[Chem. Pharm. Bull. 15(12)1966~1978(1967)]
UDC 547.924.07

254. Keiji Yoshida and Fumihiko Watanabe*1: Syntheses of 1α,2α- and 1β,2β-Epithio-A-nor-5α-androstan-17β-ol and Related Compounds.

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17β-Hydroxy-A-nor-5α-androstan-1α,2α-episulfide (XXIIIa) and -1β,2β-episulfide (XIa) were prepared from 17β-acetoxy-A-nor-5α-androstan-2-one (Ib) *via* the corresponding epoxides (XXa) and (Xa) as intermediates.

(Received March 29, 1967)

Some 2,3-episulfides in the cholestane, androstane and pregnane series were recently synthesized by Takeda[1] and Klimstra.[2,3] Among them, 2α,3α-epithio-17α-methyl-5α-androstan-17β-ol has been reported[3] to have interesting hormonal activities, that is, high anabolic and low androgenic activities. Under this circumstance and also in connection with our previous studies[4] on A-norsteroids, the syntheses of episulfides in the A-norsteroid series were undertaken for biological evaluation. The present paper deals with the preparation of 1,2-episulfides in the A-nor-5α-androstane series.

The first step in the syntheses of episulfides involved the preparation of 17β-acetoxy-A-nor-5α-androst-1-ene (Vb). Treatment of 17β-acetoxy-A-nor-5α-androstan-2-one (Ib) with isopropenyl acetate containing a catalytic amount of sulfuric acid gave 2,17β-diacetoxy-A-nor-5α-androst-1-ene (II) in 61% yield with 18% recovery of the starting material. The Δ^1-structure of II was assigned by the nuclear magnetic resonance (NMR) spectrum which showed an olefinic proton at 4.40τ as a singlet. Bromination of II afforded 1α-bromo-17β-acetoxy-A-nor-5α-androstan-2-one (III) in 85% yield, whose C-1 proton appeared at 6.12τ as a singlet. The α-configuration of the bromine atom was assigned by the following spectral data. Compared with the parent ketone (Ib), the carbonyl band in the infrared (IR) spectrum shifted to higher frequency by 10 cm^{-1} and that in the ultraviolet (UV) spectrum exhibited a red shift of 21 mμ. Moreover, in the optical rotatory dispersion (ORD), the bathochromic shift was 34 mμ in the first extremum of the positive Cotton curve. These findings suggest that the C-1 bromine atom is situated as quasi-axial, that is, the 1α-configuration in a half-chair conformation[5,6] of the 2-oxo-A-nor ring. The above-mentioned results for the enol acetylation and bromination were similar to those obtained in the A-norcholestane series by Dauben.[7]

Reduction of III with sodium borohydride afforded predominantly *cis*-bromohydrin (IVb), together with a small amount of the *trans*-isomer (XIXa). On the other hand, lithium aluminum hydride reduction of III gave only the *cis*-bromohydrin (IVa). Acetylation of both IVa and IVb furnished the identical diacetate (IVc). Assignment of the 1α-bromo-2α-hydroxy structure in this bromohydrin was established by the following chemical transformations. The bromohydrin (IVb) was converted into Ia by alkaline

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1) *a*) K. Takeda, T. Komeno, J. Kawanami, S. Ishihara, H. Kadokawa, H. Tokura, H. Itani: Tetrahedron, **21**, 329 (1965). *b*) K. Takeda, T. Komeno: Chem. & Ind., **1962**, 1793.
2) P.D. Klimstra, E.F. Nutting, R.E. Counsell: J. Med. Chem., **9**, 693 (1966).
3) P.D. Klimstra: J. Med. Chem., **9**, 781 (1966).
4) K. Yoshida, T. Kubota: This Bulletin, **14**, 1370 (1966), and preceding papers.
5) *a*) J. Fishman, C. Djerassi: Experientia, **16**, 138 (1960). *b*) J. Fishman: Chem. & Ind., **1961**, 1078. *c*) J. Fajkos, J. Joska: Collection Czech. Chem. Commun., **26**, 1118 (1961).
6) F.V. Brutcher, W. Bauer: J. Am. Chem. Soc., **84**, 2236 (1962).
7) W.G. Dauben, G.A. Boswell, W.H. Templeton: *Ibid.*, **83**, 5006 (1961).

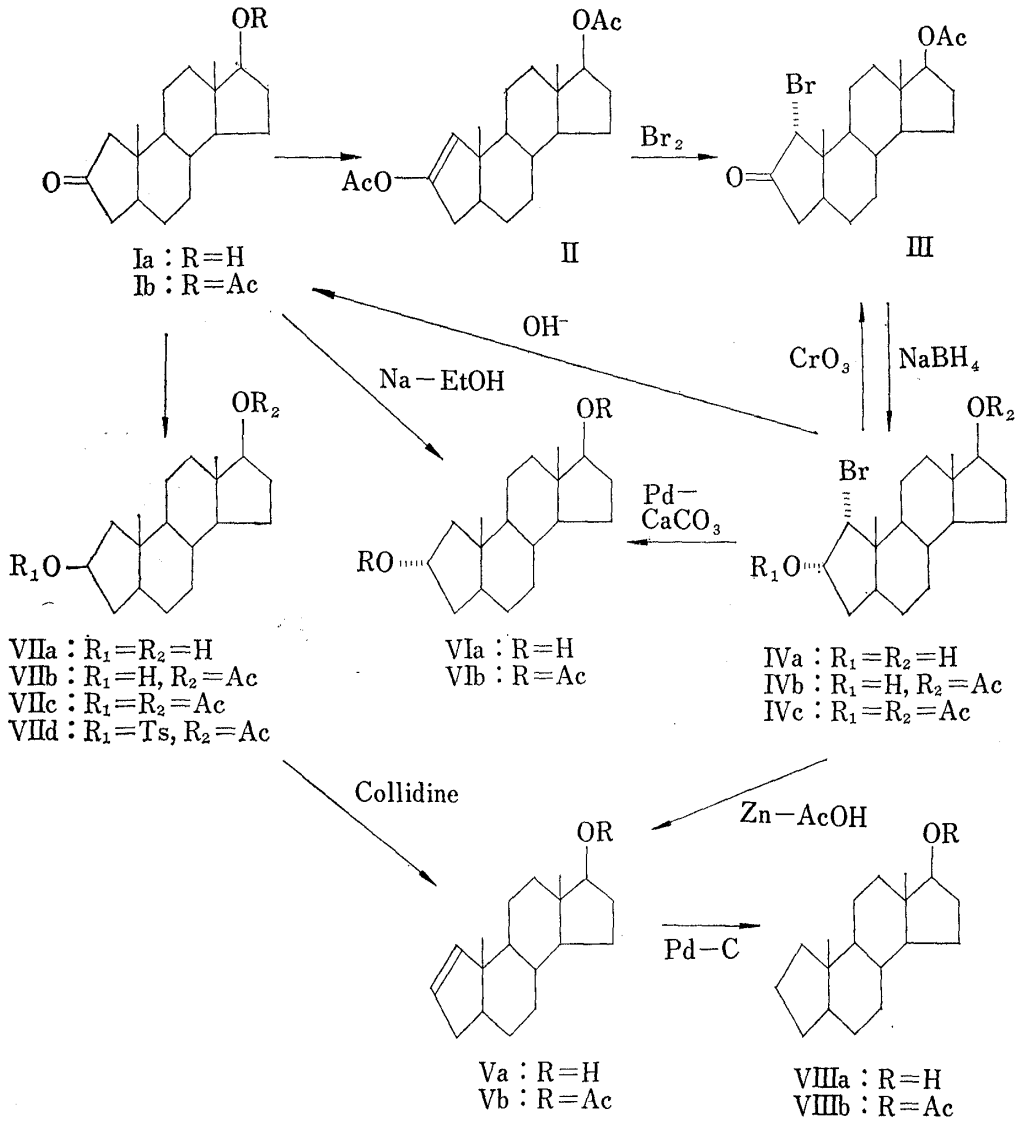

Chart 1.

hydrolysis and into III by oxidation with chromic anhydride in acetic acid. Furthermore, hydrogenation of the diacetate (IVc) over palladium-calcium carbonate led to the known 2α,17β-diacetoxy-A-nor-5α-androstane[8] (VIb). The structure of the *trans*-isomer was confirmed by identification with the authentic *trans*-bromohydrin (XIXa) described later.

When either the *cis*-bromohydrin (IVb) or a mixture with the *trans*-isomer (XIXa) was refluxed with zinc and acetic acid, 17β-acetoxy-A-nor-5α-androst-1-ene (Vb) was obtained in good yield. The over-all yield from the 2-ketone (Ib) was 45%. The olefin (Vb) was converted by saponification of the 17β-acetoxy group with methanolic potassium hydroxide into the 17β-hydroxy (Va) and by catalytic reduction on palladium-charcoal into 17β-acetoxy-A-nor-5α-androstane[9] (VIIIb) which was also obtained from Ia by the Wolff-Kishner reduction followed by acetylation.

Another route to the desired olefin involved the elimination of 2β-tosylate, according to a procedure reported[10] by Huffman for preparation of the Δ^{16}-olefin. The 2-ketone (Ib) was converted into A-nor-5α-androstane-2β,17β-diol 17-acetate (VIIb) by lithium

8) J. Jacques, M. Minssen, D. Varech : Bull. soc. chim. France, **1964**, 77.
9) E. Caspi, S.K. Malhota, Y. Shimizu, K. Maheshwari, M.J. Gasic : Tetrahedron, **22**, 595 (1966).
10) M.N. Huffman, M.H. Lott, A. Tillotson : J. Biol. Chem., **217**, 103 (1955).

tri-*tert*-butoxyaluminum hydride reduction followed by purification with preparative thin-layer chromatography (TLC). Treatment of Ⅶb with *p*-toluenesulfonyl chloride in pyridine afforded the tosylate (Ⅶd) which on boiling with collidine yielded the above-mentioned olefin (Vb) in an over-all yield of 23%.

The olefin (Vb) thus prepared was treated with *m*-chloroperbenzoic acid leading to an epoxide, whose structure was assigned to have 1α,2α-configuration assuming a rear side attack of the reagent toward the double bond. In order to clarify this assignment, reductive cleavage of the epoxide was carried out with lithium aluminum hydride. The formed single diol, m.p. 177~179°, $[\alpha]_D$ +36°, was converted by oxidation with chromic anhydride in acetic acid into the corresponding diketone which, on reduction with lithium aluminum hydride, gave another diol, m.p. 187~188°, $[\alpha]_D$ −21°. These two diols, however, differed from the known 2α,17β-diol[11] (Ⅵa) or 2β,17β-diol[11] (Ⅷa) and

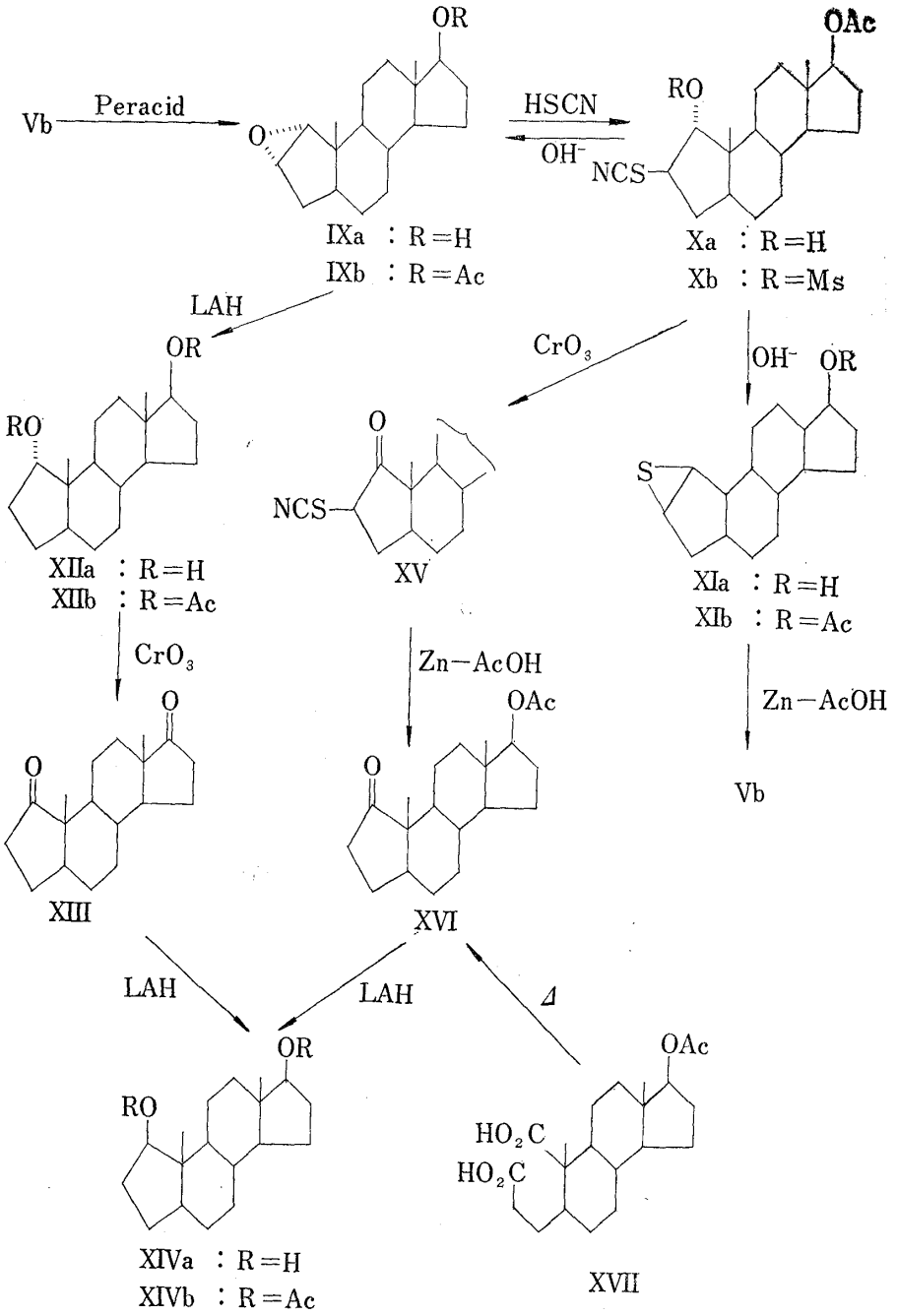

Chart 2.

11) M. Minssen, J. Jacques : Bull. soc. chim. France, **1964**, 71.

hence should be the unknown epimers with respect to the C-1 hydroxy group. Hereupon, the unknown 1,17β-diol was synthesized, using 17β-acetoxy-A-nor-5α-androstan-1-one (XVI). This ketone, prepared by pyrolysis of 1,2-seco-17β-acetoxy-5α-androstane-1,2-dioic acid (XVII), was reduced with lithium aluminum hydride to give a single 1ξ,17β-diol, identical with the above-mentioned diol, m.p. 187~188°. Shoppee reported[12] that reduction of A-norcholestan-1-one with lithium aluminum hydride, sodium in alcohol or hydrogen-platinum in acetic acid gave 1β-hydroxy-A-norcholestane. In view of this fact, it was assumed that the diol, m.p. 187~188°, derived from the 1-ketones should be A-nor-5α-androstane-1β,17β-diol (XIVa) and therefore the epimeric diol, m.p. 177~179°, derived from the epoxide could be the 1α,17β-diol (XIIIa). The C-1 proton in the NMR spectra of the diacetate (XIVb) appeared as a quartet like signal centered at 5.38τ overlapping with that of the C-17 proton, suggesting the 1β-acetoxy structure, while the same proton in XIIIb was shown as a doublet at 5.15τ (J=6.6 c.p.s.), indicating the 1α-acetoxy configuration in a half chair conformation of the A-nor ring by using Karplus' correlation.[13] The correctness of the structure of XIVa was thus established by identification with an authentic sample of the 1β,17β-diol resulted from reductive cleavage of the 1β,2β-epoxide (XXb) described later. With establishment of the structure of XIIIa, the parent epoxide was determined to be 1α,2α-epoxy-A-nor-5α-androstan-17β-ol acetate (IXb).

When IXb was treated with thiocyanic acid in ether, a thiocyanatohydrin was obtained along with a small amount of a by-product which had the formula of $C_{21}H_{31}O_3NS$. The by-product showed strong absorption bands at 2160 and 2120 cm^{-1} corresponding to an isothiocyanato group in the IR spectrum and thus appeared to belong to an isothiocyanatohydrin.[14] The former thiocyanatohydrin was considered to be 2β-thiocyanato-A-nor-5α-androstane-1α,17β-diol 17-acetate (Xa), since the direction of ring opening of the 1α,2α-epoxide with thiocyanic acid was assumed to be analogous to that[15] of 16α,17α-epoxide. This structure was confirmed by the following reactions. Oxidation of the hydroxy group with chromic anhydride in acetic acid gave the thiocyanatoketone (XV) and then, reductive removal of the thiocyanato function with zinc and acetic acid resulted in the formation of the 1-ketone (XVI), indicating the C-1 hydroxy structure of the parent thiocyanatohydrin (Xa).

In contrast to the episulfides formation[1~3] from 2,3-thiocyanatohydrins in the steroidal A-ring, alkaline treatment of Xa did not lead to the desired β-episulfide (XIa) but regenerated the parent α-epoxide (IXa) besides other two products described later. Thus, Xa was converted into the mesylate (Xb) by treatment with methanesulfonyl chloride in pyridine and subsequent treatment of Xb with methanolic potassium hydroxide led to 1β,2β-epithio-A-nor-5α-androstan-17β-ol (XIa) in good yield, as expected.

The 1α,2α-episulfide was obtained through 1β,2β-epoxide by the same method as described for the preparation of the 1β,2β-episulfide. Treatment of Vb with N-bromosuccinimide and perchloric acid in *tert*-butyl alcohol gave a *trans*-bromohydrin in 50% yield and an unexpected dibromide in 27% yield. The *trans*-bromohydrin on oxidation with chromic anhydride in acetic acid gave III and on acetylation followed by hydrogenation over palladium-calcium carbonate afforded the known 2β,17β-diacetoxy compound[8] (VIIc) accompanied by VIIIb. From the above results, the *trans*-bromohydrin was defined as 1α-bromo-A-nor-5α-androstane-2β,17β-diol 17-acetate (XIXa). The above-mentioned dibromide was also obtained by bromination of Vb and assumed to possess the

12) C.W. Shoppee, S.K. Roy, B.S. Goodrich : J. Chem. Soc., **1961**, 1583.
13) *a*) M. Karplus : J. Phys. Chem., **31**, 11 (1959). *b*) M. Karplus : J. Am. Chem. Soc., **85**, 2870 (1963).
14) D. Satoh, M. Horie, J. Morita : This Bulletin, **14**, 613 (1966).
15) T. Komeno : This Bulletin, **8**, 680 (1960).

1α,2β-*trans*-structure formulated as XVIII. This assumption was confirmed by the following NMR spectral data. The dibromide as well as the *trans*-bromohydrin (XIXa) exhibited the NMR signal as a singlet due to the C-1 proton, as expected for 1α,2β- but not for 1β,2α-disubstituted structure.

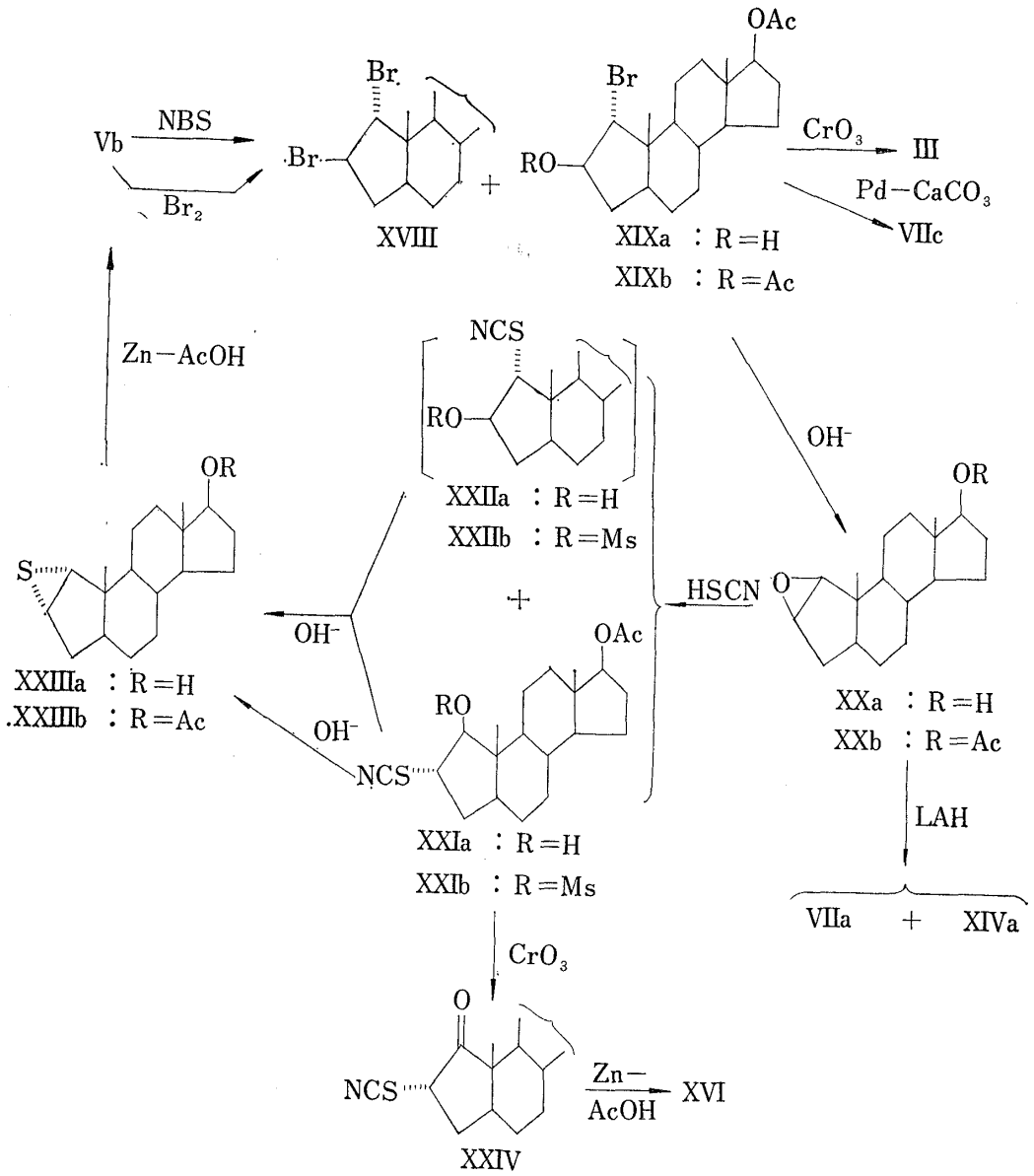

Chart 3.

The action of methanolic potassium hydroxide on XIXa furnished, in good yield, 1β, 2β-epoxy-A-nor-5α-androstan-17β-ol (XXa) as expected. Acetylation of XXa and subsequent treatment with thiocyanic acid in ether afforded a thiocyanatohydrin as an oily product. Crystallization of the product from ether gave only a small amount of crystals (A), m.p. 197~198°, and the residual oil was shown to be a mixture of (A) and another substance (B) on TLC. When the crystalline product (A) and the residual oily mixture, respectively, were submitted to mesylation followed by alkaline treatment, the identical 1α,2α-epithio-A-nor-5α-androstan-17β-ol (XXIIIa) was obtained in high yield. Accordingly, it is apparent that (A) and (B) must be the isomers of *trans*-thiocyanatohydrin with respect to the C-1 and C-2. Determination of the location of respective hydroxy groups was carried out as follows: Oxidation of (A) with chromic anhydride gave the

corresponding thiocyanatoketone which on treatment with zinc in acetic acid led to the 1-ketone (XVI). On the other hand, without isolation of the intermediates, the β-epoxide (XXb) was converted by treatment with thiocyanic acid followed by oxidation with chromic anhydride and finally reduction with zinc in acetic acid into 23% of XVI and 69% of the 2-ketone (Ib). From the above results, it was concluded that the crystalline product (A), m.p. 197~198°, was 2α-thiocyanato-A-nor-5α-androstane-1β,17β-diol 17-acetate (XXIa) and the isomer (B) must be the 1α-thiocyanato-2β-hydroxy structure (XXIIa). It was found, moreover, that reaction of the α-epoxide with thiocyanic acid or lithium aluminum hydride gave the single product with cleavage of the C-2~O bond, (Xa) or (XIIa), respectively, whereas ring opening of the β-epoxide with thiocyanic acid afforded the isomers (XXIa) and (XXIIa) in a ratio of 1:3.

In connection with this finding, it was of interest to examine the hydride cleavage of the β-epoxide. Reductive cleavage of the epoxide (XXb) with lithium aluminum hydride gave a mixture from which two fractions were separated by preparative TLC. The one gave the 2β,17β-diol (VIIa) but the other was still a mixture which on fractional recrystallization afforded the previously obtained 1β,17β-diol (XIVa) as expected.

The 1α,2α- (XXIIIa) and 1β,2β-episulfide (XIa) were prepared from the olefin (Vb) in an over-all yield of 29% and 60%, respectively, and exhibited a band at 259 mμ (ε=62) and 265 mμ (ε=50) in their UV spectra.[16] The acetates (XXIIIb) and (XIb) could be converted into the olefin (Vb) by treatment with zinc in acetic acid. The NMR spectral signals of the C-1 and C-2 protons in the epoxides and episulfides were respectively in agreement with the pattern for the steroidal 16,17-epoxides and -episulfides reported by Tori.[17]

As mentioned above, alkaline treatment of Xa gave two unknown products, 26.6% of XXVa and 47.7% of XXVIa, and 23.5% regeneration of the α-epoxide (IXa). Acetylation of the unknown products afforded the respective triacetate (XXVb) and tetraacetate (XXVIb). The former showed characteristic absorption bands at 234 mμ (ε=4410) in the UV and at 1692 cm^{-1} in the IR spectrum, as expected for a -S-Ac group,[18] which lacks in the latter. From the above spectral data and the molecular weight measurements, these substances were concluded to be 2β-mercapto-A-nor-5α-androstane-1α,17β-diol (XXVa) and the corresponding disulfide (XXVIa).

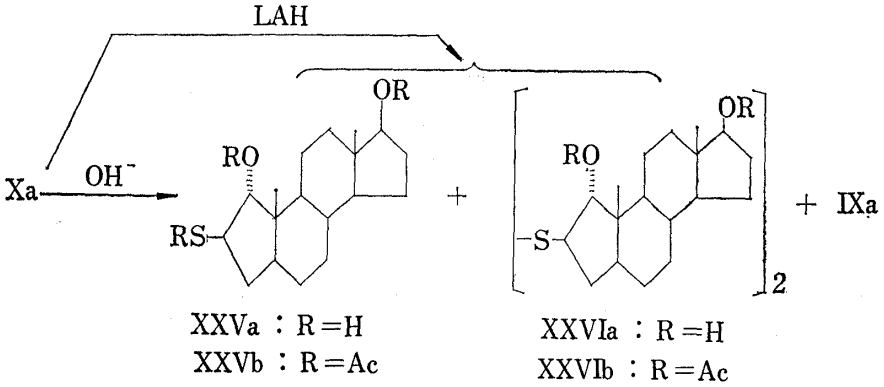

Chart 4.

For the purpose of identification of XXVa, Xa was reduced with lithium aluminum hydride to give 73% of the mercaptol[1] accompanied by 21.8% of the disulfide. These

16) T. Komeno : This Bulletin, 8, 672 (1960).
17) K. Tori, T. Komeno, T. Nakagawa : J. Org. Chem., **29**, 1136 (1964).
18) T. Komeno : This Bulletin, 8, 668 (1960).

two compounds were identical with the respective samples obtained by alkaline treatment of Xa. The formation of the disulfide (XXVIa) under reductive condition is believed to be caused by further oxidation of the mercaptol (XXVa) in the isolating process from the reaction mixture. The physiological properties of the episulfides will be discussed elsewhere.

Experimental

All melting points were determined in capillary tube and uncorrected. Optical rotations were measured in dioxane solutions at *ca.* 25°. Unless otherwise stated, IR spectra were recorded in Nujol mull with a NaCl prism and UV spectra in 95% EtOH solutions. NMR spectra were determined at 60 Mc in $CDCl_3$ solutions containing tetramethylsilane as an internal standard. ORD curves were run in MeOH solutions.

Absorbents——Merck Silica Gel 0.2~0.5 mm. was used for column chromatography and for thin-layer chromatography, Merck Silica Gel G according to Stahl was used.

17β-Acetoxy-A-nor-5α-androstan-2-one (Ib)——The 2-ketone (Ib) was prepared by pyrolysis[11] of 2,3-seco-17β-acetoxy-5α-androstane-2,3-dioic acid and showed the following constants: m.p. 114~115°, $[\alpha]_D$+133° (c=0.50). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1744,1246 (CO, OAc),[19] 1412 (CH_2). UV λ_{max} mμ (ε): 294 (36). ORD (c=0.019): $[\phi]_{314.5}$+12867, $[\phi]_{277.5}$−13263.

2,17β-Diacetoxy-A-nor-5α-androst-1-one (II)——To a solution of Ib (13.9 g.) in isopropenyl acetate (200 ml.), the catalyst solution (5 ml. of isopropenyl acetate and 0.1 ml. of conc. H_2SO_4) was added and approximately 100 ml. of the solvent was distilled over a period of 2 hr. An additional isopropenyl acetate (100 ml.) containing the catalyst solution (2.5 ml.) was added and the solvent of the reaction mixture was concentrated to one-half of its volume by slow distillation over another 2 hr. The solution was extracted with petr. ether and the organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated. The crystalline residue was chromatographed on silica gel (250 g.). The fractions (11.38 g.) eluted with petr. ether–benzene (1:1) and benzene were recrystallized from MeOH giving II (9.61 g., 61%) as plates, m.p. 122~124° The analytical sample was obtained by further recrystallization from the same solvent and melted at 123.5~125°. $[\alpha]_D$+42° (c=1.08). IR ν_{max} cm^{-1}: 3075, 1646, 848 (double bond), 1753, 1745, 1252 (OAc). NMR τ: 4.40 (singlet, C-1 H). *Anal.* Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.16; H, 8.96.

The next fractions (3.362 g.) eluted with benzene–$CHCl_3$ (9:1 to 1:1), on recrystallization from *n*-hexane, recovered the starting material (Ib) (2.49 g., 17.9%) as plates, m.p. 105~110°.

1α-Bromo-17β-acetoxy-A-nor-5α-androstan-2-one (III)——To a solution of II (1.081 g.) in CCl_4 (60 ml.), a solution of Br_2 (480 mg.) in $CHCl_3$ (10 ml.) was added dropwise with stirring over 10 min. at −10° and the solution was stirred at the same temperature for 20 min. Removal of the solvent under reduced pressure afforded a crystalline residue which was recrystallized from MeOH giving plates (783 mg.) of III, m.p. 152~153°. Concentration of the mother liquor afforded the second crop (231 mg.), m.p. 142~145°. 85% yield. Further recrystallization of the first crop from MeOH provided the analytical sample with the following constants: m.p. 153~154°. $[\alpha]_D$+85° (c=1.02). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1754 (CO), 1742, 1245 (OAc), 1414 (CH_2). UV λ_{max} mμ (ε): 315 (93). NMR τ: 6.12 (singlet, C-1 H). ORD (c=0.056): $[\phi]_{348.5}$+4321, $[\phi]_{307}$−549. *Anal.* Calcd. for $C_{20}H_{29}O_3Br$: C, 60.45; H, 7.36; Br, 20.11. Found: C, 60.34; H, 7.41; Br, 19.91.

Reduction of III with Sodium Borohydride——To a solution of III (150 mg.) in EtOH (16 ml.), $NaBH_4$ (30 mg.) was added in several portions with stirring at room temperature. After 1 hr. a few drops of dil. HCl were added to decompose the excess reagent. The mixture was extracted with AcOEt and the organic solution was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated. The residue was separated by preparative TLC (benzene–AcOEt=3:1) into the more mobile fraction (11 mg., 7.3%) and the less mobile fraction (129 mg., 85.5%). Recrystallization of the major fraction from acetone–petr. ether gave plates (54 mg.) of 1α-bromo-A-nor-5α-androstane-2α,17β-diol 17-acetate (IVb), m.p. 119~121°. $[\alpha]_D$+78° (c=0.53). IR ν_{max} cm^{-1}: 3500 (OH), 1739, 1254, 1248 (OAc). *Anal.* Calcd. for $C_{20}H_{31}O_3Br$: C, 60.15; H, 7.82; Br, 20.01. Found: C, 60.42; H, 7.89; Br, 19.93. Concentration of the mother liquor gave the second crop (38 mg.), m.p. 116~120°.

The minor fraction, on recrystallization from acetone–*n*-hexane, afforded the plates, m.p. 126~127°, identical with the *trans*-bromohydrin (XIXa) described later by the IR comparison and a mixed melting point determination.

Reduction of III with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (50 mg.) in dry tetrahydrofuran (2 ml.), a solution of III (100 mg.) in dry tetrahydrofuran (2 ml.) was added dropwise with stirring at room temperature. The reaction mixture was stirred for additional 1 hr. and decomposed by careful addition of a small portion of H_2O and dil.HCl. After extraction with AcOEt, the extract was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to dryness. Purification of the residue by preparative TLC (benzene–AcOEt=1:3) gave crystals which were recrystallized from acetone yielding 1α-bromo-A-nor-5α-androstane-2α,17β-diol (IVa) (64 mg.) as plates, m.p. 196~197° (decomp.). $[\alpha]_D$+88° (c=0.60). IR

19) K. Yoshida, T. Kubota: This Bulletin, **13**, 165 (1965).

ν_{max} cm^{-1} : 3320 (OH). *Anal.* Calcd. for $C_{18}H_{29}O_2Br$: C, 60.50; H, 8.18; Br, 22.36. Found : C, 60.65; H, 8.23; Br, 22.44.

1α-Bromo-A-nor-5α-androstane-2α,17β-diol Diacetate (IVc)——a) From the diol (Ⅳa). A solution of Ⅳa (190 mg.) in Ac_2O (1 ml.) and pyridine (2 ml.) was allowed to stand at room temperature overnight and extracted with ether. The ethereal solution was washed with dil.HCl, 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from petr. ether yielding Ⅳc (201 mg.) as needles, m.p. 118～119°, $[\alpha]_D$ −2° (c=1.04). IR ν_{max} cm^{-1} : 1742, 1240 (OAc). NMR τ : 5.47 (doublet, J=5.4 c.p.s., C-1 H). *Anal.* Calcd. for $C_{22}H_{33}O_4Br$: C, 59.86; H, 7.54; Br, 18.10. Found : C, 60.10; H, 7.74; Br, 18.20.

b) From the 17β-acetate (Ⅳb). The Ⅳb was acetylated with Ac_2O in pyridine in the same manner as described above, giving the above-mentioned diacetate (Ⅳc) in quantitative yield.

Alkaline Treatment of IVb——A mixture of Ⅳb (132 mg.) dissolved in MeOH (20 ml.) and KOH (200 mg.) was heated to reflux during 2 hr. The cooled solution was extracted with AcOEt and the extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Recrystallization from MeOH gave plates (71 mg.) of 17β-hydroxy-A-nor-5α-androstan-2-one (Ia), m.p. 193～194°, $[\alpha]_D$ +169° (c=1.00) (reported[20] m.p. 195～196.5°, $[\alpha]_D$ +174°). IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3620 (OH), 1746 (CO), 1408 (CH_2).

Oxidation of IVb with Chromic Anhydride——To a solution of Ⅳb (33 mg.) in AcOH (1 ml.), a solution of CrO_3 (11 mg.) in H_2O (0.2 ml.) was added and the solution was allowed to stand at room temperature for 20 hr. After extraction with AcOEt, the organic layer was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated. The crystalline residue was recrystallized from MeOH yielding plates (22 mg.), m.p. 153～154°, identical with a specimen of the bromoketone (Ⅲ) described above by the IR comparison and a mixed melting point determination.

Hydrogenation of IVc with Palladium-Calcium Carbonate——The bromohydrin (Ⅳc) (50 mg.) in EtOH (10 ml.) was hydrogenated on Pd-$CaCO_3$ (250 mg.) in H_2 for 15 hr. After removal of the catalyst by filtration, the filtrate was extracted with AcOEt. The organic solution was washed with dil.HCl, 5% $NaHCO_3$ and H_2O, dried and evaporated. The residue was purified by preparative TLC (benzene-AcOEt=10:1) giving a crystalline product (39 mg.) which on recrystallization from petr. ether gave 2α,17β-diacetoxy-A-nor-5α-androstane (Ⅵb) (35 mg.) as plates, m.p. 140.5～141°, $[\alpha]_D$ 0° (c=1.06) (reported[8] m.p. 135～136°, $[\alpha]_D$ 0°). IR ν_{max} cm^{-1}: 1739, 1730, 1250 (OAc).

This compound was identical with a sample of the diacetate (Ⅵb) prepared by reduction of the 2-ketone (Ib) with Na and EtOH[11] followed by acetylation with Ac_2O in pyridine.

A-Nor-5α-androstane-2β,17β-diol (VIIa), the 17-Acetate (VIIb) and the Diacetate (VIIc)——A mixture of Ib (350 mg.) and LiAl (*tert*-$BuO)_3H$ (700 mg.) in tetrahydrofuran (14 ml.) was stirred at room temperature for 16 hr. and decomposed by addition of a small portion of dil.HCl. After extraction with AcOEt, the extract was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated to give a crystalline residue. Purification by preparative TLC (benzene-AcOEt=3:1) gave crystals (281 mg.) which on recrystallization from *n*-hexane afforded Ⅶb (269 mg., 76.4%) as needles, m.p. 164～165°. $[\alpha]_D$ +3° (c=1.02). IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3620 (OH), 1740, 1249 (OAc). *Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found : C, 74.68; H, 10.10.

The Ⅶb was acetylated with Ac_2O in pyridine by standing at room temperature overnight. The product, isolated in the usual way, was recrystallized from acetone giving Ⅶc as plates in quantitative yield, m.p. 156～157°. $[\alpha]_D$ +1° (c=0.58) (reported[8] m.p. 156°, $[\alpha]_D$ +1°). IR ν_{max} cm^{-1} : 1741, 1240 (OAc).

The Ⅶb was saponified by refluxing with methanolic NaOH, yielding Ⅶa as needles (from acetone), m.p. 207～208°, $[\alpha]_D$ +10° (c=1.05) (reported[11] m.p. 215～216°, $[\alpha]_D$ +10°). IR ν_{max} cm^{-1} : 3365 (OH). This compound was identical with a sample of the 2β,17β-diol (Ⅶa) obtained by reductin of Ia with $LiAlH_4$ by a mixed melting point and the IR comparison.

2β-Tosyloxy-A-nor-5α-androstan-17β-ol Acetate (VIId)——To a solution of Ⅶb (259 mg.) in pyridine (10 ml.), *p*-toluenesulfonyl chloride (500 mg.) was added in several portions under cooling. The solution was allowed to stand at room temperature for 3 days, poured into iced H_2O and extracted with AcOEt. The organic solution was washed with dil.HCl, 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated leaving a crystalline residue. Purification by preparative TLC (benzene-AcOEt=15:1) gave crystals which on recrystallization from acetone afforded Ⅶd (204 mg., 53.1%) as plates, m.p. 175～175.5°, $[\alpha]_D$ +3° (c=0.51). IR ν_{max} cm^{-1}; 1740, 1598, 1359, 1245, 1169, 817. *Anal.* Calcd. for $C_{27}H_{38}O_5S$: C, 68.32; H, 8.07; S, 6.76. Found : C, 68.49; H, 8.20; S, 6.56.

A-Nor-5α-androst-1-en-17β-ol (Va) and the Acetate (Vb)——a) From the bromohydrin (Ⅳb). To a solution of Ⅳb (201 mg.) in AcOH (10 ml.), Zn dust (360 mg.) was added with stirring and the mixture was refluxed for 2 hr. After cooling, the Zn dust was removed by filtration and the filtrate was extracted with ether. The ethereal solution was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated. The resulting semisolid was chromatographed over silica gel (2.5 g.). Elution with petr. ether-benzene (8:2) gave a crystalline material (143 mg.) which on recrystallizatiion from MeOH afforded Vb (121 mg.) as long needles, m.p. 81～82°, $[\alpha]_D$ +28° (c=1.01). IR ν_{max} cm^{-1} : 3049, 1588, 725 (double bond), 1740, 1242 (OAc). UV $\lambda_{max}^{CH_3CN}$ mμ (ε) : 195 (10,700). NMR τ : 4.03 (quartet, $J_{1,2}$=6 c.p.s., $J_{1,3}$=1.5 c.p.s., C-1 H), 4.30 (sextet, $J_{2,1}$=6 c.p.s., $J_{2,3}$=2 c.p.s., C-2 H). *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found : C, 79.50; H, 10.00.

20) F.L. Weisenborn, H.E. Applegate : J. Am. Chem. Soc., **81**, 1960 (1959).

The olefin (Vb) was also prepared from III by reduction with $NaBH_4$ followed by treatment with Zn and AcOH in 86.3% yield without isolation of the bromohydrins.

A solution of Vb (26 mg.) in MeOH (5 ml.) and KOH (50 mg.) was refluxed for 1 hr. in a stream of N_2. The product, isolated in the usual manner, was recrystallized from *n*-hexane yielding needles (18 mg.) of Va, m.p. 131~133°. $[\alpha]_D$ +30° (c=0.61). IR ν_{max} cm^{-1} : 3300 (broad) (OH), 3050, 1590, 723 (double bond). *Anal.* Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found : C, 82.78; H, 10.94.

b) From the 2β-tosylate (VIId). A solution of VIId (66 mg.) in collidine (6 ml.) was heated to reflux during 2 hr. The cooled solution was extracted with ether and the ether layer was washed with dil.HCl, 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4. Removal of the solvent gave a crystalline residue which on recrystallization from MeOH gave Vb (24 mg., 57.1%) as needles, m.p. 73~75°. Further recrystallization from the same solvent raised the melting point to 78~79°. Identity with the above-mentioned olefin was established by the IR spectra and mixed melting point determination.

A-Nor-5α-androstan-17β-ol (VIIIa) and the Acetate (VIIIb)——a) From the 2-ketone (Ib). The Ib (1 g.) was refluxed for 1 hr. in ethylene glycol (24 ml.) with 80% hydrazine hydrate (2.4 ml.). To the cooled solution KOH (2 g.) was added and the mixture was distilled until the vapor temperature reached 180°. The reflux was continued for additional 3 hr. The cooled reaction mixture was extracted with AcOEt and the organic solution was washed with H_2O, dried and evaporated. The residue was recrystallized from MeOH giving VIIIa (456 mg.) as needles, m.p. 140~142°. Purification of the mother liquor by column chromatography on silica gel gave the additional crop (215 mg.), m.p. 140~142°. Further recrystallization from MeOH provided the analytical sample of VIIIa, m.p. 142~143°, $[\alpha]_D$ +5° (c=1.04) (reported[8] m.p. 142°, $[\alpha]_D$ +5°). IR ν_{max} cm^{-1} : 3280, 3200 (OH).

b) From the olefin (Vb). The Vb (200 mg.) in MeOH (10 ml.) and AcOEt (10 ml.) was hydrogenated over 5% Pd-C (200 mg.) for 30 min. After removals of the catalyst and the solvent, the residue was recrystallized from MeOH yielding plates (130 mg.), m.p. 82~84°. Further recrystallization from the same solvent gave VIIIb as long plates, m.p. 86~87° (reported[9] m.p. 86.5~87.5°). $[\alpha]_D$ +1° (c=1.01). IR ν_{max} cm^{-1} : 1743, 1255 (OAc).

A solution of VIIIb (158 mg.) in MeOH (9 ml.) and 20% NaOH (1 ml.) was refluxed for 30 min. The product, isolated in the usual way, was twice recrystallized from MeOH giving the above-mentioned VIIIa (53 mg.) as needles, m.p. 140~142°.

1α,2α-Epoxy-A-nor-5α-androstan-17β-ol (IXa) and the Acetate (IX)——To a solution of the olefin (Vb) (3.36 g.) in $CHCl_3$ (30 ml.), a solution of 0.0122*M* of *m*-chloroperbenzoic acid in $CHCl_3$ (50 ml.) was added dropwise with stirring at 5°. The solution was allowed to stand at room temperature for 48 hr. and diluted with ether. The ethereal solution was washed with 10% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel (55 g.). The eluates (130 mg.) eluted with petr. ether–benzene (1:1) were recrystallized from MeOH yielding the unchanged starting material (60 mg.), m.p. 72~76°.

The further eluates (3.34 g.) eluted with petr. ether–benzene (1:1) and benzene–$CHCl_3$ (1:1), on recrystallization from *n*-hexane, gave IXb (3.14 g., 88.5%) as needles, m.p. 136~137°, $[\alpha]_D$ +4° (c=1.05). IR ν_{max} cm^{-1}: 1722, 1255 (OAc), 847 (epoxy). *Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found : C, 75.63; H, 9.61.

The IXb (115 mg.) was refluxed with a solution of K_2CO_3 (150 mg.) in 90% MeOH (15 ml.) for 2hr. After working up in the usual way, the product was recrystallized from MeOH affording prisms (80 mg.) of IXa, m.p. 178~179°. $[\alpha]_D$ 0° (c=1.04). IR ν_{max} cm^{-1} : 3440 (OH), 837 (epoxy). *Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found : C, 78.38; H, 10.26.

A-Nor-5α-androstane-1α,17β-diol (XIIa) and the Diacetate (XIIb)——To a suspension of $LiAlH_4$ (300 mg.) in dry tetrahydrofuran (15 ml.), a solution of IXb (300 mg.) in dry tetrahydrofuran (15 ml.) was added dropwise with stirring at room temperature and the mixture was refluxed for 7 hr. After cooling, a small portion of H_2O and dil. HCl was added carefully to decompose the complex. The product, isolated by extraction with AcOEt, was recrystallized from acetone giving XIIa (203 mg., 77.5%) as needles, m.p. 177~179°. $[\alpha]_D$ +36° (c=0.54). IR ν_{max} cm^{-1} : 3420 (OH). *Anal.* Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found : C, 77.55; H, 10.67.

Acetylation of XIIa with Ac_2O in pyridine at room temperature overnight yielded, following the usual work-up, XIIb as needles (from dil.MeOH), m.p. 104~105°, $[\alpha]_D$ +34° (c=0.60). IR ν_{max} cm^{-1} : 1730, 1255 (OAc). NMR τ : 5.15 (doublet, J=6.6 c.p.s., C-1 H). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found : C, 73.03; H, 9.51.

A-Nor-5α-androstane-1,17-dione (XIII)——A mixture of XIIa (90 mg.) in AcOH (10 ml.) and CrO_3 (60 mg.) in H_2O (1 ml.) was left aside at room temperature for 20 hr. The reaction mixture was extracted with AcOEt and the organic layer was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated to dryness. Recrystallization from acetone–petr. ether afforded XIII (70 mg., 79%) as plates, m.p. 156~157°. $[\alpha]_D$ +71° (c=0.61). IR ν_{max} cm^{-1} : 1730 (CO). *Anal.* Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found : C, 79.05; H, 9.51.

1,2-Seco-17β-acetoxy-5α-androstane-1,2-dioic Acid (XVII)——The dioic acid (XVII) was prepared from 17β-acetoxy-5α-androst-1-ene[21] (m.p. 124~126°) in the manner reported for the preparation of

21) A. Bowers, A.D. Cross, J.A. Edwards, H. Carpio, M.C. Calzada, E. Denot : J. Med. Chem., **6**, 156 (1963).

1,2-seco-5α-cholestane-1,2-dioic acid by Shoppee[12] and showed the following constants: m.p. 220~222°, $[\alpha]_D$ +1° (c=1.00). *Anal.* Calcd. for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.43; H, 8.60.

17β-Acetoxy-A-nor-5α-androstan-1-one (XVI)——A solution of XVII (1.29 g.) in Ac_2O (10 ml.) was refluxed for 1 hr. and then heated slowly to 250°, distilling off the excess Ac_2O. The residual oil was distilled at 270~280° at 5 mm. pressure. The distillate was recrystallized from MeOH giving XVI (540 mg.) as plates, m.p. 163~165°. Purification by preparative TLC (benzene-AcOEt=10:1) raised the melting point to 167~168°. $[\alpha]_D$ −6° (c=0.51). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1739, 1247 (OAc), 1408 (CH_2). ORD (c=0.058): $[\phi]_{323.5}$ −3540, $[\phi]_{282}$ +4726. *Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.38; H, 9.78.

A-Nor-5α-androstane-1β,17β-diol (XIVa) and the Diacetate (XIVb)——a) From the 1-ketone (XVI). To a suspension of $LiAlH_4$ (80 mg.) in dry tetrahydrofuran (5 ml.), a solution of XVI (80 mg.) in dry tetrahydrofuran (5 ml.) was added dropwise with stirring. The mixture was stirred at room temperature for 1 hr. The product was isolated in the usual manner and recrystallized from acetone yielding XIVa (55 mg., 78.5%) as needles, m.p. 187~188°, $[\alpha]_D$ −21° (c=0.55). IR ν_{max} cm^{-1}: 3304 (OH). *Anal.* Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.76; H, 10.95.

Acetylation of XIVa with Ac_2O in pyridine at room temperature overnight gave XIVb as square plates (from petr. ether), m.p. 142~143°, in quantitative yield. $[\alpha]_D$ −28° (c=0.56). IR ν_{max} cm^{-1}: 1738 (shoulder), 1733, 1255 (OAc). NMR τ: 5.38 (quartet like signal overlapping with C-17 H from 5.21 τ to 5.55τ, C-1 H). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.10; H, 9.41.

b) From the diketone (XIII). A solution of XIII (36 mg.) in dry tetrahydrofuran (2 ml.) was treated with $LiAlH_4$ (36 mg.) in dry tetrahydrofuran (2 ml.) in the same manner as described above, The product was recrystallized from acetone giving the above-mentioned diol (XIVa) (31 mg., 84.9%) as needles, m.p. 187~188°, which was identified by a mixed melting point determination and the IR comparison.

2β-Thiocyanato-A-nor-5α-androstane-1α,17β-diol 17-Acetate (Xa)——To a solution of Xb (1.08 g.) in ether (90 ml.), the thiocyanic acid solution[2] prepared from KSCN (6.6 g.), H_3PO_4 (9.9 g.) and ether (30 ml.) was added and the solution was allowed to stand at room temperature for 70 hr. The ethereal solution was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated to dryness. The product was recrystallized from MeOH giving Xa (934 mg.) as plates, m.p. 220~222°. Concentration of the mother liquor afforded the second crop (171 mg.), m.p. 217~220°. Purification of the first crop by preparative TLC (benzene-AcOEt =3:1) raised the melting point to 223~224.5°. $[\alpha]_D$ +22° (c=1.03). IR ν_{max} cm^{-1}: 3480 (OH), 2150 (-SCN), 1710, 1275 (OAc). *Anal.* Calcd. for $C_{21}H_{31}O_3NS$: C, 66.80; H, 8.28; N, 3.71; S, 8.49. Found: C, 66.51; H, 8.41; N, 3.94; S, 8.29.

In another experiment, the crude product of the thiocyanatohydrin was separated by preparative TLC (benzene-AcOEt=3:1) into two fractions. The less mobile fraction (90%) gave the above-mentioned Xa. The more mobile fraction (9%) was recrystallized from MeOH yielding needles, m.p. 178~179°. $[\alpha]_D$ −112° (c= 0.50). IR ν_{max} cm^{-1}: 3510, 3460 (OH), 2160, 2120 (-NCS), 1716, 1273 (OAc). *Anal.* Calcd. for $C_{21}H_{31}O_3NS$: C, 66.80; H, 8.28; N, 3.71; S, 8.49. Found: C, 66.74; H, 8.41; N, 3.80; S, 8.48. This compound was assumed to be 2β-isothiocyanato-A-nor-5α-androstane-1α,17β-diol 17-acetate.

2β-Thiocyanato-17β-acetoxy-A-nor-5α-androstan-1-one (XV)——A mixture of Xa (150 mg.) in AcOH (20 ml.) and CrO_3 (50 mg.) in H_2O (1 ml.) was allowed to stand at room temperature for 20 hr. and then extracted with AcOEt. The extract was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated leaving a residue. Recrystallization from MeOH gave XV (128 mg.) as needles, m.p. 161~163°. $[\alpha]_D$ −84° (c=0.59). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2165 (-SCN), 1746 (CO), 1730 (OAc). NMR τ: 6.45 (multiplet, C-2 H). *Anal.* Calcd. for $C_{21}H_{29}O_3NS$: C, 67.16; H, 7.78; N, 3.73; S, 8.54. Found: C, 67.34; H, 7.82; N, 3.82; S, 8.69.

Treatment of XV with Zinc and Acetic Acid——A mixture of XV (33 mg.) in AcOH (2 ml.) and Zn dust (165 mg.) was refluxed for 1 hr. After cooling, the Zn dust was filtered off and the filtrate was diluted with AcOEt. The organic solution was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated to dryness. Recrystallization from dil.MeOH gave needles (22 mg.), m.p. 167~168°, identical with an authentic sample of the 1-ketone (XVI) by the IR and a mixed melting point determination.

1α-Mesyloxy-2β-thiocyanato-A-nor-5α-androstan-17β-ol Acetate (Xb)——To a solution of Xa (100 mg.) in pyridine (2 ml.), methanesulfonyl chloride (0.2 ml.) was added under cooling. The reaction mixture was allowed to stand at room temperature overnight, poured into iced H_2O and extracted with AcOEt. The organic solution was washed with dil.HCl, 5% $NaHCO_3$ and H_2O, dried and evaporated. The residue was recrystallized from acetone-petr. ether yielding Xb (100 mg., 82.8%) as plates, m.p. 144~146°. $[\alpha]_D$ −27° (c= 0.58). IR ν_{max} cm^{-1}: 2168 (-SCN), 1727, 1250 (ester). *Anal.* Calcd. for $C_{22}H_{33}O_5NS_2$: C, 57.99; H, 7.30; N, 3.07; S, 14.08. Found: C, 58.01; H, 7.28; N, 3.17; S, 14.11.

1β,2β-Epithio-A-nor-5α-androstan-17β-ol (XIa) and the Acetate (XIb)——A solution of Xb (628 mg.) in MeOH (63 ml.) and KOH (630 mg.) was refluxed for 1 hr. The cooled solution was diluted with ether and the ethereal solution was washed with H_2O and dried (Na_2SO_4). Removal of the solvent gave a crystalline residue which on recrystallization from acetone afforded XIa (314 mg., 78%) as needles, m.p. 169~170°, $[\alpha]_D$ −69° (c=1.03). IR ν_{max} cm^{-1}: 3320 (OH). UV λ_{max} mμ (ε): 265 (50). *Anal.* Calcd. for $C_{18}H_{28}OS$: C, 73.92; H, 9.65; S, 10.96. Found: C, 73.89; H, 9.72; S, 10.99.

Acetylation of XIa was carried out with Ac_2O in pyridine by standing at room temperature overnight and the product was recrystallized from MeOH giving XIb as needles, m.p. 155~156°, in quantitative yield.

$[\alpha]_D$ −74° (c=1.13). IR ν_{max} cm^{-1} : 1740, 1244 (OAc). UV λ_{max} mμ (ε) : 265 (51). *Anal.* Calcd. for $C_{20}H_{30}O_2S$: C, 71.81; H, 9.04; S, 9.59. Found : C, 72.09; H, 9.23; S, 9.59.

The β-episulfide (XIa) was obtained from the α-epoxide (IXb) in an over-all yield of 68% by the successive treatments.

Treatment of XIb with Zinc and Acetic Acid——A mixture of XIb (192 mg.) in AcOH (22 ml.) and Zn dust (2.66 g.) was refluxed with stirring for 3 hr. After cooling, the Zn dust was removed by filtration and the filtrate was extracted with ether. The ethereal layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to dryness. Recrystallization from MeOH gave needles (136 mg.), m.p. 81~82°, which were identified with an authentic sample of the olefin (Vb) by the IR comparison and a mixed melting point determination.

Treatment of the Olefin (Vb) with N-Bromosuccinimide——To a solution of Vb (151 mg.) in 95% *tert*-BuOH (15 ml.), NBS (94 mg.) in 95% *tert*-BuOH (5 ml.) and 1*N* $HClO_4$ (0.75 ml.) were added in succession with stirring at room temperature. The solution was stirred for additional 4 hr. and extracted with ether. The ethereal layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was separated into two fractions by preparative TLC (benzene-AcOEt=10:1). The more mobile fraction (63 mg., 27.3%), on recrystallization from MeOH, gave needles, m.p. 168~172°, identical with a specimen of the 1α,2β-dibromide (XVIII) described in the next experiment by the IR comparison and a mixed melting point determination.

The less mobile fraction (98 mg., 49.3%) was recrystallized from acetone-*n*-hexane giving 1α-bromo-A-nor-5α-androstane-2β,17β-diol 17-acetate (XIXa) (73 mg.) as plates, m.p. 126~127°. $[\alpha]_D$ +60° (c=1.02). IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3600, 3478 (OH), 1738, 1248 (OAc). NMR τ : 6.03 (singlet, C-1 H). *Anal.* Calcd. for $C_{20}H_{31}O_3Br$: C, 60.15; H, 7.82; Br, 20.01. Found : C, 60.38: H, 7.87; Br, 20.14.

1α,2β-Dibromo-A-nor-5α-androstan-17β-ol Acetate (XVIII)——To a solution of Vb (97 mg.) in CCl_4 (8 ml.), Br_2 (56 mg.) in $CHCl_3$ (8 ml.) was added dropwise with stirring under cooling. Removal of the solvent under reduced pressure gave crystals which were recrystallized from petr. ether, yielding XVIII (102 mg.) as needles, m.p. 172~174°. The analytical sample was prepared by recrystallization from the same solvent and melted at 176~177°. $[\alpha]_D$ −4° (c=0.59). IR ν_{max} cm^{-1} : 1736, 1250 (OAc). NMR τ : 5.61 (singlet, C-1 H). *Anal.* Calcd. for $C_{20}H_{30}O_2Br_2$: C, 51.95; H, 6.54; Br, 34.60. Found : C, 52.16; H, 6.71; Br, 34.46.

1α-Bromo-A-nor-5α-androstane-2β,17β-diol Diacetate (XIXb)——A solution of XIXa (69 mg.) in Ac_2O (0.4 ml.) and pyridine (1 ml.) was allowed to stand at room temperature overnight. After working up in the usual way, the product was recrystallized from petr. ether affording XIXb (53 mg.) as plates, m.p. 107~108°. $[\alpha]_D$ +31° (c=0.53). IR ν_{max} cm^{-1} : 1738, 1731, 1250, 1228 (OAC). NMR τ : 6.02 (singlet, C-1 H). *Anal.* Calcd. for $C_{22}H_{33}O_4Br$: C, 59.86; H, 7.54; Br, 18.10. Found : C, 60.14; H, 7.66; Br, 18.05.

Oxidation of XIXa with Chromic Anhydride——A mixture of CrO_3 (15 mg.) in H_2O (0.3 ml.) and XIXa (45 mg.) in AcOH (1.2 ml.) was allowed to stand at room temperature for 20 hr. The product, isolated in the manner described for oxidation of IVb, was recrystallized from MeOH yielding the bromoketone (III) (34 mg.) as plates, m.p. 152~153°. Identity with an authentic sample was established by the IR comparison and a mixed melting point determination.

Hydrogenation of XIXb with Palladium-Calcium Carbonate——The bromohydrin (XIXb) (49 mg.) in EtOH (10 ml.) was hydrogenated on Pd-$CaCO_3$ (250 mg.) in H_2 for 15 hr. The catalyst was filtered off and the filtrate was extracted with AcOEt. After washing of the organic solution with H_2O, removal of the solvent gave a residue which was separated by preparative TLC (benzene-AcOEt=3:1) into two fractions. The more mobile fraction (12 mg.) was recrystallized from MeOH affording VIIIb as plates, m.p. 82~84°. The less mobile fraction (24 mg.) on recrystallization from acetone provided the 2β,17β-diacetate (VIIc) as plates. These two compounds were identified with the respective authentic samples by mixed melting points and IR comparisons.

1β,2β-Epoxy-A-nor-5α-androstan-17β-ol (XXa) and the Acetate (XXb)——A solution of XIXa (192 mg.) in MeOH (30 ml.) and KOH (300 mg.) was refluxed for 2 hr. and diluted with AcOEt. The organic solution was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. Recrystallization from MeOH afforded XXa (115 mg., 86.5%) as plates, m.p. 150~152°. Further recrystallization from MeOH gave the analytical sample of XXa, m.p. 153~154.5°. $[\alpha]_D$ +16° (c=1.06). IR ν_{max} cm^{-1} : 3490 (OH), 835 (epoxy). *Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21: H, 10.21. Found : C, 77.96; H, 10.30.

Acetylation of XXa with Ac_2O in pyridine at room temperature overnight afforded, following the usual work-up, XXb as long plates (from *n*-hexane), m.p. 172~173°, in quantitative yield. $[\alpha]_D$ +7° (c=1.04). IR ν_{max} cm^{-1} : 1730, 1252 (OAc), 838 (epoxy). *Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found : C, 75.55; H, 9.64.

The epoxide (XXb) was obtained from the olefin (Vb) in an over-all yield of 42% by the successive treatments.

Cleavage of the 1β,2β-Epoxide (XXb) with Thiocyanic Acid——The thiocyanic acid solution[2] prepared with KSCN (4.4 g.), H_3PO_4 (6.6 g.) and ether (20 ml.) was added to a solution of XXb (720 mg.) in ether (60 ml.) and the solution was allowed to stand at room temperature for 70 hr. The reaction mixture was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to dryness. The glassy residue (853 mg.) was crystallized by addition of ether giving crystals, m.p. 190~194°, which on recrystallization from acetone-*n*-hexane afforded 2α-thiocyanato-A-nor-5α-androstane-1β,17β-diol 17-acetate (XXIa) (116 mg., 13.6%) as long

plates, m.p. 197～198°. $[\alpha]_D$ +88° (c=0.60). IR ν_{max} cm^{-1} : 3480 (OH), 2155 (-SCN), 1710, 1277 (OAc). *Anal.* Calcd. for $C_{21}H_{31}O_3NS$: C, 66.80; H, 8.28; N, 3.71; S, 8.49. Found : C, 66.94; H, 8.42; N, 3.76; S, 8.61.

Concentration of the combined mother liquors gave an oil (725 mg.) which showed the presence of XXIa and XXIIa besides a few by-products on TLC and could be utilized for preparation of the 1α,2α-episulfide (XXIIIa) described below.

1β-Mesyloxy-2α-thiocyanato-A-nor-5α-androstan-17β-ol Acetate (XXIb)——Methanesulfonyl chloride (0.1 ml.) was added to a solution of XXIa (94 mg.) in pyridine (1 ml.) under cooling and the solution was left aside at room temperature overnight. After pouring into iced H_2O, the solution was extracted with AcOEt and the extract was washed with dil.HCl, 5% $NaHCO_3$ and H_2O, and dried (Na_2SO_4). Removal of the solvent gave a residue which was recrystallized from acetone-*n*-hexane affording XXIb (67 mg.) as rhombes, m.p. 160～161.5°. $[\alpha]_D$ +112° (c=0.55). IR ν_{max} cm^{-1} : 2170 (-SCN), 1735, 1251 (OAc). *Anal.* Calcd. for $C_{22}H_{33}O_5NS_2$: C, 57.99; H, 7.30; N, 3.07; S, 14.08. Found : C, 58.23; H, 7.44; N, 3.02; S, 13.86. Concentration of the mother liquor afforded the second crop (19 mg.), m.p. 156～159°.

1α,2α-Epithio-A-nor-5α-androstan-17β-ol (XXIIIa) and the Acetate (XXIIIb)——a) From the mesylate (XXIb). A solution of XXIb (80 mg.) in MeOH (8 ml.) and KOH (80 mg.) was refluxed for 1 hr. and extracted with ether. The ethereal layer was washed with H_2O, dried over Na_2SO_4 and evaporated leaving crystals. Recrystallization from CCl_4 gave fine needles, m.p. 68～70°, which were dried at 55°/1～2 mm. for 7 hr. giving XXIIIa (38 mg., 74.1%), m.p. 96～97°, $[\alpha]_D$ +59° (c=1.12). IR ν_{max} cm^{-1} : 3310 (OH). UV λ_{max} mμ (ε): 259 (62). *Anal.* Calcd. for $C_{18}H_{28}OS$: C, 73.92; H, 9.65; S, 10.96. Found : C, 74.07; H, 9.89; S, 11.10.

Acetylation of XXIIIa with Ac_2O in pyridine by standing at room temperature overnight gave, after the usual work-up, XXIIIb as scales (from MeOH), m.p. 125～126° in quantitative yield. $[\alpha]_D$ +57° (c=1.08). IR ν_{max} cm^{-1} : 1740, 1241 (OAc). UV λ_{max} mμ (ε) : 259 (68). *Anal.* Calcd. for $C_{20}H_{30}O_2S$: C, 71.81; H, 9.04; S, 9.59. Found : C, 71.88; H, 9.22; S, 9.71.

b) From the mixture of XXIa and XXIIa. The residual oil (725 mg.), described in the cleavage of XXb with HSCN, was treated with methanesulfonyl chloride (0.8 ml.) in pyridine (8 ml.) and subsequently with a solution of KOH (850 mg.) in MeOH (85 ml.) in the above-mentioned manner. The resulting crude product was chromatographed over Al_2O_3 (Woelm. neutral, act II., 15 g.). Elution with petr. ether-benzene (1:1) and recrystallization of the eluates (480 mg.) from CCl_4 afforded fine needles, m.p. 68～70°, which on drying at 55°/1～2 mm. for 7 hr. gave the above-mentioned XXIIIa (422 mg., 75.1%), m.p. 96～97°.

This 1α,2α-episulfide (XXIIIa) was obtained from the β-epoxide (XXb) in an over-all yield of 69% without isolation of the thiocyanatohydrin.

Treatment of XXIIIb with Zinc and Acetic Acid——A mixture of XXIIIb (36 mg.) in AcOH (4 ml.) and Zn dust (500 mg.) was refluxed with stirring for 3 hr. The product, isolated in the manner described for the same treatment of XIb, was recrystallized from MeOH afforded needles (26 mg.), m.p. 81～82°, identical with a specimen of the olefin (Vb) by a mixed melting point determination and the IR comparison.

2α-Thiocyanato-17β-acetoxy-A-nor-5α-androstan-1-one (XXIV)——A mixture of XXIa (67 mg.) in AcOH (6 ml.) and CrO_3 (23 mg.) in H_2O (0.5 ml.) was allowed to stand at room temperature for 20 hr. The product, isolated in the similar manner to the preparation of XV, was recrystallized from acetone giving XXIV (55 mg.) as fine needles, m.p. 200～202°. Further recrystallization from the same solvent raised the melting point to 201～203°. $[\alpha]_D$ +171° (c=0.54). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2180 (-SCN), 1740 (CO), 1726 (OAc). NMR τ: 5.91 (quartet, $J_{2,3}$=7.2 c.p.s., 3.0 c.p.s., C-2 H). *Anal.* Calcd. for $C_{21}H_{29}O_3NS$: C, 67.16; H, 7.78; N, 3.73; S, 8.54. Found : C, 67.40; H, 7.67; N, 3.78; S, 8.73.

Treatment of XXIV with Zinc and Acetic Acid——A mixture of XXIV (33 mg.) in AcOH (2 ml.) and Zn dust (165 mg.) was refluxed for 1 hr. The product, isolated in the manner described for the same treatment of XV, was recrystallized from dil.MeOH giving needles (22 mg.), m.p. 167～168°, identical with the above-mentioned 1-ketone (XVI) by the IR comparison and the mixed melting point determination.

Convertion of a Mixture of the Thiocyanatohydrins, (XXIa) and (XXIIa), into the 1-Ketone (XVI) and 2-Ketone (Ib)——A mixture of the β-epoxide (XXb) (150 mg.) in ether (20 ml.) was treated with the thiocyanic acid solution[2] prepared with KSCN (1.4 g.), H_3PO_4 (2.1 g.) and ether (10 ml.) as described above. A mixture (178 mg.) of the resulting thiocyanatohydrins was oxidized with CrO_3 (62 mg.) in H_2O (1.5 ml.) and subsequent treatment of the thiocyanatoketones (176 mg.) with Zn dust (880 mg.) and AcOH (10 ml.) gave a mixture of the ketones (147 mg.). The product was separated into two fractions by preparative TLC (benzene-AcOEt=10:1). The more mobile fraction (35 mg., 23.3%) was recrystallized from MeOH giving the 1-ketone (XVI) (20 mg.) as needles, m.p. 167～168°. The less mobile fraction (104 mg., 69.3%), on recrystallization from MeOH, gave the 2-ketone (Ib) (86 mg.) as plates, m.p. 114～115°.

These two ketones were identified with respective samples by mixed melting points and IR comparisons.

Reduction of the 1β,2β-Epoxide (XXb) with Lithium Aluminum Hydride——A solution of XXb (125 mg.) in dry tetrahydrofuran (10 ml.) was added to a suspension of $LiAlH_4$ (125 mg.) in dry tetrahydrofuran (10 ml.) dropwise with stirring and the mixture was refluxed for 7 hr. The crude product, isolated in the usual manner, was separated into two fractions by preparative TLC (benzene-AcOEt=3:1). The more mobile fraction (50 mg.) was recrystallized from acetone giving the 2β,17β-diol (VIIa) (39 mg.) as plates, m.p. 207～

208°. The less mobile fraction (44 mg.) was shown to be still a mixture consisting of the original two products. Fractional recrystallization from acetone gave needles (13 mg.) of the 1β,17β-diol (XIVa), m.p. 178~183°, which on further recrystallization from acetone raised the melting point to 185~188°. These two diols were identified with samples of the respective diols by mixed melting points and IR comparisons.

Reduction of the Thiocyanatohydrin (Xa) with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (53 mg.) in dry tetrahydrofuran (7 ml.), a solution of Xa (106 mg.) in dry tetrahydrofuran (7 ml.) was added dropwise with stirring under cooling. After 1 hr., the product, isolated in the usual manner, was separated into two fractions by preparative TLC (benzene-AcOEt=3:1). The more mobile fraction (64 mg., 73.4%) was recrystallized from dil.MeOH yielding 2β-mercapto-A-nor-5α-androstane-1α,17β-diol (XXVa) (45 mg.) as plates, m.p. 160~162°. The analytical sample was obtained by further recrystallization from the same solvent and melted at 162~163.5°. $[\alpha]_D$ +18° (c=0.54). IR ν_{max} cm^{-1} : 3370 (OH). *Anal.* Calcd. for $C_{18}H_{30}O_2S$: C, 69.64; H, 9.74; S, 10.31. Found : C, 69.73; H, 9.81; S, 10.21.

The less mobile fraction (19 mg., 21.8%), on recrystallization from MeOH-$CHCl_3$, afforded the disulfide (XXVIa) (13 mg.) as needles, m.p. 271~272°, $[\alpha]_D$ +152° (c=0.59). IR ν_{max} cm^{-1} : 3370 (OH). *Anal.* Calcd. for $2(C_{18}H_{29}O_2S)$: C, 69.87; H, 9.45; S, 10.34. Found : C, 69.88; H, 9.61; S, 10.43.

Alkaline Treatment of Xa——A mixture of the thiocyanatohydrin (Xa) (87 mg.) in MeOH (9 ml.) and KOH (90 mg.) was refluxed for 1 hr. The product, isolated in the usual way, was separated into three fractions by preparative TLC (benzene-AcOEt=3:1). The less polar fraction (15 mg., 23.5%) was recrystallized from dil.MeOH giving the 1α,2α-epoxide (IXa) as prisms, m.p. 178~179°. The more polar fraction (19 mg., 26.6%), on recrystallization from MeOH, afforded the above-mentioned mercaptol (XXVa) as plates, m.p. 160~162°. The most polar fraction (34 mg., 47.7%) was recrystallized from MeOH-$CHCl_3$ giving the disulfide (XXVIa) as fine needles, m.p. 270~272°. These three products were identified with respective authentic samples by mixed melting points and IR spectral comparisons.

2β-Mercapto-A-nor-5α-androstane-1α,17β-diol Triacetate (XXVb)——A solutions of XXVa (74 mg.) in Ac_2O (0.5 ml.) and pyridine (1 ml.) was allowed to stand at room temperature overnight. The product, isolated in the usual way, was recrystallized from petr. ether giving XXVb (91 mg.) as plates, m.p. 171~173°, $[\alpha]_D$ +42° (c=0.53). IR ν_{max} cm^{-1} : 1692 (SAc), 1738, 1256, 1237, 1226 (OAc). UV λ_{max} mμ (ε) : 234 (4410). *Anal.* Calcd. for $C_{24}H_{36}O_5S$: C, 66.02; H, 8.31; S, 7.34. Found : C, 65.76; H, 8.11; S, 7.06.

The Disulfide Tetraacetate (XXVIb)——The XXVIa (30 mg.) was acetylated with Ac_2O (0.5 ml.) in pyridine (1 ml.) by standing at room temperature overnight. After working up in the usual way, the product was recrystallized from acetone giving XXVIb (31 mg.) as needles, m.p. 246~247°. $[\alpha]_D$ −65° (c=0.45). IR ν_{max} cm^{-1} : 1731, 1253 (OAc). *Anal.* Calcd. for $2(C_{22}H_{33}O_4S)$: C, 67.14; H, 8.45: S, 8.15; mol. wt., 787.1. Found : C, 67.14; H, 8.34; S, 8.33; mol. wt., 766 (Vapor pressure lowering method).

The authors express their deep gratitude to Dr. Ken'ichi Takeda, Director of this laboratory, for his interest and encouragement throughout the course of this work. The authors are also grateful to Dr. T. Kubota and Dr. T. Komeno for valuable discussions and their interest in this work.