STEROIDS CCLIX[1]. THE SYNTHESIS OF 5β,19 AND 6β,19-CYCLO STEROIDS[2]

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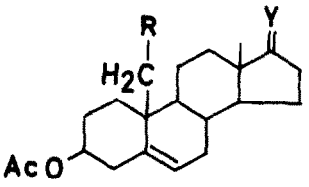
The solvolysis of 3β,19-dihydroxyandrost-5-ene-17-one-3-acetate 19-tosylate (Ib) led to the Δ6-5,19-cyclo steroid IIa or a variety of 6α-substituted 5,19-cyclopropanes V depending upon the reaction conditions. The possibility that these reactions proceed through an intermediate homoallylic bridged cation is discussed. The formation of 6β,19-cyclobutanes from 19-hydroxyandrost-4-ene 3,17-dione tosylate (VIb) is described

Recent work from these laboratories[3-5] and independent studies by the Ciba group[6,7] have made 19-hydroxy-Δ^5-olefines readily available. These compounds have found important use as intermediates for improved syntheses of 19-nor steroid hormones[3-7]. Further studies of the chemistry of this interesting β,γ-unsaturated neopentyl primary alcohol system are now possible and this paper describes the conversion of 3β,19-dihydroxyandrost-5-ene-17-one 3-acetate (Ia) into various 5β,19-cyclopropanes and the preparation of some 6β,19-cyclobutanes.

A solution of 3β,19-dihydroxyandrost-5-ene-17-one

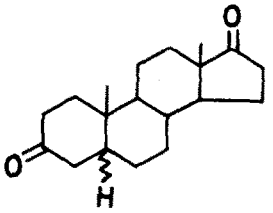


I a, R= OH; Y= O

b, R= OTs; Y= O

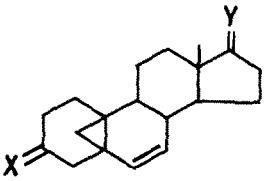
c, R= OTs; Y= 

d, R= Cl ; Y= O



IV a, 5α-H

b, 5β-H



II a, X=  ; Y= O

b, X=  ; Y= 

c, X=  ; Y= 

d, X=  ; Y= 

e, X= O; Y= 

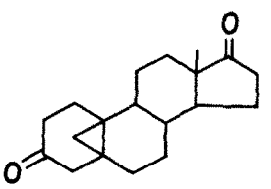
f, X= Y=

g, X= Y= O

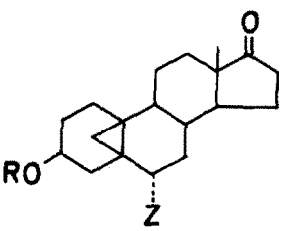
h, X=  ; Y= O

i, X=  ; Y= 

j, X= O; Y= 



III



V a, R= Ac; Z= OAc

b, R= Ac; Z= OH

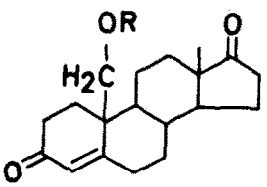
c, R= Ac; Z= N_3

d, R= Ac; Z= OEt

e, R= Ac; Z= OiPr

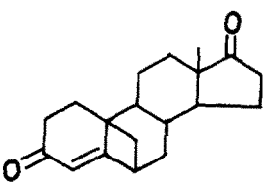
f, R= H; Z= N_3

g, R= N_3; 3-ketone

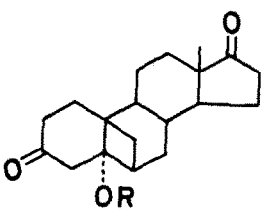


VI a, R= H

b, R= Ts



VII



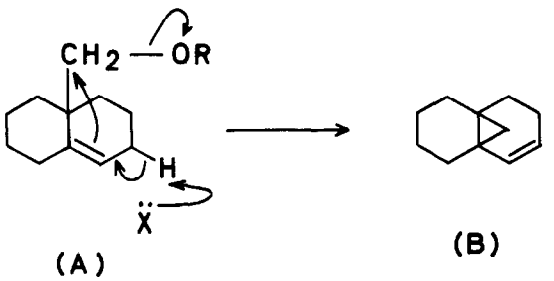
VIII a, R= H

b, R= Me

3-acetate 19-tosylate (Ib)[4] was heated under reflux in pyridine solution for 16 hours to afford 3β-hydroxy-5,19-

cycloandrost-6-en-17-one acetate (IIa) in good yield. The nuclear magnetic resonance (N.M.R.) spectrum[8] of IIa (see Table 1) revealed that the 19-proton resonance at ca. 244 c.p.s. in the tosylate Ib, had shifted to high field characteristic of cyclopropyl protons. Moreover, the splitting pattern for this resonance, an AB quartet with J 4.9 c.p.s., is typical of cyclopropyl methylene with no adjacent cyclopropyl protons. Deshielding of one cyclopropyl proton to 70.8 c.p.s. is due to the magnetic anisotropy of the neighbouring 6,7-double bond. The protons of the latter appeared as the AB portion of an ABX pattern (J_{AB} = 9.8 c.p.s., J_{AX} = 2 c.p.s.). Olefinic proton resonance appearing as a pair of doublets was assigned to the C-6 rather than to the C-7 proton (doublet) since the stereochemical disposition of these two protons relative to the axial 8β-proton is such as to favor long-range 6H-8βH coupling[9] while minimising 7H-8βH coupling.

The formation of IIa from Ib is analogous to the conversion of the bicyclic alcohol $\Delta^{1,9}$-10-hydroxymethyl-octaline benzenesulfonate (A) into [0,1,4,4]-Δ^{1}-tricyclo-undecene (B)[10] and clearly proceeds as shown (A⟶B).[11]



Various hormone analogs containing the Δ^6-5,19-cyclo system were prepared by conventional procedures. Reduction of the 17 ketone (IIa) with sodium borohydride in aqueous dioxane solution gave the corresponding 17β-alcohol (IIb) which was converted into the pyranyl ether IIc. Alkaline hydrolysis of the 3-acetate group to the alcohol IId followed by oxidation at C-3 with chromium trioxide in pyridine solution and acid hydrolysis of the protecting pyranyl ether group gave 17β-hydroxy-5,19-cycloandrost-6-ene-3-one (IIe).

Alkaline hydrolysis of the diol monoacetate IIb gave the diol IIf which was oxidized with Jones reagent[12] to the dione IIg. In the N.M.R. spectrum of the dione IIg a quartet for the protons of the cyclopropyl methylene were clearly visible and assignments of a doublet to the proton at C-7 and a pair of doublets to the C-6 proton were made on the basis of arguments outlined above. Hydrogenation of IIg in benzene solution with a 5% palladium-carbon catalyst led to the uptake of 1.07 mols of hydrogen. Purification of the product by alumina chromatography led to 5,19-cycloandrosta-3,17-dione (III). In ethanol solution the uptake of hydrogen was 2 mols affording a mixture of 5α-androstane-3,17-dione (IVa) and 5β-androstane-3,17-dione (IVb). A possible explanation for the formation of IVb is that androst-4-ene-3,17-dione is an intermediate in the hydrogenation reaction. The N.M.R. spectrum of the saturated dione III revealed that the chemical

shift, $\Delta\nu$, between the cyclopropyl protons was substantially smaller than for the Δ^6-compounds IIa and IIg, in full agreement with the suggestion (vide supra) that in the unsaturated derivatives one of these protons suffers long-range deshielding by the olefinic double bond. In IIg the second cyclopropyl methylene proton is also deshielded.

Hydrolysis of the acetoxy ketone IIa with potassium carbonate gave the corresponding alcohol IIh, and reaction of IIa with methyl magnesium bromide gave the 17α-methyl diol (IIi). Oxidation of IIi afforded the 3-ketone (IIj).

A series of reactions of the Δ^5-19-tosylate Ib with different nucleophiles was then investigated. Previously[4] we have reported on the preparation of 3β-hydroxy-19-chloroandrost-5-ene-17-one (Id) via treatment of the tosylate Ib with lithium chloride in isopropanol solution[13]. It now appears, however, from our accumulated experience of reactions of this Δ^5-19-tosylate system that displacements of this type (i.e., Ib ⟶ Id) are the exception rather than the rule and that the normal course of nucleophilic attack of a Δ^5-19-tosylate results in the formation of 6α-substituted or Δ^6-5,19-cyclopropane structures. These reactions are analogous to the conversion of Δ^5-3β-tosylates into 6α-substituted 3,5-i-steroids[14].

Treatment of Ib with potassium acetate in aqueous dioxan afforded a mixture of the 6α-acetoxy-5,19-cyclo-

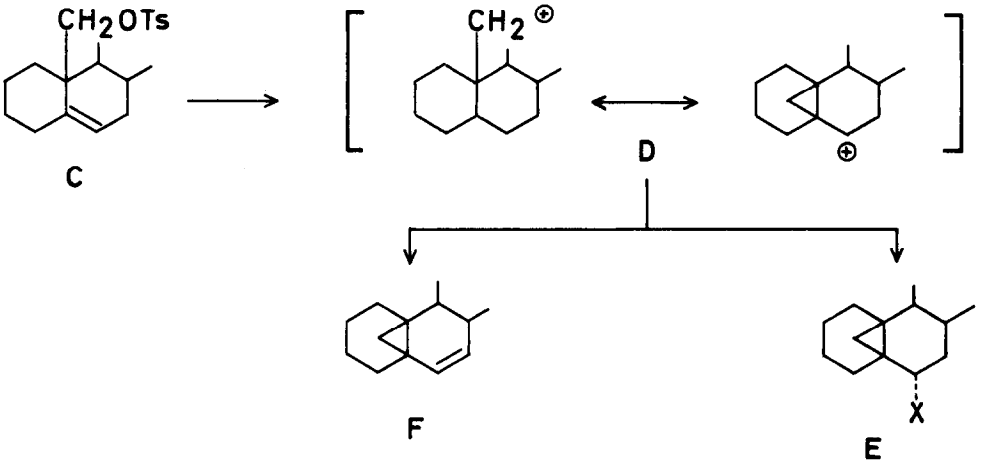
steroid Va and the corresponding diol monoacetate Vb. In contrast to lithium chloride[4] or lithium bromide[13] displacements of the Δ^5-19-tosylate Ib it was found that sodium azide in ethanol solution smoothly reacted with Ib to afford a mixture of the 6α-azide Vc and the 6α-ethoxide Vd. Similarly, in isopropanol solution both the azide Vc and the 6α-isopropoxide Ve were obtained. Hydrolysis of the 6α-azide 3-acetate Vc led to the free 3β-alcohol Vf oxidation of which furnished the corresponding 3,17-dione Vg. N.M.R. spectroscopy aided elucidation of the structures of several of these compounds (table 1). For the derivatives Vd-g either two or four peaks of the AB quartet for cyclopropyl methylene protons were clearly visible at high fields. Characteristic triplet and quartet patterns for ethoxy disclosed this structural feature of Vd. Similarly the isopropoxy unit in Ve was revealed in a 6-proton doublet and a 1-proton quartet. The change from 3β-hydroxyl, Vf, to 3-ketone, Vg, results in deshielding of one cyclopropyl proton as observed earlier with the conversion of IIa to IIg.

The solvolysis reactions which have been noted above for the Δ^5-19-tosylate system can be rationalized as proceeding via a rate controlled unimolecular reaction to a homoallylic bridge ion which is stabilized by distribution of the charge between C-19 and C-6 (C → D → E or F).

Experiments are under way to clarify this point and

to establish the kinetic order of the reaction as well as to determine whether anchimeric assistance by the double bond or steric factors control the rate of the solvolysis of the Δ^5-19-tosylate[15].

The availability of 19-hydroxyandrost-4-ene 3,17-dione[3-7] (VIa) encouraged us to study the formation of 6,19-cyclobutanes by a base promoted intramolecular alkylation reaction[16] of the corresponding tosylate VIb.



In a nitrogen atmosphere treatment of VIb with sodium methoxide in anhydrous methanol under reflux for 24 hr. led to three products which were separated by chromatography over alumina. The major product formed in over 50% yield was the 6,19-cyclobutane (VII),[11] the structural assignment of which rested on analytical U.V. and I.R. and N.M.R. data. In the ultraviolet VII exhibited maximum absorption at 242 mμ, log ε 4.19 characteristic of a Δ^4-3-keto group and strong bands in the infra red (solution in CCl_4) at 5.73 (17-ketone), 5.98 (conjugated

Table 1

N.m.r. spectral data for 19 substituted androstanes.[8,a,b]

Compound	18-H	19-H	Other protons
Ib	46.2[c]	242.0 and 245.7 (inner peaks of AB quartet)	118.9 (OAc); 145.3 ($ArCH_3$); 337 (6-H), m
IIa	54.3	33.6 and 38.4, 68.3 and 73.2 (AB quartet, J, 4.9 c.p.s.)	120.3 (OAc); 342.3 and 344.3, 352.1 and 354.0 (6-H, $J_{6,7}$, 9.8 c.p.s., $J_{6,8}$ 2 c.p.s.) 313.5 and 323.3 (7-H, $J_{6,7}$, 9.8 c.p.s.)
IIg	54.8	44.6 and 49.5, 67 and *ca.* 72 (AB quartet, J 4.9 c.p.s.)	321.6 and 331.5, d. (7-H); 342.9 (d) and 353.2 (d) (6-H; $J_{6,7}$, 9.9 c.p.s., $J_{6,8}$, *ca.* 2 c.p.s.)
III	53.4	23.9, 30.0, 31.3 and 37.5 (AB quartet, J, 6.1 c.p.s.)	152 ($4\text{-}CH_2$)
Vd	52.2	19.1 and 24.1 (only visible pair of AB quartet, J, 5.0 c.p.s.)	120.3 (OAc); 71.5,t. (CH_3 of ethoxy J,6.8 c.p.s.); 206.5, q. (methylene of ethoxy J, 6.8 c.p.s.); 221,t. (6β-H).
Ve	52.1	17.8 and 22.6 (only visible pair of AB quartet, J,4.8 c.p.s.)	120.4 (OAc); 65.3 and 72.0,d. (equivalent methyls of isopropoxy, $J_{H,Me}$, 6.7 c.p.s.); 219.8, q. ($OCHMe_2$, $J_{H,Me}$, 6.6 c.p.s.) *ca.* 228 m. (6β-H).

Vf	51.5	31.5 and 36.4, 58.9 and 63.7 (AB quartet, J, 4.9 c.p.s.	ca. 243, m., half bond width 8 c.p.s. (6β-H)
Vg	53.9	37.3 and 43.4, (only visible pair of AB quartet, J, 6.1 c.p.s.)	161.0 (4-CH_2); ca. 239, m. (6β-H)
VII	58.7	e	196,t. (6α-H); 338 (4-H).
VIIIa	56.1	e	e,153.7, 171.8 and 187.4,q. (4-CH_2)
VIIIb	56.0	e	164.3 (4-CH_2; 189.0 (OMe).

[a]Except where indicated to the contrary resonances are singlets; [b]d = doublet, q = quartet, t = triplet, m = multiplet [c]This resonance illustrates a powerful shielding of the 18-protons by the 19-tosylate substituent. A detailed discussion of various spectral data for 19-substituted steroids will be presented elsewhere, P. Crabbé, L.H. Knox and A.D. Cross, manuscript in preparation; [e]Resonance not discernible from surrounding proton resonance.

ketone), and 6.02 (shoulder) (double bond in conjugation with carbonyl group).

The N.M.R. spectrum of the enone VII showed only one three-proton singlet and this, at 58.7 c.p.s., is downfield by ca. 3 c.p.s. from the normal resonance frequency of 17-ketoandrostanes (for androst-4-ene-3,17-dione, $\upsilon_{18\text{-H}}$ = 55.8 c.p.s.[17]) No resonance assignable to protons on C-19 was locatable as was to be expected

from their aliphatic character. It was held significant that the C-4 proton resonance is a sharp singlet since it is now known[9] that such protons give rise to a broadened 'singlet' where a 6β-proton is present. The presence of a 6β-substituent in compound VII was therefore indicated. A triplet at 196 c.p.s. was assignable to the allylic 6α-cyclobutane proton coupled to both of the adjacent C-7 protons.

Two minor products VIIIa and VIIIb were isolated from the chromatogram of the reaction, both in less than 3% yield. One was less and the other more polar towards alumina than the α,β-unsaturated ketone VII. Treatment of the less polar product VIIIb with concentrated hydrochloric acid in dioxane solution gave the Δ^4-3-ketone VII. Similarly VIIIa was converted into VII when an attempted acetylation was carried out with acetic anhydride in pyridine solution. These data taken together with the spectral and analytical data for these compounds led to their formulation as the 5α-methoxy and 5α-hydroxy compounds VIIIa and VIIIb respectively. The N.M.R. spectrum of VIIIa showed a singlet for the 18-protons (56.1 c.p.s.) and three peaks of an AB quartet, J_{HH} ca. 15.5 c.p.s. were also visible. The quartet was assigned to the methylene at C-4 flanked on either side by carbon carrying no hydrogen. Conversely, the methyl ether VIIIb, which showed an extra three-proton singlet at 189 c.p.s. for the methoxyl, showed only a two-proton singlet for the

C-4 methylene. Apparently the influence of adjacent methoxyl is to render both methylene protons accidentally equivalent.

The α-configuration assigned to the substituent at C-5, in compounds VIIIa and VIIIb, was deduced from the Cotton effect observed by Circular Dichroism (C.D.)[18].

From a stereochemical point of view, the addition of an hydroxyl function, as in VIIIa, and methoxy-grouping, as in VIIIb, on the activated Δ^4-double bond, should occur from the α-side of the molecule, since the 6,19-bridge considerably hinders the approach of the reagent from the β-side. This assumption was confirmed when the C.D. curves of these three substances VII, VIIIa,b were obtained.[19] The Δ^4-3-keto bridged compound (VII) showed a positive C.D. maximum[20] at 296mμ ([θ] = 7.790), corresponding to the 17-keto-chromophore. This maximum is well resolved from the intense negative maxima associated with the Δ^4-3-keto-chromophore, around 340 mμ. The C.D. curves of the diketo-bridged compounds VIIIa and VIIIb, both show a stronger positive Cotton effect than the parent compound VII (see experimental section). This considerable increase of the C.D. positive maximum in VIIIa and VIIIb is attributable to an α-configuration of the substituent at C-5, since 3-keto 5β-(A-B-cis)-steroids are known to show a negative Cotton effect by optical rotatory dispersion[21] and Circular Dichroism.[22] Would this be the case, the C.D.

maximum of diketones VIIIa and VIIIb should be lower than in VII. The observed results are opposite, thus indicating a 5α-configuration for the substituent at C-5 in both VIIIa and VIIIb.

EXPERIMENTAL

Microanalyses are due to Dr. A. Bernhardt, Max Planck Institut, Mülheim (Ruhr), Germany. Rotations were taken at room temperature with a 1 dm tube at sodium D-light (5890Å). Infra-red spectra were taken with a Perkin-Elmer, Model 21, NaCl prism and ultra-violet absorption spectra with a Beckman spectrophotometer Model D.U. (EtOH: 95% alcohol).

3β-Hydroxy-5β,19-cycloandrost-6-en-17-one Acetate (IIa). - A solution of the 19-tosylate Ib (9.4 g.) in pyridine (188 ml.) was heated under reflux for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with water, 2N hydrochloric acid and water, dried and evaporated to dryness. The oily residue solidified upon swirling with methanol, giving 4.7 g. of 3β-hydroxy-5β,19-cycloandrost-6-en-17-one acetate (IIa). The analytical sample from methanol had m.p. 115-117°; $[\alpha]_D$ +79°; λmax 213 mμ, log ε 3.77.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; O, 14.61. Found: C, 76.51; H, 8.79; O, 14.36.

5β,19-Cycloandrost-6-ene-3β,17β-diol, 3-Acetate

(IIb). - A solution of sodium borohydride (0.28 g.) in dioxane (3 ml.) containing a few drops of water, was added to a solution of 3β-hydroxy-5β,19-cycloandrost-6-en-17-one acetate (IIa) (0.57 g.) in dioxane (9 ml.). After 3 hrs. at room temperature, acetic acid was slowly added to the mixture to destroy the excess of reagent. Addition of water and filtration afforded 5β,19-cycloandrost-6-ene-3β,17β diol 3-acetate (IIb) (535 mg.) raised by crystallizations from acetone water and methanol-water to 83-87°; $[\alpha]_D$ +11°; λmax 213 mμ, log ε 3.76.

Anal. Calcd. for $C_{21}H_{30}O_3 1/3\ H_2O$: C, 74.96; H, 9.19; O, 15.84. Found: C, 74.72; H, 9.23; O. 15.65.

5β,19-Cycloandrost-6-ene-3β,17β-diol 3-acetate-17-tetrahydropyranyl ether (IIc). - To an anhydrous solution of 5β,19-cycloandrost-6-ene-3β,17β-diol 3-acetate (IIb, 9 g.) in benzene (630 ml.) was added dihydropyran (23 ml.) and p-toluenesulfonic acid (4.5 g.). The mixture was left at room temperature for 16 hours and then poured into aqueous saturated potassium carbonate solution (500 ml.). The aqueous layer was separated, the benzene layer was washed with water (2 x 200 ml.), dried and concentrated to a small volume. This solution was then filtered over a short column of washed alumina (50 g.) Removal of the solvent gave a residue which was dissolved in hexane solution and again passed through a column of alumina (50 g.) in hexane. Removal of the hexane gave a product which was boiled for a few minutes in methanol

solution with charcoal, filtered and crystallized by the addition of water. The crude material (8.1 g., m.p. 114-120°) was recrystallized from methanol-water to give pure 5β,19-cycloandrost-6-ene-3β,17β-diol, 3-acetate-17-tetrahydropyranyl ether (IIc, 7.3 g.), m.p. 120-122°; $[\alpha]_D$ +6°; λmax 213 mμ, log ε 3.78.

Anal. Calcd. for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24; O, 15.44. Found: C, 75.24; H, 9.10, O. 15.38.

5β,19-Cycloandrost-6-ene-3β,17β-diol 17-tetrahydropyranyl ether (IId). - 5β,19-Cycloandrost-6-ene-3β,17β-diol 3-acetate 17-tetrahydropyranyl ether (IIc, 4 g.) was dissolved in 95% methanol (100 ml.) containing potassium carbonate (5 g.) and the solution was heated under reflux for 1 hour. The methanol was removed under reduced pressure, the residue was diluted with water and the product isolated by extraction with ethyl acetate. The combined extracts were washed well with water, dried and evaporated. Crystallization from acetone-hexane afforded 5β,19-cycloandrost-6-ene 3β,17β-diol 17-tetrahydropyranyl ether (IId) (3.25 g.) m.p. 162-167°, raised by crystallizations from acetone-hexane to 170-175°; $[\alpha]_D$ -59°; λmax 213 mμ, log ε 3.49.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74; O, 12.88. Found: C, 77.61; H, 9.99; O, 12.70.

17β-Hydroxy-5β,19-cycloandrost-6-en-3-one (IIe).- 5β,19-Cycloandrost-6-ene-3β,17β-diol 17-tetrahydropyranyl

ether (IId; 2.82 g.) was added to a mixture of chromic anhydride (2.8 g.) in pyridine (28 cc.) and kept at room temperature for 16 hrs. The reaction mixture was then diluted with ethyl acetate, filtered over celite, washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution and water. After drying over sodium sulfate, removal of the solvent gave a product which was dissolved in tetrahydrofuran (90 ml.) containing hydrochloric acid (2N, 1.5 ml.). After 5 hours at room temperature, the solution was poured into water, extracted with ethyl-acetate, the organic layer was washed with an aqueous bicarbonate solution and water, dried and evaporated. Chromatography of the residue on washed alumina and crystallization from acetone-hexane gave the 3-ketone (IIe) (80 mg.) m.p. 145-149°; $[\alpha]_D$ +24°; λmax 213 mμ, log ε 3.69.

Anal. Calcd. for $C_{19}H_{26}O_2 \cdot 1/2\ CH_3COCH_3$: C, 78.05; H, 9.27; O, 12.68. Found: C, 77.99; H, 9.18; O, 12.28.

5β,19-Cycloandrost-6-ene-3β,17β-diol (IIf). - A solution of 5β,19-cycloandrost-6-ene-3β,17β-diol, 3-acetate (IIb, 500 mg.) in methanol (25 ml.) containing potassium carbonate (1 g.) in water (3 ml.) was heated under reflux for 30 mins. The methanol was removed under reduced pressure, the residue was diluted with water and extracted with ethyl acetate. The extracts were washed well with water, dried and evaporated. Crystallization of the residue from acetone-hexane

afforded 350 mg. of 5β,19-cycloandrost-6-ene-3β,17β-diol (IIf), m.p. 185-188°; $[\alpha]_D$ +16°; λmax 213 mμ, log ε 3.73.

Anal. Calcd. for $C_{19}H_{28}O_2 \cdot 1/2\ CH_3COCH_3$: C, 77.56; H, 9.84; O, 12.60. Found: C, 77.75; H, 9.73; O, 12.86.

5β,19-Cycloandrost-6-ene-3,17-dione (IIg). - Oxidation of 370 mg. of the diol IIf with CrO_3-pyridine complex as described above (IId → IIe) afforded 200 mg. of the pure dione IIg, which showed m.p. 147-149°; $[\alpha]_D$ +101°; λmax 213 mμ, log ε 3.72.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51; O, 11.25. Found: C, 80.67; H, 8.59; O, 10.87.

3β-Hydroxy-5β,19-cycloandrost-6-en-17-one (IIh).- A solution of 3β-hydroxy-5β,19-cycloandrost-6-en-17-one acetate (IIa,1 g.) in methanol (25 ml.) containing potassium carbonate (1 g.) in water (3 ml.) was heated under reflux for 1/2 hour. After concentrating under reduced pressure, the residue was dissolved in ethyl acetate (25 ml.) and water (25 ml.) and the organic layer was then washed with water, dried and evaporated. The residue was percolated over washed alumina (5 g.) in benzene solution, the filtrates were evaporated and the residue was crystallized from acetone-hexane, thus giving 760 mg. of 3β-hydroxy-5β,19-cycloandrost-6-en-17-one (IIh), m.p.204-207.° The analytical sample was obtained from acetone-hexane, m.p. 208-209° with crystal change at 180°; $[\alpha]_D$ +55°,

λmax 213 mμ, log ε 3.75.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.31; H, 8.90; O, 11.75.

5β,19-Cycloandrostane-3,17-dione (III). - Hydrogenation of the Δ^6-dione (IIg) (57 mg.) in benzene solution (5 cc.) over a 5% Pd/C catalyst (6 mg.) led to the uptake of 1.07 moles of hydrogen. The benzene solution was filtered, evaporated and the residue was adsorbed from benzene onto silica-gel (2 g.). Elution with benzene-chloroform (3:1) and crystallization from methanol-water gave 5β,19-cycloandrostane-3,17-dione (III) m.p. 128-135°, raised by further crystallizations to 135-137°, undepressed upon admixture with a sample of III prepared by an alternate procedure.[11,23] The infra-red spectra of the two samples were identical.

5α and 5β-Androstane-3,17-dione (IVa and IVb).- A solution of the Δ^6-dione IIg (1.26 g.) in ethanol (25 cc.) was hydrogenated at atmospheric pressure in the presence of a 5% palladium on carbon catalyst (125 mg.). The hydrogen uptake corresponded to 2.0 mols. Filtration and removal of the solvent gave a product which was adsorbed from benzene onto silica gel. Elution with benzene-chloroform (95:5) and crystallization from aqueous methanol gave 5α-androstane-3,17-dione (IVa) (430 mg.) m.p. 135-136°; $[\alpha]_D$ +101°. The m.p. of IVa was undepressed upon

admixture with an authentic sample and the infra-red spectra were identical.

Further elution with the same solvent system and crystallization from acetone-hexane gave 5β-androstane-3,17-dione (IVb) (370 mg.) m.p. 135-136°; $[\alpha]_D$ +103°. The m.p. of IVb was depressed to 120° upon admixture with IVa but undepressed upon admixture with an authentic sample of IVb. The infra-red spectra of IVb was different from that of IVa but identical with that of the authentic sample.

3β-Hydroxy-5β,19-cycloandrost-6-en-17-one (IIh).- 3β-Hydroxy-5β,19-cycloandrost-6-en-17-one acetate (IIa, 1 g.) was dissolved in methanol (25 ml.) containing potassium carbonate (1 g.) in water (3 ml.) and the solution was heated under reflux for 0.5 hours. The methanol was removed under reduced pressure, the residue was diluted with water and extracted with ethyl acetate. The extracts were washed well with water, dried and evaporated. The residue was crystallized from acetone-hexane to give 840 mg. of 3β-hydroxy-5β,19-cycloandrost-6-en-17-one (IIh), m.p. 206-208°. The analytical sample had m.p. 208-209°, with crystal change at ca. 180°; $[\alpha]_D$ +55°; λmax 213 mμ, log ε 3.75.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.31; H, 8.90; O, 11.75.

17α-Methyl-5β,19-cycloandrost-6-ene-3β,17β-diol (IIi). - A solution of 3β-hydroxy-5β,19-cycloandrost-

6-en-17-one acetate (IIa 2 g.) in tetrahydrofuran (60 ml.) was added to an excess of an ethereal solution of 3M-methyl magnesium bromide. After stirring for 16 hours at room temperature, the excess of reagent was carefully destroyed with aqueous ammonium chloride solution. This mixture was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water, dried and evaporated. The residue was filtered in benzene solution over a short column of washed alumina and the filtrates evaporated. The crude residue (1.1 g., m.p. ca. 160°) was recrystallized several times from acetone-hexane. The product had m.p. 170-178°; $[\alpha]_D$ ±0°; λ_{max}^{EtOH} 213 mμ, log ε 3.64. It was not possible to obtain a satisfactory elemental analysis of IIi although it was chromatographically homogeneous as evidenced by thin plate chromatography.

17β-Hydroxy-17α-methyl-5β,19-cycloandrost-6-en-3-one (IIj). - To a solution of 17α-methyl-5β,19-cycloandrost-6-ene-3β,17β-diol (IIi, 0.93 g.) in pyridine (93 ml.) was added a mixture of chromic anhydride (0.93 g.) in pyridine (93 ml.). After 16 hours at room temperature, the reaction mixture was diluted with ethyl acetate, filtered over celite, washed with water, dilute hydrochloric acid, aqueous sodium bicarbonate solution and water. The organic phase was then dried and evaporated and the residue adsorbed from benzene-hexane (2:3) onto washed alumina (30 g.). Elution with the same

solvent pair gave 17β-hydroxy-17α-methyl-5β,19-cyclo-androst-6-en-3-one (IIi, 350 mg.), m.p. 165-175° raised by crystallizations from acetone-hexane to m.p. 178-180° with a crystal change at ca. 160°; $[\alpha]_D$ +15°; log ε 3.81 at 210 mμ.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.77; H, 9.66; O. 11.08.

Further elution with chloroform gave 200 mg. of unchanged starting material IIi.

Solvolysis of 3β,19-dihydroxyandrost-5-en-17-one 3-acetate 19-tosylate (Ib). - A solution of 27.6 g. of the tosylate Ib in 1 l. of dioxan and 530 ml. of water was treated with 36.7 g. of sodium acetate and heated under reflux for 1 hr. The reaction mixture was concentrated to a small volume in vacuo, diluted with saturated sodium chloride solution, and the product isolated with ethyl acetate. The resulting oil (20.8 g.) was dissolved in hexane and adsorbed on a column of 1.7 kg. of alumina. Crystallization of the product eluted with benzene-hexane (9:1) from methanol afforded 3 g. of 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one 3,6-diacetate (Va) m.p. 112-113°. Several crystallizations of a small sample furnished the analytical sample m.p. 119-120°; $[\alpha]_D$ +103°; υmax 3400, 1730 and 1250 cm^{-1}.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; O, 20.59. Found: C, 71.05; H, 8.43; O, 20.80.

Continued elution with pure benzene gave a second

series of crystalline fractions which were combined and crystallized from acetone-hexane to yield 3β,6α-dihydroxy-5β,19-cycloandrostan-17-one 3-acetate (Vb) with melting point 127-129°. A pure specimen of Vb exhibited m.p. 135-136°; $[\alpha]_D$ +106°; υmax 1730, and 1250 cm^{-1}.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.86; H, 8.90; O, 18.65.

Acetylation of a small sample of Vb with acetic anhydride-pyridine mixture afforded a product m.p.119-120° identical in all respects with the diacetate Va.

3β-Hydroxy-6α-ethoxy-5β,19-cycloandrostan-17-one acetate (Vd) and 3β-hydroxy-6α-azido-5β,19-cycloandrostan-17-one acetate (Vc). - A mixture of the 19-tosylate Ib (1 g.), sodium azide (1 g.) and ethanol (25 ml.) was heated under reflux for 24 hours, diluted with water (25 ml.) and concentrated in vacuo. The resulting precipitate was filtered and dried, then crystallized from methanol-water and from hexane to give 625 mg. of the 6-azide Vc, m.p. 114-116°. The analytical sample was obtained by several recrystallizations from acetone-hexane, m.p. 119-120°; $[\alpha]_D$ +158°;

Anal. Calcd. for $C_{21}H_{29}O_3N_3$: C, 67.90; H, 7.87; N, 11.31. Found: C, 68.06; H, 7.75; N, 11.43.

The mother liquors of the azide Vc were adsorbed onto alumina (35 g.) in hexane solution. Elution with hexane gave the 6α-ethoxy compound Vd (270 mg.) of m.p.

145-150°. The analytical sample[25], from hexane, had m.p. 150-150.5°; $[\alpha]_D$ +103°;

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.62; H, 9.07.

3β-Hydroxy-6α-isopropoxy-5β,19-cycloandrostan-17-one acetate (Ve) and 3β-hydroxy-6α-azido-5β,19-cycloandrostan-17-one acetate (Vc). - The 19-tosylate (Ib, 1 g.) was dissolved in isopropanol (25 ml.) and heated under reflux for 24 hours in the presence of sodium azide (1 g.). The reaction mixture was filtered, the filtrate evaporated to dryness, the residue was dissolved in ethyl acetate (50 ml.) and washed with water (2 x 50 ml.). The dried extracts were then evaporated to dryness, the residue was dissolved in hexane and adsorbed onto a column of washed alumina (30 g.). Elution with hexane-benzene (95:5) gave compound Ve (238 mg.), m.p.75-85°. Recrystallization from hexane and from acetone-water gave the analytical sample, m.p. 90-91°; $[\alpha]_D$ +97°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.44; H, 9.45; O, 15.75.

Further elution of the column with benzene gave compound Vc (484 mg.) m.p. 110-116°, undepressed upon admixture with the azide obtained above. The infra-red spectra of the two samples were identical.

3β-Hydroxy-6α-azido-5β,19-cycloandrostan-17-one (Vf). - A solution of the azide acetate Vc (1.5 g.) in methanol (100 ml.) containing potassium carbonate (5 g.)

was heated under reflux for one hour. The reaction mixture was then neutralized with acetic acid, concentrated under reduced pressure and poured into water. The resulting precipitate was collected and dried (1.22 g. m.p. 150-155°). The analytical sample was obtained by dissolving the crude material in acetone, filtering over washed alumina (1 g.) and crystallizing from hexane. Compound Vf showed m.p. 165-166°; $[\alpha]_D$ +212°.

Anal. Calcd. for $C_{19}H_{27}O_2N_3$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.47; H, 8.43; N, 12.83.

6α-Azido-5β,19-cycloandrostane-3,17-dione (Vg).- A solution of 3β-hydroxy-6α-azido-5β,19-cycloandrostan-17-one (Vf, 250 mg.) in toluene (25 ml.) was heated to remove moisture and then mixed with cyclohexanone (5 ml.) and aluminum isopropoxide (500 mg.). The resultant mixture was heated under reflux for one hour and poured into dilute hydrochloric acid (100 ml, 2N). Extraction of the suspension with ethyl acetate and evaporation of the dried extracts furnished the crude dione Vg, m.p. 140-145°, (200 mg.) raised by several recrystallizations from acetone-hexane to 156-157°; $[\alpha]_D$ +140°. The infra-red spectrum showed 2 carbonyl bands, 1710 and 1730 cm^{-1} and an azide band, 2090 cm^{-1}.

Anal. Calcd. for $C_{19}H_{25}O_2N_3$: C, 69.70; H, 7.70; N, 12.84. Found: C, 70.42; H, 7.53; N, 12.49.

19-Hydroxyandrost-4-en-3,17-dione 19-tosylate (VIb)

A solution of 300 mg. of 19-hydroxyandrost-4-en-3,17-dione (VIa)[3-7] in 15 ml. anhydrous pyridine containing 600 mg. p-toluene sulfonyl chloride was left at room temperature for 116 h. Water was added and then a cooled 10% hydrochloric acid solution until the solution was acid. The ethyl acetate extracts were washed with a 5% sodium bicarbonate solution and finally with water until neutral. After drying over anhydrous sodium sulfate, the solution was filtered and concentrated to 10 ml. in vacuum and the product allowed to crystallize at 0°. Filtration afforded the tosylate (VIb) (180 mg.) m.p. 160-164° λ_{max}^{EtOH} 228 mμ (log ε 4.37). Recrystallizations from ethyl alcohol provided the analytical sample of 19-hydroxyandrost-4-en-3,17-dione 19-tosylate (VIb) m.p. 164-166°, $[\alpha]_D$ +165° (C, 1; $CHCl_3$); λ_{max}^{EtOH} 228 mμ (log ε 4.36), 290-292 mμ (log ε 2.00); λ_{max}^{KBr} 5.77, 5.99, 6.16, 6.26, 7.4, 8.38, 8.46 and 10.25 μ.

Anal. Calcd. for $C_{26}H_{32}O_5S$: C, 68.39; H, 7.07; O, 17.52; S, 7.02. Found: C, 68.16; H, 7.22; O,17.30 S, 6.85.

Treatment of the Tosylate VIb with sodium methoxide

Sodium methoxide (1.45 g.) was added to a solution of 4.35 g. of the tosylate (VIb) in 135 ml. of anhydrous methanol and the reaction mixture allowed to reflux for 24 hrs.in a nitrogen atmosphere. After dilution of the cooled solution with water and acidification with 10%

hydrochloric acid extraction with ethyl acetate afforded 2.82 g. of amorphous material which was adsorbed from hexane-benzene (4:1) onto neutral alumina (140 g.). Elution with hexane-benzene (6-4) and crystallization from acetone-hexane gave 5α-methoxy-6β,19-cycloandrostan-3,17-dione (VIIIb) (60 mg.) m.p. 139-142°; $[\alpha]_D$ +85° (C, 0.9; $CHCl_3$); λmax 288-294 mμ (log ε 1.96); in alkaline medium[26] λmax 288-294 mμ (log ε 1.94); in acid medium[26b] λmax 242-244 mμ (log ε 3.39), 286-292 mμ (log ε 1.75). $\lambda_{max}^{CCl_4}$ 5.73 and 5.80 μ. Nuclear magnetic resonance (N.M.R.) spectrum: 18-methyl: 56 c.p.s., 4-methylene: 164 c.p.s., 5-methoxyl: 189 c.p.s. Circular Dichroism (C.D.) curve[27]: (C, 0.28; Dioxane) $[\theta]_{302}$ + 15.700; $[\theta]_{296}$ + 15.480; $[\theta]_{246}$ 0.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.01; H, 9.19.

The Swiss authors report[11]: m.p. 135°, $[\alpha]_D$ +77° (C, 0.59; $CHCl_3$); λ_{max}^{EtOH} 244 mμ (ε 269), 298 mμ (ε 84); υmax 1733 and 1711 cm^{-1}; N.M.R.: δ = 0.94/S CH_3-18, 3.14/S 5-OCH_3

Further elution with hexane-benzene (6-4) gave a compound (2 g.) which was recrystallized from acetone-hexane to provide 6β,19-cycloandrost-4-en-3,17-dione (VII), m.p. 130-132°; $[\alpha]_D$ -79° (C, 1; $CHCl_3$); λ_{max}^{EtOH} 242-244 mμ (log ε 4.19), 296-300 mμ (log ε 2.12); in alkaline medium: λmax 242 mμ (log ε 4.19), 296-302 mμ

(log ε 2.12); λ_{max}^{CCl4} 5.73, 5.98 μ, 6.02 μ (shoulder). N.M.R.: 18-methyl: 58.9 c.p.s.; 6α-H (1 proton) as a triplet: 195.5 c.p.s.; 4-H (1 proton); 337.7 c.p.s. C.D.[27] (C, 0.34; Dioxane): $[\theta]_{374}$ 0; $[\theta]_{354}$ - 3.960; $[\theta]_{340}$ -7.890; $[\theta]_{328}$ - 7.260; $[\theta]_{316}$ 0; $[\theta]_{296}$ +7.790; $[\theta]_{269}$ + 1.620.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.21; H, 8.34.

The Swiss authors report[11] m.p. 132°; $[\alpha]_D$ -73° (C, 0.83; $CHCl_3$); λmax 244 mμ (ε 15.460); υmax 1735 and 1660 cm^{-1}. N.M.R.: δ = 0.97/S CH_3-18; 5.59/S CH-4

Further elution with benzene-chloroform and crystallization from acetone-hexane gave 5α-hydroxy-6β,19-cyclo-androstan-3,17-dione (VIIIa) (90 mg.) m.p. 190-192°; $[\alpha]_D$ +99° (C, 0.25; $CHCl_3$); λ_{max}^{EtOH} 286-292 mμ (log ε 2.03); in alkaline medium[26] λmax 284-292 mμ (log ε 2.07); in acid medium[26] λmax 242-244 mμ (log ε 3.33). $\lambda_{max}^{CHCl_3}$ 2.8, 5.76 and 5.83 μ. N.M.R.: 18-methyl: 55.7 c.p.s.; 4-methylene as a quadruplet: 185.5 c.p.s., 170 c.p.s. 152 and 135 c.p.s., no olefinic proton and no proton on carbon bearing the hydroxyl group. C.D.[27] (C, 0.12; Dioxane): $[\theta]_{334}$ 0; $[\theta]_{303}$ + 17.300; $[\theta]_{297}$ + 17.000; $[\theta]_{248}$ 0.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.22; H, 8.65.

Acid treatment of VIIIb. - To a solution of 500 mg. of VIIIb in 10 ml. dioxane, 1 ml. concentrated hydrochloric acid was added. The reaction mixture was allowed to stand overnight at room temperature. Excess of sodium bicarbonate was then added and the solvent evaporated to dryness. The residual material was dissolved in acetone and the inorganic salts were filtered off. The filtrate was concentrated and hexane was added. Further recrystallization from acetone-hexane provided the unsaturated ketone (VII) m.p. 130-132°; λ_{max}^{EtOH} 242 mμ (log ε 4.16).

The m.p. was undepressed upon admixture with an authentic sample of VII and the infra-red spectra were identical.

Attempted acetylation of VIIIa. - A solution of VIIIa (200 mg.) in 3 ml. anhydrous pyridine and 3 ml. acetic anhydride was allowed to stand overnight at room temperature. Water was then added and an excess of 10% hydrochloric acid solution and the product extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate, water and dried over anhydrous sodium sulfate. After evaporation of the solvent in vacuo, the amorphous product was chromatographed onto 10 g. neutral alumina. Elution with benzene provided the α,β-unsaturated ketone (VII) (140 mg.): m.p.120-123°. Recrystallization from acetone-hexane gave a pure sample of VII, the m.p. of which was not depressed with an

authentic sample. The infra-red spectra were superimposable. Further elution with benzene-chloroform (1-1) gave 30 mg. of starting material VIIIa.

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23. We wish to offer our best thanks to Dr. K. Schaffner for his kindness in sending us a sample of III.

24. This experiment was carried out by Dr. J.A.Edwards of our laboratories and forms part of a study which will be reported by him in full at a later date. Our best thanks are due to Dr. Edwards for this information.

25. Prepared independently in these laboratories by Dr. L. Knox by a different route, to be published. Both samples were identical in every respect.

26. (a) The ultra-violet spectrum in alkaline medium refers to the ethanolic solution to which two drops of 10% KOH solution were added and the spectrum taken immediately; (b) The ultra-violet spectrum in acid medium refers to the ethanolic solution to which two drops of 10% HCl solution were added and the solution allowed to stand 1/2 hour at room temperature before taking the spectrum.

27. Curve kindly taken in Prof. Ourisson's laboratory, University of Strasbourg (France), on a Roussel-Jouan Dichrograph.