[Chem. Pharm. Bull. 17(2) 375—380 (1969)] UDC 547.92.04

The Synthesis and Conformational Analysis of α-Bromo-16-ketones of 13α-Androstanes[1]

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(Received June 29, 1968)

15α- and 17α-bromo-3β-hydroxy-5α,13α-androstan-16-one acetates (VI, VII) were synthesized starting from the parent 16-oxosteroid (Ib) by way of the enol acetate (V). Configuration of both bromine atoms introduced was established to be α by the standard method of Fieser and Ettorre. These two positional isomers were readily distinguished by leading to the Δ^{15}- and Δ^{16}-unsaturated compounds (X, XI), respectively. On the basis of infrared, ultraviolet, rotatory dispersion and circular dichroism spectral data, the nature of 15α- and 17α- bonds and the conformation of rign D with a ketone at C-16 were discussed.

The ring D α-bromoketones are of particular interest in that the spectroscopic properties provide the valuable informations on the nature of the C-bromine bond and hence the conformation of the fused cyclopentanone ring. These works were sufficiently performed with the common C/D-*trans* steroid having the oxo group at C-17 or C-16. As for the C/D-*cis* series the 16-bromo-17-ketones have previously been studied in these respects,[3] but the α-bromo-16-ketones have not yet been examined. In connection with these investigations the 16,17-ketol rearrangement of 13α-steroids was explored on the steric and conformational grounds and in consequence the most stable ketol was found to be the 17α-hydroxy-16-ketone.[4] An interest in the conformation of ring D with ketone at C-16 prompted us to prepare the pertinent α-bromo-16-ketones in order to obtain their spectral data.

An initial project was directed to the preparation of the epimeric 3β,16-dihydroxy compounds for the necessity as the authentic sample. Reduction of 3β-acetoxy-5α,13α-androstan-16-one (Ib) with lithium aluminum hydride gave the 3β,16α-diol (IIa) and potassium borohydride reduction yielded the 3-acetate (IIb) accompanied with a trace of 16β-epimer. The 3-monoacetate was transformed into the 16α-tosylate (IIc), which in turn was led to the 3β,16β-diol (IIIa) by refluxing with tetrabutylammonium acetate in N-methylpyrrolidone[5] followed by alkaline hydrolysis. The structures of the epimeric 3β,16-diols were confirmed by leading to the same 3,16-diketone (IV) by oxidation with Jones reagent. The configuration of C-16-hydroxyl group of a pair of epimers was evidently assigned on the basis of the chemical shift of the 18-methyl protons. The presence of hydroxyl group at C-16α exerted the downfield shift of 18-proton signal with 0.23 ppm due to 1,3-interaction in contrast to the 16β-hydroxyl group with a slight upfield shift value.

On treatment with isopropenyl acetate and catalytic amount of conc. sulfuric acid[6] the 16-ketone was converted to the enol acetate almost quantitatively, judged from the result

1) This paper constitutes Part XXI of the series entitled "Analytical Chemical Studies on Steroids"; Part XX: M. Katō, M. Ohnishi and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **16**, 2398 (1968).
2) Location: *Kita-4-bancho, Sendai.*
3) *a*) T. Nambara and J. Fishman, *J. Org. Chem.*, **26**, 4569 (1961); *b*) *Idem, Chem. Ind.* (London), **1961**, 79; *c*) T. Nambara, H. Hosoda and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **16**, 374 (1968); *d*) *Idem, Chem. Ind.* (London), **1967**, 1703; *e*) *Idem, Chem. Pharm. Bull.* (Tokyo),**16**, **1266** (1968).
4) T. Nambara, H. Hosoda and M. Usui, *Chem. Pharm. Bull.* (Tokyo), inpress.
5) H.B. Henbest and W.R. Jackson, *J. Chem. Soc.*, **1962**, 954.
6) N.S. Leeds, D.K. Fukushima and T.F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

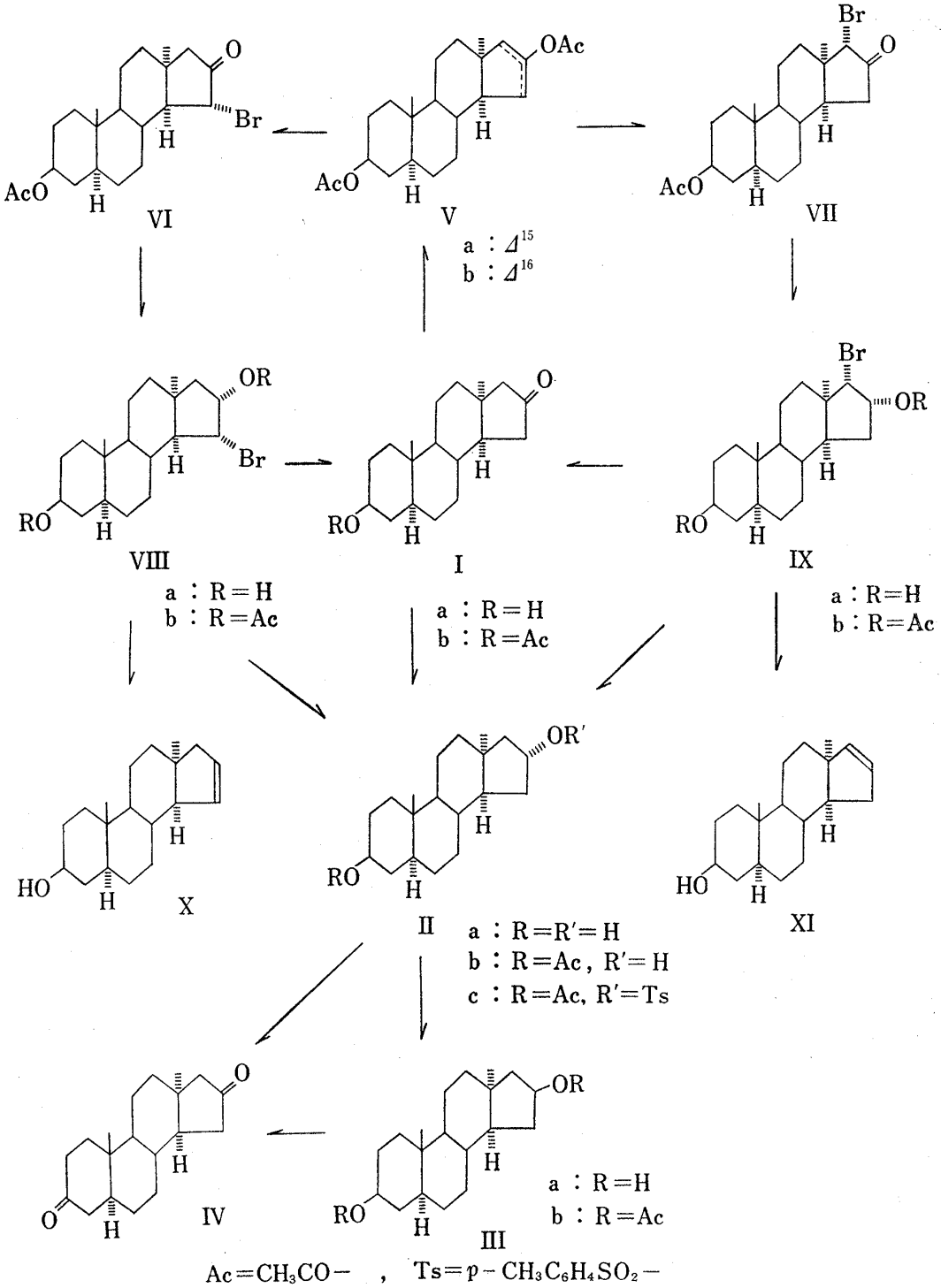

Chart 1

of thin-layer chromatography (TLC). Inspection of nuclear magnetic resonance spectra, however, indicated that the product appeared to be a mixture of Δ^{15}-and Δ^{16}-enol acetates (Va, b) in a ratio of *ca.* 1 to 1, whose separation could not be attained. It is to be noted that in the 13α-steroids enolization of the 16-ketone takes place in the both directions to almost the same degree, while in the C/D-*trans* steroids the 16-oxo function does enolize predominantly toward C-17.[7]

7) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publ., Co., New York, 1959, p. 282; J. Fajkos and J. Joska, *Collection Czech. Chem. Commun.*, **25**, 2863 (1960); *idem*, *Chem. Ind.* (London), **1960**, 872; J. Fishman, *J. Org. Chem.*, **27**, 1745 (1962).

Treatment of the enol acetates with one equivalent amount of bromine under non-enolizing conditions furnished a mixture of two isomeric α-bromo-16-ketones, which were efficiently separated into the 15α-bromo- and 17α-bromo-16-ketones (VI, VII) by means of the preparative thin-layer chromatography. Elucidation of the structure of these two isomers was achieved by the standard method of Fieser and Ettorre. Upon lithium aluminum hydride reduction at −15°, these α-bromo-16-ketones were transformed into the bromohydrins (VIIIa, IXa), respectively. The *cis*-bromohydrin structure of VIII and IX was rationalized by the formation of the same 16-ketone (Ia), when refluxed in methanolic potassium hydroxide. On the other hand reductive dehalogenation of both bromohydrins with hydrogen over palladium-on-barium carbonate gave 5α,13α-androstane-3β,16α-diol (IIa), which proved to be identical with the authentic sample mentioned above. It was therefore necessary to establish the position of the bromine to arrive at the complete structure of these α-bromo-16-ketones.

Table I. Polarographic and Spectral Data

Substance	PG	IR	UV	RD		CD	
	$E_{1/2}$(*vs.* SCE)	$\nu_{max}^{CCl_4}\Delta\nu$	$\lambda_{max}^{EtOH}\Delta\lambda$	First extremu $\lambda^{MeOH}\Delta\lambda$	$[\phi]$	$m\lambda_{max}^{MeOH}\Delta\lambda$	$[\theta]$
	V	cm^{-1}	(mμ)	(mμ)		(mμ)	
16-Ketone (Ib)		1746[a]	296	312	+7120°	292	+6530
15α-Bromo-16-ketone (VI)	−0.14	1758 +12	310 +14	330 +18	+3010°	308 +16	+1880
17α-Bromo-16-ketone (VII)	−0.53	1762 +16	296 0	320 + 8	+8400°	297 + 5	+8340

a) The 3-hydroxy compound (Ia) was used for measurement.

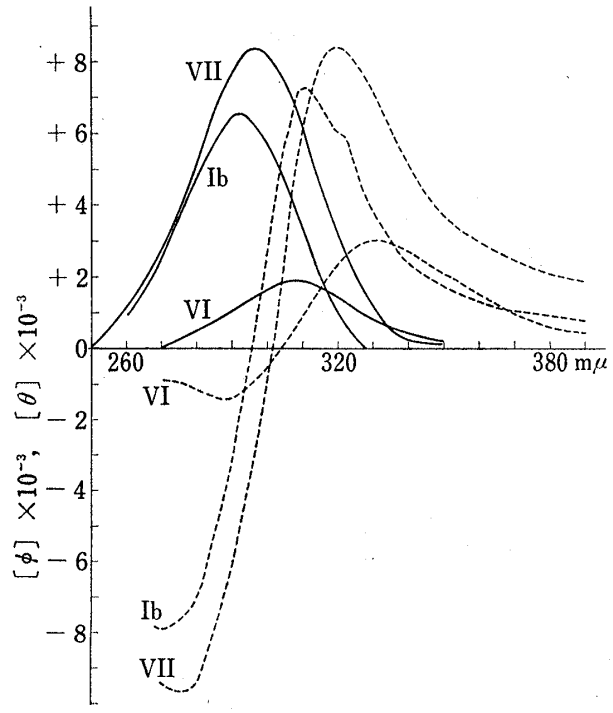

Fig. 1. Optical Rotatory Dispersion (------) and Circular Dichroism Curves (——) of Ib,VI and VII in Methanol (at 13°)

The nature of the double bond in ring D produced from the bromohydrin served to distinguish these two positional isomers. Reduction of the bromohydrin diacetate (VIIIb) with zinc dust in acetic acid and subsequent hydrolysis resulted in formation of 5α,13α-androst-15-en-3β-ol (X), which could be readily distinguished from the authentic Δ^{16}-isomer (XI) by thin-layer chromatography on silica gel plate impregnated with silver nitrate.[8] Indeed, on similar treatment the isomeric 16,17-bromohydrin diacetate (IXb) was converted to the Δ^{16}-compound (XI)[9] as was expected. Treatment of the 15α-bromo-16-ketone with hydrogen bromide in acetic acid gave an isomerization mixture, whose composition was found to be the 17α-bromo-16-ketone and the unchanged 15α-bromo compound in a ratio of *ca.* 4 to 1.

It has already been established that with several pairs of the epimeric α-bromo-16- and -17-oxosteroids the ther-

8) A.S. Gupta and S. Dev, *J. Chromatog.*, **12**, 189 (1963); R. Ikan, *ibid.*, **17**, 591 (1965); R. Ikan and M. Cudzinovski, *ibid.*, **18**, 422 (1965).
9) T. Nambara, H. Hosoda, M. Usui and J. Fishman, *Chem. Pharm. Bull.* (Tokyo), **16**, 1802 (1968).

modynamically less stable epimer is polarographically reducible with more ease than the more stable one.[10] Diagnosis by this criteria tells us that the ratio of the isomeric 15α- and 17α-bromo-16-ketones at an equilibrated state is also in qualitative agreement with a difference in the half-wave potentials (see Table I).

The spectral results of the two isomeric α-bromo-16-ketones (VI, VII) and the parent ketone (Ib) are listed in Table I. The shift values in the infrared (IR) and ultraviolet (UV) absorptions in VII reflect the quasi-equatorial nature of the 17α-bond, while those in VI indicate the bisectional character of the 15α-bond. The rotatory dispersion and circular dichroism spectral data also support the conformational assignments of these α-bromoketones. In addition the results show that the axial haloketone rule is applicable to cyclopentanone in the fused ring system.[3e,11] As illustrated in Fig. 1, the 17α-bromo derivative exhibits the positive Cotton effect with a somewhat larger amplitude than the parent ketone in contrast to the 15α-bromo compound with a smaller amplitude. All the spectroscopic data together would support the half-chair conformation for the ring D in 13α-steroids with a ketone at C-16. It is not surprising that the shift value observed in the 15α-bromo-16-ketone is somewhat less axial in comparison with the expected. This can be explained by a slight distortion in ring D caused by a non-bonded interaction between 18-methyl group and bromine atom.

Further work in progress in this laboratory will provide the data necessary for the more precise definition of the 13α-ring D conformation.

Experimental[12]

5α,13α-Androstane-3β,16α-diol 3-Acetate (IIb)——To a solution of 3β-hydroxy-5α,13α-androstan-16-one acetate (Ib) (50 mg) in THF (3 ml) was added a methanolic solution of KBH_4 (50 mg) dropwise at $-10°$. After allowing to stand for 4 hr the excess reagent was decomposed by addition of a few drops of AcOH. The reaction mixture was diluted with AcOEt and washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up an oily product obtained was submitted to preparative TLC using benzene–ether (6:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.36) with AcOEt and recrystallization of the eluate from acetone–hexane gave IIb (20 mg) as colorless needles. mp 96—97°. $[\alpha]_D^{15}$ $-85.5°$ ($c=0.10$). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.79; H, 10.16. Elution of the adsorbent obtained from another spot (*Rf* 0.40) gave the 16β-epimer (8 mg) as an oily substance.

5α,13α-Androstane-3β,16α-diol (IIa)——i) To a solution of Ib (52 mg) in ether (3 ml) was added $LiAlH_4$ (50 mg) and the resulting solution was allowed to stand at room temperature for 1 hr. The excess reagent was decomposed with moistened ether and the reaction mixture was acidified with 10% H_2SO_4. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crystalline residue obtained was submitted to preparative TLC using benzene–ether (1:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.31) with AcOEt and recrystallization of the eluate from acetone–hexane gave IIa (22 mg) as colorless needles. mp 207°. $[\alpha]_D^{15}$ $-58.4°$ ($c=0.10$). *Anal.* Calcd. for $C_{19}H_{32}O_2 \cdot 1/2\ H_2O$: C, 75.70; H, 11.03. Found: C, 75.39; H, 11.05. NMR (5% solution in $CDCl_3$) δ: 1.09 (3H, s, 18-CH_3), 0.71 (3H, s, 19-CH_3).

ii) To a solution of IIb (3 mg) in MeOH (2 ml) was added 10% K_2CO_3 (1 ml) and the resulting solution was refluxed for 2 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

10) S. Goya, H. Hosoda, T. Kudo, C. Anzo and T. Nambara, *Yakugaku Zasshi*, in press.

11) C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958); A. Lardon, H.P. Sigg and T. Reichstein, *Helv. Chim. Acta*, **42**, 1462 (1959); J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960).

12) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were determined in $CHCl_3$ solution unless otherwise stated. Infrared and ultraviolet spectra were obtained on carefully calibrated Hitachi Model 225 and EPS-3 spectrophotometers, respectively. Optical rotatory dispersion and circular dichroism measurements were carried out on Nihon-Bunko Model ORD/UV-5 recorder. Nuclear magnetic resonance spectra were run on Hitachi H-60 spectrometer at 60 Mcps in $CDCl_3$ using $(CH_3)_4Si$ as an internal standard. For preparative TLC silica gel H (E. Merck, Co.) was used as an adsorbent.

acetone–hexane gave IIa (1 mg) as colorless needles, mp 208.5—209.5°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

5α,13α-Androstane-3β,16β-diol Diacetate (IIIb)——To a solution of IIb (45 mg) in pyridine (3 ml) was added *p*-TsCl (90 mg) under ice–cooling and the reaction mixture was stirred for 44 hr. The resulting solution was poured into ice–water and extracted with ether. The organic layer was washed with 5% HCl, H_2O and dried over anhydrous Na_2SO_4. On usual work–up an oily residue was obtained. The 16-tosylate (IIc) seemed to be homogeneous according to TLC and therefore submitted to further elaboration without purification. To a solution of IIc in N-methylpyrrolidone (0.8 ml) was added tetrabutylammonium acetate (250 mg) and the resulting solution was refluxed for 8 hr. The reaction mixture was diluted with ether and washed with 5% HCl, 5% $NaHCO_3$ and H_2O successively, and dried over anhydrous Na_2SO_4. After usual work–up an oily residue obtained was chromatographed on silica gel (3 g). Elution with benzene gave IIIb (15 mg) as an oily product. According to TLC the product seemed to be homogeneous and therefore was submitted to further elaboration.

5α13α-Androstane-3β,16β-diol (IIIa)——i) A solution of IIIb (15 mg) dissolved in 5% methanolic KOH (2 ml) was refluxed for 1.5 hr. The resulting solution was diluted with AcOEt and washed with H_2O and dried over anhydrous Na_2SO_4. After usual work–up an oily product obtained was submitted to preparative TLC using benzene–ether (1:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.28) with AcOEt and recrystallization of the eluate from acetone–hexane gave IIIa (8 mg) as colorless needles. mp 152—154°. $[\alpha]_D^{15}$ −54.7° (c=0.08). *Anal.* Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.32; H, 10.93. NMR (5% solution in $CDCl_3$) δ: 0.83 (3H, s, 18–CH_3), 0.74 (3H, s, 19–CH_3).

ii) A solution of 5α,13α-androstane-3β,16β-diol 3-acetate (8 mg) in aq. MeOH containing K_2CO_3 was refluxed for 2 hr. After usual work–up an oily residue obtained was submitted to preparative TLC using benzene–ether (1:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.28) and recrystallization of the eluate from acetone–hexane gave IIIa (2 mg) as colorless needles. mp 150—152°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

5α,13α-Androstane-3,16-dione (IV)——i) To a solution of IIa (20 mg) in acetone (2 ml) was added 8 N CrO_3 solution (0.048 ml) and the resulting solution was allowed to stand at room temperature for 20 min. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work–up the crystalline residue was obtained. Recrystallization from acetone–hexane gave IV (12 mg) as colorless prisms. mp 117—119°. $[\alpha]_D^{15}$ +64.7° (c=0.10). *Anal.* Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.48; H, 9.68.

ii) IIIa (5 mg) was oxidized with 8 N CrO_3 solution in the same manner as described in i). Recrystallization from acetone–hexane gave IV (3 mg) as colorless prisms. mp 117—119°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

5α,13α-Androst-15-ene-3β,16-diol Diacetate (Va), 5α,13α-Androst-16-ene-3β,16-diol Diacetate (Vb)——To a solution of Ib (100 mg) in isopropenyl acetate (10 ml) was added 12 drops of the catalyst solution (isopropenyl acetate (1 ml) and conc. H_2SO_4 (0.01 ml)) and refluxed for 3 hr. The reaction mixture was concentrated to one–half of its volume by slow distillation over 1 hr. An additional 5 ml of isopropenyl acetate containing 6 drops of catalyst solution was added and the solution was again concentrated to *ca.* 5 ml over another 1 hr. The resulting solution was diluted with ether and washed with cold 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work–up the product obtained was dissolved in hexane and diltered through Al_2O_3 (7 g). Upon concentration of the filtrate the crystalline product was obtained. Recrystallization from MeOH gave a mixture of Va and Vb (74 mg) as colorless needles. mp 116—118°. $[\alpha]_D^{14}$ −70.5° (c=0.10). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.55; H, 9.06.

3β-Acetoxy-15α-bromo-5α,13α-androstan-16-one (VI), 3β-Acetoxy-17α-bromo-5α,13α-androstan-16- one (VII)——To a solution of Va and Vb (180 mg) in CCl_4 (40 ml) containing anhydrous K_2CO_3 (160 mg) was added a solution of the calculated amount of Br_2 in CCl_4 dropwise with stirring at 0°. The resulting solution was washed with $NaHSO_3$ solution, H_2O and dried over anhydrous Na_2SO_4. On usual work–up the crystalline product was obtained. Recrystallization from acetone–MeOH gave VI (68 mg) as colorless needles. mp 203—205°. $[\alpha]_D^{18}$ +9.7° (c=0.10). *Anal.* Calcd. for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.59. Found: C, 61.46; H, 7.48. The mother liquor of VI was submitted to preparative TLC using hexane–benzene (2:8) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.14) with acetone and recrystallization of the eluate from acetone–MeOH gave VII (60 mg) as colorless needles. mp 214—216°. $[\alpha]_D^{18}$ +53.1° (c=0.10). *Anal.* Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59. Found: C, 61.19; H, 7.66.

15α-Bromo-5α,13α-androstane-3β,16α-diol (VIIIa)——To a solution of VI (40 mg) in THF (4 ml) was added $LiAlH_4$ (80 mg) under cooling at −13 to −14° portionwise and the resulting solution was allowed to stand for 5 min. The reaction mixture was decomposed with moistened ether and acidified with 10% H_2SO_4. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work–up the crystalline product obtained was chromatographed on silica gel (3 g). Elution with benzene–ether (20:1 to 15:1) and recrystallization of the eluate from acetone–hexane gave VIIIa (16 mg) as colorless needles. mp 147—149°. $[\alpha]_D^{15}$+24.3° (c=0.10). *Anal.* Calcd. for $C_{19}H_{31}BrO_2$: C, 61.45; H, 8.41. Found: C, 61.82; H, 8.39.

15α-Bromo-5α,13α-androstane-3β,16α-diol Diacetate (VIIIb)——Usual treatment of VIIIa (17 mg) with pyridine (0.8 ml) and Ac_2O (0.4 ml) followed by recrystallization from MeOH gave VIIIb (16 mg) as colorless needles. mp 152—153°. $[\alpha]_D^{18}$ −33.4° (c=0.10). *Anal.* Calcd. for $C_{23}H_{35}O_4Br$: C, 60.65; H, 7.75. Found: C, 60.94; H, 7.93.

17α-Bromo-5α,13α-androstane-3β,16α-diol (IXa)——VII (35 mg) was submitted to reduction with $LiAlH_4$ (70 mg) in the same manner as described above. The crude product obtained was chromatographed on silica gel (3.5 g). Elution with benzene–ether (20:1) and recrystallization of the eluate from acetone–hexane gave IXa (22 mg) as colorless needles. mp 133°. $[\alpha]_D^{18}$ −46.8° (c=0.11). *Anal.* Calcd. for $C_{19}H_{31}O_2Br$: C, 61.45; H, 8.41. Found: C, 61.70; H, 8.49.

17α-Bromo-5α,13α-androstane-3β,16α-diol Diacetate (IXb)——Usual treatment of IXa (30 mg) with pyridine (0.8 ml) and Ac_2O (0.4 ml) followed by recrystallization from MeOH gave IXb (26 mg) as colorless prisms. mp 177—179°. $[\alpha]_D^{14}$ −37.7° (c=0.11). *Anal.* Calcd. for $C_{23}H_{35}O_4Br$: C, 60.65; H, 7.75. Found: C, 61.41; H, 8.17.

Transformation of VIIIa and IXa into Ia with Potassium Hydroxide——i) A solution of VIIIa (5 mg) in 5% methanolic KOH (1 ml) was refluxed for 1.5 hr. The resulting solution was diluted with AcOEt and 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 Ia (2 mg) as colorless needles. mp 192—194°. Mixed melting point on admixture with the authentic sample showed no depression.

ii) Similar treatment of IXa (5 mg) with 5% methanolic KOH and recrystallization of the crude product from acetone–hexane gave Ia (3 mg) as colorless. mp 189—191°. Mixed melting point on admixture with the authentic sample showed no depression.

Debromination of VIIIa and IXa——i) A solution of VIIIa (7 mg) in EtOH (4 ml) was shaken with 5% $Pd/BaCO_3$ (30 mg) under a stream of H_2 for 63 hr. After removal of catalyst by filtration the filtrate was concentrated to give crystalline product. Recrystallization from acetone–hexane gave IIa (4 mg) as colorless needles. mp 206—208°. Mixed melting point on admixture with the authentic sample mentioned above showed no depression.

ii) Similar treatment of IXa (10 mg) with 5% $Pd/BaCO_3$ (60 mg) under a stream of H_2 and recrystallization of the crude product from acetone–hexane gave IIa (4 mg) as colorless needles. mp 206—207°. Mixed melting point on admixture with the authentic sample showed no depression.

5α,13α-Androst-15-en-3β-ol (X)——To a boiled solution of VIIIb (30 mg) in AcOH (10 ml) – Ac_2O (1 ml) was added Zn dust (300 mg) portionwise and the resulting solution was refluxed for 8 hr. After removal of the precipitate by filtration the filtrate was concentrated and dissolved in ether. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. An oily product obtained seemed to be homogeneous and therefore was submitted to further elaboration without purification. To a solution of the crude product (15 mg) in ether (2 ml) was added $LiAlH_4$ (20 mg) and allowed to stand at room temperature for 1 hr. On usual work-up the crystalline product was obtained. Recrystallization from dil. MeOH gave X (9 mg) as colorless needles. mp 96—99°. $[\alpha]_D^{15}$ −120.4° (c=0.07). *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.41; H, 11.20. When developed on silica gel G–$AgNO_3$ plate with benzene–ether (3:1) as solvent, X exhibited *Rf* 0.28, distinctly different from that of XI (*Rf* 0.24).

5α,13α-Androst-16-en-3β-ol (XI)——Similar treatment of IXb (15 mg) with Zn (200 mg) in AcOH (8 ml) – Ac_2O (1 ml) as described above gave an oily product (6 mg). Hydrolysis of the crude product with $LiAlH_4$ (15 mg) in ether (2 ml) and recrystallization from dil. MeOH gave XI (2 mg) as colorless needles. The product proved to be entirely identical with the authentic sample in every respect.

Equilibration of Isomeric α-Bromo-16-ketones——i) To a solution of VII (27 mg) in glacial AcOH (0.5 ml) was added AcOH saturated with HBr (0.1 ml). The solution was heated at 50° for 1 hr, and then poured into ice–water. The precipitate was filtered off, washed with H_2O and was submitted to preparative TLC using hexane–benzene (2:8) as developing solvent. Elution of the adsorbent corresponding to the spots (*Rf* 0.22, 0.14) and recrystallization of the eluates gave VI (2 mg) and VII (13 mg), respectively.

ii) Similar treatment of VI (20 mg) with HBr in AcOH followed by preparative TLC gave VI (3 mg) and VII (12 mg).

Polarography Polarographic reductions were run by a Yanagimoto Model PA-102 polarograph equipped with a capillary of the following characteristics: m=6.58 mg/sec, t= 4.8 sec at a mercury height of 68.5 cm. The polarographic cell was an H-cell containing a saturated calomel anode. An electrolysis solution was prepared by weighing the sample into a 10 ml volumetric flask, dissolving it in iso-PrOH (*ca.* 5 ml) and adding the acetate buffer (pH 6.0) (2 ml). The solution was then made up to 10 ml with additional iso-PrOH. The sample solution thus prepared was deaerated by bubbling N_2 gas and then polarographed at 25.0±0.2°. Half-wave potential was expressed in volt *vs.* the saturated calomel electrode.

Acknowledgement The authors are indebted to all the staff of central analytical laboratoty of this Institute for elemental analyses, ultraviolet absorption, nuclear magnetic resonance, optical rotatory dispersion and circular dichroism spectral measurements. Thanks are also due to Hitachi, Ltd., for measurement of infrared spectra. This work was supported in part by a Grant-in-Aid from the Ministry of Education, which is gratefully acknowledged.