Regiospecific Syntheses of Modified Steroid Hormones. Part VI.[1] α-, α′-, and β-Mode Reactions of Hydrogen Halides with 1,2-Epoxy- and 4,5-Epoxy-3-oxo-androstanes and -estranes

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The reaction of **A/B** *cis*-4β,5β-epoxy-17β-hydroxyandrostan-3-one acetate **1***b* with hydrogen fluoride in chloroform gave 5α-fluoro-4α,17β-dihydroxyandrostan-3-one acetate **10***b* by β-mode oxirane opening to **10***a*, followed by epimerization at C-4. Reactions of **A/B** *cis*-α,β-epoxyketones **1***a* and **1***c* in acetone containing aqueous hydrogen chloride resulted in α-mode regiospecific oxirane opening, followed by β-dehydration to 4-chloro-4-en-3-ones **4***a* and **4***c*. Reaction of hydrogen chloride in "10%" ethanol–chloroform with 4β,5β-epoxy-17β-hydroxyandrostan-3-one **1***a* gave non-regioselectively **3***a* and **4***a* (α:α′, 1:1), whereas the reactions with 4α,5α-epoxy-17β-hydroxyandrostan-3-one acetate **2**, 1α,2α-epoxy-17β-hydroxy-5α-androstan-3-one **6***a*, and 1β,2β-epoxy-17β-hydroxy-5α-androstan-3-one acetate **5** were α-mode regiospecific. Epoxyketone **5** was readily converted to the *trans*-diequatorial 2α-chloro-1β,17β-dihydroxy-5α-androstan-3-one acetate **7**. The reactions of hydrogen fluoride with 4β,5β-epoxy-17β-hydroxy androstan-3-one **1***a* in "10%" ethanol–chloroform or in *N,N*-dimethylformamide, and with 1α,2α-epoxy-17β-hydroxy-5α-androstan-3-one **6***a* in *N,N*-dimethylformamide were α′-regioselective. Mechanisms are proposed for the observed α-, β-, and α′-mode reactions of hydrogen halides with steroidal α,β-epoxyketones **1**, **2**, **5**, and **6**.

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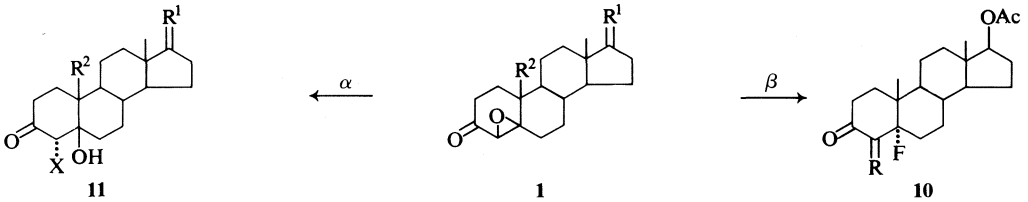
La réaction de l'acétate de l'époxy-4β,5β hydroxy-17β androstanone-3 **A/B** *cis* (**1***b*) avec l'acide fluorhydrique dans le chloroforme conduit à l'acétate du fluoro-5α dihydroxy-4α,17β androstanone-3 (**10***b*); cette transformation s'effectue par une ouverture du type β de l'oxiranne conduisant au produit (**10***a*) qui s'épimérise ensuite en position C-4. La réaction des époxy-α,β cétones **A/B** *cis* **1***a* et **1***c* dans l'acétone contenant de l'acide chlorhydrique aqueux conduit à des ouvertures régiospécifiques de l'oxiranne par un mode α; ces ouvertures sont suivies par une déshydration-β fournissant les chloro-4 èn-4 one-3 **4***a* et **4***c*. L'acide chlorhydrique dans un mélange éthanol–chloroforme à 10% réagit avec l'époxy-4β,5β hydroxy-17β androstanone-3 (**1***a*) et conduit d'une façon non-régiosélective aux produits **3***a* et **4***a* (α:α′, 1:1) alors que les réactions de l'acétate de l'époxy-4α,5α hydroxy-17β androstanone-3 (**2**), de l'époxy-1α,2α hydroxy-17β androstane-5α one-3 (**6***a*) et de l'acétate de l'époxy-1β,2β hydroxy-17β androstane-5α one-3 se produisent d'une façon régiospécifique avec un mode α. L'époxycétone **5** se transforme rapidement en produit *trans* diéquatorial, acétate de chloro-2α dihydroxy-1β,17β androstane-5α one-3 (**7**). Les réactions de l'acide fluorhydrique avec l'époxy-4β,5β hydroxy-17β androstanone-3 (**1***a*) dans un mélange d'éthanol–chloroforme à 10% ou dans la *N,N*-diméthylformamide et avec l'époxy-1α,2α hydroxy-17β androstane-5α one-3 (**6***a*) dans la *N,N*-diméthylformamide sont régiosélectives α′. On propose des mécanismes pour les modes de réaction α,β et α′ observés lors des réactions des halogénures d'hydrogène avec les cétones stéroïdales α,β époxydées **1**, **2**, **5** et **6**.

[Traduit par le journal]

Introduction

Recently we reported reactions of hydrogen halides with steroidal 4,5-epoxy-3-ones (1). These studies have led to revision of several erroneous structure assignments based on mechanistic misconceptions (1*a*, 2) and the development of regiospecific routes, via 19-norsteroid intermediates, to 2-fluoro and 4-bromo- ring-A-aromatic steroids (3*a* and *b*). The present paper gives a full account of these reactions and extends the study to 1α,2α- and 1β,2β-epoxy-5α-androstan-3-ones. The α,β-epoxyketones **1**, **2**, **5**, and **6**, (Schemes 1 and 3) were selected as model compounds in which stereoelectronically normal *trans*-diaxial oxirane cleavage could occur either by α-mode, or by β-mode reactions. These conformational determinants did, however, not account for all the observed reactions: several "abnormal" re-

[1]Part V, see ref. 3*c*.



11

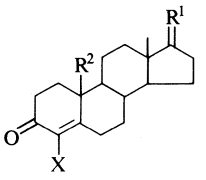
a R^1 = α-H, β-OH; R^2 = Me; X = Cl
b R^1 = α-H, β-OH; R^2 = H; X = Cl
c R^1 = α-H, β-OH; R^2 = H; X = Br

1

a R^1 = α-H, β-OH; R^2 = Me
b R^1 = α-H, β-OAc; R^2 = Me
c R^1 = α-H, β-OH; R^2 = H
d R^1 = α-H, β-OH; R^2 = OH
e R^1 = O; R^2 = OH

10

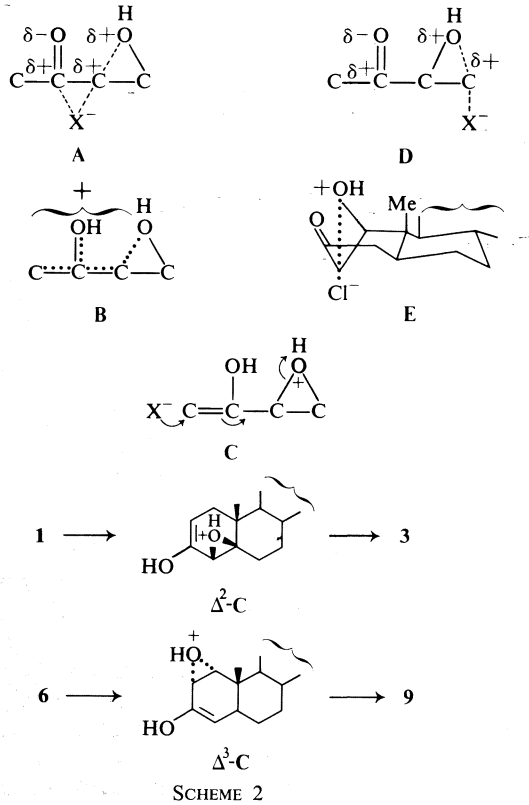
a R = α-H, β-OH
b R = α-OH, β-H
c R = α-OD, β-H
d R = α-OAc, β-H



4

a R^1 = α-H, β-OH; R^2 = Me; X = Cl
b R^1 = α-H, β-OAc; R^2 = Me; X = Cl
c R^1 = α-H, β-OH; R^2 = H; X = Cl
d R^1 = α-H, β-OH; R^2 = H; X = Br
e R^1 = α-H, β-OH; R^2 = OH; X = Br
f R^1 = O; R^2 = OH; X = Br

SCHEME 1

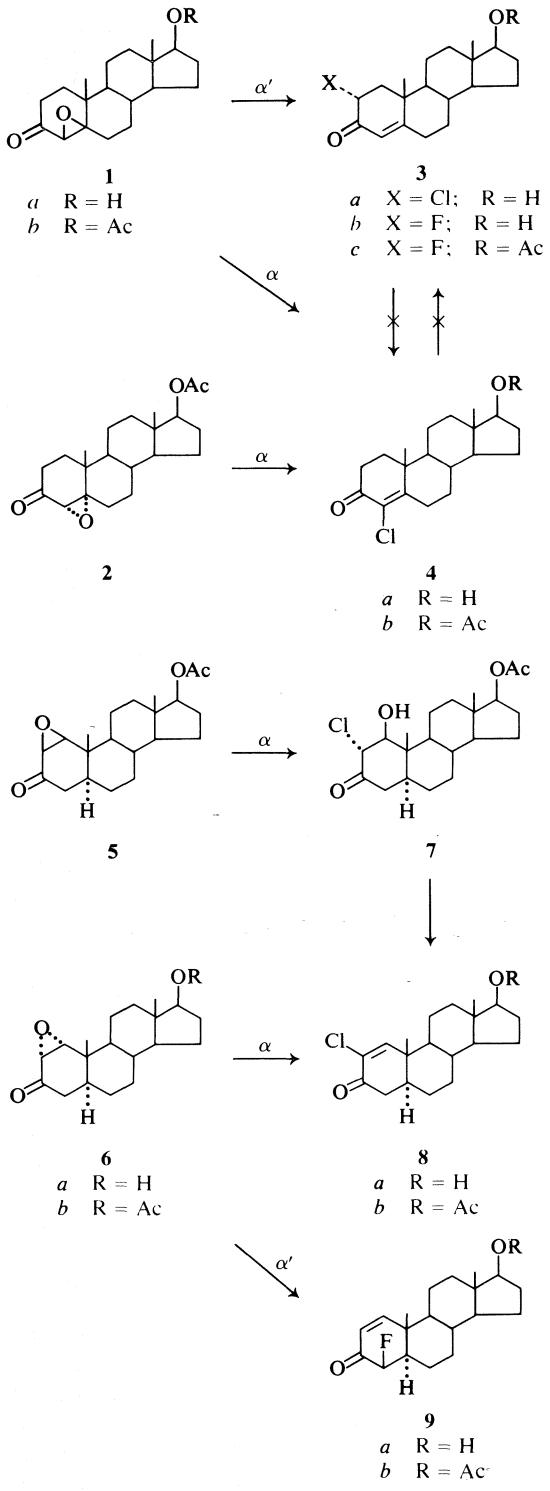


SCHEME 2

actions occurred, such as facile *trans*-diequatorial α-mode oxirane cleavage by chloride; and α′-mode *cine*-halogenations by chloride (non-regioselective) and by fluoride (regioselective). The present study is addressed to mechanistic interpretations of these reactions with regard to halide polarizabilities and steric requirements, as well as the interaction of neighboring orbitals in nucleophilic oxirane cleavage (Scheme 2).

Results and Discussion

Reaction of **A**/**B** *cis*-4β,5β-epoxy-17β-hydroxyandrostan-3-one acetate **1***b* with hydrogen fluoride in neat chloroform proceeded by β-mode (Scheme 1) and gave, as the only isolable product, the 5α,4α-fluorohydrin **10***b*, ν_{max} (KBr) 3462, 3510 (OH), 1731 (17-ester C=O), 1715 cm^{-1} (C(3)=O); δ($CDCl_3$) 4.71(1H, t, J = 7.5 Hz, 17α-H), 4.64 (1H, q, J_{H_a,F_a} = 33 Hz (4), J_{HH} = 6.5 Hz, 4-H), 3.45 (1H, d, J_{HH} = 6.5 Hz, 4-OH), 1.13 (3H, s, 19-H_3), 0.89 (3H, s, 18-H_3). The 6.5 Hz coupling between the 4-H and the 4-OH proton was removed by spin decoupling; as well as by conversion of **10***b* to the diacetate **10***d*, or by exchange of the hydroxyl proton of **10***b* for deuterium in **10***c*, ν_{max} (KBr) 2580, 2405 cm^{-1}



SCHEME 3

(associated OD (5)). The OH stretching band at 3510 cm^{-1} of the 5α,4α-fluorohydrin **10***b* was concentration independent in the range 0.005–0.015 *M* in carbon tetrachloride solution, as was the C=O stretching band at 1715 cm^{-1}. These data are interpreted as supporting an OH···F hydrogen bonded structure for the *cis*-fluorohydrin **10***b*. The β-mode reaction is envisaged to produce initially the *trans*-diaxial fluorohydrin **10***a*, via a transition state **D** (Scheme 2) of the protonated oxirane bearing a partial positive charge at C-5, where it can be more readily accommodated than at C-4, adjacent to the positive end of the carbonyl dipole. A fractional positive charge at C-5 in **D** could, in part, be the consequence of the positive charge on the leaving group, the protonated oxirane oxygen (6*a*). The nature of the transition state **D** is akin to that proposed by Diggle and co-workers (6*b*) for acid catalyzed ring opening of steroidal 5α,6α-epoxides in largely non-aqueous medium (butanone containing 0.05 *N* perchloric acid); bond-breaking at C-6 in the protonated oxirane was considered more advanced than bond-making, with a partial positive charge developing at C-6 in the transition state. A similar mechanism would allow a close approach to C-5 of the small nucleophile of low polarizability F^- (or its equivalent HF_2^-) from the steroid's hindered α-side. The *cis*-5α,4α-fluorohydrin **10***b* is regarded as the end product of facile acid-catalyzed epimerization at C-4 of the primary reaction product, the *trans*-diaxial 5α,4β-fluorohydrin **10***a*.[2] In contrast to the β-mode regioselectivity of the hydrogen fluoride reaction with epoxyketone **1***a*, hydrogen chloride in chloroform reacted α-mode regiospecifically with **1***a*, giving 4-chlorotestosterone **4***a*.

Attempted reaction of hydrogen fluoride with **A**/**B** *cis*-epoxyketone **1***c* in the presence of a small amount of water (acetone containing aqueous 30% hydrofluoric acid; 1.8 *N* in HF) led to re-

[2]The reaction of boron trifluoride etherate in benzene with 4β,5β-epoxycholestan-6-one and 5β,6β-epoxycholestan-4-one afforded respectively the *trans*-diaxial fluorohydrin 4β-fluoro-5β-hydroxycholestan-6-one and the *trans*-diequatorial fluorohydrin 6α-fluoro-5β-hydroxycholestan-4-one (7). In contrast to the predictable instability of the axial C-4 carbinol in **10***a*, the configurations of the tertiary C-5 carbinols in the heteroannular cholestanone β,α-fluorohydrins are stable. These β-regiospecific *trans*-oxirane cleavages are thus akin to the *trans*-oxirane opening of **1***a* to **10***a* via **D**.

covery of **1***c*, reflecting the expected lowered nucleophilicity of fluoride on hydration (8). Hydrogen chloride, however, reacted under similar conditions (acetone containing aqueous 10 *N* hydrochloric acid; 1.0 *N* in HCl) with the **A**/**B** *cis*-epoxyketone **1***a* α-mode regiospecifically, affording 4-chlorotestosterone **4***a*. That this reaction proceeds through the intermediate *trans*-diaxial 4α,5β-chlorohydrin **11***a* is evidenced by the isolation of the corresponding 4α,5β-chlorohydrin **11***b* after reaction of **A**/**B** *cis*-19-norepoxyketone **1***c* with hydrochloric acid in acetone (0°, 15 min). The analogous 19-nor-4α,5β-bromohydrin **11***c* was obtained by reaction of **1***c* with hydrogen bromide in acetone at 20° for 15 min, whereas reaction at 57° for 1 h of either the α,β-epoxyketone **1***c* or the β,α-bromohydrin **11***c* afforded 4-bromo-19-nortestosterone **4***d*. The α-mode regiospecific oxirane cleavage of the **A**/**B** *cis*-10β-hydroxyepoxyketones **1***d* and **1***e* with hydrogen bromide was utilized in the regiospecific syntheses of 4-bromo-17β-estradiol and -estrone via 19-norsteroid intermediates **4***e* and **4***f* (3*b*). The regiospecific α-mode oxirane opening of the **A**/**B** *cis*-epoxyketones **1***a*, **1***c*, **1***d*, and **1***e* was envisaged to pass through a transition state **A** stabilized by orbital overlap with carbonyl, and the observed difference in α vs. β regioselectivity between hydrogen chloride and hydrogen fluoride (in chloroform) was viewed as a reflection of the polarizability of chloride, in contrast to fluoride (1*b*).

Reaction of **A**/**B** *cis*-4β,5β-epoxy-17β-hydroxyandrostan-3-one **1***a* in "10%" ethanol–chloroform with hydrogen chloride (3 min, 23°) was non-regioselective, affording a 1:1 mixture of the α-mode product 4-chlorotestosterone **4***a* and the α′-mode product 2α-chlorotestosterone **3***a* (Scheme 3).[3] This finding could suggest as an intermediate a delocalized allylic cation **B**, which is attacked by nucleophile at α and α′ (9), however, such a rationalization of the non-regioselectivity would involve the unwarranted presumption that the charge distribution in **B** would not be rendered unsymmetrical by overlap with the C-5β oxygen. The observed non-regioselectivity may reflect competing reactions: α-mode oxirane opening **A** at C-4α of the 4β,5β-epoxyketone **1***a* by chloride assisted by neighboring orbital overlap with carbonyl (10), and concurrent α′-mode reaction of chloride at C-2α of the Δ^2-enol **C** of **1***a* concomitant with opening of the protonated 4β,5β-oxirane and fast β-elimination in the resulting 5β-hydroxy-Δ^3-enol.

The plausibility of these mechanisms, **A** and **C**, for the concurrent α- and α′-mode reactions of the **A**/**B** *cis*-epoxyketone **1***a* with hydrogen chloride is supported by the finding that hydrogen fluoride, in contrast to hydrogen chloride, reacted α′-mode regioselectively with **1***a* in "10%" ethanol–chloroform (3.5 min, 43°), or in *N*,*N*-dimethylformamide (22 *N*, 3 h, 23°) affording 2α-fluorotestosterone **3***b* as the sole isolable product. In contrast to the polarizable nucleophile Cl^- with a relatively large bonding orbital, the small and non-polarizable F^- would not be capable of orbital overlap (as in **A**) and thus oxirane cleavage adjacent to carbonyl by fluoride would be precluded. In the presence of protic solvent, solvated fluoride would not be sufficiently nucleophilic to effect β-mode oxirane opening **D** and due to its solvent shell it would encounter hindrance in the approach to C-5α in the **A**/**B** *cis*-epoxyketone **1***a*. The α′-mode *cine*-fluorination was exploited in the regiospecific synthesis of 2α-fluoro-10β-hydroxyestr-4-ene-3,17-dione from 4β,5β-epoxy-10β-hydroxyestr-4-ene-3,17-dione **1***e*, the key intermediate in the synthesis of 2-fluoroestrone via 19-norsteroid intermediates (1*a*, 3*a*).

The **A**/**B** *trans*-1α,2α-epoxy-3-one **6***a* gave the α′-mode reaction product **9***a* with 22 *N* hydrogen fluoride in *N*,*N*-dimethylformamide. The mechanism of the α′-mode fluorination of **6***b* to **9***b*, proposed by Kerb and co-workers (11) (rearrangement involving fluoride migration) is implausible and contradicted by available experimental evidence (1*a*). Plausible reactive intermediates in the α′-mode reactions of epoxyketones **1** and **6** are the respective enols Δ^2-**C** and Δ^3-**C** protonated on oxirane oxygen (Scheme 2), which give rise to the halogen configurations observed in the products **3** and **6** on nucleophilic displacement by halide entering *trans* to the oxonium leaving group. Precedents for *trans* S_N2' type reactions are the displacement by hy-

[3]The two products **3***a* and **4***a* were shown not to be interconvertible by migration of chloride. The α-mode chlorohydrin 4α-chloro-5β,17β-dihydroxyestran-3-one **11***b* gave 4-chloro-19-nortestosterone **4***c* on reaction with hydrogen chloride in "10%" ethanol–chloroform, which rules out α,β-chlorohydrins **11** as intermediates in the α′-mode reaction.

dride in diastereomeric 1,3-*t*-butylpropargyl sulfonates (12*a*) and acylolyzes of steroidal α-bromoketones (12*b*).[4]

In contrast to the α′-mode reaction of hydrogen fluoride with **A/B** *trans*-1α,2α-epoxy-3-one **6***a*, its reaction with hydrogen chloride in "10%" ethanol–chloroform proceeded regiospecifically by α-mode, as did the same reaction with **A/B** *trans*-4α,5α-epoxy-3-one **2**. These α-mode regiospecific reactions of **6***a* and **2**, as contrasted with the non-regioselective reaction of the **A/B** *cis*-4β,5β-epoxy-3-one **1***a* with hydrogen chloride, may reflect a relatively more hindered approach of solvated chloride to C-4α in the **A/B** *cis*-epoxyketone **1***a* than to C-2β and C-4β in the **A/B** *trans*-epoxyketones **6***a* and **2**. Consequently, the α′-mode reaction can successfully compete with the normally favored α-mode reaction, when the latter is sterically impeded, as in **1***a*, provided the reaction milieu is favorable to enolization.

In contrast to the **A/B** *trans*-epoxyketones **2** and **6***a*, in which α-mode oxirane opening by hydrogen chloride leads to the stereoelectronically normal *trans*-diaxial product, the **A/B** *trans*-1β,2β-epoxy-3-one **5** would give the diaxial chlorohydrin if it reacted by β-mode, which was not realized. In fact, the reaction of **5** with hydrogen chloride in "10%" ethanol–chloroform was fast (1 min, 23°) and α-mode regiospecific, affording the *trans*-diequatorial chlorohydrin **7** together with its dehydration product, the 2-chloro-enone **8**.

An α-mode oxirane opening in epoxyketone **5** via a transition state with ring **A** in a half-boat conformation **E**, followed by conformational change to the diequatorial chlorohydrin **7**, would have to overcome severe non-bonded interactions in the near-eclipsed conformation of the incipient chlorohydrin hydroxyl and the C-19 methyl, as well as the hindrance by H-5α to the approach of chloride in forming the "flagpole" bond at C-2α. This mechanism would therefore not be conducive to a fast reaction.

[4]Bordwell (13*a*–*c*) has questioned whether the concerted S_N2' mechanism can be realized. He favored alternative step-wise carbonium-type mechanisms involving reversible formation of ion-pair intermediates, pointing out the difficulty of distinguishing experimentally between these mechanisms. The C=C bonds in the enols **Δ²-C** and **Δ³-C** are not akin to the unactivated C=C bonds discussed by Bordwell, and the C-halogen bond-making may well assist significantly in the bond-breaking of the protonated oxirane.

The facile diequatorial α-mode oxirane opening of epoxide **5** can be envisaged to pass through a transition state **A** sufficiently stabilized to compensate for the oxirane conformation in **5**, which is stereoelectronically unfavorable for α-mode ring opening. Transition state **A** reflects the mechanistic concepts of Dewar (10*a*) or Streitwieser (13*b*). This reaction is stereochemically akin to the accelerated S_N2 reaction of the conformationally fixed axial α-chloroketone *trans*-2-chloro-4-*t*-butyl-cyclohexanone, in which both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were found to be lowered relative to these parameters in *trans*-3-*t*-butylchlorocyclohexane (10*d*). The expected lower activation energy due to delocalized bonding in transition state **A**, although partly offset by entropic loss reflecting the geometric requirements of the three-center reaction, would account for the observed fast diequatorial oxirane opening of epoxyketone **5** to chlorohydrin **7**.

Experimental

Melting points were determined with a Thomas microstage and are corrected. The u.v. spectra were recorded with a Cary 14 spectrophotometer and the i.r. spectra with a Beckman IR-9 spectrophotometer, n.m.r. spectra were determined at 60 MHz with a Varian A60A spectrometer, with tetramethylsilane as internal standard; o.r.d. and c.d. measurements were made with a Jasco ORD/UV 5 spectropolarimeter with c.d. attachment. Microanalyses were performed by Huffman Laboratories, Wheatridge, Colorado. Mass spectral analyses were performed by Morgan Schaffer Corporation, Montreal. Nylon tubing used for dry columns was obtained from Walter Coles and Co., 47/49 Tanner Street, London, England. Dry column adsorbent was Woelm silica gel, obtained from Waters Associates, Framingham, Massachusetts, pre-equilibrated with 10% by weight of benzene – ethyl acetate – ethanol (80:20:1); t.l.c. was performed on Eastman "Chromagram" silica gel with benzene – ethyl acetate – ethanol (80:20:1) as the developing solvent, unless otherwise specified.

4β,5β-Epoxy-17β-hydroxyandrostan-3-one (***1a***)

Melting point 155–158° (lit. (14) 157–158°, (17) 156–157°); δ ($CDCl_3$) 3.00 (1H, s, 4α-H), 3.72 (1H, t, J = 7.5 Hz, 17α-H), 1.07 (3H, s, 19-H_3), and 0.69 (3H, s, 18-H_3); o.r.d. (*c* 0117, chloroform) $[\Phi]_{700}$ + 260°, $[\Phi]_{589}$ + 417°, $[\Phi]_{334}$ + 9750°, $[\Phi]_{310}$ 0°, $[\Phi]_{290}$ −7580°; $[\alpha]_D^{23}$ + 137° (lit. (14) + 136°, (17) + 145°); c.d. (0.00158 *M* in methanol) $\Delta\varepsilon_{313}$ + 3.80; t.l.c. R_f 0.58; mass spectrum *m/e* 304 (M^+).

4β,5β-Epoxy-17β-hydroxyandrostan-3-one Acetate (***1b***)

ν_{max} (CCl_4) 1735 (17-ester C=O), 1715 (C(3)=O), and 1245 cm^{-1} (17-ester C—O); δ ($CDCl_3$) 4.67 (1H, t, J = 7.5 Hz, 17α-H), 3.00 (1H, s, 4α-H), 2.03 (3H, s, 17-OAc), 1.15 (3H, s, 19-H_3), and 0.82 (3H, s, 18-H_3); o.r.d. (*c* 0.052, chloroform) $[\Phi]_{700}$ +261°, $[\Phi]_{589}$ +460°, $[\Phi]_{329}$ +

11 000°, $[\Phi]_{309}$ 0°, $[\Phi]_{284}$ −10 600°; $[\alpha]_D^{23}$ +134° (lit. (17) +130°); c.d. (0.00134 *M* in chloroform) $\Delta\varepsilon_{310}$ +4.30 (lit. (15) +4.2); t.l.c. R_f 0.82.

*4α,5α-Epoxy-17β-hydroxyandrostan-3-one Acetate (**2**)*

Melting point 171–172° (lit. (17) 172–173°); ν_{max} ($CHCl_3$) broad 1722 cm^{-1} (C(3)=O and 17 ester C=O); δ ($CDCl_3$) 4.70 (1H, t, J = 7.5 Hz, 17α-H), 3.05 (1H, s, 4β-H), 2.04 (3H, s, 17-OAc), 1.07 (3H, s, 19-H_3), and 0.82 (3H, s, 18-H_3); o.r.d. (*c* 0.178, dioxane) $[\Phi]_{700}$ −135°, $[\Phi]_{589}$ −194°, $[\Phi]_{342}$ −8400°, $[\Phi]_{332}$ −8760°, $[\Phi]_{312}$ 0°, $[\Phi]_{287}$ +10 000°; c.d. (0.00515 *M* in dioxane) $\Delta\varepsilon_{311}$ −3.50, shoulder at 320 nm; t.l.c. R_f 0.82.

*1β,2β-Epoxy-17β-hydroxy-5α-androstan-3-one Acetate (**5**)*

Melting point 178–179° (lit. (18) 179–180°); ν_{max} (KBr) 1730 (C(3)=O and 17 ester C=O) and 1245 cm^{-1} (17 ester C—O); δ ($CDCl_3$) 4.68 (1H, t, J = 7.5 Hz, 17α-H), 3.50 (1H, d, J = 3.5 Hz, 1-H), 3.12 (1H, d, J = 3.5 Hz, 2-H, $w_{1/2}$ 3 Hz), 2.07 (3H, s, 17-OAc), 1.09 (3H, s, 19-H_3), and 0.86 (3H, s, 18-H_3); c.d. (0.00527 *M* in dioxane) $\Delta\varepsilon_{302}$ −0.23; $[\alpha]_D^{23}$ +43.7° (lit. (18) +38.5°); t.l.c. R_f 0.83; mass spectrum *m/e* 347 (M^+).

*1α,2α-Epoxy-17β-hydroxy-5α-androstan-3-one (**6a**)*

Melting point 159–161° (lit. (20) 161–162°); ν_{max} (KBr) 1712 cm^{-1} (C(3)=O); δ ($CDCl_3$) 3.72 (1H, t, J = 7.5 Hz, 17α-H), 3.58 (1H, d, J = 3.5 Hz, 1-H), 3.27 (1H, d, J = 3.5 Hz, 2-H) 0.93 (3H, s, 19-H_3), and 0.78 (3H, s, 18-H_3); o.r.d. (*c* 0.08, dioxane) $[\Phi]_{589}$ +178°, $[\Phi]_{328}$ +6030°, $[\Phi]_{310}$ 0°, $[\Phi]_{278}$ −5800°; c.d. (0.00277 *M* in dioxane) $\Delta\varepsilon_{310}$ +2.08; $[\alpha]_D^{23}$ +58.7°; t.l.c. R_f 0.50; mass spectrum *m/e* 304 (M^+).

*1α,2α-Epoxy-17β-hydroxy-5α-androstan-3-one Acetate (**6b**)*

Melting point 160–161° (lit. (20) 160–161°); δ ($CDCl_3$) 3.73 (1H, t, J = 7.5 H, 17α-H), 3.57 (1H, d, J = 3.5 Hz, 1-H), 3.25 (1H, d, J = 3.5 Hz, 2-H), 0.90 (3H, s, 19-H_3), and 0.77 (3H, s, 18-H_3); t.l.c. R_f 0.78.

*5α-Fluoro-4α,17β-dihydroxyandrostan-3-one 17-Acetate (**10b**)*

Anhydrous hydrogen fluoride was bubbled into chloroform (50 ml, ethanol-free) for 7 min. A solution of 4β,5β-epoxy-17β-hydroxyandrostan-3-one acetate **1***b* (1.365 g) in chloroform (15 ml, ethanol-free) was added to the hydrogen fluoride solution at 25°. After 2 h a portion (47 ml) was poured into sodium hydroxide (2.0 *N*, 200 ml, 0°), extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated. The residue was placed on a column (2 × 77 in.) of dry column adsorbent (1020 g) (21). The column was developed with benzene–ethyl acetate–ethanol (80:20:1). The fraction R_f 0.18 to 0.44 was rechromatographed on a column (1 × 65 in.) of dry column adsorbent (290 g) and gave **10***b* (22%), needles of m.p. 186–189° (from ethyl acetate–ligroin); o.r.d. (*c* 0.236, dioxane) $[\Phi]_{700}$ 0°, $[\Phi]_{589}$ +9°, $[\Phi]_{298}$ −575°, $[\Phi]_{282}$ 0°, $[\Phi]_{254}$ +770°; c.d. (0.00646 *M* in dioxane) $\Delta\varepsilon_{284}$ −0.88; t.l.c. R_f 0.57.

Anal. Calcd. for $C_{21}H_{31}FO_4$: C, 68.82; H, 8.53; F, 5.19. Found: C, 68.66; H, 8.08; F, 5.04.

The diacetate **10***d* was prepared in the usual manner, m.p. 189–193° (from methanol–water); ν_{max} ($CHCl_3$) 1751 (4 ester C=O), 1733 (17 ester C=O), 1255 cm^{-1} (ester C—O); δ ($CDCl_3$) 5.75 (1H, d, $^3J_{H_a,F_a}$ = 33 Hz, 4-H), 4.68 (1H, t, J = 7.5 Hz, 17α-H), 2.25 (3H, s, 4-OAc), 2.05 (3H, s, 17-OAc), 1.10 (3H, s, 19-H_3), and 0.82 (3H, s, 18-H_3); c.d. (0.00823 *M* in dioxane) $\Delta\varepsilon_{302}$ +0.098, shoulder at 308 nm, $\Delta\varepsilon_{272}$ −0.088; t.l.c. R_f 0.72.

*4-Chlorotestosterone (**4a**)*

(*a*) Hydrogen chloride was bubbled into chloroform (ethanol-free) for 15 min (0.6 *N* HCl). To the stirred hydrogen chloride solution (19.0 ml) was added 4β,5β-epoxy-17β-hydroxyandrostan-3-one **1***a* (1.008 g) in chloroform (15.0 ml, ethanol-free) at 0°. After 10 min at 0°, a 3.5-ml portion of the mixture was poured into aqueous sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated. The residue contained starting material **1***a* and 4-chlorotestosterone **4***a* (33% by u.v.). After 35 min at 0°, a 3.5-ml portion was worked up and yielded 4-chlorotestosterone **4***a* (67% by u.v.), m.p. 188–189° (from acetone–ligroin) (lit. (14, 16) 188–189°); λ_{max} (EtOH) 256 nm (ε 14 700); t.l.c. R_f 0.43.

(*b*) To a stirred solution of **1***a* (0.350 g) in acetone (8.6 ml) at 23° was added hydrochloric acid (10 *N*, 0.86 ml). After 40 min at 23°, the reaction mixture was worked up as in *a*, yielding **4***a* (99% by u.v.) identical (t.l.c., i.r., u.v., m.p.) with **4***a* from *a*.

*4α-Chloro-5β,17β-dihydroxyestran-3-one (**11b**)*

To a stirred solution of 4β,5β-epoxy-17β-hydroxyestran-3-one **1***c* (19) (0.604 g) in acetone (2.0 ml) at 0° was added aqueous hydrochloric acid (10 *N*, 0.43 ml). After 10 min at 0°, the crystalline precipitate formed was filtered and washed with acetone, yielding **11***b* (30%), m.p. 189–190°; ν_{max} (KBr) 3480 and 3270 (OH) and 1735 cm^{-1} (C(3)=O); δ (DMSO) 4.10 (1H, s, 4β-H), and 0.67 (3H, s, 18-H_3); o.r.d. (*c* 0.120, methanol) $[\Phi]_{700}$ +127°, $[\Phi]_{589}$ +127°, $[\Phi]_{315}$ +3720°, $[\Phi]_{294}$ 0°, $[\Phi]_{272}$ −3370°; c.d. (0.00352 *M* in methanol) $\Delta\varepsilon_{303}$ +1.42; m.p. 198–200°.

Anal. Calcd. for $C_{18}H_{27}ClO_3$: C, 66.14; H, 8.34; Cl, 10.85. Found: C, 65.61; H, 8.60; Cl, 10.51.

A second crop of crystals (15%) was identical (i.r.) with the first crop of **11***b*. The filtrate was worked up yielding a material (0.265 g) which showed the 4-chloro-4-en-3-one chromophore λ_{max} (EtOH) 256 nm (ε 6800).

*4α-Bromo-5β,17β-dihydroxyestran-3-one (**11c**)*

To a stirred solution of 4β,5β-epoxy-17β-hydroxyestran-3-one **1***c* (19) (0.6804 g) in acetone (10 ml) at 20° was added aqueous hydrobromic acid (30%, 1.2 ml). After 15 min at 20°, the crystalline precipitate formed was filtered and washed with acetone, yielding **11***c* (45%), m.p. 128–129°; ν_{max} (KBr) 3487 and 3270 (OH) and 1714 cm^{-1} (C(3)=O); δ (DMSO) 4.13 (1H, s, 4β-H) and 0.68 (3H, s, 18-H_3); o.r.d. (*c* 0.034, methanol) $[\Phi]_{700}$ +260°, $[\Phi]_{589}$ +260°, $[\Phi]_{332}$ +5600, $[\Phi]_{287}$ −8860°, $[\Phi]_{278}$ −9300°; c.d. (0.00108 *M* in dioxane) $\Delta\varepsilon_{308}$ +3.52, $\Delta\varepsilon_{311}$ +3.06 (inflection), $\Delta\varepsilon_{313}$ +3.46 (inflection). A second crop of crystals (24%) was identical (i.r., o.r.d.) with the first crop of **11***c*.

Anal. Calcd. for $C_{18}H_{27}BrO_3$; C, 58.22; H, 7.33; Br. 21.52. Found: C, 58.43; H, 7.35; Br, 21.22.

*4-Bromo-19-nortestosterone (**4d**)*

(*a*) To a solution of 4α-bromo-5β,17β-dihydroxy estran-3-one **11***c* (0.145 g) in acetone (12.0 ml) was added aqueous hydrobromic acid (30%, 2.0 ml) and the mixture heated to 60° for 75 min. After cooling to 23°, the crystal-

line **4***d* was filtered (41% by u.v.). The product was placed on a column of Fluorisil (6.0 g). Elution with heptane–acetone (19:1) gave **4***d*, m.p. 149–152° (lit. (22) 125–128°); λ_{max} (EtOH) 262 nm (ε 11 800) (lit. (22) 262 nm (ε 8000)); ν_{max} (KBr) 1677 (conjugated C=O) and 1576 cm^{-1} (conjugated C=C); δ ($CDCl_3$) 0.77 (3H, s, 18-H_3); t.l.c. (Eastman "Chromagram" alumina sheets, benzene – ethyl acetate, 4:1) R_f 0.49.

(*b*) To a solution of 4β,5β-epoxy-17β-hydroxyestran-3-one **1***c* (0.540 g) in acetone (4.0 ml) was added aqueous hydrobromic acid (30%, 1.0 ml). The mixture was warmed to 60° for 1 h, and water was added to turbidity. The product **4***d* which crystallized was identical (t.l.c., u.v., i.r., n.m.r.) with **4***d* described in *a*.

*Attempted α-Mode Reaction of 4β,5β-Epoxy-17β-hydroxyestran-3-one (**1***c*) with Hydrogen Fluoride*

To a stirred solution of **1***c* (0.830 g) in acetone (3.0 ml) at 0° was added aqueous hydrofluoric acid (30%, 0.40 ml). After 3 h at 0°, the mixture was poured into sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated, yielding starting material **1***c*.

*4-Chlorotestosterone (**4***a*) and 2α-Chlorotestosterone (**3***a*) from 4β,5β-Epoxy-17β-hydroxyandrostan-3-one (**1***a*)*

To a stirred solution of 1.9 *N* hydrogen chloride in "10%" ethanol–chloroform (2.0 ml) was added at 23° **1***a* (0.063 g) in "10%" ethanol–chloroform (1.0 ml). After 1 min at 23°, the reaction mixture was poured into aqueous sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated, leaving a 1:1 mixture[5] of 4-chlorotestosterone **4***a* and 2α-chlorotestosterone **3***a* (by n.m.r.) which was placed on a column (1 × 22 in.) of dry column adsorbent (140 g) (21). The column was developed with benzene – ethyl acetate – ethanol (80:20:1). The fraction R_f 0.13 to 0.18 yielded **4***a*, m.p. 188–189°; λ_{max} (EtOH) 256 nm (ε 14 700); ν_{max} ($CHCl_3$) 3620 and 3450 (OH), 1688 (conjugated C=O), and 1582 cm^{-1} (conjugated C=C); δ ($CDCl_3$) 1.26 (3H, s, 19-H_3) and 0.80 (3H, s, 18-H_3); t.l.c. R_f 0.51. The fraction R_f 0.25 to 0.54 yielded **3***a*; λ_{max} (EtOH) 244 nm (ε 14 800) (from ether) (lit. (23) 243 nm (ε 14 500)); ν_{max} (KBr) 3500–3400 (OH), 1695 (conjugated C=O), 1618 (conjugated C=C) cm^{-1}, δ ($CDCl_3$) 5.90 (1H, broad s, 4-H), 4.70 (1H, q, J_{ae} = 5.5 Hz, J_{aa} = 14 Hz, 2β-H), 1.31 (3H, s, 19-H_3), and 0.79 (3H, s, 18-H_3); t.l.c. R_f 0.59.

*4-Chlorotestosterone Acetate (**3***c*) from 4α,5α-Epoxy-17β-hydroxyandrostan-3-one Acetate (**2**)*

To a stirred solution of 1.9 *N* hydrogen chloride in "10%" ethanol–chloroform (9.0 ml) was added at 23° **2** (0.300 g) in "10%" ethanol–chloroform (3.0 ml). After 1 min at 23°, a 4.0 ml portion of the mixture was worked up as usual, affording a mixture of **3***c* (66% by u.v.) and unreacted starting material **2** (25% by n.m.r.). Dry column chromatography gave **3***c*, m.p. 225–227° (from methanol–water) (lit. (16) 228–230°); λ_{max} (EtOH) 255 nm (ε 12 900) (lit. (16) 255 nm (ε 13 300)).

*2-Chloro-17β-hydroxy-5α-androst-1-en-3-one (**8***a*) from 1α,2α-Epoxy-17β-hydroxy-5α-androstan-3-one (**6***a*)*

To a stirred solution of 1.9 *N* hydrogen chloride in "10%" ethanol–chloroform (2.0 ml) was added at 23° **6***a* (0.063 g) in "10%" ethanol–chloroform (1.0 ml). After 1 min at 23° the reaction mixture was worked up as usual, affording **8***a* (82% by u.v.). This material was placed on a column (1 × 21 in.) of dry column adsorbent (140 g). This column was developed with benzene – ethyl acetate – ethanol (80:20:1) and yielded (R_f 0.25–0.81) **8***a*, m.p. 224–225° (from methanol) (lit. (24) 224–226°); λ_{max} (EtOH) 248 nm (ε 11 400); ν_{max} (KBr) 3510 (OH), 1693 (conjugated C=O), 1600 cm^{-1} (conjugated C=C); δ ($CDCl_3$) 7.41 (1H, s, 1-H), 3.73 (1H, t, *J* = 7.5 Hz, 17α-H), 1.10 (3H, s, 19-H_3), 0.80 (3H, s, 18-H_3); t.l.c. R_f 0.56.

*2-Chloro-17β-hydroxy-5α-androst-1-en-3-one Acetate (**8***b*) and 2α-Chloro-1β,17β-dihydroxy-5α-androstan-3-one 17-Acetate (**7**) from 1β,2β-Epoxy-17β-hydroxy-5α-androstan-3-one Acetate (**5**)*

To a stirred solution of 1.9 *N* hydrogen chloride in "10%" ethanol–chloroform (2.0 ml) was added **5** (0.700 g) in "10%" ethanol–chloroform (1.0 ml). After 1 min at 23°, the reaction mixture was worked up as usual, yielding a mixture of **8***b* (48% by u.v.) and **7** (50% by n.m.r.). The mixture was placed on a column (1 × 2 in.) of dry column adsorbent (140 g) and developed with benzene – ethyl acetate – ethanol (80:20:1). The fraction R_f 0.68 to 0.86 yielded **8***b*, m.p. 155–157° (from methanol) (lit. (24) 155.5–156.5°); λ_{max} (EtOH) 247 nm (ε 11 200); ν_{max} ($CHCl_3$) 3460 (OH), 1735 (17 ester C=O), and 1717 cm^{-1} (conjugated C=O); δ ($CDCl_3$) 7.40 (1H, s, 1-H), 4.63 (1H, t, *J* = 7.5 Hz, 17α-H), 2.06 (3H, s, 17-OAc), 1.10 (3H, s, 19-H_3), and 0.83 (3H, s, 19-H_3); t.l.c. R_f 0.89. The fraction from R_f 0.41 to 0.59 yielded **7** (52%), m.p. 220–222° (from diethyl ether); ν_{max} ($CHCl_3$) 3580 (OH), 1733 (17 ester C=O), and 1727 cm^{-1} (C(3)=O); δ ($CDCl_3$) 4.68 (1H, t, *J* = 7.5 Hz, 17α-H) 4.61 (1H, d, $J_{1\alpha,2\beta}$ = 9.5 Hz, 2-H), 3.60 (1H, d, $J_{1\alpha,2\beta}$ = 9.5 Hz, 1-H), 2.08 (3H, s, 17-OAc), 1.22 (3H, s, 19-H_3), and 0.80 (3H, s, 18-H_3); o.r.d. (*c* 0.032, methanol) $[\Phi]_{700}$ +97.3°, $[\Phi]_{589}$ +194°, $[\Phi]_{310}$ +3180°, $[\Phi]_{281}$ 0°, $[\Phi]_{262}$ −3300°; t.l.c. R_f 0.75; mass spectrum *m/e* 382 (M^+).

*2-Chloro-17β-hydroxy-5α-androst-1-en-3-one Acetate (**8***b*) from 2α-Chloro-1β,17β-dihydroxy-5α-androstan-3-one 17-Acetate (**7**)*

To a stirred solution of 1.9 *N* hydrogen chloride in "10%" ethanol–chloroform (2.0 ml) was added at 23° the 2α,1β-chlorohydrin **7** (0.015 g) in "10%" ethanol–chloroform (1.0 ml). After 2 min at 23° the reaction mixture was worked up as usual, affording a mixture of the 2-chloro-1-en-3-one **8***b* and starting material **7** in a 2:1 ratio (by u.v. and n.m.r.).

*Attempted Rearrangement of 4-Chlorotestosterone (**4***a*)*

To a stirred solution of 2.46 *N* hydrogen chloride in "10%" ethanol–chloroform (6.6 ml) was added 4-chlorotestosterone **4***a* (0.150 g) at 23°. After 7 min at 23° the reaction mixture was poured into sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried, and evaporated, yielding unchanged **4***a* (t.l.c., u.v., i.r., n.m.r.).

*4-Chloro-19-nortestosterone (**4***c*) from 4α-Chloro-5β,17β-dihydroxyestran-3-one (**11***b*)*

A solution of the chlorohydrin **11***b* (0.100 g) in "10%" ethanol–chloroform (11.0 ml) was added to a solution of

[5]The ratio α:α′ was 3:2 after 3 min reaction at 0° and 7:3 after 0.5 min reaction at 40°.

1.15 *N* hydrogen chloride in "10%" ethanol–chloroform (4.4 ml). The mixture was stirred at 21° for 7 min, poured into sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried, and evaporated, yielding **4***c* (25) (70% by u.v.), m.p. 220–222° (from methanol–water) (lit. (25) 220–223°); λ_{max} (EtOH) 255 nm (ε 13 500).

*Attempted Interconversion of 2α-Chlorotestosterone (**3a**) and 4-Chlorotestosterone (**4a**)*

To a stirred solution of 7.63 *N* hydrogen chloride in tetrahydrofuran (7.0 ml) was added a 1:1 mixture of **3***a* and **4***a* (0.358 g) in tetrahydrofuran (7.0 ml) at 0°. After 10 min at 0° the reaction mixture was poured into sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried, and evaporated, giving unchanged starting mixture (1:1) of **3***a* and **4***a*; δ ($CDCl_3$) 5.89 (0.50 H, s, 4-H) 4.20 (0.50 H, q, J_{ae} = 5.5 Hz, J_{aa} = 14 Hz, 2β-H), 1.3 (1.5 H, s, 19-H_3 of **3***a*), and 1.26 (1.5 H, s, 19-H_3 of **4***a*).

*2α-Fluorotestosterone (**3b**)*

(*a*) Anhydrous hydrogen fluoride was bubbled into "10%" ethanol–chloroform (68.2 ml) for 7 min, while the temperature rose to 43°. Two phases separated: the concentration of hydrogen fluoride was 44 *N* in the upper phase and 0.7 *N* in the lower phase. Powdered 4β,5β-epoxy-17β-hydroxyandrostan-3-one **1***a* (1.562 g) was added in one batch. A portion (17.0 ml) was removed after 1 min, poured into sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried, and evaporated. The product was placed on a column (1½ × 32 in.) of neutral alumina ("Woelm"), pre-equilibrated with water (6% by weight). The column was developed with benzene – ethyl acetate – ethanol (80:20:1) and gave (R_f 0.18 to 0.45) **3***b* (44%), m.p. 152–153° (lit. (26) 150–151°); λ_{max} (EtOH) 240 nm (ε 16 100); ν_{max} (KBr) 1698 (conjugated C=O), 1664 cm^{-1} (conjugated C=C); δ ($CDCl_3$) 5.79 (1H, d, $^4J_{HF}$ = 5 Hz, 4-H), 5.04 (1H, octet, $^2J_{HF}$ = 49 Hz, J_{aa} = 5.5 Hz, J_{ae} = 13 Hz, 2β-H), 3.67 (1H, t, *J* = 7.5 Hz, 17α-H), 1.30 (3H, s, 19-H_3), and 0.78 (3H, s, 18-H_3); o.r.d. (*c* 0.04, dioxane) $[\Phi]_{700}$ +480°, $[\Phi]_{589}$ +815°, $[\Phi]_{360}$ −2540°, $[\Phi]_{300}$ +13 700°; c.d. (0.00131 *M* in dioxane) $\Delta\varepsilon_{335}$ −2.60; t.l.c. R_f 0.47. This specimen of **3***b*, R=H) was identical (i.r., u.v., o.r.d., t.l.c., m.p.) with an authentic sample of 2α-fluorotestosterone **3***b* synthesized by an independent route (26).

(*b*) To a stirred solution of 22 *N* hydrogen fluoride in *N*,*N*-dimethylformamide, was added **1***a* (0.340 g). After 1 h at 23° the reaction mixture contained **3***b* (42% by n.m.r.) and starting material **1***a* (50% by n.m.r.). After 3 h at 23°, the reaction mixture was worked up yielding **3***b* (80% by n.m.r.), which was placed on a column (1 × 12 in.) of dry column adsorbent (84 g). The column was developed with benzene – ethyl acetate – enol (80:20:1), yielding **3***b* (65%), identical (i.r., u.v., o.r.d., t.l.c., m.p.) with the specimen from reaction *a*.

*2α-Fluorotestosterone Acetate (**3c**)*

Hydrogen fluoride was bubbled through a solution of 4β,5β-epoxy-17β-hydroxyandrostan-3-one acetate **1***a* (1.913 g, 5.56 mmol) in "10%" ethanol–chloroform (83.6 ml). Portions (8.8 ml) were removed at 1 min intervals, poured into sodium hydroxide (2.0 *N*, 0°), extracted with chloroform, washed with water, dried, and evaporated. The portions from 1 to 5 min gave unreacted **1***a* (as determined by n.m.r.). The 7-min portion yielded **3***c* (76% by n.m.r.), m.p. 179–181° (from methanol) (lit. (26) 180–182°); λ_{max} (EtOH) 240 nm (ε 14 800); ν_{max} (KBr) 1738 (17 ester C=O), 1704 (conjugated C=O), and 1618 cm^{-1} (conjugated C=C); t.l.c. R_f 0.69.

*4β-Fluoro-17β-hydroxy-5α-androst-1-en-3-one (**9a**)*

To a stirred solution of 22 *N* hydrogen fluoride in *N*,*N*-dimethylformamide (9.0 ml) at 23° was added 1α,2α-epoxy-17β-hydroxy-5α-androstan-3-one **6***a* (0.150 g). After 3 h at 23°, the reaction mixture was worked up in the usual manner, yielding **10***d* (83% by n.m.r.), which was placed on a column (1 × 14 in.) of dry column adsorbent (100 g). The column was developed with benzene – ethyl acetate – ethanol (80:20:1) yielding (R_f 0.14 to 0.78) **9***a*, m.p. 156–158° (from acetone–water); λ_{max} (EtOH) 234 nm (ε 10 400); δ ($CDCl_3$) 7.44 (1H, d, *J* = 10 Hz, H-1), 6.08 (1H, d, *J* = 10 Hz, 2-H), 4.53 (1H, q, $^2J_{HF}$ = 49 Hz, J_{ae} = 3 Hz, 4α-H), 1.20 (3H, d, $^5J_{HF}$ = 2 Hz, 19-H_3), and 0.80 (3H, s, 18-H_3); t.l.c. R_f 0.47; mass spectrum *m*/*e* 306 (M^+).

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