REACTIONS OF 4β,5-EPOXY-5β-ANDROSTAN-3-ONES WITH HYDROGEN FLUORIDE IN PYRIDINE

Bojan Hamlin Jennings and Joan Marie Bengtson

Department of Chemistry, Wheaton College
Norton, Massachusetts 02766

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ABSTRACT

4β,5-Epoxy-5β-androstane-3,17-dione (1a), 17β-hydroxy-4β,5-epoxy-5β-androstan-3-one (1b) and 17β-acetoxy-4β,5-epoxy-5β-androstan-3-one (1c) were treated with anhydrous hydrogen fluoride in pyridine (70% solution) at 55° and yielded the corresponding 4-en-4-ols, e.g. 4-hydroxy-4-androstene-3,17-dione (2a).

As the reaction temperature was lowered each epoxide formed a second product which, at -75°, was the major component of the reaction mixture and was identified as the 5α-fluoro-4α-ol derivative of the parent enone, e.g. 4α-hydroxy-5-fluoro-5α-androstane-3,17-dione (3a). These fluorohydrins are thermally unstable, losing hydrogen fluoride.

The acetates of the fluorohydrins were also prepared, characterized, and shown to be more stable than the parent alcohols.

INTRODUCTION

Brodie and co-workers have demonstrated that several synthetic steroids are estrogen synthetase inhibitors, highly effective against estrogen-dependent processes, including the growth of mammary tumors (1). As these authors point out in their excellent discussion, such inhibitors could offer a desirable alternative to ablative surgery as a method for treating breast cancer. From a consideration of their published data (2), as well as unpublished information made available to us, we were prompted to prepare fluorosteroids which might also be of use as inhibitors.

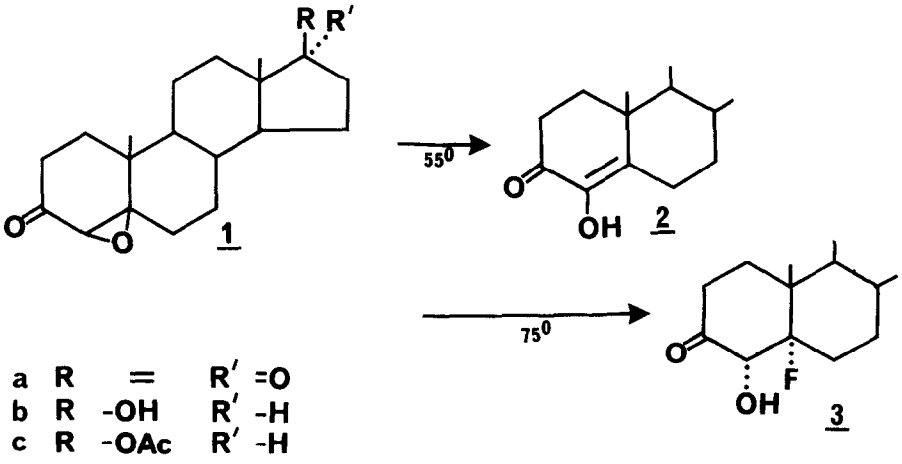
An attractive route to such compounds is through their epoxides which have traditionally been cleaved with boron trifluoride etherate or gaseous

hydrogen fluoride (3). We have studied reactions between three 4,5-β-epoxides and a 70% solution of hydrogen fluoride in pyridine (4).

RESULTS

At moderate temperature the reaction produced 4-en-4-ols (2a, 2b, and 2c) which were characterized by their ultraviolet, infrared, and nuclear magnetic resonance spectra (Experimental Section and Table I).

Reaction temperatures below 55° favored the formation of a saturated compound from each epoxide, detected by thin layer chromatography, infrared and nuclear magnetic resonance spectra of the crude products; at -75°, only traces of unsaturated products were found (uv).



The assignment of structure 3a to the product from 1a was based on spectral data. The ultraviolet spectrum showed no significant absorption. The infrared spectrum indicated the presence of an intramolecularly hydrogen bonded hydroxyl group (3475 cm^{-1}, $C_4OH\cdots FC_5$) as well as the expected carbonyls (1740 and 1720 cm^{-1}), but gave no indication of an α,β-unsaturated ketone.

Table I

Nuclear Magnetic Resonance Data for Products of Reactions Between 4β,5-Epoxy-5β-androstan-3-ones and Hydrogen Fluoride in Pyridine at 55°C[a].

Product from	Chemical Shift	Multiplicity	#H	Assignment	Deduced Structure
4β,5-epoxy-5β-androstane-3,17-dione (1a)	55	s	3	$C_{18}\underline{H}_3$	4-hydroxy-4-androstene-3,17-dione (2a)
	72	s	3	$C_{19}\underline{H}_3$	
	363[b]	s	1	$C_4O\underline{H}$	
17β-hydroxy-4β,5-epoxy-5β-androstan-3-one (1b)	47	s	3	$C_{18}\underline{H}_3$	4,17β-dihydroxy-4-androsten-3-one (2b)
	71	s	3	$C_{19}\underline{H}_3$	
	218	m	1	$C_{17}\underline{H}$	
	364[b]	s	1	$C_4O\underline{H}$	
17β-acetoxy-4β,5-epoxy-5β-androstan-3-one (1c)	48	s	3	$C_{18}\underline{H}_3$	4-hydroxy-17β-acetoxy-4-androsten-3-one (2c)
	69	s	3	$C_{19}\underline{H}_3$	
	279	t	1	$C_{17}\underline{H}$	
	362[b]	s	1	$C_4O\underline{H}$	

[a]All chemical shift values are given in Hz relative to tetramethylsilane as internal standard; $\delta = \frac{Hz}{60}$. S, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Hz given for triplets and multiplets are for their centers.

[b]Disappeared when D_2O added.

Nuclear magnetic resonance spectra (Table II) served further to define the structure as 4α-hydroxy-5-fluoro-5α-androstane-3,17-dione (3a). The spectrum taken in deuterated chloroform showed no absorption lower that 289 Hz (4.82δ); consequently, the fluorine must be tertiary at the 5-position: a secondary hydrogen geminal to fluorine would be immediately obvious by a resonance centered at somewhat lower field and split with a large $J_{\underline{H}-\underline{F}}$ value (45-80 Hz) (5).

The hydroxylic proton, expected at C_4, appeared as a doublet ($J_{\underline{H}-O\underline{H}}$ = 6 Hz, centered at 201 Hz; 3.35δ; 1H), which disappeared when D_2O was added. This chemical shift value reinforced the infrared data, both criteria suggesting intramolecular hydrogen bonding, presumably to fluorine at the 5α position. Although bonding between $C_4\alpha O\underline{H}$ and C_3=O is also a possibility, the significantly greater electronegativity of fluorine (4.0) as compared with oxygen (3.5) should favor H-F bonding despite the somewhat larger nearest distance between H and F (approximately 2.4 Å from Dreiding models) as compared with the nearest distance between C_3=O and $C_4\alpha O\underline{H}$ (2.1 Å). The splitting of the $O\underline{H}$ peaks was shown to result from coupling of the $C_4O\underline{H}$ with the $C_4\underline{H}$, whose resonance, in the absence of D_2O, appeared as a quartet ($J_{\underline{H}-\underline{F}}$ = 31 Hz, $J_{\underline{H}-O\underline{H}}$ = 6 Hz) centered at 270.5 Hz (4.51δ; 1H). Addition of D_2O destroyed the $C_4O\underline{H}$-$C_4\underline{H}$ interaction and the quartet ($C_4\underline{H}$) was replaced by a doublet ($J_{\underline{H}-\underline{F}}$ = 31 Hz). The chemical shift (270.5 Hz) is reasonable for a proton both geminal to hydroxyl and vicinal to fluorine and the coupling constant of 31 Hz indicates that the $C_4\underline{H}$ is oriented diaxially to the $C_5\underline{F}$ (dihedral angle of 180°); an axial-equtorial arrangement (dihedral angle near 40°) would produce a much smaller J-value (6).

Table II

Nuclear Magnetic Resonance Data for Product of Reaction Between 4β,5-Epoxy-5β-androstane-3,17-dione (1a) and Hydrogen Fluoride in Pyridine at -75°C[a].

Chemical Shift (Hz) $CDCl_3$	Multiplicity[d]	Chemical Shift (Hz) ϕH_d	Multiplicity[d]	# H	Assignment
54	s	31	s	3	$C_{18}\underline{H}_3$
63 64	d $J_{\underline{H}-\underline{F}}$=1	43 44	d $J_{\underline{H}-\underline{F}}$=1	3	$C_{19}\underline{H}_3$
198 204	d[b,c] $J_{\underline{H}-O\underline{H}}$=6	214 220	d $J_{\underline{H}-O\underline{H}}$=6	1	$C_4O\underline{H}$
252 258 283 289	q[c] $J_{\underline{H}-\underline{F}}$=31 $J_{\underline{H}-O\underline{H}}$=6	227 233 259 265	q $J_{\underline{H}-\underline{F}}$=32 $J_{\underline{H}-O\underline{H}}$=6	1	$C_4\underline{H}$
	When D_2O added, this quartet collapsed to doublet:				
255 286	d $J_{\underline{H}-\underline{F}}$=31	230 262	d $J_{\underline{H}-\underline{F}}$=32		

Deduced Structure:

4α-hydroxy-5-fluoro-5α-androstane-3,17-dione (3a)

[a,b] See footnotes for Table I.

[c] The hydroxylic proton appeared as a doublet only in spectra of highly purified samples; otherwise it showed as a broad multiplet, with the $C_4\underline{H}$ a doublet (J_{H-F}=31 Hz, $W_{1/2}$~4 Hz).

[d] J values are given in Hz.

Additional evidence for the axial orientation of the $C_4\underline{H}$ was obtained by observing the spectrum of the compound in deuterated benzene solution. In this solvent axial C_4-protons of 3-ketosteroids are shifted upfield from their positions in deuterated chloroform solutions, whereas equatorial protons are little affected (7). The $\underline{H}$-$\underline{F}$ doublet assigned to $C_4\underline{H}$ of our fluorohydrin was shifted upfield by 25 Hz (to 246 Hz, center) in the spectrum of the compound taken in benzene (see Table II), exactly as would be expected for an axial $C_4\underline{H}$ (7).

There is thus no doubt that the hydrogen and fluorine are diaxial, with the hydroxyl cis to the fluorine. The question as to whether hydroxyl and fluorine are both alpha (ring A/B trans) or both beta (ring A/B cis) was settled by noting that the nuclear magnetic resonance for the $C_{19}\underline{H}$'s of the fluorohydrin is a doublet ($J_{\underline{H}\text{-}\underline{F}}$ = 1 Hz, centered at 63.5 Hz in chloroform, 43.5 Hz in benzene) which would result only if the fluorine at C_5, and therefore the hydroxyl at C_4, are oriented alpha. Long range coupling between atoms separated by four sigma bonds (H at C_{19} and F at C_5) is observed only if they are aligned in an "M" arrangement (8). A beta fluorine at C_5 would not satisfy this requirement with respect to any of the conformations of the C_{19} methyl protons, whereas an alpha fluorine does.

The cumulative evidence thus establishes the structure as 4α-hydroxy-5-fluoro-5α-androstane-3,17-dione (3a).

The mass spectrum of the compound obtained by gas chromatographic-mass spectral analysis gave no parent peak for fluorhydrin (m/e = 322), the highest mass being at m/e = 302 (fluorohydrin minus HF); indeed, the spectrum was identical with that of 2a. Dehydrofluorination also occurred as the compound melted, on treatment with base, and when

chromatographed. These observations are consistent with the diaxial 4H, 5F assignment. It is well known that base catalyzed E_2 dehydrohalogenation requires trans H-C-C-X geometry and Dale Hoff has shown that thermal dehydrofluorination also proceeds by trans elimination (9).

That structure 3b is appropriate for the product from 1b follows from analysis of its nuclear magnetic resonance spectra in various solvents (Table III). Absence of low-field resonance requires that the fluorine be at C_5. In the spectrum taken in $CDCl_3$, the $C_{17}\underline{H}$ appeared as a multiplet centered at ~216 Hz (3.60δ) but the size of the peak relative to other resonances indicated two protons and suggested that the signal for a hydrogen-bonded hydroxyl proton at C_4 coincided with that for the $C_{17}H$. A doublet ($J_{\underline{H}-\underline{F}}$ = 31 Hz), centered at 271.5 Hz (4.53δ; 1H) was attributable to $C_4\underline{H}$ and, as with 3a, this $C_4\underline{H}$ resonance was shifted upfield by 25 Hz in the spectrum taken of the compound in deuterated benzene. The diaxial character of the H-C-C-F bond was thus established and, again as with 3a, 5αF,4αOH orientation was inferred from the split (1 Hz) signal of the C_{19} methyl protons.

The spectrum taken in deuterated dimethyl sulfoxide gave interesting confirmatory evidence for the structure. This solvent hydrogen bonds strongly with hydroxyl protons which are thus shifted downfield relative to their positions in deuterated chloroform solution (10). The spectrum of the low temperature product in dimethyl sulfoxide (Table III) displayed broad peaks centered at approximately 208 Hz (3.47δ; 1H), 261 Hz (4.35δ; 1½ H), and 292 Hz (4.87δ; 1½ H). Addition of D_2O caused the broad peaks at 261 and 292 Hz to be replaced by sharp peaks at 261 Hz (1 H) and 294 Hz (4.90δ; 1 H). Clearly, in the dimethyl sulfoxide spectrum taken before addition of D_2O, the hydroxyl protons at C_4 and C_{17} appeared

Table III

Nuclear Magnetic Resonance Data for Product of Reaction Between 17β-Hydroxy-4β,5-Epoxy-5β-androstan-3-one (1b) and Hydrogen Fluoride in Pyridine at -75°C[a].

Chemical Shift (Hz) $CDCl_3$	Chemical Shift (Hz) ϕH_d	Chemical Shift (Hz) $DMSO_d$	Multiplicity[b]	# H	Assignment
46	48	40	s	3	$C_{18}\underline{H}_3$
63 64	58 59	57 58	d $J_{\underline{H}-\underline{F}}$=1	3	$C_{19}\underline{H}_3$
216	204		m,b	2	$C_{17}\underline{H}$ $C_4\underline{OH}$
256 287	231 262		d $J_{\underline{H}-\underline{F}}$=31	1	$C_4\underline{H}$
		208	m,b	1	$C_{17}\underline{H}$
		261 292	m,b m,b	1½ 1½	$C_{17}\underline{OH}$, ½$C_4\underline{H}$ $C_4\underline{OH}$, ½$C_4\underline{H}$
		When D_2O added, these broad multiplets changed to sharp peaks:			
		261 294	d $J_{\underline{H}-\underline{F}}$=33	1	$C_4\underline{H}$

Deduced Structure:
4α,17β-dihydroxy-5-fluoro-5α-androstan-3-one (3b)

[a] See footnote for Table I.

[b] J values are given in Hz.

downfield from their positions in chloroform solution, the $C_{17}\underline{OH}$ coinciding with one half of the $C_4\underline{H}$ doublet, centered at 261 Hz ($C_{17}\underline{OH}$ of 17β-hydroxyandrostane, split to a doublet by $C_{17}\underline{H}$, is centered at 260 Hz (4.33δ)), and the $C_4\underline{OH}$ with the other half, centered at 292 Hz. Addition of D_2O disposed of both hydroxyl signals and the doublet from the $C_4\underline{H}$ appeared in sharp focus, free of overlap.

The mass spectrum of the fluorohydrin was identical with that of 2b; loss of hydrogen fluoride also occurred on heating and on treatment with base.

Ultraviolet, infrared, and nuclear magnetic resonance spectra (Table IV) of the low temperature product from 1c were consistent with assignment on structure 3c. All spectra differed somewhat from those reported by Neeman and O'Grodnick for 3c obtained by treating the beta epoxide with anhydrous hydrogen fluoride in neat chloroform (11), but they were analogous to the corresponding spectra of our other fluorohydrins. The nuclear magnetic resonance spectrum taken in deuterated chloroform showed coincidence of the resonance from the $C_{17}\underline{H}$ with the downfield half of the quartet belonging to $C_4\underline{H}$ which was split by both $C_4\underline{OH}$ and $C_5\underline{F}$ (see Table IV). Collapse of this quartet to a doublet in the presence of D_2O clarified this assignment.

Like the other two fluorohydrins, 3c was easily dehydrofluorinated.

Acetates of the Fluorohydrins

Treatment of the fluorohydrins with acetic anhydride in dry pyridine produced 4α-acetoxy-5-fluoro-5α-androstane-3,17-dione from 3a and 4α,17β-diacetoxy-5-fluoro-5α-androstan-3-one from 3b and 3c. The infrared and nuclear magnetic resonance spectra (Table V) of the acetylated

Table IV

Nuclear Magnetic Resonance Data for Product of Reaction Between 17β-Acetoxy-4β,5-Epoxy-5β-androstan-3-one (1c) and Hydrogen Fluoride in Pyridine at -75°C[a].

Chemical Shift ($CDCl_3$)	Multiplicity[c]	Chemical Shift ($\phi\underline{H}_d$)	Multiplicity[c]	# H	Assignment
49	s	40	s	3	$C_{18}\underline{H}_3$
62 63	d $J_{\underline{H}-\underline{F}}=1$	45 46	d $J_{\underline{H}-\underline{F}}=1$	3	$C_{19}\underline{H}_3$
121	s	105	s	3	$C_{17}{}^{O\underline{C}\underline{C}H}_{\underline{\underline{O}}}{}_3$
198 202	d[b] $J_{\underline{H}-O\underline{H}}=4$	220	b	1	$C_4O\underline{H}$
253 257	d (part of q) $J_{\underline{H}-O\underline{H}}=4$			½	$C_4\underline{H}$
274 to 292	m,b (d part of q plus m)			1½	$C_4\underline{H}$,$C_{17}\underline{H}$

Table IV - Continued

Chemical Shift ($CDCl_3$)	Multiplicity	Chemical Shift ($\emptyset H_d$)	Multiplicity	# H	Assignment
When D_2O added, the quartet collapsed to doublet clearly visible on either side of the $C_{17}\underline{H}$ multiplet:					
255 286	d $J_{\underline{H}-\underline{F}}$=31	234 265	d $J_{\underline{H}-\underline{F}}$=31	1	$C_4\underline{H}$
275	t $J_{\underline{H}-\underline{F}}$=8	282	t $J_{\underline{H}-\underline{F}}$=8	1	$C_{17}\underline{H}$

Deduced Structure:

4α-hydroxy-17β-acetoxy-5-fluoro-5α-androstan-3-one (3c)

[a,b] See footnotes for Table I.

[c] J values are given in Hz.

Table V

Nuclear Magnetic Resonance Data for Acetates of the Fluorohydrins[a].

Acetate from	Chemical Shift (Hz) $CDCl_3$	Chemical Shift (Hz) $\emptyset H_d$	Multiplicity[b]	# H	Assignment
4α-hydroxy-5-fluoro-5α-androstane-3,17-dione (3a)	54	30	s	3	$C_{18}\underline{H}_3$
	65 66	44 45	d $J_{\underline{H}-\underline{F}}=1$	3	$C_{19}\underline{H}_3$
	134	114	s	3	$C_4OC\underline{CH}_3$ (O)
	323 356	324 357	d $J_{\underline{H}-\underline{F}}=33$	1	$C_4\underline{H}$
4α,17β-dihydroxy-5-fluoro-5α-androstan-3-one (3b) and 4α-hydroxy-17β-acetoxy-5-fluoro-5α-androstan-3-one (3c)	48	43	s	3	$C_{18}\underline{H}_3$
	63 64	50 51	d $J_{\underline{H}-\underline{F}}=1$	3	$C_{19}\underline{H}_3$
	120	108	s	3	$C_{17}OC\underline{CH}_3$ (O)
	133	116	s	3	$C_4OC\underline{CH}_3$ (O)
	276	284	t $J_{\underline{H}-\underline{H}}=8$	1	$C_{17}\underline{H}$
	322 355	332 365	d $J_{\underline{H}-\underline{F}}=33$	1	$C_4\underline{H}$

[a] See footnote for Table I.

[b] J values are given in Hz.

compounds confirmed their structures; moreover, the spectra of the diacetate were essentially the same as those reported by Neeman and O'Grodnick for the same compound (11).

In contrast with the fluorohydrins, the acetates did not evolve hydrogen fluoride on melting, were stable at 100° in vacuo, and could be purified by chromatography, with no sign of decomposition. Treatment with methanolic sodium hydroxide converted them immediately to 4-en-4-ol-3-ones (2a, 2b).

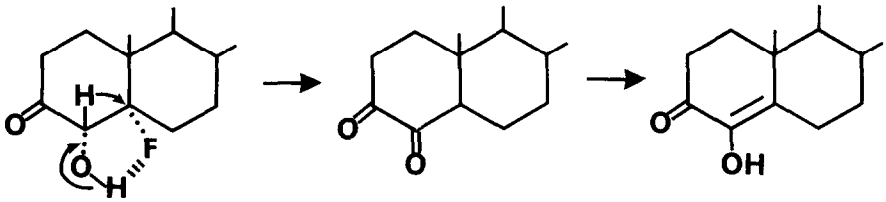
DISCUSSION

The accepted mechanism for cleavage of an epoxide ring (12,13) would lead, in our case, to the production of 5α-fluoro-4β-ols. To account for the fact that, instead, 4α-ols are formed, rapid epimerization at C_4 must be invoked (11). Driving force for this conversion could be the destabilizing diaxial interaction between the 4βOH and the methyl group at C_{10} coupled with a stabilizing contribution from hydrogen bonding (between 4αOH and 5αF), available to the 4α-ol product but not to the intermediate 4β-ol. Furthermore, as pointed out by a referee, the epimerized product should be thermodynamically more stable on conformational grounds alone.

It is mechanistically significant that dehydrohalogenation does not occur to any marked extent during low temperature reaction whereas epimerization takes place rapidly. The accepted route for epimerization of a ketone substituted in an alpha position is by way of the enol or enolate ion, depending on whether acid or base catalysis is operative. Hydrogen fluoride in pyridine contains both HF and F^- in a molar ratio of 3.5 to 0.4, assuming all the available pyridine has reacted with HF

to produce pyridinium and fluoride ions. The degree of independence of the latter from hydrogen bonding to excess HF is not clear, but any free fluoride ion should serve as a powerful base catalyst (14). At any rate, either the enol or the enolate ion, once formed, might well be expected to serve as an intermediate not only for the observed isomerization, but also for dehydrohalogenation. Progression to unsaturated compounds does not, however, occur at -75°.

A mechanism can be imagined for the observed thermal dehydrofluorination of the 5α,4α-fluorohydrins by taking into account the evidence for strong hydrogen bonding between the $C_4\alpha O\underline{H}$ and the $C_5\alpha\underline{F}$. Transition from a hydrogen bond to a covalent H-F bond, accompanied by a hydride shift to the back side of C_5, and realignment of electrons, would result in the diketo form of the enolic products.



The conversion would be facilitated both because the migrating hydride can provide anchimeric assistance for breaking the C-F bond and because the fluorine is already partially bonded to the hydrogen and well situated for the concerted mechanism. The observation that the 4-acetates do not lose hydrogen fluoride on heating lends credence to this suggestion.

The dehydrofluorination of both the fluorohydrins and their acetates in a basic medium is unexceptional and falls within the category of normal base-catalyzed <u>trans</u> elimination.

EXPERIMENTAL

Steroids used as starting materials were obtained from Steraloids, Inc. (Wilton, N.H.) and Sigma Chemical Co. (St. Louis, Mo.); 70% HF in pyridine from Aldrich Chemical Co. (Milwaukee, Wi.). Spectra were taken on a Perkin-Elmer Ultraviolet-Visible Spectrophotometer 202, Infrared 137 and 337, and a Variant T-60 Nuclear Magnetic Resonance Spectrometer. All Hz are reported relative to TMS. Mass spectra were taken with a Finnigan Model 3200 fitted with a 3% OV-1, 5 ft. column, at temperatures ranging from 200-240°; retention times were 4-5 min. at pressures between 7-9 psi. A Perkin-Elmer Polarimeter 241 was used. Thin layer chromatography was carried out on Eastman Silica Gel Chromagram Sheets (13179) using 10% or 25% ethyl acetate-benzene and the spots were visualized by exposure to iodine vapor or by spraying with a saturated solution of antimony chloride in chloroform. Silica Gel 60 (Brinkmann, 70-230 mesh) was used for column chromatography unless otherwise noted. Samples were applied to the column in benzene solution. All chromatographic solvents were Analytical Reagent grade, dried over 3 Å molecular sieves. Melting points (°C) are uncorrected. Microchemical analyses were done by Schwartzkopf (Woodside, N.Y.) and Sanda, Inc. (Philadelphia, Pa.).

Preparation and purification of the β-epoxides (1a, 1b, and 1c).

1a: Androstendione (2.0 g, 6.9 mmole), dissolved in 200 ml methanol-water (80:20) and cooled to 0°, was treated with 13 ml 30% H_2O_2 and 8.6 ml 4H NaOH (15). The mixture was stirred for 2.5 hr at 0-5° in the dark, filtered, and the filtrate taken up in CH_2Cl_2. The organic layer, washed with H_2O, dried, and evaporated, yielded 1.5 g white solid whose nmr showed a 1:4 ratio of α:β (α,182 Hz; β,178 Hz). Some runs still contained starting material (346 Hz, λmax(EtOH), 241 nm).

In our hands chromatography on alumina (Woelm, neutral) (15) resulted in breakdown on the column to yellow oils and, although the α and β isomers could be separated from unreacted dione on silica gel, they were not cleanly separated from each other. Pure β-epoxide (180 mg) was obtained by recrystallization of 1.03 g crude from benzene. A second crop (133 mg) consisted of an α:β mixture (1:9, nmr). The pure material (first crop) showed 1 spot on tlc; mp: 201-203° (lit. 202-203° [15]); uv: no absorption at 241 nm; ir: ν(KBr, cm^{-1}) 1730 (C_{17}=O), 1710 (C_3=O), 1244 (epoxy C-O); nmr: ($CDCl_3$, Hz) 53 ($C_{18}\underline{H}_3$), 70 ($C_{19}\underline{H}_3$), 178 ($C_4\underline{H}$), no signal at 64 ($C_{19}\underline{H}_3$ for α) or 180 ($C_4\underline{H}$ for α).

1b: In a typical synthesis, from 2.00 g testosterone, the procedure described above furnished 1.71 g product, α:β ~ 1:7 (nmr: $C_4\underline{H}$ α,181 Hz; β,177 Hz) and unreacted testosterone (nmr: $C_4\underline{H}$, 341 Hz; λmax(EtOH) 243 nm). Crude product (1.97 g) was chromatographed on 70 g silica gel: 25% ether-benzene (50 ml fractions) eluted first a mixture of α:β ~1:3, followed by 1.16 g pure β epoxide; testosterone (150 mg) came off with 50% ether-benzene. The pure fraction gave one spot on

tlc; mp: 155-156°; (lit 158-159°; 156-157° [15]); uv: no absorption at 243 nm; ir: ν(KBr, cm^{-1}) 3535 (O-H), 1710 sh, 1700 (C_3=O), 1252, 1248 (epoxy C-O); nmr: ($CDCl_3$, Hz) 46,($C_{18}\underline{H}_3$), 70 ($C_{19}\underline{H}_3$), 178 ($C_4\underline{H}$), no signal at 64 ($C_{19}\underline{H}_3$ for α) or 181 ($C_4\underline{H}$ for α).

1c: The above procedure gave, from 5.75 g testosterone acetate, 5.42 g white solid which contained unreacted starting material (nmr $C_4\underline{H}$, 343 Hz; λmax(EtOH) 241 nm) and α:β≅1:8 ($C_4\underline{H}$ α, 180 Hz; β,177 Hz). The amount of testosterone acetate was approximately equal to the amount of α compound (nmr).

Part of the crude (855 mg) was chromatographed on 22 g silica gel. The first four fractions (25 ml each), eluted by 5% ether-benzene, consisted of (1) 175 mg α:β = 1:1, (2) 301 mg 1:4, (3 and 4) 137 mg pure β. These were followed by unreacted testosterone (147 mg), eluted by 10% ether-benzene. Pure β-epoxide (142 mg) could also be obtained from recrystallization of crude product (301 mg) from ether. The purified material gave one spot in tlc; mp: 141-142°; uv: no absorption at 241 nm; ir: ν(KBr, cm^{-1}) 1726 (aceto C=O), 1711 (C_3=O), 1256, 1247 (epoxy C-O); nmr: ($CDCl_3$, Hz) 49 ($C_{18}\underline{H}_3$), 69 ($C_{19}\underline{H}_3$), 177 ($C_4\underline{H}$), no signal at 64 ($C_{19}\underline{H}_3$ for α) or 183 ($C_4\underline{H}$ for α).

Reactions of the β-epoxides with hydrogen fluoride in pyridine.

At 55±5°. 2a: A polyethylene bottle was fitted with a Claisen type adapter one arm of which held a reflux condenser topped with a drying tube; the other arm was fitted with an adapter holding a nitrogen inlet. 1a (364 mg, 1.20 mmole), dried overnight in vacuo at room temperature, was placed in the apparatus which had been thoroughly flushed with nitrogen. Hydrogen fluoride solution (30 ml) was added all at once and the apparatus lowered into an oil bath maintained at 55±5°. The mixture was stirred in diffuse light for 20 min, after which the rust colored solution was poured over ice water, CH_2Cl_2 was added, and layers separated. The aqueous layer was washed twice with CH_2Cl_2 and the combined organic layers washed with water, 2% $NaHCO_3$, and saturated NaCl. The organic layer, dried and evaporated, gave 235 mg orange solid, which displayed 2 spots on tlc, the major one having the same R_f value as a sample of 2a prepared by treating the epoxide with 2% H_2SO_4 in glacial acetic acid for 2 hr (16). Trituration with ether gave 93 mg white solid which still showed an unidentified impurity by tlc. Recrystallization from ether yielded 24 mg material having one spot, tlc; mp: 205-206°; uv: λmax(EtOH) 279 nm; ir: ν(KBr, cm^{-1}) 3400, 3380 (H-bonded OH), 1735 (C_{17}=O), 1665 (C=C-C=O), 1625 (C=C), 1100, 1089, 1069, 1052, 1028, 1019 (C-F 1110-1000); nmr: see Table I; in addition to the tabulated data, an unassigned sharply defined doublet (J=4, 1H), centered at 147 Hz and two characteristic doublets (J=4) centered at 178 and 192 Hz. The nmr spectrum matched that of the compound obtained by treatment of the epoxide with H_2SO_4.

2b: The procedure (1 hr) and work-up described above gave, from 500 mg 1b, 210 mg yellow solid having one major and two minor spots on tlc. Recrystallization of 101 mg from benzene-ether gave 68 mg pure material: one spot tlc; mp: 225-226° (lit. 222° [16]); uv: λmax(EtOH) 279 nm, λmax(EtOH, N/200 NaOH) 330 nm; ir: ν(KBr, cm^{-1}) sh 3520, 3425 (H-bonded OH), 1665, sh 1650 (C=C-C=O), 1625 (C=C); nmr: see Table I; also unassigned but characteristic sets of doublets centered at 145 and 187 Hz (J=4). Both ir and nmr spectra were identical with these from acid treatment of the epoxide (see above).

2c: 1c (239 mg, above procedure, 15 min) yielded 251 mg orange solid which, on trituration with ether gave 49 mg white solid having one major and one minor spot on tlc. Recrystallization (83 mg) gave 15 mg pure 2c: tlc, one spot; mp: 194-195°; uv: λmax(EtOH) 279 nm; ir: ν(KBr, cm^{-1}) 3425 (H-bonded OH), 1740 (ester C=O), 1670 (C=C-C=O), 1640 (C=C); nmr; see Table I; an unassigned doublet (J=4, 1H) typical of the 4OH-Δ4 system (cf above) was centered at 144 Hz, with broad multiplets at 174 and 186 Hz. Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.94; H, 8.51.

At -75±5°. 3a: The reaction vessel, flushed with N_2 and charged with 487 mg 1a, (dried at 100° for several hours in vacuo) and 39 ml HF solution was lowered into a dry ice-ether bath maintained at -75±5°. The mixture was stirred for 30 min, after which it was poured over ice and the organic products taken up in CH_2Cl_2, which was then washed with water, 5% $NaHCO_3$, again with water, dried, and evaporated to give 443 mg white solid. This gave one major and three minor spots on tlc and slight absorption at 237 and 278 nm. The product (230 mg) was crystallized from acetone (which did not dissolve 7.6 mg, the latter having an unidentified ir spectrum) to give an analytical sample. Mp: 207-208°, d, HF evolved; uv: no absorption; ir: ν(KBr, cm^{-1}) 3475 (intramolecular H-bonded OH), 1740 (C_{17}=O), 1720 (C_3=O), 1090, 1053, 1006 (C-F: 1110-1000); nmr: see Table II; ms: (P^+-20) = 302, spectrum identical with that of 2a; rd (2.36 x 10^{-5}M, dioxane [θ] 25°) (589) 0, (578) 12, (546) 53, (436) 345, (365) 1073. Anal. Calc'd for $C_{19}H_{27}O_3F$: C, 70.78; H, 8.44; F, 5.89. Found: C, 70.84; H, 8.32; F, 5.81.

3b: Epoxide 1b (481 mg, 1.60 mmole), dried overnight at 100° in vacuo, was treated at -75° with 33 ml HF in pyridine in the dark for 20 min and worked up as above. The uv spectrum of the white solid product (442 mg) showed trace unsaturation; ir: (KBr, cm^{-1}) 3430 (intramolecular H-bonded OH), 3395 (intermolecular H-bonded OH), 1730 (C_3=O), 1079, 1009 (C-F: 1110-1000); nmr: see Table III; ms: (P^+-20) = 304, spectrum of 2b.

The compound could not be further purified by crystallization; chromatography on silica gel, silver impregnated silica gel, florisil, or alumina was, with one exception, totally unsuccessful: extensive decomposition occurred, yellow oils formed in the columns, and fractions contained from four to eight compounds, including 2b (tlc; uv, 280 nm)

and testosterone (tlc; uv, 243 nm). One run, on silica gel, fortuitously yielded 6.8 mg material (from 111 mg crude) which gave the following analysis: Anal. Calc'd for $C_{19}H_{29}O_3F$: C, 70.34; H, 9.01. Found: C, 70.31; H, 9.08.

3c: The above procedure (40 min) gave, from 409 mg (1.2 mmole) 1a and 31 ml HF solution, 434 mg light yellow solid. A small amount of ether was added to take up the yellow impurity and the undissolved white solid (113 mg) was filtered. Combined material from two runs (246 mg) was recrystallized from ether to give 72 mg 3c. Mp: 180-181°, d, HF evolved; uv: no absorption; ir: ν(KBr, cm^{-1}) 3470 (H-bonded OH), 1730 (aceto C=O), sh 1720 (C_3=O), 1092, 1082, 1043, 1024 (C-F: 1110-1000); nmr: see Table IV; rd (1.28 x 10^{-5}M, dioxane [θ] 25°) (589) 1, (578) 2, (546) 4, (436) -3, (365) -94. Anal. Calc'd for $C_{21}H_{31}O_4F$: C, 68.83; H, 8.53; F, 5.18. Found: C, 68.72; H, 8.58; F, 4.77.

Stability of the Fluorohydrins

The uv spectra of the cooled solid residues left after melting 3a, 3b, and 3c absorbed strongly at 279 nm (4-en-4-ols). When heated overnight at 100° in a vacuum drying apparatus, both 3b and 3c partially decomposed (ir and uv); 3a was unchanged.

Chromatography of all three crude fluorohydrins on silica gel was disastrous, yielding yellow oils which absorbed at 279 nm. Decomposition of analytical samples also occurred on tlc (2 spots).

Solutions of fluorohydrins in 15% methanolic NaOH were allowed to remain at room temperature a few hours, after which they were neutralized with dilute HCl. Chloroform was added, layers separated, the organic layer washed with saturated salt solution, dried, and evaporated. The uv and ir spectra of the residues were identical with those of the androst-4-en-4-ols corresponding to the parent fluorohydrins. The uv spectra of basic methanolic solutions of the fluorohydrins taken immediately after dissolving showed strong absorption at 320 nm, characteristic of 4-en-4-ol-3-ones in basic solution (17).

Preparation of Acetates of the Fluorohydrins

Fluorohydrin 3a (101 mg, 0.31 mmole), dried overnight at room temperature in vacuo, was dissolved in 1 ml dry pyridine and 0.5 ml acetic anhydride, both freshly distilled, and left at room temperature overnight. Ice, water, and CH_2Cl_2 were added and layers separated. The organic extract was washed with water, 5% HCl, again with water, and filtered through phase separating paper. On evaporation of solvent, 96 mg (85% yield) nearly pure 4α-acetoxy-5-fluoro-5α-androstane-3-17-dione (4) was obtained, having 1 spot on tlc and a trace of absorption at 252 nm. The material was further purified by chromatography on 7 g silica gel: 43 mg was eluted by 10% ether-benzene. Mp: 217-218° sealed tube; ir: ν(KBr, cm^{-1}) 1760 (acetate C=O, C_{17}=O), 1730 (C_3=O), 1091, 1076, 1051, 1028, 1012, 1008 (C-F: 1110-1000); nmr:

see Table V; rd (1.84 x 10^{-5}M, dioxane [θ] 25°)(589) 0, (578) 15, (546) 76, (436) 502, (365) 1470. Anal. Calc'd for $C_{21}H_{29}O_4F$: C, 69.21; H, 8.02; F, 5.21. Found: C, 69.14; H, 8.13; F, 5.11.

From 442 mg crude 2b, 4.5 ml pyridine and 2.3 ml acetic anhydride, 361 mg crude 4,17β-diacetoxy-5-fluoro-5α-androstan-3-one (5) was obtained, having one major and four minor spots on tlc. On chromatography of 350 mg of this sample, 103 mg pure diacetate was eluted by 5% ether-benzene. Mp: 192-193°, sealed tube [lit. 189-193° (11)]; ir: ν(KBr, cm^{-1}) 1755 (acetate C=O), 1735 (C_3=O), 1090, 1078, 1045, 1030 (C-F: 1110-1000); nmr: see Table V; rd (1.64 x 10^{-5}M, dioxane [θ] 25°) (589) 143, (578) 150, (546) 171, (436) 296, (365) 454. Anal. Calc'd for $C_{23}H_{33}O_5F$: C, 67.63; H, 8.14; F, 4.65. Found: C, 67.63; H, 8.17; F, 4.31.

The same diacetate (5, 85 mg) was obtained from 89 mg crude 3c. Chromatography on silica gel gave 50% yield of pure 5, eluted by 10% ether-benzene.

Stability of the acetates:

Melted acetates were allowed to re-solidify to white solids, the uv spectra of which showed no significant absorption. Infrared spectra of the compounds, taken after heating overnight at 100° in a vacuum drying apparatus, were identical with the spectra of pure acetates. The uv spectra of the acetates, dissolved in 15% methanolic NaOH, gave λmax at 317 nm for the monoacetate and 321 nm for the diacetate; these absorptions are typical for basic solutions of diosphenols (17) which would result from combined hydrolysis-dehydrofluorination of the acetates.

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