[Chem. Pharm. Bull. 17(5) 947—953 (1969)] UDC 547.92.04.07

Rearrangements of the 16,17-Ketols of 13α-Androstanes[1]

Toshio Nambara, Hiroshi Hosoda and Masahiro Usui

Pharmaceutical Institute, Tohoku University[2]

(Received August 24, 1968)

Four isomeric 16,17-ketols of 13α-androstanes were prepared as illustrated in Chart 1. The rearrangements and stabilities of these ketols with acid or base were investigated. The results were compared with those of the corresponding compounds having 13β,14α- and 13β,14β-ring systems (see Fig. 1). The stability sequence of these ketols is discussed on the steric and conformational grounds.

The rearrangement of four isomeric 16,17-ketols with the common 14α- and 14β-ring systems and their sequential stability have already been explored on the steric and conformational grounds.[3] In connection with these studies an interest in the altered steric environment of ring D of 13α-steroids prompted us to examine the rearrangement of the 16,17-ketols.

The synthesis of these compounds was initially performed according to the general method developed by Gallagher and his co-workers[4] starting from the Δ^{16}-enol acetate (I).[5] Treatment with perbenzoic acid gave a mixture of the epimeric 16,17-epoxides in a ratio of 3 to 1, from which the major product (II) was isolated by fractional crystallization. Configuration of the epoxy group was assigned to be β rather than α on the basis of the shift values of 18-proton signal (see Table I). This result was in qualitative agreement with the previous finding on the epoxidation of 5α,13α-androst-16-en-3β-ol acetate.[6] When the β-epoxyacetate (II) was treated with sulfuric acid, the 16β-hydroxy-17-ketone (IIIa) and its 3-monoacetate (IIIb) were provided almost quantitatively. The structure of this ketol was confirmed through

Table I. Effect of Substituents on the Chemical Shifts of C-18 and C-19 Protons

Compound	Shift value[a]			
	C-18-H		C-19-H	
	τ	Δτ	τ	Δτ
5α,13α-Androstan-3β-ol acetate	9.14		9.26	
5α,13α-Androstane-3β,17α-diol diacetate	9.07	−0.07	9.22	−0.04
5α,13α-Androstane-3β,17β-diol diacetate	9.12	−0.02	9.23	−0.03
16α,17α-Epoxy-5α,13α-androstan-3β-ol acetate	8.88	−0.26	9.26	0
16β,17β-Epoxy-5α,13α-androstan-3β-ol acetate	9.15	+0.01	9.26	0
Enol acetate epoxide (II)	9.07	−0.07	9.26	0

a) Plus sign represents an upfield shift.

1) This paper constitutes Part XXIII of the series entitled "Analytical Chemical Studies on Steroids"; Part XXII: S. Goya, H. Hosoda, T. Kudo, C. Anzo, and T. Nambara, *Yakugaku Zasshi*, **89**, 336 (1969).
2) Location: *Aobayama, Sendai.*
3) *a*) T. Nambara and J. Fishman, *J. Org. Chem.*, **27**, 2131 (1962); *b*) J. Fishman, *J. Am. Chem. Soc.*, **82**, 6143 (1960).
4) N.S. Leeds, D.K. Fukushima, and T.F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).
5) T. Nambara, H. Hosoda, and S. Goya, *Chem. Ind.* (London), **1967**, 1090; *idem*, *Chem. Pharm. Bull.* (Tokyo), **16**, 1266 (1968).

an alternative synthetic way employing the known 3β,16β,17α-triol 3,16-diacetate (IV).[6] Oxidation with Jones reagent[7] gave the ketol diacetate (IIIc), which proved to be identical with the 3,16-diacetate derived from IIIa and IIIb on usual acetylation.

On similar treatment with mineral acid followed by acetylation the mother liquor of II gave the second 16,17-ketol. The new ketol also lacked the infrared (IR) absorption arising from the active methylene adjacent to ketone, and hence it seemed very likely to be the 16α-

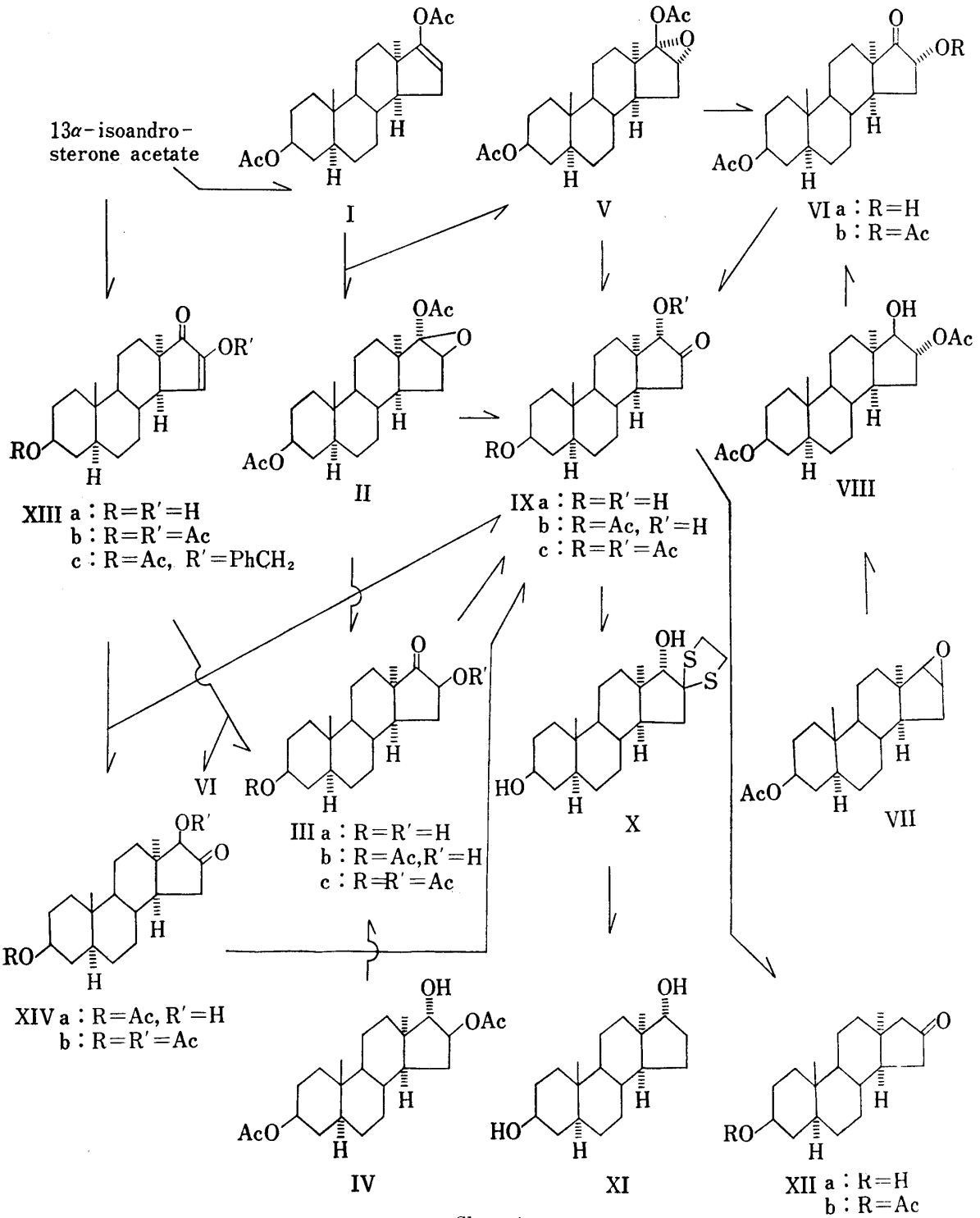

Chart 1

6) T. Nambara, H. Hosoda, M. Usui, and J. Fishman, *Chem. Pharm. Bull.* (Tokyo), **16**, 1802 (1968).
7) K. Bowden, I.M. Heilbron, E.R.H. Jones, and B.C.L. Weedon, *J. Chem. Soc.*, **1946**, 39.

epimer. The synthesis starting from the epoxide established the structure unequivocally. The 16β,17β-epoxide 3-acetate (VII) prepared by the known method[6] was refluxed in glacial acetic acid. Acetolysis occurred preferentially at C-16 furnishing the desired 3β,16α,17β-triol 3,16-diacetate (VIII). The assignment of its structure was justified by the presence of the C-17-proton signal which appeared at 6.40 τ (J=3.8 cps) as a sharp doublet. It is to be noted that cleavage of the epoxide ring with acetic acid takes a same course as with lithium aluminum hydride previously observed. Subsequent oxidation with chromium trioxide gave the 16α-hydroxy-17-ketone diacetate (VIb), entirely identical with the above-mentioned ketol by usual criteria. It must be now emphasized that acid-catalyzed rearrangement of the enol acetate epoxide has been shown to involve acetyl migration with retention of configuration.[8]

Alternatively, on brief exposure to alkali both the epoxyacetates were transformed into the third ketol. The infrared absorption at 1405 cm^{-1} due to the active methylene served to distinguish it from the isomeric 16-hydroxy-17-ketones. In actuality, the ketol diacetate (IXc) being refluxed with zinc dust in acetic acid, removal of α-acetoxyl group took place readily to furnish 3β-hydroxy-5α,13α-androstan-16-one acetate (XIIb). Then, configuration of the oxygen function at C-17 was elucidated by the degradative means. On treatment with ethanedithiol and catalytic amount of boron trifluoride[9] the 17-hydroxy-16-ketone (IXa) was converted to the ethylenedithioketal (X). Desulfurization with Raney nickel proceeded without any evident hydrogenolysis at C-17 to give 5α,13α-androstane-3β,17α-diol (XI), identical with the authentic sample[5] in all respects. Thus the structure of the third ketol should be defined as the 17α-hydroxy-16-ketone (IXa).

The synthesis of the epimeric 16-hydroxy-17-ketones was accomplished through the more accessible route. Oxidation of the 17-ketone with oxygen in the presence of potassium t-butoxide followed by usual acetylation furnished 3β,16-dihydroxy-5α,13α-androst-15-en-17-one diacetate (XIIIb) in satisfactory yield. On catalytic hydrogenation over palladium-on-charcoal this unsaturated compound was transformed into two saturated C-16-epimers (VIb, IIIc), which were efficiently separated by fractional crystallization.

The preparation of the remaining 17β-hydroxy-16-ketone was somewhat more tedious. The starting material, 3β,16-dihydroxy-5α,13α-androst-15-en-17-one (XIIIa), was converted into the 3-acetylated 16-benzyl ether (XIIIc), which in turn was reduced with potassium borohydride. The reduction product appeared to consist of three compounds, whose separation, however, could not be attained because of the close similarity in chromatographic behaviors. Upon brief treatment with mineral acid followed by chromatographic purification the fourth desired ketol, 17β-hydroxy-16-ketone (XIVa), was provided together with the isomeric 17α-hydroxy-16-ketone and 16ξ-benzyloxy-5α,13α-androstane-3β,17ξ-diol 3-acetate. Unfortunately the new ketol could not be isolated in the crystalline state. However, the color reaction with tetrazolium blue and infrared and nuclear magnetic resonance (NMR) spectra together rationalized the assignment of the structure of 17β-hydroxy-16-ketone.

On treatment with mineral acid the 17β-hydroxy-16-ketone acetate (XIVb) did easily undergo the rearrangement to yield the 17α-hydroxy-16-ketone. In contrast to this ketol both the 16-hydroxy-17-ketones did not change under the similar conditions, but on prolonged standing they rearranged to the same 17α-hydroxy-16-ketone. This rerrangement was also observed when exposed to alkali for a short period.

It has been demonstrated that in 13α-steroids three of the ketols rearrange to the most stable 17α-hydroxy-16-ketone under various conditions and thence the stability of the four isomeric 16,17-ketols has the sequence as shown in Fig. 1. These results are in accord with those of 14α- and 14β-steroids in that the 16-ketone is most stable. However, in contrast

8) K.L. Williamson, J.I. Coburn, and M.F. Herr, *J. Org. Chem.*, **32**, 3934 (1967).
9) L.F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

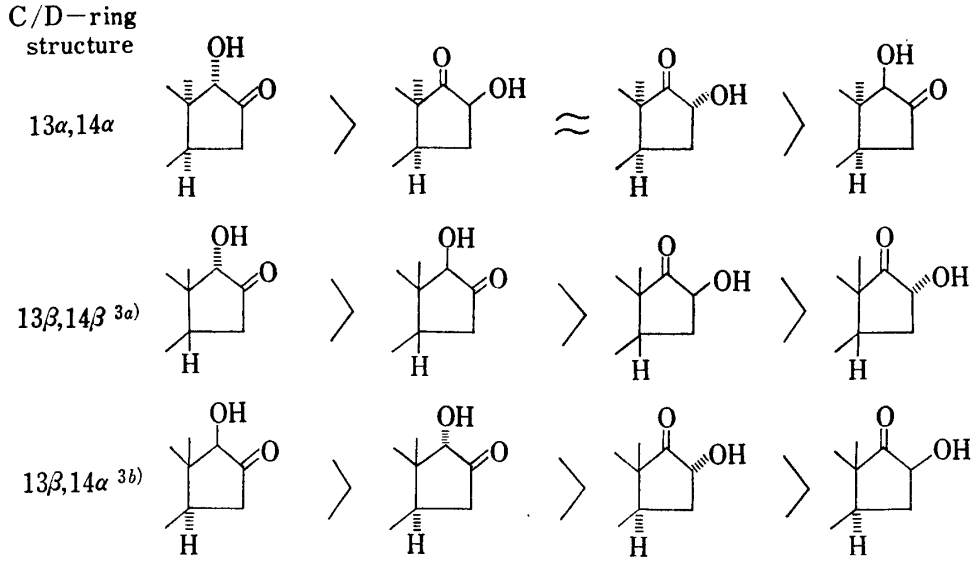

Fig. 1. Sequential Stability of Isomeric 16,17-Ketols

to the other series the 17β-hydroxy-16-ketone, which rearranged on even brief exposure to acid, was least stable among the four isomeric ketols. In addition, the epimeric 16-hydroxy-17-ketones were not changed by mild acid treatment, but isomerized by prolongation of the exposing time. Further, there could be seen no distinct difference in stability between these two epimers. The authors have already reported that in 13α-series ring D with ketone at C-17 would probably exist in β-envelope form, while that of the 16-ketone in half-chair form.[5,10] Conformational difference in ring D may provide the plausible explanation for the preference of the 16-ketone rather than the 17-ketone, unless any significant steric hindrance due to the substituents may exist. The greater stability of the 17α-hydroxy-16-ketone, which was unchanged with both acid and base, appears to be the case. On the other hand the susceptibility of the 17β-hydroxy-16-ketone to acid may be ascribable to the interaction between the 17β-hydroxyl group and the 11β- and 8β-hydrogens, which may cancel the conformational stability of the 16-ketone. Similar behaviors observed with the epimeric 16-hydroxy-17-ketones can be attributed to the spatial arrangement of the *cis*-linked ring D characteristic to the 13α-steroids, where the β-side of the molecule is crowded due to the cage-like structure and the α-side is also sterically hindered by the presence of the 18-methyl group. The rate-determining step in enolization is abstraction of the proton alpha to ketone. Accordingly both C-16-hydrogens in the epimeric 16-hydroxy-17-ketones may require the similar conditions to effect enolization and thence rearrangement. It is of particular interest that the sequential stability of the four isomeric 16,17-ketols depends on the alteration in steric environment involving the C/D-ring fusion.

Experimental[11]

16β,17β-Epoxy-5α,13α-androstane-3β,17α-diol Diacetate (II)——To a solution of 5α,13α-androst-16-ene-3β,17-diol diacetate (I) (120 mg) in $CHCl_3$ (4 ml) was added perbenzoic acid–$CHCl_3$ solution (0.3M, 4 ml), and the resulting solution was allowed to stand at room temperature for 2 hr. The reaction mixture was diluted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from MeOH gave II (30 mg) as colorless plates.

10) T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.* (Tokyo), **17**, 375 (1969).

11) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated. For thin-layer chromatography (TLC) silicagel H (E. Merck, Co.) was used. Nuclear magnetic resonance spectra were obtained on Hitachi Model H-60 spectrometer at 60 Mc using tetramethylsilane as an internal standard. Abbreviation used s=singlet, t=triplet, q=quartet and m=multiplet.

mp 164—166°. $[\alpha]_D^{14}$ −51.7° (c=0.11). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.51; H, 8.77.

3β,16β-Dihydroxy-5α,13α-androstan-17-one 3-Acetate (IIIb)——To a solution of II (100 mg) in acetone–MeOH (1:3) (8 ml) was added 6N H_2SO_4 (2 ml), and the resulting solution was allowed to stand at room temperature for 40 min. The reaction mixture was diluted with ether, washed with cold 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from acetone–hexane gave IIIb (60 mg) as colorless leaflets. mp 140—142°. $[\alpha]_D^{12}$ −87.5° (c=0.12). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.31; H, 9.10.

3β,16β-Dihydroxy-5α,13α-androstan-17-one (IIIa)——II (100 mg) was treated with dil. H_2SO_4 in the same manner as described above for 48 hr. The oily substance obtained was submitted to preparative TLC using benzene–ether (5:3) as developing solvent. Elution of the adsorbent corresponding to the spot (Rf 0.22) and recrystallization of the eluate from acetone–hexane gave IIIa (55 mg) as colorless needles. mp 156—158°. $[\alpha]_D^{18}$ −65.7° (c=0.11, MeOH). *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 73.79; H, 9.73. NMR (5% solution in $CDCl_3$) τ: 9.35 (3H, s, 19-CH_3), 8.96 (3H, s, 18-CH_3), 6.40 (1H, m, 3α-H), 5.73 (1H, q, 16α-H). Elution of the adsorbent corresponding to the spot (Rf 0.65) gave IIIb (6 mg).

3β,16β-Dihydroxy-5α,13α-androstan-17-one Diacetate (IIIc)——i) Usual acetylation of IIIa with pyridine and Ac_2O followed by recrystallization from aq. MeOH gave IIIc as colorless leaflets. mp 95—96°/121—123°. $[\alpha]_D^{18}$ −57.4° (c=0.10). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.73; H, 8.83. NMR (5% solution in $CDCl_3$) τ: 9.32 (3H, s, 19-CH_3), 8.96 (3H, s, 18-CH_3), 8.01 (3H, s, 3β-$OCOCH_3$), 7.91 (3H, s, 16β-$OCOCH_3$), 5.35 (1H, m, 3α-H), 4.61 (1H, q, 16α-H).

ii) To a solution of 5α,13α-androstane-3β,16β,17α-triol 3,16-diacetate (IV) (10 mg) in acetone (1 ml) was added Jones reagent (0.012 ml), and the resulting solution was allowed to stand at room temperature for 5 min. The reaction mixture was diluted with cold H_2O and extracted with ether. After usual work-up the crude product obtained was chromatographed on silicagel (3 g). Elution with benzene and recrystallization of the eluate from aq. MeOH gave IIIc (6 mg) as colorless leaflets. Mixed melting point measurement on admixture with the sample obtained in i) and IR spectra comparison showed the identity of two samples.

3β,16α-Dihydroxy-5α,13α-androstan-17-one 3-Acetate (VIa)——From the mother liquor of II 16α,17α-epoxy-5α,13α-androstane-3β,17β-diol diacetate (V) (60 mg) was obtained as the oily substance. To a solution of this crude product in acetone–MeOH (1:3) (4 ml) was added 6N H_2SO_4 (1 ml), and the resulting solution was allowed to stand at room temperature for 50 min. The reaction mixture was diluted with ether, washed with cold 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up the oily residue obtained was submitted to preparative TLC using benzene–ether (10:1) as developing solvent. Elution of the adsorbent corresponding to the spot (Rf 0.13) gave VIa (15 mg) as an oil.

3β,16α-Dihydroxy-5α,13α-androstan-17-one Diacetate (VIb)——i) To a solution of VIII (20 mg) in acetone (2 ml) was added Jones reagent (0.025 ml), and allowed to stand at room temperature for 5 min. The reaction mixture was diluted with cold H_2O and extracted with ether. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from aq. MeOH gave VIb (15 mg) as colorless needles. mp 144—145°. $[\alpha]_D^{17}$ −68.2° (c=0.11). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.80; H, 8.99. NMR (5% solution in $CDCl_3$) τ: 9.34 (3H, s, 19-CH_3), 8.96 (3H, s, 18-CH_3), 8.00 (3H, s, 3β-$OCOCH_3$), 7.91 (3H, s, 16α-$OCOCH_3$), 5.35 (1H, m, 3α-H), 4.87 (1H,t,16β-H).

ii) Treatment of VIa (15 mg) with pyridine (0.2 ml) and Ac_2O (0.1 ml) followed by usual work-up gave the crystalline product. The crude product was submitted to preparative TLC using benzene–ether (20:1) as developing solvent. The adsorbent corresponding to the spot (Rf 0.36) was eluted with acetone and recrystallization of the eluate from aq. MeOH gave VIb (8 mg) as colorless needles. mp 144—145°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

5α,13α-Androstane-3β,16α,17β-triol 3,16-Diacetate (VIII)——A solution of 16β,17β-epoxy-5α,13α-androstan-3β-ol acetate (VII)[6] (100 mg) in AcOH (10 ml) was refluxed for 30 min. The resulting solution was concentrated *in vacuo* and extracted with ether. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up the oily residue obtained was submitted to preparative TLC using benzene–ether (5:1) as developing solvent. Elution of the adsorbent corresponding to the spot (Rf 0.40) with acetone and recrystallization of the eluate from hexane–acetone gave VIII (30 mg) as colorless plates. mp 206—207°. $[\alpha]_D^{14}$ −21.4° (c=0.07). *Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.26; H, 9.52.

3β,17α-Dihydroxy-5α,13α-androstan-16-one (IXa)——i) To a solution of II (50 mg) in MeOH (20 ml) was added 0.2N NaOH (5 ml) and refluxed for 20 min. The reaction mixture was concentrated and extracted with AcOEt. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from acetone–hexane gave IXa (35 mg) as colorless needles. mp 161—163°. $[\alpha]_D^{29}$ +32.9° (c=4.61). *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 73.87; H, 9.81. NMR (5% solution in $CDCl_3$) τ: 9.24 (3H, s, 19-CH_3), 9.21 (3H, s, 18-CH_3), 6.40 (1H, m, 3α-H), 5.75 (1H, s, 17β-H).

ii) To a solution of VIb (20 mg) in MeOH (2 ml) was added 6N H_2SO_4 (0.8 ml), and the resulting solution was allowed to stand at 25° for 6 days. The reaction mixture was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from $CHCl_3$ gave IXa (10 mg) as colorless needles. mp 161—163°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

iii) To a solution of VIb (10 mg) in MeOH (3.6 ml) was added 0.1N NaOH (2.4 ml) and allowed to stand at 25° for 4 hr. The reaction mixture was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from $CHCl_3$ gave IXa (3 mg) as colorless needles. mp 154—156°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

iv) To a solution of IIIc (20 mg) in MeOH (2 ml) was added 6N H_2SO_4 (0.8 ml) and allowed to stand at 25° for 6 days. The reaction mixture was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crude product was submitted to preparative TLC using benzene–ether (5:3) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.20) with acetone and recrystallization of the eluate from $CHCl_3$ gave IXa (7 mg) as colorless plates. mp 161—163°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

v) To a solution of IIIc (10 mg) in MeOH (3.6 ml) was added 0.1N NaOH (2.4 ml), and the resulting solution was treated in the same manner as described in iii). The crude product was submitted to preparative TLC. Recrystallization from $CHCl_3$ gave IXa (3 mg) as colorless plates. mp 160—162°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

vi) To a solution of XIVb (10 mg) in MeOH (1 ml) was added 6N H_2SO_4 (0.4 ml) and allowed to stand at 25° for 48 hr. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work-up the semicrystalline product was obtained. TLC and NMR spectra comparison proved it to be identical with IXa.

3β,17α-Dihydroxy-5α,13α-androstan-16-one Diacetate (IXc)——Usual acetylation of IXa with pyridine and Ac_2O followed by recrystallization from MeOH gave IXc as colorless needles. mp 201—203°. $[\alpha]_D^{28}$ +8.4° (*c*=3.75). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.77; H, 8.82. NMR (5% solution in $CDCl_3$) τ: 9.21 (3H, s, 19-CH_3), 9.10 (3H, s, 18-CH_3), 8.00 (3H, s, 3β-OCOCH_3), 7.86 (3H, s, 17α-OCO-CH_3), 5.35 (1H, m, 3α-H), 4.50 (1H, s, 17β-H).

16,16-Ethylenedithio-5α,13α-androstane-3β,17α-diol (X)——To a solution of IXa (60 mg) in AcOH (1.8 ml) were added ethanedithiol (0.15 ml) and BF_3-etherate (0.15 ml) and allowed to stand at room temperature for 16 hr. The reaction mixture was diluted with ether, washed with 5% NaOH, H_2O and dried over anhydrous Na_2SO_4. After usual work-up the oily residue obtained was dissolved in 5% methanolic KOH and refluxed for 1 hr. The resulting solution was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the oily residue was chromatographed on silicagel (3 g). Elution with benzene–ether (5:1) and recrystallization of the eluate from acetone–hexane gave X (55 mg) as colorless needles. mp 148—150°. $[\alpha]_D^{20}$ −47.4° (*c*=0.10). *Anal.* Calcd. for $C_{21}H_{34}O_2S_2$: C, 65.94; H, 8.96. Found: C, 65.80; H, 8.97.

Desulfurization of X with Raney Nickel——To a solution of X (36 mg) in EtOH (2 ml) was added Raney Ni (W2) (*ca.* 0.75 g) and refluxed for 6 hr. After removal of catalyst by filtration the filtrate was concentrated to give the crystalline product. Recrystallization from acetone–hexane gave 5α,13α-androstane-3β,17α-diol (XI) (15 mg) as colorless needles. mp 193—195°. Mixed melting point measurement on admixture with the authentic sample and IR spectra comparison showed identity of two samples.

3β-Hydroxy-5α,13α-androstan-16-one Acetate (XIIb)——To a stirred solution of IXc (200 mg) in AcOH (30 ml)–Ac_2O (3 ml) was added Zn dust (10 g) portionwise and refluxed for 16 hr. During this period an additional amount of Zn dust (6 g) was added in two portions. The cake was filtered off and washed with EtOH. The filtrate and washing were combined and concentrated *in vacuo*. The residue was extracted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from MeOH gave XIIb (105 mg) as colorless needles. mp 140—141°. $[\alpha]_D^{17}$ +43.0° (*c*=0.10). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.00; H, 9.61.

3β-Hydroxy-5α, 13α-androstan-16-one (XIIa)——To a solution of XIIb (25 mg) in MeOH (2 ml) was added 10% K_2CO_3 (4 ml) and refluxed for 1 hr. The resulting solution was concentrated and extracted with AcOEt. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from acetone–hexane gave XIIa (20 mg) as colorless needles. mp 191—193°. $[\alpha]_D^{14}$ +56.9° (*c*=0.11). *Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.93; H, 10.44.

3β,16-Dihydroxy-5α,13α-androst-15-en-17-one (XIIIa)——To a *t*-BuOK solution prepared from K (50 mg) and *t*-BuOH (2 ml) was added a solution of 3β-hydroxy-5α,13α-androstan-17-one (100 mg) in *t*-BuOH (3 ml), and the resulting solution was stirred at room temperature for 20 hr. The reaction mixture was neutralized with dil. H_2SO_4 and concentrated to give the crystalline product. Recrystallization from AcOEt gave XIIIa (40 mg) as colorless prisms. mp 257—260°. $[\alpha]_D^{27}$ −112.5° (*c*=0.08 ,MeOH). *Anal.*

Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.77; H, 9.33. This compound exhibited brown color with $FeCl_3$ reagent.

3β,16-Dihydroxy-5α,13α-androst-15-en-17-one Diacetate (XIIIb)——Usual acetylation of XIIIa with pyridine and Ac_2O followed by recrystallization from aq. MeOH gave XIIIb as colorless prisms. mp 150—152°. $[\alpha]_D^{27}$ −92.3° (c=0.13). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.90; H, 8.31.

Catalytic Hydrogenation of XIIIb——A solution of XIIIb (100 mg) in AcOEt (3 ml) was shaken with 5% Pd/C (60 mg) under a stream of H_2 for 48 hr. After removal of catalyst by filtration the filtrate was concentrated to give the crystalline product. GLC indicated that the product consisted of VIb and IIIc in a ratio of *ca.* 2 to 1. Fractional crystallization from aq. MeOH gave VIb (40 mg) as colorless leaflets. mp 140—141°. Concentration of mother liquor and recrystallization from aq. MeOH gave IIIc (15 mg) as colorless needles. mp 120—122°.

3β-Hydroxy-16-benzyloxy-5α,13α-androst-15-en-17-one Acetate (XIIIc)——To a solution of XIIIa (140 mg) in EtOH (10 ml) were added anhydrous K_2CO_3 (280 mg) and $C_6H_5CH_2Cl$ (72 mg) and refluxed for 8 hr. The resulting solution was diluted with ether, washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the oily residue (180 mg) was obtained. Treatment with pyridine and Ac_2O followed by recrystallization from aq. MeOH gave XIIIc (120 mg) as colorless plates. mp 117—118°. $[\alpha]_D^{27}$ −59.1° (c=0.11). *Anal.* Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.31; 8.26.

Potassium Borohydride Reduction of XIIIc and Subsequent Acid Treatment——To a solution of XIIIc (790 mg) in THF (30 ml) was added aq. solution (5 ml) of KBH_4 (900 mg) at 0° and allowed to stand for 5 hr. After addition of AcOH to decompose the excess KBH_4, the reaction mixture was extracted with ether, washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the oily residue (750 mg) was obtained. Tc a solution of this crude product in MeOH (20 ml) was added 6N H_2SO_4 (0.8 ml) at −5° and allowed to stand at room temperature for 20 min. The resulting solution was diluted with ether, washed with cold 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the oily residue obtained was chromatographed on silica gel (10 g). Elution with hexane–benzene (1:1) gave the semicrystalline product (100 mg). Further elution with benzene–ether (2:1) and recrystallization of the eluate from acetone–hexane gave 3β,17α-dihydroxy-5α,13α-androstan-16-one 3-acetate (IXb) (370 mg) as colorless plates. mp 111—113°. $[\alpha]_D^{27}$ +29.4° (c=0.63). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.75; H, 9.22. Usual acetylation with pyridine and Ac_2O gave IXc. To a solution of the 1st eluate (100 mg) in MeOH (20 ml) was added 6 N H_2SO_4 (0.8 ml) and allowed to stand at room temperature for 40 min. The resulting solution was diluted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the oily residue obtained was chromatographed on silicagel (3.5 g). Elution with benzene–ether (30:1) and recrystallization of the eluate from aq. MeOH gave 16ξ-benzyloxy-5α,13α-androstane-3β,17ξ-diol 3-acetate (60 mg) as colorless plates. mp 151—152°. $[\alpha]_D^{26}$ −60.0° (c=0.10). *Anal.* Calcd. for $C_{28}H_{40}O_4$: C, 76.32; H, 9.15. Found: C, 76.31; H, 9.00. NMR (5% solution in CCl_4) τ: 9.28 (3H, s, 19-CH_3), 9.13 (3H, s, 18-CH_3), 8.10 (3H, s, 3β-$OCOCH_3$), 5.50 (2H, s, -OCH_2Ph), 5.40 (1H, m, 3α-H), 2.73 (5H, s, C_6H_5-). Further elution with benzene–ether (10:1) gave 3β,17β-dihydroxy-5α,13α-androstan-16-one 3-acetate (XIVa) (20 mg) as colorless oil. This substance showed positive reaction with tetrazolium blue and a single spot at *Rf* 0.26 in contrast to IXb (*Rf* 0.19), IIIb (*Rf* 0.21) and VIb (*Rf* 0.13) on TLC using benzene–ether (10:1) as solvent. Usual acetylation of XIVa (20 mg) with pyridine (0.3 ml) and Ac_2O (0.15 ml) followed by preparative TLC gave 3β,17β-dihydroxy-5α,13α-androstan-16-one diacetate (XIVb) (12 mg) as colorless oil. This substance showed a single spot at *Rf* 0.26 in contrast to IXc (*Rf* 0.25), IIc (*Rf* 0.29) and VIb (*Rf* 0.36) on TLC using benzene–ether (20:1) as solvent. NMR (5% solution in $CDCl_3$) τ: 9.25 (3H, s, 19-CH_3), 8.88 (3H, s, 18-CH_3), 7.98 (3 H, s, 3β-$OCOCH_3$), 7.91 (3H, s, 17β-$OCOCH_3$), 5.35 (1H, m, 3α-H), 5.14 (1H, s, 17α-H). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1733, 1761.

Acknowledgement The authors are indebted to all the staff of central analytical laboratory of this Institute for elemental analyses and nuclear magnetic resonance spectral measurements. This work was supported in part by a Grant-in-Aid from the Ministry of Education, which is gratefully acknowledged.