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The Synthesis and Nuclear Magnetic Resonance Spectra of Epimeric 16-Deuterio-14β-androstan-17-ols[1]

Toshio Nambara, Masahiro Usui and Hiroshi Hosoda

Pharmaceutical Institute, Tohoku University[2]

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Four epimeric 16-deuterio-5α,14β-androstan-17-ols were prepared from 3β-hydroxy-5α,14β-androstan-17-one by the reaction sequence illustrated in Chart 1. The conformation of ring D in 14β-steroids is discussed based upon the correlation of dihedral angles with the observed coupling constants of H16,17 (see Table I).

In the preceding paper the authors reported the conformation of ring D having 13α,14α-ring system on the basis of the nuclear magnetic resonance spectra of the 16-deuterio-13α-androstan-17-ols.[3] An interest in the characteristic feature of C/D-*cis* junction prompted us to explore the conformation of the fused cyclopentane ring in 14β-steroids. It has already been demonstrated that the C–16 deuterated compounds are particularly suitable for the study of the C–17 proton resonance, since the deuterium substitution simplifies the ABX pattern to the AX without electronic influence and/or steric distortion of ring D.[3,4] Accordingly the authors have attempted to prepare the four epimeric 16-deuterio-5α,14β-androstan-17-ols as the pertinent compounds for the conformational analysis.

An initial project was directed to removal of the oxygen function at C–3 to facilitate the elaboration of ring D. The starting material, 3β-hydroxy-5α,14β-androstan-17-one[5] (Ia), was transformed into the tosylate (Ib), which on treatment with dimethyl sulfoxide was led to the Δ^2-unsaturated compound (II). Catalytic hydrogenation over palladium-on-charcoal gave the desired 14β-androstan-17-one (III) in satisfactory yield. In order to ensure the stereoselectivity the reductive cleavage of the epoxide with metal hydride was attempted for preparation of the 17-hydroxy derivatives. Treatment of III with isopropenyl acetate and conc. sulfuric acid as catalyst gave the Δ^{16}-enol acetate (IV) almost quantitatively. Reaction with an equimolar amount of bromine under non-enolizing condition proceeded from the less hindered β-side yielding the 16β-bromo-17-ketone (V). Subsequent reduction with lithium aluminum hydride furnished the 16,17-*trans*-bromohydrin (VIa) accompanied with a debromination product (VIIIa). The stereochemistry of 14β-ring D has already been established by the authors[6] and therefore the structural assignments of these derivatives are unequivocal. When the *trans*-bromohydrin was refluxed with base, facile dehydrobromination took place to give the 16α,17α-epoxide (VII). The cleavage of this α-epoxide with lithium aluminum deuteride gave solely the 16β-deuterio-17α-ol (VIIIb), which proved to be substantially identical with the product (VIIIa) derivable from III upon metal hydride reduction. Epimerization of the C–17 substituent was accomplished by the method of Henbest, *et al.*[7] When

1) This paper constitutes Part XXVIII of the series entitled "Analytical Chemical Studies on Steroids," Part XXVII: T. Nambara and T. Kudo, *Chem. Pharm. Bull.* (Tokyo), **17**, 1585 (1969).
2) Location: *Aobayama, Sendai.*
3) T. Nambara, H. Hosoda, M. Usui and J. Fishman, *Chem. Pharm. Bull.* (Tokyo), **16**, 1802 (1968).
4) J. Fishman, *J. Am. Chem. Soc.*, **87**, 3455 (1965).
5) A.F. St. André, H.B. MacPhillamy, J.A. Nelson, A.C. Shabica and C.R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).
6) T. Nambara and J. Fishman, *J. Org. Chem.*, **26**, 4569 (1961).
7) H.B. Henbest and W.R. Jackson, *J. Chem. Soc.*, **1962**, 954.

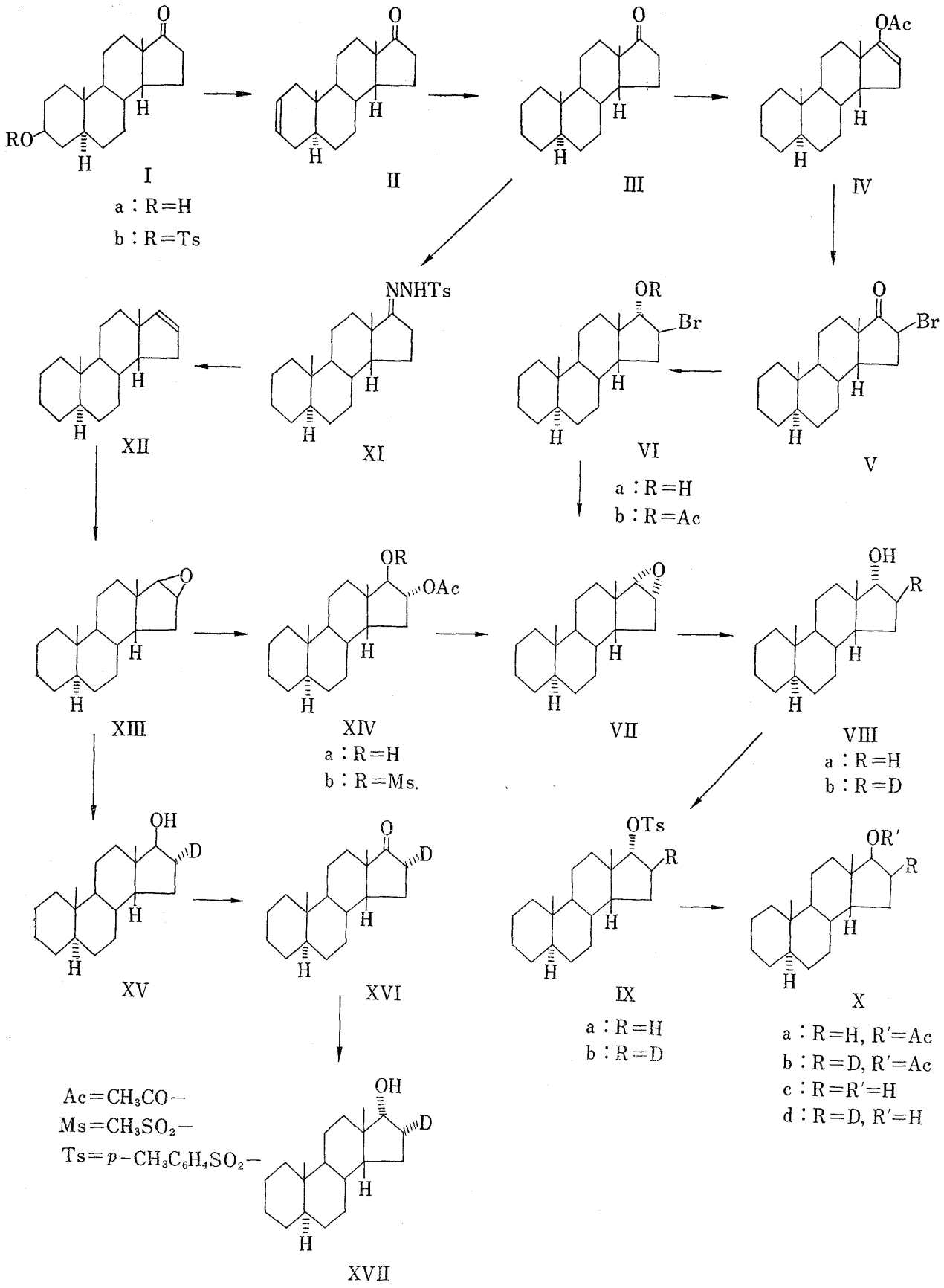


Chart 1

the 17α-tosylate (IXa) derived from VIIIa was refluxed in N-methylpyrrolidone with tetrabutylammonium acetate, the 17β-acetate (Xa) was obtained in reasonable yield. Then, saponification with alkali provided the epimeric 17β-hydroxy compound (Xc). The synthetic sequence thus established was extended in a similar fashion to preparation of the 16β-deuterated derivatives. The 16β-deuterio-17α-hydroxy compound (VIIIb) was converted into the tosylate (IXb), epimerized to the 17β-acetate (Xb) and then led to the desired 16β-deuterio-17β-ol (Xd) by alkaline hydrolysis.

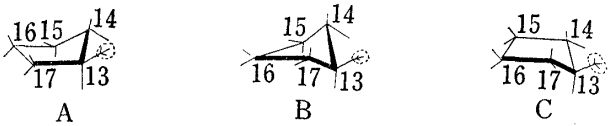
The synthesis of another pair of the 16α-deuterio-17-ols was undertaken employing the 16β,17β-epoxide as a key intermediate. In usual manner the 17-ketone (III) was transformed into the *p*-tosylhydrazone (XI), which on reduction with lithium aluminum hydride was led to the Δ^{16}-unsaturated compound (XII).[8,9] The crude product being treated with perbenzoic acid, the reagent attacked the Δ^{16}-double bond from the β-side to give the 16β,17β-epoxide (XIII), whose structure was confirmed by leading it to the epimeric α-epoxide. When refluxed with acetic acid, the β-epoxide underwent acetolysis at C–16 to give the 16α,17β-glycol 16-acetate (XIVa). This monoacetate was further led to the 17-methanesulfonate (XIVb), which in turn was converted into the known 16α,17α-epoxide with alkali. The ring opening of the 16β,17β-epoxide with lithium aluminum deuteride also occurred preferentially at C–16 to give the desired 16α-deuterio-17β-ol (XV).[10] The preparation of the epimeric 17α-hydroxy derivative was achieved with ease starting from XV. Oxidation with chromium trioxide in acetic acid and subsequent work-up proceeded without loss of isotope at C–16[3,12] to furnish the 16α-deuterio-17-ketone (XVI). Then, reduction with lithium aluminum hydride resulted in formation of the remaining 16α-deuterio-17α-ol (XVII). All these C–16 deuterated compounds exhibited the infrared absorption band due to C–D stretching frequency at 2173—2191 cm^{-1}.

The coupling constants of the C–17 protons were measured with the four epimeric 16-deuterio-5α,14β-androstan-17-ols thus obtained. It appears to be strange that the coupling of H16β,17β is somewhat larger than that of H16α,17α despite the similarity of their dihedral angles. These phenomena were also recognized with the H16,17 coupling of 13β,14α- and 13α,14α-ring systems[3,4] and were tentatively explained as an analogy of Williams and Bhacca's

Table I. Coupling Constants of H16, 17 of Epimeric 16-Deuterio-5α,14β-androstan-17-ols[a]

Configuration of H-16 and -17	Conformation A	B	C	Found[b]
16β,17α (XV)	2.2	0	0	0
16α,17α (Xd)	8.2	7.4	5.2	5.1
16α,17β (VIIIb)	2.2	5.1	7.7	6.5
16β,17β (XVII)	8.2	7.4	5.2	8.6

a) All *J* values are in cycles per second.
b) The H-17α and H-17β signals appeared at 6.36 and 6.30 τ, respectively.



8) L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963).
9) T. Nambara and M. Yano, *Chem. Pharm. Bull.* (Tokyo), **13**, 1004 (1965).
10) The previous report[11] dealing with the mode of reductive cleavage of 16β,17β-epoxy-5α,14β-androstan-3β-ol acetate with lithium aluminum hydride should be corrected (T. Nambara, M. Usui and H. Hosoda, to be published).
11) T. Nambara and K. Hirai, *Chem. Pharm. Bull.* (Tokyo), **12**, 836 (1964).
12) G.K. Helkamp and B.F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957).

observation.[13] They reported that in the cyclohexane ring the coupling constant of a proton attached to a carbon bearing an equatorial hydroxyl group is 2—3 cps larger than that of the epimeric proton. This finding, if extended to the five-membered ring, would account for the apparent discrepancy. Accordingly the observed coupling constant for 17β-proton should be reduced by an intermediate value up to 2 cps for comparison with the calculated value.

The torsional angles estimated by vector analytical technique for cyclopentane ring[14] permit the calculation of H16,17 dihedral angles for the three common conformations A, B and C, if ring C would exist in the chair form. In Table I the coupling constants calculated by the Karplus equation[15] are listed in comparison with the observed values. It is evident that the experimental values are in qualitative agreement with those expected for conformation B or C, but not A. The data available exclude conformation A with certainty, but do not permit a definite choice between the remaining two conformations due to the limitation of the Karplus equation. It is noteworthy that the coupling constants of 17-proton in this series are almost equal to those of the corresponding resonance in 13α-steroids. The close similarity observed strongly suggests that the prefered ring D conformation would be common to both C/D-*cis* ring systems.

It is hoped that these findings will be helpful to interpret the chemistry of ring D in14β-series, which includes the important cardiotonic steroids.

Experimental[16]

3β-Hydroxy-5α,14β-androstan-17-one 3-*p*-Toluenesulfonate (Ib)——To a solution of 3β-hydroxy-5α,14β-androstan-17-one (Ia)[5] (600 mg) in pyridine (20 ml) was added *p*-TsCl (600 mg) under ice–cooling, and the resulting solution was stirred for 25 hr. The reaction mixture was poured into ice–water and the precipitate was filtered and then dried. Recrystallization from acetone gave Ib (920 mg) as colorless needles. mp 158—159°. $[\alpha]_D^{16}$ +46.1° (c=0.10). *Anal.* Calcd. for $C_{26}H_{36}O_4S$: C, 70.24; H, 8.16. Found: C, 70.55; H, 8.28.

5α,14β-Androst-2-en-17-one (II)——A solution of Ib (140 mg) dissolved in DMSO (5 ml) was heated at 100° for 3 hr. The reaction mixture was diluted with ether, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work–up the crystalline product was recrystallized from dil. MeOH to give II (70 mg) as colorless needles. mp 83—85°. $[\alpha]_D^{16}$ +159.8° (c=0.10). *Anal.* Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.96; H, 10.37.

5α,14β-Androstan-17-one (III)——A solution of II (380 mg) dissolved in AcOEt (10 ml) was shaken with 5% Pd/C (200 mg) under a current of H_2 for 53 hr. After removal of the catalyst by filtration, the filtrate was concentrated to give a crystalline product. Recrystallization from dil. MeOH gave III (310 mg) as colorless needles. mp 115—117°. $[\alpha]_D^{24}$ +92.1° (c=0.10). *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.40; H, 11.05.

5α,14β-Androst-16-en-17-ol Acetate (IV)——To a solution of III (920 mg) in isopropenyl acetate (20 ml) was added a catalyst solution (isopropenyl acetate (1 ml) and conc. H_2SO_4 (0.02 ml)), and the resulting solution was refluxed for 3 hr. The reaction mixture was concentrated to one–half of its volume by slow distillation over a period of 1 hr. An additional 10 ml of isopropenyl acetate containing the catalyst solution (0.5 ml) was added, and the resulting solution was refluxed for 1 hr and again concentrated to *ca.* 10 ml. The reaction mixture was diluted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work–up the residue obtained was passed through a column of Al_2O_3 (40 g). Elution with hexane and recrystallization of the eluate from MeOH gave (750 mg) as colorless needles. mp 58.5—59.5°. $[\alpha]_D^{26}$ +60.6° (c=0.10). *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.93; H, 9.87.

16β-Bromo-5α,14β-androstan-17-one (V)——To a solution of IV (720 mg) in CCl_4 (40 ml) containing anhydrous K_2CO_3 (650 mg) was added a calculated amount of Br_2, and the reaction mixture was washed with 5% $NaHSO_3$ solution, H_2O and dried over anhydrous Na_2SO_4. On usual work–up a crystalline product was obtained. Recrystallization from dil. MeOH gave V (820 mg) as colorless needles. mp 110—112°, $[\alpha]_D^{26}$

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14) F.V. Brutcher, Jr. and W. Bauer, Jr., *J. Am. Chem. Soc.*, **84**, 2233, 2236 (1962).
15) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).
16) All melting points were taken on a micro hot–stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated. Nuclear magnetic resonance spectra were obtained on Hitachi Model H–60 spectrometer operated at 60 Mcps in $CDCl_3$ containing tetramethylsilane as an internal standard.

+156.3° (c=0.11). *Anal.* Calcd. for $C_{19}H_{29}OBr$: C, 64.58; H, 8.27. Found: C, 64.89; H, 8.11.

16β-Bromo-5α,14β-androstan-17α-ol (VIa)——To a solution of V (800 mg) in anhydrous ether (40 ml) was added $LiAlH_4$ (1.1 g) portionwise at −10°, and the resulting solution was allowed to stand at 0° for 2 hr. The reaction mixture was decomposed with moist ether and acidified with 10% H_2SO_4. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the residue obtained was chromatographed on silica gel (25 g). Elution with benzene gave VIa (190 mg) as an oily product. Further elution with benzene gave VIIIa (190 mg) as a by-product. Acetylation of VIa with Ac_2O and pyridine followed by recrystallization of the crude product from dil. MeOH gave 16β-bromo-5α,14β-androstan-17α-ol acetate (VIb) as colorless needles. mp 109—110°. $[\alpha]_D^{23}$+81.6° (c=0.10). *Anal.* Calcd. for $C_{21}H_{33}O_2Br$: C, 63.47; H, 8.37. Found: C, 63.36; H, 8.29.

16α,17α-Epoxy-5α,14β-androstane (VII)——i) A solution of VIa (160 mg) dissolved in 5% methanolic KOH (12 ml) was refluxed for 4 hr. The resulting solution was concentrated and then extracted with ether. The extract was washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up a crystalline product was obtained. Recrystallization from dil. MeOH gave VII (115 mg) as colorless needles. mp 72—73°. $[\alpha]_D^{26}$+47.0° (c=0.11). *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.57; H, 10.82.
ii) To a solution of XIVa (110 mg) in pyridine (1 ml) was added $MeSO_2Cl$ (0.12 ml) under ice-cooling, and the resulting solution was kept in refrigerator for 4 hr. The reaction mixture was diluted with ether, washed with 5% $NaHCO_3$ and H_2O, and dried over anhydrous Na_2SO_4. On usual work-up the mesylate (XIVb) was obtained as an oily substance. This product appeared to be homogeneous according to TLC and therefore submitted to further step without purification. The crude product was dissolved in 5% methanolic KOH (10 ml) and refluxed for 2 hr. After usual work-up the crystalline product obtained was recrystallized from dil. MeOH to give VII (50 mg) as colorless needles. mp 68—73°. Mixed mp on admixture with the sample obtained in i) showed no depression and infrared (IR) spectra of two samples were entirely identical.

16β-Deuterio-5α,14β-androstan-17α-ol (VIIIb)——To a solution of VII (50 mg) in THF (5 ml) was added $LiAlD_4$ (50 mg) and refluxed for 5 hr. The reaction mixture was decomposed with moist ether and then processed in the usual manner. Recrystallization from dil. MeOH gave VIIIb (40 mg) as colorless needles. mp 119—122°. Mixed mp on admixture with VIIIa showed no depression.

5α,14β-Androstan-17α-ol (VIIIa)——To a solution of III (100 mg) in anhydrous ether (5 ml) was added $LiAlH_4$ (100 mg) under ice-cooling and allowed to stand at room temperature for 1 hr. The reaction mixture was decomposed with moist ether and then processed in the usual manner. Recrystallization from dil. MeOH gave VIIIa (82 mg) as colorless needles. mp 121—123°. $[\alpha]_D^{24}$+34.5° (c=0.10). *Anal.* Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.87; H, 11.73.

5α,14β-Androstan-17β-ol Acetate (Xa)——To a solution of VIIIa (110 mg) in pyridine (15 ml) was added p-TsCl (600 mg) in several portions and stirred for 5 days. The reaction mixture was diluted with ether, washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up an oily substance was obtained. This product appeared to be homogeneous according to TLC and therefore submitted to further step. A solution of the tosylate (IXa) (125 mg) dissolved in N-methylpyrrolidone (1.6 ml) was heated with tetrabutylammonium acetate (500 mg) at 160° for 8 hr. The reaction mixture was diluted with ether, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up an oily residue obtained was chromatographed on silica gel (4 g). Elution with hexane–benzene (1:1) and recrystallization of the eluate from dil. MeOH gave Xa (30 mg) as colorless needles. mp 122—123°. $[\alpha]_D^{26}$+63.5° (c=0.10). *Anal.* Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.93; H, 11.09.

16β-Deuterio-5α,14β-androstan-17β-ol Acetate (Xb)——VIIIb (60 mg) was treated in the same manner as in Xa. Recrystallization from dil. MeOH gave Xb (25 mg) as colorless needles. mp 120—121°. Mixed mp on admixture with Xa showed no depression.

5α,14β-Androstan-17β-ol (Xc)——A solution of Xa (25 mg) dissolved in 5% methanolic KOH (4 ml) was refluxed for 2 hr. After usual work-up the crude product obtained was recrystallized from dil. MeOH to give Xc (15 mg) as colorless needles. mp 123—125°. $[\alpha]_D^{23}$+38.5° (c=0.10). *Anal.* Calcd. for $C_{19}H_{32}O \cdot 1/2H_2O$: C, 79.94; H, 11.65. Found: C, 80.79; H, 11.11.

16β-Deuterio-5α,14β-androstan-17β-ol (Xd)——Xb (23 mg) was treated with 5% methanolic KOH in the same manner as in Xc. Recrystallization from dil. MeOH gave Xd (15 mg) as colorless needles. mp 122—123°. Mixed mp on admixture with Xc showed no depression.

5α,14β-Androstan-17-one p-Tosylhydrazone (XI)——To a solution of III (770 mg) in MeOH (40 ml) were added p-$TsNHNH_2$ (640 mg) and AcOH (0.5 ml), and the resulting solution was refluxed for 16 hr. After usual work-up a crude product obtained was recrystallized from dil. MeOH to give XI (800 mg) as colorless needles. mp 143—145°. $[\alpha]_D^{22}$+55.7° (c=0.10). *Anal.* Calcd. for $C_{26}H_{38}O_2N_2S$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.67; H, 8.55; N, 6.25.

16β,17β-Epoxy-5α,14β-androstane (XIII)——To a solution of XI (780 mg) in THF (50 ml) was added $LiAlH_4$ (1.8 g), and the resulting solution was refluxed for 12 hr. The reaction mixture was decomposed with moist ether and acidified with 10% H_2SO_4. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up an oily product obtained was chromatographed on silica gel (15 g).

Elution with hexane gave 5α,14β-androst-16-ene (XII) (405 mg) as an oily substance. To a solution of XII (400 mg) in $CHCl_3$ (5 ml) was added perbenzoic acid–$CHCl_3$ solution (0.40M, 5 ml) and allowed to stand at room temperature for 2 hr. The reaction mixture was diluted with ether, washed with 5% $NaHCO_3$ and H_2O, and dried over anhydrous Na_2SO_4. After usual work-up an oily product obtained was chromatographed on silica gel (20 g). Elution with hexane–benzene (3:1) and recrystallization of the eluate from dil. MeOH gave XIII (230 mg) as colorless needles. mp 61—62°. $[\alpha]_D^{24}+71.9°$ ($c=0.10$). *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.15; H, 10.88.

16α-Deuterio-5α,14β-androstan-17β-ol (XV)——A solution of XIII (100 mg) dissolved in THF (10 ml) was refluxed with $LiAlD_4$ (80 mg) for 5 hr. The reaction mixture was processed in the same manner as in VII. Recrystallization from dil. MeOH gave XV (60 mg) as colorless needles. mp 124—126°. Mixed mp on admixture with Xc showed no depression.

16α-Deuterio-5α,14β-androstan-17-one (XVI)——To a solution of XV (60 mg) in glacial AcOH (5 ml) was added 2% CrO_3 solution in 98% AcOH (1 ml), and the resulting solution was allowed to stand at room temperature for 3 hr. After addition of MeOH to decompose the excess CrO_3 the reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with cold 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up recrystallization of the crude product gave XVI (37 mg) as colorless needles. mp 114—116°. Mixed mp on admixture with III showed no depression.

16α-Deuterio-5α,14β-androstan-17α-ol (XVII)——To a solution of XVI (30 mg) in anhydrous ether (5 ml) was added $LiAlH_4$ (100 mg)and allowed to stand at room temperature for 3 hr. After usual work-up the crude product obtained was recrystallized from dil. MeOH to give XVII (25 mg) as colorless needles. mp 123—125°. Mixed mp on admixture with VIIIa showed no depression.

5α,14β-Androstane-16α,17β-diol 16-Acetate (XIVa)——A solution of XIII (210 mg) dissolved in glacial AcOH (6 ml) was refluxed for 80 min. The reaction mixture was diluted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crude product obtained was chromatographed on silica gel (10 g). Elution with benzene and recrystallization of the eluate from dil. MeOH gave XIVa (153 mg) as colorless needles. mp 112—114°. $[\alpha]_D^{18}+18.4°$ ($c=0.11$). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.72; H, 10.19.

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