Tetrahedron. Vol. 29, pp. 4053 to 4064. Pergamon Press 1973. Printed in Great Britain

SYNTHESIS AND CONFORMATION OF 2-FLUORO-3-KETOESTRANE DERIVATIVES

J. PATAKI*

The Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, Illinois 60637

(*Received in the USA* 14 *May* 1973; *Received in the UK for publication* 20 *August* 1973)

Abstract—Treatment of 3-methoxy-17β-acetoxyestra-2,5(10)-diene with perchloryl fluoride in aqueous dioxane or tetrahydrofuran yielded a 2-fluoro-3-ketosteroid with unusual properties. Unlike the known 2α-fluoro-19-nortestosterone, this fluoroketone possessing a 5(10) double bond easily lost hydrogen fluoride to form estradiol 17-acetate; aromatization took place on melting, on exposure to pyridine or acid or even during chromatography on silica gel or Florisil. Because of the Δ-5(10) structure and the absence of the C_{19} Me group, it is difficult to infer the exact orientation of the 2-fluorine substituent from its effect on the NMR spectrum, CD or the CO absorption in the IR. However, the properties of certain derivatives suggested that the fluorine substituent was 2β. Treatment of the unsaturated fluorketone with peracid gave a mixture of epoxides which on basic hydrolysis furnished two 2-fluoro-10-hydroxy-17-acetoxyestr-4-en-3-ones epimeric at C_{10}. The UV and NMR spectra of the 10α-hydroxy epimer indicated an equatorial 2β-orientation of fluorine, whereas the 10β-hydroxy epimer showed an axial 2β-fluorine substituent which could be isomerized by acid to the more stable equatorial 2α-configuration.

The discovery that, in absence of acid, the F atom of perchloryl fluoride behaves as an electrophile[1a,b,c] led, especially in the steroid field, to the synthesis of a series of fluorinated compounds which, by any other means, would have been difficult to prepare.[2] Thus, the synthesis of fluoroketone **2** via reaction of perchloryl fluoride with the enolether **1** appeared feasible.

Initially, however, no definite product could be secured from the reaction of **1** with perchloryl fluoride, although the starting material was consumed. In pyridine, mainly water-soluble products were formed while in other solvents only intractable material was obtained. Use of the acetate **1a** instead of the free alcohol **1**, and mixtures of tetrahydrofuran or dioxane with water as solvent led to crystalline **2a** in about 35% yield. Under identical conditions, **1b** gave the fluoro-diketone **2b** in similar yield. For reasons given below, we assigned to both compounds structures of 2β-fluoroestr-5(10)-en-3-one derivatives.

The fluoroketone **2a** does not show a definite m.p., but rather decomposes between 160° and 185° to yield a solid melting at 215°. The IR spectrum of the resolidified product is identical with that of estradiol 17-acetate, **3a**, which also melts at 215°. The same compound is also formed on mild treatment of the fluoroketone **2a** with acid or with base, or when it is desorbed from Florisil, silica gel or neutral alumina, thus it could not be isolated or purified by chromatography. The ketone is dimorphic, and the two forms show different solid phase IR spectra; in one form the ketone C=O is at 1745 cm^{-1} and overlaps with the acetate band, in the other form it appears as a distinct band at 1724 cm^{-1}, same as the C=O band of the parent ketone **8a**. The form with the higher-frequency C=O band also shows a single C—F stretching peak at 1096 cm^{-1}, while the second form exhibits two peaks at 1091 cm^{-1} and 1082 cm^{-1} of different intensity. The solution spectra of both forms are, of course, the same with the ketone band at 1745 cm^{-1} and the C—F band at 1093 cm^{-1}. The 1745 cm^{-1} form could be converted to the 1724 cm^{-1} form by rapid crystallization, but the reverse transformation could not be effected. The diketone **2b** was obtained in one form with the C=O band at the higher frequency. Upon heating, or with acid, base or adsorbents, **2b** decomposed analogously yielding estrone.

In α-haloketones, both the C=O and carbon-halogen stretching frequencies are indicative of the conformation of the halogen atom.[3,4] However, in contrast to other α-haloketones, the C=O frequencies of axial as well as of equatorial α-fluoroketones are higher than those of the corresponding unsubstituted ketones.[5,6] In addition, the published stretching frequencies of axial and equatorial C—F bands lack sufficient consistency of pattern to be of help in determining the stereochemistry of the fluorine substituent. For this reason we sought to correlate the orientation of the fluorine in compound **2a** to that of the known 2α-fluoro-19-nortestosterone acetate **4a**[7] by preparing the ethylene

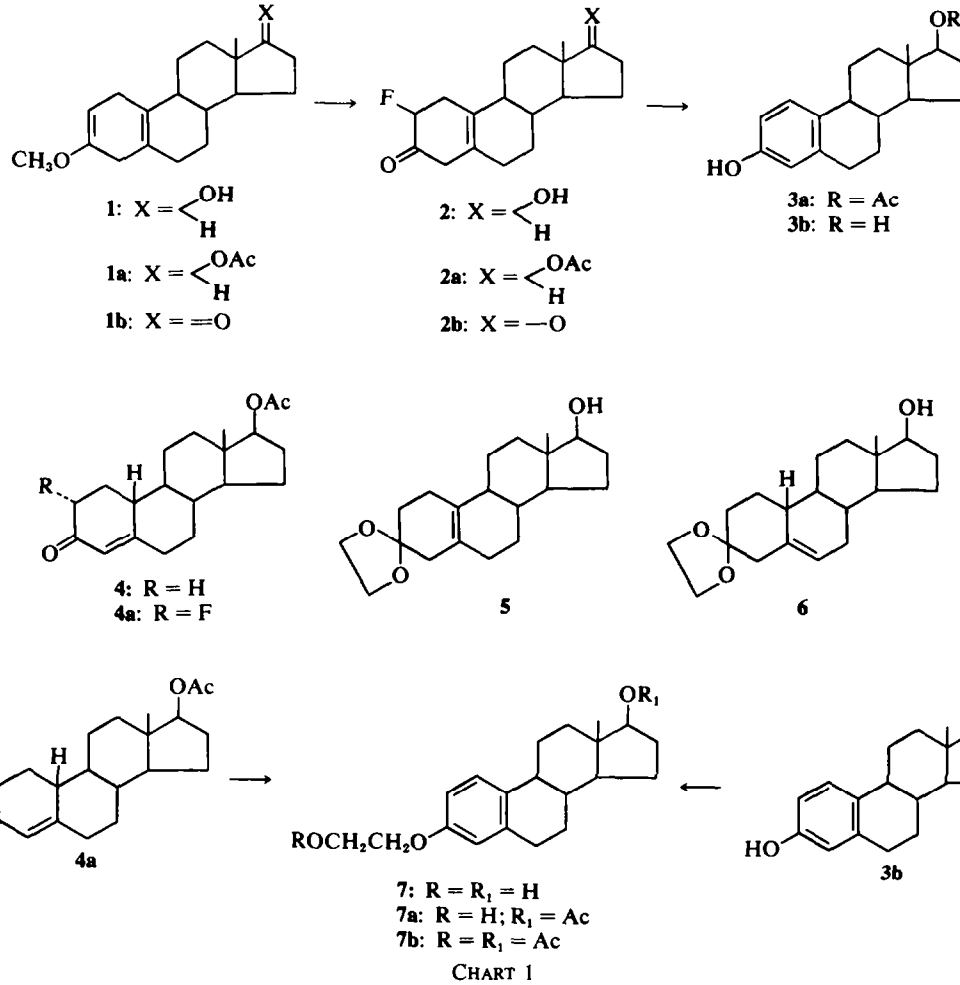

CHART 1

ketals derived from **4a**, and to isolate and hydrolyze the isomer corresponding to compound **5**. However, *p*-toluenesulfonic acid catalyzed reaction of **4a** with ethylene glycol in benzene gave a product whose IR spectrum showed the presence of an aromatic ring and of a free OH group which could be acetylated. Elemental analysis and IR spectrum indicated that the triene **7a** was formed. This was confirmed by synthesis of the diacetate **7b** from estradiol, **3b** and ethylene chlorohydrin, according to the method of Birch and Mukherji,[8] and subsequent acetylation of the reaction product.[9] The formation of **7a** might be initiated (Chart 2) by elimination of hydroxonium ion from the intermediate postulated by Djerassi and Gorman;[10] the resulting homoconjugated diene then could lose elements of HF and aromatize to give compound **7a** if elimination of HF occurred more rapidly than the nucleophilic attack at C-3 by the primary OH group forming the ethylene ketal.

Introduction of a F atom in the conformationally rather rigid ring A of saturated and α,β-unsaturated 3-ketosteroids by means of perchloryl fluoride under conditions which provide thermodynamic control of the reaction leads exclusively to equatorial α-fluoroketones.[1a, b, c, 11, 12, 13] However, in conformationally less rigid systems mixtures of axial and equatorial α-fluoroketones were obtained by Allinger and Blatter.[5]

In a 5(10)-unsaturated 3-ketosteroid (e.g., **8**) the rigidity of ring A is lost so that the two possible half-chair conformations are interconvertible,[14, 15] and the small energy difference (e.g., 2·7 kcal/mole for cyclohexene[16]) between the half-chair and half-boat conformations is further reduced by the sp^2 hybrodized C atom of the ketone.* Applied to the fluoroketone **2a** this means that the four conforma-

*The experimentally found energy difference of 2·8 kcal/mole between the chair and boat (flexible) forms of cyclohexanone is about 3·1 kcal/mole less than the difference between the chair and boat forms of cyclohexane.[17] For cyclohexenone this would mean that the half-chair and half-boat forms are energetically quasi equivalent.

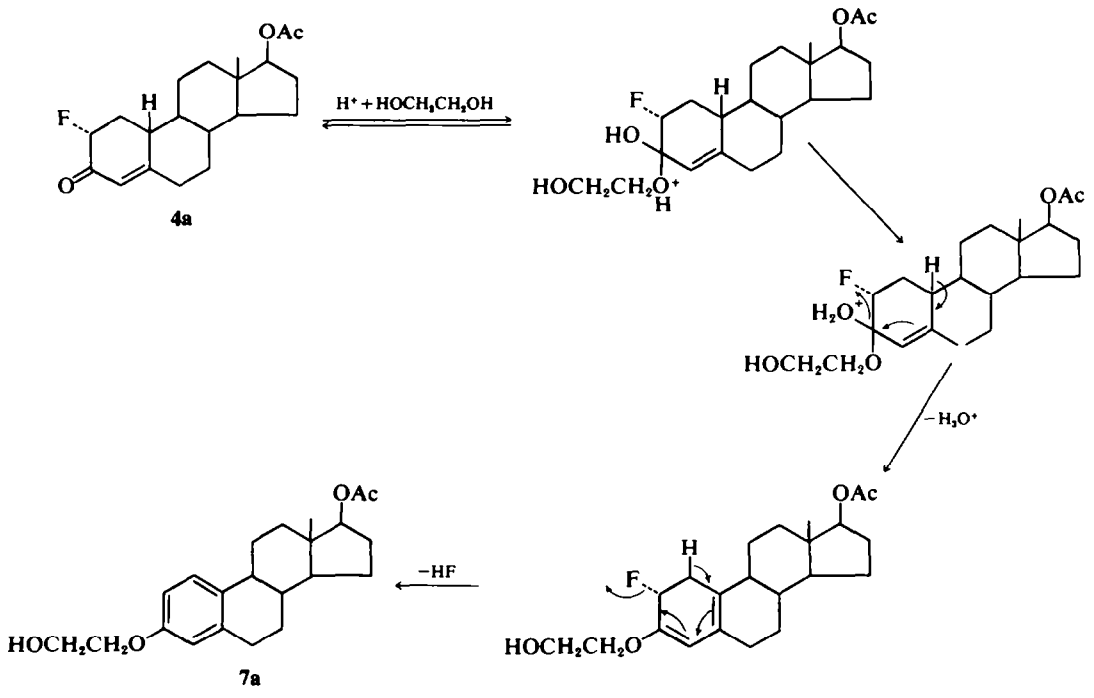

CHART 2

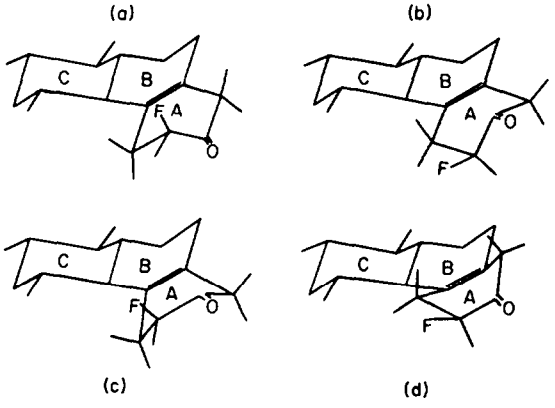

Fig 1.

tions of ring A (Fig 1) would be energetically more or less equivalent.* However, Levine *et al.*[15] point out that in conformations A and C the pseudo-equatorial 1 β- and the equatorial 11 α-hydrogens interact, the distance between the two being only about 1·8 Å.† They concluded that, in the case of the 3-alcohols, the ring A of a 5(10)-unsaturated steroid assumes the half-chair conformation as in B, with the 2β-substituent in equatorial position. Although their data, which were based on NMR studies, did not exclude the possibility that the half-boat conformation as in D might be preferred, they decided in favor of the half-chair form because of the calculated energy difference of 2·7 kcal/mole.[20] However, since this energy difference practically disappears in the ketones **2a** or **8**, the two conformers B and D cannot be differentiated.‡ We hoped to gain further insight into the stereochemistry of the fluoroketone from spectroscopic evidence.

Due to stabilization of their excited state, axial α-fluoroketones show a bathochromic shift of their peak UV absorption relative to the corresponding unsubstituted ketones. These red shifts are, generally, of the order of 10 nm.[22] On the other hand, an adjacent equatorial halogen has little or no effect on the $n \rightarrow \pi^*$ transition of the CO group, and significant change in the position of the absorption maximum is not expected. Maximum absorption of the fluoroketone **2a** was found at 285 nm ($\epsilon = 28$) in dioxane, and at 288 nm ($\epsilon = 32$) in cyclohexane,

*In the two boat conformations C and D, the bond opposition strain involving the carbonyl group[16] is about half that of the chair conformations A and B, because in the former the carbonyl oxygen is eclipsed only by one of the adjacent equatorial hydrogens, while in the latter it is eclipsed by both of the flanking equatorial hydrogens.

†By using the potential energy values for non-bonded hydrogen-hydrogen interactions calculated by Fieser and Fieser,[19] one can estimate conformations A and C to be about 5–7 kcal/mole less stable than B and D.

‡As they undoubtedly come near to represent conformational energy minima, the use of "conformers" for conformations B and D appears to be justified.[21]

while that of the unsubstituted ketone was at 284 nm ($\epsilon = 36$) in dioxane and at 287 nm ($\epsilon = 39$) in cyclohexane. These data are in accord with equatorial orientation of the 2-fluorine in **2a**, as present in both of the conformers B and D.

The NMR spectrum of **2a** showed for the C-2 proton a triplet signal centered at 337 c/s with an apparent coupling constant of 9·4 c/s. (The second half of the pair overlaps with the C-17 proton signal and is not resolved.) Since the expected signal would be a quartet, a triplet would indicate that the proton lies between the two C-1 protons and, being equidistant from both, is equally coupled to them. This would place the C-2 proton in the equatorial, the fluorine in the C-2 axial position, in contradiction to the UV spectrum. However, since only the X part of the ABX system is discernible, a complete analysis is not possible and the Abraham-Holker rule[23] cannot be applied in this case; thus, no conclusions can be drawn from the magnitude of the apparent coupling constants.*

In the NMR spectrum of **2b**, owing to the absence of a C-17 proton, the pair of triplets becomes visible. One is centered at 288·2 c/s and the other at 337·6 c/s. Again, first order approximation gives a coupling constant of 9·4 c/s between the C-2 proton and the two C-1 protons. The observed geminal fluorine-proton coupling constant of 49·4 c/s is in good agreement with the values of 49 to 50 c/s found by Allinger and coworkers[24a] and Wittstruck and coworkers.[24b]

We hoped to resolve the question of the stereochemistry of the F atom and the conformation of ring A in **2a** by CD measurements, but again the interpretation of the obtained curves was not unambiguous. The measurements were kindly performed by Dr. G. Snatzke, and we quote his analysis:† "The positive Cotton effect of the CD curve of **8a** (Fig 2) with a maximum at 298 nm ($[\theta] = +1980$ and a shoulder at 289 nm ($[\theta] = +1780$) can accomodate only conformers B and D. In both, the twistlike conformations of ring A are slightly positive and this determines the sign of the Cotton effect,[25] but it does not allow to decide which of the two is actually present, though the low molecular ellipticity might favor conformer B, where the contribution of the rest of the molecule is slightly negative, while *in the half-boat conformer* D the residual molecular contribution is positive. Conformations A and C should give a negative Cotton effect.

"The fluoroketone **2a** shows, at room temperature, a double-humped curve with a negative maximum at 304 ($[\theta] = -495$, a positive one at 272 nm ($[\theta] = +297$), and a more positive wing toward lower wavelengths. At a temperature of −183° the curious situation arises that there is a bathochromic shift for both bands, while in most cases a blue shift is found at lower temperatures. The main negative maximum is now at 309 nm ($[\theta] = -518$). The positive low-wavelength maximum moved to 279 nm and is very much increased ($[\theta] = +924$).

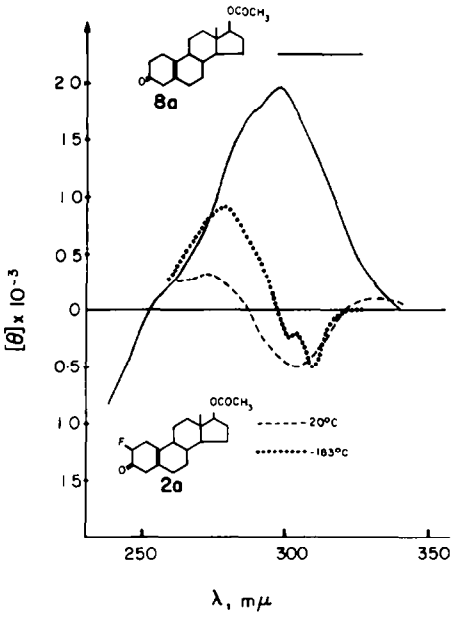

Fig 2.

A band at 309 nm could already be ascribed to an axial fluorine. The shift of this maximum could, however, be only apparent if one assumes that the band at lower wavelengths increases and shifts to the red for some reason. This maximum at 309 nm must, therefore, not necessarily be taken as an indication that an axial species is present at lower temperatures. Furthermore, one would face the odd situation that the population of the axial and equatorial conformers increases at the same time. It is more likely that we have one of those cases where there are two series of vibrational bands, one allowed, one forbidden. The curve with positive and negative maxima should then not be interpreted in the sense that there are two conformational species present. Nevertheless, the increase of the 270 nm band shows that probably one conformation with an equatorial fluorine accumulates at lower temperature. A tentative interpretation would then be that the preferred conformation of **2a** is that of the half-boat D, with a 2β-equatorial fluorine. The reason could be that the angle between the C—F and carbonyl dipoles is here greater than in the 2β-equatorial half-chair form B, and in this manner some dipole-dipole interaction is relieved. Conformer D should give a more positive Cotton effect than conformer B, and this would explain the decrease of the 279 nm band by warming up the solu-

*This was pointed out by one of the referees.

†We are greatly indebted to Dr. Günther Snatzke of the University of Bonn, Germany, for his interpretation.

tion to room temperature. That the molecular ellipticity of the CD curve is not as great as that of the nonfluorinated ketone **8a** might arise from the fact that in the half-boat conformer the fluorine is already a little in the positive, upper left octant, which could give some negative contribution if, indeed, fluorine shows also here the opposite contribution of other halogen substituents."

In summary, with the exception of the UV absorption spectrum, no straightforward stereochemical assignment can be made for the F atom in the 2-fluoro-Δ5(10)-ketone, based on purely spectroscopic evidence. Consequently, we tried to establish the configuration of the fluorine by chemical transformation of **2a**.

It is known that the hydroxyketone **8** reacts with perbenzoic or monoperphthalic acids to give the 5,10-epoxide which with base yields the α,β-unsaturated ketone corresponding to **11** (Chart 3).[26] In the case of **2a**, we hoped that this sequence of reactions would lead to a 2β-fluoro-10β-hydroxyketone. The β-oriented fluorine in the new compound would be axial and it should undergo acid catalyzed isomerization to the thermodynamically more stable equatorial 2α-fluoroketone.

In a model experiment, we oxidized the acetoxyketone **8a** with *m*-chloroperbenzoic acid and adsorbed the crude oxidation product on Florisil to effect opening of the epoxide ring. Surprisingly, we could isolate not only the known 10β-hydroxyketone **11**, but also the 10α-hydroxy isomer **12** which was not found by others describing the oxidation of 5(10)-unsaturated 3-ketones with peracids,[26] although the formation of epimeric 10-hydroxyketones has been claimed in a patent.[26c] This difference in results may be due to the oxidizing agent used here. The two isomers were obtained in a ratio of 2:1 in favor of the 10β-hydroxy compound. The molecular rotation difference between the two compounds is 800° which is in agreement with the values observed with other C-10 epimeric pairs[26c,27] (Table 1). The ORD curves show the pre-

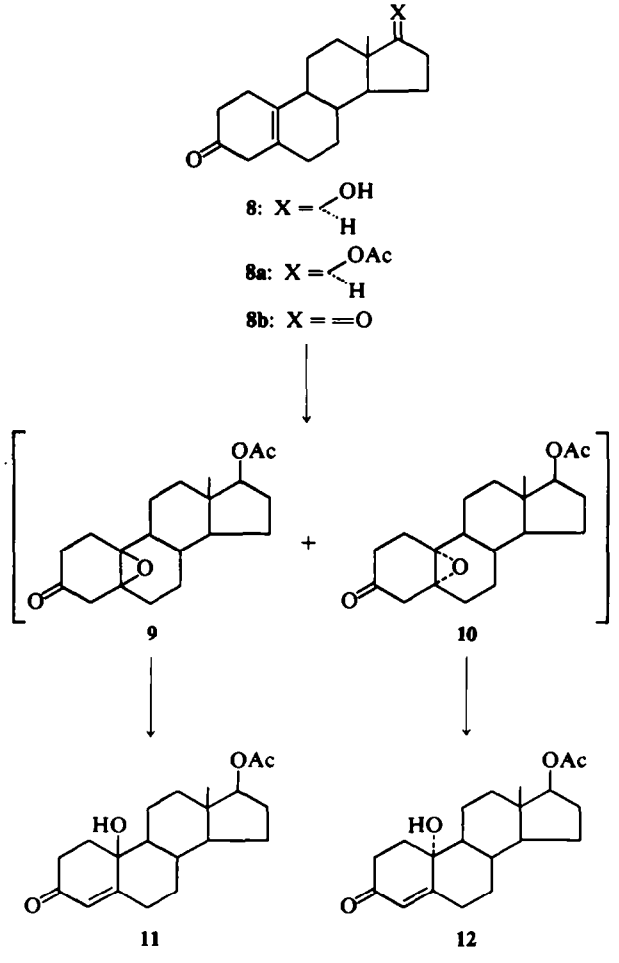

CHART 3

Table 1. Molecular rotation differences between C-2 halogenated steroidal 4-en-3-ones and their parent compounds

Compound	M_D Unsubst. (I)	2-Equat. (II)	2-Axial (III)	ΔM_D(II–I)	ΔM_D(III–I)
2-Fluorotestosterone	+314	+402		+88	
2-Fluoro-19-nortestosterone	+148	+291		+143	
2-Fluoro-19-nortestosterone acetate	+120	+275		+155	
2-Fluoro-estr-4-en-10β,17β-diol-3-one 17-acetate	+159	+293	0	+134	−159
2-Fluoro-estr-4-en-10α,17β-diol-3-one 17-acetate	−661	−588		+73	
2-Chloro-6β-bromocholest-4-en-3-one	28	+194	−194	+166	−222
2,6β-Dibromocholest-4-en-3-one	28	+282	−226	+254	−254

dicted Cotton effects (Fig 3).* In the neighborhood of the $\pi \rightarrow \pi^*$ transition, which determines the chirality of the α,β-unsaturated ketone chromophore,[28] the ORD curve of the 10β-hydroxyketone is strongly positive, while that of the 10α-hydroxyketone is negative. The NMR spectrum of **11** exhibits a doublet centered at 344·5 c/s (J = 1·4 c/s) for the C-4 vinylic proton. The small splitting is probably due to spin-spin coupling with the axial 6β-proton, although in general this gives rise only to a broadened singlet.[29] The C-18 protons appear as a singlet at 52·1 c/s. A similar upfield shift of the C-18 proton signal occurs in 10α-19-nortestosterone (as compared to 19-nortestosterone);[30] it results from the difference in the long-range shielding effected by the ring A system and is indicative of its orientation.

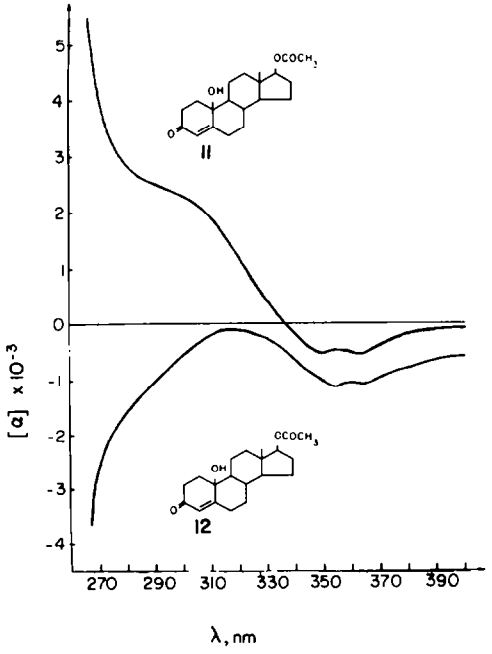

Fig 3.

When the corresponding sequence was carried out with the fluoroketone **2a**, two α,β-unsaturated hydroxyketones were obtained to which the structures **15** and **16** could be assigned (Chart 4) based on their molecular rotational differences (Table 1) and their UV absorption spectra (Table 2). However, the formation of the 10α-hydroxyketone was favored in a ratio of 2:1. This already might indicate that the fluorine is in the β-position, because, the chelative mechanism of epoxidation being nonoperative, the general polar directive effect of the β-fluorine causes the *trans*-epoxide to be formed predominantly.†

In the NMR spectrum of **16**, the C-18 proton signal is found upfield (6·3 c/s) from the corresponding signal of **15** which substantiates the stereochemical assignments at C-10. For **16**, a quartet centered at 303·2 c/s is visible corresponding to half of the resonance signal of the C-2 proton, with coupling constants of 5·8 and 11·9 c/s. The quartet signal and the observed coupling constants are in accord with a 2α-axial proton, thus with a 2β-equatorial fluorine. The 2β-equatorial position of the fluorine is confirmed by the C-4 proton signal which is a doublet at 347·4 and 352·4 c/s ($J_{2\beta F,4H}$ = 5·0 c/s), split by spin-spin coupling with the fluorine. It has been pointed out[24b] that in order for H—F coupling to occur over the 3-C=O group, the C—F bond at C-2, the C=O group and the vinylic C—H bond must be nearly in the same plane. An equatorial 2β-fluorine fulfills this requirement. There is no substantial difference between the UV

*We are indebted to Dr. Eugene Farkas, Eli Lilly and Company for the ORD measurements.

†I thank the referee for this suggestion. See H. B. Henbest, *Proc. Chem. Soc.* 159 (1963).

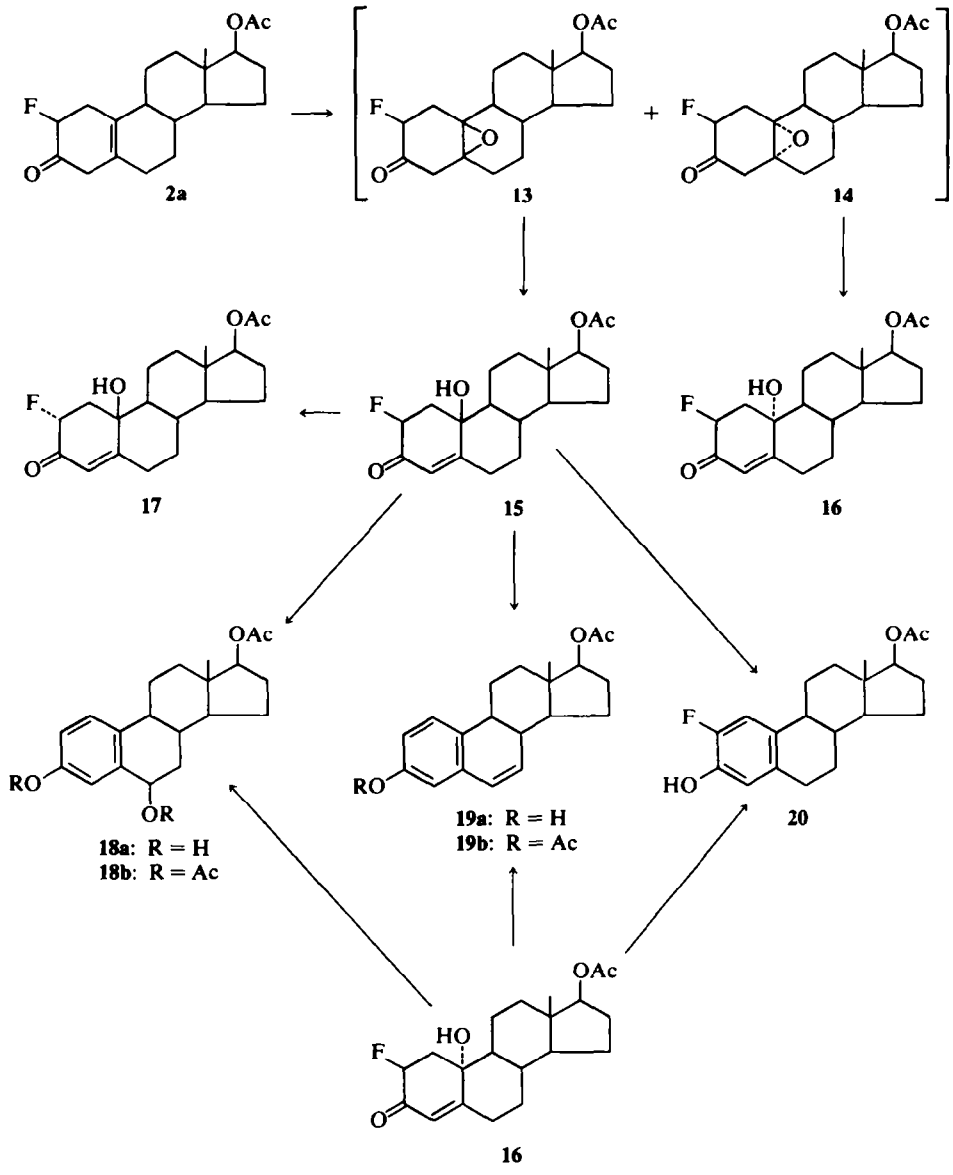

CHART 4

absorption maxima of **16** and **12** (Table 2). This is as expected if the fluorine is equatorial in **16**.

The CD curve of **16** (Fig 4) is rather different from the curve of the parent ketone **12**. The intensity of the negative Cotton effect is greatly reduced. At the same time, there is a pronounced positive Cotton effect with a maximum at about 326 nm. This could well be due to a distortion of ring A which probably approximates the twist conformation and to the quasi equatorial position of the fluorine in which it could exert its negative contribution. Also, due to a distorted ring A, the flexible conformation of ring B is probably different from the flexible conformation of ring B in **12** in such a way that in **12** carbon atoms 5 and 8 are flagpoles of ring B, while in **16** carbon atoms 6 and 9 become flagpoles of the flexible form. In any event, the chirality of the ketone chromophore of **16** must be the same as that of **12** because the Cotton effect turns strongly negative as the curve approaches the $\pi \rightarrow \pi^*$ transition.

The fluorine atom in **15** is undoubtedly 2β-axially oriented. Both the molecular rotation difference between **15** and **11** (Table 1) and the UV absorption maximum of **15** (Table 2) are in agreement with that structure. The bathochromic shift of 5 nm observed

Table 2. Shifts in the ultraviolet UV maxima of steroidal 2-fluoro ketones

Parent ketone	λ_{max}, mμ 2-Eq. F-	2-Ax. F-	Unsubst.	Contribution of 2-F Equat.	Axial
5α-Androstan-17β-ol-3-one acetate	280(M)	289(M)	280(M)	0	+9·0
5α-Androstan-3,17-dione	291(D)	298(D)	291(D)	0	+7·0
Estr-5(10)-en-17β-ol-3-one acetate	285–287 (D)		284–286 (D)	+1·0	
Testosterone	242(E)		241(E)	+1·0	
19-Nortestosterone	239(E)		240(E)	−1·0	
Estr-4-en-10β,17β-diol-3-one 17-acetate	234(E)	239(E)	234(E)	0	+5·0
	227·5(C)	236·5(C)	227(C)	+0·5	+9·5
Estr-4-en-10α,17β-diol-3-one 17-acetate	233(E)		232·5(E)	+0·5	
	225(C)		224(C)	+1·0	

M = Methyl alcohol; D = Dioxane; E = Ethyl alcohol; C = Cyclohexane.

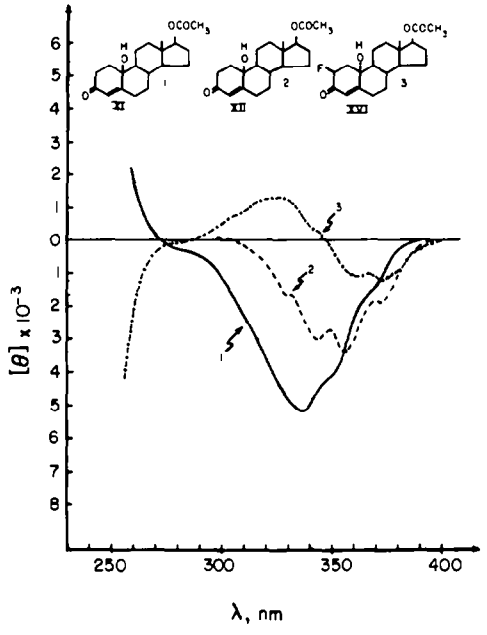

Fig 4.

in absolute ethyl alcohol is relatively small. However, this might be expected[5,24a] with ring A approximately in a twist conformation[31] orienting the C—F bond nearer to the plane of the C=O group than in a normal half-chair, thus decreasing the magnitude of the red shift. Accordingly, the greater bathochromic shift (9·5 nm) in cyclohexane solution suggests that the conformation of ring A in this nonpolar solvent is nearer to a normal half-chair with the C—F bond almost orthogonal to the plane of the C=O group. Probably the compound exists in solution as a mixture of ring A conformations whose proportion changes with the polarity of the solvent. Such an interpretation is strongly supported by its CD curve in which both a negative and a positive maximum are present (Fig 5) and also by its NMR spectrum.

Assuming that ring A in **15** existed in the normal half-chair conformation, one would expect the visible part of the 2α-equatorial proton to appear as a triplet in the NMR spectrum. Nevertheless, a quartet centered at 313·3 c/s is observed. The apparent coupling constants of 4·9 c/s and 8·9 c/s cannot be reconciled with any definite conformation of ring A, as with these values no reasonable dihedral angles can be obtained between the C-2 hydrogen and the geminal hydrogens at C-1, using the Karplus equation or any of its modifications. There is no long range spin–spin coupling between the fluorine at C-2 and the C-4 vinylic proton, the signal of the latter being a broad singlet; thus the C—F and vin-

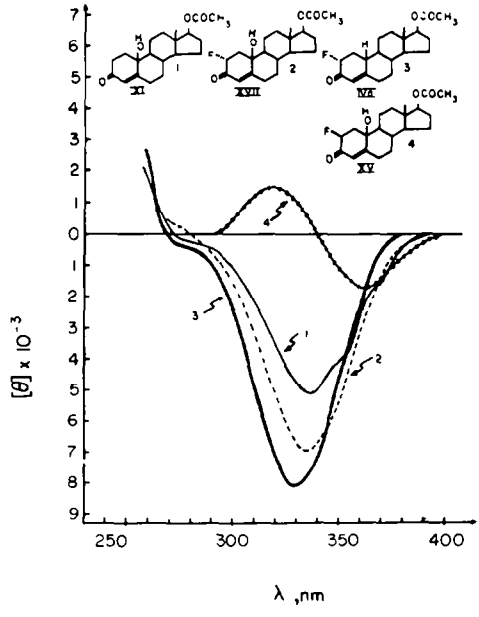

Fig 5.

ylic C—H bonds must be perpendicular to each other, indicating that the fluorine is axially or near axially oriented.

It appears rather surprising that ring A of **15** is not in the expected half-chair conformation. Allinger and coworkers[24a] found that ring A of 2β-fluoro - 5α - androstan - 3, 17 - dione is preferentially in a normal chair conformation. There is no reason to assume that in **15** the 1,3-diaxial interaction between the 2- and 10-substituents should be more severe than in the androstan derivative, if not by dipole–dipole repulsion. In this connection it is interesting to note that both 2β - methyl - 17β - hydroxyestr - 4 - en - 3 - one and 2β, 17β - diacetoxyestr - 4 - en - 3 - one, where there is minimal 1,3-nonbonded interaction between the 2β-substituents and the 10β-hydrogen, have their ring A in a twist conformation.[32]

Isomerization of **15** with acid confirmed the 2β-axial orientation of the F atom. It gave, besides several ring A aromatic compounds (see below), a new α,β-unsaturated ketone in about 50% yield. The spectral properties are in complete agreement with the assigned structure of 2α-fluoro-17β-acetoxyestr-4-en-10β-ol-3-one, **17**. Its UV absorption maximum is essentially the same as that of the parent ketone (Table 2). The NMR spectrum (taken in dimethylsulfoxide-d_6) showed the C-4 proton split by the equatorial fluorine as a doublet centered at 342·0 c/s ($J_{2\alpha F,4H}$ = 5·0 c/s). From the predicted pair of quartets for the 2β-axial proton, one is visible centered at 296 c/s. The first approximation coupling constants are 5·5 c/s and 12·8 c/s. These values agree well with those found for **4a**. The negative Cotton effect of its CD curve closely resembles those of **11** and **4a**. It is worthy to note that the molecular ellipticities of the fluoroketones are significantly greater than that of the unsubstituted ketone and the maxima show slight hypsochromic shifts.

In the acid treatment of **15**, in addition to **17**, three phenolic compounds identified as **18a**, **19a**, and **20** were isolated in yields of 3·6 and 6%, respectively. The last three compounds were the exclusive reaction products when identical conditions were applied to **16**. In this case, the yields were 35%, 6% and 3%. Estra - 1,3,5(10) - trien - 3,6β 17β-triol 17-acetate, **18a**, was identified by conversion to and direct comparison with the known triacetate **18b**.[33] Both 6-dehydroestradiol 17-acetate **19a** and its acetylation product, **19b**, showed the physical characteristics already described,[34] and gave no depression of m.p. on admixture with authentic materials.

The IR spectrum and elemental analysis of **20** are in agreement with the proposed formula. Its UV spectrum (λ_{MAX}^{EtOH} 281 nm ϵ = 2,600) is very similar to that of estradiol acetate.[34] In the NMR spectrum, both the C-1 and C-4 protons are spin–spin coupled to the 2-fluorine and appear as doublets, $J_{1H,2F}$ = 12·1 c/s and $J_{4H,2F}$ = 8·9 c/s. Attempts to prepare **20** by dehydrogenation of **4a** with dichlorodicyanobenzoquinone[35] or with palladium magnesium oxide catalyst[36] were unsuccessful. The first reagent gave only unchanged starting material,[37] while with the second dehydrohalogenation took place and estradiol 17-acetate was the sole product isolated.

Biological evaluation. 2β - Fluoro - 17β - acetoxyestr - 5(10) - en - 3 - one, **2a**, possesses 60% of the uterotropic activity of estrone. It has an androgenic activity of about 5–10% of that of testosterone, **2a** is inactive as an antiandrogen. Its antigonadotropic activity is about as great as that of estrone. For antitumor activity see Table 3.

Table 3. Inhibition of R-35 mammary adenocarcinoma in Sprague-Dawley rats

Compound	Inhibition, % of control Subcutaneous	Oral
2β-Fluoro-17β-acetoxyestr-5(10)-en-3-one	58	62
Estradiol	50	0
Testosterone	45	0
Provera (6α-Methyl-17α-acetoxyprogesterone)	75	0
Oxylone (9α-Fluoro-11β,17α-dihydroxy-6α-methyl-pregna-1,4-dien-3,20-dione)	80*	75*

*but large net weight loss

2β-Fluoro-17β-acetoxyestr-5(10)-en-3-one exhibits 28% inhibition and 45% prolongation of life in 7,12-DMBA induced mammary carcinoma at a dose level of 2·5 mg, administered subcutaneously. It has no effect in leukemias and lymphomas.

EXPERIMENTAL

M.ps were determined in capillary tubes and are not corrected. The specific rotations were taken in chloroform solns where not otherwise indicated. The UV spectra were obtained on a Cary II Recording Spectrophotometer and the IR spectra on a Perkin Elmer "Infracord" Spectrophotometer, in the solvents indicated. The NMR spectra were run on a Varian A-60 instrument in $CDCl_3$ using TMS as internal standard with the exceptions noted. Microanalyses were performed by Mr. Joseph Alicino, Metuchen, N.J.

3-Methoxy-17β-acetoxyestra-2,5(10)-diene (**1a**). **1**[38] (30 g) was dissolved in 60 ml pyridine and 20 ml Ac_2O. The soln was allowed to stand in a N_2 atmosphere for 24 hr at room temp. The solvents were removed *in vacuo* and the residue (34·36 g) was dissolved in 200 ml ether. The soln was passed through a column of 15 g of Florisil and the column was washed with an additional 300 ml ether. The residue, left after evaporation of the ether, crystallized from MeOH, yield 26·19 g of **1a**, m.p. 103–105°. The analytical sample melted at 104–106·5. (Found: C, 76·24; H, 9·17. $C_{21}H_{30}O_3$ requires: C, 76·32; H, 9·15%).

2β-Fluoro-17β-acetoxyestr-5(10)-en-3-one (**2a**). A soln of **1a** (26·00 g) in 1300 ml THF and 650 ml water was placed in an ice-bath. Perchloryl fluoride was bubbled into

the stirred soln for 10 min. The soln was then poured into 5 litres ice water and the mixture was extracted 3 times with methylene chloride. The extracts were washed repeatedly with water and once with sat NaCl aq. After drying (Na_2SO_4), the solvent was removed under reduced pressure. The evaporation residue (25·48 g) gave from ether–hexane 11·42 g of crystalline material which was recrystallized immediately in acetone–hexane to give **2a** (8·19 g), m.p. 185–187° (dec with darkening and resolidification), 210–213°. In other runs, dec points between 160° and 180° were observed. The IR spectra showed also variations. One modification had ν_{KBr} 1745, 1724, 1091, 1082 cm^{-1}, the other ν_{KBr} 1745, 1093 cm^{-1}. νCCl_4 (for both modification) 1745, 1093 cm^{-1}. $[\alpha]_D = +135·8°$. NMR: 49·5 (s, 3, 13-CH_3), 337·0 c/s (t, 1/2, 2α-H; J = 9·4 c/s). (Found: C, 71·66; 71·94; H, 8·29; 8·16; F, 5·89; 5·68. $C_{20}H_{27}FO_3$ requires: C, 71·82; H, 8·13; F, 5·68%). The two analyses correspond to the different modifications.

Estradiol 17-*acetate* (**3a**) *from* **2a**. **2a** (50 mg) was heated to reflux in 10 ml of 50% AcOH for 1 hr. The soln was cooled and a soln of $NaHCO_3$ (3 g) in 45 ml water was added with caution. The crystals which separated were collected, washed well with water and dried to give **2a** (44 mg), m.p. 212–215° (Lit:[34] m.p. 217–219°). Mixture m.p. with authentic sample (m.p. 216–219°) 215–218°.

2β-*Fluoroestr*-5(10)-*en*-3,17-*dione* (**2b**). A slow stream of perchloryl fluoride was introduced into a soln of 3 - methoxyestra - 2,5(10) - dien - 17 - one[39] (3·34 g) in 140 ml THF and 38 ml water kept in an ice bath for 15 min. The excess reagent was removed on the water pump at room temp and the soln was poured into 600 ml ice water. After standing for 10 min, the mixture was extracted with ether, the extracts were washed with $NaHCO_3$ aq, water and sat NaCl aq. The dried (Na_2SO_4) soln was reduced to a small volume and allowed to stand overnight at 0°. The fluoroketone (1·51 g, m.p. 164–168° with dec) was isolated by filtration. Three recrystallizations from acetone–hexane afforded analytically pure material, melting at 176–177·5° (with dec and resolidification), 246–251°. $[\alpha]_D = +261·1°$. $\lambda_{max}^{dioxane}$ 294 nm (ε = 48), ν_{KBr} 1745, 1088 cm^{-1}, NMR: 54·3 (s, 3, 13-CH_3), 288·2 (t, 1/2, 2α-H), 337·6 c/s (t, 1·2, 2α-H), J = 9·4, 9·4 c/s. $J_{2\alpha H1F} = 49·4$ c/s. (Found: C, 74·72; H, 7·92; F, 6·37. $C_{18}H_{23}FO_2$ requires: C, 74·45; H, 7·98; F, 6·54%).

17β-*Acetoxyestr*-5(10)-*en*-3-*one* (**8a**). **1a** (500 mg) in 42 ml MeOH was allowed to stand with a soln of oxalic acid dihydrate (500 mg) in 8 ml water during 40 min at room temp. The soln was then diluted with water and extracted with ether. The extract was washed successively with $NaHCO_3$ aq, water and sat NaCl aq. After removal of the ether from the dried (Na_2SO_4) soln, the residue was crystallized from MeOH–water and yielded **8a** (438 mg), m.p. 130·5–132·5°. M.p. of the analytical sample 132–134°, $[\alpha] = 114·2°$ ν_{KBr} 1742, 1724 cm^{-1}. (Found: C, 75·69; H, 8·88. $C_{20}H_{28}O_3$ requires: C, 75·91; H, 8·91%).

17β - *Acetoxyestr* - 4 - *en* - 10β - *ol* - 3 - *one* (**11**) *and* 17β - *acetoxyestr* - 4 - *en* - 10α - *ol* - 3 - *one* (**12**). The soln of **8a** (350 mg) and 85% *m*-chloroperbenzoic acid (500 ml) in 50 ml ether was allowed to remain 17 hr at room temp. Acidic material was removed by washing with 5% Na_2CO_3 aq. The solvent was evaporated from the dried (Na_2SO_4) soln and the residue (352 mg) was dissolved in a small amount of methylene chloride and adsorbed on 12 g of Florisil. After 2 hr, the column was eluted with 400 ml ether. Evaporation of the ether left 333 mg crystalline material which was chromatographed on 10 g Florisil. The column was eluted with hexane containing increasing amounts of acetone. The fractions with 4–5% acetone contained the 10β-hydroxy isomer. The 10α-hydroxy compound was obtained from fractions eluted with 5–7% acetone.

17β - *Acetoxyestr* - 4 - *en* - 10β - *ol* - 3 - *one* (**11**). The crude crystals (181 mg) gave after two recrystallizations from acetone–hexane 114 mg of pure **11**, m.p. 179–181°, which was homogeneous on TLC plate, $[\alpha] = +48°$; $M_D = +159°$, λ_{max}^{EtOH} 234 nm (ε = 14,100); $\lambda_{max}^{Cyclohexane}$ 227 nm (ε = 14,900), ν_{KBr} 3413, 1718, 1689, 1629 cm^{-1}, NMR: 52·1 (s, 3, 13-CH_3), 344·5 c/s (d, 1, 4-CH; J = 1·4 c/s). (Found: C, 72·09; H, 8·55. $C_{20}H_{28}O_4$ requires: C, 72·26; H, 8·49%).

17β - *Acetoxyestr* - 4 - *en* - 10α - *ol* - 3 - *one* (**7**). The combined fractions (82 mg) obtained with 5–7% acetone afforded, after two recrystallizations from acetone–hexane, 51 mg of pure **12**, m.p. 194–196°. $[\alpha]_D = -198·9°$; $M_D = -661°$, λ_{max}^{EtOH} 232·5 nm (ε = 17,900); $\lambda_{max}^{cyclohexane}$ 224 nm (ε = 17,000), ν_{KBr} 3448, 1715, 1675, 1631 cm^{-1}, NMR: 45·7 (s, 3, 13-CH_3), 347·3 c/s (s, 1, 4-CH). (Found: C, 72·38; H, 8·54. $C_{20}H_{28}O_4$ requires: C, 72·26; H, 8·49%).

Diacetate of 3-(2-*hydroxyethoxy* - *estra* - 1,3,5(10) - *trien* - 17β - *ol* (**7b**)

(a) *From* 2α - *fluoro* - 17β - *acetoxyestr* - 4 - *en* - 3 - *one* (**4a**). A soln of **4a** (250 mg) in 40 ml benzene was heated under reflux with 1·2 ml ethylene glycol and *p*-toluenesulfonic acid monohydrate (30 mg) for 19 hr, using a Dean-Stark water separator. After cooling, the soln was washed with $NaHCO_3$ aq and with water. After the solvent was removed under reduced pressure, the foamy residue (284 mg) showed a strong OH band and a band at 1499 cm^{-1} (aromatic ring) in its IR spectrum. The crude product was acetylated with 2 ml Ac_2O and 5 ml pyridine at room temp. After the usual workup, 324 mg of a partly crystalline product was obtained which was chromatographed on 12 g of Florisil. The bulk of the material (255 mg) was eluted with hexane-2% acetone. Crystallization from MeOH–water gave **7b** (139 mg), m.p. 78–79°. The analytical sample melted at 79–80°. $[\alpha]_D = +37°$, ν_{KBr} 1754, 1739, 1610, 1567, 1497, 1233–1252 cm^{-1}. (Found: C, 71·96; H, 8·01. $C_{24}H_{32}O_5$ requires: C, 71·97; H, 8·06%).

(b) *From estradiol* (**3b**). To a warm (80°) soln of NaOH (1·5 g) in 30 ml water, estradiol (250 mg) in 5 ml hot EtOH and 2·5 ml freshly distilled ethylene chlorohydrine were added simultaneously. After stirring for 30 min at 80–83°, the same amounts of NaOH and ethylene chlorohydrine were again added and stirring was continued for another 15 min. The mixture was filtered warm and the solid collected was washed well with warm water. The dried product (284 mg) was acetylated with 2 ml Ac_2O in 3 ml pyridine. Usual workup afforded an oil (355 mg) which crystallized from MeOH to give **7b** (182 mg), m.p. 79·5–80·5°; a second crop (45 mg) melted at 78–79°. Mixture m.p. with material obtained from **4a** 79·5–80·5°. $[\alpha]_D = +37·3°$, ν_{KBr} 1751, 1739, 1610, 1567, 1499, 1233–1250 cm^{-1}. (Found: C, 71·86; H, 8·06. $C_{24}H_{32}O_5$ requires: C, 71·97; H, 8·06%).

2β - *Fluoro* - 17β - *acetoxyestr* - 4 - *en* - 10β - *ol* - 3 - *one* (**15**) *and* 2β - *fluoro* - 17β - *acetoxyestr* - 4 - *en* - 10α - *ol* - 3 - *one* (**16**). To a soln of **2a** (5·0 g) in 750 ml anhyd ether, 85% *m*-chloroperbenzoic acid (7·5 g) in 250 ml ether was added. After standing for 17 hr at room temp, the soln was washed with 5% Na_2CO_3 aq, water and dried (Na_2SO_4). The ether was distilled off under reduced pressure leaving 5·41 g of a colorless foam. This was dissolved in a small amount of methylene chloride and adsorbed on

a column of 100 g of florisil. After 2 hr, the column was eluted with 800 ml of an ether–acetone (9:1) mixture. Evaporation of the solvent left 5·34 g of a crystalline product which was chromatographed on 200 g of florisil. The compounds were eluted with hexane containing increasing amounts of acetone.

2β - Fluoro - 17β - acetoxyestr - 4 - en - 10β - ol - 3 - one (**15**). The fractions obtained with 8 to 10% acetone gave after crystallization from acetone–hexane pure **15** (1·13 g), m.p. 190–192·5°. The analytical sample melted at 191–193°. $[\alpha]_D = 0°$, $M_D = 0°$, λ_{max}^{EtOH} 239 nm (ϵ = 12,170); $\lambda_{max}^{cyclohexane}$ 236·5 nm (ϵ = 12,600), ν_{KBr} 3546, 1739, 1692, 1618 cm^{-1}, NMR: 52·4 (s, 3, 13-CH_3), 313·2 (q, 1/2, 2α-H; J = 4·9 and 8·9 c/s), 349·3 c/s (s, 1, 4-H). (Found: C, 68·81; H, 7·73; F, 5·61. $C_{20}H_{27}FO_4$ requires: C, 68·54; H, 7·76, F, 5·42%).

2β - Fluoro - 17β - acetoxyestr - 4 - en - 10α - ol - 3 - one (**16**). Isomer **16** was obtained from the fractions eluted with 10–15% acetone. After recrystallization from acetone, the yield was 2·21 g. The product melted at 201–204°. The analytical sample had a m.p. of 203–206°. $[\alpha]_D = -167·8°$, $M_D = -588°$, λ_{max}^{EtOH} 233 nm (ϵ = 14,100); $\lambda_{max}^{cyclohexane}$ 225 nm (ϵ = 12,900), ν_{KBr} 3425, 1718, 1695, 1631 cm^{-1}, NMR: 46·1 (s, 3, 13-CH_3), 303·2 (q, 1/2, 2α-H; J = 5·8 and 11·9 c/s), 349·9 c/s (d, 1, 4-CH). (Found: C, 68·49; H, 7·85; F, 5·72. $C_{20}H_{27}FO_4$ requires: C, 68·54; H, 7·76; F, 5·42%).

Acid isomerization of 2β - fluoro - 17β-acetoxyestr - 4 - en - 10β - ol - 3 - one. **15** (400 mg) in 20 ml acetone was heated under reflux with 0·2 ml conc HCl for 45 min. The cooled soln was diluted with ether and washed with $NaHCO_3$ aq and with water. After drying (Na_2SO_4), the solvent was removed. The residue (400 mg) was triturated with ether, the crystalline material was collected by filtration and washed well with ether. In this way, *2α - fluoro - 17β - acetoxyestr - 4 - en - 10β - ol - 3 - one*, **17** (208 mg), m.p. 218–222° (with dec) was obtained. Two recrystallizations from acetone gave 144 mg of analytically pure **17**, melting at 240–242° (with dec). $[\alpha]_D = +83·5°$, $M_D = +292°$, λ_{max}^{EtOH} 234 nm (ϵ = 13,000); $\lambda_{max}^{cyclohexane}$ 227·5 nm (ϵ = 13,400), ν_{KBr} 3356, 1709, 1711, 1618 cm^{-1}, NMR (in DMSO-d_6): 48·2 (s, 3, 13-CH_3), 296 (q, 1/2, 2β-H; J = 5·5 and 12·8 c/s), 341·9 c/s (d, 1, 4-CH). (Found: C, 68·71; H, 7·85; F, 5·24. $C_{20}H_{27}FO_4$ requires: C, 68·54; H, 7·76; F, 5·42%).

All mother liquors were combined and the solvents evaporated. The residue (230 mg) was chromatographed on 10 g of Florisil. The first two fractions, obtained with hexane-2% acetone, gave 33 mg of crystalline material which, after two recrystallizations from acetone–hexane, melted at 195–196°. The product was identified as 2 - *fluoroestra - 1,3,5(10) - trien - 3,17β - diol - 17 - acetate* (**20**). $[\alpha]_D = +48·1°$, λ_{max}^{EtOH} 281 nm (ϵ = 2,600), ν_{KBr} 3425, 1718, 1597, 1506, 1266 cm^{-1}, NMR: 49·6 (s, 3, 13-CH_3), 401·0 (d, 1, 4-H; J = 8·9 c/s), 417 c/s (d, 1, 1-H; J = 12·1 c/s). (Found: C, 72·34; H, 7·75; F, 5·58. $C_{20}H_{25}FO_3$ requires: C, 72·26; H, 7·58; F, 5·71%).

Subsequent fractions with the same solvent mixture and with hexane-3% acetone gave from acetone–hexane 26 mg of *6-dehydroestra-diol 17-acetate* (**19a**), m.p. 244–246° (see below). Finally, hexane-10% acetone eluted 15 mg of material which from acetone gave **18a** (11 mg), m.p. 172–175° (with dec).

Acid treatment of 2β-fluoro-17β-acetoxyestr-4-en-10α-ol-3-one (**16**). The soln of **16** (600 mg) in 30 ml acetone was heated to reflux with 0·3 ml conc HCl for 45 min. The soln was cooled, diluted with ether and washed with $NaHCO_3$ aq and with water. After drying (Na_2SO_4), the solvents were removed and the residue (586 mg) was triturated with ether. The insoluble material (206 mg), gave from acetone–hexane of *6β-hydroxyestradiol 17 acetate*, **18a** (138 mg), m.p. 175–176° (with dec). The analytical sample melted at 176–176·5 (with dec). $[\alpha]_D = +4·8°$ (in dioxane), λ_{max}^{EtOH} 221 nm (ϵ = 7,125); 283 nm (ϵ = 2,010); 288 nm (shoulder) (ϵ = 1,870), ν_{KBr} 3460, 3322, 1718, 1616, 1585, 1499, 1274 cm^{-1}. (Found: C, 72·52; H, 8·03. $C_{20}H_{26}O_4$ requires: C, 72·70; H, 7·92%).

All mother liquors were evaporated and the residue (441 mg) was chromatographed on 20 g of Florisil. The early hexane-2% acetone eluates (36 mg) afforded 2-fluoroestradiol 17-acetate, **20** (17 mg), m.p. 194–196°.

6-Dehydroestradiol 17-acetate, **19a** (46 mg) was eluted next with the same solvent mixture and hexane-3% acetone. Two recrystallizations from MeOH gave the analytical sample, m.p. 246–249° (Lit,[34] m.p. 250–252°). $[\alpha]_D = -223·5°$ (Lit,[34] $[\alpha]_D = -203°$). ν_{KBr} 3472, 1715, 1613, 1570, 1493, 1267 cm^{-1}, λ_{max}^{EtOH} 221 nm (ϵ = 26,300), 262 nm (ϵ = 7,900), 303 nm (ϵ = 3,040), (Lit,[34] λ_{max}^{EtOH} 222 nm (ϵ = 28,800), 262 nm (ϵ = 8,500), 303 nm (ϵ = 2,950)). (Found: C, 76·64; H, 7·73. $C_{20}H_{24}O_3$ requires: C, 76·89; H, 7·74%).

Hexane-8% acetone eluted starting material **16** (26 mg). Additional **18a** was recovered from the fractions obtained with hexane-10% acetone. Recrystallization of the crude product from acetone–hexane gave 74 mg of material melting at 173–175° (with dec).

6-Dehydroestradiol diacetate (**19b**). **19a** (13 mg) was acetylated in 0·2 ml pyridine with 0·05 ml Ac_2O at room temp. After the usual work-up, the material was recrystallized from MeOH–water. The diacetate (10 mg) melted at 151–152° (Lit,[34] 153·5–155°). $[\alpha]_D = -203·5°$ (Lit,[34] $[\alpha] = -162°$). λ_{max}^{EtOH} 219 nm (ϵ = 29,400), 263 nm (ϵ = 9,800) (Lit,[34] λ_{max}^{EtOH} 262 nm (ϵ = 10,200)), ν_{KBr} 1770, 1727, 1595, 1567, 1479, 1252, 1205, 1189 cm^{-1}. Mixture m.p. with authentic 6-dehydroestradiol diacetate (m.p. 151·5–153°; $[\alpha]_D = -206·7°$): 151·5–153°.

6β-Hydroxyestradiol triacetate (**18b**). **18a** (50 mg) was acetylated with 0·2 ml Ac_2O and 0·5 ml pyridine overnight at room temp. After the usual work-up, the crude crystalline triacetate (61 mg) was recrystallized from MeOH. The pure **18b** melted at 177·5–178·5°. (Lit[33a] 176–178°. Lit[33b] 173–175°). Mixture m.p. with authentic sample* (m.p. 173–175°); 175–177°, $[\alpha]_D = +52·7°$ (Lit,[33a] +53°; Lit,[33b] +57°), λ_{max}^{EtOH} 268 nm (ϵ = 701), 275·5 nm (ϵ = 699), ν_{KBr} 1767, 1733 (shoulder), 1720, 1493, 1247, 1205 cm^{-1}. (Found: C, 69·27; H, 7·52. $C_{24}H_{30}O_6$ requires: C, 69·53; H, 7·30%).

6-Dehydroestradiol 17-acetate (**19a**) *from* **18a**. **18a** (5 mg) in 2 ml acetone was refluxed with 0∓2 ml conc HCl for 90 min. KOAc (20 mg) in 0·1 ml water was added, and the acetone was evaporated *in vacuo*. The residue was extracted with hot hexane. The concentrated extracts deposited **19a** (3 mg), m.p. 243–248°; no depression of m.p. with the product obtained in the acid treatment of **15** or **16**.

Attempted dehydrogenation of 2α-fluoro-19-nortestosterone acetate (**4a**). A soln of **4a** (250 mg) in 30 ml 95% EtOH was refluxed with a palladium–magnesium oxide catalyst[36] (300 mg) for 48 hr in a N_2 atmosphere. After 24 hr of refluxing, another 250 mg of catalyst was added.

*We are indebted to Dr. Josef Fried for the comparison sample.

The mixture was cooled, filtered from the catalyst, and the solvent was removed. The semi-crystalline residue (219 mg) gave from ether 97 mg estradiol 17-acetate, m.p. 213–216°. Mixture m.p. with authentic sample (m.p. 216–219°): 215–219°.

Acknowledgments—I am greatly indebted to Dr. Elwood V. Jensen for suggesting the problem and for helpful discussions. I also thank Dr. Ivan I. Salamon for reading the manuscript.

REFERENCES

[1a] R. B. Gabbard and E. V. Jensen, *J. Org. Chem.* **23**, 1406 (1958); [b] S. Nakanishi, K. Morita and E. V. Jensen, *J. Am. Chem. Soc.* **81**, 5259 (1959); [c] S. Nakanishi, R. L. Morgan and E. V. Jensen, *Chem. & Ind.* 1136 (1960)

[2] J. L. Mills, *J. Am. Chem. Soc.* **81**, 5515 (1959)

[3] E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 240 and refs cited. McGraw-Hill, New York (1962)

[4] E. L. Eliel, N. L. Allinger, L. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 142. Interscience, New York (1965)

[5] N. L. Allinger and H. M. Blatter, *J. Org. Chem.* **27**, 1523 (1962)

[6] P. D. Klimstra and R. E. Counsell, *J. Med. Pharm. Chem.* **5**, 1216 (1962)

[7] The Upjohn Co., Brit. Pat. 866,995; *Chem. Abstr.* **57**, 3524[e] (1962)

[8] A. J. Birch and S. M. Mukherji, *J. Chem. Soc.* 2531 (1949)

[9] The diol 7 was first described by F. A. Kincl, H. J. Ringold and G. Rosenkranz, *J. Org. Chem.* **22**, 1127 (1957). No acetylated derivatives were prepared

[10] C. Djerassi and M. Gorman, *J. Am. Chem. Soc.* **75**, 3704 (1953)

[11] J. W. Chamberlain, *Steroid Reactions* (Edited by C. Djerassi), p. 164. Holden-Day, San Francisco (1963)

[12] A. S. Kende, *Tetrahedron Letters* 13 (1959)

[13a] E. J. Corey, *J. Am. Chem. Soc.* **75**, 2301 (1953); [b] E. J. Corey, *Experientia* **9**, 329 (1953); [c] J. Allinger and N. L. Allinger, *Tetrahedron* **2**, 64 (1958)

[14] D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chem. & Ind.* 21 (1954)

[15a] S. G. Levine, N. H. Eudy and C. F. Leffler, *J. Org. Chem.* **31**, 3995 (1966); [b] S. G. Levine, N. H. Eudy and E. C. Farthing, *Tetrahedron Letters* 1517 (1963)

[16] C. W. Beckett, N. K. Freeman and K. Pitzer, *J. Am. Chem. Soc.* **70**, 4227 (1948)

[17] N. L. Allinger and F. M. Karkowski, *Tetrahedron Letters* 2171 (1965)

[18] Ref 5, p. 112

[19] L. F. Fieser and M. Fieser, *Steroids* p. 825. Reinhold, New York (1959)

[20] Ref 15*a*, footnote 25, p. 3998

[21] N. L. Allinger, P. Crabbé and G. Pérez, *Tetrahedron* **22**, footnote 13, p. 1616

[22] Ref 4, p. 151

[23a] R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.* 806 (1963); [b] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field* p. 145. Holden-Day, San Francisco (1964)

[24a] N. L. Allinger, M. A. DaRooge, M. A. Miller and B. Waegell, *J. Org. Chem.* **28**, 780 (1963); [b] T. A. Wittstruck, S. K. Malhotra, H. J. Ringold and A. D. Cross, *J. Am. Chem. Soc.* **85**, 3039 (1963)

[25a] G. Snatzke, *Tetrahedron* **21**, 413 (1965); [b] C. Djerassi and W. Klyne, *Proc. Nat. Acad. Sci.* **48**, 1093 (1962)

[26a] R. J. Kirdani and D. S. Layne, *J. Med. Chem.* **7**, 592 (1964); [b] A. D. Cross, E. Denot, R. Acevedo, R. Urquiza and A. Bowers, *J. Org. Chem.* **29**, 2195 (1964); [c] R. Gardi, C. Pedrali and A. Ercoli, *Gazz. Chim. Ital.* **93**, 1504 (1963); [d] J. Perez-Ruelas, J. Iriarte, F. Kincl and C. Djerassi, *J. Org. Chem.* **23**, 1744 (1958); [e] F. B. Colton, U.S. Pat. 2,729,654, *Chem. Abstr.* **50**, 11372[b] (1956)

[27] F. Sondheimer, R. Mechoulam and M. Sprecher, *Tetrahedron* **20**, 2473 (1964), and earlier references cited

[28a] W. B. Whalley, *Chem. & Ind.* 1024 (1962); [b] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, *J. Am. Chem. Soc.* **84**, 870 (1962)

[29a] T. A. Wittstruck, S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.* **85**, 1699 (1963); [b] D. J. Collins, J. J. Hobbs and S. Sternhell, *Tetrahedron Letters* 197 (1963)

[30] E. Farkas, J. M. Owen, M. Debono, R. M. Molloy and M. M. Marsh, *Ibid.* 1023 (1966)

[31a] G. Snatzke, *Tetrahedron* **21**, 421 (1965); [b] K. Kuriyama, E. Kondo and K. Tori, *Tetrahedron Letters* 1485 (1963)

[32] J. Jamamoto and H. Kaneko, *Tetrahedron* **21**, 2501 (1965)

[33a] A. J. Laskin, P. Grabovich, B. Junta, C. deLisle Meyers and J. Fried, *J. Org. Chem.* **29**, 1333 (1964); [b] O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.* **81**, 442 (1959)

[34] C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, *Ibid.* **72**, 4534 (1950)

[35] D. Burn, D. N. Kirk and V. Petrow, *Proc. Chem. Soc.* 14 (1960)

[36] W. F. Johns and J. Laos, *J. Org. Chem.* **30**, 123 (1965); Roussell-Uclaf, Belgian Pat. 617,259, *Chem. Abstr.* **59**, 2905[b] (1963)

[37] J. Zderic, H. Carpio, A. Bowers and C. Djerassi, *Steroids* **1**, 233 (1963), have reported that estra-4, 7-dien-3, 17-dione did not react with dichlordicyanobenzoquinone

[38] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.* **75**, 5366 (1953)

[39] F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *J. Am. Chem. Soc.* **79**, 1123 (1957)