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26. Kenyu Shibata, Joji Yamada, and Hiromu Mori : Further Preparation of Steroidal Diosphenols. II.*1 Synthesis of 2,16α,17β- and 2,16β,17β-Trihydroxy-4,4-dimethylandrosta-1,5-dien-3-ones.

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2,16β,17β-Trihydroxy-4,4-dimethylandrosta-1,5-dien-3-one (VI) was prepared from 2,16β,17β-trihydroxyandrost-5-ene 16,17-acetonide in 4 steps. 2,16α,17β-Trihydroxy-4,4-dimethylandrosta-1,5-dien-3-one (XVIII) was prepared from 2,17β-dihydroxy-4,4-dimethylandrosta-1,5-dien-3-one (VII) in 8 steps. It was found that the 2,3-ketol was converted to the 2,3-diketone by autoxidation without influence on 16,17-glycol.

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In continuous studies on preparations of steroidal diosphenols, it seemed interesting for us that diosphenols with 16,17-glycol were prepared and examined their antitumor activities. This paper describes synthesis of 2,16α,17β- and 2,16β,17β-trihydroxy-4,4-dimethylandrosta-1,5-dien-3-ones (VI and XVIII).

Preparation of 16β,17β-Dihydroxy Diosphenol (VI)

In general, the enol structure of 2,3-diketone (diosphenol) is not stable to alkali,[1] peracid,[2] and oxidation.[3] Therefore, it seemed to be desirable that the construction of the diosphenol structure is performed after introduction of hydroxy group at C-16 and then protection of glycol in ring D. This attempt was easily carried out in the case of the synthesis of 16β-hydroxy derivative (VI) because 16β,17β-glycol structure

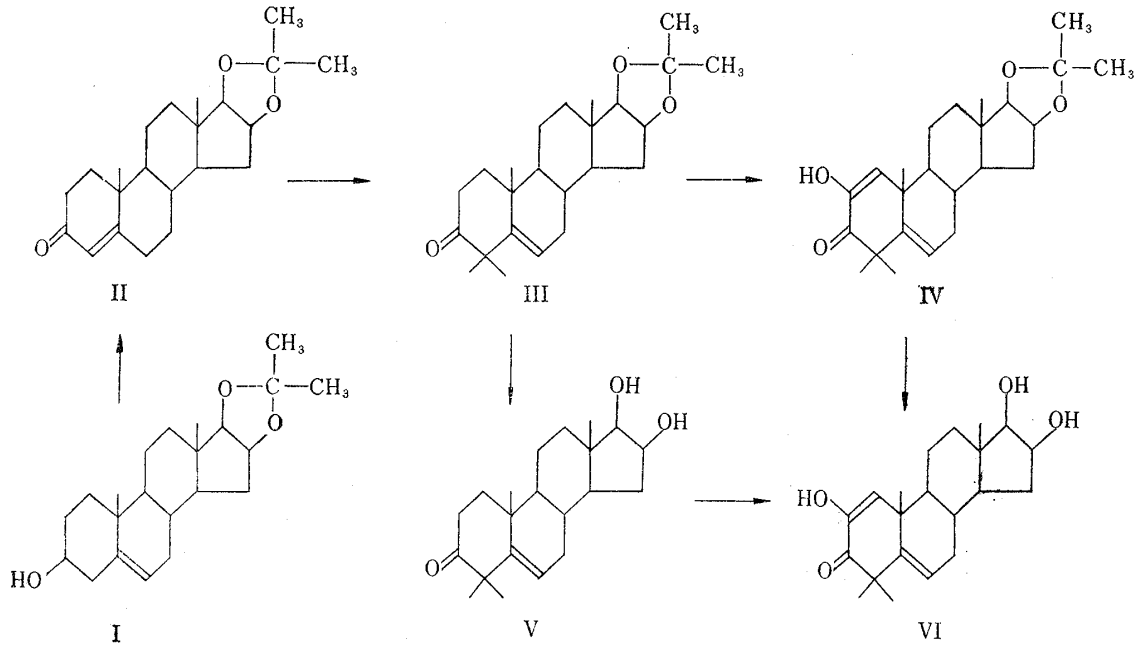

Chart 1.

*1 Part I : To be published.

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1) H. Mori, V. S. Gandhi, E. Schwenk : This Bulletin, **10**, 842 (1961).
2) G. R. Chaudhry, T. G. Halsall, E. R. H. Jones : J. Chem. Soc., **1961**, 2725.
3) D. Lavie, E. Glotter, Y. Shvo : Tetrahedron, **19**, 1377 (1963).

could be protected as acetonide. 16β,17β-Dihydroxyandrost-4-en-3-one 16,17-acetonide (II) was used as the starting material.

Dodson and Mizuba[4] have already reported the preparation of 16β,17β-dihydroxyandrost-4-en-3-one from testosterone by microbiological method and of its acetonide (II) by treatment with acetone containing *p*-toluenesulfonic acid, but physical constants of the acetonide (II) have not been shown except melting point. The starting material (II) was prepared from androst-5-ene-3β,16β,17β-triol 16,17-acetonide (I) by Oppenauer oxidation. The treatment of II with excess potassium *tert*-butoxide and methyl iodide in *tert*-butanol[5] at room temperature led to 4,4-dimethyl compound (III) in about 70%

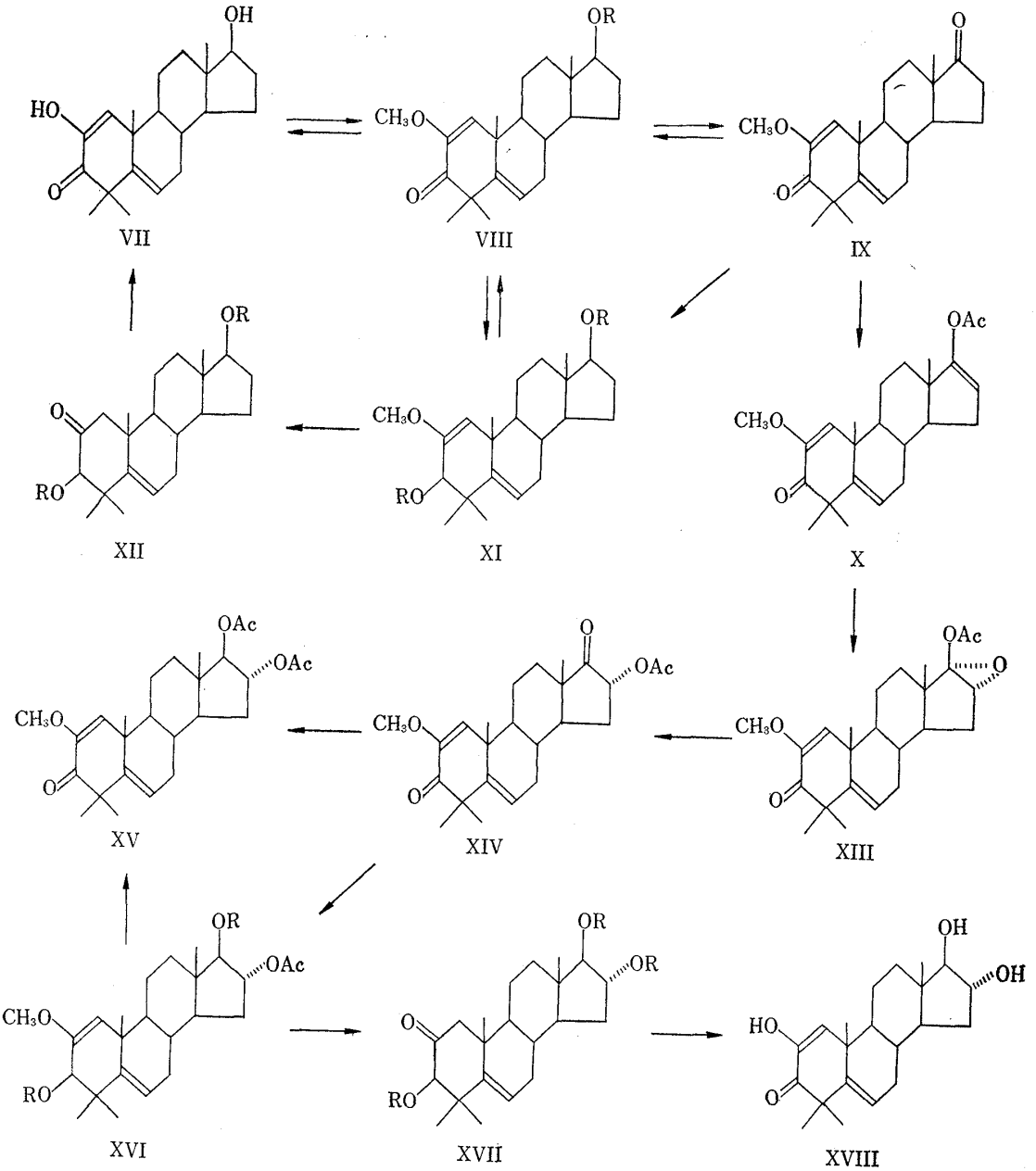


Chart 2.

4) R. M. Dodson, S. Mizuba : J. Org. Chem., **27**, 698 (1962).
5) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. I. Ives, R. B. Kelly : J. Chem. Soc., **1957**, 1131.

yield. The autoxidation[6] of III afforded the diosphenol (IV), which was hydrolyzed by phosphoric acid to the objective diosphenol (VI) in satisfactory yield. VI was also prepared from III by hydrolysis to V, followed by autoxidation.

Preparation of 16α,17β-Dihydroxy Diosphenol (XVIII)

The preparation of the diosphenol (XVIII) was somewhat difficult comparing with that of the diosphenol (VI), because no protecting method of glycol structure seemed to be found in literature for our purpose. Fortunately, it has already described the methyl ether of the diosphenol is considerably stable in structure to diluted acid[7] and periodic acid.[8] For this reason, the methyl ether (VIIIa), prepared easily from the diosphenol (VII),[1] was chosen as a starting material.

At first, VIIIa was transformed into 17-oxo compound (IX) by Jones oxidation,[9] and the treatment of IX with isopropenyl acetate in the presence of acid catalyst afforded the enol acetate (X). In this step, the preparative method of 16α,17β-glycol, developed by Gallagher and his co-workers,[10] was used for the enol acetate (X). In our case, the partial epoxidation of C-16~C-17 double bond was necessary for the preparation of the diosphenol (XVIII). Many examples of such partial epoxidation have been found in literature.[11] The enol acetate (X) was treated with 1.4 equivalent of monoperphthalic acid or 1.07 equivalent of perbenzoic acid to give the epoxide (XIII), and the crude epoxide (XIII) was treated with perchloric acid without purification to give the ketol acetate (XIV). It was suggested from the yield of the ketol acetate (XIV) that the yield of the epoxide (XIII) was higher in the case of perbenzoic acid rather than of monoperphthalic acid. In the case of perbenzoic acid, however, a crystalline by-product was isolated by chromatography from the reaction mixture, the structure of which was not fully established, but seemed to be the product from 1,2;16,17-diepoxide because of no characteristic absorption in ultraviolet absorption spectrum.

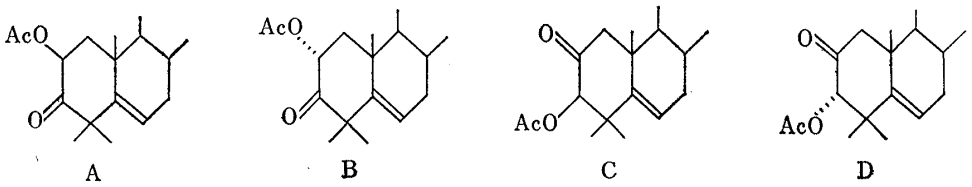
Norymberski and Wood[12] have reported on the partial reduction of androst-4-ene-3,17-dione with ca. 1.5 equivalent of sodium borohydride in methanol at 0° to testosterone. As a model compound, IX was selected and the partial reduction was attempted to give VIIIa in good yield. The partial reduction of XIV, however, gave an unsatisfactory result. Although infrared and ultraviolet absorption spectrum showed the existence of a small amount of the desired compound (XV) (after acetylation) in the reaction mixture, the isolation of an analytically pure sample was not succeeded. When 60% α,β-unsaturated oxo function in ring A was maintained (from ultraviolet spectrum), the reaction mixture was acetylated and was analysed by thin-layer chromatography. The mixture was shown to consist of XIV, XVIb and a small amount of XV. This result coincides with the suggestion that the difference of the reducing rate between 3-oxo and 17-oxo was shortened for the steric hindrance of the rear side by 16α-acetoxy function.

As the above mentioned approach was found not to be suitable one, an attempt of the process (XIV→XVIa→XV) was made. Here again, the compound (IX) was selected as a model and was reduced to XIa, which could be transformed into VIIIa without

6) D. H. R. Barton, S. K. Pradhan, S. Sternhell, J. F. Templeton : J. Chem. Soc., **1961**, 255.
7) The hydrolysis of the methyl ether was performed only by drastic treatment with concentrated hydrochloric acid (W. Reush, R. LeMahien : J. Org. Chem., **28**, 2443 (1963)).
8) D. Lavie, D. Willner : J. Am. Chem. Soc., **82**, 1668 (1960).
9) K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weeden : J. Chem. Soc., **1946**, 39.
10) N. S. Leeds, D. K. Fukushima, T. F. Gallagher : J. Am. Chem. Soc., **76**, 2943 (1954).
11) *a*) with perbenzoic acid : V. Sanda, J. Fajkos : Collection Czeckoslov. Chem. Communs, **26**, 2734 (1961). *b*) with monoperphthalic acid; H. Hasegawa, Y. Sato, K. Tsuda : This Bulletin, **9**, 409 (1961). J. P. Ruelas, C. Djerassi, H. J. Ringold : J. Am. Chem. Soc., **82**, 1230 (1960).
12) J. K. Norymberski, G. F. Woods : J. Chem. Soc., **1955**, 3426.

difficulty by manganese dioxide[13] or mild Oppenauer oxidation.[14] The compound (XIV) was reduced with excess sodium borohydride to give oily substance, which was failed to crystallize, but was found from its infrared absorption spectrum that 3- and 17-oxo group were reduced perfectly. The partial oxidation of the crude product (XVIa) with manganese dioxide or mild Oppenauer oxidation was attempted without success. The reason why such a difference was observed was not understood. It has been described that the metal hydride reduction of 4,4-dimethylcholest-5-en-3-one leads to the 3β-ol from the steric viewpoint.[15] The configuration of C-3 hydroxyl group in XIa and XVIa was tentatively assigned as β, although there was no unambiguous proof.

When XIa was refluxed with methanolic hydrochloric acid, and the product was acetylated, a ketol acetate, m.p. 203~205°, was obtained. Nuclear magnetic resonance (NMR) spectrum of this ketol acetate indicated a singlet at τ=4.93 for one hydrogen



A B C D

Chart 3.

(>CHOAc) and a broad peak at τ=7.65 for two hydrogen (-$COCH_2$-).*3 Among theoretically possible structures of 2,3-ketol acetate (A, B, C and D), structure A and B can be ruled out from NMR data. On the other hand, it is expected that there should be obtained the kinetically stable isomer in this case. Accordingly, the ketol acetate, m.p. 203~205°, should be 3β-acetoxy-2-oxo compound (XIIb), because 3β-acetoxy group is considered to be equatorial. The ketol (XIIa or XIIb) was shaken in oxygen atmosphere in *tert*-butanol containing potassium *tert*-butoxide or in ethanol and aqueous potassium hydroxide[16] to afford the diosphenol (VII). The crude reduction product (XVIa) described above was acetylated to triacetate (XVIb), and treatment of the triacetate (XVIb) with hydrochloric acid afforded the ketol (XVIIa), which was characterized as triacetate (XVIIb). The autoxidation of XVIIa or XVIIb afforded the objective diosphenol (XVIII) in satisfactory yield. The yields of autoxidation were better in potassium hydroxide-ethanol system rather than potassium *tert*-butoxide-*tert*-buthanol system in both cases.

Experimental*4

16β,17β-Dihydroxyandrost-4-en-3-one 16,17-Acetonide (II)——A solution of androst-5-ene-3β,16β,17β-triol 16,17-acetonide (I, 500 mg.) in dry benzene (20 ml.) and cyclohexanone (2.5 ml.) was heated and a trace of H_2O was removed azeotropically. A solution of aluminum isoproxide (250 mg.) in benzene (2.5 ml.) was added, and the mixture was slowly distilled for 2.5 hr., during which ca. 5 ml. of benzene was distilled out. When cooled, a saturated aqueous solution of Rochelle salt was added, and the solvent was removed by steam distillation. The product was extracted with ether, and ether solution was washed with H_2O and dried over Na_2SO_4. The solvent was removed by distillation to give white solid, which was crystallized

*3 Similar NMR spectrum of 3β-acetoxyeuphen-2-one (a singlet at τ=4.95 for one hydrogen and a broad peak at τ=7.50 for two hydrogens) has been reported by Lavie and his co-workers (See reference 4).

*4 Melting points are uncorrected. UV spectra were measured in MeOH, optical rotations in $CHCl_3$ and IR spectra in KBr unless otherwise described.

13) G. Stork, H. J. E. Loewenthal, P. C. Mukharji : J. Am. Chem. Soc., **78**, 501 (1956); F. Sondheimer, C. Amendolland, G. Rosenkranz : J. Chem. Soc., **1954**, 1226.
14) H. Hensler, J. Kalvoda, P. Wieland, A. Wettstein : Helv. Chim. Acta, **44**, 179 (1961).
15) H. J. Ringold, G. Rosenkranz : J. Org. Chem., **22**, 602 (1957).
16) R. L. Clarke : J. Am. Chem. Soc., **82**, 4629 (1960); S. M. Kupchan, S. McLean, G. W. A. Milne, P. Slade : J. Org. Chem., **27**, 147 (1962).

from MeOH to afford II (350 mg.), m.p. 180~187°. Further crystallization from MeOH gave an analytical sample as colorless needles, m.p. 187~188.5°, $[\alpha]_D^{19}$ +124° (c=1.00). UV : λ_{max} 241 mμ (ε 17,400). IR: ν_{max} cm^{-1} 1675, 1625. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found : C, 76.65; H, 9.47.

16β,17β-Dihydroxy-4,4-dimethylandrost-5-en-3-one 16,17-Acetonide (III)——To a solution of *tert*-butanol (50 ml.) containing potassium (200 mg.) was added 16β,17β-dihydroxyandrost-4-en-3-one 16,17-acetonide (II, 500 mg.) under N_2 atmosphere and the mixture was stirred until the steroid was dissolved. Methyl iodide (0.7 ml.) was dropwise added at room temperature over a period of 10 min. to the yellow solution and the mixture was stirred for 2 hr. and allowed to stand overnight. The mixture was poured into H_2O, and the product was extracted with ether. Ether solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to crystalline product, which was crystallized from MeOH to afford III (300 mg.), m.p. 183~186°, $[\alpha]_D^{19}$ +26° (c=1.00). *Anal.* Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found : C, 77.06; H, 9.68.

2,16β,17β-Trihydroxy-4,4-dimethylandrosta-1,5-dien-3-one 16,17-Acetonide (IV)——The acetonide (III, 2.4 g.) was dissolved in *N* potassium *tert*-butoxide in *tert*-butanol (240 ml.), and the solution was stirred under O_2 atmosphere for 2 hr., during which one equivalent of O_2 was absorbed. The solution was poured into H_2O and acidified with 10% HCl. The resulting product was extracted with ether, and ether solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Evaporation of the solvent gave a solid, which on crystallization from MeOH afforded colorless plates (IV, 1.5 g.), m.p. 172~175°, $[\alpha]_D^{24}$ +86° (c=1.00). UV : λ_{max} 272 mμ (ε 8,500). IR : ν_{max} cm^{-1} 3470, 1685, 1665. *Anal.* Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found : C, 74.52; H, 8.88.

16β,17β-Dihydroxy-4,4-dimethylandrost-5-en-3-one (V)——A mixture of 16β,17β-dihydroxy-4,4-dimethylandrost-5-en-3-one 16,17-acetonide (III, 300 mg.), EtOH (50 ml.) and 85% H_3PO_4 (10 ml.) was refluxed for 30 min.,[17] and poured into H_2O. The product was extracted with ether and ether solution was washed with H_2O and dried over Na_2SO_4. Removal of the solvent left crystalline solid (250 mg.), which was crystallized from MeOH to give V as colorless prisms, m.p. 205~208°, $[\alpha]_D^{19}$ −7° (c=1.00). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found : C, 75.80; H, 9.71.

2,16β,17β-Trihydroxy-4,4-dimethylandrosta-1,5-dien-3-one (VI)——a) By hydrolysis of IV. The hydrolysis of IV (1.0 g.) with H_3PO_4 (30 ml.) was performed as the same manner described above. After addition of H_2O, the resulting product was extracted with ether and the solution was washed with H_2O, and dried over Na_2SO_4. Removal of the solvent left crystalline solid (0.8 g.), which on recrystallization from MeOH gave an analytical sample (VI) as colorless plates, m.p. 158~161°, $[\alpha]_D^{23}$ +46° (c=1.00). UV : λ_{max} 272 mμ (ε 8,000). IR : ν_{max} cm^{-1} 3555, 3240 (broad), 1678, 1657. *Anal.* Calcd. for $C_{21}H_{30}O_4 \cdot MeOH$: C, 69.81; H, 9.05. Found : C, 69.74; H, 9.05.

b) By autoxidation of V. 16β,17β-Dihydroxy-4,4-dimethylandrost-5-en-3-one (V, 200 mg.) was treated with *N* potassium *tert*-butoxide in *tert*-butanol under O_2 atmosphere as described above. The solution was poured into H_2O and acidified with 10% HCl. The product was extracted with ether and ether solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. The solvent was evaporated to dryness to afford oily substance, which was crystallized from MeOH to V (62 mg.), m.p. 155~160°. The product was identical with the diosphenol (V) obtained above.

17β-Hydroxy-2-methoxy-4,4-dimethylandrosta-1,5-dien-3-one (VIIIa)——a) By methylation[18] of VII. To a solution of 2,17β-dihydroxy-4,4-dimethylandrosta-1,5-dien-3-one (VII, 2.9 g.) and $(CH_3)_2SO_4$ (18 ml.) in MeOH (300 ml.) was dropwise added 20% KOH (60 ml.) over a period of 10 min. with stirring. The solution was continued to stir for additional 30 min. and poured into H_2O and acidified with 10% HCl. Precipitates were collected by filtration, dried and crystallized from MeOH to VIIIa (2.5 g.) as colorless prisms, m.p. 230~235°, $[\alpha]_D^{11}$ +42° (c=1.00). UV : λ_{max} 265 mμ (ε 6,500). IR : ν_{max} cm^{-1} 3525, 1682, 1628. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found : C, 76.46; H, 9.15.

b) By mild Oppenauer oxidation of XIa. A suspension of 2-methoxy-4,4-dimethylandrosta-1,5-diene-3β,17β-diol (XIa, 150 mg.), aluminum isopropoxide (160 mg.), acetone (0.7 ml.) and dry benzene (10 ml.) was stirred for 14 hr. at room temperature. 2*N* H_2SO_4 (10 ml.) was added and the product was extracted with ether. Ether solution was washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the product was crystallized from MeOH to VIIIa (98 mg.), which was identical with the methyl ether obtained above.

17β-Acetoxy-2-methoxy-4,4-dimethylandrosta-1,5-dien-3-one (VIIIb)——a) By acetylation of VIIIa. 17β-Hydroxy-2-methoxy-4,4-dimethylandrosta-1,5-dien-3-one (VIIIa) was acetylated by Ac_2O-pyridine in the usual manner. The acetate (VIIIb) was crystallized from MeOH as colorless needles, m.p. 158~160°, $[\alpha]_D^{14}$ +22° (c=1.00). UV : λ_{max} 265 mμ (ε 6,500). IR : ν_{max} cm^{-1} 1733, 1700, 1628, 1250. *Anal.* Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found : C, 74.31; H, 8.72.

b) By partial reduction of IX. To a solution of 2-methoxy-4,4-dimethylandrosta-1,5-diene-3,17-dione (IX, 172 mg.) in MeOH (50 ml.) was added $NaBH_4$ (26.5 mg.) in small portions and the solution was stirred for 45 min. at 0°. The excess $NaBH_4$ was decomposed by addition of AcOH, and the solution was poured

17) M. N. Huffman, M. H. Lott : J. Am. Chem. Soc., **71**, 719 (1949).
18) D. H. R. Barton, P. J. L. Daniels, J. F. McGhie, P. J. Palmer : J. Chem. Soc., **1963**, 3675.

into H_2O. The precipitates were collected by filtration, washed with H_2O, dried and acetylated by the usual manner, and the product was chromatographed on Florisil. The fractions eluted with ether-benzene (1:9) were crystallized from MeOH to XIb (48 mg.), m.p. 137~142°. The fractions eluted with ether were crystallized from MeOH to VIIIb (84 mg.), which was identical with the compound obtained above.

c) By selective oxidation of XIa with MnO_2. A suspension of 2-methoxy-4,4-dimethylandrosta-1,5-diene-3β,17β-diol (XIa, 120 mg.) and MnO_2 (1.2 g.) in $CHCl_3$ (20 ml.) was stirred at room temperature for 16 hr. and allowed to stand overnight. After removal of MnO_2 by filtration and evaporation of the solvent, the solid residue was acetylated by Ac_2O-pyridine, and the product was chromatographed on Florisil. The fractions eluted with ether-benzene (1:9) were crystallized from MeOH to XIb (42 mg.), which was identical with the compound described below. The fractions eluted with ether were crystallized from MeOH to VIIIb (69 mg.) identical with the compound obtained above.

Hydrolysis[19] of 17β-Hydroxy-2-methoxy-4,4-dimethylandrosta-1,5-dien-3-one (VIIIa)——A solution of VIIIa (110 mg.) in dioxane (15 ml.) was refluxed with concentrated HCl (2 ml.) for 8 hr., then cooled to room temperature and poured into H_2O. The product was extracted with ether, and ether solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Removal of the solvent and repeated crystallizations from MeOH gave the diosphenol (VII, 33 mg.), m.p. 162~165°, which was identical with an authentic sample.[1]

2-Methoxy-4,4-dimethylandrosta-1,5-diene-3,17-dione (IX)——To a solution of 17β-hydroxy-2-methoxy-4,4-dimethylandrosta-1,5-dien-3-one (VIIIa, 7.0 g.) in acetone (700 ml.), 8N CrO_3 solution*5 (9.6 ml.) was dropwise added at 0° with stirring. The suspension was stirred for 5 min. and poured into H_2O. Precipitates were collected by filtration, washed with H_2O and crystallized from MeOH to afford IX (5.85 g.), m.p. 200~203.5°. Further crystallization from the same solvent gave an analytical sample as colorless prisms, m.p. 203~205°, $[\alpha]_D^{11}$ +92° (c=1.00). UV : λ_{max} 265 mμ (ε 6,500). IR : ν_{max} cm^{-1} 1736, 1694, 1635. *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.19; H, 8.77. Found : C, 76.93; H, 8.78.

2-Methoxy-4,4-dimethylandrosta-1,5-diene-3β,17β-diol 3,17-diacetate (XIb)——a) From VIIIa. A solution of 17β-hydroxy-2-methoxy-4,4-dimethylandrosta-1,5-dien-3-one (VIIIa, 1.0 g.) in MeOH (180 ml.) was stirred with $NaBH_4$ (500 mg.) for 1 hr. at room temperature. The solution was poured into H_2O and the resulting precipitates were collected by filtration, dried and crystallized from MeOH to afford Xa (700 mg.). m.p. 140~144°, UV : no characteristic absorption. IR : ν_{max} cm^{-1} 3600, 3470~3270 (broad), 1673, 1655. The diol (Xa) was acetylated in the usual manner to the diacetate (XIb), m.p. 152~155°, $[\alpha]_D^{11}$ −11° (c=1.00). IR : $\nu_{max}^{CS_2}$ cm^{-1} 1744, 1669, 1235. *Anal.* Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found : C, 72.32; H, 8.78.

b) From IX. The diketone (IX, 1.0 g.) was treated with $NaBH_4$ as described above, followed by acetylation, to give XIb (580 mg.) identical with the diacetate obtained above.

3β,17β-Diacetoxy-4,4-dimethylandrost-5-en-2-one (XIIb)——A solution of 2-methoxy-4,4-dimethylandrosta-1,5-diene-3β,17β-diol (XIa, 500 mg.) in MeOH (30 ml.) was refluxed with 16% HCl (5 ml.) for 3 hr., and poured into H_2O. The resultant precipitates were collected by filtration, dried and crystallized from Me_2CO to afford the ketol (XIIa, 300 mg.), m.p. 185~188°, IR $\nu_{max}^{CS_2}$ cm^{-1} : 3670, 3540, 1722, 1095, UV : λ_{max} 282 mμ (ε 48). The ketol (XIIa) was acetylated with Ac_2O-pyridine in the usual manner to afford the diacetate (XIIb) as colorless prisms, m.p. 203~205°, $[\alpha]_D^{11}$ −26° (c=1.01). IR : $\nu_{max}^{CS_2}$ cm^{-1} 1755, 1740, 1240, 1230. *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found : C, 71.82; H, 8.69.

Autoxidation of XIIa——a) In *tert*-butanol containing potassium *tert*-butoxide. A solution of the ketol (XIIa, 80 mg.) in *tert*-butanol (20 ml.) containing potassium (800 mg.) was stirred undre O_2 atmosphere for 30 min. The solution was poured into H_2O and acidified with 10% HCl, and the product was extracted with ether. Ether solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Removal of the solvent and crystallization from MeOH gave the diosphenol (VII, 18 mg.), which was identical with an authentic sample.

b) In aqueous EtOH containing KOH. A mixture of the ketol (XIIa, 120 mg.), 20% KOH (5 ml.) and EtOH (30 ml.) was stirred under O_2 atmosphere for 30 min. The solution was poured into H_2O and acidified with 10% HCl, and the product was extracted with ether. Ether solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Removal of the solvent and crystallization from MeOH afforded the diosphenol (VII, 36 mg.), which was identical with an authentic sample.

The ketol diacetate (XIIb, 100 mg.) was treated with the same manner described above to afford the diosphenol (VII, 52 mg.).

17-Acetoxy-2-methoxy-4,4-dimethylandrosta-1,5,16-trien-3-one (X)——To a solution of 2-methoxy-4,4-dimethylandrosta-1,5-diene-3,17-dione (IX, 10 g.) in isopropenyl acetate (70 ml.) was added 3.4 ml. of catalyst solution (5 ml. of isopropenyl acetate and 0.1 ml. of H_2SO_4). Approximately 10 ml. of the solvent was distilled over a period of 2 hr., and further isopropenyl acetate (50 ml.) and catalyst solution (3.4 ml.) were added. The solvent was concentrated to 20 ml. by slow distillation over another 2 hr. The solution was cooled, and diluted with benzene, and the solution was washed with cold 5% Na_2CO_3 and H_2O, and

*5 A solution of CrO_3 (26.72 g.) in H_2SO_4 (23 ml.) diluted with H_2O to a volume of 100 ml. was used.

19) R. Stevenson, L. F. Fieser : J. Am. Chem. Soc., **78**, 1409 (1956).

dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in benzene and chromatographed on Florisil. The crude enol acetate (X, 6.8 g.) was obtained from the fractions eluted with benzene (600 ml.), which on crystallization from MeOH afforded an analytical sample, m.p. 129~131°, $[\alpha]_D^{11}$ +47° (c=1.00). UV : λ_{max} 265 mμ (ε 6,500). IR : ν_{max} cm^{-1} 1776, 1705, 1630, 1615, 1195, 1178. *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found : C, 74.88; H, 8.57.

16α-Acetoxy-2-methoxy-4,4-dimethylandrosta-5,5-diene-3,17-dione (XXIV)——a) With monoperphthalic acid. To a solution of 17-acetoxy-2-methoxy-4,4-dimethylandrosta-1,5,16-trien-3-one (X, 2.8 g.) in $CHCl_3$ (10 ml.) and ether (90 ml.), a solution of monoperphthalic acid in ether (1.84 g. in 15.3 ml.) was added and the mixture was allowed to stand for 48 hr. at 0°. After filtration of phthalic acid, ether solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Evaporation of the solvent gave the crude epoxide (X), m.p. 169~174°, IR : ν_{max} cm^{-1} 1760, 1757, 1725, 1689, 1640, 1220, UV : λ_{max} 265 mμ (ε 6,300). Without purification, the crude epoxide was dissolved in cold AcOH (20 ml.) and a cold solution of AcOH (5 ml.) containing 60% perchloric acid (1 ml.) was added. The mixture was allowed to stand for 30 min. at room temperature. After addition of ether, the solution was washed with H_2O, 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Removal of the solvent afforded oily substance, which was acetylated with Ac_2O-pyridine in the usual manner. The product was chromatographed on Florisil, and the fractions eluted with ether-benzene (1:9) were crystallized from MeOH to the ketol acetate (XIV, 600 mg.), m.p. 155~168°. Further crystallization from the same solvent gave an analytical sample as colorless plates, m.p. 172~174°, $[\alpha]_D^{11}$ +52° (c=0.90). UV : λ_{max} 265 mμ (ε 6,600). IR : $\nu_{max}^{CS_2}$ cm^{-1} 1765, 1750, 1700, 1634, 1225. *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found : C, 72.08; H, 8.34.

b) With perbenzoic acid. To a solution of X (2.0 g.) in cold benzene (100 ml.), a solution of perbenzoic acid in cold benzene (770 mg. in 15.5 ml.) was added and the mixture was allowed to stand for 15 hr. at 0°. The solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. After removal of the solvent, the product was treated with perchloric acid as described above, followed by acetylation, to give the ketol acetate (XIV, 950 mg.) and by-product, m.p. 231~235°, UV: no characteristic absorption.

Partial Reduction of XIV——A solution of the ketol acetate (XIV, 146 mg.) in MeOH (58 ml.) was treated with $NaBH_4$ (21.2 mg.) for 30 min. at 0°. A few drops of AcOH were added and the solution was poured into H_2O. Precipitates were collected by filtration and acetylated with Ac_2O-pyridine in the usual manner. The product was chromatographed on Florisil. The fractions eluted with benzene were crystallized from MeOH to XIVb (40 mg.), m.p. 179~182°, UV : no characteristic absorption, IR : ν_{max} cm^{-1} 1745, 1675, 1245. The fractions eluted with ether-benzene (1:9) were crystallized from MeOH to the crude diacetate (XV, 32 mg.), m.p. 135~140°, UV : λ_{max} 265 mμ (ε 6,300), IR : ν_{max} cm^{-1} 1745, 1705, 1640, 1245.

2-Methoxy-4,4-dimethylandrosta-1,5-diene-3β,16α,17β-triol (XVIa) and Triacetate (XVIb)——A solution of the ketol acetate (XIV, 200 mg.) in MeOH (20 ml.) was treated with $NaBH_4$ (100 mg.) for 1 hr. at room temperature. The mixture was poured into H_2O and the product was extracted with ether. Ether solution was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave oily substance, which was failed to crystallized and used the experiment described below without purification. The oil was acetylated with Ac_2O-pyridine to the triacetate (XVIb), IR of which was identical with that of the product obtained above, and the crude triacetate was used for preparation of XVIIa.

Attempt of Selective Oxidation of XVIa——The oxidation of XVIa (crude) by MnO_2 or mild Oppenauer oxidation was made as described in the partial oxidation of XIa to VIIIa. After acetylation of the reaction product and chromatography, a small amount of substance, which was considered to be crude XV from IR, was obtained, but its purification into analytical sample was not succeeded.

3β,16α,17β-Trihydroxy-4,4-dimethylandrost-5-en-2-one (XVIIa) and Triacetate (XVIIb)——A solution of the crude triacetate (XVIb, 150 mg.) in MeOH (20 ml.) was refluxed with 16% HCl (5 ml.) for 3 hr. and poured into H_2O. The resulting precipitates were collected by filtration, dried and crystallized from acetone to afford the ketol (XVIIa, 70 mg.), m.p. 216~219°, IR : ν_{max} 1705 cm^{-1}. The ketol (XVIIa) was acetylated with Ac_2O-pyridine to triacetate (XVIIb), m.p. 216~218°, $[\alpha]_D^{14}$ −28° (c=0.90). IR : ν_{max} cm^{-1} 1730~1742 (broad), 1240. *Anal.* Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found : C, 68.52; H, 8.28.

2,16α,17β-Trihydroxy-4,4-dimethylandrosta-1,5-dien-3-one (XVIII)——a) In *tert*-butanol containing potassium *tert*-butoxide. A suspension of the ketol (XVIIa, 100 mg.) in *tert*-butanol (20 ml.) containing potassium (800 mg.) was stirred under O_2 atmosphere for 1 hr., when the steroid was dissolved. The solution was poured into H_2O and acidified with 10% HCl, and the product was extracted with ether-CH_2Cl_2 mixture. The solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Removal of the solvent and crystallization from ether-MeOH gave the diosphenol (XVIII, 12 mg.), m.p. 188~192°. Further crystallization from the same solvent afforded an analytical sample as colorless plates, m.p. 193~195°, $[\alpha]_D^{14}$ +32° (c=0.96). UV : λ_{max} 272 mμ (ε 7,700). IR : ν_{max} cm^{-1} 1680, 1665. *Anal.* Calcd. for $C_{21}H_{30}O_4 \cdot MeOH$: C, 69.81; H, 9.05. Found : C, 69.51; H, 8.81.

b) In EtOH containing aqueous KOH. A solution of the ketol triacetate (XVIIb, 200 mg.) in EtOH (40 ml.) and 20% KOH (3 ml.) was stirred under O_2 atmosphere for 20 min., when the absorption of O_2 stopped. The solution was poured into H_2O and acidified with 10% HCl, and the product was extracted with ether-CH_2Cl_2 mixture. The solution was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. Removal of

the solvent and crystallization from ether-MeOH mixture afforded the diosphenol (XVIII, 125 mg.), which was identical with the diosphenol obtained above.

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27. Masao Tomita, Shoichiro Uyeo, and Tohru Kikuchi : Pachysandra Alkaloids. II.*1 Structure of Pachysandrine-A, a New Pregnane Type Alkaloid.*2

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Structure and stereochemistry of pachysandrine-A, one of the major alkaloids isolated from the weakly basic alkaloid fraction of *Pachysandra terminalis* SIEB. et ZUCC. (Buxaceae), was discussed and assigned to the formula Ia. This presents the first example of 4-oxygenated 3,20-diamino-5α-pregnane alkaloid discovered in natural source.

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In the preceding paper,*1 we reported the isolation and characterization of a number of alkaloids of *Pachysandra terminalis* SIEB. et ZUCC. (Japanese name : Fukkiso), a Buxaceous plant. This paper deals with the full detail of the structural elucidation of pachysandrine-A (Ia), one of the major alkaloids obtained from the weakly basic alkaloid fraction. As will be clear in the sequel, this alkaloid, together with pachysandrine-B which will be discussed in the following paper, is the first pregnane type alkaloid discovered from a plant family other than Apocynaceae and also the first example of the pregnane alkaloid having an oxygen function at the 4-position.

Pachysandrine-A (Ia), m.p. 234～236°, $[\alpha]_D$ +80° ($CHCl_3$), was analyzed for $C_{33}H_{50}O_3N_2$ and demonstrated infrared bands*4 for an O-acetyl (1730 and 1245 cm^{-1}) and a conjugated tertiary amide (1620 cm^{-1}). Its NMR spectrum*5 revealed the presence of a phenyl group (2.67τ, 5H, singlet), a CH-CH-(O-Ac)-CH grouping (4.62τ, 1H, quartet, J 5 and 6 c.p.s.), an amide N-methyl (7.07τ,3H), an N-dimethyl (7.84τ,6H), an O-acetyl (7.98τ, 3H), two tertiary C-methyls (9.06 and 9.36τ, 6H), and a secondary C-methyl group (9.13τ, 3H, doublet, J 6 c.p.s.) (Fig. 3).

Hydrolysis of the alkaloid (Ia) with 5% methanolic sodium hydroxide gave an O-desacyl compound (Ib), $C_{31}H_{48}O_2N_2$, m.p. 194～195°, showing still an amide band (1610 cm^{-1}), but no O-acetyl band in the infrared spectrum. Upon acetylation, the O-desacyl compound (Ib) returned to pachysandrine-A (Ia).

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*1 Part I. M. Tomita, T. Kikuchi, S. Uyeo, Jr., T. Nishinaga, M. Yasunishi (née Ando), A. Yamamoto : Yakugaku Zasshi, **87**, 198 (1967).

*2 Preliminary report of this work appeared in Tetrahedron Letters, No. 18, 1053 (1964).

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*4 All the IR spectra were determined in chloroform solutions unless otherwise stated. For identification of compounds, spectra were measured in KBr discs using a Koken DS-301 Spectrometer.

*5 All the NMR spectra were measured on a Varian Associates A-60 High-Resolution NMR Spectrometer in deuterated chloroform using tetramethylsilane as the internal reference and chemical shifts are reported in τ values.