

When the portion insoluble in benzene was added to a small amount of EtOH and allowed to stand at room temperature for 3 to 7 days, 0.5 g. of methylglyoxal di-N-benzyl-N-phenylhydrazone separated. Recrystallization from EtOH gave an analytical sample as yellow prisms, m.p. 126°. *Anal.* Calcd. for $C_{29}H_{28}N_4$: C, 80.56; H, 6.48; N, 12.96. Found: C, 80.69; H, 6.47; N, 12.73.

Methylglyoxal Di-N-benzyl-N-phenylhydrazone—To a solution of 1.0 g. of 30% aqueous methylglyoxal was added 1.74 g. of N-benzyl-N-phenylhydrazine. The yellow precipitate was filtered and washed with H_2O . After recrystallization from EtOH it melted at 126°.

Methylglyoxal Diphenylhydrazone—A mixture of phenylhydrazine (3.3 g.) and N,N-dimethylaminoacetone (1 g.) was refluxed in 10 ml. of EtOH for 1 hr. on a steam bath. The reaction mixture was cooled and with 10 ml. H_2O added. The yellow precipitate was filtered, washed with H_2O and recrystallized from EtOH yielding 2 g. of methylglyoxal diphenylhydrazone, m.p. 148°, identified by comparison of its infrared spectrum with that of an authentic sample.⁹⁾

The authors would like to express their deep gratitude to Dr. T. Akiba, director of this laboratory, for his encouragement throughout the course of this work. Thanks are also due to Mr. Tsuneo Ito, Kitazato University, for the NMR analysis.

5) H. V. Pechmann: *Ber.*, **20**, 2539 (1887).

[*Chem. Pharm. Bull.*
15(1) 15 ~ 27 (1967)]

UDC 547.924.07

3. Katsumi Tanabe, Rinji Takasaki, Kiyoshi Sakai, Ryoza Hayashi, Yasuhiro Morisawa and Teruo Hashimoto: Steroid Series. XVI.*¹

The Preparation of 3 α ,5 α -Cyclo-6 β ,19-oxidosteroids and its Conversion to 19-Oxygenated Steroid Derivatives.*²

(*Central Research Laboratories, Sankyo Co., Ltd.*)*³

3 α ,5 α -Cyclo-6 β ,19-oxidosteroid (II) was synthesized by the lead tetraacetate oxidation of 3 α ,5 α -cyclo-6 β -hydroxysteroid (I) in benzene. The acid-catalysed solvolysis of the oxide (II) afforded 3 α ,5 α -cyclo-19-hydroxy-6 β -substituted steroid (XVI) and/or 4⁵-19-hydroxy-3 β -substituted steroid (XVII), depending upon the reaction conditions employed. Oxidation of the oxide (II) with Jones reagent gave 3 α ,5 α -cyclo-6 β ,19-dioxosteroid (XIX) with two equivalent molar oxidant, and 3 α ,5 α -cyclo-6-oxosteroid-19-oic acid (XX) with the excess reagent.

(Received February 23, 1966)

The transannular substitution reaction to introduce a functional group at a suitably located, nonactivated carbon of the steroid nucleus has recently been employed by several groups¹⁾ for preparation of the C-19 substituted steroid,²⁾ which is an useful

*¹ Part XV. Y. Morisawa: *Agr. Biol. Chem.*, **28**, 796 (1964).

*² A part of this work was presented as a communication: K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, Y. Morisawa: *This Bulletin*, **10**, 1126 (1962).

*³ 1-2-58, Hiromachi, Shinagawa-ku, Tokyo (田部克巳, 高崎林治, 酒井 浄, 林 了, 森沢靖弘, 橋本輝夫).

1) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, O. Halpern: *J. Am. Chem. Soc.*, **84**, 3204 (1962); K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner, A. Wettstein: *Experientia*, **18**, 464 (1962); M. Akhtar, D.H.R. Barton: *J. Am. Chem. Soc.*, **86**, 1528 (1964); R. Gardi, C. Pedrall: *Gazz. chim. ital.*, **91**, 1420 (1961).

2) A. Bowers, L. C. Ibáñez, M. E. Cabezas, H. J. Ringold: *Chem. & Ind.*, **1962**, 1299; *Idem.*: *J. Org. Chem.*, **27**, 1862 (1962); Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein: *Experientia*, **17**, 475 (1961); K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein: *Helv. Chim. Acta*, **45**, 1317, 2161, 2575 (1962); H. Wehrli, M. S. Heller, K. Schaffner, O. Jeger: *Ibid.*, **44**, 2162 (1961); D.H.R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet: *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961); D.H.R. Barton, J. M. Beaton: *Ibid.*, **84**, 199 (1962); J. S. Mills, V. Petrow: *Chem. & Ind.*, **1961**, 946.

appeared dealing with the same lead tetraacetate oxidation reaction of $3\alpha,5\alpha$ -cyclo- 6β -hydroxysteroids differing only in the side chain structures.

$3\alpha,5$ -Cyclo- 6β -hydroxy- 5α -androstan-17-one (Ic)⁵⁾ was treated with lead tetraacetate in boiling benzene to afford, after chromatography over neutral alumina, $3\alpha,5$ -cyclo- 6β , 19-oxido- 5α -androstan-17-one (IIc), together with a small amount of $3\alpha,5$ -cyclo- 5α -androstan-6,17-dione (IIIc).

The infrared (IR) spectrum of $3\alpha,5$ -cyclo- 6β ,19-oxido- 5α -androstan-17-one (IIc) showed, besides a weak band at 3058 cm^{-1} due to cyclopropane, five to six bands in the region of $1100\sim 850\text{ cm}^{-1}$ indicating the presence of a substituted tetrahydrofuran ring and a weak but sharp one at 1485 cm^{-1} ascribable to the bending vibration of C-19 methylene in the newly formed 6β ,19-oxide ring, as already pointed out by Bagli *et al.*⁶⁾ The nuclear magnetic resonance (NMR) spectrum had no signal characteristic to 19-methyl protons but instead a pair of doublets ($j=7.0\text{ c.p.s.}$) centered at 6.56 and 6.08τ ascribable to non-equivalent 19-methylene protons of the 6β ,19-oxide ring, together with ill-defined peaks observed in the regions of $9.1\sim 9.3\tau$ and $9.6\sim 9.8\tau$ indicating the presence of the $3\alpha,5\alpha$ -cyclo structure. Resonance signal due to 6α -proton appeared at 6.10τ as quasi doublet ($j=5.0\text{ c.p.s.}$), whereas the corresponding one in $3\alpha,5$ -cyclo- 6β -hydroxy- 5α -androstan-17-one (Ic) was observed at 6.69τ as quasi triplet ($j=2.8\text{ c.p.s.}$). These different types of splitting of 6α -protons were attributed by Sollman^{4c)} to the change of the dihedral angles between 6α -proton and 7α - or 7β -protons due to the formation of the strained oxide bridge.

Treatment of $3\alpha,5$ -cyclo- 6β ,19-oxido- 5α -androstan-17-one (IIc) with a catalytic amount of diluted sulfuric or perchloric acids in aqueous solvent at room temperature afforded $3\alpha,5$ -cyclo- 6β ,19-dihydroxy- 5α -androstan-17-one (IVc) in 92% yield, while on heating the reaction mixture at $50\sim 60^\circ$, the oxide was converted into 3β ,19-dihydroxy-androst-5-en-17-one (VIc), which was also obtainable on heating $3\alpha,5\alpha$ -cyclo- 6β ,19-diol (IVc) in an aqueous solvent containing diluted sulfuric acid at 70° . When $3\alpha,5\alpha$ -cyclo- 6β ,19-diol (IVc) or its diacetate prepared from IVc with acetic anhydride in pyridine was heated at 70° in acetic acid in the presence of concentrated sulfuric acid, there was obtained 3β ,19-dihydroxyandrost-5-en-17-one 3,19-diacetate (XIc), which was also formed directly from the oxide (IIc) under the same reaction conditions.

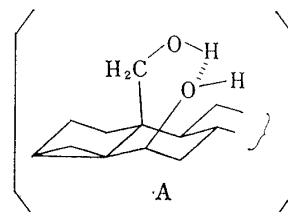
Examination of an infrared spectrum*⁴ of $3\alpha,5$ -cyclo- 6β ,19-dihydroxy- 5α -androstan-17-one (IVc) in carbon tetrachloride at a concentration of 0.0014 moles revealed the presence of free and intramolecular hydrogen bonded hydroxyl absorptions at 3613^{*5} and 3462 cm^{-1} , respectively. The NMR spectrum of $3\alpha,5\alpha$ -cyclo- 6β ,19-diol (IVc) in dry chloroform containing a drop of acetic acid displayed, besides a complex signals at $9.2\sim 9.8\tau$ due to cyclopropyl protons, a pair of doublets ($j=10.2\text{ c.p.s.}$) centered at 6.27 and 6.69τ ascribable to 19-methylene protons and a multiplet at 6.69τ assignable to 6α -proton, while in the corresponding 6β ,19-diacetate (VIc) resonance peaks due to 19-methylene protons and 6α -proton appeared as a singlet at 5.77τ and as a triplet ($j=2.5\text{ c.p.s.}$) at 5.49τ , respectively. The 19-methylene protons in $3\alpha,5\alpha$ -cyclo- 6β ,19-diol (IVc) are apparently non-equivalent which might arise from the strong intramolecular hydrogen bonding as disclosed in the infrared spectra, while the methylene protons in

*⁴ The spectrum was run on Perkin-Elmer Model 21, P-G-I.

*⁵ A weak shoulder at 3625 cm^{-1} was observed, which is assignable to a free hydroxy stretching vibration due to the primary 19-hydroxyl group. These observations suggested that $3\alpha,5\alpha$ -cyclo- 6β ,19-diol (IVc) predominantly exists as formula (A).

5) A. Butenandt, L. A. Surányi : *Ber.*, **75**, 592 (1942).

6) J. F. Bagli, P. F. Morand, R. Gaudry : *J. Org. Chem.*, **28**, 1207 (1963).



the corresponding diacetate (Vc) may become equivalent as a consequence of possible free rotation of the 19-methylene group.

The NMR spectrum of 3 β ,19-dihydroxyandrost-5-en-17-one 3,19-diacetate (Xlc) showed no multiplet at high field characteristic to cyclopropane but had ill-defined signal at 4.38 τ indicating the presence of 6-vinyl proton and a pair of doublets ($j=12.2$ c.p.s.) centered at 5.40 and 6.07 τ ascribable to 19-methylene protons. The doublet centered at 5.40 τ with 2-proton "hump" was apparently overlapped with a broad signal due to 3 α -proton.

Methanolysis of 3 α ,5-cyclo-6 β ,19-oxido-5 α -androst-17-one (IIc) in the presence of a catalytic amount of boron trifluoride etherate at -5° afforded 3 α ,5-cyclo-6 β -methoxy-19-hydroxy-5 α -androst-17-one (Vc) in 90% yield, together with a small amount of isomeric 3 β -methoxy-19-hydroxyandrost-5-en-17-one (Xc). The former compound (Vc) was convertible to the latter (Xc) on further treatment under refluxing conditions.

The infrared spectrum*⁴ of 3 α ,5 α -cyclo-6 β -methoxy-19-ol (Vc) in carbon tetrachloride at a concentration of 0.0004 moles exhibited an intense hydroxyl band at 3435 cm^{-1} due to strong intramolecular hydrogen bonding and a weak band at 3064 cm^{-1} characteristic to cyclopropane.

Acetolysis of 3 α ,5 α -cyclo-6 β ,19-oxide (IIc) either in glacial acetic acid at 80° or in glacial acetic acid with a catalytic amount of boron trifluoride etherate at room temperature proceeded smoothly to afford 3 β ,19-dihydroxyandrost-5-en-17-one 3-acetate (Xc), which was acetylated with acetic anhydride in pyridine to give the corresponding 3 β ,19-diacetate (Xlc) described above. The structure of Δ^5 -3 β -acetoxy-19-ol (Xc) was based on the fact that Jones oxidation⁷ of the monoacetate (Xc) with one equivalent molar oxidant furnished 3 β -hydroxyandrost-5-ene-17,19-dione 3-acetate (XIIIc). Multiplet signals due to 6-vinyl protons in the NMR spectra of XIIIc or the corresponding 3 β -ol (XIVc) were observed at 4.17~4.18 τ , being obviously shifted downfield compared with the corresponding resonance at 4.58 τ in 3 β -hydroxyandrost-5-en-17-one 3-acetate. Singlet resonances due to 18-methyl protons in these 19-oxo-steroids (XIIIc and XIVc) appeared at 9.14~9.15 τ ,⁸ which is slightly but surely shifted higher field, apparently due to the long range shielding of the 19-formyl group, relative to the signal at 9.11 τ in 3 β -hydroxyandrost-5-en-17-one 3-acetate.

Refluxing 3 α ,5 α -cyclo-6 β ,19-oxide (IIc) with diluted hydrochloric acid in acetone furnished 3 β -chloro-19-hydroxyandrost-5-en-17-one (VIIIc), which was converted to Δ^5 -3 β ,19-diacetate (Xlc) on refluxing with potassium acetate in acetic acid, or acetylated with acetic anhydride in pyridine to give the corresponding 19-acetate (XIIc). The Δ^5 -3 β -chloro-19-acetate (XIIc) was also prepared from 3 α ,5 α -cyclo-6 β ,19-diacetate (Vc) on treatment with diluted hydrochloric acid in chloroform at room temperature.

The infrared spectrum*⁴ of Δ^5 -3 β -chloro-19-alcohol (VIIIb) in the pregnane series in carbon tetrachloride at a concentration of 0.004 moles showed two absorption bands due to hydroxyl stretching vibration at 3632 and 3583 cm^{-1} with relative intensity of 2:1, which are assignable to free and intramolecular hydrogen bonded hydroxyl groups, respectively. The latter absorption at 3583 cm^{-1} , shifted by 49 cm^{-1} from the free band, could be ascribable to the intramolecular hydrogen bonding between 19-hydroxyl and π -electrons of 5~6 double bond, similar to the case of epicholesterol.⁹ The NMR resonances due to 6-vinyl protons of 3 β ,19-dihydroxyandrost-5-en-17-one 3-acetate (Xc) and 3 β -methoxy-19-hydroxyandrost-5-en-17-one (Xc), both having the common partial

*⁴ Δ^5 -3 β -hydroxy-6,19-dione (XIVc) had two peaks due to 18-methyl protons at 9.06 and 9.15 τ , having relative intensity of ca. 1:5. The minor peak at 9.06 τ might be attributable to the signal for Δ^5 -3 β ,19-hemiacetal existing as an equilibrium mixture in deuteriochloroform.

7) K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. C. Weedon: J. Chem. Soc., **1946**, 39.

8) P. von R. Schleyer, D. S. Trifan, R. Bacsikai: J. Am. Chem. Soc., **80**, 6691 (1958).

structure of Δ^5 -19-hydroxyl appeared respectively at 4.18 and 4.20 τ , which were shifted downfield by 0.25 to 0.30 p.p.m. in comparison with the corresponding signal at 4.58 τ in 3 β -hydroxyandrost-5-en-17-one 3-acetate. These paramagnetic shifts may be attributable to the intramolecular hydrogen bonding between the hydroxyl and olefinic π -bond as revealed in the infrared spectrum of Δ^5 -3 β -chloro-19-alcohol (VIIIc). In fact, acetylation of the 19-hydroxyl of Kc caused the signal to shift upfield by 0.20 p.p.m., just similar to the case of epicholesterol.⁹⁾

All the results on the acid-catalysed solvolysis reactions of 3 α ,5 α -cyclo-6 β ,19-oxide (IIc) described thus far clearly suggested that an initial cleavage of the oxide bridge occurred at C₆-position with a consequent formation of 19-hydroxylated homoallylic cation (XV) and a subsequent β -attack of anions at C₆- or C₃-positions, depending upon the reaction conditions employed, gave rise to 3 α ,5 α -cyclo-6 β - (XVI) or Δ^5 -3 β -substituted steroids (XVII). These observations strongly support the Tadaniel's conclusion^{4a)} that the 19-hydroxylated homoallylic cation (XV) has the the same stereochemistry at C₃- or C₆-positions as the well-established one for 19-methyl homoallylic cation (XVIII).³⁾ The high yield formation of 3 α ,5 α -cyclo-6 β ,19-disubstituted steroids (IVc and Vc) implies that the acid-catalysed solvolysis reactions of 3 α ,5 α -cyclo-6 β ,19-oxide (II) proceeded more rapidly to form the intermedial 19-hydroxylated homoallylic cation (XV), probably owing to the presence of the strained oxide bridge in the compound (II), than the initially formed, kinetically controlled product,¹⁰⁾ 3 α ,5 α -cyclo-6 β -substituted-19-alcohol (XVI) regenerates the same intermediate (XV), which in turn rearranges to the more stable Δ^5 -3 β -substituted-19-alcohol (XVII).

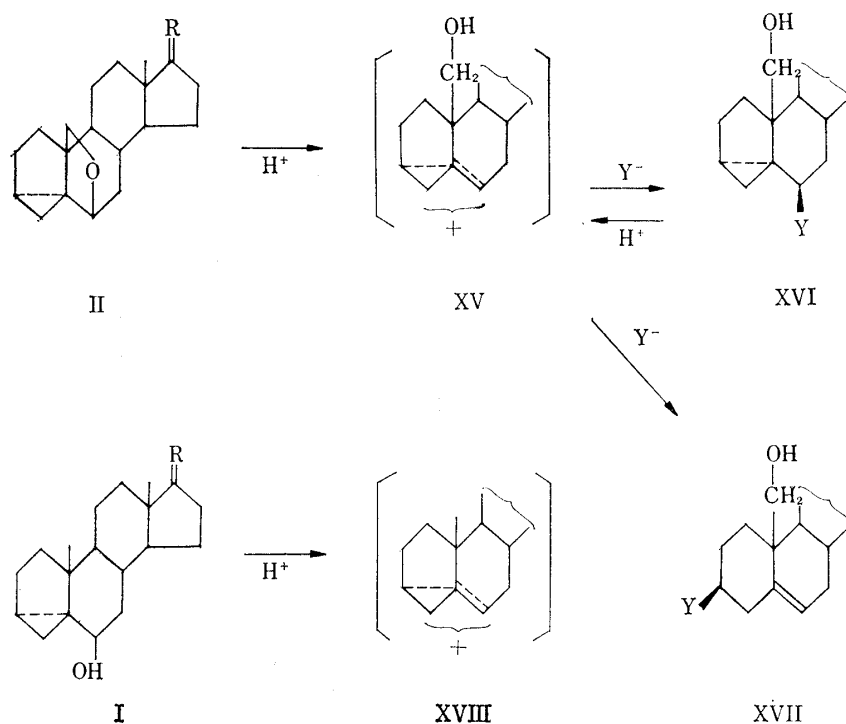


Chart 2.

In fact, 3 α ,5-cyclo-6 β ,19-oxido-5 α -cholestane (IIa) gave 3 α ,5-cyclo-6 β ,19-dihydroxy-5 α -cholestane (IVa) in a mild acidic medium at room temperature for 4 hours, whereas the latter compound could be converted into 3 β ,19-dihydroxycholest-5-ene (VIIa) only after prolonged refluxing conditions.

9) T. Okamoto, Y. Kawazoe : This Bulletin, **11**, 643 (1963).

10) Y. Pocker : Proc. Chem. Soc. (London), **1959**, 226.

Oxidation of 3 α ,5-cyclo-6 β ,19-oxido-5 α -androstan-17-one (IIc) afforded in high yields 3 α ,5-cyclo-5 α -androstan-6,17,19-trione (XXc) with two equivalent molar of Jones reagent⁷⁾ and 3 α ,5-cyclo-5 α -androstan-6,17-dione-19-oic acid (XXc) with the excess reagent. These were also prepared by oxidation of 3 α ,5 α -cyclo-6 β ,19-diol (IVc) with the same reagent.

3 α ,5-Cyclo-5 α -androstan-6,17,19-trione (XXc) showed a formyl and 3 α ,5 α -cyclo-6-ketone bands at 1718 and 1683 cm^{-1} , respectively, in the infrared spectrum and displayed a singlet at 0.19 τ due to a formyl proton attached to a quarternally substituted carbon atom in the NMR spectrum. Resonance signal due to 3 α ,5-cyclo-propyl protons was observed as a rather simple multiplet centered at 9.20 τ just similar to the case of 3 α ,5-cyclo-5 α -androstan-6,17-dione (IIIc).

Sodium borohydride reduction of 3 α ,5-cyclo-5 α -androstan-6,17,19-trione (XXc) in tetrahydrofuran afforded, after chromatography over alumina, a mixture of 3 α ,5-cyclo-5 α -androstan-6 α ,17 β ,19-triol (XXII) and 3 α ,5-cyclo-5 α -androstan-6 β ,17 β ,19-triol (XXI) in a ratio of 11:1, both of which were converted to the same 3 β ,17 β ,19-trihydroxyandrost-5-ene (XXIII) on treatment with perchloric acid in aqueous dioxane. The structure of the minor reduction product, 3 α ,5 α -cyclo-6 β ,17 β ,19-triol (XXI), was established by its identity with the reduction product of 3 α ,5-cyclo-6 β ,19-dihydroxy-5 α -androstan-17-one (IVc) with sodium borohydride. The major triol (XXII) must therefore be 6 α -alcohol.

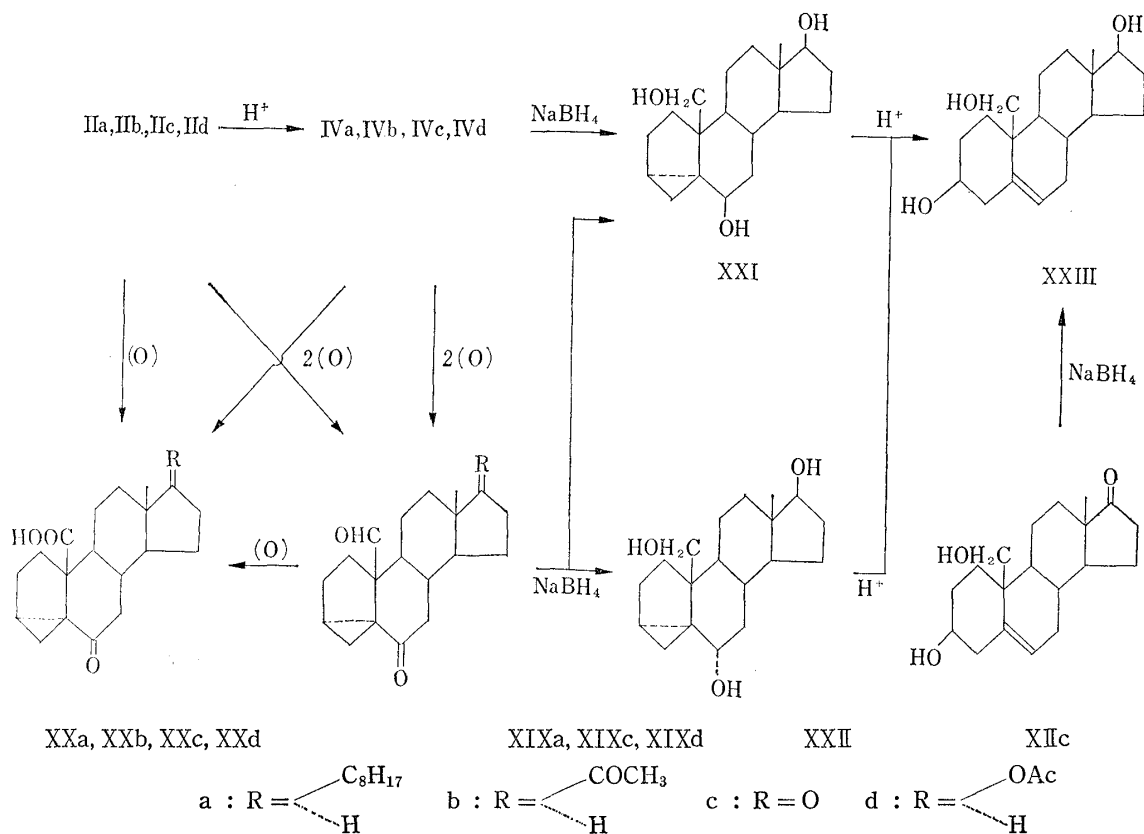


Chart 3.

The relative rates of the acid-catalysed solvolysis reactions of the C₆-epimeric triols (XXI and XXII) were also in accord with this assignment: The $[\alpha]_D$ value of a solution of the 6 β -ol (XXI) decreased rapidly from the initial +52.8° to -42.5°, a close value for 4 β -3 β ,17 β ,19-triol (XXIII), during 4 hours in aqueous dioxane containing concentrated perchloric acid, while the 6 α -epimer (XXII) rearranged under the same conditions only in 62% for 66 hours and in order to finish reaction further heating at

70° for 4 hours^{*7} was required. These results were coincided with the observation for epimeric 3 α ,5-cyclo-5 α -cholestan-6 α - and 6 β -ols.¹¹⁾ However, the elution order of the triols (XXI and XXII) from an alumina column was found to be reversed to the one¹²⁾ observed for the 3 α ,5 α -cyclo-6-alcohols, the 3 α ,5 α -cyclo-6 α ,17 β ,19-triol (XXIII) with an C₆-equatorial hydroxyl group being eluted more rapidly than the 6 β -axial alcohol (XXI).

Experimental^{*8}

Lead Tetraacetate Oxidation of 3 α ,5-Cyclo-6 β -hydroxy-5 α -androstan-17-one (Ic)—A solution of 1.0 g. of Ic and 2.0 g. of Pb(OAc)₄ in 50 ml. of dry benzene was refluxed for 20 hr. under anhydrous conditions. The reaction mixture was cooled, filtered from the inorganic salts and the benzene solution was washed with 5% aq. KI, water, 5% aq. Na₂S₂O₃, and water, successively and dried over anhyd. Na₂SO₄. Removal of the solvent yielded a syrupy residue, which was chromatographed over 30 g. of Al₂O₃. Elution with hexane-benzene (4:1) afforded 0.366 g. of a crystalline product melting at 126~128°. Recrystallization from hexane afforded needles of IIc, m.p. 137~138°, [α]_D +150.1° (c=2.16). *Anal.* Calcd. for C₁₉H₂₆O₂: C, 79.68; H, 9.15. Found: C, 79.31; H, 9.21. IR $\nu_{\max}$ cm⁻¹: 3058 (cyclopropane), 1485 (19-CH₂-). NMR τ : 9.10~9.30 and 9.60~9.80 (3 α ,5-cyclopropyl protons), 9.06 (18-CH₃), 6.56 (doublet) and 6.08 (doublet) (j=7.0 c.p.s., 19-CH₂-), 6.10 (doublet, j=5.0 c.p.s., 6 α -H).

Further elution with hexane-benzene (1:1) gave a small amount of a crystalline material, which was recrystallized from hexane-benzene to give IIc as needles of m.p. 185~187°. The identity with an authentic sample prepared by oxidation of Ic with CrO₃ in AcOH was confirmed by mixed melting point determination and infrared spectral comparison.

Elution with benzene afforded 0.480 g. of a starting material recovered, which was recrystallized from hexane to give Ic of m.p. 136~138°.

Lead Tetraacetate Oxidation of 3 α ,5-Cyclo-6 β -hydroxy-5 α -cholestane (Ia)¹³⁾—To a solution of 10 g. of Ia in 500 ml. of benzene was added 20 g. of Pb(OAc)₄ and 1.0 g. of benzoyl peroxide and the mixture was refluxed for 18.5 hr. under moisture-free conditions. The reaction mixture was cooled, filtered through celite to remove inorganic material. The filtrate was successively washed with 5% aq. KI, water, 5% aq. Na₂S₂O₃, and water and dried over anhyd. Na₂SO₄. Evaporation of the solvent yielded an oily residue, which was chromatographed over Al₂O₃. First elution with a mixture of benzene-hexane (1:3) afforded 3.6 g. of a crystalline substance, which was recrystallized from acetone to give IIa as needles of m.p. 81~82°. [α]_D +74° (c=2.16). *Anal.* Calcd. for C₂₇H₄₄O: C, 84.32; H, 11.53. Found: C, 83.99; H, 11.64. IR $\nu_{\max}$ cm⁻¹: 1493 (19-CH₂-). NMR τ : 9.5~9.7 (cyclopropane), 9.27 (18-CH₃), 6.07 (doublet) and 6.60 (doublet) (j=7.5 c.p.s., 19-CH₂-), 6.13 (6 α -H).

Subsequent elution with the same eluant gave 4.2 g. of the starting material unchanged.

Lead Tetraacetate Oxidation of 3 α ,5-Cyclo-6 β -hydroxy-5 α -pregnan-20-one (Ib)¹⁴⁾—To a solution of 10 g. of Ib in 500 ml. of benzene was added 20 g. of Pb(OAc)₄ and 1.0 g. of benzoyl peroxide and the mixture was refluxed under anhydrous conditions for 15 hr. The reaction mixture was worked up as described for Ia to yield an oily residue, which was chromatographed over Al₂O₃.

The eluate with a mixture of benzene-hexane (2:3) afforded 1.56 g. of a crystalline product having m.p. 165~175°, which was recrystallized from benzene-hexane to furnish IIb as prisms of m.p. 173~175°. *Anal.* Calcd. for C₂₁H₃₀O₂: C, 80.21; H, 9.62. Found: C, 80.02; H, 9.55. IR $\nu_{\max}$ cm⁻¹: 1488 (19-CH₂-).

3 α ,5-Cyclo-6 β ,19-oxido-17 β -hydroxy-5 α -androstan-17-Acetate (IIId)—To a stirred suspension of 2.0 g. of LiAlH₄ in 150 ml. of anhyd. ether, 3.05 g. of IIc in 150 ml. of anhyd. ether was added dropwise under ice-cooling and stirring was further continued for 1.5 hr. The reaction mixture was treated with water to decompose the excess reagent and acidified with dil. HCl. The ether layer was separated, washed with aq. NaHCO₃ and water, dried over anhyd. Na₂SO₄, and condensed to dryness to yield 2.9 g. of a crystalline material. Recrystallization from benzene-hexane afforded 2.1 g. of 3 α ,5-cyclo-6 β ,19-oxido-17 β -

^{*7} See Experimental Part.

^{*8} All melting points were uncorrected. The NMR spectra were recorded on Varian A-60 in deuteriochloroform containing tetramethylsilane as an internal standard. The IR spectra were taken with Perkin Elmer Model-21 and refer to Nujol mull, [α]_D values relate to chloroform and Al₂O₃ for chromatography was neutral, Woelm grade III, unless otherwise mentioned.

11) S. Winstein, E. M. Kosower: J. Am. Chem. Soc., **81**, 4399 (1959).

12) E. M. Kosower, S. Winstein: *Ibid.*, **78**, 4347 (1956).

13) J. H. Beynon, I. M. Heibron, F. S. Spring: J. Chem. Soc., **1937**, 1459; E. M. Kosower, S. Winstein: J. Am. Chem. Soc., **78**, 4347 (1956).

14) A. Butenandt, W. Gross: Ber., **70**, 1446 (1937); D. K. Patel, V. Petrow, I. A. Stuart-Webb: J. Chem. Soc., **1957**, 665.

hydroxy-5 α -androstane as plates, m.p. 181~183°. $[\alpha]_D +73.4^\circ$ ($c=2.35$). *Anal.* Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.75; H, 10.34.

A sample of 0.508 g. of the 17 β -ol obtained above was acetylated with 5 ml. of Ac_2O in 7 ml. of Py. at room temperature. The reaction mixture was diluted with ice-water, extracted with ether and the extract was washed with dil. HCl, aq. $NaHCO_3$ and water, and dried over anhyd. Na_2SO_4 . Removal of the solvent gave 0.543 g. of a crystalline product, which was chromatographed over Al_2O_3 . The combined eluates with hexane and hexane-benzene (9:1 to 4:1) furnished 0.337 g. of **Id** melting at 125.5~127°. $[\alpha]_D +55.6^\circ$ ($c=2.61$). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.25.

3 α ,5-Cyclo-6 β ,19-dihydroxy-5 α -androstan-17-one (IVc)—A solution of 3.0 g. of **Ic** in 300 ml. of 90% aq. acetone and 3.0 ml. of 10% H_2SO_4 was set aside at room temperature for 16 hr. The reaction mixture was diluted with water and extracted with ether. The extract was washed with aq. $NaHCO_3$, water and dried over anhyd. Na_2SO_4 . Evaporation of the solvent yielded a crystalline residue, which was recrystallized from hexane-benzene to afford 2.93 g. of **IVc** as plates, m.p. 175~175.5°, $[\alpha]_D +147.3^\circ$. *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.63; H, 9.10. IR $\nu_{max}^{ccl_4}$ cm^{-1} : 3060 (cyclopropane), 3613 (6-OH), 3462 (intramolecular hydrogen bonded hydroxyl). NMR τ : 9.2~9.8 (cyclopropane), 9.03 (18- CH_3), 6.27 (doublet) and 6.70 (doublet, $j=10.2$ c.p.s., 19- CH_2 -), 6.69 (6 α -H).

3 α ,5-Cyclo-6 β ,17 β ,19-trihydroxy-5 α -androstane 17-Monoacetate (IVd)—A solution of 10.5 g. of **Id** in 1.30 L. of 90% aq. acetone and 3.7 ml. of 10% H_2SO_4 was set aside at room temperature for 19 hr. The solution was condensed *in vacuo* to ca. 300 ml. in a bath at 40° and poured into ca. 600 ml. of water to separate crystals, which was collected by filtration, washed with water and EtOH, dried to weigh 11.0 g. of a crystalline product melting at 168~177°. Recrystallization from benzene-hexane gave 10.1 g. of **IVd** as needles, m.p. 180~183°. $[\alpha]_D +50^\circ$ ($c=1.20$). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.96; H, 9.12. IR ν_{max} cm^{-1} : 3226 (OH), 1740 (17-OAc).

3 α ,5-Cyclo-6 β ,19-dihydroxy-5 α -cholestane (IVa)—A solution of 60 g. of **Ia** in 7.0 L. of acetone, 700 ml. of water and 20 ml. of 10% H_2SO_4 was allowed to stand at room temperature for 18 hr. The solution was condensed *in vacuo* in a bath at 40° to separate out crystalline material, which was filtered on a funnel, washed with water and dried to yield 55 g. of a crystalline product (m.p. 133~136°). Recrystallization from hexane afforded silky needles of **IVa** melting at 137~138°. $[\alpha]_D +65.6^\circ$ ($c=1.42$). *Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.51, H, 11.41. IR ν_{max} cm^{-1} : 3356 and 3195 (OH). NMR τ : 9.3~9.9 (cyclopropane), 9.23 (18- CH_3), 6.35 (doublet) and 6.75 (doublet) ($j=10.5$ c.p.s., 19- CH_2 -), 6.80 (triplet, $j=2.7$ c.p.s., 6 α -H), 6.0 (broad, hydrogen bonded OH).

The mother liquor of recrystallization was extracted with ether, which, after washing and drying, was condensed to give ca. 4.5 g. of a crystalline residue, showing two spots of **IVa** (minor) and **VIIa** in TLC. Recrystallization from benzene-hexane afforded **VIIa** as leaflets of m.p. 151~153°.

Treatment of 3 α ,5-Cyclo-6 β ,19-oxido-5 α -pregnan-20-one (IIb) with Diluted Sulfuric Acid in Acetone—A solution of 1.70 g. of **IIb** in 350 ml. of acetone and 30 ml. of 5% H_2SO_4 was set aside at room temperature over night. The solution was condensed *in vacuo* at below 30° and poured into ice-water to separate crystals, which was collected by filtration and taken up into ether. The ether solution was washed with aq. $NaHCO_3$, water and dried over anhyd. Na_2SO_4 . Removal of the solvent yielded 1.70 g. of an oily residue, which crystallized by adding isopropyl ether. Recrystallization from benzene afforded 0.320 g. of **VIIb**, m.p. 193~194°. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.46; H, 9.60. IR ν_{max} cm^{-1} : 3420 (OH), 1695 and 1680 (20-CO).

The mother-liquor of recrystallization was chromatographed over Al_2O_3 and the combined eluates with benzene-ether (4:1) and ether gave 1.105 g. of a crystalline product, which was recrystallized from acetone-hexane to give **IVb** of m.p. 167~168°. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.51; H, 9.58. IR ν_{max} cm^{-1} : 3200 (broad, OH), 1708 (20-CO).

Further elution with MeOH afforded additional 0.230 g. of **VIIb**.

3 α ,5-Cyclo-6 β ,19-dihydroxy-5 α -androstan-17-one 6,19-Diacetate (VIc)—A solution of 0.10 g. of **IVc** in 1.0 ml. of Ac_2O and 2.0 ml. of pyridine was set aside at room temperature for 15 hr. The solution was poured onto ice-water, extracted with ether. The extract was washed with dil. HCl, aq. $NaHCO_3$ and water, and dried. Evaporation of the solvent yielded a syrup substance, which was chromatographed over Al_2O_3 . Elution with hexane-benzene (4:1) gave, after recrystallization from hexane, **VIc** as granules of m.p. 114~115°. *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.30; H, 8.52. NMR τ : 9.5 (cyclopropane), 9.03 (18- CH_3), 7.98 (OAc), 5.77 (19- CH_2 -).

3 β ,19-Dihydroxyandrost-5-en-17-one (VIIc)—i) A solution of 3.40 g. of **Ic** in 340 ml. of 90% aq. acetone and 1.0 ml. of concd. H_2SO_4 was warmed at 55~60° for 5 hr. The reaction mixture was concentrated *in vacuo* and diluted with water to separate a crystalline material, which was taken by filtration, washed and dried to yield 3.35 g. of a product melting at 188~192°. Recrystallization from benzene gave **VIIc** as leaflets of m.p. 207~210°, $[\alpha]_D +8.8^\circ$. *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.85; H, 9.41. IR ν_{max} cm^{-1} : 3378 and 3125 (OH), 1739 (17-CO).

ii) A solution of 0.50 g. of **IVc** in 50 ml. of 90% aq. dioxane and 0.7 ml. of 10% H_2SO_4 was heated at 70° for 3 hr. The solution was diluted with water and extracted with ether. The extract was washed

with aq. NaHCO_3 , water, and dried. Evaporation of the solvent and recrystallization from benzene afforded 0.42 g. of VIIc, m.p. 202~207°.

3 β ,17 β ,19-Trihydroxyandrost-5-ene 17-Monoacetate (VIIId)—A mixture of 1.0 g. of IIId, 100 ml. of 90% aq. dioxane and 1.0 ml. of 60% HClO_4 was heated at 60° for 5 hr. and the solution was condensed *in vacuo* to a half volume, diluted with water to separate crystals, which was collected by filtration, washed with water, dried and recrystallized from benzene to afford 0.90 g. of leaflets of VIIId, m.p. 201~203°. $[\alpha]_D^{25}$ -59.5° (c=1.81). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{32}\text{O}_4$: C, 72.38; H, 9.26. Found: C, 72.54; H, 9.18.

3 β ,19-Dihydroxycholest-5-ene (VIIa)—A solution of 4.5 g. of Ia in 220 ml. of 80% aq. acetone and 30 drops of 70% HClO_4 was refluxed for 8 hr. The reaction mixture was condensed *in vacuo*, diluted with water and extracted with ether. The extract was washed with aq. NaHCO_3 and water, dried over anhyd. Na_2SO_4 . Removal of the solvent yielded 4.76 g. of a crystalline product, which was recrystallized from MeOH to afford 3.8 g. of VIIa as leaflets, m.p. 151~153°. $[\alpha]_D^{25}$ -27° (c=2.18). An analytical sample was evacuated at 80° for 4 hr. *Anal.* Calcd. for $\text{C}_{27}\text{H}_{46}\text{O}_2$: C, 80.54; H, 11.52. Found: C, 80.23; H, 11.50.

Methanolysis of 3 α ,5-Cyclo-6 β ,19-oxido-5 α -androst-17-one (IIc)—i) with sulfuric acid under refluxing. A solution of 0.615 g. of IIc in 60 ml. of MeOH containing 4 drops of 5.5% H_2SO_4 was refluxed on a water bath for 1 hr. The reaction mixture was diluted with water, extracted with ether. The ether extract was washed with aq. NaHCO_3 and water, dried and condensed to dryness to yield 0.64 g. of a crystalline residue, which was chromatographed over Al_2O_3 . The eluate with hexane-benzene (2:1) gave 0.217 g. of a crystalline product. Recrystallization from hexane afforded needles of 3 α ,5-cyclo-6 β -methoxy-5 α -androst-17-one (Vc), m.p. 104~105°. $[\alpha]_D^{25}$ +145.2°. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{30}\text{O}_3$: C, 75.43; H, 9.50. Found: C, 75.04; H, 9.76. NMR τ : 9.2~9.4 (cyclopropane), 9.01 (18- CH_3), 6.57 (OCH_3). IR $\nu_{\text{max}}^{\text{C}=\text{O}}$ cm^{-1} : 3435 (intramolecular hydrogen bonded OH), 3064 (cyclopropane).

Further elution with benzene-methanol (4:1), after recrystallization from hexane-ether, gave 0.29 g. of 3 β -methoxy-19-hydroxyandrost-5-en-17-one (Xc) as needles melting at 145°, $[\alpha]_D^{25}$ +8.6°. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{30}\text{O}_3$: C, 75.43; H, 9.50. Found: C, 75.13; H, 9.64. NMR τ : 9.05 (18- CH_3), 6.63 (OCH_3), 6.08 (doublet) and 6.43 (doublet) (j=12 c.p.s., 19- CH_2 -), 4.20 (6-H).

ii) with BF_3 -etherate at -5°. A solution of 1.0 g. of IIc in 30 ml. of abs. MeOH and 0.05 ml. of BF_3 -etherate was stirred at -5° for 3.5 hr. The solution was neutralized with aq. NaHCO_3 , condensed *in vacuo* and extracted with ether. The extract was washed with water, dried and condensed to dryness to yield 1.13 g. of a crystalline residue, which was recrystallized from hexane to give 0.525 g. of Vc melting at 101~102°. Chromatography of the mother liquor over 24 g. of Al_2O_3 afforded additional 0.489 g. of Vc (combined yield, 1.014 g.) from the hexane-benzene (4:1) eluate.

Further elution with ether gave a small amount (ca. 0.06 g.) of Xc of m.p. 145~147°.

Methanolysis of 3 α ,5-Cyclo-6 β -methoxy-19-hydroxy-5 α -androst-17-one (IVc)—A solution of 0.08 g. of IVc in 8 ml. of MeOH with 2 drops of 5.5% H_2SO_4 was refluxed for 1.5 hr. The solution was diluted with water and extracted with ether. The extract was washed with water and dried over anhyd. Na_2SO_4 . Evaporation of the solvent gave a crystalline residue, which was recrystallized from hexane-benzene to afford Xc melting at 145~146°.

3 β ,19-Dihydroxyandrost-5-en-17-one 3,19-Diacetate (XIc)—i) A solution of 0.10 g. of IIc in 12 ml. of glac. AcOH containing 3 drops of conc. H_2SO_4 was allowed to stand at 22° for 12 hr. The solution was diluted with water and extracted with ether. The extract was washed with aq. NaHCO_3 and water, dried, and condensed to dryness to give 0.116 g. of a syrupy residue, which was chromatographed over 8 g. of Al_2O_3 . Elution with benzene-hexane (1:1) afforded 0.072 g. of a crystalline product. Recrystallization from hexane furnished prisms of XIc, m.p. 107~108°. *Anal.* Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_5$: C, 71.10; H, 8.30. Found: C, 71.41; H, 8.39. NMR τ : 9.08 (18- CH_3), 7.94 and 7.97 (OAc), 5.46 (doublet) and 6.07 (doublet) (j=12.5 c.p.s., 19- CH_2 -), 4.40 (6-H).

ii) A mixture of 0.30 g. of VIIc, 20 ml. of glac. AcOH and 6 drops of conc. H_2SO_4 was heated on a boiling water bath for ca. 15 min. The colored solution was poured onto ice-water and extracted with ether. The extract was washed with 5% NaHCO_3 , water, and dried over anhyd. Na_2SO_4 , condensed to dryness to yield 0.327 g. of a syrupy residue, which was chromatographed over Al_2O_3 . The eluate with hexane-benzene (1:3), after recrystallization from hexane, gave plates of XIc melting at 106.5~108°.

The same result was obtained on treating the reaction mixture at room temperature for 12 hr.

iii) A solution of 0.10 g. of VIIc in 10 ml. of glac. AcOH containing a drop of 5.5% H_2SO_4 was set aside at room temperature for 19 hr. The solution was worked up as described above to afford an oily residue. Chromatography over Al_2O_3 gave 0.048 g. of XIc melting at 107~108°.

iv) A sample (0.048 g., m.p. 207°) of VIIc was treated with 1.0 ml. of Ac_2O and 3.0 ml. of pyridine at room temperature for 15 hr. The reaction mixture was condensed to dryness *in vacuo* to give a crystalline product, which was recrystallized from hexane to afford prisms of XIc melting at 106~108°.

3 β ,19-Dihydroxyandrost-5-en-17-one 3-Monoacetate (IXc)—i) A solution of 1.35 g. of IIc in 135 ml. of glac. AcOH containing 20 drops of BF_3 -etherate was set aside at room temperature for 8.5 hr. The reaction mixture was poured onto ice-water and extracted with ether. The extract was washed with aq. NaHCO_3 , water, dried over anhyd. Na_2SO_4 , and condensed to dryness to yield a crystalline residue, which

was chromatographed over 50 g. of Al_2O_3 . The benzene eluate gave 1.397 g. of a crystalline product. Recrystallization from hexane-benzene afforded needles of Kc, m.p. 161° . *Anal.* Calcd. for $\text{C}_{21}\text{H}_{30}\text{O}_4$: C, 72.80, H, 8.73. Found: C, 72.91; H, 8.54. IR $\nu_{\max}$ cm^{-1} : 3623 (OH), 1736 (17-CO and OAc), 1256 and 1042 (OAc).

ii) A solution of 0.10 g. of IIc in 10 ml. of glac. AcOH was heated at 80° for 1 hr. and worked up as described above. Chromatography of the product over Al_2O_3 afforded 0.044 g. of Kc melting at 161° .

The 3-monoacetate (Kc) was acetylated with Ac_2O in pyridine at room temperature to afford XIc of m.p. $106\sim 108^\circ$.

3 β ,17 β ,19-Trihydroxyandrost-5-ene 3,17-Diacetate (IXd)—A solution of 3.2 g. of IIc in 320 ml. of glac. AcOH and 1.0 ml. of BF_3 -etherate was set aside at 29° for 7 hr. The reaction mixture was poured into ice-water, extracted with ether, the extract was washed with NaHCO_3 , water, dried over MgSO_4 and condensed to dryness to give 3.7 g. of a crystalline residue, which was chromatographed over 100 g. of Al_2O_3 . Elutions with benzene and benzene-ether (5:1) afforded 3.128 g. of a crystalline product. Recrystallization from benzene-hexane furnished prisms of IXd melting at $149.5\sim 150.5^\circ$. $[\alpha]_D -58.4^\circ$ ($c=2.82$). *Anal.* Calcd. for $\text{C}_{29}\text{H}_{34}\text{O}_5$: C, 70.74; H, 8.78. Found: C, 70.85; H, 8.57.

3 β -Chloro-19-hydroxyandrost-5-en-17-one (VIIIc)—A mixture of 1.0 g. of IIc, 80 ml. of acetone and 5 ml. of 12% HCl was refluxed for 1 hr. The solution was condensed *in vacuo*, diluted with water and extracted with ether. The extract was washed with aq. NaHCO_3 , water, dried and condensed to dryness to afford 1.07 g. of a crystalline product. Recrystallization from benzene-hexane furnished VIIIc, m.p. $164\sim 166^\circ$. $[\alpha]_D +30.4^\circ$ ($c=1.87$). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_2\text{Cl}$: C, 70.69; H, 8.37; Cl, 11.01. Found: C, 70.57; H, 8.26; Cl, 11.21.

3 β -Chloro-19-hydroxyandrost-5-en-17-one 19-Acetate (XIIC)—i) A solution of 0.10 g. of VIc in 10 ml. of CHCl_3 containing a small amount of water was saturated with HCl gas and the mixture was set aside at room temperature for 12 hr. The solution was added with water, extracted with ether and the ether extract was washed with 5% NaHCO_3 , water, and dried over anhyd. Na_2SO_4 . Evaporation of the solvent yielded an oily residue, which was chromatographed over Al_2O_3 . The benzene eluate, after recrystallization from hexane, afforded XIc as needles of m.p. $99\sim 101^\circ$. $[\alpha]_D -22^\circ$ ($c=2.18$). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{29}\text{O}_3\text{Cl}$: C, 69.12; H, 8.01; Cl, 9.72. Found: C, 68.87; H, 8.04; Cl, 9.80.

ii) A sample of VIc was treated with Ac_2O in pyridine at room temperature. The reaction mixture was worked up as usual to give, after recrystallization from hexane, needles of XIc melting at $98\sim 100^\circ$.

Treatment of 3 β -Chloro-19-hydroxyandrost-5-en-17-one (VIIIc) with Anhydrous Potassium Acetate in Acetic Acid—A mixture of 0.15 g. of VIIIc, 10 ml. of glac. AcOH and 0.30 g. of freshly melted anhyd. AcOK was refluxed for 5 hr. The reaction mixture was poured into water, extracted with ether and the extract was washed with 5% NaHCO_3 , water, and dried over anhyd. Na_2SO_4 . Removal of the solvent yielded 0.155 g. of XIc as an oily product, which was taken in 10 ml. of 3% KOH-EtOH and refluxed on the water bath for 40 min. The reaction mixture was poured into water and extracted with ether. The extract was washed with water, dried and condensed to dryness to yield 0.113 g. of a crystalline residue, which was chromatographed over Al_2O_3 . Elution with CHCl_3 and recrystallization of the product from benzene-hexane gave XIc as needles of m.p. $205\sim 209^\circ$.

3 β -Chloro-19-hydroxypregn-5-en-20-one (VIIIb)—A solution of 0.50 g. of IIb in 400 ml. of acetone and 5 ml. of 10% HCl was heated under reflux for 1 hr. The solution was condensed *in vacuo*, diluted with water and extracted with ether. The extract was washed with aq. NaHCO_3 , water, dried over anhyd. Na_2SO_4 , and condensed to dryness to give 0.493 g. of a crystalline residue melting at $138\sim 145^\circ$. Recrystallization from acetone-hexane yielded VIIIb, m.p. $145\sim 146^\circ$. $[\alpha]_D +43^\circ$ ($c=3.41$). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{31}\text{O}_2\text{Cl}$: C, 71.87; H, 8.90; Cl, 10.14. Found: C, 72.34; H, 8.91; Cl, 9.83. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : *4 3632 (free OH), 3583 (OH- π bond), 1710 (20-CO). IR $\nu_{\max}$ cm^{-1} : 3510 and 3425 (OH), 1712 and 1692 (20-CO).

3 β ,17 β -Dihydroxyandrost-5-en-19-one 3,17-Diacetate (XIId)—To a stirred solution of 0.39 g. (0.001 mole) of IXd in 40 ml. of purified acetone with bubbling dry N_2 , 0.30 ml. (0.001 $\times$ 1.2 moles) of 8N $\text{CrO}_3\text{-H}_2\text{SO}_4$ reagent was added dropwise under ice-cooling and stirring was continued for 5 min. The reaction mixture was treated with EtOH to decompose the excess reagent, diluted with water and extracted with ether. The extract was washed with aq. NaHCO_3 and water, and dried over anhyd. MgSO_4 . Evaporation of the solvent yielded 0.35 g. of a crystalline residue, which was chromatographed over 12 g. of Al_2O_3 . The benzene-hexane (1:1) eluate afforded 0.364 g. of a crystalline product. Recrystallization from hexane gave needles of XIId, m.p. $152\sim 153^\circ$. $[\alpha]_D -246^\circ$ ($c=0.95$). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_5$: C, 71.10; H, 8.30. Found: C, 70.94; H, 8.18.

3 β -Hydroxyandrost-5-ene-17,19-dione 3-Acetate (XIIC)—To a stirred solution of 0.108 g. of Kc in 10 ml. of acetone with bubbling of N_2 gas, 0.09 ml. of Jones reagent was added at $12\sim 14^\circ$ and stirred continued for 8 min. The reaction mixture was treated as described for XIId to yield 0.103 g. of a crystalline product, which was recrystallized from benzene-hexane to give 0.083 g. of XIIC melting at $143\sim 146^\circ$. An analytical sample was obtained by further recrystallization from hexane as needles of m.p. $147\sim 150^\circ$. $[\alpha]_D -228.3^\circ$. *Anal.* Calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_4$: C, 73.22; H, 8.19. Found: C, 73.66; H, 8.27. IR $\nu_{\max}$ cm^{-1} : 1745, 1727 and 1718 (shoulder). UV $\lambda_{\max}^{\text{EtOH}}$ m μ : 305 (ϵ 140). NMR τ : 9.14 (18- CH_3), 4.17 (6-vinyl H), 0.05 (CHO).

3 β -Hydroxyandrost-5-ene-17,19-dione (XIVc)—A solution of 0.057 g. of XIIIc in 25 ml. of 2% KOH-MeOH and 2 ml. of benzene was allowed to stand at room temperature for 13 hr. and worked up as usual to give 0.044 g. of a crystalline product. Recrystallization from benzene-hexane afforded needles of XIVa, m.p. 149~150°. $[\alpha]_D -177.6^\circ$ ($c=1.72$). *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.38; H, 8.80. IR $\nu_{\max}^{CCl_4}$ cm^{-1} : 3623 and 3613 (OH), 2700 and 1727 (CHO), 1748 (17-CO). UV $\lambda_{\max}^{EtOH}$ $m\mu$: 305 (ϵ 145). NMR τ : 9.15 (18-CH₃), 4.18 (6-vinyl H), 0.03 (CHO).

Jones Oxidation of 3 α ,5-Cyclo-6 β ,19-oxido-5 α -androstane-17-one (IIc)—i) with two equivalent molar oxidant. To a stirred solution of 0.20 g. of IIc in 20 ml. of purified acetone with N₂-bubbling, 0.35 ml. of Jones reagent was added dropwise at 10° and stirring was continued for 10 min. The reaction mixture was treated with MeOH to decompose the excess oxidant, diluted with water, condensed *in vacuo* at 40° and extracted with AcOEt. The extract was washed with 5% NaHCO₃ and water, dried, and condensed to dryness *in vacuo* yielded 0.188 g. of a crystalline material, which was recrystallized from benzene-hexane to afford 0.172 g. of 3 α ,5-cyclo-5 α -androstane-6,17,19-trione (XIXc), m.p. 222~225°, $[\alpha]_D +108.5^\circ$ ($c=1.76$). *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.92; H, 8.04. IR $\nu_{\max}$ cm^{-1} : 1733 (17-CO), 1717 (CHO), 1683 (6-CO). NMR τ : 9.3 (cyclopropane), 9.04 (18-CH₃), 0.23 (CHO).

ii) with the excess oxidant. To a stirring solution of 2.0 g. of IIc in 200 ml. of acetone at 10~15° under N₂ atmosphere, 27 ml. of Jones reagent was added dropwise for 10 min. and stirring was further continued for 20 min. at room temperature. MeOH was added to decompose the excess reagent and the reaction mixture was diluted with water, condensed *in vacuo* and extracted with AcOEt. The extract was shaken with aq. NaHCO₃. The aqueous layer was separated, acidified with dil. HCl, and extracted with AcOEt. The extract was washed with satd. aq. NaCl, dried, and evaporated to give a crystalline product, which was recrystallized from AcOEt-hexane to afford 1.90 g. of 3 α ,5-cyclo-5 α -androstane-6,17-dion-19-oic acid (XXc), m.p. 260~262°, $[\alpha]_D +118.7^\circ$. *Anal.* Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.91; H, 7.58. IR $\nu_{\max}$ cm^{-1} : 1736, 1715, 1658 and 1645. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1738, 1706, 1701 (shoulder) and 1695.

Jones Oxidation of 3 α ,5-Cyclo-6 β ,19-oxido-17 β -hydroxy-5 α -androstane 17-Acetate (IIId)—To a solution of 32.5 g. of IIId in 3.5 L. of purified acetone with vigorous stirring and N₂ bubbling, 51 ml. of Jones reagent was added dropwise for several minutes at 9°. After stirring for additional 10 min., the reaction mixture was added with 50 ml. of EtOH to decompose the excess oxidant, diluted with ca. 500 ml. of water, condensed *in vacuo* to ca. 1.5 L. at below 25° under N₂ atmosphere, and extracted with ether. The extract was washed with aq. NaHCO₃, water, dried, and condensed to dryness to give 28 g. of a crystalline product, which was recrystallized from benzene-hexane to afford 12 g. of 3 α ,5-cyclo-17 β -hydroxy-5 α -androstane-6,19-dione 17-acetate (XIXd) melting at 138~144°. The mother liquor of recrystallization was chromatographed over 250 g. of Al₂O₃. Elution with benzene gave 10.4 g. of a crystalline material, which was recrystallized from benzene-hexane to afford additional 7.2 g. of XIXd (combined yield, 19.2 g., 56%). Further recrystallization afforded an analytical sample as needles of m.p. 149~151°. $[\alpha]_D +4.3^\circ$ ($c=3.49$). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.55; H, 8.12. IR $\nu_{\max}$ cm^{-1} : 1733 (OAc), 1706 (CHO), 1686 (6-CO).

The aq. NaHCO₃ layer described above was acidified with dil. HCl and extracted with CHCl₃-ether. The extract was washed with water, dried, and condensed to dryness to give 5.5 g. of a crystalline, acidic material. Recrystallization from EtOH-hexane afforded 3 α ,5-cyclo-17 β -hydroxy-5 α -androstane-6-on-19-oic acid 17-acetate (XXd) as scales, m.p. 271~274° (decomp.). $[\alpha]_D +9.2^\circ$ ($c=4.40$). *Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.76; H, 7.77. IR $\nu_{\max}$ cm^{-1} : 1742 and 1238 (OAc), 1695 and 1684 (6-CO and COOH). NMR τ : 9.24 (cyclopropane), 9.17 (18-CH₃), 7.93 (OAc).

3 α ,5-Cyclo-5 α -cholestane-6,19-dione (XIXa)—i) To a solution of 12.0 g. of IVa in 1.5 L. of acetone at 4~8°, 19.5 ml. of Jones reagent was added rapidly for ca. 30 sec. with vigorous stirring and stirring was further continued for 4 min. The reaction mixture was treated as described above to yield, after recrystallization from MeOH, 5.7 g. of a crystalline product melting at 114~117°. The mother liquor was condensed to dryness and chromatography over Al₂O₃ afforded additional 2.01 g. of a crystalline material from the benzene-hexane (1:1) eluate. The combined crystals were further recrystallized from MeOH to give XIXa as prisms, m.p. 119.5~121.5°. $[\alpha]_D +20.8^\circ$ ($c=1.30$). *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.14; H, 10.56. IR $\nu_{\max}$ cm^{-1} : 1718 (CHO), 1684 (6-CO). NMR τ : 9.27 (18-CH₃), 0.19 (CHO).

ii) To a stirred solution of 0.385 g. of IIa in 46 ml. of acetone with bubbling N₂ stream, 0.5 ml. of Jones reagent was added dropwise at 6~8°. After stirring for 4 min., the reaction mixture was worked up as described above to yield 0.41 g. of a reaction product. Chromatography over Al₂O₃ gave XIXa melting at 118~122° from the benzene eluate.

3 α ,5-Cyclo-5 α -cholestan-6-on-19-oic Acid (XXa)—To a solution of 5.0 g. of IIa in 500 ml. of acetone with vigorous stirring was added dropwise 48 ml. of Jones reagent at 10~15° and stirring was further continued for 30 min. at room temperature. The reaction mixture was treated as described above to yield 4.2 g. of an acidic material, which was recrystallized from hexane to afford XXa melting at 220~221°. $[\alpha]_D +49^\circ$ ($c=1.90$). *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.21; H, 10.08. IR $\nu_{\max}$ cm^{-1} : 1718 (COOH), 1689 (6-CO), 1650.

3 α ,5-Cyclo-5 α -pregnane-6,20-dione-19-oic Acid (XXb)—To a stirred solution of 8.0 g. of IIb in 1.6 L. of acetone, 80 ml. of Jones reagent was added dropwise for 20 min. at 10–15° and stirring was continued at 11° for 20 min., then at 18° for additional 30 min. The excess oxidant was decomposed by adding ca. 100 ml. of MeOH and the reaction mixture was condensed *in vacuo*, poured into ice-water and extracted with AcOEt. The extract was shaken with 5% NaHCO₃ and the alkaline layer was acidified with dil. HCl and again extracted with AcOEt. The extract was washed with water, dried, and condensed to dryness *in vacuo* to leave 5.9 g. of a crystalline product, which was recrystallized from acetone-hexane to give 4.7 g. of XXb melting at 234–243°. Further recrystallizations afforded an analytically pure sample of m.p. 244–245° (decomp.). *Anal.* Calcd. for C₂₁H₂₈O₄: C, 73.22; H, 8.19. Found: C, 72.94; H, 8.22. IR $\nu_{\max}$ cm⁻¹: 3300 (broad, OH), 1740 (COOH), 1700 (20-CO), 1690 (3 α ,5-cyclo-6-CO).

Jones Oxidation of 3 α ,5-Cyclo-6 β ,19-dihydroxy-5 α -androstane-17-one (IVc)—i) with two equivalent molar oxidant. To a stirred solution of 0.20 g. of IVc in 20 ml. of acetone with dry N₂-stream, 0.35 ml. of Jones reagent was added dropwise at 10° and stirring was further continued for 5 min. The reaction mixture was worked up as the manner described for IIc to afford, after recrystallization from benzene-hexane, 0.184 g. of XIXc melting at 219–221°.

ii) with the excess oxidant. To a solution of 0.80 g. of IVc in 500 ml. of purified acetone with vigorous stirring, 1.25 g. of Jones reagent was added dropwise at 15–17°. After stirring for 25 min., the reaction mixture was treated as described for IIc to give, after recrystallization from AcOEt-hexane, 0.735 g. of XXc melting at 259–261°.

Jones Oxidation of 3 α ,5-Cyclo-6 β ,17 β ,19-trihydroxy-5 α -androstane 17-Monoacetate (IVd)—To a solution of 10.1 g. of IVd in 1.3 L. of acetone with vigorous stirring and dry N₂-bubbling, 7.2 ml. of Jones reagent was added for 1.5 min. at 10–12°. After stirring for 1.5 min., additional 7.2 ml. of the oxidant was added for 1.5 min. and stirring continued for 3 min. The reaction mixture was worked up as described for IIc to give 9.5 g. of a crystalline material, which was recrystallized from benzene-hexane to afford 5.40 g. of needles of XIXd, m.p. 140–147°. Chromatography of the mother liquor over Al₂O₃ gave further 1.10 g. of XIXd from the benzene eluate.

Sodium Borohydride Reduction of 3 α ,5-Cyclo-5 α -androstane-6,17,19-trione (XIXc) in Tetrahydrofuran—To a stirred solution of 0.50 g. of XIXc in 25 ml. of purified tetrahydrofuran was added 0.10 g. of NaBH₄ in 2.0 ml. of water and stirring was continued for 3 hr. at room temperature. AcOH was added to decompose the excess reagent and the reaction mixture was diluted with water, extracted with AcOEt. The extract was washed with 5% NaHCO₃ and water, dried over Na₂SO₄, and condensed to dryness *in vacuo* to leave a crystalline product, which was chromatographed over 20 g. of Al₂O₃ (neutral, Woelm grade I). The first fraction eluted with benzene-ether (1:1) gave 0.409 g. of a crystalline product, which was recrystallized from MeOH to afford 3 α ,5-cyclo-5 α -androstane-6 α ,17 β ,19-triol (XXII) as needles of m.p. 164.5–165°, [α]_D +90.0° (dioxane). *Anal.* Calcd. for C₁₉H₃₀O₃: C, 72.34; H, 9.91. Found: C, 71.92; H, 9.94.

Further elution with the same mixture of solvents yielded 0.037 g. of another product, which was recrystallized from MeOH to give needles of 3 α ,5-cyclo-5 α -androstane-6 β ,17 β ,19-triol (XXI), m.p. 127–131°. This was identified with the authentic specimen prepared by NaBH₄ reduction of 3 α ,5-cyclo-5 α -androstane-17-one-6 β ,19-diol (IVc).

3 α ,5-Cyclo-5 α -androstane-6 β ,17 β ,19-triol (XXI)—To a solution of 0.20 g. of IVc in 20 ml. of MeOH, 0.050 g. of NaBH₄ in water was added at room temperature and stirring was continued for 3 hr. The reaction mixture was treated as described above to yield a crystalline product, which was chromatographed over 7.0 g. of Al₂O₃. The combined eluates with benzene-ether (4:1 and 7:3) gave 0.175 g. of crystals, which was recrystallized from MeOH to afford XXI as needles melting at 133–135° (sintering at 127°), [α]_D +52.8° (dioxane). *Anal.* Calcd. for C₁₉H₃₀O₃ · ½ H₂O: C, 72.34; H, 9.91. Found: C, 72.10; H, 9.82.

TABLE I.

6 β ,17 β ,19-triol (XXI)		6 α ,17 β ,19-triol (XXII)	
time (min.)	[α] _D	time (min.)	[α] _D
0 ^{a)}	+52.8°	0 ^{a)}	+90°
6	+26	10	+95
10	+9.4	15	+81.7
15	+4.7	60	+81.7
25	–4.7	600	+80
70	–32.8	1560	+41.7 (37% rearranged)
240	–42.2	3960	+9.3 (62% rearranged)
540	–42.2		

a) Values in dioxane in the absence of acid.

Treatment of 3 α ,5-Cyclo-5 α -androstane-6 β ,17 β ,19-triol (XXI) and its 6 α -Epimer (XXII) with 60% Perchloric Acid in 90% aq. Dioxane—Each solution prepared from 0.04272 g. of 6 β ,17 β ,19-triol (XXI) and 0.04283 g. of 6 α ,17 β ,19-triol (XXII) in 5 ml. of 90% dioxane containing 6 drops of 60% HClO₄ was let stand at 27~28° and the changes of optical rotations were measured separately as shown in Table I.

When the solution of 6 α ,17 β ,19-triol (XXII), after allowing to stand at 27~28° for 66 hr., was heated at 70° for 4 hr., the observed $[\alpha]_D^{25}$ value was finally reached at -40°, the value for 3 β ,17 β ,19-trihydroxyandrost-5-ene (XXIII). The solutions were separately made alkaline with aq. NaHCO₃, concentrated *in vacuo*, and extracted with CHCl₃. Each extract was washed with water, dried, and condensed to dryness to give a crystalline product of the same 3 β ,17 β ,19-trihydroxyandrost-5-ene (XXIII) melting at 222~228°.

3 β ,17 β ,19-Trihydroxyandrost-5-ene (XXIII)—To a solution of 0.10 g. of VIIc in 50 ml. of EtOH was added 0.05 g. of NaBH₄ in water and stirring continued for 2 hr. at room temperature. The reaction mixture was worked up as described for XXI to give a crystalline product, which was recrystallized from EtOH-H₂O to afford needles of XXIII, m.p. 227~232°. An analytical sample was evacuated at 70° for 10 hr. *Anal.* Calcd. for C₁₉H₃₀O₃: C, 74.47; H, 9.87. Found: C, 74.00; H, 9.67. $[\alpha]_D^{25}$ -42.1° (EtOH).

The authors are grateful to Prof. K. Tsuda, Director of Institute of Applied Microbiology, the Univ. of Tokyo and Dr. G. Sunagawa, Director of this Laboratories for their continuing encouragement. Thanks are also due to Mr. Nakazawa for skilled technical help and to the members of Section of Physical Chemistry in this Laboratories for measurements of physical and elemental analytical data.

[Chem. Pharm. Bull.
15(1) 27 ~ 37 (1967)]

UDC 547.92.07

4. Katsumi Tanabe, Rinji Takasaki, Ryoza Hayashi, Yasuhiro Morisawa, and Teruo Hashimoto: Steroid Series. XVII.*¹ New Synthetic Routes to 19-Norsteroids (1).*²

(Central Research Laboratories, Sankyo Co., Ltd.*³)

19-Nor- Δ^4 -3-oxosteroid (IX) was synthesized starting from 3 α ,5 α -cyclo-6 β ,19-oxidosteroid (I) through 3 β -substituted- Δ^5 -steroid-19-oic acid (VII), whose synthesis was achieved by the three methods: i) Hydrolysis of 3 β -hydroxy- Δ^5 -steroid-19-oic acid 3,19-lactone (VI) which was prepared by oxidizing either 3 β ,19-dihydroxy- Δ^5 -steroid (III) or 3 β -hydroxy-19-oxo- Δ^5 -steroid (V) with Jones reagent or Oppenauer reaction, ii) Oxidation of 3 β ,19-dihydroxy- Δ^5 -steroid 3-acetate (III) with the excess Jones reagent, iii) Reduction of 3 α ,5 α -cyclo-6-oxo-19-oic acid (IV) with sodium borohydride and subsequent acid-catalysed solvolysis of a mixture of resultant 6-epimeric hydroxy acids (XIII and XIV) in a suitable solvent. 3 β -Substituted- Δ^5 -steroid-19-oic acid (VII) was in turn converted to 19-nor- Δ^4 -3-oxosteroid (IX) in two ways: i) Oxidation of 3 β -hydroxy compound and subsequent acid-treatment of the resultant Δ^5 -3-oxosteroid-19-oic acid (VIII), ii) Pyrolysis of the 3 β -acetoxo- Δ^5 -steroid-19-oic acid (VII) to afford 3 β -acetoxo- Δ^5 (¹⁰)-steroid (XI), followed by alkaline hydrolysis, Jones oxidation, and acid-treatment, successively.

(Received February 23, 1966)

In a preceding paper*¹ we described the preparation of 3 α ,5 α -cyclo-6 β ,19-oxido-steroids (I) by the action of lead tetraacetate on 3 α ,5 α -cyclo-6 β -hydroxysteroids and acid-catalysed solvolysis reactions of the products to afford, depending upon the reaction conditions, 19-hydroxylated 3 α ,5 α -cyclo-6 β - (II) or Δ^5 -3 β -substituted steroids (III). Oxidation of the oxido compounds (I) leading directly to 3 α ,5 α -cyclo-6-oxosteroid-19-oic acids (IV) was also described. The present investigation was undertaken in order

*¹ Part XVI: This Bulletin, 15, 15 (1967).

*² A part of this work was presented at the 82th Annual Meeting of the Pharmaceutical Society of Japan at Shizuoka, Oct. 1962.

*³ 1-2-58, Hiromachi, Shinagawa-ku, Tokyo (田部克巳, 高崎林治, 林 了三, 森沢靖弘, 橋本輝夫).