was heated under reflux 1 hr. The gross product was passed through a column of washed alumina (600 g.) and eluted with hexane (ten 250-ml. fractions) followed by methylene chloride. The first partially crystalline fractions eluted with hexane were combined (11.7 g.) and recrystallized from methanol to give 3β-acetoxy-5β,6β-methylene-19-norpregn-1(10)-en-20-one (**8a**, 5.69 g., 57.0%), m.p. 95–102°. Further recrystallization from methanol yielded the analytical sample: m.p. 104–105°; $[\alpha]_D$ +77°; no absorption in the ultraviolet (215–250 mμ); ν_{max} 1738, 1700, 1245, 1065, 1025, 990, 890, 852, and 780 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.49; H, 9.16.

The mother liquors and oily fractions further eluted with hexane and with methylene chloride were rechromatographed on washed alumina (300 g.). The crystalline fractions eluted with hexane–ether (4:1) consisted of the 5β,6β-methylene-Δ^9 isomer **4d** (2.01 g., 20.0%): m.p. 76–78° after recrystallization from methanol; $[\alpha]_D$ +72°; λ_{max} 217–218 mμ (log ϵ 3.89); ν_{max} 1740, 1712, 1243, 1060, 922, and 728 cm.$^{-1}$; n.m.r. 40 (18-H, s), 35–47 and obscured resonance (cyclopropyl H, m), 123 (OAc, s), 127 (21-H, s), and 305 (3α-H, m) c.p.s.

Anal. Found: C, 77.54; H, 9.33.

3β-Hydroxy-7ξ-fluoro-B-homo-19-norpregn-5(10)-en-20-one (3f).—A solution of the acetate **3e** (5.0 g.) in 5% methanolic potassium hydroxide was set aside overnight at room temperature. The product was isolated by dilution with water and filtration. Recrystallization from methanol afforded the ketol **3f** (4.1 g.): m.p. 71–73°; $[\alpha]_D$ +56°; ν_{max} 3400, 1700, 1080, 995, and 965 cm.$^{-1}$; n.m.r. 41 (18-H, s), 126 (21-H, s), 121 (OH, s), 234 (3α-H, m), 268, and 318 (7ξ-H, pair of m, J_{HF} = 50 c.p.s.) c.p.s.

Anal. Calcd. for $C_{21}H_{31}FO_2 \cdot 0.5H_2O$: C, 73.43; H, 9.39; F, 5.53. Found: C, 73.24; H, 9.55; F, 5.55.

7ξ-Fluoro-B-homo-19-norpregn-5(10)-ene-3,20-dione (3g).—A solution of the ketol **3f** (125 mg.) in purified acetone (10 ml.) was oxidized at 0–5° with an excess of 8 *N* chromic acid.[8] The product was isolated by dilution with water and ether extraction. Recrystallization from methanol afforded the unconjugated dione **3g** (105 mg.): m.p. 103–104°; $[\alpha]D$ +135°; no absorption in the ultraviolet (220–250 mμ); ν_{max} 1710, 1698, 1060, 960, and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}FO_2 \cdot 0.5H_2O$: C, 73.86; H, 8.86; F, 5.56. Found: C, 73.92; H, 8.52; F, 5.55.

7ξ-Fluoro-B-homo-19-norpregn-4-ene-3,20-dione (7e).—A mixture of the dione **3g** (520 mg.), oxalic acid (520 mg.), and 96% ethanol (25 ml.) was heated under reflux for 16 hr. The mixture was concentrated and the product was isolated by precipitation in water and extraction with ether. Evaporation of the dried (Na_2SO_4) ether extract and recrystallization of the crude product from methanol gave the conjugated dione **7e** (460 mg.): m.p. 157–158°; $[\alpha]D$ +20°; λ_{max} 238–240 mμ (log ε 4.19); ν_{max} 1705, 1680, 1625, 1005, and 885 cm.$^{-1}$; n.m.r. 39.5 (18-H, s), 128.5 (21-H, s), 358 (4-H, broad s), *ca.* 275 and 323 (7H, pair of m) c.p.s.

Anal. Calcd. for $C_{21}H_{29}FO_2$: C, 75.87; H, 8.79; F, 5.71. Found: C, 76.24; H, 8.81; F, 6.39.

3β-Hydroxy-5β,6β-methylene-19-norpregn-1(10)-en-20-one (8b).—A solution of the ester **8a** (1.0 g.) in 5% methanolic potassium hydroxide (25 ml.) was kept at room temperature overnight. The product was isolated by dilution with water and filtration. Recrystalization from methanol afforded the ketol **8b** (0.76 g.): m.p. 175–176°; $[\alpha]D$ +114°; no absorption in the ultraviolet (215–230 mμ); ν_{max} 3460, 3030, 1698, 1082, 990, 870, 785, and 765 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.45; H, 9.65.

5β,6β-Methylene-19-norpregn-1(10)-ene-3,20-dione (8c).—To a solution of sodium dichromate (9.0 g.) and sulfuric acid (6 ml.) in water (140 ml.) at 0–5°, there was added a solution of the ketol **8b** (2.0 g.) in ether (800 ml.). The mixture was vigorously stirred for 1.5 hr., the ether layer was then separated, and the aqueous phase was extracted with ether (two 25-ml. portions). The total organic solution was passed through a column of washed alumina (100 g.) and the eluate was evaporated to a crystalline residue. Recrystallization from acetone–hexane gave the dione **8c** (0.5 g.): m.p. 117–118°; $[\alpha]D$ −129°; no absorption in the ultraviolet (215–230 mμ); ν_{max} 1722, 1710, 1030, 978, and 897 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.94; H, 9.24.

3β-Hydroxy-5β,6β-methylene-19-norpregn-9-en-20-one (4e).—Saponification of the ester **4d** (1.0 g.) in 5% methanolic potassium hydroxide as described above and recrystallization of the crude product from methanol afforded the ketol **4e** (0.81 g.): m.p. 182–183°; $[\alpha]D$ +115°; λ_{max} 217–218 mμ (log ε 3.96); ν_{max} 3450, 1698, 1082, 965, 892, 833, and 765 cm.$^{-1}$; n.m.r. 38.5 (18-H), 117 (OH, s), 126.5 (21-H, s), and *ca.* 247 (3α-H, m) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.26; H, 9.54.

5β,6β-Methylene-19-norpregn-9-ene-3,20-dione (4f).—To a solution of sodium dichromate dihydrate (6.75 g.) in sulfuric acid (4.5 ml.) and water (105 ml.) at 0–5° there was added a solution of the above ketol **4e** (1.48 g.) in ether (2 l.), and the mixture was stirred at ice-bath temperature for 1.5 hr. The product was isolated as described above and crystallized twice from methanol to give the corresponding dione **4f** (0.39 g.): m.p. 142–144°; $[\alpha]D$ −124°; λ_{max} 214–215 mμ (log ε 3.82); ν_{max} 1725, 1700, 1015, 970, 900, and 772 cm.$^{-1}$; n.m.r. 40.5 (18-H, s), 128.5 (21-H, s), *ca.* 130, *ca.* 147, 163, and 180 (C-4 methylene, AB pattern) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.78; H, 9.10.

3β-Acetoxy-6β-methyl-5α,10α,19-norpregnan-20-one (9).—A solution of the cyclopropane **8a** (250 mg.) in 95% ethanol (50 ml.) was shaken with hydrogen over 5% palladium on charcoal (250 mg.) at room temperature and 3 atm. After 6 hr. the product was isolated and chromatographed on Florisil (7.5 g.). Eluting with hexane afforded an oil (40 mg.). Further elution with chloroform yielded the title compound **9** (170 mg.): m.p. 125–126° after recrystallization from methanol; $[\alpha]D$ +116°; ν_{max} 1730, 1700, 1250, and 1043 cm.$^{-1}$; n.m.r. 40 (18-H, s), 57.5, 64.5 (6β-Me, d), 122 (3β-OAc, s), 127 (21-H, s), and 299 (3α-H, m) c.p.s.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.79; H, 9.64.

Reaction of 17α,20:20,21-Bismethylenedioxypregn-5-ene-3β,-19-diol 3β-Acetate (2c) with the Fluoramine 1. A.—A solution of the 19-hydroxy steroid **2c** (20.0 g.) and the reagent **1** (14.3 g., 1.5 mole equiv.) in dry methylene chloride (250 ml.) was kept at −20° for 48 hr. The gross reaction mixture was passed through a column of washed alumina (800 g.) and eluted first with hexane (fractions 1–6) followed by methylene chloride (fractions 7–9), collecting 700-ml. fractions. The crystalline fractions (2–9) were combined and recrystallized from methanol to give the 7ξ-fluoro-B-homo derivative **3h** (15.0 g.), m.p. 138–140°. Recrystallization from methanol afforded the analytical sample: m.p. 138–140°; $[\alpha]D$ −93°; ν_{max} 1735, 1255, 1085, and 935 cm.$^{-1}$; n.m.r. 53.5 (18-H, s), 121 (OAc, s), 249.5 (21-H, s), 302 (two protons, s), 301, 311.5 (two protons, two s) (methylenedioxy protons), and 285–330 (3α- and 7ξ-H, m) c.p.s.

Anal. Calcd. for $C_{25}H_{35}FO_6$: C, 66.64; H, 7.83; F, 4.20. Found: C, 67.13; H, 7.70; F, 4.30.

The total mother liquors were chromatographed on washed alumina (500 g.). Elution with hexane afforded additional **3h** (300 mg.) giving a total yield of 15.3 g. (76.5%).

B.—A mixture of the 19-hydroxy steroid **2c** (4.49 g., 10 mmoles), the fluoramine **1** (2.85 g., 15 mmoles), and dry acetonitrile (50 ml.) was heated under reflux 1 hr. The mixture was then cooled and passed through a column of washed alumina. The fractions eluted with hexane and with methylene chloride were combined and chromatographed on washed alumina (250 g.). The first crystalline fractions eluted with hexane–ether (9:1) consisted of the 5β,6β-methylene-Δ^9 derivative **4g** (3.01 g., 70.0%) as determined by infrared analyses. Recrystallization from methanol afforded the analytical sample: m.p. 163.5–164.5°; $[\alpha]D$ −89°; λ_{max} 217–218 mμ (log ε 3.94); ν_{max} 3010, 1730, 1260, 1240, 1085, and 940 cm.$^{-1}$; n.m.r. 51.5 (18-H, s), 122.5 (OAc, s), 239 (21-H, s), 302.5 (two protons, s), 302.5, and 311.7 (2 s, methylenedioxy protons) c.p.s.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.94; H, 7.90.

Further elution with the same solvent system yielded the 5β,6β-methylene-$\Delta^{1(10)}$ isomer **8d** (0.85 g., 20.0%). Recrystallization from methanol gave the analytical sample: m.p. 172–175°; $[\alpha]D$ −87°; no absorption in the ultraviolet (215–250 mμ); ν_{max} 1730, 1255, 1085, 940, and 885 cm.$^{-1}$; n.m.r. 48 (18-H, s), 123.5 (OAc, s), 240.5 (21-H), 304.5 (three protons, s), and 314 (one proton, s, methylenedioxy protons), 290–335 (3α-H, m), and 328 (1-H, m) c.p.s.

Anal. Found: C, 69.94; H, 7.97.

7ξ-Fluoro-17,20:20,21-bismethylenedioxy-B-homo-19-norpregn-5(10)-en-3β-ol (3j).—The acetate **3h** (300 mg.) was saponified in 5% methanolic potassium hydroxide (25 ml.) at room temperature (16 hr.). Recrystallization from acetone–hexane afforded the analytical sample: m.p. 145–147°; $[\alpha]D$ −98°; ν_{max} 3600, 1095, 1085, and 940 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}O_5$: C, 67.63; H, 8.12; F, 4.65. Found: C, 67.68; H, 8.23; F, 5.05.

7ξ-Fluoro-17,20:20,21-bismethylenedioxy-B-homo-19-norpregn-5(10)-en-3-one (3k).—Chromic acid (5 ml. of 8 *N*)[8] was added dropwise with stirring to a solution of **3j** (5 g.) in acetone (125 ml.) at 0–5°. The cooling bath was then removed and the mixture was stirred for an additional 5 min. The product, as isolated by dilution with water and filtration, exhibited weak absorption in the ultraviolet at 240 mμ. Crystallization from acetone afforded purer **3k** (2.8 g.), m.p. 76–78°, and further recrystallization from acetone gave the analytical sample: m.p. 79–80°; $[\alpha]D$ −29°; no absorption in the ultraviolet (220–250 mμ); ν_{max} 1720, 1708, 1095, 1085, 940, and 870 cm.$^{-1}$; n.m.r. 55.5 (18-H, s), 240 (21-H s), 302, 303.5, 312 (methylenedioxy protons, 3 s), and 172 (C-4 methylene H, AB pattern) c.p.s.

Anal. Calcd. for $C_{23}H_{31}FO_5$: C, 67.97; H, 7.69; F, 4.67. Found: C, 68.04; H, 8.04; F, 4.24.

The mother liquors were chromatographed on Florisil (100 g.). Crystalline fractions eluted with hexane–ether (4:1) consisted of more unconjugated dione **3k** (300 mg.), and the crystalline

fractions eluted with hexane–ether (7:3) consisted of the isomeric Δ^4 3-ketone **7f** (120 mg.), identical with a sample prepared as described below.

7ξ-Fluoro-17,20:20,21-bismethylenedioxy-B-homo-19-norpregn-4-en-3-one (**7f**).—A solution of the unconjugated ketone **3k** (1.0 g.) in 95% ethanol (25 ml.) containing oxalic acid (1.0 g.) was heated under reflux for 16 hr. The product (850 mg.) was isolated by dilution with water and filtration. Several recrystallizations from acetone afforded the analytical sample: m.p. 246–247°; $[\alpha]_D$ −137°; λ_{max} 240 mμ (log ε 4.17); ν_{max} 1670, 1625, 1095, 1080, and 940 cm.$^{-1}$; n.m.r. 50 (18-H, s), 240 (21-H, s), 304.5 (two protons), 303, 312.5 (methylenedioxy protons), 356 (4-H, s), 275, and 325 (7ξ-H, pair of m, J_{HF} = *ca.* 50 c.p.s.) c.p.s.

Anal. Calcd. for $C_{23}H_{31}FO_6$: C, 67.97; H, 7.69; F, 4.67. Found: C, 68.35; H, 7.62; F, 4.18.

17α,21-Dihydroxy-7ξ-fluoro-B-homo-19-norpregn-4-ene-3,20-dione (**7g**).—Ketone **7f** (215 mg.) was added to concentrated hydrochloric acid at 0° with good stirring. The steroid dissolved completely in 2.5 min. The mixture was stirred an additional minute and the product was then isolated by precipitation in aqueous sodium bicarbonate and extraction with ethyl acetate. Recrystallization from methanol afforded the analytical sample: m.p. 204–205°; $[\alpha]_D$ −60°; λ_{max} 238 mμ (log ε 4.19); ν_{max} 3350–3400, 1708, 1655, 1615, and 885 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}FO_4$: C, 69.18; H, 8.01; F, 5.21. Found: C, 69.13; H, 8.15; F, 5.57.

Product Development Control in the Reduction of 17-Keto-13α-androst-5-en-3β-ol

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Reduction of 17-keto-13α-androst-5-en-3β-ol with either sodium and isopropyl alcohol, lithium aluminum hydride, or sodium borohydride yields a mixture of epimeric 17-ols in which the 17α-ol predominates. The configurations of the products were deduced from rotational, infrared, and n.m.r. data. The results support the conclusion that the reductions with lithium aluminum hydride and sodium borohydride are product development controlled.

In a previous publication,[1] we indicated that the hydride reduction of a 17-keto-13α,14α steroid, as well as a 17-keto-13β,14α and a 17-keto-13β,14β steroid, was product development controlled. This paper presents additional evidence in support of this conclusion.

17-Keto-13α-androst-5-en-3β-ol (I)[2] was reduced with lithium aluminum hydride, sodium borohydride, and sodium in isopropyl alcohol. All three reductions were observed to give a mixture of products in which the predominant product is the more levorotatory epimer having the hydroxyl group at C-17 α oriented.[2] The crude mixture of products from each of the reductions was analyzed by paper chromatography.[3] The results reveal that the 17β epimer is also present in all three reduction mixtures; 17–20% when lithium aluminum hydride is used, 8–10% when the reduction is carried out with sodium and isopropyl alcohol, and 20–25% when the reducing agent is sodium borohydride.

Fractional crystallization of each of the reduction mixtures affords 13α-androst-5-ene-3β,17α-diol of comparable purity in 77, 87, and 48% yields when lithium aluminum hydride, sodium and isopropyl alcohol, and sodium borohydride are, respectively, employed.

The configurations at C-17 of the two reduction products were deduced from rotational, infrared, and n.m.r. data. Of a pair of 17-hydroxy steroids which are epimeric at C-17, the epimer having the greater levorotation has the 17α-hydroxy configuration.[2] For example, the specific rotation of 13α,17α-testosterone is about 40° more levorotatory than that of 13α-testosterone.[1,2]

The major product obtained from the reduction of 17-keto-13α-androst-5-en-3β-ol (I) exhibits a specific rotation of −122° while the minor product shows a rotation of −99°. Oppenauer oxidation of the former affords 13α,17α-testosterone in 38% yield, thereby establishing that the configuration at C-17 of the major reduction product is the same as that of 13α,17α-testosterone.

The molecular rotation difference ($\Delta MD^{13\beta-13\alpha}$) was found to be +53° for testosterone and 13α-testosterone and +65° for 17α-testosterone and 13α,17α-testosterone.[2]

Barton and Cox[4] reported the specific rotation of androst-5-ene-3β,17α-diol to be −61° in chloroform while Muller, *et al.*,[5] found that of androst-5-ene-3β,17β-diol to be −55° in the same solvent. Hence, the molecular rotation difference ($\Delta MD^{13\beta-14\alpha}$) is +128° for androst-5-ene-3β,17β-diol and 13α-androst-5-ene-3β,-17β-diol, and +177° for androst-5-ene-3β,17α-diol and 13α-androst-5-ene-3β,17α-diol. These results, together with the molecular rotation difference of 17α-estradiol 3-methyl ether and 13α,17α-estradiol 3-methyl ether, are tabulated in Table I.

The infrared spectrum of 13α-androst-5-ene-3β,17α-diol shows C–O stretching bands at 9.32 and 9.43 μ while the spectrum of the 3β,17β-diol displays the C–O band at 9.50 μ. Previous investigators[2,6] have reported that the C–O stretching band of an equatorial hydroxyl group appears at a lower wave length than that of an axial hydroxyl group. Our results suggest that the hydroxyl group at C-17 of the 3β,17β-diol has greater axial character than the corresponding group of the 3β,17α epimer. This is in accord with molecular models assembled on the premise that ring C has the chair conformation, ring D is puckered, and the C-17 substituents are not eclipsed by those of C-16.[1]

The n.m.r. spectrum of 13α,17α-testosterone reveals a triplet centered at 254 c.p.s. (τ 5.77) with observed splittings of 7.5 c.p.s. This triplet, which is due to the resonance of the 17β-proton, is reminiscent of the triplet centered at τ 6.33

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