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.[5]

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, Ryozo Hayashi, Yasuhiro Morisawa and Teruo Hashimoto : Steroid Series. XVI.*1 The Preparation of 3α,5α-Cyclo-6β,19-oxidosteroids and its Conversion to 19-Oxygenated Steroid Derivatives.*2

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

3α,5α-Cyclo-6β,19-oxidosteroid (II) was synthesized by the lead tetraacetate oxidation of 3α,5α-cyclo-6β-hydroxysteroid (I) in benzene. The acid-catalysed solvolysis of the oxide (II) afforded 3α,5α-cyclo-19-hydroxy-6β-substituted steroid (XVI) and/or Δ^5-19-hydroxy-3β-substituted steroid (XVII), depending upon the reaction conditions employed. Oxidation of the oxide (II) with Jones reagent gave 3α,5α-cyclo-6β,19-dioxosteroid (XIX) with two equivalent molar oxidant, and 3α,5α-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 groups[1] for preparation of the C-19 substituted steroid,[2] which is an useful

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

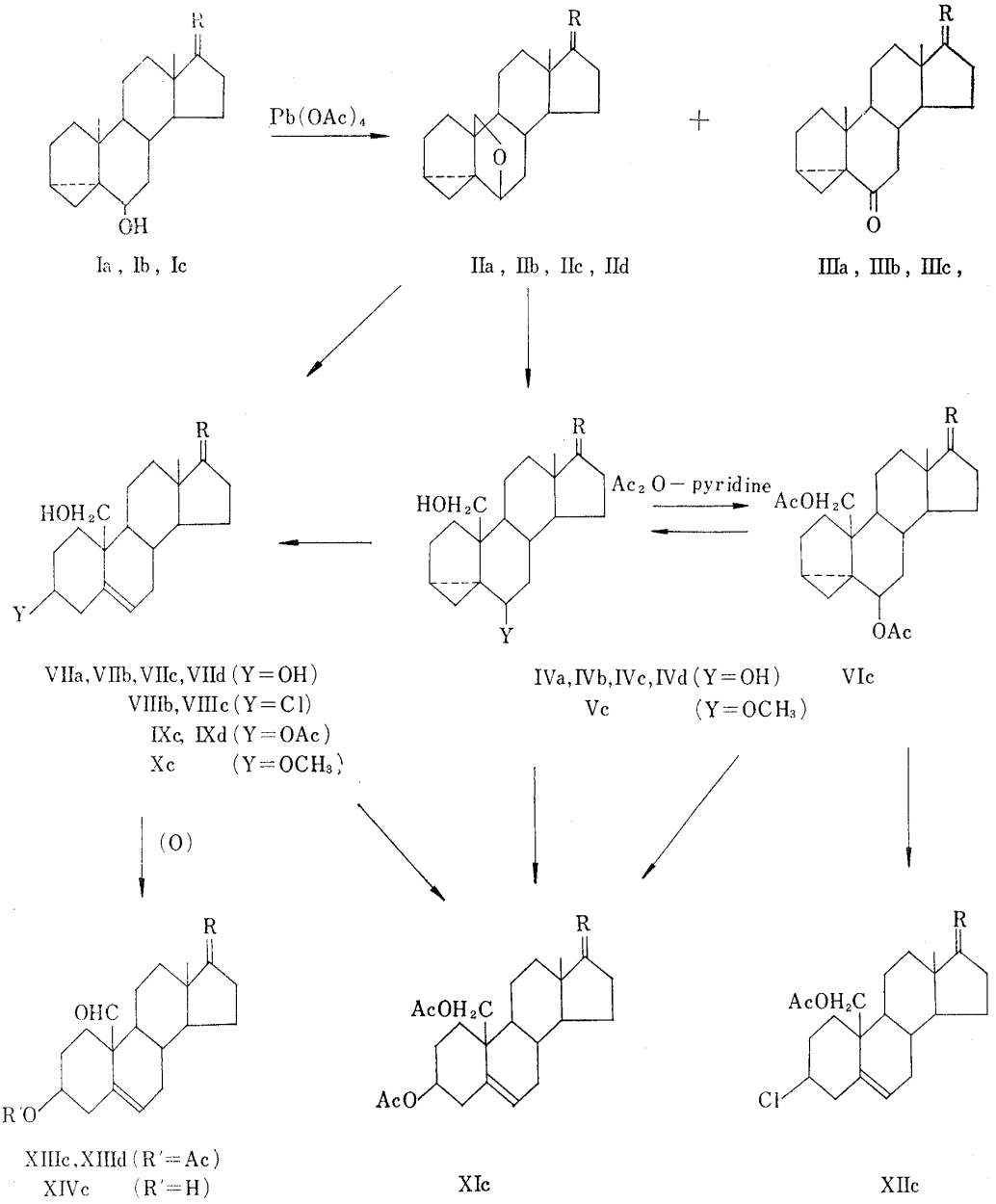
*2 A part of this work was presented as a communication : K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, Y. Morisawa : This Bulletin, **10**, 1126 (1962).

*3 1-2-58, Hiromachi, Shinagawa-ku, Tokyo (田部克巳, 高崎林治, 酒井 浄, 林 了三, 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. Ibánêz, 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.

intermediate for synthesis of the biologically important 19-norsteroid. In this connection we have synthesized 3α,5α-cyclo-6β,19-oxidosteroids (II) which were anticipated to exhibit reactivities toward acidic conditions, similar to those of 3α,5α-cyclo-6β-oxygenated steroid (I)[3] from the structural similarity and thus might be convertible under mild conditions to Δ^5-3β, 19-dioxygenated steroids. In a previous communication*[2] we have briefly reported the preparation of 3α,5-cyclo-6β,19-oxido-5α-androstan-17-one (IIc) by oxidation of 3α,5-cyclo-6β-hydroxy-5α-androstan-17-one (Ic) with lead tetraacetate and its conversion to 19-oxygenated derivatives by the acid-catalysed solvolysis or oxidation reactions. Subsequent to our publication, three independent papers[4] have



a : R=—C_8H_{17}, b : R=—$COCH_3$, c : R=O, d : R=—OAc

Chart 1.

3) L. Fieser & M. Fieser : "Steroids," Reinhold Publishing Corp., New York, 314 (1959).
4) *a*) J. Tadaniel : J. Org. Chem., **28**, 1744 (1963); *b*) R. Moriarty, T. D. D'Silver : *Ibid.*, **28**, 2445(1963); *c*) P. B. Sollman : *Ibid.*, **28**, 3559 (1963).

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

3α,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, 3α,5-cyclo-6β, 19-oxido-5α-androstan-17-one (IIc), together with a small amount of 3α,5-cyclo-5α-androstane-6,17-dione (IIIc).

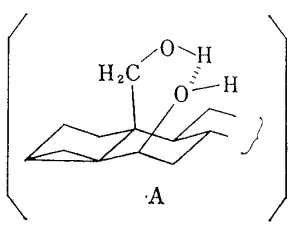
The infrared (IR) spectrum of 3α,5-cyclo-6β,19-oxido-5α-androstan-17-one (IIc) showed, besides a weak band at 3058 cm^{-1} due to cyclopropane, five to six bands in the region of 1100~850 cm^{-1} indicating the presence of a substituted tetrahydrofuran ring and a weak but sharp one at 1485 cm^{-1} ascribable 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 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 9.1~9.3τ and 9.6~9.8τ indicating the presence of the 3α,5α-cyclo structure. Resonance signal due to 6α-proton appeared at 6.10τ as quasi doublet (j=5.0 c.p.s.), whereas the corresponding one in 3α,5-cyclo-6β-hydroxy-5α-androstan-17-one (Ic) was observed at 6.69τ as quasi triplet (j=2.8 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 3α,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 3α,5-cyclo-6β,19-dihydroxy-5α-androstan-17-one (IVc) in 92% yield, while on heating the reaction mixture at 50~60°, the oxide was converted into 3β,19-dihydroxy-androst-5-en-17-one (VIc), which was also obtainable on heating 3α,5α-cyclo-6β,19-diol (IVc) in an aqueous solvent containing diluted sulfuric acid at 70°. When 3α,5α-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 (VIIc), which was also formed directly from the oxide (IIc) under the same reaction conditions.

Examination of an infrared spectrum*4 of 3α,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 3α,5α-cyclo-6β,19-diol (IVc) in dry chloroform containing a drop of acetic acid displayed, besides a complex signals at 9.2~9.8τ due to cyclopropyl protons, a pair of doublets (j=10.2 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 (Vc) resonance peaks due to 19-methylene protons and 6α-proton appeared as a singlet at 5.77τ and as a triplet (j=2.5 c.p.s.) at 5.49τ, respectively. The 19-methylene protons in 3α,5α-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 runned 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 3α,5α-cyclo-6β,19-diol (IVc) predominantly exists as formula (A).



A

5) A. Butenandt, L. A. Surányl : Ber., **75**, 592 (1942).
6) J. F. Bagli, P. F. Morand, R. Gaudry : J. Org. Chem., **28**, 1207 (1963).

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

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

Methanolysis of 3α,5-cyclo-6β,19-oxido-5α-androstan-17-one (Ⅱc) in the presence of a catalytic amount of boron trifluoride etherate at $-5°$ afforded 3α,5-cyclo-6β-methoxy-19-hydroxy-5α-androstan-17-one (Ⅴc) in 90% yield, together with a small amount of isomeric 3β-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 3α,5α-cyclo-6β-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 3α,5α-cyclo-6β,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 3β,19-dihydroxyandrost-5-en-17-one 3-acetate (Ⅸc), which was acetylated with acetic anhydride in pyridine to give the corresponding 3β,19-diacetate (Ⅸc) described above. The structure of Δ^5-3β-acetoxy-19-ol (Ⅸc) was based on the fact that Jones oxidation[7] of the monoacetate (Ⅸc) with one equivalent molar oxidant furnished 3β-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 3β-ol (XⅣc) were observed at 4.17~4.18τ, being obviously shifted downfield compared with the corresponding resonance at 4.58τ in 3β-hydroxyandrost-5-en-17-one 3-acetate. Singlet resonances due to 18-methyl protons in these 19-oxo-steroids (XⅢc and XⅣc) appeared at 9.14~9.15τ,*6 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 9.11τ in 3β-hydroxyandrost-5-en-17-one 3-acetate.

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

The infrared spectrum*4 of Δ^5-3β-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.[8] The NMR resonances due to 6-vinyl protons of 3β,19-dihydroxyandrost-5-en-17-one 3-acetate (Ⅸc) and 3β-methoxy-19-hydroxyandrost-5-en-17-one (Ⅹc), both having the common partial

*6 Δ^5-3β-hydroxy-6,19-dione (XⅣc) had two peaks due to 18-methyl protons at 9.06 and 9.15τ, having relative intensity of ca. 1:5. The minor peak at 9.06τ might be attributable to the signal for Δ^5-3β,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. Bacskai : J. Am. Chem. Soc., **80**, 6691 (1958).

structure of Δ^5-19-hydroxyl appeared respectively at 4.18 and 4.20τ, which were shifted downfield by 0.25 to 0.30 p.p.m. in comparison with the corresponding signal at 4.58τ in 3β-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^5-3β-chloro-19-alcohol (VIIIc). In fact, acetylation of the 19-hydroxyl of IXc 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 3α,5α-cyclo-6β,19-oxide (IIc) described thus far clearly suggested that an initial cleavage of the oxide bridge occurred at C_6-position with a consequent formation of 19-hydroxylated homoallylic cation (XV) and a subsequent β-attack of anions at C_6- or C_3-positions, depending upon the reaction conditions employed, gave rise to 3α,5α-cyclo-6β- (XVI) or Δ^5-3β-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 C_3- or C_6-positions as the well-established one for 19-methyl homoallylic cation (XVIII).[3] The high yield formation of 3α,5α-cyclo-6β,19-disubstituted steroids (IVc and Vc) implies that the acid-catalysed solvolysis reactions of 3α,5α-cyclo-6β,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] 3α,5α-cyclo-6β-substituted-19-alcohol (XVI) regenerates the same intermediate (XV), which in turn rearranges to the more stable Δ^5-3β-substituted-19-alcohol (XVII).

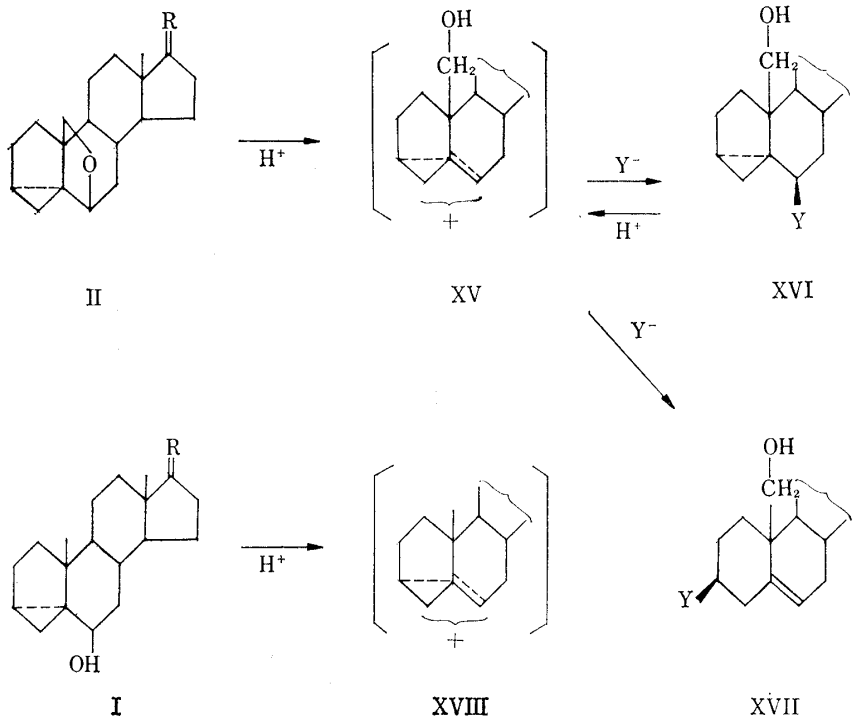


Chart 2.

In fact, 3α,5-cyclo-6β,19-oxido-5α-cholestane (IIa) gave 3α,5-cyclo-6β,19-dihydroxy-5α-cholestane (IVa) in a mild acidic medium at room temperature for 4 hours, whereas the latter compound could be converted into 3β,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 3α,5-cyclo-6β,19-oxido-5α-androstan-17-one (IIc) afforded in high yields 3α,5-cyclo-5α-androstane-6,17,19-trione (XIXc) with two equivalent molar of Jones reagent[7] and 3α,5-cyclo-5α-androstane-6,17-dione-19-oic acid (XXc) with the excess reagent. These were also prepared by oxidation of 3α,5α-cyclo-6β,19-diol (IVc) with the same reagent.

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

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

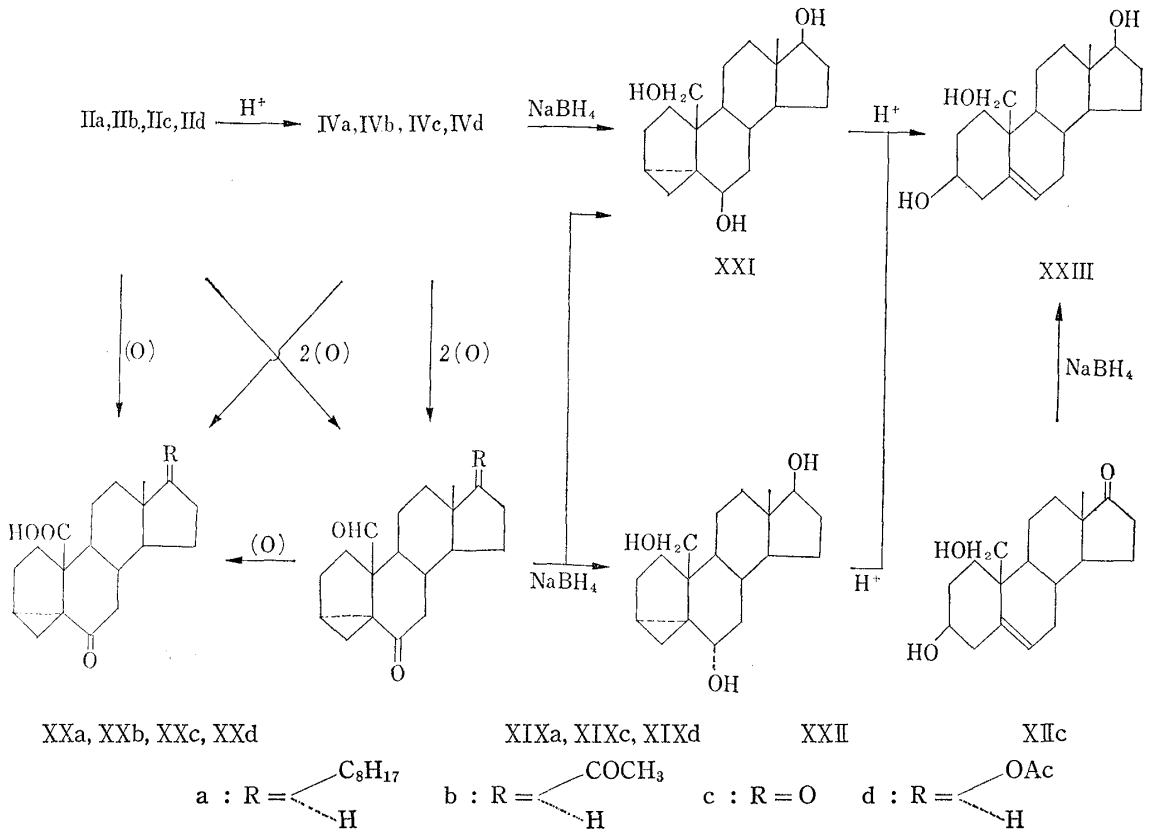


Chart 3.

The relative rates of the acid-catalysed solvolysis reactions of the C_6-epimeric triols (XXI and XXII) were also in accord with this assignment: The $[\alpha]_D$ value of a solution of the 6β-ol (XXI) decreased rapidly from the initial +52.8° to −42.5°, a close value for Δ^5-3β,17β,19-triol (XXIII), during 4 hours in aqueous dioxane containing concentrated perchloric acid, while the 6α-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 3α,5-cyclo-5α-cholestan-6α- and 6β-ols.[11] However, the elution order of the triols (XXI and XXII) from an alumina column was found to be reversed to the one[12] observed for the 3α,5α-cyclo-6-alcohols, the 3α,5α-cyclo-6α,17β,19-triol (XXII) with an C_6-equatorial hydroxyl group being eluted more rapidly than the 6β-axial alcohol (XXI).

Experimental*8

Lead Tetraacetate Oxidation of 3α,5-Cyclo-6β-hydroxy-5α-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. $Na_2S_2O_3$, and water, successively and dried over anhyd. Na_2SO_4. Removal of the solvent yielded a syrupy residue, which was chromatographed over 30 g. of Al_2O_3. 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°, $[\alpha]_D$ +150.1° (c=2.16). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.31; H, 9.21. IR ν_{max} cm^{-1}: 3058 (cyclopropane), 1485 (19-CH_2-). NMR τ: 9.10~9.30 and 9.60~9.80 (3α,5-cyclopropyl protons), 9.06 (18-CH_3), 6.56 (doublet) and 6.08 (doublet) (j=7.0 c.p.s., 19-CH_2-), 6.10 (doublet, j=5.0 c.p.s., 6α-H).

Further elution with hexane-benzene (1:1) gave a small amount of a crystalline material, which was recrystallized from hexane-benzene to give IIIc as needles of m.p. 185~187°. The identity with an authentic sample prepared by oxidation of Ic with CrO_3 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 3α,5-Cyclo-6β-hydroxy-5α-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. $Na_2S_2O_3$, and water and dried over anhyd. Na_2SO_4. Evaporation of the solvent yielded an oily residue, which was chromatographed over Al_2O_3. 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°. $[\alpha]_D$ +74° (c=2.16). *Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.32; H, 11.53. Found: C, 83.99; H, 11.64. IR ν_{max} cm^{-1}: 1493 (19-CH_2-). NMR τ: 9.5~9.7 (cyclopropane), 9.27 (18-CH_3), 6.07 (doublet) and 6.60 (doublet) (j=7.5 c.p.s., 19-CH_2-), 6.13 (6α-H).

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

Lead Tetraacetate Oxidation of 3α,5-Cyclo-6β-hydroxy-5α-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 Al_2O_3.

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 $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.02; H, 9.55. IR ν_{max} cm^{-1}: 1488 (19-CH_2-).

3α,5-Cyclo-6β,19-oxido-17β-hydroxy-5α-androstane 17-Acetate (IId)——To a stirred suspension of 2.0 g. of $LiAlH_4$ 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. $NaHCO_3$ and water, dried over anhyd. Na_2SO_4, and condensed to dryness to yield 2.9 g. of a crystalline material. Recrystallization from benzene-hexane afforded 2.1 g. of 3α,5-cyclo-6β,19-oxido-17β-

*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, $[\alpha]_D$ values relate to chloroform and Al_2O_3 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).
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hydroxy-5α-androstane as plates, m.p. 181~183°. $[\alpha]_D$ +73.4° (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 17β-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 IId melting at 125.5~127°. $[\alpha]_D$ +55.6° (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.

3α,5-Cyclo-6β,19-dihydroxy-5α-androstan-17-one (IVc)——A solution of 3.0 g. of IIc 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°. *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}:*4 3060 (cyclopropane), 3613 (6-OH), 3462 (intramolecular hydrogen bonded hydroxyl). NMRτ: 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 (6α-H).

3α,5-Cyclo-6β,17β,19-trihydroxy-5α-androstane 17-Monoacetate (IVd)——A solution of 10.5 g. of IId 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° (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).

3α,5-Cyclo-6β,19-dihydroxy-5α-cholestane (IVa)——A solution of 60 g. of IIa 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° (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). NMRτ: 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., 6α-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 3α,5-Cyclo-6β,19-oxido-5α-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.

3α,5-Cyclo-6β,19-dihydroxy-5α-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. NMRτ: 9.5 (cyclopropane), 9.03 (18-CH_3), 7.98 (OAc), 5.77 (19-CH_2-).

3β,19-Dihydroxyandrost-5-en-17-one (VIIc)——i) A solution of 3.40 g. of IIc 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°. *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°.

3β,17β,19-Trihydroxyandrost-5-ene 17-Monoacetate (VIId)——A mixture of 1.0 g. of IId, 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 VIId, m.p. 201~203°. $[\alpha]_D$ −59.5° (c=1.81). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.54; H, 9.18.

3β,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°. $[\alpha]_D$ −27° (c=2.18). An analytical sample was evacuated at 80° for 4 hr. *Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.23; H, 11.50.

Methanolysis of 3α,5-Cyclo-6β,19-oxido-5α-androstan-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 3α,5-cyclo-6β-methoxy-5α-androstan-17-one (Vc), m.p. 104~105°. $[\alpha]_D$ +145.2°. *Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.04; H, 9.76. NMRτ: 9.2~9.4 (cyclopropane), 9.01 (18-CH_3), 6.57 (OCH_3). IR $\nu_{max}^{CCl_4}$ 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 3β-methoxy-19-hydroxyandrost-5-en-17-one (Xc) as needles melting at 145°, $[\alpha]_D$ +8.6°. *Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.13; H, 9.64. NMRτ: 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 3α,5-Cyclo-6β-methoxy-19-hydroxy-5α-androstan-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°.

3β,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 $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.41; H, 8.39. NMRτ: 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°.

3β,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 IXc, m.p. 161°. *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80, H, 8.73. Found: C, 72.91; H, 8.54. IR ν_{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 IXc melting at 161°.

The 3-monoacetate (IXc) was acetylated with Ac_2O in pyridine at room temperature to afford Xc of m.p. 106~108°.

3β,17β,19-Trihydroxyandrost-5-ene 3,17-Diacetate (IXd)——A solution of 3.2 g. of IId 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 149.5~150.5°. $[\alpha]_D$ −58.4° (c=2.82). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.85; H, 8.57.

3β-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. 164~166°. $[\alpha]_D$ +30.4° (c=1.87). *Anal.* Calcd. for $C_{19}H_{27}O_2Cl$: C, 70.69; H, 8.37; Cl, 11.01. Found: C, 70.57; H, 8.26; Cl, 11.21.

3β-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 XIIc as needles of m.p. 99~101°. $[\alpha]_D$ −22° (c=2.18). *Anal.* Calcd. for $C_{21}H_{29}O_3Cl$: C, 69.12; H, 8.01; Cl, 9.72. Found: C, 68.87; H, 8.04; Cl, 9.80.

ii) A sample of VIIIc 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 XIIc melting at 98~100°.

Treatment of 3β-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 Xc 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 VIIc as needles of m.p. 205~209°.

3β-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 138~145°. Recrystallization from acetone-hexane yielded VIIIb, m.p. 145~146°. $[\alpha]_D$ +43° (c=3.41). *Anal.* Calcd. for $C_{21}H_{31}O_2Cl$: C, 71.87; H, 8.90; Cl, 10.14. Found: C, 72.34; H, 8.91; Cl, 9.83. IR $\nu_{max}^{CCl_4}$ cm^{-1}:*4 3632 (free OH), 3583 (OH-π bond), 1710 (20-CO). IR ν_{max} cm^{-1}: 3510 and 3425 (OH), 1712 and 1692 (20-CO).

3β,17β-Dihydroxyandrost-5-en-19-one 3,17-Diacetate (XIIId)——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. (0.001×1.2 moles) of 8*N* CrO_3-H_2SO_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 XIIId, m.p. 152~153°. $[\alpha]_D$ −246° (c=0.95). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.94; H, 8.18.

3β-Hydroxyandrost-5-ene-17,19-dione 3-Acetate (XIIIc)——To a stirred solution of 0.108 g. of IXc in 10 ml. of acetone with bubbling of N_2 gas, 0.09 ml. of Jones reagent was added at 12~14° and stirred continued for 8 min. The reaction mixture was treated as described for XIIId to yield 0.103 g. of a crystalline product, which was recrystallized from benzene-hexane to give 0.083 g. of XIIIc melting at 143~146°. An analytical sample was obtained by further recrystallization from hexane as needles of m.p. 147~150°. $[\alpha]_D$ −228.3°. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.66; H, 8.27. IR ν_{max} cm^{-1}: 1745, 1727 and 1718 (shoulder). UV λ_{max}^{EtOH} mμ: 305 (ε 140). NMR τ: 9.14 (18-CH_3), 4.17 (6-vinyl H), 0.05 (CHO).

3β-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° (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 λ_{max}^{EtOH} mμ: 305 (ε 145). NMRτ: 9.15 (18-CH_3), 4.18 (6-vinyl H), 0.03 (CHO).

Jones Oxidation of 3α,5-Cyclo-6β,19-oxido-5α-androstan-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 N_2-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% $NaHCO_3$ 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 3α,5-cyclo-5α-androstane-6,17,19-trione (XIXc), m.p. 222~225°, $[\alpha]_D$ +108.5° (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 ν_{max} cm^{-1}: 1733 (17-CO), 1717 (CHO), 1683 (6-CO). NMRτ: 9.3 (cyclopropane), 9.04 (18-CH_3), 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 N_2 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. $NaHCO_3$. 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 3α,5-cyclo-5α-androstane-6,17-dion-19-oic acid (XXc), m.p. 260~262°, $[\alpha]_D$ +118.7°. *Anal.* Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.91; H, 7.58. IR ν_{max} cm^{-1}: 1736, 1715, 1658 and 1645. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738, 1706, 1701 (shoulder) and 1695.

Jones Oxidation of 3α,5-Cyclo-6β,19-oxido-17β-hydroxy-5α-androstane 17-Acetate (IId)——To a solution of 32.5 g. of IId in 3.5 L. of purified acetone with vigorous stirring and N_2 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 N_2 atmosphere, and extracted with ether. The extract was washed with aq. $NaHCO_3$, 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 3α,5-cyclo-17β-hydroxy-5α-androstane-6,19-dione 17-acetate (XIXd) melting at 138~144°. The mother liquor of recrystallization was chromatographed over 250 g. of Al_2O_3. 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° (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 ν_{max} cm^{-1}: 1733 (OAc), 1706 (CHO), 1686 (6-CO).

The aq. $NaHCO_3$ layer described above was acidified with dil. HCl and extracted with $CHCl_3$-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 3α,5-cyclo-17β-hydroxy-5α-androstan-6-on-19-oic acid 17-acetate (XXd) as scales, m.p. 271~274° (decomp.). $[\alpha]_D$ +9.2° (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 ν_{max} cm^{-1}: 1742 and 1238 (OAc), 1695 and 1684 (6-CO and COOH). NMRτ: 9.24 (cyclopropane), 9.17 (18-CH_3), 7.93 (OAc).

3α,5-Cyclo-5α-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 Al_2O_3 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° (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 ν_{max} cm^{-1}: 1718 (CHO), 1684 (6-CO). NMRτ: 9.27 (18-CH_3), 0.19 (CHO).

ii) To a stirred solution of 0.385 g. of IIa in 46 ml. of acetone with bubbling N_2 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 Al_2O_3 gave XIXa melting at 118~122° from the benzene eluate.

3α,5-Cyclo-5α-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° (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 ν_{max} cm^{-1}: 1718 (COOH), 1689 (6-CO), 1650.

3α,5-Cyclo-5α-pregnane-6,20-dion-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% $NaHCO_3$ 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 $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found : C, 72.94; H, 8.22. IR ν_{max} cm^{-1}: 3300 (broad, OH), 1740 (COOH), 1700 (20-CO), 1690 (3α,5-cyclo-6-CO).

Jones Oxidation of 3α,5-Cyclo-6β,19-dihydroxy-5α-androstan-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 N_2-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 3α,5-Cyclo-6β,17β,19-trihydroxy-5α-androstane 17-Monoacetate (IVd)——To a solution of 10.1 g. of IVd in 1.3 L. of acetone with vigorous stirring and dry N_2-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 IId 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 Al_2O_3 gave further 1.10 g. of XIXd from the benzene eluate.

Sodium Borohydride Reduction of 3α,5-Cyclo-5α-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 $NaBH_4$ 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% $NaHCO_3$ and water, dried over Na_2SO_4, and condensed to dryness *in vacuo* to leave a crystalline product, which was chromatographed over 20 g. of Al_2O_3 (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 3α,5-cyclo-5α-androstane-6α,17β,19-triol (XXII) as needles of m.p. 164.5～165°, $[\alpha]_D$ +90.0° (dioxane). *Anal.* Calcd. for $C_{19}H_{30}O_3$: 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 3α,5-cyclo-5α-androstane-6β,17β,19-triol (XXI), m.p. 127～131°. This was identified with the authentic specimen prepared by $NaBH_4$ reduction of 3α,5-cyclo-5α-androstan-17-one-6β,19-diol (IVc).

3α,5-Cyclo-5α-androstane-6β,17β,19-triol (XXI)——To a solution of 0.20 g. of IVc in 20 ml. of MeOH, 0.050 g. of $NaBH_4$ 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 Al_2O_3. 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°), $[\alpha]_D$ +52.8° (dioxane). *Anal.* Calcd. for $C_{19}H_{30}O_3 \cdot \frac{1}{2} H_2O$: C, 72.34; H, 9.91. Found : C, 72.10; H, 9.82.

Table I.

6β,17β,19-triol (XXI)		6α,17β,19-triol (XXII)	
time (min.)	$[\alpha]_D$	time (min.)	$[\alpha]_D$
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 absense of acid.

Treatment of 3α,5-Cyclo-5α-androstane-6β,17β,19-triol (XXI) and its 6α-Epimer (XXII) with 60% Perchloric Acid in 90% aq. Dioxane——Each solution prepared from 0.04272 g. of 6β,17β,19-triol (XXI) and 0.04283 g. of 6α,17β,19-triol (XXII) in 5 ml. of 90% dioxane containing 6 drops of 60% $HClO_4$ was let stand at 27~28° and the changes of optical rotations were measured separately as shown in Table I.

When the solution of 6α,17β,19-triol (XXII), after allowing to stand at 27~28° for 66 hr., was heated at 70° for 4 hr., the observed $[\alpha]_D$ value was finally reached at −40°, the value for 3β,17β,19-trihydroxyandrost-5-ene (XXIII). The solutions were separately made alkaline with aq. $NaHCO_3$, concentrated *in vacuo*, and extracted with $CHCl_3$. Each extract was washed with water, dried, and condensed to dryness to give a crystalline product of the same 3β,17β,19-trihydroxyandrost-5-ene (XXIII) melting at 222~228°.

3β,17β,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 $NaBH_4$ 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-H_2O to afford needles of XXIII, m.p. 227~232°. An analytical sample was evacuated at 70° for 10 hr. *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.00; H, 9.67. $[\alpha]_D^{29}$ −42.1° (EtOH).

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4. Katsumi Tanabe, Rinji Takasaki, Ryozo 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 3α,5α-cyclo-6β,19-oxidosteroid (I) through 3β-substituted-Δ^5-steroid-19-oic acid (VII), whose synthesis was achieved by the three methods: i) Hydrolysis of 3β-hydroxy-Δ^5-steroid-19-oic acid 3,19-lactone (VI) which was prepared by oxidizing either 3β,19-dihydroxy-Δ^5-steroid (III) or 3β-hydroxy-19-oxo-Δ^5-steroid (V) with Jones reagent or Oppenauer reaction, ii) Oxidation of 3β,19-dihydroxy-Δ^5-steroid 3-acetate (III) with the excess Jones reagent, iii) Reduction of 3α,5α-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. 3β-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 3β-hydroxy compound and subsequent acid-treatment of the resultant Δ^5-3-oxosteroid-19-oic acid (VIII), ii) Pyrolysis of the 3β-acetoxy-Δ^5-steroid-19-oic acid (VII) to afford 3β-acetoxy-$\Delta^{5(10)}$-steroid (XI), followed by alkaline hydrolysis, Jones oxidation, and acid-treatment, successively.

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

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*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).