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The Synthesis and Conformational Analysis of 17-Bromo-estratrien-16-ones and -androst-5-en-16-ones[1]

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In order to explain the rate difference of Zimmermann reaction with the 16-oxosteroids[3] in terms of the conformational concepts, two pairs of the epimeric 17-bromo-16-ketones in estratriene and androst-5-ene series have been synthesized (Chart 1 and 2). The conformation of ring D with a ketone at C-16 was examined on the basis of their spectral data litsed in Table I. Contrary to the expectations, however, no definite evidence for the long-range effect on the conformation of ring D due to the structure alteration in distant part of the molecule has been obtained.

As a part of our program dealing with the mechanism of Zimmermann reaction we have investigated the specificity of this rection with various oxosteroids.[3] It was thereby observed that the presence of aromatic ring A or Δ^5-double bond in steroid nucleus exerted the significant influence on the reactivity of the active methylenes adjacent to the 16-ketone. These results led to the assumption that the rate difference of reaction might be ascribable to the long-range conformational effect[4] due to the structure alteration in distant part of the molecule. An interest in these respects prompted us to explore the conformation of ring D with a ketone at C-16. The present paper describes the synthesis of the epimeic 17-bromo-16-ketones having estratriene and androst-5-ene skeletons and the conformational analysis on the basis of their spectral data. The starting material, 3-hydroxyestra-1,3,5(10)-trien-16-one (IVa), was

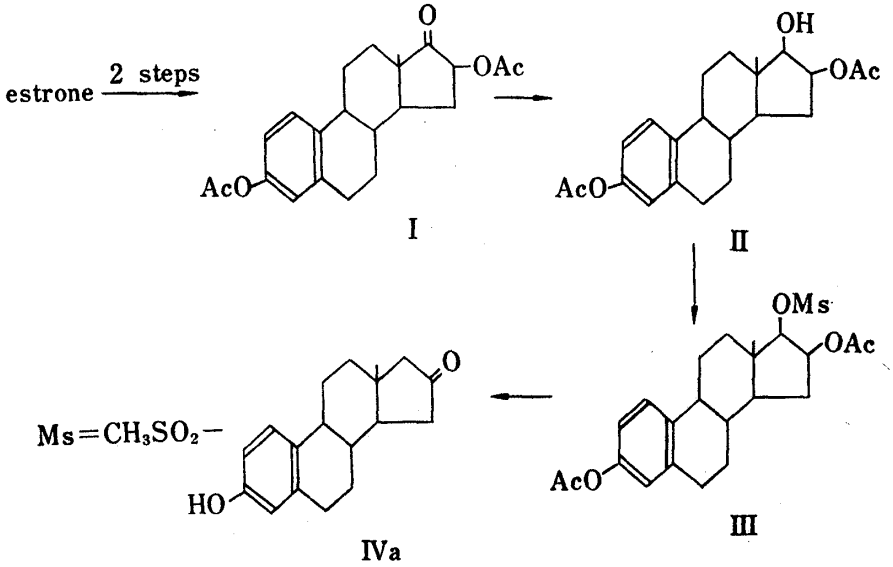

Chart 1

1) This paper constitutes Part XXVII of the series entitled "Analytical Chemical Studies on Steroids"; Part XXVI: T. Nambara, K. Yamanouchi, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), in press.
2) Location: *Aobayama, Sendai.*
3) T. Nambara and M. Katō, *Chem. Pharm. Bull.* (Tokyo), **13**, 78 (1965); T. Nambara, M. Katō, R. Imanari, and T. Kudo, *Chem. Pharm. Bull.* (Tokyo), **16**, 126 (1968).
4) D.H.R. Barton, F. McCapra, P.J. May, and F. Thudium, *J. Chem. Soc.*, **1960**, 1297, and references quoted therein.

prepared from 3,16β-dihydroxyestra-1,3,5(10)-trien-17-one diacetate (I) according to the method developed by Hara.[5] Reduction of I with sodium borohydride followed by repeated fractional crystallization[6] gave the 3,16β,17β-triol 3,16-diacetate (II), which was in turn transformed into the 17-methanesulfonate (III). Subsequent treatment with alkali provided the desired estrone-16 (IVa) in satisfactory yield.

It has already been reported that the difficulties were encountered with enolacetylation of the 16-keto estrogen in contrast to the androstan-16-one under the usual conditions employing isopropenyl acetate and conc. sulfuric acid as catalyst. Recently, Rhone, *et al.* succeeded in preparation of the enol acetate with use of anhydrous *p*-toluenesulfonic acid instead of sulfuric acid.[7] Indeed, the Δ^{16}-en-16-ol acetate (Va) was produced under the proposed conditions in 61% yield. Reaction of Va with an equivalent amount of bromine in carbon tetrachloride under non-enolizing conditions furnished the 17α-bromo-16-ketone (VIa) as a sole product. Configuration of bromine introduced is unequivocal since the stereochemistry of ring D in 14α-steroids is sufficiently substantiated.[8] Epimerization of the 17α-bromoketone was readily achieved by treatment with base. Subsequent reacetylation and purification by preparative thin-layer chromatography provided the desired 17β-bromo-16-ketone (VIIa). The existence of bromine atom at C-17 was confirmed by leading to estra-1,3,5(10),16-tetraen-3-ol(IXa). Reduction of VIIa with lithium aluminum hydride gave the *cis*-bromohydrin (VIIIa), which on treatment with zinc dust in acetic acid[9] was converted to IXa, idential with the authentic sample.[10] The structure of VIIa was thus fully established.

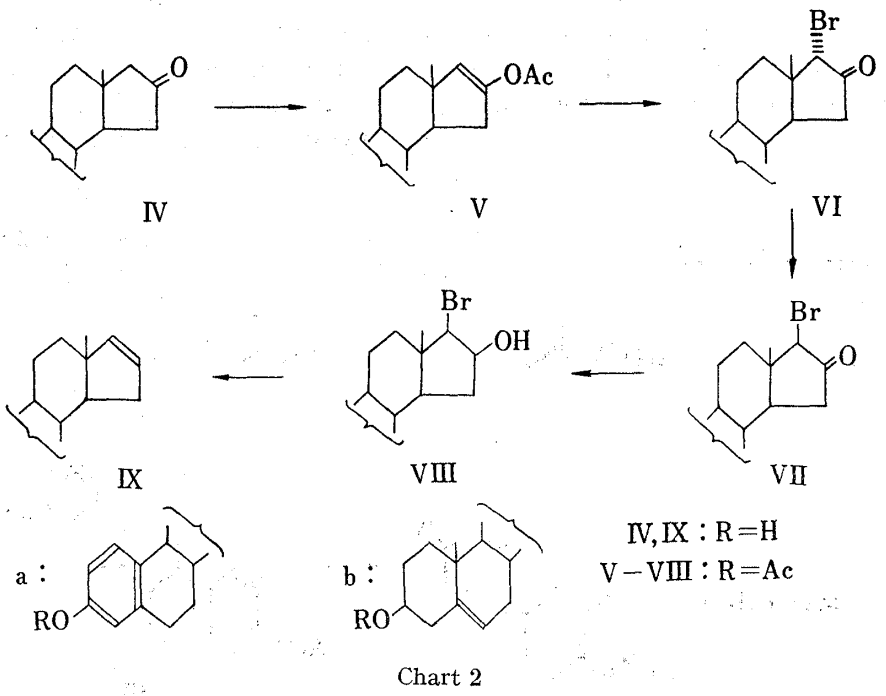

Chart 2

5) S. Hara, *Yakugaku Zasshi*, **87**, 1573 (1967).
6) Otherwise the expected product, II, would be contaminated with the isomeric 3,17-diacetate since acetyl migration took place in part together with the reduction of the 17-ketone (T. Nambara, Y. Matsuki and T. Kudo, unpublished data).
7) J.R. Rhone and M.N. Huffman, *Tetrahedron Letters*, **1965**, 1395. Detailed procedure, however, was not described therein.
8) It was also reported that per-acid would attack the Δ^{16}-double bond of Va from the α-side of the molecule to give the corresponding 16α,17α-epoxy derivative.[7] See also references 11 and 12.
9) L.F. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, **75**, 1700 (1953).
10) M.F. Huffman, M.H. Lott, and A. Tillotson, *J. Biol. Chem.*, **217**, 103 (1955).

As for the androst-5-ene series the same reaction sequence was used for the synthesis of the epimeric 17-bromo-16-ketones and their structural elucidation. 3β-Hydroxyandrost-5-en-16-one (IVb) was transformed into the Δ^{16}-en-16-ol acetate (Vb), which was then led to the 17α-bromo-16-ketone (VIb) by reaction with bromine. Treatment of VIb with base in the similar manner as in the 16-keto estrogen gave the epimeric 17β-bromo-16-ketone (VIIb) as was expected. The retention of bromine at C-17 was justified by leading it to the 16,17-bromohydrin (VIIIb) by metal hydride reduction and then to the Δ^{16}-unsaturated compound (IXb) by reductive debromination with zinc dust in acetic acid.

Table I. Rotatory Dispersion and Spectral Data

	IR $\nu_{max}^{CCl_4}$ (cm^{-1})	$\Delta\nu$ (cm^{-1})	UV λ_{max}^{EtOH} (mμ)	$\Delta\lambda$ (mμ)	RD$^{1st\ extremum}_{MeOH}$ (mμ)	[ϕ]	$\Delta\lambda$ (mμ)
Androst-5-ene series							
16-Ketone(IVb-Ac)	1747[a]		291		314	−13449°	
17α-Bromo-16-ketone (VIb)	1756	9	316	25	346	− 2148°	32
17β-Bromo-16-ketone (VIIb)	1763	16	297	6	324	− 7697°	10
Estratriene series							
16-Ketone (IVa-Ac)	1747		—		314	−11723°	
17α-Bromo-16-ketone (VIa)	1757	10	—	—	349	− 1674°	35
17β-Bromo-16-ketone (VIIa)	1763	16	—	—	322	−11341°	8
5α-Androstane series[b]							
16-Ketone	1746		299[c]		314	−15885°	
17α-Bromo-16-ketone	1754	8	316	17	350	− 2159°	36
17β-Bromo-16-ketone	1764	18	—	—	—	—	—

a) Free alcohol was used for this determination.
b) J. Fishman and C.Djerassi, *Experientia*, **16**, 138 (1960) and reference 12
c) The authors observed λ_{max} at 291 mμ.

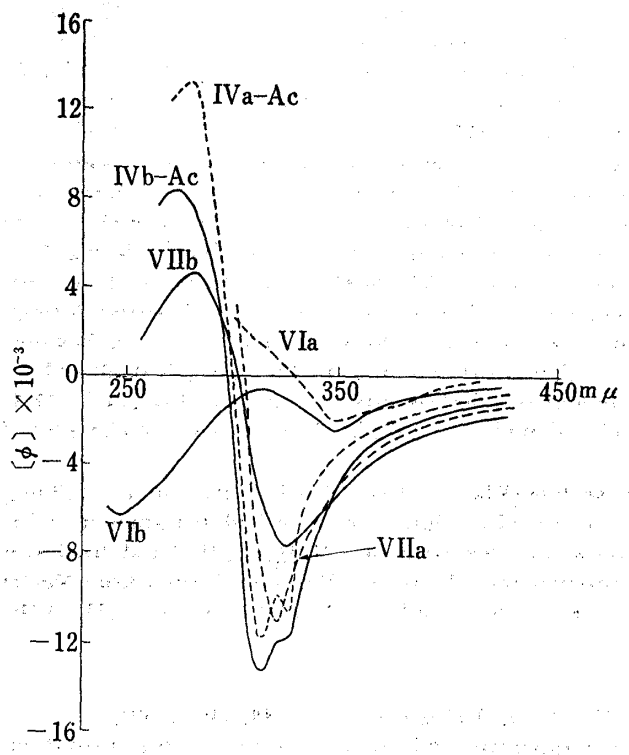

Fig. 1. Optical Rotatory Dispersion Curves of 16-Oxosteroids in Methanol

The spectral data of two pairs of epimeric 17-bromo-16-ketones and their parent 16-ketones are collected in Table I. It is apparent from these shift values that in both series the two 17-positions are not equivalent. Infrared shifts are such as to assign to the 17α bond quasiaxial and to the 17β bond quasiequatorial character. In addition, ultraviolet displacements show the expected reverse relationship. The optical rotatory dispersion curves also support these conformational assignments in that quasiaxial 17α-epimer exhibits the much larger bathochromic shift of the first extremum (see Fig. 1). There can be seen no substantial difference in spectroscopic properties between the estratriene and androst-5-ene derivatives. It should be emphasized that the magnitudes of these shift values are almost equal to those of the 17-bromoandrostan-16-ones having no unsaturation.[11,12] The present findings

11) J. Fajkoš and J. Joska, *Collection Czech. Chem. Commun.*, **25**, 2863 (1960); **26**, 1188 (1961).
12) J. Fishman, *J. Org. Chem.*, **27**, 1745 (1962).

together with the polarographic data[13] permit the assignment of the half-chair conformation to ring D with a ketone at C-16. Contrary to the expectations the long-range conformational effects are not apparent for the C-halogen bond of these 16-oxosteroids. The angular distortion due to the distant effect may be of a more subtle nature and therefore they may not be reflected to the parameters employed. Anyhow, the conformational argument used to explain the less reactivity in Zimmermann reaction should be extended along the more adequate approach. It is hoped that further studies in progress will provide the more precise knowledge on this problem.

Experimental[14]

Estra-1,3,5(10)-triene-3,16β,17β-triol 3,16-Diacetate (II)——To a stirred solution of 3,16β-dihydroxyestra-1,3,5(10)-trien-17-one diacetate (I) (500 mg) in MeOH (14 ml) was added dropwise a solution of $NaBH_4$ (76 mg) in 70% MeOH (3 ml) under ice-cooling. After stirring for 60 min, the reaction mixture was acidified with AcOH (1 drop), poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up a crystalline procudt was obtained. Repeated recrystallization from acetone-hexane gave II (360 mg) as colorless needles. mp 136—138°, $[\alpha]_D^{12}$ +68.9° (c=0.19). *Anal.* Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.02; H, 7.78.

17β-Methanesulfonyloxyestra-1,3,5(10)-triene-3,16β-diol Diacetate (III)——To a stirred solution of II (250 mg) in pyridine (2 ml) was added $MeSO_2Cl$ (1.1 ml) dropwise under ice-cooling. After stirring for 60 min, the reaction mixture was poured into H_2O and extracted with $CHCl_3$. The organic layer was washed with 10% HCl, 5% $NaHCO_3$ and H_2O and dried over anhydrous Na_2SO_4. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave III (231 mg) as colorless needles. mp 182—184°, $[\alpha]_D^{13}$+24.2° (c=0.12). *Anal.* Calcd. for $C_{23}H_{30}O_7S$: C, 61.32; H, 6.71. Found: C, 61.56; H, 6.67.

3-Hydroxyestra-1,3,5(10)-trien-16-one (IVa)——A solution of III (183 mg) in methanolic 1N KOH (20 ml) was refluxed under a current of N_2 for 5 hr. The resulting solution was acidified with 10% HCl and concentrated *in vacuo*. The crystalline residue was dissolved in AcOEt, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up a crystalline product obtained was chromatographed on Al_2O_3 (5 g). Elution with benzene and recrystallization of the eluate from MeOH gave IVa (100 mg) as colorless needles. mp 239—241°, $[\alpha]_D^{22}$−92.5° (c=0.19, EtOH). *Anal.* Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.58; H, 8.27. No contamination of the isomeric 17-ketone was confirmed by gas-liquid chromatography upon leading to the O-trimethylsilyl oxime derivative.[15] Huffman, *et al.* prepared this compound by the different method and reported it mp 243.5—244.5°, $[\alpha]_D^{25}$−87.5° (c=0.43, EtOH).[16]

Estra-1,3,5(10),16-tetraene-3,16-diol Diacetate (Va)——To a solution of IVa (680 mg) in isopropenyl acetate (20 ml) was added anhydrous *p*-TsOH (100 mg) and refluxed for 25 hr. The resulting solution was concentrated to its half volume by slow distillation over a period of 2 hr. Additional isopropenyl acetate (10 ml) and anhydrous *p*-TsOH (50 mg) were added and concentrated again to its half volume during 7 hr. The reaction mixture was diluted with ether, washed with ice-cooled 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up the residue was dissolved in hexane-benzene (2:1) and filtered through Al_2O_3 (20 g). After evaporation of solvent an oily residue was submitted to preparative TLC using hexane-AcOEt (3:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.59) and recrystallization of the eluate from MeOH gave Va (450 mg) as colorless prisms. mp 136—137°, $[\alpha]_D^{22}$+41.4° (c=0.11). *Anal.* Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.40. Found: C, 74.32; H, 7.19. Rhone, *et al.* reported it mp 136—137°.[7]

3-Hydroxy-17α-bromoestra-1,3,5(10)-trien-16-one Acetate (VIa)——Toa s tirred solution of Va (170 mg) in CCl_4 (20 ml) containing anhydrous K_2CO_3 (140 mg) was added a solution of the calculated amount of Br_2 dissolved in CCl_4 dropwise at 0°. The resulting solution was washed with 10% $NaHSO_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave VIa (68 mg) as colorless needles. mp 116—118°, $[\alpha]_D^{15}$+3.9° (c=0.13). *Anal.* Calcd. for $C_{20}H_{23}O_3Br$: C, 61.38; H, 5.92. Found: C, 61.27; H, 6.03.

13) S. Goya, H. Hosoda, T. Kudo, C. Anzo, and T. Nambara, *Yakugaku Zasshi*, **89**, 336 (1969).
14) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated. Infrared and ultraviolet spectra were obtained on carefully calibrated Hitachi Model 225 and EPS-3 spectrophotometers, respectively. Optical rotatory dispersion measurements were carried out on Nihon-Bunko Model ORD/UV-5 recorder. For preparative TLC silica gel H (E. Merck AG) was used as an adsorbent.
15) T. Nambara, T. Kudo, and H. Ikeda, *J. Chromatog.*, **34**, 526 (1968).
16) M.N. Huffman and M.H. Lott, *J. Am. Chem. Soc.*, **75**, 4327 (1953).

3-Hydroxy-17β-bromoestra-1,3,5(10)-trien-16-one Acetate (VIIa)——To a solution of VIa (50 mg) in EtOH (3 ml)-THF (1 ml) was added 1% ethanolic KOH (2 ml), and the resulting solution was allowed to stand at 18° for 40 min. The reaction mixture was poured into H_2O, acidified with 10% HCl and extracted with ether. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue obtained was treated with pyridine (1 ml) and Ac_2O (0.5 ml). After usual work-up the crude product was submitted to preparative TLC using hexane–AcOEt (3:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.42) and recrystallization of the eluate from MeOH gave VIIa (7 mg) as colorless needles. mp 141—143°, $[\alpha]_D^{22}$ −112.5° (c=0.13). *Anal.* Calcd. for $C_{20}H_{23}O_3Br$: C, 61.38; H 5.92. Found: C, 61.53; H, 6.19.

Transformation of VIIa into Estra-1,3,5(10),16-tetraen-3-ol (IXa)——To a solution of VIIa (45 mg) in anhydrous ether (6 ml) was added $LiAlH_4$ (60 mg) at 0° and allowed to stand for 1 hr. The reaction mixture was decomposed with moist ether, acidified with 10% H_2SO_4 and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crude product was submitted to further step without purification. To a solution of the crude bromohydrin (VIIIa) (40 mg) in AcOH (10 ml)–Ac_2O (1 ml) was added Zn dust (200 mg) and refluxed for 8 hr. After separation of the cake by filtration the filtrate was concentrated to give a crystalline residue. The crude product was then dissolved in 1% methanolic KOH (8 ml) and refluxed for 1 hr. After usual work-up the hydrolyzate was submitted to preparative TLC using hexane–AcOEt (3:2) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.60) and recrystallization of the eluate from acetone–hexane gave IXa (7 mg) as colorless needles. mp 122—123°. *Anal.* Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.39; H, 8.62. Mixed mp on admixture with the authentic sample[10] showed no depression, and IR spectra and *Rf* values (on thin-layer silica gel H impregnated with $AgNO_3$) of two samples were entirely identical.

Androsta-5,16-diene-3β,16-diol Diacetate (Vb)——To a solution of 3β-hydroxyandrost-5-en-16-one (IVb) (300 mg) in isopropenyl acetate (3 ml) was added catalyst solution (1 ml of isopropenyl acetate and 0.02 ml of conc. H_2SO_4) (0.15 ml), and the resulting solution was refluxed for 2 hr and then, approximately 1.5 ml was distilled off for 2 hr. Additional isopropenyl acetate (3 ml) and catalyst solution (0.15 ml) were added and concentrated to one-half of its volume by slow distillation over another 2 hr. The reaction mixture was diluted with ether, washed with ice-cooled 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was dissolved in hexane–benzene (2:1) and filtered through Al_2O_3 (8 g). Upon concentration of the filtrate a crystalline product was obtained. Recrystallization from MeOH gave Vb (230 mg) as colorless needles. mp 128—130°, $[\alpha]_D^{19}$ −130° (c=0.10). *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 74.16; H, 8.66. Found: C, 74.18; H, 8.67.

3β-Hydroxy-17α-bromoandrost-5-en-16-one Acetate (VIb)——To a stirred solution of Vb (400 mg) in CCl_4 (40 ml) containing anhydrous K_2CO_3 (340 mg) was added a solution of the calculated amount of Br_2 dissolved in CCl_4 dropwise at 0°. The resulting solution was washed with 10% $NaHSO_3$ solution, H_2O and dried over anhydrous Na_2SO_4. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave VIb (300 mg) as colorless leaflets. mp 132—133°, $[\alpha]_D^{17}$ −120° (c=0.11). *Anal.* Calcd. for $C_{21}H_{29}O_3Br$: C, 61.61; H, 7.14. Found: C, 61.83; H, 7.15.

3β-Hydroxy-17β-bromoandrost-5-en-16-one Acetate (VIIb)——To a solution of VIb (300 mg) in EtOH (13 ml)–THF (2 ml) was added 1% ethanolic KOH (10 ml) and the resulting solution was allowed to stand at 18° for 20 min. The reaction mixture was poured into H_2O and extracted with ether. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the residue was treated with pyridine (2 ml) and Ac_2O (1 ml). On usual work-up the crude product was submitted to preparative TLC using hexane–AcOEt (3:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.50) and recrystallization of the eluate from MeOH gave VIIb (58 mg) as colorless needles. mp 232—234°, $[\alpha]_D^{14}$ −184.6° (c=0.23). *Anal.* Calcd. for $C_{21}H_{29}O_3Br$: C, 61.61; H, 7.14. Found: C, 61.83; H, 7.29.

17β-Bromoandrost-5-ene-3β,16β-diol (VIIIb)——To a solution of VIIb (55 mg) in anhydrous ether (6 ml) was added $LiAlH_4$ (83 mg) at 0° and allowed to stand for 1 hr. The reaction mixture was decomposed with moist ether, acidified with 10% H_2SO_4 and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up a crystalline product was recrystallized from acetone–hexane to give VIIIb (35 mg) as colorless plates. mp 200.5—202.5°. 3,16-Diacetate: Usual acetylation of VIIIb with Ac_2O and pyridine and recrystallization from MeOH gave the 3,16-diacetate as colorless needles. mp 141—142.5°, $[\alpha]_D^{15}$ −64.5° (c=0.12). *Anal.* Calcd. for $C_{23}H_{33}O_4Br$: C, 60.92; H, 7.34. Found: C, 60.98; H, 6.92.

Transformation of VIIIb into Androsta-5,16-dien-3β-ol (IXb)——To a solution of VIIIb (35 mg) in AcOH (10 ml)–Ac_2O (1 ml) was added Zn dust (200 mg) and refluxed for 8 hr. After separation of the cake by filtration the filtrate was concentrated to give an oily residue. The crude product was then dissolved in 1% methanolic KOH (10 ml) and refluxed for 1 hr. After usual work-up a crude product was recrystallized from MeOH to give IXb (6 mg) as colorless prisms. mp 132—134°. *Anal.* Calcd. for $C_{19}H_{28}O$: C, 83.77;

17) F. Sondheimer, O. Mancera, M. Urquiza, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 4145 (1955).

H, 10.36. Found: C, 83.58; H, 10.14. TLC: *Rf* 0.52 (silica gel G impregnated with $AgNO_3$, hexane–AcOEt (3:1)). Mixed mp on admixture with the authentic sample[17] showed no depression and IR spectra and *Rf* values (on thin-layer silica gel G impregnated with $AgNO_3$) of two samples were entirely identical.

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