The addition of 1-ethoxypyridinium ethyl sulfate to sodium *n*-butylmercaptide in 1-butanethiol and subsequent reaction at 100° for 0.5 hr. gave, after the usual work-up (see A), butylmercaptopyridines listed in Table I.

G. As 1-Ethoxypyridinium *p*-Toluenesulfonate.—Pyridine N-oxide (4.75 g., 0.05 mole) was heated with ethyl *p*-toluenesulfonate (10.0 g., 0.05 mole) at 100° for 1.5 hr. The sirup was washed with ether and the resultant salt was added to a suspension of sodium *n*-butylmercaptide in excess 1-butanethiol as in B. Work-up according to the general method (see A) gave the sulfides listed in Table I.

Acknowledgment.—The authors would like to thank the National Science Foundation for their generous support of this work through a research grant (G-22191). They would also like to thank Dr. Charles L. Bell for valuable comments.

Steroids. CCXL.[1,2] The Reaction of Steroidal Alcohols with 2-Chloro-1,1,2-trifluorotriethylamine

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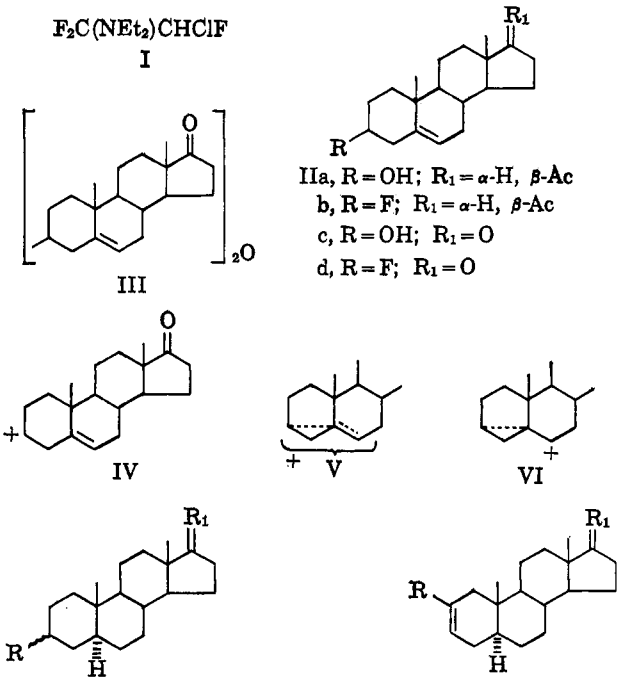
The reaction of 2-chloro-1,1,2-trifluorotriethylamine (I) with steroidal alcohols is described. Primary and secondary hydroxy steroids generally yield products resulting from replacement of hydroxyl by fluorine, ester formation, simple dehydration, dehydration accompanied by rearrangement, and ether formation. Tertiary alcohols undergo dehydration with or without concomitant rearrangement. The dependence of product formation on the nature of the steroidal alcohol, solvent, and reaction temperature is discussed. Nuclear magnetic resonance spectral data are analyzed for the various alcohols and reaction products.

The remarkable enhancement of biological activity in steroid hormones resulting from introduction of fluorine at various sites in the steroid molecule is well documented in the chemical literature.[3] During the past decade a number of synthetic routes to fluoro steroids have been developed in pursuit of further derivatives.[4] The recent observation of Yarovenko and Raksha that 2-chloro-1,1,2-trifluorotriethylamine (I) reacts readily under mild conditions with primary aliphatic alcohols to give replacement of hydroxyl by fluorine,[5] prompted us to investigate the utility of this reagent for the preparation of fluoro steroids.[2] Ayer, in a preliminary communication, has recently described a similar investigation of the reactions of the amine I with steroidal alcohols.[6]

When 3β-hydroxypregn-5-en-20-one (IIa) was treated with the fluorinating reagent I in dry tetrahydrofuran, there was obtained the 3β-fluoro derivative IIb.[3,7] Reaction proceeded with over-all retention of configuration. However, when a mixture of 3β-hydroxyandrost-5-en-17-one (IIc), 1.5 molar equiv. of the reagent I, and dry methylene chloride were refluxed briefly, two products could be isolated by chromatography on Florisil.[8] The less polar product consisted of the known 3β-fluoro derivative IId[6,7] (58%). The more polar product proved to be the ether III (4.8%), the structure of which was established by elementary analysis, n.m.r. spectroscopy, and mass spectrometry.[9] Ayer,[6] using different reaction conditions, obtained only



(1) Steroids CCXXXIX: L. H. Knox, E. Velarde, and A. D. Cross *J. Am. Chem. Soc.*, **85**, 2533 (1963). The present paper also constitutes Spectra and Stereochemistry, part X; part IX, A. D. Cross and P. Crabbé, *ibid.*, **86**, 1221 (1964).

(2) A preliminary account of this work was published by L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962).

(3) For leading references, see A. Bowers, P. G. Holton, E. Denot, M. C. Loza, and R. Urquiza, *J. Am. Chem. Soc.*, **84**, 1050 (1962).

(4) For a review of methods currently available for the introduction of fluorine into the steroid system, see J. W. Chamberlin, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p. 155.

(5) N. N. Yarovenko and M. A. Raksha, *Zh. Obskch. Khim.*, **29**, 2159 (1959); *cf. Chem. Abstr.*, **54**, 9724*h* (1960).

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

(7) (a) T. N. Jacobsen and E. V. Jensen, *Chem. Ind.* (London), 172, (1957); (b) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 4813 (1957).

(8) Florisil is a magnesium silicate marketed by the Floridin Co., Hancock, W. Va.

(9) Determinations carried out on a C.E.C. 21-1036 mass spectrometer equipped with a "direct inlet" system [see J. F. Lynch, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Experientia*, **19**, 211 (1963)].

TABLE I

N.M.R. SPECTRAL DATA FOR SOME STEROID ALCOHOLS, DEHYDRATION PRODUCTS, RELATED FLUORO STEROIDS, AND OTHER DERIVATIVES[a]

Compound	18-H	19-H	Other protons
IIa[b,c]	38.3	60.8	127.5 (21-H), 322 (6-H), 210 (h.b.w.[d] 20) (3α-H)
IIb	38.8	62.2	127.3 (21-H), *ca.* 325 (6-H), *ca.* 237 and *ca.* 287 (h.b.w. *ca.* 23) (3α-H), J_{HF} = *ca.* 50
IIc[e,f]	52.8	62.0	328 (6-H), 211 (3α-H)
IId	53.5	64.9	327 (6-H), 238 and 289 (h.b.w. *ca.* 22) (3α-H), J_{HF} = 51
III	52.9	61.8	320 (6-H), 193 (h.b.w. *ca.* 23) (3α-H)
VIIa[g]	51.3	50.1	215 (h.b.w. 23) (3α-H)
VIIb	51.3	48.7	265 and 313 (h.b.w. 7) (3β-H), J_{HF} = 48
VIIc	52.9	52.9	293 (h.b.w. 22) (3α-H), 349.9 and 400.6 ($O_2CCHClF$), J_{HF} = 50.7
VIId	52.9	49.8	118.8 (Nac), 250 (h.b.w. 16) (3β-H), 494 (NH)
VIIf	47.6	49.1	119.2 (NAc), 122.4 (OAc), 250 (h.b.w. 14) (3β-H), 277 (17α-H), 355 (NH).
VIIh	47.5	47.5	117.4 (NAc), 121.5 (OAc), 225 (h.b.w. 25) (3α-H), 276 (17α-H), 324 (NH).
VIIj[h]	51.9	48.8	243 (h.b.w. 7) (3βH)
IX	46.5	52.8	57.8 (2α- and 2β-Me), 121.4 (OAc)
Xa	47.7	40.0	121.6 (OAc), 96.3 (vinylic Me)
Xb	47.4	43.6	122.1 (OAc), 98 (h.b.w. 5) (vinylic Me), 317 (2-H), 277 (17α-H)
XI	46.5 and	44.2	71.2 (3β-Me), 121.1 (OAc), 276 (17αH)
XVIId[i-k]	47.6	72.0	344 (h.b.w. 3.1) (4-H)
XVIIe	38.8, 40.9 J_{HF} = 2.1	70.6	344 (4-H), 239.5 and 294.7 (17βH), J_{HF} = 55.2
XVIIf	52.9	71.7	344.5 (h.b.w. 3.4) (4-H), 352.0 and 402.8 ($O_2CCHClF$), J_{HF} = 50.8
XVIIg	42.8	71.9	222.2, 228.0 (17βH), $J_{16\beta,17\beta}$ = 5.8, 344 (4-H)
XVIIh	49.8	71.3	344 (h.b.w. 3.0) (4-H), 295.0 and 301.2 (17β-H), $J_{17\beta,16\beta}$ = 6.2, 350.3 and 401.4 ($O_2CCHClF$), J_{HF} = 51.1
XVIIj[l,m]	54.9	73.0	73.0 (17α-Me), 345 (h.b.w. 3.4) (4-H)
XIXb	53.5	75.7, 80.2 J_{HF} = 4.5	123.0 (OAc), 268 and 318 (6-H), J_{HF} = 50, 326 (h.b.w. 21) (3α-H)
XXIIa		69.9	55.0 and 61.6 (17β-Me), $J_{apparent}$ = 6.6, 344 (4-H)
XXIIb[n]		70.5	58 (allylic methyls)
XXIIb[n] (4,5-dihydro)		58.4	58.4 (alylic methyls)
XXIII		70.5	55.3 and 61.0 (17β-Me), $J_{apparent}$ = 5.7, 344 (4-H)
XXVa	47.0		227.3 (OMe)
XXVb	40.8, 42.6 J_{HF} = 1.8		226.5 (OMe)
XXVc	51.8		226.2 (OMe), 294 (17α-H), 351.6 and 402.6 ($O_2CCHClF$), J_{HF} = 51
XXVI			226.3 (OMe), 57.5 and 63.0 (17β-Me), $J_{apparent}$ = 5.5
XXVII	47.3	44.2	121.3 (OAc), 334 (3-H), 223 (=C—CH_2—O)

[a] See ref. 10. For comparison with various data reported in the literature the following chemical shift values have been employed: $\nu_{benzene} - \nu_{TMS}$ = 384 c.p.s.; $\nu_{H_2O} - \nu_{TMS}$ = 282; $\nu_{cyclohexane} - \nu_{TMS}$ = 86 c.p.s. Where necessary, resonances recorded elsewhere at 40 Mc.p.s. have been multiplied by $^3/_2$ for the same reason. [b] J. N. Shoolery and M. T. Rogers [*J. Am. Chem. Soc.* **80**, 5121 (1958)] give $\nu_{18\text{-H}}$ 39 and $\nu_{19\text{-H}}$ 61.5. [c] R. F. Zürcher [*Helv. Chim. Acta*, **44**, 1380 (1961)] gives $\nu_{19\text{-H}}$ 60.5. [d] h.b.w. = half-band width; values in c.p.s. [e] Lit.[b] $\nu_{18\text{-H}}$ 54 and $\nu_{19\text{-H}}$ 61.5. [f] W. R. Nes and U. H. Kim [*Steroids*, **1**, 594 (1963)] report $\nu_{18\text{-H}}$ 52.2 and $\nu_{19\text{-H}}$ 62.4. [g] Lit.[b] $\nu_{18\text{-H}}$ and $\nu_{19\text{-H}}$ 52.5. [h] Lit.[b] $\nu_{18\text{-H}}$ 52.5, $\nu_{19\text{-H}}$ 49.5, and $\nu_{3\beta\text{-H}}$ 249; lit.[c] $\nu_{19\text{-H}}$ 48.4. [i] Lit.[b] $\nu_{18\text{-H}}$ 48, $\nu_{19\text{-H}}$ 72, and $\nu_{4\text{-H}}$ 343.5; lit.[c] $\nu_{19\text{-H}}$ 71.9. [j] T. Okamoto and Y. Kawazoe [*Chem. Pharm. Bull.* (Tokyo), **11**, 643 (1963)] give $\nu_{18\text{-H}}$ 48.8. [k] T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold [*J. Am. Chem. Soc.*, **85**, 1699 (1963)] give $\nu_{4\text{-H}}$ 344 (h.b.w. 3.4). [l] Lit.[b] $\nu_{18\text{-H}}$ 54, $\nu_{19\text{-H}}$ 72, and $\nu_{4\text{-H}}$ 343.5; lit.[c] $\nu_{19\text{-H}}$ 72.9. [m] E. Caspi and D. M. Piatak [*Can. J. Chem.*, **41**, 2294 (1963)] give $\nu_{18\text{-H}}$ 54.0, $\nu_{19\text{-H}}$ 70.8, $\nu_{17\alpha\text{-Me}}$ 70.8, and $\nu_{4\text{-H}}$ 342.6. [n] Lit.[m] $\nu_{19\text{-H}}$ 70.2, $\nu_{allylic\ Me}$ 57.0, and $\nu_{4\text{-H}}$ 345.

the fluoro derivative IId. In the n.m.r. spectrum[10] (see Table I) the ether showed only two resonances attributable to angular methyl groups which is indicative of symmetry of substitution about the ether link. Moreover, both protons in the environment —CH—O—CH— resonated at the same frequency (180–210 c.p.s., broad multiplet, half-band width *ca.* 20 c.p.s.) and both must therefore be *axially* oriented. Structure III, involving ether formation with retention of configuration, is in accord with our interpretation of the mechanism of action of the reagent (*vide infra*). The mass spectrum of the ether III showed a small peak for the molecular ion at 558 but very few other peaks with *m/e* ratios greater than 271. The primary fission occurs therefore at a homoallylic C–O bond to give an *m/e* peak at 271 (IV, strongest peak in the spectrum). The charged species IV would be expected to achieve stabilization through charge delocalization (IV ↔ V ↔ VI).[11]

The marked influence of solvent and temperature on product composition in these reactions is illustrated by results obtained with 3β-hydroxy-5α-androst-17-one (VIIa) where the products arise by (1) elimination, with formation of the Δ²-derivative VIIIa,[2,6,12] (2) substitution of hydroxyl by fluorine with inversion

(10) N.m.r. spectra were recorded on a Varian A-60 spectrometer using 5% w./v. solutions in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Chemical shifts, ν, are quoted as c.p.s. downfield from the TMS reference (0.0 c.p.s.) and are accurate to ±1 c.p.s. Coupling constants, *J*, also expressed in c.p.s. units are accurate to ±0.5 c.p.s. A.D.C. thanks the Universidad Nacional Autonoma de México for time on the spectrometer.

(11) For a general discussion of the mass spectra of ethers, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 3.

(12) (a) R. E. Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *J. Am. Chem. Soc.*, **59**, 1363 (1937); (b) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963); (c) V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, *Helv. Chim. Acta*, **28**, 618 (1945).

to form VIIb,[2,6] (3) formation of the chlorofluoroacetate ester VIIc, and (4), in one case, formation of the amide VIId. In all cases the variety of reaction product is easily rationalized in terms of a common reaction mechanism (*vide infra*). The structures of the products VIIb–d were elucidated by n.m.r. spectroscopy and further supported by analyses and infrared spectral examination (see Experimental section). Low-field resonance (below 200 c.p.s.) in the spectrum of the fluoro steroid VIIb was limited to one proton only and this appeared as a pair of multiplets, each with a half-band width of 7 c.p.s. This resonance is interpreted as being due to an equatorial 3β-proton coupled to an axial 3α-fluorine, J_{HF} = 48 c.p.s. The ester VIIc showed a characteristic broad multiplet at 293 c.p.s. with a half-band width *ca.* 22 c.p.s. for the axial 3α-proton, and a pair of sharp singlet resonances at 349.9 and 400.6 c.p.s. for the single proton of the chlorofluoroacetate group strongly coupled to the fluorine on the same carbon atom, J_{HF} = 50.7 c.p.s. This easily detected, widely split, low-field doublet proved of great utility in the recognition of chlorofluoroacetate esters. An extra singlet resonance for three protons at 118.8 c.p.s. was surprisingly observed in the fourth reaction product VIId, which was formed only where acetonitrile was employed as solvent for the reaction. It appeared likely therefore that the solvent had participated in the reaction leading to an acetamido steroid. Infrared absorption bands at 3280, 1650, and 1545 cm.$^{-1}$ for a secondary amide group supported this conclusion. A multiplet resonance at 494 c.p.s. for NH and a multiplet resonance at 250 c.p.s. for an equatorial 3β-proton provided further evidence. The latter resonance was broader (half-band width 16 c.p.s.) than is usually observed for equatorial 3β-protons owing to coupling with the adjacent proton on nitrogen. Proof of structure came from reduction of the amide VIId with sodium borohydride to 3α-acetamido-5α-androstan-17β-ol (VIIe)[13a] followed by acetylation to the known 3α-acetamido-5α-androstan-17β-ol acetate (VIIf)[13a] which was identified by comparison with an authentic sample.[13b]

When 1 molar equiv. of the reagent I was added to a solution of 3α-hydroxy-(5α)-androstan-17-one (VIIj) in tetrahydrofuran (Table II) and the mixture was immediately evaporated *in vacuo*, an essentially quantitative yield of the Δ^2-derivative VIIIa was obtained. Ayer[6] obtained also a little of the 3β-fluoro derivative. Under similar conditions, reaction of the amine I with 2,2-dimethylandrostane-3β,17β-diol 17-acetate (IX), prepared by sodium borohydride reduction of the corresponding 3-ketone,[14] yielded 2,3-dimethylandrost-2-en-17β-ol acetate (Xa) which, as reported earlier,[2] was identified by n.m.r. spectroscopy (see Table I). In tetrahydrofuran 3β-methylandrostane-3α,17β-diol 17-acetate (XI)[15] apparently failed to react with 1 molar equiv. of the reagent I after refluxing for 10 min. When 2 molar equiv. of I were employed and the reflux period extended to 1 hr., the dehydration product Xb[15] was isolated in 62% yield. N.m.r. spectral data (Table I) were consistent with the assigned structure.

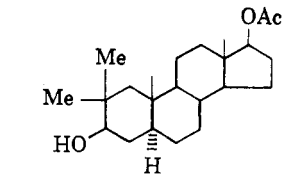
Having discussed the multitude of products which arise from various steroidal 3-alcohols it is pertinent to consider next the mechanism of action of the reagent to facilitate discussion of reactions at other centers. The amine I is suitably constructed to undergo an

TABLE II

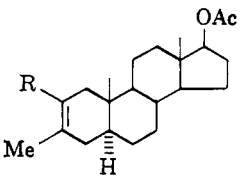
EFFECT OF REACTION CONDITIONS ON PRODUCT COMPOSITION IN THE TREATMENT OF 3β-HYDROXY-5α-ANDROSTAN-17-ONE (VIIa, 6 MMOLES) WITH THE REAGENT I (9 MMOLES)[a]

Reaction conditions			Products isolated, % yield			
Solvent	Temp., °C.	Time, hr.	Δ^2- (VIIIa)	3α-F (VIIb)	Ester (VIIc)	Amide (VIId)
CH_2Cl_2	0	16	34	42	3	0
CH_3CN	0	16	23	0	3	21
Tetrahydrofuran	0	16	19	18	17	0
Tetrahydrofuran	25	0.1	63	0	0	0

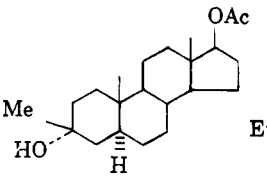
[a] In 25 ml. of solvent.



IX



Xa, R = Me
b, R = H



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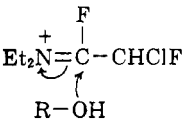
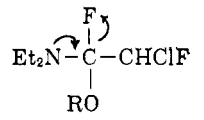
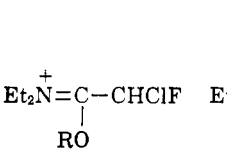


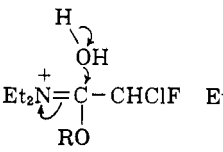
XII



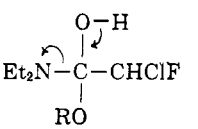
XIII



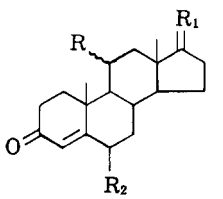
XIV

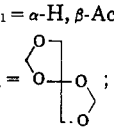


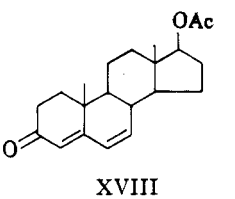
XV



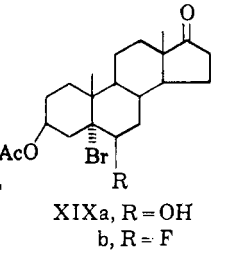
XVI



XVIIa, R = H; R_1 = α-H, β-OAc; R_2 = OH
b, R = α-OH; R_1 = α-H, β-Ac; R_2 = H
c, R = β-OH; R_1 =  ; R_2 = H
d, R = R_2 = H; R_1 = α-H, β-OH
e, R = R_2 = H; R_1 = α-F, β-H
f, R = R_2 = H; R_1 = α-H, β-O_2CCHClF
g, R = R_2 = H; R_1 = α-OH, β-H
h, R = R_2 = H; R_1 = α-O_2CCHClF, β-H
j, R = R_2 = H; R_1 = α-Me, β-OH



XVIII



XIXa, R = OH
b, R = F

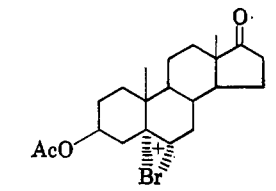
(13) (a) M. M. Janot, Q. Khuong-Hun, and R. Goutarel, *Bull. soc. chim. France*, 1640 (1960). (b) We wish to thank Dr. J. Schmitt, Etablissements Clin-Byla, Paris, for a sample of the amino alcohol VIIg which proved identical with the 3α-amino compound obtained by us from hydrogenation of 4,5-dihydrotestosterone oxime. Both samples of this amino alcohol VIIg on acetylation gave the same O,N-diacetyl derivative VIIf, indistinguishable from the derivative VIIf arrived at from the fluoramine reaction product (see Experimental section). The 3β-amino isomer which was also formed by hydrogenation of the oxime was converted to the 3β-acetamido derivative VIIh.

(14) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

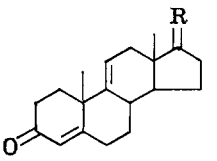
(15) B. Pelc, *Collection Czech. Chem. Commun.*, **25**, 1624 (1960).

internal displacement of fluorine and the resultant charged ammonium species XII adds to any alcohol as illustrated (I → XII, + alcohol → XIII). Further internal displacement of fluoride leads to another charged species XIV.[2,6,16] According to the nature and substitution of R, the species XIV can react further by SN1 or SN2 reactions with liberation of a stable neutral amide, N,N-diethyl chlorofluoroacetamide. Thus, an SN2 displacement by fluoride ion leads to substitution with inversion (*e.g.*, VIIa → VIIb), while a suitable solvent can similarly intervene [*e.g.*, VIIa (as XIV) + CH_3CN → VIId]. For Δ^5-3-alcohols internal displacement at C-3 with formation of the more stable *i*-steroid nonclassical carbonium ion, leading to over-all substitution with retention of configuration, is expected and observed (IIa → IIb). Formation of the ether III constitutes a special case of this reaction with a second molecule of steroid acting in place of fluoride ion. For these alcohols the possibility of 3β-fluoro Δ^5-steroid formation by an SNi-type substitution reaction (four-centered cyclic intermediate from XIV) cannot be excluded on the basis of the available evidence. Where water is present in the reaction mixture as a contaminant, then the chlorofluoroacetate esters are formed (XV → XVI) with expulsion of diethylamino ion. A further possible mode of collapse of an incipient or developed carbonium ion is loss of a proton either before or subsequent to a carbon skeleton rearrangement (*e.g.*, VIIa → VIII, and IX → X). Similar examples have been described elsewhere.[1]

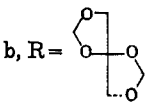
Two C-6 alcohols were examined. Brief warming with the amine I in tetrahydrofuran did not affect 6β-hydroxytestosterone acetate[17] (XVIIa), but in diglyme, under reflux, dehydration occurred with formation of the dienone (XVIII).[18,19] Another case of substitution with retention of configuration was discovered when 5α-bromo-3β,6β-dihydroxyandrostan-17-one 3-acetate (XIXa)[20] was treated with the amine I. The product was quickly identified as the 6β-fluoro derivative XIXb since the resonance of the 19-protons was split by long-range coupling, $J_{19\text{-H},6\beta\text{-F}} = 4.5$ c.p.s. The latter phenomenon is known to occur only when a certain steric relationship of the 19-protons and fluorine atom is maintained,[21] and this condition is fulfilled by 6β-, but not 6α-fluoro steroids. It is apparent that the action of the amine I on the 6β-hydroxy steroid XIXa leads to a charged species (*cf.* XV) which can undergo internal displacement of the amide moiety by bromine leading to the bromonium ion XX. Fluoride ion attack then leads to the 6β-fluoro steroid XIXb.

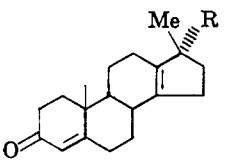


XX

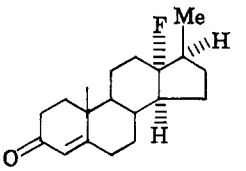


XXIa, R = α-H, β-Ac

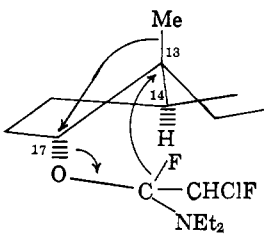




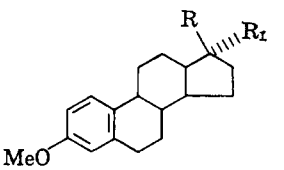
XXIIa, R = H
b, R = Me



XXIII



XXIV



XXVa, R = OH; R1 = H
b, R = H; R1 = F
c, R = O2CCHClF; R1 = H

A significant difference in the reactivity of 11α- and 11β-alcohols was observed. While 11α-hydroxypregn-4-ene-3,20-dione (XVIIb)[22] reacted with the amine I in methylene chloride at 0° to give the $\Delta^{4,9(11)}$-derivative XXIa[23] in 86% yield, hydrocortisone bismethylenedioxy derivative XVIIc,[24] under the same conditions, was recovered quantitatively. When the latter was refluxed for 1 hr. with the reagent I in methylene chloride, the dehydration product XXIb[25] could be isolated in 82% yield based on unrecovered starting material.[26]

Without exception, 17β-secondary alcohols gave three products, these being the dehydration product with migration of the 13β-methyl group, the 17α-fluoro derivative, and the 17β-chlorofluoroacetate. Thus, testosterone XVIId reacted with the amine I in tetrahydrofuran at room temperature with formation of 17β-methyl-18-norandrosta-4,13-dien-3-one (XXIIa), 17α-fluoroandrost-4-en-3-one (XVIIe),[2,6] and testosterone chlorofluoroacetate (XVIIf) in crude yields of 25, 18, and 26%, respectively. The structure of the dehydration product XXIIa was demonstrated by elementary and n.m.r. spectral analyses (see Table I). The absence of any signal in the vinyl region excluded the alternative structure containing a Δ^{12}-double bond.

During the course of our work, a synthesis of the 17α-fluoro derivative XVIIe was described by Henbest and Jackson[27] which involved a nucleophilic displacement reaction with testosterone *p*-toluenesulfonate

(16) The electrons of both nitrogen and oxygen of XIII assist the expulsion of fluoride ion. Although the resultant positive charge is placed on nitrogen in XIV, the oxygen atom obviously also bears partial charge which facilitates carbonium ion formation.

(17) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(18) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(19) Using different experimental conditions Ayer[6] was able to convert 6β,11α-dihydroxypregn-4-ene-3,20-dione to 6α-fluoropregna-4,9(11)-diene-3,20-dione in low yield.

(20) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

(21) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736, 3784 (1962); see also L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *ibid.*, **85**, 1851 (1963), footnote 29.

(22) D. H. Peterson, H. C. Murray, S. H. Epstein, L. M. Reineke, A. Weinstraub, P. D. Meister, and H. M. Leigh, *ibid.*, **74**, 5933 (1952).

(23) C. W. Shoppee and I. Reichstein, *Helv. Chim. Acta*, **24**, 351 (1941).

(24) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

(25) R. E. Beyler and L. H. Sarett, U. S. Patent 2,888,457 (1959).

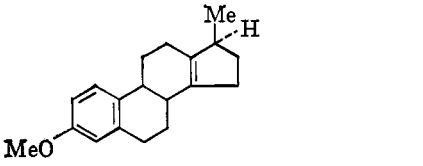
(26) Ayer[6] was able to isolate also a little of the 11β-fluoro derivative from 11α-hydroxyprogesterone.

(27) H. B. Henbest and W. A. Jackson, *J. Chem. Soc.*, 954 (1962).

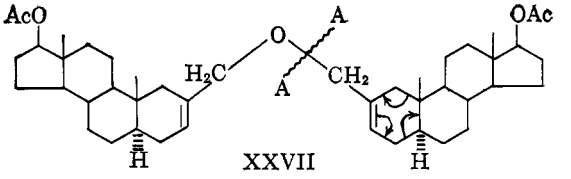
and tetrabutylammonium fluoride. The chlorofluoroacetate XVIIf, in common with similar esters isolated in this study, showed a characteristic strong band at *ca.* 1770 cm.$^{-1}$ in the infrared spectrum and was readily hydrolyzed to testosterone. In the n.m.r. spectrum the highly characteristic doublet, J_{HF} = *ca.* 50 c.p.s., for the lone proton in the chlorofluoroacetate ester group was clearly visible. Epitestosterone (XVIIg) under similar conditions afforded the 18-norsteroid XXIIa (80%, identified by mixture melting point and comparative spectra with a sample obtained from testosterone), the chlorofluoroacetate XVIIh (2%), and a third product for which we propose structure XXIII (7%). This last compound shows no proton resonance, other than that for the C-4 proton, at low fields thus excluding protons in the environment H–C–F. Since analysis shows the presence of one fluorine substituent, this has to be attached to quaternary carbon. Structure XXIII is suggested by consideration of the stereochemically favored mechanism (*cf.* XXIV) in which the 13β-methyl group migrates to the 17β-position as the 17α-carbon–oxygen bond polarizes. Simultaneously, the developing fluoride ion can attack C-13 from the α-face. Other structures (*e.g.*, 13α-H, 14ξ-fluoro) involving hydride ion migration 14$\alpha \rightarrow$ 13α) cannot be excluded, but are less attractive possibilities. The presence of the 17β-methyl group is supported by proton resonance for three methyl protons as a doublet, $J_{apparent}$ = 5.7 c.p.s.,[28] with each arm of the doublet broadened by long-range coupling, probably with fluorine. These results are in contrast to certain acid-catalyzed dehydrations of 17β- and 17α-ols which are reported to give Δ^{16}- and $\Delta^{13(17)}$-derivatives, respectively.[29] Estradiol-3-methyl ether (XXVa) reacted with the amine I in tetrahydrofuran at room temperature with formation of the 18-norsteroid XXVI, the 17α-fluoro derivative XXVb, and the chlorofluoroacetate XXVc in crude yields of 47, 26, and 9%, respectively. Chemical shift data for these and other compounds described above, which support the assigned structures, are summarized in Table I.

Under relatively mild conditions, and in a variety of solvents, tertiary steroidal alcohols are inert to the amine I (*vide supra*). At elevated temperatures, however, tertiary alcohols yield exclusively, and in high yield, products resulting from dehydration, with or without rearrangement. When 17α-methyltestosterone (XVIIj) was briefly refluxed in acetonitrile with the amine (I), 17,17-dimethyl-18-norandrosta-4,13-dien-3-one (XXIIb)[30] was obtained. The structure of XXIIb was established by n.m.r. and elemental analyses. Several other examples of rearrangement with 13β-methyl migration to C-17 have been reported in the recent literature, with structure determinations by the n.m.r. method.[30,31] In each case the diagnostic changes are the disappearance of the 18-proton resonance and the appearance of a new methyl resonance at higher frequencies as either a doublet or singlet dependent upon the secondary or tertiary nature of the original C-17 alcohol. In a further example, 17α-methyldihydrotestosterone (XVIIj, 4,5-dihydro) was treated with the reagent I to obtain the analogous 17,17-dimethyl derivative (XXIIb, 4,5-dihydro).

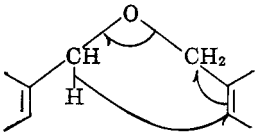
We reported earlier[2] that the fluorinating reagent I converted 2-hydroxymethylandrost-2-en-17β-ol acetate (VIIIb)[32] into 2-fluoromethylandrost-2-en-17β-ol acetate (VIIIc), identical with a sample of the same fluoromethyl compound prepared by an alternative route.[33] Further studies of the n.m.r. spectra of several preparations of this product reveal that it is in fact an inseparable mixture of the 2-fluoromethyl compound VIIIc and the 3β-fluoro-2-methylene isomer.[34] The mixture shows melting point and chromatographic behavior of a pure compound. A second product from the reaction of the allylic alcohol VIIIb with the reagent I was shown to be the ether XXVII. In the n.m.r. spectrum only two angular methyl proton resonance singlets were observed which suggested symmetry of structure about the ether link. Resonance for the two C-3 olefinic protons occurred at 334 c.p.s., while there was no sign of *exo*-methylene proton resonances. The allylic methylenes attached to ethereal oxygen gave a broad (half-band width 6 c.p.s.) 'singlet' resonance at 223 c.p.s. In the mass spectrum[9] the molecular ion was detected as m/e = 674. As with the other ether III examined, it was apparent that the primary cleavages take place at the ether link since there were only a few low intensity peaks above m/e = 330. A peak



XXVI



XXVII



XXVIIa

at m/e = 330 corresponds to the charged specie remaining after cleavage (fission at AA in XXVII) and transfer of a hydrogen (XXVIIa). Other peaks may arise from a breakdown of ring A in the ether or derived primary fission particles by the cyclic electron shift mechanism shown in XXVII. Very recently a report has appeared describing mass spectral patterns

(28) An important paper by F. A. L. Anet [*Can. J. Chem.*, **39**, 2262 (1961)] has drawn attention to the fact that for many methyl groups the observed splitting is not the true magnitude of the coupling constant.

(29) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, p. 529.

(30) E. Capsi and D. M. Piatak, *Can. J. Chem.*, **41**, 2294 (1963).

(31) *Inter alia*, (a) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963); (b) A. J. Mason, *et al.*, *ibid.*, **6**, 1 (1963); (c) R. Kirdani, R. I. Dorfman, and W. R. Nes, *Steroids*, **1**, 219 (1963); (d) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961); (e) E. Caspi and D. M. Piatak, *Chem. Ind.* (London), 1984 (1962); (f) V. Tortorella, G. Lucente, and A. Romeo, *Ann. chim.*, **50**, 1198 (1960); *cf. Varian Tech. Info. Bull.*, **3**, No. 2 (1961).

(32) J. C. Orr, *et al.*, *J. Med. Chem.*, **6**, 166 (1963).

(33) J. A. Edwards, *et al.*, *ibid.*, **6**, 174 (1963).

(34) A. D. Cross and P. W. Landis, forthcoming publication.

for other types of Δ^2-steroids for which the same mechanism of ring A fission is proposed.[35]

There are a number of features concerning the n.m.r. data which merit comment. First, by using standard values for the chemical shifts of the angular methyl protons in 5α-androstane ($\nu_{18\text{-H}}$ = 41.5 c.p.s. and $\nu_{19\text{-H}}$ = 47.5 c.p.s.[36]), it is possible to calculate the shifts of each of these frequencies owing to substituent groups at various points in the steroid nucleus. In Table III

TABLE III

N.M.R. SPECTRAL DATA[10] FOR 5α,14α-ANDROSTANE AND SOME SIMPLE DERIVATIVES[a]

Compound	$\nu_{18\text{-H}}$	$\nu_{19\text{-H}}$	Other protons
5α,14α-Androstane	41.5 (41.5)	47.5 (47.5)	
5α-Androstan-3-one	43.5	61.1	
5α-Androstan-3α-ol	41.7	47.3	243, h.b.w.[b] 7 (3β-H)
5α-Androstan-3β-ol	41.9	48.8	215, h.b.w. 24 (3α-H)

[a] Values are given in c.p.s.; values in parentheses are those of Zürcher (ref. 37b). [b] h.b.w. = half-band width; values are in c.p.s.

are collected angular methyl proton resonance frequency data for 5α,14α-androstane and three 3-substituted derivatives. From this information the frequency shifts due to each functional group were calculated. These values are assembled in Table IV. With knowledge of these frequency shifts it was possible, by simple additions and subtractions, to calculate the frequency shifts due to other substituents in the compounds studied.[38,39] These data are also collected in Table IV.

From Table IV it is seen that in almost no case did the shifts calculated in this work differ by more than 0.5 c.p.s. from the values found by Zürcher. This agreement lends further support to the principle of shift additivity since the observed differences are well within experimental error.

The resonance patterns of the 17-proton in 17-monosubstituted 16-unsubstituted steroids offer a simple means of assigning the stereochemistry of the substituent (*cf.* Table I). For 17β-substituted steroids

TABLE IV

FREQUENCY SHIFTS OF ANGULAR METHYL PROTON RESONANCES DUE TO SUBSTITUENT GROUPS[a-c]

Substituent group	$\Delta\nu_{18\text{-H}}$	$\Delta\nu_{19\text{-H}}$
3-C=O*	2 (2.5)	13.5 (14.5)
3α-OH*	0 (0.5)	0 (0)
3β-OH*	0.5 (0.5)	1.5 (2.0)
3α-F	0	0
3β-F	1	3.5
3α-AcNH*	1.5	1.5
3β-AcNH*	1.5	0
3β-O_2CCHClF*	1.5	4.5
3-Methyl-Δ^2-*	1.0	4.0
2,3-Dimethyl-Δ^2-	1.0	−7.5
Δ^4-3-C=O[d]	4.0 (4.5)	24.5 (25.0)
3-Methoxy-$\Delta^{1,3,5(10)}$[e]	4.0	
17-C=O	10.0 (10.0)	0.5 (1.0)
17β-OAc*	4.5 (5.0)	0 (0)
17α-OH*	−3	0
17α-F*	−5.5	−1.5
17β-O_2CCHClF*	7	0
17α-O_2CCHClF*	4	−0.5
17α-Me, 17β-OH*	9 (9)	1 (0.5)

[a] Shifts are relative to values for 5α,14α-androstane and are quoted to the nearest 0.5 c.p.s. Zürcher's values[37b] are given in parentheses. All values are for 8β,9α,14α stereochemistry, and 5α where applicable. [b] Data marked by an asterisk in this table are derived from a consideration of only one example of each functional group and hence must be considered less reliable than Zürcher's data where the latter were compiled from numerous examples. [c] Positive values of $\Delta\nu$ indicate a downfield shift. [d] Calculated using Zürcher's values of $\Delta\nu_{18\text{-H}}$ = 2 and $\Delta\nu_{19\text{-H}}$ = 0 for the 17β-OH function. [e] This value is calculated making the assumption that an aromatic ring A does not alter the conformation of ring D relative to nonaromatic ring A steroids.

the 17α-proton appears as a characteristic ill-resolved triplet.[41] However, the 17β-proton resonance in the epimeric 17α compounds is an apparent doublet, J = *ca.* 6 c.p.s. (*cf.* XVIIg and XVIIh). The reason for this is clear from models[42] which demonstrate that the angle subtended by the adjacent 17β- and 16α-C–H bonds is close to 90° and coupling between 17β- and 16α-protons is therefore predictably very small.[43] Conversely, the 17β-C–H to 16β-C–H subtended angle is less than 20° and strong coupling will occur, the magnitude being dependent upon numerous factors.[44]

An interesting situation occurs with Δ^2-steroids where an inspection of models[42] reveals that the 10β-angular methyl group during rotation brings the 19-protons near to the shielding cone of the double bond. From Tables III and IV and Zürcher's[37b] value of $\Delta\nu_{19\text{-H}}$ = 0 for a Δ^2-double bond, it may be noted that progressive substitution of the double bond by methyl groups results in an upfield shift of $\nu_{19\text{-H}}$ by *ca.* 4 c.p.s. per methyl group.[45]

Experimental[46]

2-chloro-1,1-2-trifluorotriethylamine (I) was prepared essentially as described by Yarovenko and Raksha.[5] Chlorotrifluoro-

(35) H. Audier, M. Fétizon, and W. Vetter, *Bull. soc. chim. France*, 1971 (1963).

(36) Zürcher reported earlier[37a] a value of 46.5 c.p.s. for $\nu_{19\text{-H}}$ of 5α-androstane. During our studies it became apparent that this figure required revision to 47.5 c.p.s. It is most important to note that many previously published $\Delta\nu_{19\text{-H}}$ shift values due to substituents on the steroid nucleus which were based on the earlier reference frequency of 46.5 c.p.s. must now be revised and reduced by 1 c.p.s. Zürcher subsequently revised his value of $\nu_{19\text{-H}}$ to 47.5 c.p.s.[37b] and, in fact, his new reference values for both $\nu_{18\text{-H}}$ and $\nu_{19\text{-H}}$ are in excellent agreement with those recorded by us (Table III). Much of the task of retabulating additivity shifts of angular methyl frequencies has been performed by Zürcher.[37b]

(37) (a) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); (b) **46**, 2054 (1963).

(38) The concept of frequency shift additivities is of considerable importance in alicyclic chemistry. However considerable care must be exercised in its application. Several cases have been reported where the additivity principle is no longer valid because of conformational distortion.[37,39] It appears unlikely, for example, that widespread use of this rule will be possible with ring-D 16,17-disubstituted steroids since this ring can readily adopt any one of three conformations to relieve strain.[40] Table IV contains only data which have been derived from studies of steroids where marked conformational distortions are unlikely.

(39) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); A. D. Cross, *ibid.*, **84**, 3206 (1962); A. D. Cross and I. T. Harrison, *ibid.*, **85**, 3223 (1963); T. Okamoto and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **11**, 643 (1963).

(40) F. V. Brutcher, Jr. and W. Bauer, Jr., *J. Am. Chem. Soc.*, **84**, 2236 (1963); A. D. Cross and P. Crabbe, *ibid.*, **86**, 1221 (1964); C. Beard and A. D. Cross, unpublished observations.

(41) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

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

(43) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(44) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); *cf.*, also, part IX in the series, Spectra and Stereochemistry.

(45) A 2-methyl substituent has a similar effect (A. D. Cross, unpublished observations).

(46) Melting points are uncorrected. Optical rotations were determined in chloroform solutions and ultraviolet spectra were measured in 95% ethanol. Infrared spectra, determined in potassium bromide disks on a Perkin-Elmer Model 21 spectrometer equipped with sodium chloride optics, were recorded by Dr. Matthews and his staff.

ethylene was bubbled for 8 hr. into diethylamine (50.0 g.) maintained at −5 to −10°. Distillation *in vacuo* afforded 48.0 g. (44%) of the reagent I, b.p. 28–30° (8 mm.), lit.[5] b.p. 32–33° (6 mm.).

3β-Fluoropregn-5-en-20-one (IIb).—A solution of 1.9 g. (6 mmoles) of 3α-hydroxypregn-5-en-20-one (IIa) and 1.1 g. (6 mmoles) of the amine I in dry tetrahydrofuran (20 ml.) was kept at room temperature for 10 min. and then evaporated to dryness *in vacuo* at steam bath temperature. Recrystallization of the solid residue from methanol gave the fluoro derivative IIb (0.97 g. 52%), m.p. 155–160°, which was identical by infrared comparison and mixture melting point with a sample prepared by an alternative route.[3]

Reaction of 3β-Hydroxyandrost-5-en-17-one (IIc) with the Amine I.—A mixture of 3β-hydroxyandrost-5-en-17-one (2.9 g., 10 mmoles), the amine I (2.85 g., 15 mmoles), and dry methylene chloride (25 ml.) was heated under reflux for 15 min. and then evaporated *in vacuo* on the steam bath. The residue was adsorbed from hexane containing a little benzene onto Florisil (90 g.). The crystalline fractions eluted with hexane and hexane–ether (4:1) were combined (2.43 g.) and recrystallized from hexane yielding 1.67 g. (57.5%) of 3β-fluoroandrost-5-en-17-one (IId),[6,7] m.p. 155–157°, raised to 157–158° by recrystallization from hexane; $[\alpha]_D$ −13°; ν_{max} 1743 cm.$^{-1}$ (17-ketone).

Anal. Calcd. for $C_{19}H_{27}FO$: C, 78.57; H, 9.37; F, 6.54. Found: C, 78.61; H, 9.49; F, 6.53.

Further elution with ether afforded the ether III (0.27 g., 4.6%), m.p. 276–278°, raised to 278–280° by recrystallization from acetone; $[\alpha]_D$ −5°; ν_{max} 1745 and 1100 cm.$^{-1}$.

Anal. Calcd. for $C_{38}H_{54}O$: C, 81.67; H, 9.74. Found: C, 81.38; H, 9.78.

Reaction of 3β-Hydroxy-5α-androstan-17-one (VIIa) with the Amine I. A.—A solution of 1.7 g. (6 mmoles) of 3β-hydroxy-5α-androstan-17-one and 1.7 g. (9 mmoles) of the reagent I in dry methylene chloride (25 ml.) was kept at 0° for 16 hr. Solvent was removed by evaporation *in vacuo* at room temperature and the residual oil was adsorbed from hexane onto Florisil (100 g.) The first crystalline fractions eluted with hexane–ether (9:1) consisted of androst-2-en-17-one (VIIIa, 0.55 g., 33.7%), m.p. 105–107° after recrystallization from hexane, and identical by mixture melting point and infrared spectral comparison with an authentic sample.[12] Further elution with the same solvent system afforded 3α-fluoroandrostan-17-one (VIIb, 0.73 g., 41.7%), m.p. 118–119°, $[\alpha]_D$ +95°, ν_{max} 1745 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}FO$: C, 78.03; H, 9.97; F, 6.49. Found: C, 78.10; H, 10.19; F, 6.10.

Finally, elution with hexane–ether (1:1) and ether yielded the chlorofluoroacetate VIIc (0.07 g., 3.0%), m.p. 149–151° after recrystallization from methanol; $[\alpha]_D$ +52°; ν_{max} 1740 (17-ketone), 1205, and 1770 cm.$^{-1}$ (chlorofluoroacetate ester).

Anal. Calcd. for $C_{21}H_{30}FO_3Cl$: C, 65.52; H, 7.85; Cl, 9.21; F, 4.93. Found: C, 65.52; H, 7.58; Cl, 9.47; F, 4.40.

B.—The above procedure was repeated at 0 and 25°, substituting dry tetrahydrofuran for methylene chloride, with the results shown in Table II.

C.—When dry acetonitrile was substituted for methylene chloride in procedure A, chromatography afforded, in addition to androst-2-en-17-one (VIIIa) and the ester VIIc, the amide VIId (370 mg., 21%), m.p. 246–248° after recrystallization from acetone; $[\alpha]_D$ +107°; ν_{max} 3280, 1650, and 1545 (secondary amide), and 1745 cm.$^{-1}$ (17-ketone).

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23; O, 9.65. Found: C, 75.95; H, 10.04; N, 4.09; O, 9.82.

3α-Acetamido-5α-androstan-17β-ol (VIIe).—To a solution of the amido ketone VIId (150 mg.) in dioxane (2 ml.) there was added a solution of sodium borohydride (75 mg.) in a mixture of dioxane (1 ml.) and water (0.5 ml.). The mixture was stirred at room temperature for 1 hr., neutralized with acetic acid, and the crude product (m.p. 255–257°) was isolated in the usual manner. A sample recrystallized from acetone afforded pure 3α-acetamido-5α-androstan-17β-ol (VIIe), m.p. 258–260°, $[\alpha]_D$ +34°; lit.[13a] m.p. 250°, $[\alpha]_D$ +33°.

Anal. Calcd. for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.49; H, 10.56; N, 4.58.

3α-Acetamido-5α-androstan-17β-ol 17-Acetate (VIIf).—Acetylation of the alcohol (VIIe, 100 mg.) obtained above in a pyridine–acetic anhydride mixture yielded the O,N-diacetylated derivative VIIf which was recrystallized from acetone, m.p. 199–200°, $[\alpha]_D$ +29°; lit.[13a] m.p. 185°, $[\alpha]_D$ +32°. The melting point was undepressed on admixture with an authentic sample obtained by acetylation of the corresponding amino alcohol VIIg (*vide infra*).[13b] Infrared spectra were indistinguishable.

Anal. Calcd. for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.31; H, 9.88, N, 3.90.

3α-Amino-5α-androstan-17β-ol (VIIg).—3-Oximino-5α-androstan-17β-ol was first prepared as described by Janot.[13a] After recrystallization from acetone the sample had m.p. 220–222°, $[\alpha]_D$ +22°, lit.[13a] m.p. 215°.

Anal. Calcd. for $C_{19}H_{31}NO_2$: N, 4.59. Found: N, 4.58.

Hydrogenation of this oxime (3.0 g.) in acetic acid (30 ml.) over platinum oxide (600 mg.) overnight at an initial hydrogen pressure of 50 p.s.i. and isolation of the product by filtration and distillation of the solvent under reduced pressure afforded the 3α-amino derivative contaminated with a small amount of the 3β-isomer (3.0 g.), m.p. 187–193°. Two crystallizations of a 100-mg. sample from methanol afforded the pure 3α-isomer, m.p. 190–192°. A mixture melting point with an authentic sample[13b] showed no depression, and infrared spectra of the two specimens were identical.

Anal. Calcd. for $C_{19}H_{33}NO$: C, 78.29; H, 11.41; N, 4.70. Found: C, 78.34; H, 11.62; N, 4.58.

3α- and 3β-Acetamido-5α-androstan-17β-ol 17-Acetates (VIIf and VIIh).—The mixture of amino alcohols obtained above (2.9 g.) was acetylated in a pyridine–acetic anhydride mixture. The crude product, m.p. 185–187°, on recrystallization from methanol afforded the 3β-isomer (VIIh, 0.43 g.), m.p. 274–276°, raised to 277–279° by a second recrystallization from methanol (lit.[13a] m.p. 278°).

Anal. Calcd. for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93, N, 3.73. Found: C, 73.65; H, 9.89; N, 3.85.

From the mother liquors there was obtained the 3α-isomer which, after two crystallizations from acetone, amounted to 1.3 g., m.p. 198–200°. This was identical by mixture melting point and infrared spectral comparison with 3α-acetamido-5α-androstan-17β-ol acetate (VIIf) prepared from VIId (*vide supra*).

Reaction of 3α-Hydroxy-5α-androstan-17-one (VIIj) with the Reagent I.—To a solution of 1.48 g. (5 mmoles) of the alcohol VIIj in dry methylene chloride (9 ml.) at room temperature, there was added 0.95 g. (5 mmoles) of the reagent I, and the mixture was evaporated to dryness *in vacuo*. The residue was adsorbed from hexane onto neutral alumina (50 g.). The crystalline fractions eluted with hexane consisted of androst-2-en-17-one[12] (VIIIa, 1.15 g.), m.p. 97–100° after crystallization from hexane. Further elution with hexane–ether (1:1) afforded unchanged alcohol VIIf (0.30 g.), m.p. 188–189°. Based on unrecovered starting material, the yield of the olefin VIIIa was essentially quantitative.

2,2-Dimethyl-5α-androstane-3β,17β-diol 17-Acetate (IX).—To a solution of 2,2-dimethyl-17β-hydroxy-5α-androstan-3-one acetate[14] (2.2 g.) in dioxane (20 ml.) there was added dropwise with stirring a solution of sodium borohydride (1.0 g.) in a mixture of dioxane (25 ml.) and water (2 ml.). Stirring was continued for 1 hr. and the product was isolated by dilution with cold water and filtration. Recrystallization from methanol afforded the 3β-alcohol IX (1.53 g., 69.0%), m.p. 174–175°, raised to 177–178° by a further recrystallization from methanol; $[\alpha]_D$ +18°; ν_{max} 3480 (OH) and 1735 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.46; H, 10.56.

Reaction of the Alcohol IX with the Reagent I.—A solution of 1.17 g. (3.2 mmoles) of the above alcohol IX and 0.75 g. (4 mmoles) of the reagent I in dry tetrahydrofuran (8 ml.) was warmed briefly (10 min.) on the steam bath and then evaporated *in vacuo*. The crude product was adsorbed from hexane onto Florisil (50 g.). The crystalline fractions eluted with hexane consisted of 2,3-dimethylandrost-2-en-17β-ol acetate (Xa, 0.540 g., 50%), m.p. 130–131°. Recrystallization from methanol afforded a pure sample, m.p. 141–143°, $[\alpha]_D$ +36°, ν_{max} 1735 and 1255 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.39; H, 10.89.

3-Methyl-5α-androst-2-en-17β-ol Acetate (Xb).—A solution of 3β-methylandrostane-3α,17β-diol 17-acetate[15] (1.56 g., 4 mmoles) and the reagent I (1.56 g., 8 mmoles) in tetrahydrofuran (25 ml.) was refluxed for 1 hr. Evaporation to dryness and recrystallization of the crude residue from methanol afforded 0.63 g. of 3-methyl-5α-androst-2-en-17β-ol acetate (Xb), m.p. 95–97°. Chromatography of the mother liquors on Florisil gave an additional 0.19 g. of this product, m.p. 97–98°, raising the yield to 0.82 g. (62%). Recrystallization from methanol afforded a

pure sample, m.p. 99–100°, $[\alpha]_D$ +51° (lit.[15] m.p. 105–107°, $[\alpha]_D$ +47°), ν_{max} 1738 and 1250 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.13; H, 10.42.

Reaction of 6β-Hydroxytestosterone 17-Acetate (XVIIa) with the Reagent I.—A mixture of 340 mg. (1.04 mmoles) of the 6β-hydroxy steroid XVIIa,[17] 400 mg. (2.2 mmoles) of the reagent I, and diglyme (10 ml.) was heated under reflux for 1 hr. The product was isolated by dilution with water and filtration, and then was adsorbed from hexane onto Florisil (25 g.). Crystalline fractions eluted with hexane–ether (1:1) were combined (150 mg., 44%) and recrystallized from acetone affording 6-dehydrotestosterone acetate (XVIII), m.p. 145–147°, $[\alpha]_D$ +45°, λ_{max} 282–284 mμ (log ε 4.28); lit.[18] m.p. 143–144°, $[\alpha]_D$ +36° (chloroform), λ_{max} 284 mμ (log ε 4.53). Identification was further established by infrared spectral comparison with an authentic sample.

When tetrahydrofuran was employed as solvent in place of diglyme, the alcohol XVIIa was recovered.

5α-Bromo-6β-fluoro-3β-hydroxyandrostan-17-one 3-Acetate (XIXb).[47]—To a solution of 250 mg. of 3β,6β-dihydroxy-5α-bromoandrostan-17-one 3-acetate[20] in 40 ml. of dry methylene chloride was added 0.4 ml. of the reagent I and the solution was allowed to stand at room temperature for 24 hr. Evaporation of the solvent and chromatography of the residue on alumina gave, after crystallization of the product from methylene chloride–hexane, 5α-bromo-6β-fluoro-3β-hydroxyandrostan-17-one acetate (60 mg.), m.p. 186–188°, $[\alpha]_D$ ±0°, λ_{max} 278–282 mμ (log ε 1.63), ν_{max} 1744 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}BrFO_3$: C, 58.70; H, 7.03. Found: C, 59.02; H, 7.31.

Reaction of 11α-Hydroxypregn-4-ene-3,20-dione (XVIIb) with the Reagent I.—A mixture of 2.0 g. (6 mmoles) of the 11α-alcohol XVIIb,[22] 1.70 g. (9 mmoles) of the reagent I, and dry methylene chloride (25 ml.) was kept at 0° for 16 hr. The mixture was evaporated and the residue was crystallized from methanol yielding 1.35 g. of pregna-4,9(11)-diene-3,20-dione (XXIa), m.p. 123–125°. Chromatography of the mother liquors on Florisil afforded an additional 200 mg. of XXIa, raising the yield to 1.55 g. (86.0%).

Reaction of 11β-Hydroxy-17,20,20-21-methylenedioxypregn-4-en-3-one (XVIIc) with the Reagent I.—A solution of 2.30 g. (6 mmoles) of the 11β-alcohol XVIIc[24] and 1.70 g. (9 mmoles) of the reagent I in methylene chloride (25 ml.) was heated under reflux for 1 hr. Solvent was evaporated under reduced pressure and the residue was recrystallized from acetone yielding the $\Delta^{9(11)}$-derivative XXIb[25] (1.62 g.), m.p. 235–236°, identical with an authentic sample by infrared comparison. The mother liquor was adsorbed from benzene onto Florisil (50 g.). The first crystalline fractions eluted with benzene–ether (4:1) consisted of the dehydration product XXIb (0.15 g.). Further elution with the same solvent system yielded unchanged alcohol XVIIc (0.18 g.). Based on unrecovered starting material, the yield of XXIb amounted to 82.4%.

A similar reaction using methylene chloride solvent, but at reaction temperature of 0°, afforded only unchanged starting material.

Reaction of Testosterone (XVIId) with the Reagent I.—A mixture of 1.72 g. (6 mmoles) of testosterone, 1.71 g. (9 mmoles) of the reagent I, and dry acetonitrile (20 ml.) was kept at room temperature for 30 min. and then evaporated *in vacuo* at room temperature. The residue was adsorbed from hexane onto Florisil (100 g.). The partially crystalline fraction eluted with hexane consisted of 17β-methylandrosta-4,13-dien-3-one (XXIIa, 0.40 g., 24.7%), m.p. 112–113° after recrystallization from hexane, $[\alpha]_D$ +69°, λ_{max} 238–240 mμ (log ε 4.23), ν_{max} 1680 and 1620 cm.$^{-1}$ (enone).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 83.97; H, 9.82; O, 6.38.

Further elution with hexane–ether (9:1) afforded 0.31 g. (18.0%) of 17α-fluoroandrost-4-en-3-one (XVIIe), m.p. 100–105°, raised to 146–148° after recrystallization from methanol; $[\alpha]_D$ +96°; λ_{max} 240–242 mμ (log ε 4.23); ν_{max} 1685 and 1615 cm.$^{-1}$ (enone).

Anal. Calcd. for $C_{19}H_{27}FO$: C, 78.57; H, 9.37. Found: C, 78.09; H, 9.01.

Further elution with hexane–ether (1:1) gave 0.61 g. (26.5%) of testosterone chlorofluoroacetate (XVIIf), m.p. 177–179° after recrystallization from methanol; $[\alpha]_D$ +81°; λ_{max} 240–242 mμ (log ε 4.21); ν_{max} 1660 and 1615 (enone), 1775 and 1205 cm.$^{-1}$ (chlorofluoroacetate ester).

Anal. Calcd. for $C_{21}H_{28}ClFO_3$: C, 65.86; H, 7.36; Cl, 9.26; F, 4.96. Found: C, 66.08; H, 7.45; Cl, 9.05; F, 5.36.

Finally, elution with ether afforded 0.11 g. of testosterone.

Reaction of 17α-Hydroxyandrost-4-en-3-one (Epitestosterone) (XVIIg) with the Reagent I.—A mixture of 8.7 g. (30 mmoles) of epitestosterone, 8.5 g. (45 mmoles) of the reagent I, and dry tetrahydrofuran (100 ml.) was stirred at room temperature overnight (14 hr.). Solvent was removed by evaporation *in vacuo*, and the residue was adsorbed onto Florisil (400 g.). The partially crystalline fractions eluted with hexane–ether (9:1, 250-ml. fractions) consisted of the dehydration product XXIIa (6.45 g., 79.6%), m.p. 110–112°, identical by infrared comparison with a sample obtained by similar treatment of testosterone (*vide supra*). Further elution with the same solvent system afforded 0.59 g. (7.0%) of a product considered to be 13α-fluoro-17β-methylandrost-4-en-3-one (XXIII), m.p. 118–119° after recrystallization from methanol, $[\alpha]_D$ +101°, λ_{max} 240–242 mμ (log ε 4.34), ν_{max} 1670 and 1615 cm.$^{-1}$ (enone).

Anal. Calcd. for $C_{19}H_{27}FO$: C, 78.57; H, 9.37; F, 6.54. Found: C, 78.79; H, 9.51; F, 6.49.

Continued elution with the same solvent system yielded epitestosterone chlorofluoroacetate (XVIIh, 0.21 g., 1.8%), m.p. 155–156° after recrystallization from methanol; $[\alpha]_D$ +70°; λ_{max} 240 mμ (log ε 4.26); ν_{max} 1680 and 1620 (enone), and 1770 and 1208 cm.$^{-1}$ (chlorofluoroacetate ester).

Anal. Calcd. for $C_{21}H_{28}ClF$: C, 65.88; H, 7.37; Cl, 9.26; F, 4.96. Found: C, 66.04; H, 7.52; Cl, 9.36; F, 5.58.

Reaction of Estradiol-3-methyl Ether (XXVa) with the Reagent I.—A solution of-8.58 g. (30 mmoles) of estradiol-3-methyl ether and 8.50 g. (45 mmoles) of the reagent I in dry tetrahydrofuran (100 ml.) was kept at room temperature for 30 min. Solvent was removed by evaporation *in vacuo* at room temperature, and the residual oil was adsorbed from hexane onto Florisil (300 g.). The first crystalline fractions eluted with hexane consisted of 3-hydroxy-17β-methylgona-1,3,5(10),13-tetraene-3-methyl ether (XXVI, 3.79 g., 47.1%), m.p. 65–75°. Two crystallizations from methanol afforded the analytical sample, m.p. 107–108°; $[\alpha]_D$ +42°; λ_{max} 280 mμ (log ε 3.30) and 287 mμ (log ε 3.20); ν_{max} 1615, 1575, 1507, 810, and 782 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.92; H, 9.10.

The latter crystalline fractions eluted with hexane consisted of the 17α-fluoro derivative XXVb (2.35 g., 26.0%), m.p. 96–98° after recrystallization from methanol; $[\alpha]_D$ +62°; λ_{max} 278–280 mμ (log ε 3.31) and 287 mμ (log ε 3.27); ν_{max} 1612, 1580, and 1505 cm.$^{-1}$ (benzene ring).

Anal. Calcd. for $C_{19}H_{25}FO$: C, 79.47; H, 8.74. F, 6.58. Found: 79.37; H, 8.67; F, 7.04.

The final crystalline fractions eluted with hexane–ether (9:1) consisted of the chlorofluoroacetate XXVc (1.0 g., 8.7%), m.p. 145–147° after recrystallization from methanol; $[\alpha]_D$ +41°; λ_{max} 278 mμ (log ε 3.35) and 287 mμ (log ε 3.29); ν_{max} 1780 and 1215 (chlorofluoroacetate ester), 1618, 1585, and 1510 cm.$^{-1}$ (aromatic ring).

Anal. Calcd. for $C_{21}H_{26}ClFO_3$: C, 66.22; H, 6.88; Cl, 9.31; F, 4.99. Found: C, 66.62; H, 6.96; Cl, 8.93; F, 5.30.

Reaction of 17β-Hydroxy-17α-methylandrostan-3-one (XVIIi, 4,5-dihydro) with the Reagent I.—A solution of 1.80 g. (6 mmoles) of the alcohol (XVIIj, 4,5-dihydro) and 2.26 g. (12 mmoles) of the reagent I in tetrahydrofuran (40 ml.) was heated under reflux for 10 min. Recrystallization of the crude product from methanol afforded 0.38 g. of 17,17-dimethyl-18-norandrost-13-en-3-one (XXIIb, 4,5-dihydro), m.p. 140–141°. Chromatography of the mother liquors on Florisil gave an additional 0.56 g. of this product, m.p. 140–141°, for a total yield of 55.4%. Recrystallization from methanol gave the analytical sample, m.p. 142–143°, $[\alpha]_D$ ±0°, ν_{max} 1712 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{30}O$ C, 83.86; H, 10.56. Found: C, 83.36; H, 10.62.

Reaction of 17α-Methylandrost-4-en-17β-ol-3-one (XVIIj) with the Reagent I.—A mixture of 1.8 g. (6 mmoles) of XVIIj, 2.3 g. (12 mmoles) of the reagent I, and dry acetonitrile (25 ml.) was heated under reflux for 5 min. Solvent was distilled on the steam bath under reduced pressure and the residual oil was chromatographed on Florisil (100 g.). The crystalline fractions eluted with hexane–ether (4:1) consisted of 17,17-dimethyl-18-norandrostane-4,13-dien-3-one (XXIIb), 700 mg. (41.4%), m.p.

(47) This reaction was carried out by Dr. I. T. Harrison of these laboratories.

68.70°. Recrystallization from methanol furnished the analytical sample, m.p. 74–75°, $[\alpha]_D$ +58°.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.85; H, 9.92. Found: C, 84.73; H, 9.90.

Reaction of 2-Hydroxymethyl-5α-androst-2-en-17β-ol 17-Acetate (VIIIb) with the Reagent I.—A solution of 1.73 g. (5 mmoles of 2-hydroxymethyl-5α-androst-2-en-17β-ol acetate (VIIIb, 1.0 g., 5 mmoles) of the reagent I, and dry tetrahydrofuran (20 ml.) was warmed gently on the steam bath for 10 min. Solvent was removed by evaporation under reduced pressure and the residual oil was adsorbed from hexane onto Florisil (100 g.). Elution with hexane–ether (9:1) afforded the mixed fluorinated products (see Discussion) (1.13 g., 65%), m.p. 110–117°, m.p. 115–117° after recrystallization from methanol, $[\alpha]_D$ +40°. Further elution with the same solvent system yielded the ether XXVII (0.59 g., 38%), m.p. 180–183°, raised to 203–205° by recrystallization from ethyl acetate; $[\alpha]_D$ +61°; ν_{max} 1738 and 1255 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{44}H_{66}O_5$: C, 78.31; H, 10.16. Found: C, 78.45; H, 10.05.

Acknowledgment.—The authors are indebted to Professor C. Djerassi for the mass spectra and for consultations on their significance.

Steroids. CCLVII.[1] 5,10-Disubstituted Estranes

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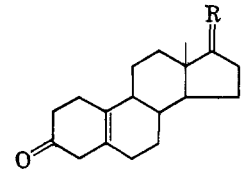
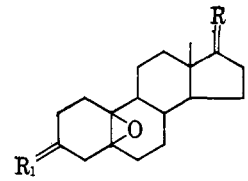
Epoxidations of various 3,17-disubstituted estr-5(10)-enes have been effected. Additions to the 5β,10β-epoxides, with ring opening, gave a variety of 5,10-disubstituted estranes including some stereoisomeric 3,5,10,17-tetrols and their derivatives. Assignment of configuration in estran-3α-ol 5β,10β-epoxide 3-acetates was facilitated by the occurrence of an intramolecular acetylation to give 5α-acetates.

Although strenuous efforts have been directed to the synthesis of 19-norsteroids bearing a 10β-hydrogen,[2] relatively little has been reported concering 19-norsteroids derived by electrophilic addition to estr-5(10)-enes. Rapala and Farkas described the hydrogenation of the latter compounds[3] and, with co-workers, converted a series of estr-5(10)-en-3-ones to estra-4,9-dien-3-ones by addition of bromine across the 5(10)-double bond followed by dehydrohalogenation.[4] An earlier communication from the Syntex laboratories revealed the conversion of 17β-hydroxyestr-5(10)-en-3-one (Ia) to the corresponding 5β,10β-epoxide (IIa).[5] Isomerization of the latter (IIa) with base afforded 10β-hydroxy-19-nortestosterone (IIIa), whose stereochemical identity had been established previously by optical rotatory dispersion studies.[6] Cleavage of the epoxide (IIa) by boron trifluoride led to the corresponding 5α-fluoro-10β-hydroxy derivative.[5] β-Addition of osmium tetroxide to the estra-5(10)-ene (Ia) is described in the patent literature, but no constants are given for the product.[7] Another patent claims that peracid oxidation of estr-5(10)-ene-3,17-dione (Ib) leads to a mixture of 10α- and 10β-hydroxyestr-4-ene-3,17-dione.[8] No firm evidence for the formation of the 10α-hydroxy compound is provided.

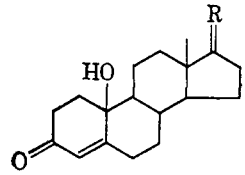
In view of the pre-eminent position occupied by estrane derivatives in the realm of ovulation inhibition by oral administration, we continued researches into electrophilic additions to nonconjugated 5(10)-double bonds.[9]



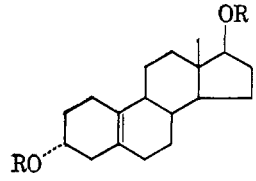
Ia, R = α-H, β-OH
b, R = O



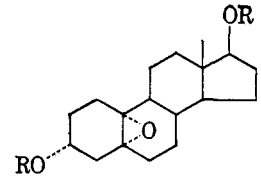
IIa, R = α-H, β-OH; R_1 = O
b, R = R_1 = O
c, R = R_1 = α-H, β-OH
d, R = α-H, β-OH; R_1 = α-OH, β-H
e, R = α-H, β-OAc; R_1 = α-OAc, β-H
f, R = R_1 = α-H, β-OAc
g, R = O; R_1 = α-OH, β-H



IIIa, R = αH, βOH
b, R = O



IVa, R=H
b, R=Ac



Va, R=H
b, R=Ac

Peracid oxidation of estr-5(10)-ene-3,17-dione (Ib) afforded the corresponding 5β,10β-epoxide (IIb).[11]

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(9) During the final stages of our work, we became aware of independent and simultaneous studies by Dr. S. G. Levine in this field. Very few of our results overlap with his and, generally, the two separate studies utilized different substituents at C-17. We wish to acknowledge a most friendly exchange of information with Dr. Levine and express thanks for a copy of his recent communication[10] prior to publication.

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(11) After completion of our work (1962), R. Gardi, C. Pedrali, and A. Ercoli [*Gazz. chim. ital.*, **93**, 1503 (1963)] reported bromination and epoxidation of estr-5(10)-enes.