($CDCl_3$) τ 7.95 (3, s, $COCH_3$), 7.40–8.70 (*ca.* 8, m, methylene and methine protons), 8.97, 9.08, and 9.16 [9, s, $C(CH_3)_2$ and $CHCH_3$]; mass spectral mol wt 196.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.42.

p-Nitrobenzoylation of 7.—Treatment of **7** (0.15 g) with *p*-nitrobenzoyl chloride (0.25 g) in dry pyridine (2 ml) at room temperature for 40 hr and work-up gave 0.2 g (68%) of the *p*-nitrobenzoate of **7** (**10**): mp 125° (EtOH); ir (KBr) 3120, 2964, 1720, 1605, 1526, 1350, 1295, 1122, 1110, and 715 cm^{-1}; nmr ($CDCl_3$) τ 1.79 (4, s, phenyl protons), 7.50–8.80 (8, methylene and methine protons), 8.91 and 9.02 [6, s, $C(CH_3)_2$], and 9.17 (3, d, J = 8.0 Hz, $CHCH_3$).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.29; H, 7.01; N, 4.63.

Formation of 2 from 7.—A mixture of **7** (0.15 g) and benzonitrile (0.20 g) was treated with sulfuric acid (2.0 g) for 1 day at room temperature. Work-up gave 0.14 g of crude product which exhibited a peak having the same retention time (7.5 min) with that of the main peak of **2** (the minor peak, 6.5 min) on vpc (silicone SE-30, at 250°).

Formation of 9 from 7.—A mixture of **7** (0.19 g) and acetonitrile (1.0 g) was treated with sulfuric acid (1.5 g) similarly. Vpc analysis (200°) of the products showed a peak having the same retention time with **9** (4.7 min).

Conversion of 7 to *exo*-Isocamphane.—Treatment of **7** (0.15 g) with *p*-toluenesulfonyl chloride (0.20 g) in pyridine (2 ml) gave **7**-tosylate (0.15 g) as an oil: ir (neat) 2960, 1603, 1365, 1195, 1180, 1043, 1030, 880, and 675 cm^{-1}. The tosylate was reduced with lithium aluminum hydride (0.5 g) in tetrahydrofuran (5 ml) under refluxing for 1 week. The product was taken in ether and was analyzed on vpc to reveal two main peaks. The major peak was recovered tosylate and the minor (*ca.* 5% peak area of the main peak) had the same retention time (6 min) with that of *exo*-isocamphane, which was prepared as a mixture of *exo* (85%) and *endo* (15%) isomers by catalytic reduction of camphene with Pd-C (10%) in ethanol,[13b] and had bp 160–165° and mp 54–60°.[24] Similar treatment of the alcohol from **8** revealed also isocamphane peaks in a low yield (*ca.* 3%).

Reaction of 1 with a Mixture of Sulfuric Acid and Acetic Acid. vi.—**1** (1.0 g, 0.008 mol) was stirred into an ice-cooled mixture of sulfuric acid (2.5 g) and acetic acid (4 ml), and the mixture was stirred for 20 hr at room temperature. Work-up as above afforded 0.45 g of paraffin-like oil, 0.16 g (13%) of the acetate **8**, and 0.38 g (34%) of the alcohol **7** in addition to a trace amount of **6**.

Registry No.—**1**, 16626-39-4; **2** (*exo*), 24454-04-4; **3**, 24454-00-0; **4**, 24454-01-1; **5**, 24454-02-2; **6**, 24454-03-3; **7**, 24454-05-5; **7** acetate, 24454-07-7; **9**, 24454-08-8; **10**, 24454-06-6; **8** (*endo*), 24454-35-1; **2** (*endo*), 24454-36-2.

(24) The isomer ratio was estimated from the relative peak area on vpc and nmr signal at τ 9.51; *cf.* ref 11.

Steroid Rearrangements. Reactions of a 16,17α-Epoxypregnan-20-one with Hydrogen Fluoride and Thermal Dehydrofluorinations

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Treatment of 16,17α-epoxypregnan-3α-ol-11,20-dione acetate (**1**) with anhydrous hydrogen fluoride afforded a mixture from which three fluorine-containing steroids and three rearranged olefins were separated and their structures established. Two of the products were the unrearranged 16β-fluoro- and 17α-fluoropregnanes **11** and **12**, respectively. The remaining four products had formed as a result of migration of the 18-methyl to C-17, and were identified as the three isomeric C-ring olefins **2**, **3**, and **6**, and the 14-fluoro steroid **8**. Stereospecific thermal elimination of hydrogen fluoride from the tertiary fluoro steroids was employed to interrelate certain of the reaction products and as an aid to elucidation of their stereochemistry.

The reaction of steroid epoxides with hydrogen fluoride is a frequently used method for introduction of fluorine into various selected ring positions. Utility of this reaction for synthesis of 16-fluoro steroids, however, has been hampered by the well-documented[1,2] tendency for 16,17α-epoxy-20-keto steroids to undergo Wagner–Meerwein rearrangements involving shift of the angular methyl group from C-13 to C-17. Shapiro and coworkers,[3] for example, found that 16,17α-epoxyprogesterone was transformed into a rearranged Δ^{13} steroid upon treatment with hydrogen fluoride in chloroform containing ethanol.

Beyler and Hoffman[4] reported lack of success in preparing 16-fluoropregnanes by the action of hydrogen fluoride on the epoxy steroid **1** under a variety of conditions. An early patent report[5] claims synthesis of a 9,16-difluoro steroid by means of simultaneous opening of both oxirane rings in a 9,11β:16,17α-bisepoxy steroid with HF, but the properties of the 16-fluoro steroid were not described.

The original objective of this investigation, *i.e.*, synthesis of 16-fluorinated cortical steroids,[6] was broadened as the complexity of the HF-catalyzed reactions of **1** became apparent. Structures of the several reaction products were determined in order to provide a more detailed understanding of the multiple transformations involved.

Results

When **1** was allowed to react in a 1:1 HF–THF mixture for 5 hr at room temperature, about 70% of the epoxide was consumed, giving rise to a complex mixture of products. Examination of the mixture using tlc revealed six well-defined spots, and combinations of

(1) N. L. Wendler in "Molecular Rearrangements," Vol. II, P. DeMayo, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 16.

(2) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961), and references cited therein.

(3) E. L. Shapiro, M. Steinberg, D. Gould, M. J. Gentles, H. L. Herzog, M. Gilmore, W. Charney, E. B. Hershberg, and L. Mandel, *J. Amer. Chem. Soc.*, **81**, 6483 (1959).

(4) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

(5) C. G. Bergstrom, U. S. Patent 2,703,799 (March 8, 1955); *Chem. Abstr.*, **50**, 1935 (1956).

(6) Fluorohydrin E (**11**) served as an intermediate for synthesis of 16β-fluoroprednisone, mp 243–246°, $[\alpha]^{25}D$ +108° ($CHCl_3$), using standard procedures (D. R. Hoff, J. K. Bennett, and G. E. Arth, unpublished). Entirely different syntheses of the closely related 16β-fluorohydrocortisone acetate and 16β-fluoroprednisolone acetate were subsequently disclosed by other workers.[7]

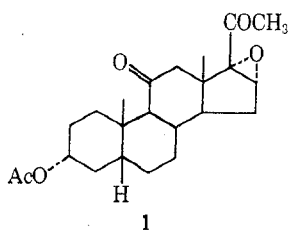
(7) (a) D. E. Ayer and M. P. Schneider, *J. Amer. Chem. Soc.*, **82**, 1249 (1960); (b) Fred Kagan, B. J. Magerlein, and R. D. Birkenmeyer, *J. Org. Chem.*, **28**, 3477 (1963).

preparative chromatography and fractional crystallization allowed resolution of the mixture into six components plus unchanged starting material.

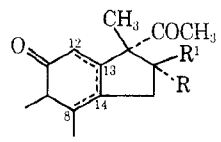
Each of three of the reaction products was the result of isomerization of the starting epoxy ketone, a process which generated an acetylatable hydroxy group and a double bond. In addition to the olefins, three fluorine-containing products, representing addition of hydrogen fluoride to the oxirane with or without subsequent rearrangements, were obtained.

For convenience in discussion, the reaction products will be designated olefins A, B, C and fluorohydrins D, E, and F, respectively. The assigned structures for these substances are shown in Chart I. Selected nmr data are presented in Table I.

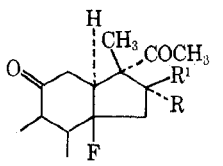
CHART I



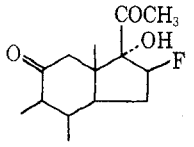
1



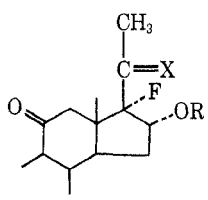
2, Δ^{12}; R = OAc; R¹ = H (olefin A)
3, Δ^{13}; R = OH; R¹ = H (olefin B)
4, Δ^{13}; R = OAc; R¹ = H
5, Δ^{13}; R = H; R¹ = OAc
6, $\Delta^{8(14)}$; R = OAc; R¹ = H (olefin C)
7, $\Delta^{8(14)}$; R = H; R¹ = OAc



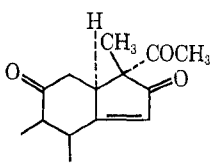
8, R = OH; R¹ = H (fluorohydrin D)
9, R = OAc; R¹ = H
10, R = H; R¹ = OAc



11 (fluorohydrin E)



12, R = H; X = O (fluorohydrin F)
13, R = Ac; X = O
14, R = H; X = NOCH₃



15

CrO_3
C_5H_5N

8

The structural assignments for the olefinic products rest on their elemental composition and spectral properties. Migration of the angular methyl group from C-13 to C-17 was assumed by analogy with the earlier reports,[1,2] and this assumption was supported in all three cases by shifts of the pertinent methyl signal downfield in the nmr spectrum. Finally, satisfactory assignment of the double bond positions required a methyl migration, since the signal due to the C-16 proton was observed in the 16-acetate of each compound, and vinyl protons were present only in olefin A, in which the double bond is conjugated with the 11-carbonyl group.

Placement of the double bond in olefin A (**2**) at the 12 position was dictated by the ultraviolet ($\lambda_{max}^{CH_3OH}$ 239, mμ, ε 11,000) and infrared spectra and by the C-12 vinyl proton resonance at τ 4.21 appearing as a doublet (allylic coupling with the C-14 proton, J = 2.4 Hz) in the nmr spectrum. The downfield position of the 10-methyl resonance (τ 8.63) and the intermediate position of the 17-methyl signal (τ 8.97) relative to that of olefins B and C (Table I) are consistent with the effects to be expected from polarization of the 11-keto-Δ^{12} system.

Olefins B (**3**) and C (**6**) are tetrasubstituted, as deduced from lack of vinyl proton resonances in the nmr spectra and from strong end absorption in the ultraviolet. Differentiation between the alternative Δ^{13} and $\Delta^{8(14)}$ bond position follows from the position of the nmr signal due to the shifted 17-methyl group. The 17-methyl in olefin B is strongly deshielded (τ 8.77), requiring placement of the double bond at the 12 position. That olefin C has the $\Delta^{8(14)}$ structure is supported by the higher position of its 17-methyl resonance at τ 9.10.

Olefin B 16-acetate (**4**), exhibits a strong positive Cotton effect in the ORD (a = +187) which is a composite of the strong dispersion curve expected from the 20-carbonyl and the weaker curve attributed to the 11-carbonyl. The ORD curve shown by olefin C 16-acetate is, on the other hand, characterized by a strong negative Cotton effect (a = −167). Although distinction between the $\Delta^{8(14)}$ and Δ^{13} olefins rests on the chemical shift of the rearranged 17-methyl protons, these ORD curves provided useful supportive information for correlating structures with unsaturation in these positions. In each of the four isomers **3** through **7**, those with the double bond at 13 exhibited the characteristic strong positive curve, whereas the $\Delta^{8(14)}$ olefins were characterized by similar strong negative curves. Furthermore, the shape and magnitude of the curves were substantially identical whether the acetoxy group at C-16 was α or β. These observations can be satisfyingly rationalized by inspections of models. In contrast to 17β-acetyl steroids, in which the dispersion curves are influenced by orientation of substituents at C-16, the ORD curves and hence the 17α-acetyl side-chain disposition in the rearranged steroids depend on the geometry of the C–D ring junction but not at all on the nature of substitution at C-16.

Fluorohydrin E was readily recognized as the normally expected 16β-fluoro-17α-ol (**11**) by its easy reconversion to the starting epoxide **1** by means of mild alkaline treatment. Protons at C-21 are coupled with the fluorine (J = 4 cps), but the C-18 hydrogens appear as a singlet in the 60-MHz spectrum.

Location of the fluorine in fluorohydrin F (**12**) at the 17 position was established by these observations. The C-21 protons are split into a doublet (J = 6 cps). Acetylation gave the 3,16-diacetate (**13**) in which the C-16 hydrogen was revealed as a pair of triplets centered at τ 4.59. The vicinal H–F coupling constant was 16.2 Hz. The angular methyl resonances in **12** appeared at the expected positions (τ 8.86 and 9.33, respectively) for an unrearranged steroid, and the C-18 protons were not coupled to the fluorine. Thus the gross structure was revealed as a 16-hydroxy-17-fluoro steroid. The ORD curve of fluorohydrin F

TABLE I

NMR ASSIGNMENTS[a]

Compound	Methyl resonances[b] C-21	C-19	C-18	17-CH_3	16-H	Other
2	7.82	8.63		8.97	4.81	C-12 proton: τ 4.21; J = 2.4 Hz
3	7.77	8.77		8.77		
4	7.82	8.77		8.75	4.78	
5	7.77	8.88		8.78	4.49	
6	7.88	8.88		9.10	4.73	
7	7.93	8.83		9.00	4.33	
8	7.76	8.92		9.03		
9	7.86	8.82		9.03	4.78	C-13 proton: τ 6.86[c]
10	7.80	8.89		9.03	4.45	
11	7.63[d]	8.83	9.00		5.00[e]	17α-OH doublet: τ 5.72; J = 1.8 Hz
12	7.77[f]	8.86	9.33			
13	7.83[f]	8.84	9.32		4.59[g]	
14	8.19	8.86	9.38			
15	7.68	8.87		8.69		C-15 proton: τ 4.06[h]
16	8.16	8.82	9.22			
17	8.16	8.82	9.03		4.03[i]	
18	8.22	8.82	8.72		4.76[j]	
20	8.22	8.88		8.88	4.65	
21	8.22	8.87		8.87		
22	8.16	8.88	9.15		6.18	
23	8.00	8.88	9.21		6.20	
24	8.17	8.89		8.78	4.63	
26	7.76	8.85	8.90		4.23	

[a] Determined in $CDCl_3$, using TMS as the internal standard, with Varian Associates A-60D spectrometer. The observations in footnotes *c*, *i*, and *j* were taken from spectra obtained with the Varian HA-100 instrument. [b] Singlets, except where noted. [c] Octet, J_{FH} = 35 Hz; J_{HH} = 14, 6 Hz. [d] Doublet, J = 4 Hz. [e] Pair of multiplets, J_{FH} = 48 Hz. [f] Doublet, J = 6 Hz. [g] Pair of triplets, J_{FH} = 16.2 Hz. [h] Quartet, J = 2.1, 0.9 Hz. [i] Octet, J_{FH} = 22 Hz. [j] Octet, J_{FH} = 24 Hz.

reveals a strong positive Cotton effect (a = +154), suggesting a 17α-fluoro-17β-acetyl configuration. Furthermore, the ORD curve measured in methanol was identical with that in dioxane. Danielewicz and Klyne[8] showed, in related models, that 16β substitution diminishes the amplitude of the positive Cotton effect arising from the 20-carbonyl in 17β-acetyl steroids, whereas 16α substitution has little effect. More significantly, 16β-hydroxy-5α-pregnan-20-one showed a positive Cotton effect in hexane, but a plain curve in methanol. This finding was explained as owing to hydrogen bonding with the solvent, resulting in loss of the preferred conformation which gives rise to the anomalous dispersion curve in the aprotic solvent. Applying this analogy to fluorohydrin F requires placement of the 16-hydroxy group in the α position. Thus the complete structure of fluorohydrin F is established as 17α-fluoropregnane-3α-16α-diol-11,20-dione 3-acetate (**12**). Assignment of the *cis*-fluorohydrin structure is supported by the high stability of this substance to prolonged treatment with alkali. It was unaffected (except for ester hydrolysis) by 18 hr of standing in a solution of 40% potassium hydroxide in 1:1 aqueous methanol.

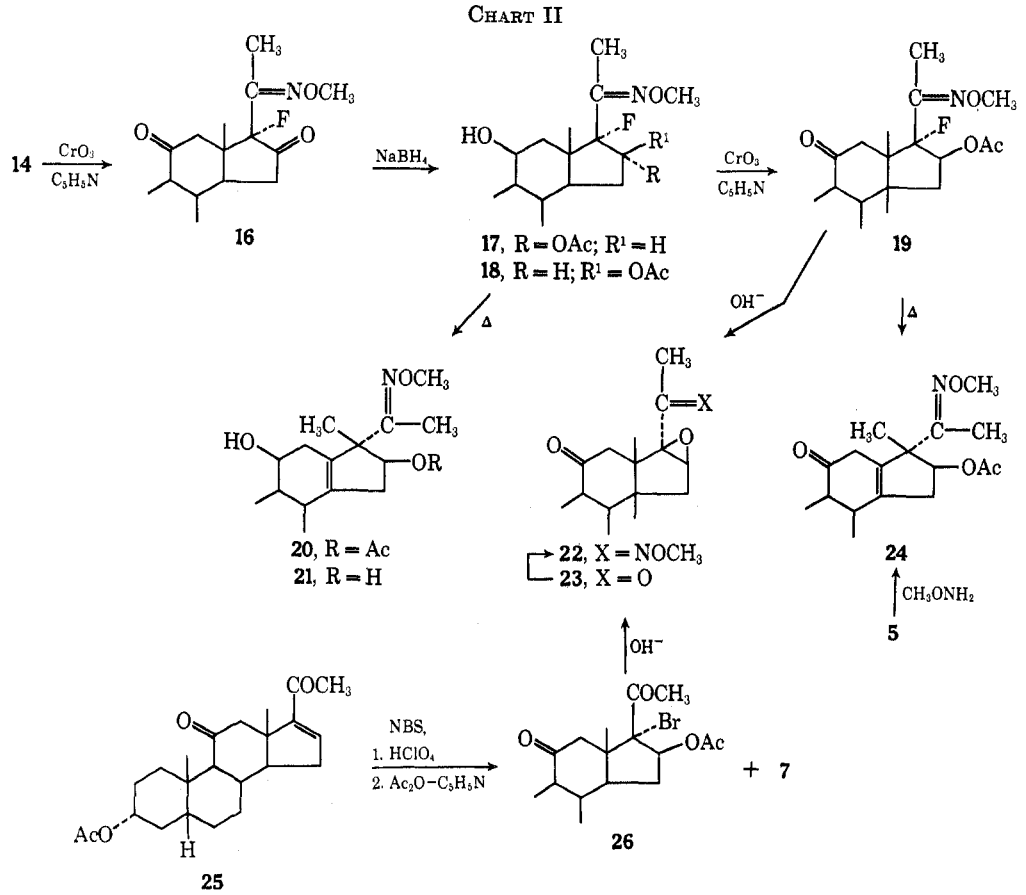
The assigned structure for fluorohydrin F was confirmed unambiguously by means of the transformations outlined in Chart II. Its 20-methoxime **14** was prepared and oxidized to the 16 ketone **16**. Sodium borohydride reduction followed by acetylation then afforded the pair of isomeric 16 acetoxy steroids **17** and **18**. Independent preparation of the 16α-acetoxy isomer **17** by sodium borohydride reduction of **14** allowed differentiation of the two isomers. The 16β-acetoxy isomer **18** was characterized by a low-field position of the C-18 methyl protons at τ 8.72. The 16,17 F–H coupling constants for **17** and **18** were 22 and 24 Hz, respectively. Determination of the nmr spectrum of **18** at 100 MHz allowed resolution of the C-18 methyl proton signal into a doublet (J = 1.3 Hz). Reoxidation of the 11-hydroxy in **18** gave the 11 ketone **19**, which readily afforded the 16,17β-oxide **22** upon alkaline treatment followed by reacetylation. When the *cis*-fluorohydrin acetate **17** was subjected to identical conditions, unchanged starting material was recovered in good yield after reacetylation. The 16,17β-epoxy steroid **22** was independently prepared from the bromohydrin acetate **26**, using similar ring-closure conditions, subsequent acetylation, and 20-methoxime formation.

The presence of the fluorine atom in fluorohydrin D had no obvious effect on the features of the 60-MHz pmr spectrum; *i.e.*, neither the angular methyl hydrogens nor the protons at C-16 and C-21 were coupled to the fluorine. The ^{19}F mr spectrum (94.1 MHz) was symmetrical and centered at −20.26 ppm relative to internal C_6F_6.[9] The 16-line pattern (five lines superimposed) yielded to a first-order analysis, fitting apparent F–H coupling constants of 35, 29, 29, and 23 Hz. One proton, located vicinal to the fluorine, moreover, was visible in the 100-MHz pmr spectrum of the 16-acetate **9**. It appeared as eight lines centered at τ 6.86, with coupling constants of 35, 14, and 6 Hz. These observations are interpreted as requiring the presence of the $(-CH)_2CFCH_2-$ grouping, since the observed F–H splittings are in the normal range for vicinal F–H coupling constants. This requirement excludes C-13 but ideally fits C-14 for the location at the fluorine atom. The eight-line methine signal at τ 6.86 is then assigned to the C-13 proton which is coupled to the 14-fluorine (35 Hz) and to the two C-12 protons (14 and 6 Hz). The alternative C-15 location for this proton is excluded

(8) J. C. Danielewicz and W. Klyne, *J. Chem. Soc.*, 1306 (1965).

(9) The author is indebted to Dr. W. L. Budde, Midwestern Research Institute, Kansas City, Mo., for measurement of this spectrum.

CHART II



since the observed splittings did not coincide with the known H-15,H-16 coupling constants.

The provisional formulation of fluorohydrin D as a 14-fluoro-17-methyl-18-nor-17-isopregnane-3,16-diol-11,20-dione (**8**) is further supported by the position (τ 9.03) of the 17-methyl resonance and the appearance of the ORD curve of its 16-acetate, which exhibits a strong negative Cotton effect (a = −166). These two features are comparable to the corresponding observations with olefin C, in which the corresponding C-methyl peak appears at τ 9.10, and the ORD has the same sign and amplitude (−169) of the Cotton effect.

Confirmation of the proposed fluorohydrin D formulation was obtained in the following ways.

(1) Oxidation with chromic anhydride in pyridine[10] resulted in spontaneous loss of hydrogen fluoride, yielding the Δ^{14}-16-one **15**: λ_{max}^{Nujol} 1695, 1613 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 237 mμ (ϵ 13,000). The C-15 proton resonance in **15** appeared as a quartet (τ 4.06) with splittings of 2.1 and 0.9 Hz, respectively, due to allylic coupling with the protons at C-8 and C-13. By way of contrast, fluorohydrin D itself experienced no loss of fluorine even under conditions of drastic alkaline treatment.

(2) Fluorohydrin D is unstable at its melting point, spontaneously eliminating hydrogen fluoride. When a sample of its 16-acetate (**9**) was subjected to a temperature of 211° for 2 min *in vacuo*, an elimination of hydrogen fluoride was complete, and an excellent yield (81%) of olefin B 16-acetate (**4**), was obtained.

(3) Solvolysis of fluorohydrin D 16-acetate (**9**), in the presence of aqueous sodium bicarbonate gave rise to a 60:40 mixture of two substances, separable by chromatography after reacetylation. The lesser component was identified as recovered starting material. The other was a product isomeric with **9**. The new isomer was identified as the 16β-acetoxy epimer **10** from these data: In the nmr spectra of **9** and **10**, only the resonances of the protons at C-16 differ appreciably between the two isomers. This signal shifted downfield from τ 4.78 in **9** to τ 4.45 in **10**. The ORD curves of **9** and **10** show Cotton effects with essentially the same sign, shape, and amplitude (−166 and −174, respectively), and, in fact, the two curves are distinguishable only in that **10** is shifted to more positive rotations at all wavelengths. The same product mixture was obtained by solvolysis of **10** demonstrating establishment of an equilibrium between **9** and **10**. This observation is of consequence for fixing the stereochemical assignments at C-13 and C-14 in fluorohydrin D, a subject which is conveniently deferred to the discussion section.

Although a complete quantitative separation of the products obtained by the actions of HF on **1** was not attempted, the major products were clearly the unconjugated olefins **3** and **6** and the fluorinated steroids **8** and **12**, each obtained in at least 5–10% yield. The best yield of the normally expected product **11** was 1.8%. The conjugated olefin **2** was formed in negligible (*ca.* 0.1%) quantity, and its presence could not be detected even by measurement of the ultraviolet absorption spectrum of the crude reaction mixture.

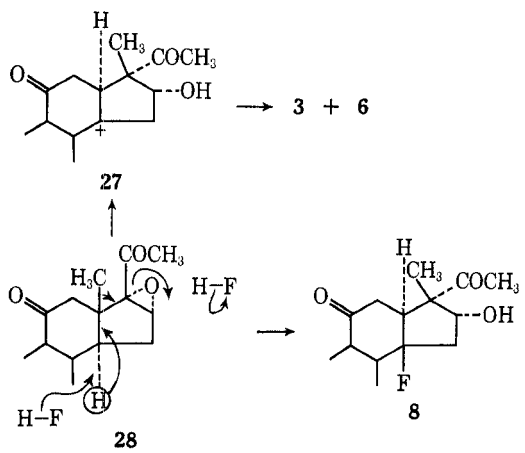
Synthesis of the bromohydrin acetate **26** by addition of HOBr to **25** followed by acetylation was complicated by formation of a bromine-free by-product. The

(10) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

elemental analysis, a negative Cotton effect in the ORD ($a = -153$), and the appearance in the nmr spectrum of a C-methyl resonance at τ 9.00 and a proton signal at τ 4.33 (16 H) allow assignment of the $\Delta^{8(14)}$ structure **7** to this product.

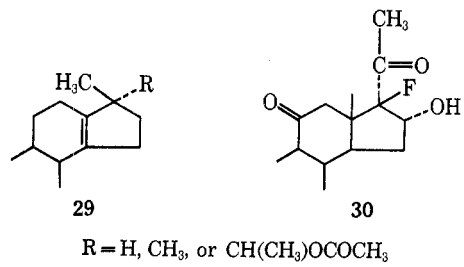
Discussion

Rearrangements Induced by Hydrogen Fluoride.—Prominence of the nonconjugated olefins **3** and **6** and of the 14-fluoro steroid **8** in the reaction mixture, coupled with the very minor amount of conjugated olefin **2** observed, elevates the significance of the center at C-14 in the rearrangement under discussion. The apparent stereochemical homogeneity in the series of observed products favors a fully concerted mechanism involving migration of the 14α hydrogen to C-13.



Alternative multistep processes entailing, for example, double-bond migration from Δ^{13} to $\Delta^{8(14)}$ or intermediate formation of a transient C-13 cation, must be considered, though the further possibility of HF addition to a tetrasubstituted olefin is not likely. Evidence, to be developed later, for the 14β orientation of the entering fluorine atom provides support for the proposed mechanism.

Numerous examples of steroid rearrangements with C-13 → C-17 methyl migration have been reported,[1,10] and the olefinic products were usually assumed to have the unsaturation at Δ^{13} position. Survey of the recent examples for which nmr data are supplied showed 13 different products assigned the C/D part structure



R = H, CH_3, or $CH(CH_3)OCOCH_3$

29. Two of these,[11] both having R = CH_3, had 17-methyl signals at τ 8.48 and 8.52 ($CDCl_3$, 60 MHz). The remaining 11 examples had 17-methyl resonances in the range of τ 9.00–9.04.[12–16] In keeping with the findings of the present study, the rearrangement products with the higher field position of the 17-methyl might reasonably be reformulated as $\Delta^{8(14)}$ olefins.

It is clear from a review of these many rearrangements that the final location of the unsaturation is determined by the reaction conditions. When the rearrangement was brought about by prolonged acid treatment, particularly in protic solvents, the $\Delta^{8(14)}$ product was formed. In the few cases where the Δ^{13} product could be isolated, the reaction conditions are found to have been much milder and briefer.

The *cis*-fluorohydrin **12** may be rationalized as a secondary product arising from a reverse epoxide cleavage, affording the 17β-fluoro steroid **30** followed by inversion of the configuration at C-17 *via* a retro-aldol–realdolization sequence. An immediate precedent for this possibility is provided by the cleavage of 16,-17β-epoxy-17-iso-5-pregnen-3β-ol-20-one acetate with hydrazoic acid, affording a mixture of *cis* and *trans* azidohydrins.[17] Direct *cis*-epoxide opening in rigid rings has been observed,[18] but the explanation invoked in that instance is not directly applicable here, since alternatives to fluorine attack at C-17 clearly exist.

The extraordinarily facile interconversion of the epimers **9** and **10** must likewise be attributed to D-ring opening and reclosure.

Thermal Dehydrofluorination Reactions.—The smooth thermal elimination of hydrogen fluoride from fluorohydrin D 16-acetate (**9**), affording **4**, was paralleled by an equally facile conversion of the 16 epimer **10** to a new tetrasubstituted olefin. The position of the 17-methyl proton resonance at τ 8.78 and the negative Cotton effect in the ORD ($a = -182$) readily established the identity of the new product as the 16β-epimer (**5**) of olefin B 16-acetate.

Although alkyl fluorides, particularly tertiary fluorides, are known to be thermally unstable, the mechanism and stereochemical significance of the thermal HF elimination appears to have been little investigated.

Decomposition of the 14-fluoro steroids **9** and **10** was virtually instantaneous at around 205°. At lower temperatures the dehydrofluorination was equally fast, but an induction period of up to several minutes was required. Plots of induction time *vs.* temperature of a variety of tertiary fluorides are smooth curves characteristic of the particular compound and provide estimates of the relative ease with which any given fluoride can undergo this elimination. As an example, 9α-fluorohydrocortisone acetate requires a temperature of 282° to promote HF elimination within 30 sec. Preparative thermal dehydrohalogenations with this steroid were unpromising owing to the higher temperatures required. Presence of impurities often hastens onset of the reaction.

Rather unexpectedly, the 17α-fluoropregnane **18** also eliminated hydrogen fluoride with ease at moderate

(11) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

(12) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

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(17) K. Ponsold, B. Schönecker, and I. Pfaff, *Chem. Ber.*, **100**, 2957 (1967).

(18) N. G. Bisset, *Tetrahedron Lett.*, **27**, 3107 (1968).

temperatures. In a preparative run, a 60% yield of a single fluorine-free product **20** was obtained. Noncrystalline **20** was characterized by means of its mass spectrum (parent peak at *m/e* 462) and nmr spectrum [τ 4.65, (16 H), 8.88, (angular methyls)] which allowed its formulation as a rearranged Δ^{13} steroid. Mild hydrolysis of **20** afforded the crystalline triol **21** which was fully characterized by its mass and nmr spectra and its elemental composition.

The corresponding 11 ketone **19** similarly evolved hydrogen fluoride, yielding **24** in 90% yield. The mass and nmr spectra were again in full accord with the structure shown. The rearranged product **24** was identical with the 20-methoxime of the independently obtained Δ^{13} steroid **5**, as shown by comparison of the ir, nmr, and high resolution mass spectra of the two samples. This comparison confirmed structures previously assigned to **10** and **5**.

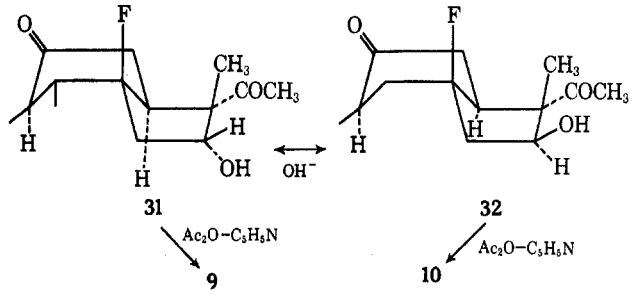
The thermal dehydrofluorination reaction is most likely an acid-catalyzed (by HF) *trans* elimination. Observation of an induction period is suggestive, and the reaction is enormously faster than uncatalyzed gas-phase eliminations of other hydrohalides. Vapor-phase elimination of HCl, HBr, or HI is presently considered to be a two-step process initiated by heterolysis of the C–X bond,[19] rather than the concerted *cis* elimination which had previously been postulated.[20] In the case of HF eliminations, two separate mechanisms are probably operating. The initial uncatalyzed elimination would be too slow to observe directly, but a buildup of product HF could promote the fast acid-catalyzed reaction.

The postulate of a *trans* elimination accounting for at least the majority of the product is buttressed by observation of eliminations with methyl migration in **18** and **19**. The migrating methyl is *trans* to the departing fluoride and the *cis*-16 proton is undisturbed.

Stereochemistry.—Use of the thermal dehydrofluorination reaction served to interrelate the olefin B and fluorohydrin D series, and the fluorohydrins D and F series were independently converted to the common product **24**. As a result of these manipulations, configurations at C-16 and C-17 were defined for all three series. Any prior uncertainty on this point arises from the demonstrated opportunity for 16-hydroxy-20-ketopregnanes to undergo ring-opening reactions which may lead to inversion at C-16 or C-17. Since no such inversion was encountered under the conditions of the HF reactions, it seems safe to assume the regular C-16 and C-17 assignments made for the olefins A and C series.

Configuration at the C–D ring junction in **8**, **9**, and **10** was initially assigned as shown (13α-H,14β-F) from consideration of the probable mechanism by which these compounds might have been formed. Several independent lines of evidence converge in support of the proposed formulation.

If the thermal HF elimination (**9** → **4** and **10** → **5**) is indeed *trans*, and if the hydrogen at C-13 arrives initially *via* a stereospecific C-14 → C-13 migration, the postulated 13α-H,14β-F configuration must be correct. The observed equilibrium between **9** and **10** in the presence of mild aqueous base is fully in accord with this conclusion. Inspection of Dreiding models of all four possible configurations about the 13–14 bond reveals that only in the 13α-H,14β-F arrangement (**29** and **30**) are the 16α and 16β substituents projected in conformations of approximately equal energy. The C-ring is in the boat form with the 9α and 13α hydrogens in the flagpole positions. Furthermore, the 17α bond has a pronounced pseudoequatorial character, an observation consonant with the finding that the more bulky acetyl group remains at the preferred 17α position in both components, **31** and **32**, of the equilibrium mixture.



The major alternative formulation to be considered, with 14α-F and 13α-H is clearly ruled out. Whether the C ring assumes a boat (or worse) chair conformation, the 16β position is overwhelmingly less favorable for substitution. Similar analysis of the remaining 13β-H, 14β-F, and 14α-F possibilities rule them out as serious competitors, with the slight reservation that the flexibility allowed the D ring in some isomers leaves a residue of uncertainty as to the actual conformation of the D ring.

Consideration of the apparent vicinal F–H coupling constants in **9** provides further corroboration for the assumed stereochemistry. The intuitive supposition that the dihedral angle dependence for F–H vicinal couplings should be qualitatively similar to the parallel H–H coupling (Karplus) relationship was supported to a degree by data collected by Williamson, Hsu, Hall, Swager, and Coulter.[21] These workers estimated maximum F–H coupling constants of 31 $COS^2\phi$ for angles (ϕ) between 0 and 90° and 44 $COS^2\phi$ for angles between 90 and 180°.

These estimated values fit the observed coupling constants in **9** quite well. The required assumption of a boat configuration for the C ring in the 13α-H,14β-F structure confers a degree of rigidity which may allow a fairly accurate estimate of the associated dihedral angles from the Dreiding model. The measured angles, along with the calculated and observed coupling constants for this structure are listed in Table II.

TABLE II

Dihedral angle		F–H, Hz	
Between 14β-F and	Degree	Calcd	Obsd[a]
13α-H	165	42	35
8β-H	150	33	29
15α-H	155	32	29
15β-H	25	26	23

[a] Individual assignments are of course arbitrary except for that of the 13α-H–14β-F coupling constant which was observed in the proton spectrum.

(19) A. Maccoll, *Advan. Phys. Org. Chem.*, 91 (1965).
(20) D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949).
(21) K. L. Williamson, Y-F. L. Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *J. Amer. Chem. Soc.*, **90**, 6717 (1968).

Although analogous analyses are possible for the remaining isomeric possibilities, conclusions are necessarily hazardous because of the greater flexibility in these models and related uncertainty surrounding the actual D-ring conformation. Nonetheless, the 13α-H,-14α-F possibility again seems clearly ruled out. Regardless of the conformation (C-ring boat or chair, or twist form), models show that one of the protons at C-15 must assume a dihedral angle with the C–F bond close to 90°, thus observation of at least one smaller coupling constant would be expected in this isomer.

Long-Range F–H Coupling.—Having in hand three new classes of D-ring fluorinated steroids, discussion of geometrical effects on long-range F–H coupling is appropriate.

Since F–H coupling constants may be quite large, long-range splitting is frequently visible in fluorinated hydrocarbons, and much discussion in the literature surrounds the questions of the mechanism and the spatial requirements for such long-range coupling. Cross and Landis[22–25] surveyed a group of fluoro steroids and formulated the "converging vector rule" defining geometric conditions which must be met if coupling between the fluorine and one of the angular methyl groups is to occur through five or more intervening σ bonds. The rule states that vectors drawn away from the carbon along the C–F bond, and the C–H bond must be capable of intersecting. The rule but states the minimum requirement for long-range coupling. Other factors may certainly prevent coupling even when the rule is satisfied. Excessive length of the σ chain[24] and internuclear distance[25] are two such factors.

Data from the present study suggest that when the angular methyl group and the fluorine are both situated on the five-membered D ring, caution is required in the application of the converging vector rule to assignment of structures.

Fluorohydrin E (**11**), with firmly established stereochemistry, provides an anchor point for the discussion. The converging vector rule predicts that long-range coupling between the 16β-fluorine and the angular methyl (C-18) protons, and the 21-methyl protons may occur. These hydrogens and the fluorine are separated by five σ bonds. In fact, the 21-methyl hydrogens were coupled to the fluorine (J = 4 Hz), but no splitting or even line broadening of the 18-methyl signal was observed. Cross and Landis[23,24] presented examples of 16β-fluoro steroids in which 16-F–18-H coupling (0.5–1.5 Hz) was seen. These examples were 17 ketones, suggesting the possibility that transmission of spin information through a sp^2-hybridized carbon atom may be more efficient than through a fully saturated σ skeleton. This possibility is enhanced by the observation of substantial (4 Hz) coupling of fluorine with the 21-methyl protons in fluorohydrin E. More likely, ring deformations in certain fused five-membered rings may interfere with effective coupling. Bonds to substituents on a cyclopentane ring, moreover, lack the parallel relationship of those to *trans* diaxial substituents on a cyclohexane ring. In the former case, the combination of greater internuclear distances and intervening bond angle distortions may suffice to prevent coupling.

Turning now to the fluorohydrin D series (**8** through **10**), it will be noted that acceptance of a β orientation for fluorine at C-14 requires consideration of the converging vector rule in this instance as well. The observation was made that the C-17 angular methyl group must possess a pseudoaxial configuration. The rule predicts the possibility that the angular methyl protons may couple with the fluorine, whereas no coupling was observed. Except for the reservations brought forth in the foregoing discussions, lack of coupling here might be taken as evidence *against* the 14β-F orientation. Because of the lack of 18-H–16β-F coupling in fluorohydrin E, however, the force of this contrary evidence is great diminished.

Finally, attention is called to the 17α-fluoropregnanes **12** to **14** and **16** to **19**. The converging vector rule does not apply (18-methyl and 21-methyl hydrogens separated from the fluorine by 4 σ bonds). A small 18-H–17α-F coupling was observed in one case (**18**, J_{FH} = 1.3 Hz). More interestingly, 21-H–F coupling to the extent of 6 Hz was seen in the ketones **12** and **13** but not with the methoxime derivatives **14** and **16** to **19**. Either the methoximino grouping does not alow transmission of spin information, or derivatization changes the side-chain orientation in a way that is unfavorable to spin coupling.

Experimental Section[26]

Reaction of 16,17α-Epoxypregnan-3α-ol-11,20-dione Acetate[27] (1) with Hydrogen Fluoride.—Anhydrous hydrogen fluoride (113.7 g, 5.68 mol) was condensed in a dry polyethylene bottle surrounded by a Dry Ice–acetone bath. Tetrahydrofuran (57.4 g, 7.96 mol) was cooled in a Dry Ice bath and added to the HF in 1 portion. To this reagent mixture was added a solution of 1 (44.6 g, 0.114 mol) in 600 ml of chloroform and 112.5 ml of tetrahydrofuran. The solution was cooled to about −30° before adding it to the HF reagent. The reaction mixture was then allowed to stand exposed to room temperature for 5 hr, after which time it was poured over a slurry of ice and water containing about 500 g of sodium bicarbonate. The steroid mixture was extracted with 3 l. of chloroform which, after washing with water and drying (Na_2SO_4), was concentrated *in vacuo* to a red oil. The oily product was dissolved twice in ether and evaporated to remove traces of chloroform, and then was dissolved in about 200 ml of ether, and the resulting solution was filtered and allowed to stand. The crystalline product, fluorohydrin F (**12**), amounted to 1.3 g, mp 239–253°. An additional 0.5 g was obtained by repeating the crystallization in ether from the total reaction product. The combined fluorohydrin F fraction was purified by recrystallization from acetone: first crop 1.30 g, mp 257–261°; second crop, 0.21 g, mp 251–259°. The analytical sample was obtained from acetone: mp 258–260°; $[\alpha]^{23}D$ +86° (*c* 1.11, $CHCl_3$).

Anal. Calcd for $C_{23}H_{33}FO_5$: C, 67.62; H, 8.14; F, 4.65. Found: C, 67.83; H, 8.24; F, 4.41.

Acetylation afforded the diacetate **13**: mp 179–181° (acetone–ether); $[\alpha]^{23}D$ +142° (*c* 1.015, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}O_6F$: C, 66.64; H, 7.83; F, 4.22. Found: C, 66.57; H, 7.65; F, 4.46.

Hydrolysis of fluorohydrin F in refluxing aqueous methanol containing sodium bicarbonate gave the diol: mp 215–216°; $[\alpha]^{23}D$ +68° (*c* 0.84, $CHCl_3$).

(22) A. D. Cross and P. W. Landis, *J. Amer. Chem. Soc.*, **84**, 1736 (1962).
(23) A. D. Cross and P. W. Landis, *ibid.*, **84**, 3784 (1962).
(24) A. D. Cross and P. W. Landis, *ibid.*, **86**, 4005 (1964).
(25) A. D. Cross, *ibid.*, **86**, 4011 (1964).

(26) Melting points are uncorrected. Ultraviolet spectra were determined with the Cary Model 11 recording spectrophotometer, and the ir spectra were measured with the Perkin-Elmer Model 137 infracord. ORD dispersion curves were obtained with a Cary 60 spectropolarimeter, and mass spectra were obtained with CEC 21-110 high-resolution spectrometer.
(27) P. L. Julian, W. Cole, E. W. Meyer, and B. M. Regan, *J. Amer. Chem. Soc.*, **77**, 4601 (1955).

Anal. Calcd for $C_{21}H_{31}O_4F$: C, 68.82; H, 8.53; F, 5.18. Found: C, 68.52; H, 8.57; F, 4.84.

All filtrates after isolation of fluorohydrin F were recombined. One-tenth of this material, amounting to 4.54 g, was chromatographed over a column of silica gel (1 lb). Initial elution with 20% ether–petroleum ether afforded, after a small amount of oily impurity, 1.31 g of unchanged **1**, amounting to 29%.

Continued elution with 50% ether–petroleum ether gave a mixture containing chiefly olefin B (**3**) contaminated with some fluorohydrin F. Later fractions were nearly pure olefin B. Recrystallization several times from ethyl acetate yielded a sample melting at 189–192°.

Anal. Calcd for $C_{23}H_{32}O_6$: C, 71.10; H, 8.30. Found: C, 70.97; H, 8.04.

Contaminants in the olefin B fractions were more readily removed after acetylation to give the 3,16-diacetates. Thus, 605 mg of acetylated material was chromatographed over 60 g of silica gel. Elution with 33% ether–petroleum ether removed fluorohydrin F diacetate, and pure olefin B diacetate was obtained by elution with 50% ether–petroleum ether. Crystallization from 2-propanol afforded a solvate, mp 46–49°, containing 2 mol of 2-propanol.

Anal. Calcd for $C_{25}H_{34}O_6 \cdot 2C_3H_8O$: C, 67.60; H, 9.15. Found: C, 67.69; H, 8.86.

Composition of the solvate was confirmed by the nmr spectrum. Unsolvated noncrystalline olefin C diacetate, homogeneous by nmr, was employed for the rotation measurements, $[\alpha]^{25}D$ −4.0° (*c* 0.512, $CHCl_3$).

Continued elution after removal of olefin B diacetate yielded about 75 mg of crystalline olefin A (**2**): mp 188–189° (ethyl acetate–hexane); $[\alpha]^{25}D$ −98.2 (*c* 0.7965, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 11,000).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.37; H, 8.06.

After removal of the olefin B and olefin A fractions, the original column was stripped with ether, yielding a complex mixture whose major components were fluorohydrins D (**8**) and E (**11**), and additional olefin B. This fraction, amounting to 1.35 g, was rechromatographed over 135 g of silica gel. Elution with 70% ether–petroleum ether gave first the olefin B fraction, then intractable mixtures, then pure fluorohydrin D: mp 205–206° dec; $[\alpha]^{25}D$ −156.3° (*c* 1.005, $CHCl_3$). The analytical sample was obtained from ethyl acetate, mp 206° dec.

Anal. Calcd for $C_{23}H_{33}FO_5$: C, 67.62; H, 8.14; F, 4.65. Found: C, 67.65; H, 8.19; F, 4.58.

Acetylation afforded the diacetate **9**, mp 201–203° dec. Recrystallization from acetone–ether afforded the analytical sample: mp 201–202.5° dec; $[\alpha]^{23}D$ −159° (*c* 1.145, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}FO_6$: C, 66.64; H, 7.83; F, 4.22. Found: C, 66.75; H, 8.10; F, 4.0.

After removal of as much olefin B and fluorohydrin D as possible from the fraction under investigation (obtained by eluting the original column with ether), all filtrates were recombined and acetylated. This procedure allowed isolation of fluorohydrin E (**11**) in pure form. A total of 507 mg of acetylated materials was chromatographed over 50 g of silica gel. Flurohydrin E was obtained by elution with 50% ether–petroleum ether, mp 224–230°. After three recrystallizations from ethyl acetate, material melting at 238–242° was obtained: $[\alpha]^{24}D$ +54° (*c* 0.94, $CHCl_3$).

Anal. Calcd for $C_{23}H_{33}O_5F$: C, 67.62; H, 8.14; F, 4.65. Found: C, 67.52; H, 8.37; F, 4.54.

Continued elution with ether afforded the diacetate **9** of fluorohydrin D.

The procedures outlined above served for isolation of fluorohydrins D, E, and F and olefins A and B. Separations were not always quantitative, and no effort was made to maximize the yield of any individual fraction. Olefin C was not found in the silica gel fractions, but was readily separated from the original reaction mixture after acetylation by means of chromatography over acid-washed alumina. Fluorohydrin E and the diacetate of fluorohydrin D were also obtained from the mixture of acetates by alumina chromatography. The order of elution was (1) olefin C, 20% chloroform–ether, after extensive washing of the column with 80% ether–petroleum ether; (2) fluorohydrin D diacetate, 50% chloroform–ether, early fractions; and (3) fluorohydrin E, 50% chloroform–ether, later fractions.

Olefin C was purified by repeated recrystallization from ether: mp 167–168°; $[\alpha]^{23}D$ −146° (*c* 0.92, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.90; H, 7.84.

Hydrolysis of olefin C (a diacetate) in aqueous methanol containing potassium carbonate (18 hr, room temperature) afforded the diol, mp 198–201°. After three recrystallizations from acetone–ether, the material melted at 202.5–204.5°, $[\alpha]^{24}D$ −158° (*c* 0.835, $CHCl_3$).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.72; H, 8.60.

Formation of 16,17α-Epoxypregnan-3α-ol-11,20-dione from Fluorohydrin E.—Fluorohydrin E (95 mg) was treated with 211 mg of anhydrous potassium carbonate in 70 ml of methanol and 10 ml of water at room temperature for 24 hr. Most of the methanol was removed by evaporation *in vacuo* at 45°, and the precipitated residue was extracted into chloroform. After washing with water and drying ($MgSO_4$), the solvent was removed *in vacuo*, and the product (65 mg, 80%) was recrystallized from ether, mp 222–225°. It was identified as 16,17α-epoxypregnan-3α-ol-11,20-dione by comparison of the infrared spectra and by a mixture melting point.

Base-Catalyzed Isomerization of Fluorohydrin D.—Fluorohydrin D diacetate (**9**) (206.6 mg) and sodium bicarbonate (256.5 mg) were dissolved in 3.5 ml of methanol and 3.5 ml of water, respectively, and then combined and heated under reflux for 15 hr. The mixture was cooled and distributed between ethyl acetate and water. The ethyl acetate layer was separated and concentrated to yield 194.3 mg of oily product which was acetylated in the usual way. The mixture of acetates was resolved by chromatography over 20 g of silica gel. The isomeric fluorohydrin **10** was eluted first with 20% ether–petroleum ether. The crude weight was 127 mg. After recrystallization from ether, 73.1 mg of material, mp 163–167°, was obtained. Recrystallizafrom ether twice for analysis raised the melting point to 166–169°, $[\alpha]^{25}D$ −71.7° (*c* 1.185, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}FO_6$: C, 66.64; H, 7.83; F, 4.22. Found: C, 66.90; H, 7.65; F, 4.10.

Continued elution of the column with 33% ether–petroleum ether gave 74.8 mg of recovered **9**, diminishing to 48 mg, mp 199–201° dec, after recrystallization from methanol.

Thermal Dehydrofluorination of 9.—A sample of 39.2 mg of **9** was placed in a 5-cc round-bottom flask which was evacuated (oil pump) and then immersed in an oil bath at 211° for 2 min. The rapid evolution of hydrogen fluoride commenced after melting of the sample and subsided within 90 sec. After the flask had cooled, the contents (39.3 mg) were applied to a column of 4 g of silica gel. A small amount of impurities was removed by washing the column with 20% ether–petroleum ether. Elution with 15-cc fractions of 33% ether–petroleum afforded the major reaction product followed by a mixture of three minor components (total 5.4 mg) which were not identified. The major product, identified by ir and nmr spectra as olefin B 16-acetate (**4**), was noncrystalline and amounted to 30.3 mg (81%). Crystallization from 2-propanol afforded material, mp 44–47°, identical by nmr and ir with the material prepared by acetylation of **3**.

Thermal Dehydrofluorination of 10.—A sample (90.3 mg) of **10** was placed in an evacuated flask which was immersed for 90 sec in an oil bath which has been heated to 236°. After cooling, the product (**5**) was recrystallized from ether: 81.1 mg (94%), mp 120–124°. Recrystallization from ether twice afforded a sample melting at 121–124°, $[\alpha]^{25}D$ +74.5° (*c* 0.435, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.43; H, 8.17.

Chromic Anhydride Oxidation of Fluorohydrin D (8).—A solution of **8** (75.9 mg) in 0.5 ml of pyridine was added to a suspension of CrO_3 (161.6 mg) in 0.5 ml of pyridine. After standing for 18 hr at room temperature, the reaction mixture was distributed between ethyl acetate and water. The organic layer was washed with 0.1 *N* HCl and, after removal of solids by filtration, was washed successively with water, 5% sodium bicarbonate solution, and water. Removal of the solvent afforded 68.1 mg of a complex mixture which was chromatographed over 8.5 g of silica gel. The column was developed by eluting first with 20% ether–petroleum ether and then with 33% ether–petroleum ether. The latter eluent removed 27.9 mg of **15** which was recrystallized from ether: 18 mg; mp 154–156°; $\lambda_{max}^{CH_3OH}$ 237 mμ (ε 13,000).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.62; H, 7.78.

Conversion of Fluorohydrin F (12) to the 16,17β-Oxide 22.—Fluorohydrin F (512.1 mg, 1.254 mmol) and methoxyamine hydrochloride (131.8 mg, 1.578 mmol) were combined in solution

in 4 ml of pyridine and let stand for 19.5 hr at room temperature. The mixture was distributed between ethyl acetate and water; the organic layer was washed successively with 0.1 *N* HCl, water, 5% $NaHCO_3$ solution, and water and then evaporated to dryness. The residue was crystallized from ethyl acetate–hexane to afford 499.7 mg (91%) in two crops, mp 196–198 and 194–196°, respectively, and was recrystallized from ether for analysis: mp 197–198°; $[\alpha]^{25}D$ +46.1° (*c* 1.000, $CHCl_3$).

Anal. Calcd for $C_{24}H_{36}FNO_5$: C, 65.88; H, 8.29; N, 3.20; F, 4.34. Found: C, 66.18; H, 8.36; N, 3.17; F, 4.49.

Methoxime **14** (942.9 mg, 2.16 mmol) was dissolved in 5 cc of pyridine and added to a suspension of CrO_3 (1.4946 g) in 10 cc of pyridine. After 17 hr of stirring at room temperature, the mixture was distributed between ethyl acetate and water. The ethyl acetate layer was washed with 0.1 *N* HCl and then after removal of precipitated solids by filtration, was washed with water, followed by 5% $NaHCO_3$ solution, and finally water. Removal of the solvent *in vacuo* followed by recrystallization of the residue from methanol afforded 792.0 mg (84%) of **16**, mp 170–172°. After two recrystallizations from ether–hexane for analysis, the melting point was 172–173°, $[\alpha]^{25}D$ −111.5° (*c* 0.9154, $CHCl_3$).

Anal. Calcd for $C_{24}H_{34}FO_5N$: C, 66.18; H, 7.87; N, 3.22; F, 4.36. Found: C, 65.90; H, 8.12; N, 3.26; F, 4.6.

The 16 ketone **16** (754.8 mg, 1.73 mmol) was dissolved in 60 ml of methanol, and the solution was cooled to 2° in an ice bath. A cold solution of sodium borohydride (2.3 g) in 30 ml of 0.1 *N* boric acid was added. After 1 hr of standing at room temperature, the reaction mixture was treated with a few drops of acetic acid (no evolution of hydrogen) and then acidified to pH 3.4 with 2 *N* sulfuric acid. The acid treatment was required to decompose a borate ester or complex which was otherwise obtained from the reaction. After 2 min, the acidic solution was neutralized with 5% sodium bicarbonate and then extracted with ethyl acetate. After removal of the solvent, the residual extract (785.6 mg) was acetylated as usual (786.6 mg of crude product); the mixture of acetates was resolved by chromatography over 76 g of silica gel. The column was developed by washing with petroleum ether, eluting with 20% ether–petroleum ether, and taking 100-cc fractions. The two components of the mixture overlapped, but the earliest and latest fractions afforded the pure products. Rechromatography of the intermediate mixed fractions allowed fairly efficient separation of the mixture. The faster moving component was **18**: mp 132–134° from hexane, $[\alpha]^{25}D$ +78.6° (*c* 1.005, $CHCl_3$).

Anal. Calcd for $C_{26}H_{40}FNO_6$: C, 64.85; H, 8.37; N, 2.91; F, 3.95. Found: C, 65.06; H, 8.16; N, 2.83; F, 3.8.

The slower moving component **17** was recrystallized from methanol: mp 202–204°; $[\alpha]^{25}D$ +23.7° (*c* 1.001, $CHCl_3$).

Anal. Calcd for $C_{26}H_{40}FNO_6$: C, 64.85; H, 8.37; N, 2.91; F, 3.95. Found: C, 65.00; H, 8.10; N, 2.94; F, 3.6.

The two components were present in approximately equal amounts. The best isolated yields were 34% **17** and 29% **18**.

The 16α-acetoxy isomer **17** was also obtained by sodium borohydride reduction of **14**, using the same conditions described above and allowing independent assignment of isomer identification. The products were compared by means of the infrared spectra and mixed melting point.

The 16β-acetoxy isomer **18** (51.4 mg) was converted to the 11 ketone **19** by oxidation with chromic anhydride in pyridine using the procedures described for preparation of **16** above. The product **19** was obtained in 82% yield: mp 150–154°; mp 154–156° after recrystallization twice from hexane; $[\alpha]^{25}D$ +88.7° (*c* 1.0221, $CHCl_3$).

Anal. Calcd for $C_{26}H_{38}FNO_6$: C, 65.11; H, 7.99; N, 2.92; F, 3.96. Found: C, 65.37; H, 7.77; N, 2.79; F, 3.72.

Closure of the fluorohydrin acetate **19** to the epoxide **22** was accomplished by treating 27.0 mg of the former in a refluxing solution of 136 mg of potassium hydroxide in 1 ml of 1:4 water–methanol for 1 hr. The crude oxide was acetylated in the usual way, and the acetate was purified by passage over a column of 2 g of silica gel, removing the product by elution with 20% ether petroleum ether. The crude crystalline product amounted to 18.8 mg, mp 124–126°. After recrystallization from hexane, 12 mg (mp 128–131°), was obtained identical to an authentic sample prepared from **23** and methoxyamine. Comparison was made by means of the infrared spectra and a mixture melting point.

16,17β-Oxido-17-isopregnan-3α-ol-11,20-dione Acetate (23) and Its 20-Methoxime 22.—16-Pregnen-3α-ol-11,20-dione acetate[28] (**25**) (4.6886 g, 12.59 mmol) was dissolved in a mixture of 220 ml of acetone and 22 ml of water and was cooled in an ice bath. N-Bromosuccinimide (22.5 g) was added in 1 portion; then, with stirring aud continued cooling, a solution of perchloric acid (12 cc of 70% perchloric acid diluted to 120 cc with water) was added dropwise over the space of 1 hr. The mixture was allowed to stand at room temperature for 12 hr and then was poured over a slurry of ice, water, and an excess of sodium sulfite. Enough solid sodium sulfite was added until the mixture was free from oxidizing products (starch–iodide test paper) and alkaline; then the resulting mixture was extracted with ethyl acetate. After washing with water and removing of solvent, the residual product was dissolved in ether and allowed to stand. A bromine-free by-product, 1.8126 g, mp 176–179°, separated and was collected by filtration. The filtrate was concentrated to dryness and acetylated as usual, and the impure bromohydrin acetate fraction was applied to a column of 300 g of silica gel. The product, 17α-bromopregnan-3α,16β-diol-11,20-dione 3,6-diacetate (**26**), amounting to 1.573 g, mp 173–176° (ether–hexane), was eluted with 20% ether–petroleum ether. Recrystallization from hexane raised the melting point to 181–183°, $[\alpha]^{25}D$ +124.0° (*c* 0.5025, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}BrO_6$: C, 58.70; H, 6.90; Br, 15.63. Found: C, 58.61; H, 6.84; Br, 15.51.

The nonbrominated by-product, assigned structure **7**, recrystallized from ethyl acetate–hexane for analysis: mp 200.5–202°; $[\alpha]^{25}D$ +72.0° (*c* 1.0257, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.95. Found: C, 69.45; H, 8.27.

Formation of the epoxide **23** from the bromohydrin acetate **26** was accomplished as follows; **26** (117.7 mg) was treated with potassium carbonate (218.8 mg) in 5 cc of refluxing 4:1 methanol–water for 2 hr. The product was obtained by extraction with ethyl acetate, a water wash, and removal of the solvent under reduced pressure. The crude product was acetylated, and the acetate was purified by chromatography over 9.25 g of silica gel. After washing the column with 20% ether–petroleum ether, the product was taken off with 33% ether–petroleum ether. After crystallization from ether, 77.2 mg of material melting at 133–136° was obtained. The analytical sample, mp 138–140°, was obtained after two recrystallizations from ether–hexane.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.36; H, 8.59.

The 20-methoxime **22** of the β-oxide was obtained by condensation of 155.3 mg of the ketone with 102.2 mg of methoxyamine hydrochloride in 2 cc of pyridine, using the procedure and work-up described above. The crude crystalline product (from hexane) melted at 121–127° and was judged an approximately equal mixture of *syn* and *anti* isomers from the appearance of double peaks for the OMe, 18-methyl, and 21-methyl signals in the nmr separated by 1–2 Hz. Repeated crystallization from hexane gave an inefficient separation of the isomers, allowing isolation of a single isomer, mp 125–129°, showing single methyl peaks. Seeding the *syn–anti* mixture with a crystal of **22** made by ring closure allowed rapid isolation of a pure sample (35.4 mg) of the desired isomer, mp 124–127°. Further recrystallization from hexane afforded material melting at 129–131°, $[\alpha]^{25}D$ +23.8° (*c* 0.960, $CHCl_3$).

Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.03; H, 8.45; N, 3.36. Found: C, 68.80; H, 8.46; N, 3.36.

Thermal Rearrangement of the 17α-Fluorides 18 and 19 with Loss of Hydrogen Fluoride.—The 11β-ol **18** (161.7 mg) was placed in an evacuated flask which was immersed for 80 sec in an oil bath which had been heated to 240°. A small amount of crystalline sublimate was recovered and identified as unchanged **18**. The remaining product, a light yellow oil, was chromatographed over 16 g of silica gel. Some impurities were removed by washing the column with 20% ether–petroleum ether, and the product was removed by elution with 33% ether–petroleum ether. A total of 91.5 mg (59%) of **20**, noncrystalline but homogeneous by nmr, was obtained: $[\alpha]^{25}D$ +69.7° (*c* 1.013, methanol). A 20 mg sample of the purified **20** was hydrolyzed at room temperature by the action of potassium carbonate (62 mg) in 8 ml of methanol and 2 cc of water (21 hr). The crystalline triol **21**, mp 138–140° (ether), was thus obtained: $[\alpha]^{25}D$ +48.9° (*c* 0.500, $CHCl_3$).

(28) P. L. Julian and W. J. Karpel, U. S. Patent 2,671,794; *Chem. Abstr.*, **49**, 4034 (1955).

Anal. Calcd for $C_{22}H_{35}NO_4$: C, 69.99; H, 9.35; N, 3.71. Found: C, 70.00; H, 9.64; N, 3.89.

Similarly, the corresponding 11 ketone **19** (77.4 mg) was heated *in vacuo* for 90 sec at 250°. The product was purified by chromatography over 7.5 g of silica gel. After removal of a slight impurity with 10% ether–petroleum ether, the main product was obtained by elution with 20% ether–petroleum ether. The noncrystalline product, homogeneous by nmr, amounted to 44.1 mg (59%). It was identical with the 20-methoxime **24** of the Δ^{13} olefin **5** by the following criteria. The infrared spectra (Nujol mull of solid films) and nmr spectra were identical. The mass spectra of the two preparations showed identical fragmentation patterns and were nearly superimposable, except that the methoxime prepared from **5** showed a small impurity at *m/e* 488, attributable to formation of a small amount of the **11**, 20-bis methoxime of **5**. The high-resolution spectrum of the purified pyrolysis product exhibited a molecular ion peak at a *m/e* of 459.2647 (calcd 459.26207), and an M + 1 peak at 460.2708 (calcd 460.26543).

The reference sample of the methoxime **24** was prepared by condensation of the Δ^{13} olefin **5** with methoxyamine hydrochloride in pyridine using the method described above. The product was noncrystalline though very nearly homogenous as judged by thin layer chromatography and the nmr spectrum. A high-resolution mass spectrum showed a strong molecular ion peak at a *m/e* of 459.2645 (calcd 459.26207) and an $(M + 1)^+$ peak at 460.2704 (calcd 460.26543). A small impurity, estimated to be less than 5% by nmr, was revealed by the presence of a small peak at *m/e* 488. The impurity is assumed to be the 11,20-bis-methoxime of the olefin **5**.

Registry No.—**1**, 24298-90-6; **2**, 24298-91-7; **3**, 24298-92-8; **4**, 24298-93-9; **5**, 24343-86-0; **6**, 24298-94-0; **7**, 24298-95-1; **8**, 24298-96-2; **9**, 24428-66-8; **10**, 24381-50-8; **11**, 24298-97-3; **12**, 24381-51-9; **13**, 24298-98-4; **14**, 24298-99-5; **15**, 24343-87-1; **16**, 24299-00-1; **17**, 24299-01-2; **18**, 24299-02-3; **19**, 24299-03-4; **20**, 24381-52-0; **21**, 24299-04-5; **22**, 24299-05-6; **23**, 5067-60-7; **24**, 24299-07-8; **25**, 4970-39-2; **26**, 24343-88-2; hydrogen fluoride, 7664-39-3; triol of **21**, 24298-71-3; diol of **12**, 24298-72-4; diol of **6**, 24298-70-2.

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Solvolysis of 19-Substituted Androstane Derivatives[1,2]

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Dehydromesylation of 19-hydroxy-5α-androst-2-en-17-one mesylate (**1**) by the action of hot pyridine gives a mixture of steroidal olefinic products, the principal constituent of which is shown to be B(9a)-homo-2,5(10)-estradien-17-one (**2a**). 19-Hydroxy-5α-androstan-17-one mesylate (**7b**) behaves in an analogous fashion and gives rise to B(9a)-homo-5(10)-estren-17-one (**8a**) and B(9a)-homo-5α-estr-1(10)-en-17-one (**9**). Chemical degradation and mass spectral analysis confirmed the proposed structures.

Solvolysis of 19-substituted steroids is of interest both from a mechanistic viewpoint and as a pathway to structurally modified steroid hormones. Previous studies have indicated that the products formed upon solvolysis of 19-substituted steroids depend largely on the substituents in rings A and B. For example, homoallylic participation of a double bond has been noted with 3-oxo-19-mesyloxyandrost-4-ene and 3-ethylenedioxy- (or acetoxy-) androst-5-ene systems. In these instances, solvolysis afforded 6β,19-cyclo and 5β,19-cyclo steroids,[3,4] respectively. Moreover, the expansion of ring A to the A-homo-19-nor system was reported in the case of 3-oxo-19-tosyloxyandrostane[5] and 3-oxo-19-mesyloxyandrosta-1,4-diene systems.[6] With 2-oxo-19-mesyloxy steroids, however, no ring enlargement occurred, and the corresponding 1β,19-cyclo steroid derivative was isolated.[7] It is noteworthy that in all cases no expansion of ring B was reported.

In the course of studies on the synthesis of C-19 radio-labeled steroids, we examined the solvolysis products of 19-hydroxy-5α-androst-2-en-17-one mesylate[8] (**1**) and the corresponding dihydro derivative (**7b**). Refluxing a solution of **1** in pyridine afforded a mixture of steroidal olefins which upon thin layer chromatography on silica gel G impregnated with silver nitrate indicated the presence of two products. Chromatography of the reaction mixture on alumina (activity II) yielded a crystalline product **2a** (25%), an oily product (20%),[9] and starting material (45%).

Compound **2a** was analyzed for $C_{19}H_{26}O$. The intense end absorption in the uv spectrum indicated the presence of nonconjugated double bonds as well as the presence of a highly substituted double bond. The nmr spectrum showed one angular methyl group corresponding to the C_{18} methyl at δ 0.97. This

(1) The work conducted in these laboratories was supported by the American Cancer Society Grant PRA-18 and National Institute of Health Grant CA-08349.

(2) (a) A preliminary account of this work has appeared: F. Kohen, L. K. Lala, W. Van Bever, and R. E. Counsell, *Chem. Commun.*, 347 (1969). (b) Presented in part at the VIth IUPAC Meeting on Steroids and Natural Products, Mexico City, April 1969, Abstract 5A, p 27.

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(9) This product appeared homogeneous on tlc, but it showed three C-18 methyl peaks in the nmr, indicating that it was still a mixture. Because of the difficulty in purification, it was not further investigated.