TABLE III
RELATIVE RATES OF REACTION OF BENZYL ALKYL ETHERS WITH N-BROMOSUCCINIMIDE, BROMOTRICHLOROMETHANE, AND *t*-BUTYL HYPOBROMITE[a]

Ether	*r*[b] NBS	*r*[b] $BrCCl_3$	*r*[b] *t*-BuOBr
$C_6H_5CH_2OCH_3$	1.00	1.00	1.00
$C_6H_5CH_2OC_2H_5$	1.1 ± 0.1[c]	1.3 ± 0.1[c]	1.1 ± 0.1[c]
$C_6H_5CH_2OCH(CH_3)_2$	1.5 ± 0.1	1.3 ± 0.1	1.3 ± 0.2
$C_6H_5CH_2OC(CH_3)_3$	1.7 ± 0.1	1.8 ± 0.2	1.5 ± 0.1
$C_6H_5CH_2OCH_2C_6H_5$	0.8 ± 0.1	1.3 ± 0.1	1.0 ± 0.1

[a] These reactions, initiated by irradiation with a 500-w. tungsten lamp, were carried out in refluxing (77°) carbon tetrachloride (see Experimental Section). [b] *r* is the relative reactivity per benzylic hydrogen atom. [c] The uncertainties expressed are average deviations from the mean of two or more determinations.

various ethers ($C_6H_5CH_2OR$) increase only slightly as R changes in the sequence CH_3, C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2C_6H_5$. In other words, the favorable influence of the ether function on the benzyl hydrogen abstraction process[1] is not much affected by alterations in the structure of the alkyl group. It is interesting to recall that the relative reactivities observed for the reactions of $C_6H_5CH_3$, $C_6H_5CH_2CH_3$, $C_6H_5CH(CH_3)_2$, $C_6H_5CH_2C_6H_5$, and $(C_6H_5)_3CH$ with N-bromosuccinimide are, in contrast to those of the benzyl alkyl ethers, substantially different from those observed in reactions with bromotrichloromethane. That is, the reactivity ratios of these hydrocarbons are appreciably altered when Br· is replaced by the more selective $\cdot CCl_3$ radical as the hydrogen-abstracting species.[7]

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

Steroids. CCLXXXII.[1] Some Reactions of 5β,19-Cyclo 6-Oxygenated Steroids in Acid Media

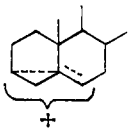
H. CARPIO, A. CRUZ BAZÁN,[2] M. G. TERÁN MEDINA,[2] AND J. A. EDWARDS[3]

The Research Laboratories of Syntex, S.A., Apartado 2679, Mexico, D.F., Mexico

Received May 12, 1965

Treatment of 3β-hydroxy-5β,19-cycloandrostane-6,17-dione (Ic) and 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one (Id) with hydrochloric acid afforded the corresponding 19-chloro derivatives IIa, b, and IV, respectively. With hydrofluoric and sulfuric acids, 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one (Id) and the acetate Ia rearranged to afford a multiplicity of products, including B-homo-19-nor steroids. Product formation is rationalized on the basis of classical carbonium ion intermediates.

The solvolysis of the *p*-toluenesulfonates of 3β-hydroxy-Δ^5 steroids in buffered medium frequently yields 3α,5α-cyclo derivatives,[4] which in turn may be rearranged to the parent Δ^5-3β alcohols in the presence of dilute mineral acid.[5] These well-known transformations have been studied extensively, and their mechanistic aspects have been explained on the basis of the nonclassical homoallylic cation.[4]



In recent communications from our laboratory[6] and from several others[7,8] it was reported that the closely related 19-tosyloxy-Δ^5 steroids underwent solvolytic displacement of tosylate with participation of the olefinic double bond to yield 5β,19-cyclo-6α-hydroxy steroids. Tadanier and Cole[8] also made the interesting observation that the 5β,19-cyclo-6α-hydroxy system was not converted to the parent 19-hydroxy-Δ^5 steroid in the presence of aqueous sulfuric acid. Instead, rearrangement to a B-homo-$\Delta^{5(10)}$-estrane derivative took place.

We have also investigated in detail the behavior of several 5β,19-cyclo 6-oxygenated steroids in hydrochloric, hydrofluoric, and sulfuric acid mixtures. It was found that both 19-substituted and more complex rearrangement products were formed and that the outcome of the rearrangement was dependent upon the acid employed. An account of our work is reported in this paper.

At the same time as these investigations were in progress, other Syntex researchers examined the action of diethyl-(2-chloro-1,1,2-trifluoroethyl)amine on 19-hydroxy-Δ^5 steroids.[9] Several products resulted, including two reported here. The same carbonium ions are considered to be generated as in our work, with the observed variance in product mix being a consequence of the different mode of collapse of the intermediate charged species.

Three cyclopropyl steroids were utilized in the present investigation: 3β-hydroxy-5β,19-cycloandrostane-6,17-dione (Ic), 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one (Id), and the corresponding acetate Ia which has been described previously.[6] Compounds Ic and Id were obtained from the acetate Ia by unexceptional methods, as outlined in the Experimental Section.

Treatment of 3β-hydroxy-5β,19-cycloandrostane-6,-17-dione (Ic) with hydrochloric acid in tetrahydrofuran

(1) Steroids. CCLXXXI: A. D. Cross and L. J. Durham, *J. Org. Chem.*, **30**, 3200 (1965).

(2) This work was reported earlier in theses submitted by A. C. B. and M. G. T. M. to the Universidad de Vera Cruz (1964) and the Universidad Nacional Autonoma de Mexico (1965), respectively.

(3) To whom enquiries should be addressed at Syntex Research Center, Stanford Industrial Park, Palo Alto, Calif.

(4) For a recent summary of the *i*-steroid rearrangement, see N. L. Wendler in "Molecular Rearrangements," part 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p. 1075.

(5) See L. F. Fieser and M. Fieser in "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 315, 316.

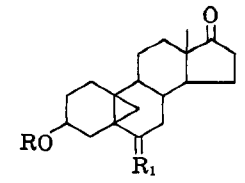
(6) O. Halpern, P. Crabbé, A. D. Cross, I. Delfín, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(7) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964).

(8) J. Tadanier and W. Cole, *Tetrahedron Letters*, 1345 (1964).

(9) See L. H. Knox, *et al.*, *J. Org. Chem.*, **30**, 4160 (1965).

CHART I



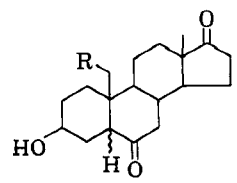
Ia, R = $COCH_3$; R_1 = 

b, R = $COCH_3$; R_1 = O

c, R = H; R_1 = O

d, R = H; R_1 = 

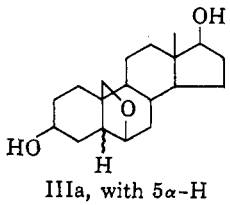
e, R = CH_3; R_1 = 



IIa, R = Cl; with 5α-H

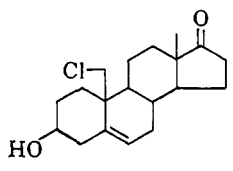
b, R = Cl; with 5β-H

c, R = H; with 5α-H



IIIa, with 5α-H

b, with 5β-H



IV

containing boron trifluoride etherate[10] for 21 hr. at room temperature smoothly opened the cyclopropane ring and afforded a mixture of two 19-chloro compounds isomeric at C-5. Careful chromatography of the mixture gave 19-chloro-3β-hydroxy-5α-androstane-6,17-dione (IIa) and the 5β isomer IIb in 44 and 20% yields, respectively (see Chart I). These structures were allocated on the basis of the following evidence. The n.m.r. spectra of IIa and IIb exhibited an AB pattern centered at *ca.* 217 c.p.s. for the protons of a chloromethyl group. Both isomers gave rise to the starting 5β,19-cyclo steroid when exposed to methanolic alkali, as expected for γ-chloro ketones, and each pure isomer was equilibrated to the same 7:3 mixture with acid. The A/B-*trans* isomer exhibited a positive Cotton effect curve virtually superimposable upon the curve of 3β-hydroxy-5α-androstan-6,17-dione (IIc) and afforded the previously described 6β,19-oxido-5α-androstane-3β,17β-diol (IIIa)[11] on reduction with lithium tri-*t*-butoxyaluminum hydride.

The A/B-*cis* isomer was characterized by a weakly positive rotatory dispersion curve, since the strongly positive Cotton effect of the 17-ketone[12] is substantially reduced by the pronounced negative contribution of the A/B-*cis* 6-ketone.[13] Similar metal hydride reduction of IIb gave a new oxide which was assigned the structure 6β,19-oxido-5β-androstane-3β,17β-diol (IIIb).[14]

(10) *Cf.* R. Villotti, O. Halpern, and A. Bowers, *Gazz. chim. ital.*, **93**, 244 (1963).

(11) A. Bowers, E. Denot, L. C. Ibáñez, M. E. Cabezas Rivera, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(12) See C. Djerassi in "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 47.

(13) C. Djerassi and W. Clossen, *J. Am. Chem. Soc.*, **78**, 3761 (1956).

(14) The accidental chemical equivalence of the 19-protons of a 6β,19-oxido-5α-androstane in n.m.r. spectroscopy was first reported by J. F. Bagli, *et al.*[15] This was also observed in the n.m.r. spectrum of IIIa (2-proton singlet at 223.5 c.p.s.). In contrast, the 19-protons of 6β,19-oxido-5β-androstane-3β,17β-diol (IIIb) were characterized by a pair of doublets centered at 218.5 c.p.s.

(15) J. F. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963).

In the 6α-hydroxy-5β,19-cyclo series, rearrangement with hydrochloric acid also gave rise to a 19-substituted product. More specifically, 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one (Id) provided 19-chloro-3β-hydroxyandrost-5-en-17-one (IV) in high yield when exposed to the same hydrochloric acid-boron trifluoride mixture. This product IV was identical in all respects with an authentic sample prepared by treating 3β-acetoxy-19-tosyloxyandrost-5-en-17-one with lithium chloride.[16]

In anhydrous hydrogen fluoride–tetrahydrofuran mixtures at −5° the 6-hydroxy- and 6-keto-5β,19-cycloandrostanes reacted in a different manner. The alcohols Ia and Id afforded complex mixtures of products, whereas the ketone Ic was recovered unchanged. Thus, 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one (Id) was converted to a mixture of five products, from which two crystalline compounds were isolated in a pure state. The substance, m.p. 150–152°, isolated in 5% yield, was identified as 3β-hydroxy-6-methylestra-1(10),5-dien-17-one (V) from its ultraviolet spectrum (λ_{max} 246 mμ with inflections at 237 and 255 mμ) and by comparison with an authentic sample prepared by an unambiguous synthesis.[17]

The second product, m.p. 176–177°, isolated in 8% yield, was isomeric with the starting diol and exhibited no selective absorption in the ultraviolet. In the n.m.r. spectrum, signals were observed at 55 (18-H protons), 119 (hydroxyl protons, peak removed by addition of deuterium oxide), and 239 c.p.s. (broad two-proton multiplet for protons in the environment C*H*OH) but no olefinic proton resonances. Since the low yield of this substance precluded an extensive chemical investigation, a more effective method was sought for its preparation. In fact, the desired rearrangement product could be obtained in better than 60% yield by treating the 5β,19-cyclocarbinol Id with 30% aqueous sulfuric acid in dioxane solution. This substance was identified as 3β,7ξ-dihydroxy-B-homoestr-5(10)-en-17-one (VIa, see Chart II)[18] from chemical and spectral data to be outlined in the sequel.

When 3β-acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia) was treated with anhydrous hydrogen fluoride, the only identifiable product was a fluorine-containing compound, m.p. 112–114°, which was isolated in *ca.* 30% yield. In the n.m.r. spectrum, this substance exhibited three ill-resolved multiplets at low field corresponding in area to two protons. The multiplet at 296 c.p.s. was assigned to a proton in the environment C*H*OAc [*cf.* n.m.r. spectral data for 3β-acetoxy-7ξ-hydroxy-B-homoestr-5(10)-en-17-one (VIb)], and the pair of multiplets (total 1H, half-band width of each multiplet *ca.* 22 cycles) at 269 and 319 c.p.s. suggested the presence of a single proton on carbon bearing fluorine and flanked by at least two methylene hydrogens.

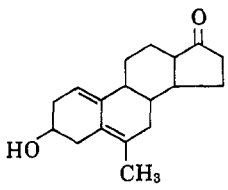
On the basis of this spectral interpretation and the demonstrated ability of the 6α-hydroxy-5β,19-cyclo

(16) O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 116 (1963).

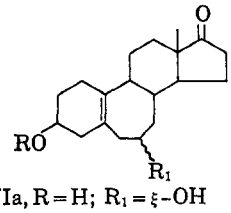
(17) O. Halpern, unpublished results from these laboratories. 17-Cycloethylenedioxy-3β-hydroxyestr-5(10)-en-6-one was treated with methyl Grignard reagent and the product was exposed to acid to yield 3β-hydroxy-6-methylestra-1(10),5-dien-17-one (V).

(18) The Abbott investigators assigned the β configuration to the C-7 substituent of their rearrangement product on the basis of mechanistic considerations. In the absence of chemical evidence, we prefer to leave the stereochemistry at this position unspecified.

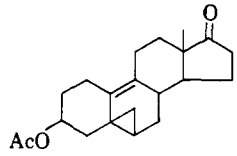
CHART II



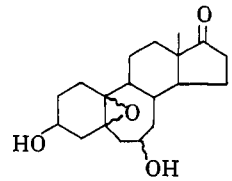
V



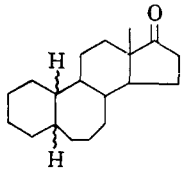
VIa, R = H; $R_1 = \xi$-OH
b, R = $COCH_3$; $R_1 = \xi$-OH
c, R = CH_3; $R_1 = \beta$-OH
d, R = $COCH_3$; $R_1 = \xi$-F



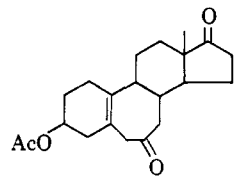
VII



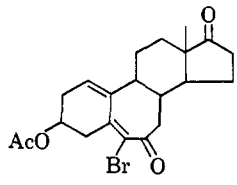
VIII



IX



X



XI

system to rearrange to B-homoestrane derivatives (see below), this new product was formulated as 3β-acetoxy-7ξ-fluoro-B-homoestr-5(10)-en-17-one (VId).[19]

Reference has already been made to the work of Tadanier and Cole concerning the rearrangement of 6α-hydroxy-3β-methoxy-5β,19-cycloandrostan-17-one (Ie) in aqueous sulfuric acid.[8] The product from this reaction was allocated the structure 7β-hydroxy-3β-methoxy-B-homoestr-5(10)-en-17-one (VIc) on the basis of limited experimental and physical data. Experiments will now be described which led to the identification of 3β,7ξ-dihydroxy-B-homoestr-5(10)-en-17-one (VIa) as the product formed by the action of aqueous sulfuric acid and anhydrous hydrogen fluoride on 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one (Id).

Initially, it was demonstrated that only the 6-hydroxyl group participated in the rearrangement, since treatment of 3β-acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia) with sulfuric acid gave 3β-acetoxy-7ξ-hydroxy-B-homoestr-5(10)-en-17-one (VIb), which in turn afforded the diol VIa after alkaline hydrolysis. A small quantity of the latter diol VIa was also produced during the acid-catalyzed rearrangement of Ia. Epoxidation of VIa with *m*-chloroperbenzoic acid produced a crystalline epoxide VIII which confirmed the presence of a double bond. This double bond must be tetrasubstituted, since the n.m.r. spectrum of the rearrangement product shows no vinyl proton resonance.

Surprisingly, hydrogenation of 3β,7ξ-dihydroxy-B-homoestr-5(10)-en-17-one (VIa) over palladium catalyst not only reduced the 5(10) double bond but also caused hydrogenolysis of the two homoallylic secondary hydroxyl functions to yield 5ξ,10ξ-B-homoestran-17-one (IX). The β,γ disposition of the 5(10) double bond to the 7-hydroxyl group was shown by oxidation of the rearrangement product VIb with chromium trioxide–pyridine complex.[20] This afforded a crystalline diketone X devoid of strong ultraviolet absorption in the 220–300-mμ region. Moreover, no appreciable ultraviolet maximum developed after the ketone X was exposed to boiling methanolic sodium hydroxide.[21] Its n.m.r. spectrum showed an ill-resolved two-proton resonance multiplet at 179 c.p.s. for the α-methylene protons of the β,γ-unsaturated ketone, an observation which parallels similar results obtained by the Abbott workers.[8]

A convenient chemical proof of the presence of a β,γ-unsaturated ketone system in the oxidation product was suggested by the work of Perelman, *et al.*[23] They showed that $\Delta^{5(10)}$-3-keto steroids in pyridine solution absorbed readily 1 mole equiv. of bromine with concomitant loss of hydrobromic acid to yield $\Delta^{4,9}$-dienones. Accordingly, the diketone X was treated with pyridinium bromide perbromide in pyridine solution, and after purification a low yield of a compound considered to be 3β-acetoxy-6-bromo-B-homoestra-1(10),5-diene-7,17-dione (XI) was obtained. The n.m.r. spectrum of the bromodienone XI showed an approximate triplet at 359 c.p.s. for the C-1 olefinic proton, and its ultraviolet spectrum exhibited maxima at 228 and 310 mμ.

When the course of the sulfuric acid rearrangement of the 5β,19-cyclocarbinols Ia was followed by thin layer chromatography (t.l.c.), the transient formation of a less polar intermediate was noted. This intermediate proved to be the principal product when reduced concentrations of acid were employed. The identification of this substance as 3β-acetoxy-5β,6β-methylenestr-9-en-17-one (VII) was based on the following considerations. The ultraviolet spectrum of this product exhibited maximal absorption at 216 mμ, as expected by analogy with related vinylcyclopropyl chromophores.[24] Signals were observed in the n.m.r. spectrum at 38–43 c.p.s. for the cyclopropyl protons, but olefinic proton resonance was absent. Finally, exposure of the cyclopropyl intermediate VII to increased concentrations of sulfuric acid led to the B-homo alcohol VIb in moderate yield.

(19) The different behavior of 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one (Id) in anhydrous hydrogen fluoride, compared with the corresponding acetate Ia, is attributed to the inadvertent introduction of moisture into the former reaction rather than to an intrinsic property of the steroid Id. Since water competes with fluoride ion for the carbonium ion species and suppresses the dissociation of hydrofluoric acid, a low yield of fluorinated product is to be expected if essentially anhydrous conditions are not maintained.

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

(21) A similar observation was made also by Tadanier and Cole.[8] This is in agreement with the findings of Johnson and co-workers, who showed that in the A-homo steroid series the β,γ-unsaturated system of a 3-keto-Δ^4a steroid did not isomerize to any appreciable extent.[22]

(22) W. S. Johnson, M. Neeman, and P. S. Birkeland, *Tetrahedron Letters*, 142 (1963).

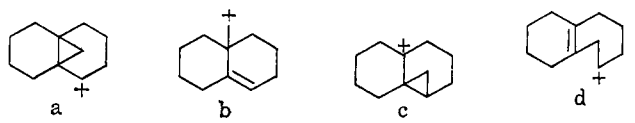
(23) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(24) J. W. Rowe, A. Melera, D. Arigoni, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **40**, 1 (1957).

The rearrangement of the 6-keto-5,19-cyclo steroid Ic to the 19-chloro compounds IIa and IIb is unexceptional and is considered to proceed by the initial protonation of the carbonyl function followed by migration of the 5,19 bond with concomitant entry of chloride ion at C-19.[25]

In the 6α-hydroxy-5β,19-cyclo series, the various acid-catalyzed rearrangement products can be formally derived from the carbonium ions a–d which are generated by protonation of the 6α-hydroxyl group (compare ref. 8).

Clearly, the experiments with sulfuric acid indicate that an equilibrium is established involving several



positively charged species[26] as judged by the formation of 3β-acetoxy-5β,6β-methylenestr-9-en-17-one (VII) in dilute acid and by the ability of this substance to yield the B-homo alcohol VIb in the presence of increased concentrations of acid. A similar situation obtains for the reactions with hydrofluoric acid which afford 3β-hydroxy-6-methylestr-1(10),5-dien-17-one (V) *via* the undetected 5β,6β-methylene compound VII as well as the 7-hydroxy and 7-fluoro-B-homo compounds VIa and VId.

The conversion of 5β,19-cyclo-6α-hydroxy steroid Id to 19-chloro-3β-hydroxyandrost-5-en-17-one (IV) parallels the hydrochloric acid catalyzed rearrangements of simple cyclopropylcarbinol derivatives which also afford the ring-opened primary chloro compounds.[27] The high yield of the 19-chloro-Δ^5 compound IV, without the apparent formation of by-products, suggests that this substance is formed by a concerted process or that IV is the thermodynamic product of this reaction since the rearrangement takes place under strongly equilibrating conditions.

The apparent reduced stability of 19-chloro-3β-hydroxy-5α-androstan-6,17-dione (IIa) merits comment. Allinger has shown that 6-ketocholestane at equilibrium contains 11.6% of the A/B-*cis* isomer.[28] In the 19-chloro-6-keto series the mixture was estimated to contain *ca.* 30% of the 5β isomer at equilibrium. This corresponds to an approximate value of 0.5 kcal./mole[29] for the free energy of isomerization, as compared to 1.2 kcal./mole reported by Allinger for 6-ketocholestane. While the environment of the 6-keto group in the 19-chloroandrostane series is altered by additional substituents at C-3 and C-19, the 3β-hydroxyl group should, if anything, reduce the quantity of the 5β isomer at equilibrium.[30] Thus, the diminished stability of 19-chloro-3β-hydroxy-5α-androstane-6,17-dione (IIa) observed experimentally is attributed to a steric effect of the 19-chloro substituent, rather than to a transmitted effect of the 17-ketone. Indeed, destabilization of the A,B-*trans* 6-ketone IIa is not unexpected, since replacement of a C-19 hydrogen by chlorine introduces a new series of nonbonded interactions between the halogen function and the adjacent axial (β) hydrogen atoms in rings A and C.

(25) For a related study in the 11-keto-12β,18-cyclo series with hydrobromic acid to yield an 18-brominated product, see J. F. Kerwin, M. E. Wolff, F. L. Owings, B. B. Lewis, B. Blank, S. Magnani, C. Karash, and V. Georgian, *J. Org. Chem.*, **27**, 3628 (1962).

(26) The importance of nonclassical carbonium ion participation in these rearrangements cannot be assessed from the available experimental data.

(27) See R. Breslow in "Molecular Rearrangements," part 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp. 260, 269.

(28) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961).

(29) Calculated on the basis of a zero value for the entropy of isomerization. See ref. 28.

(30) The introduction of a 3β-hydroxyl group into an A,B-*cis* steroid produces two 1:3 diaxial interactions between the axial 3β substituent and the axial hydrogens at C-1 and C-5.

Experimental Section[31]

3β,6α-Dihydroxy-5β,19-cycloandrostan-17-one (Id).—3β-Acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia) (0.2 g.)[6] was dissolved in 4 ml. of 1% methanolic sodium hydroxide and the resulting solution was heated under reflux for 1 hr. The reaction mixture was diluted with ice–water and the product was isolated by extraction with ethyl acetate. The resulting solid was crystallized from acetone–ether and afforded 0.13 g. of the diol Id, m.p. 167–168°. The melting point was unchanged after several additional crystallizations: $[\alpha]_D$ +130°; ν_{max} 3350 and 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.77. Found: C, 74.24; H, 9.34; O, 16.67.

3β-Acetoxy-5β,19-cycloandrostane-6,17-dione (Ib).—A solution of 0.15 g. of 3β-acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia) in 3 ml. of acetone was cooled to 5° and oxidized with 0.19 ml. of 8 *N* chromium trioxide–sulfuric acid reagent.[32] After 10 min., ice and water were added and the product was isolated by extraction with ethyl acetate. The crude product crystallized from acetone–ether, yielding 0.12 g. of the diketone Ib, m.p. 155–156°. An analytical specimen, prepared from the same solvent pair, exhibited m.p. 158–159°; $[\alpha]_D$ +1°; ν_{max} 1735, 1730, 1685, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19; O, 18.58. Found: C, 73.26; H, 8.08; O, 18.70.

3β-Hydroxy-5β,19-cycloandrostane-6,17-dione (Ic).—The foregoing diketone (1.2 g.) was hydrolyzed with 20 ml. of boiling 1% methanolic sodium hydroxide solution for 1 hr. and the reaction mixture was processed as described previously. Crystallization of the crude product from acetone–hexane provided 0.9 g. of the hydroxy diketone Ic: m.p. 200–201°, raised to 203–204° after two additional crystallizations; $[\alpha]_D$ +17°; ν_{max} 3500, 1730, and 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; O, 15.87. Found: C, 75.31; H, 8.74, O, 15.94.

Reaction of 3β-Hydroxy-5β,19-cycloandrostane-6,17-dione (Ic) with Hydrochloric Acid.—A solution of 1 g. of Ic in 50 ml. of tetrahydrofuran was cooled to 5° and treated with 2.1 ml. of boron trifluoride etherate and 5.1 ml. of concentrated hydrochloric acid.[10] The reaction mixture was left standing for 21 hr. at room temperature and then diluted with cold water, and the resulting solution was extracted with several portions of methylene chloride. The organic extracts were washed with water to neutrality, dried (Na_2SO_4), and evaporated. The crude product, shown to be a 70:30 mixture by t.l.c., was dissolved in ethyl acetate and adsorbed on a column of 100 g. of silica gel. The steroids were eluted with pure ethyl acetate (10-ml. fractions) and the progress of the chromatogram was followed by t.l.c. analysis. The fractions containing the pure less polar component were combined and crystallized from acetone–ether to yield 0.21 g. of 19-chloro-3β-hydroxy-5β-androstane-6,17-dione (IIb), m.p. 181–183°. An analytically pure specimen had m.p. 186–187°; $[\alpha]_D$ −25°; ν_{max} 3450, 1750, and 1700 cm.$^{-1}$; O.R.D. $[\phi]_{700}$ + 146°, $[\phi]_{589}$ +225°, $[\phi]_{400}$ +304°, $[\phi]_{350}$ +481°, $[\phi]_{322.5}$ +1034°,

(31) Melting points are uncorrected. All rotations are for chloroform solutions at 16–22°, and ultraviolet absorption spectra for 95% ethanol solutions. Infrared spectra determined in potassium bromide disks on a Perkin-Elmer Model 21 spectrometer equipped with sodium chloride optics are by Mr. Erlin Avila and his staff. N.m.r. spectra were taken in deuteriochloroform solution (*ca.* 10% w./v.) with a tetramethylsilane internal reference using a Varian A-60 spectrometer. Chemical shifts are quoted as cycles per second from the reference. The optical rotatory dispersion curves were obtained with a Rudolph spectropolarimeter. Microanalyses were by Midwest Micro Laboratories, Indianapolis 20, Ind., or by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

(32) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

$[\phi]_{305}$ ±0, and $[\phi]_{300}$ −328° (*c* 0.06, dioxane); n.m.r. 55 (18-H), 215 and 218 (19-H, inner peaks of a pair of doublets), and 248 c.p.s. (broad multiplet of 3α-H).

Anal. Calcd. for $C_{19}H_{27}ClO_3$: C, 67.34; H, 8.03; Cl, 10.46; O, 14.17. Found: C, 67.56; H, 8.24; Cl, 10.89; O, 14.60.

The fractions containing the pure more polar component were combined and crystallized from acetone–ether to yield 0.48 g. of 19-chloro-3β-hydroxy-5α-androstane-6,17-dione (IIa), m.p. 174–175°. The analytical sample exhibited m.p. 175–176°; $[\alpha]_D$ +27°; ν_{max} 3400, 1725, and 1710 cm.$^{-1}$; O.R.D. $[\phi]_{700}$ +129°, $[\phi]_{589}$ +182°, $[\phi]_{400}$ +641°, $[\phi]_{317.5}$ +6435°, and $[\phi]_{305}$ +2681° (*c* 0.06, dioxane); n.m.r. 56.5 (18-H), 203, 215, 218, and 228 c.p.s. (AB pattern of 19-H).

Anal. Calcd. for $C_{19}H_{27}ClO_3$: C, 67.34; H, 8.03; Cl, 10.46. Found: C, 67.63; H, 8.15; Cl, 10.06.

Treatment of the Isomeric 19-Chloro Compounds IIa and IIb with 1% Sodium Hydroxide in Methanol.—19-Chloro-3β-hydroxy-5β-androstane-6,17-dione (IIb, 0.02 g.) was dissolved in 2 ml. of 1% methanolic sodium hydroxide and heated under reflux for 1 hr. and processed as described previously. The resulting product was crystallized from acetone–ether to give 3β-hydroxy-5β,19-cycloandrostane-6,17-dione (Ic), m.p. 198–200°, identical, in all respects with an authentic sample.

19-Chloro-3β-hydroxy-5α-androstane-6,17-dione (IIa, 0.02 g.) also yielded the same product when treated in the identical manner.

Equilibration of the Isomeric 19-Chloro Compounds IIa and IIb.—Five-milligram samples of IIa and IIb were dissolved in 0.25 ml. of tetrahydrofuran in separate flasks, and the resulting solutions were cooled and treated with 0.01 ml. of boron trifluoride etherate and 0.03 ml. of concentrated hydrochloric acid. After 15 min. the solutions were permitted to warm to room temperature. Aliquots were withdrawn after 3, 5, and 24 hr. and examined by t.l.c. analysis using both starting materials as reference standards. The steroids were detected with iodine vapors and their concentrations were estimated by comparing the relative intensities and areas of the spots. After 3 hr. both samples were equilibrated to the same 70:30 mixture in which the 5α isomer IIa predominated. This ratio was unchanged after 5- and 24-hr. periods.

Reduction of 19-Chloro-3β-hydroxy-5α-androstane-6,17-dione (IIa) with Lithium Tri-*t*-butoxyaluminum Hydride.—A solution of 0.2 g. of IIa in 20 ml. of dry tetrahydrofuran was treated with 0.7 g. of lithium tri-*t*-butoxyaluminum hydride and heated under reflux for 0.5 hr. After cooling, the reaction mixture was poured into 25 ml. of 1% aqueous hydrochloric acid and the resulting solution was extracted with ethyl acetate. The organic phase was separated, washed once with 1% aqueous sodium bicarbonate and with water to neutrality, dried over sodium sulfate, and evaporated.

An ethyl acetate solution of the resulting product was filtered through a small column of silica gel and the solids eluted in the first fractions were combined and crystallized from acetone–hexane. This yielded 0.04 g. of 6β-19-oxido-5α-androstane-3β,17β-diol (IIIa), m.p. 170–175°, identical in all respects with an authentic sample.[11]

Reduction of 19-Chloro-3β-hydroxy-5β-androstane-6,17-dione (IIb) with Lithium Tri-*t*-butoxyaluminum Hydride.—The reduction of 0.24 g. of the 5β isomer IIb with 0.7 g. of lithium tri-*t*-butoxyaluminum hydride exactly as described in the preceding experiment afforded a crude product which was crystallized from acetone–ether to yield 0.13 g. of 6β,19-oxido-5β-androstane-3β,17β-diol (IIIb), m.p. 230–232°. An analytically pure specimen exhibited m.p. 232–234°; $[\alpha]_D$ +35°; n.m.r. 48 (18-H), 195, 203, 234, 242 (19-H), 213, 222, and 256 c.p.s. (ill-resolved multiplets for 3α-H, 6α-H, and 17α-H).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87; O, 15.66. Found: C, 74.63; H, 9.83; O, 15.84.

3β-Hydroxy-5α-androstane-6,17-dione (IIc).—A solution of 1.8 g. of 3β-acetoxy-5α-androstane-6,17-dione[33] in 70 ml. of 1% methanolic sodium hydroxide was heated under reflux for 1 hr., cooled, and poured into water. The product was isolated by extraction with ethyl acetate and crystallized from methanol to yield 1 g. of 3β-hydroxy-5α-androstane-6,17-dione (IIc): m.p. 186–187°, unchanged after further crystallization; $[\alpha]_D$ +60°; ν_{max} 3300, 1750, and 1715 cm.$^{-1}$; O.R.D. $[\phi]_{700}$ +140°, $[\phi]_{589}$ +167°, $[\phi]_{400}$ +850°, $[\phi]_{320}$ +6532°, and $[\phi]_{310}$ +4274° (*c* 0.1, dioxane).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.77. Found: C, 75.71; H, 9.13; O, 15.70.

Reaction of 3β,6α-Dihydroxy-5β,19-cycloandrostan-17-one (Id) with Hydrochloric Acid.—A solution of 0.05 g. of the 5β,19-cyclo-3β,6α-diol Id in 2.5 ml. of tetrahydrofuran was cooled to 5° and treated with 0.1 ml. of boron trifluoride etherate and 0.25 ml. of concentrated hydrochloric acid. The reaction mixture was left standing at room temperature for 20 hr. and then poured into 25 ml. of methylene chloride. The resulting solution was washed with water until neutral, dried (Na_2SO_4), and evaporated to yield essentially pure 19-chloro-3β-hydroxyandrost-5-en-17-one (IV). The product, obtained by crystallization from ethanol, exhibited m.p. 193–195° and was undepressed in melting point when mixed with an authentic sample[16] of the 19-chloro compound IV. The infrared spectra of the two compounds were indistinguishable.

Reaction of 3β,6α-Dihydroxy-5β,19-cycloandrostan-17-one (Id) with Hydrofluoric Acid.—An ice-cold solution of 0.9 g. of Id and 55 ml. of methylene chloride was added to a mixture of 5.4 g. of anhydrous hydrofluoric acid and 9 ml. of tetrahydrofuran previously cooled to −70° by immersion in an acetone–Dry Ice mixture. The resulting solution was stirred for 30 min. at −70° and then left standing at −5° for 24 hr. The reaction mixture was poured into an excess of sodium bicarbonate solution and the product was isolated by extraction with methylene chloride. The resulting oil was dissolved in 25 ml. of methylene chloride and adsorbed on a column of 100 g. of silica gel. Elution with methylene chloride–ethyl acetate (1:1) provided 0.05 g. of 3β-hydroxy-6-methylestra-1(10),5-dien-17-one. After several crystallizations from methanol–water, this substance exhibited m.p. 150–152°, $[\alpha]_D$ −113°, ν_{max} 246 mμ with inflections at 237 and 255 mμ (log ε 4.33), and was identical in all respects with a sample prepared by an alternative synthesis.[17]

Continued elution with pure ethyl acetate afforded 0.07 g. of 3β,7ξ-dihydroxy-B-homoestr-5(10)-en-17-one (VIa), m.p. 168–170°. The analytical sample, prepared from acetone–hexane, had m.p. 176–178°; $[\alpha]_D$ +46°; ν_{max} 3400 and 1725 cm.$^{-1}$; n.m.r. 55.1 (18-H), 118.7 (3-O*H* and 7-O*H* since band disappears on addition of D_2O), and 239.5 c.p.s. (broad multiplet of 3α-H and 7-H).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.77. Found: C, 74.49; H, 9.41; O, 16.14.

Reaction of 3β-Acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia) with Hydrofluoric Acid.—An ice-cold solution of 1.0 g. of Ia and 60 ml. of methylene chloride was added to a mixture of 6.4 g. of of anhydrous hydrogen fluoride and 12.3 g. of tetrahydrofuran previously cooled to −70° by immersion in an acetone–Dry Ice mixture. The resulting solution was stirred for 1.5 hr. at −70°, left standing at −5° for 24 hr., and processed as described previously. This afforded an oil (five compounds by t.l.c.) which was dissolved in chloroform–ethyl acetate (3:1) and adsorbed on 200 g. of silica gel. Elution with this same mixture yielded 0.29 g. of homogeneous 3β-acetoxy-7ξ-fluoro-β-homoestr-5(10)-en-17-one (VId). An analytical sample prepared by crystallization from methanol had m.p. 109–110°; $[\alpha]_D$ +54°; ν_{max} 1740 and 1250 cm.$^{-1}$; n.m.r. 57.3 (18-H), 123.4 (3-acetoxy-H), 296 (multiplet of 3α-H), 269, and 319 c.p.s. (ill-resolved multiplets of 7-H).

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.39; H, 8.39; F, 5.45. Found: C, 72.15; H, 8.33; F, 6.09.

A sample of 3β-acetoxy-7ξ-fluoro-B-homoestr-5(10)-en-17-one was undepressed in melting point when mixed with the fluoro compound obtained by treating 3β-acetoxy-19-hydroxyandrost-5-en-17-one with diethyl-(2-chloro-1,1,2-trifluoroethyl)amine.[9] The infrared spectra of the two compounds were indistinguishable.

Reaction of 3β,6α-Dihydroxy-5β,19-cycloandrostan-17-one (Id) with Sulfuric Acid.—A solution of 1.5 g. of Id in 112.5 ml. of dioxane was treated with 37.5 ml. of 30% aqueous sulfuric acid, and after 4 hr. the reaction mixture was poured into saturated sodium chloride solution. The steroid was isolated by extraction with ethyl acetate and, after crystallization from acetone–ether, there was obtained 0.78 g. of 3β,7ξ-dihydroxy-B-homoestr-5-(10)-en-17-one (VIa), m.p. 176–178°. This substance was shown to be identical with a sample of the B-homodiol obtained previously (*vide supra*) by mixture melting point determination and infrared spectral comparison.

Reaction of 3β-Acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia) with Sulfuric Acid.—Treatment of 0.5 g. of the acetate

(33) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1956).

Ia with 30% aqueous sulfuric acid in dioxane, as described in the preceding experiment, gave an oily product which was dissolved in ethyl acetate–hexane (3:1) and adsorbed on a column of 5 g. of silica gel. By crystallization (acetone–hexane) of the product eluted in the first fractions there was obtained 0.11 g. of 3β-acetoxy-7ξ-hydroxy-B-homoestr-5(10)-en-17-one (VIb): m.p. 161–163° (after several additional crystallizations, the melting point was raised to 168–169°); $[\alpha]_D$ +40°; ν_{max} 3550, 1750, and 1250 cm.$^{-1}$; n.m.r. 56.4 (18-H) and 123 c.p.s. (3-acetoxy H).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.33; H, 8.66.

Continued elution with the same solvent mixture afforded a second product, which was crystallized from acetone–hexane to yield 0.02 g. of 3β,7ξ-dihydroxy-B-homoestr-5(10)-en-17-one (VIa), m.p. 175–177°.

Epoxidation of 3β,7ξ-Dihydroxy-B-homoestr-5(10)-en-17-one (VIa).—A solution of 0.1 g. of VIa in 0.8 ml. of chloroform was treated with 0.08 g. of *m*-chloroperbenzoic acid dissolved in 1.6 ml. of chloroform, and after 1 hr. the reaction mixture was diluted in 10 ml. of chloroform. The resulting solution was washed successively with 10% aqueous sodium bisulfite, 5% aqueous sodium bicarbonate, and water, dried (Na_2SO_4), and evaporated. The resulting solid was crystallized several times from methanol to afford a sample of 3β,7ξ-dihydroxy-5ξ,10ξ-epoxido-B-homoestran-17-one (VIII), m.p. 204–207°, admixed with *ca.* 10% of the isomeric epoxide: $[\alpha]_D$ +76°; ν_{max} 3250 and 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_4 \cdot 0.25CH_3OH$: C, 70.46; H, 8.90; O, 20.66. Found: C, 70.78; H, 8.63; O, 20.96.

Catalytic Hydrogenation of 3β,7ξ-Dihydroxy-B-homoestr-5(10)-en-17-one (VIa).—A solution of 0.1 g. of VIa in 3 ml. of methanol was hydrogenated with 0.03 g. of prereduced 10% palladized charcoal. The uptake of hydrogen ceased after 3 mole equiv. was absorbed. The catalyst was removed by filtration and the filtrate was taken to dryness *in vacuo*. The resulting solid was crystallized from methanol to afford 0.06 g. of 5ξ,10ξ-B-homoestran-17-one (IX): m.p. 108–113°, raised to 116–117° after several additional crystallizations; $[\alpha]_D$ +62°; ν_{max} 1725 cm.$^{-1}$; n.m.r. 50.7 c.p.s. (18-H).

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02; O, 5.83. Found: C, 83.31; H, 11.26; O, 5.91.

3β-Acetoxy-B-homoestr-5(10)-en-7,17-dione (X).—A solution of 0.75 g. of 3β-acetoxy-7ξ-hydroxy-B-homoestr-5(10)-en-17-one (VIb) in 15 ml. of pyridine was added to a slurry of chromium trioxide–pyridine complex[19] prepared by adding 0.8 g. of chromic acid to 15 ml. of pyridine. The mixture was stirred for 15 hr. and then diluted with 7.0 ml. of ethyl acetate, and the resulting solution was filtered successively through Celite and a column of 30 g. of alumina. Crystallization of the resulting solid from ether–hexane provided 0.36 g. of the diketone X, m.p. 138–139°. An analytically pure sample prepared from the same solvent pair exhibited m.p. 142–143°; $[\alpha]_D$ −105°; λ_{max} 289 mμ (log ε 2.17); ν_{max} 1740, 1720, and 1250 cm.$^{-1}$; n.m.r. 54.5 (18-H), 124 (3-acetoxy-H), 179 (ill-resolved multiplet of 6-H), and 299 c.p.s. (multiplet of 3α-H).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19; O, 18.58. Found: C, 72.90; H, 8.43; O, 19.09.

3β-Acetoxy-6-bromo-B-homoestra-1(10),5-diene-7,17-dione (XI).—A solution of 0.2 g. of the foregoing diketone in 4 ml. of pyridine was treated with 1.1 g. of pyridinium bromide perbromide and stirred for 7 hr. The reaction mixture was partitioned between water and ethyl acetate and the organic phase was separated. This was washed successively with dilute hydrochloric acid, dilute sodium bicarbonate, and water until neutral. Evaporation of the sodium sulfate dried extract *in vacuo* yielded a solid which was taken up in hexane–ethyl acetate (7:3) and adsorbed on a column of 41 g. of silica gel. The crystalline fractions eluted with this mixture were combined with acetone, aqueous methanol was added, and the solvents were evaporated to a small volume in a stream of nitrogen. After cooling, there was obtained 0.1 g. of the bromodienone XI, m.p. 134–136°.

After several additional crystallizations following the same procedure, an analytical sample was obtained which exhibited m.p. 140–141°; $[\alpha]_D$ −476°; λ_{max} 228 and 310 mμ (log ε 3.69 and 3.97); ν_{max} 1740, 1680, 1630, and 1250 cm.$^{-1}$; n.m.r. 57 (18-H), 121.5 (3-acetoxy-H), 317 (multiplet of 3α-H), 355, 359, and 361 c.p.s. (1-H).

Anal. Calcd. for $C_{21}H_{26}BrO_4$: C, 59.86; H, 5.98; Br, 18.97. Found: C, 59.82; H, 6.05; Br, 19.61.

Reaction of 3β-Acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia) with Dilute Sulfuric Acid.—A solution of 2 g. of the cyclopropane Ia in 72 ml. of dioxane containing 9.6 ml. of acetic acid was treated with 24 ml. of 16% aqueous sulfuric acid. The mixture was stirred for 10 min. and poured into saturated brine, and the resulting solution was extracted with several portions of ethyl acetate. The organic extracts were washed with dilute sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated. This afforded a solid which was dissolved in hexane and chromatographed on 100 g. of Florisil. No products were eluted with pure hexane or mixtures of hexane–benzene. Elution with pure benzene furnished 0.58 g. of 3β-acetoxy-5β,6β-methylenestr-9-en-17-one (VII) which exhibited m.p. 124–125° after crystallization from hexane. A pure specimen of VII had m.p. 125–126°; $[\alpha]_D$ +72°; λ_{max} 216 mμ (log ε 3.95); ν_{max} 1730 and 1250 cm.$^{-1}$; n.m.r. 38.3, 46.3 (cyclopropyl-H), 58.3 (18-H), 123 (3-acetoxy H), and 306 c.p.s. (multiplet of 3α-H).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.69; H, 8.59. Found: C, 76.89; H, 8.80.

This product was identical by mixture melting point and infrared comparison with a sample of 3β-acetoxy-5β,6β-methylenestr-9-en-17-one described in the accompanying paper.

Conversion of 3β-Acetoxy-5β,6β-methylenestr-9-en-17-one (VII) to 3β-Acetoxy-7ξ-hydroxy-B-homoestr-5(10)-en-17-one (VIb).—A solution of 0.25 g. of the foregoing cyclopropane in 9 ml. of dioxane containing 1.2 ml. of acetic acid was treated with 3 ml. of 30% aqueous sulfuric acid. After 4 hr. the reaction mixture was poured into saturated brine and processed as described previously. This afforded an oil which was dissolved in hexane and chromatographed on 12.5 g. of Florisil. Elution with hexane and hexane–benzene mixtures afforded traces of noncrystalline material which were discarded. Elution with pure benzene afforded 0.08 g. of the starting compound VII. Continued elution with benzene containing 3% acetone yielded a second product which was crystallized twice from acetone–hexane. This gave 0.02 g. of 3β-acetoxy-7ξ-hydroxy-B-homoestr-5(10)-en-17-one (VIb), m.p. 159–161°, identical by mixture melting point and infrared comparison with a sample obtained from the 30% sulfuric acid rearrangement of 3β-acetoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (Ia).

Acknowledgment.—We wish to thank Dr. A. D. Cross for helpful discussions on the n.m.r. aspects of this work.