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9. Tokuo Kubota, Keiji Yoshida, Fumiko Hayashi, and Ken'ichi Takeda: Studies on A-Norsteroids. I. Synthesis of A-Nor-$\Delta^{3(5)}$-1,2-dioxo Steroids.[*1]

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During the course of the structural investigation on kogagenin, 25D-spirostane-1β,2β,3α,5β-tetrol, it has been found[1] that the treatment of 25D-spirost-4-ene-1β,2β,3α-triol (I) with manganese dioxide yielded A-nor-25D-spirost-3(5)-ene-1,2-dione (IIIa). The formation of this A-norsteroid has been explained to proceed through benzilic acid type rearrangement of an intermediate enetrione, which would probably arise from further oxidation of the primarily produced 1β,2β-dihydroxy-Δ^4-3-one (II).

In connection with recent findings[2] that some derivatives of A-norsteroids possess

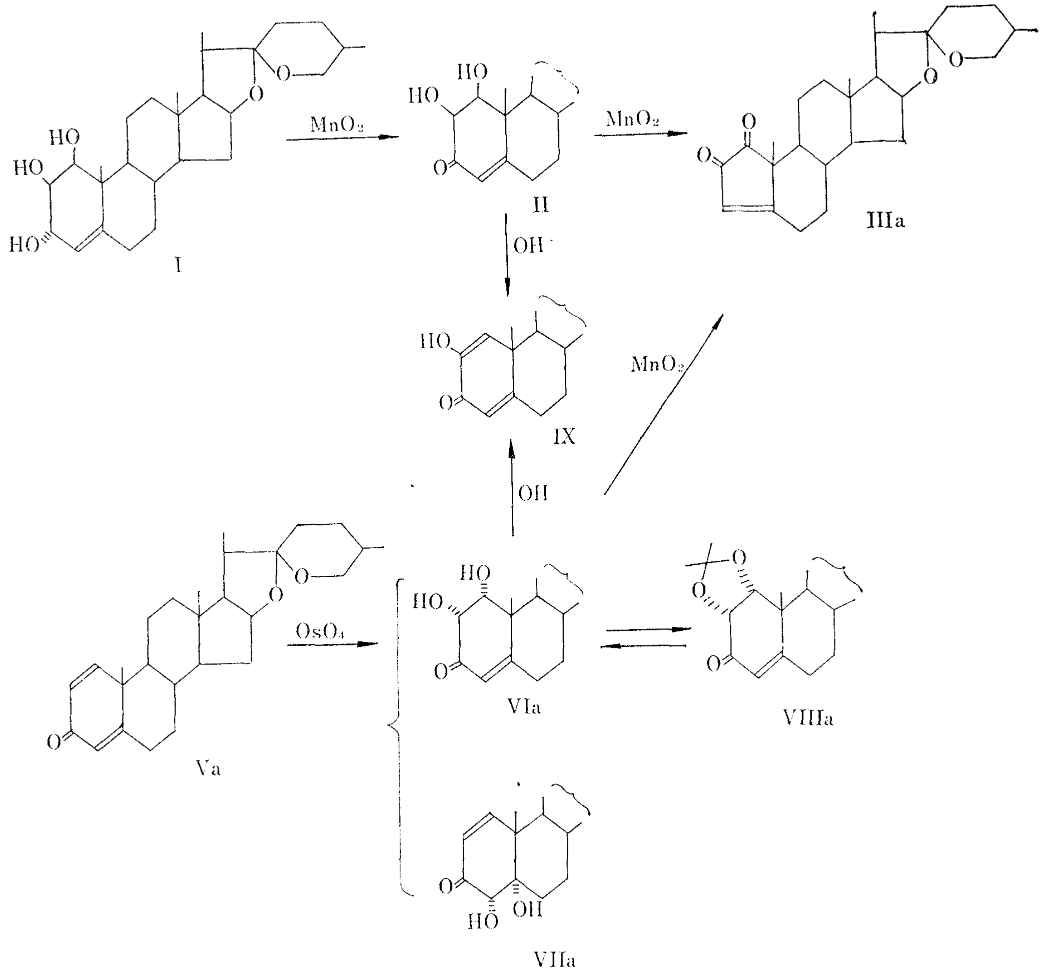

Chart 1.

[*1] An outline of this paper was presented at the Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July, 1961.

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1) T. Kubota, K. Takeda: Tetrahedron, **10**, 1 (1960).

2) *a*) L. J. Lerner, A. Bianchi, A. Borman: Proc. Soc. Exp. Med. Biol., **103**, 172 (1960). *b*) J. Jacques, G. Pincus: Excerpta Medica, **51**, 3 (1962).

interesting physiological activities, it was of interest to evaluate biological activities of steroidal hormone analogs having the novel A-nor-$\Delta^{3(5)}$-1,2-dioxo structure.

As manganese dioxide is a mild oxidizing agent, it is anticipated that this reagent gives no effect on functional groups, such as isolated carbonyl and hydroxyl groups, other than the 1,2-dihydroxy-Δ^4-3-oxo moiety in steroids. Thus the oxidative ring contraction with manganese dioxide would probably be applicable to preparation of the modified hormone analogs. On the other hand, the 1,2-dihydroxy-Δ^4-3-ones would certainly be converted into the A-norsteroids regardless of the configuration of hydroxyl groups at C_1 and C_2.

In order to prepare 1,2-dihydroxy-Δ^4-3-oxo derivatives, treatment of $\Delta^{1,4}$-3-oxo steroids with osmium tetroxide was chosen as the most desirable approach. The $\Delta^{1,4}$-3-oxo steroids (Va~f), except for commercially available prednisolone acetate (Vg), were conveniently prepared by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation[3] of the parent Δ^4-3-ones, *i.e.* 25D-spirost-4-en-3-one (IVa), cholest-4-en-3-one (IVb), testosterone propionate (IVc), progesterone (IVe) and deoxycorticosterone acetate (IVf).

Hirschmann, *et al.*[4,5] have carried out hydroxylation of the $\Delta^{1,4}$-3-oxo group in a few steroid derivatives with osmium tetroxide and they have got various results, in which 1,2- or 4,5-diol alone, or both were obtained. In this investigation, osmium tetroxide oxidation of the $\Delta^{1,4}$-3-oxo steroids (Va~g) followed essentially the procedure of Hirschmann.[4,5] The compounds were allowed to react with osmium tetroxide in pyridine and the osmates were decomposed with hydrogen sulfide. In every case, the crude hydroxylated products were predicted to consist of two isomeric diols, from their

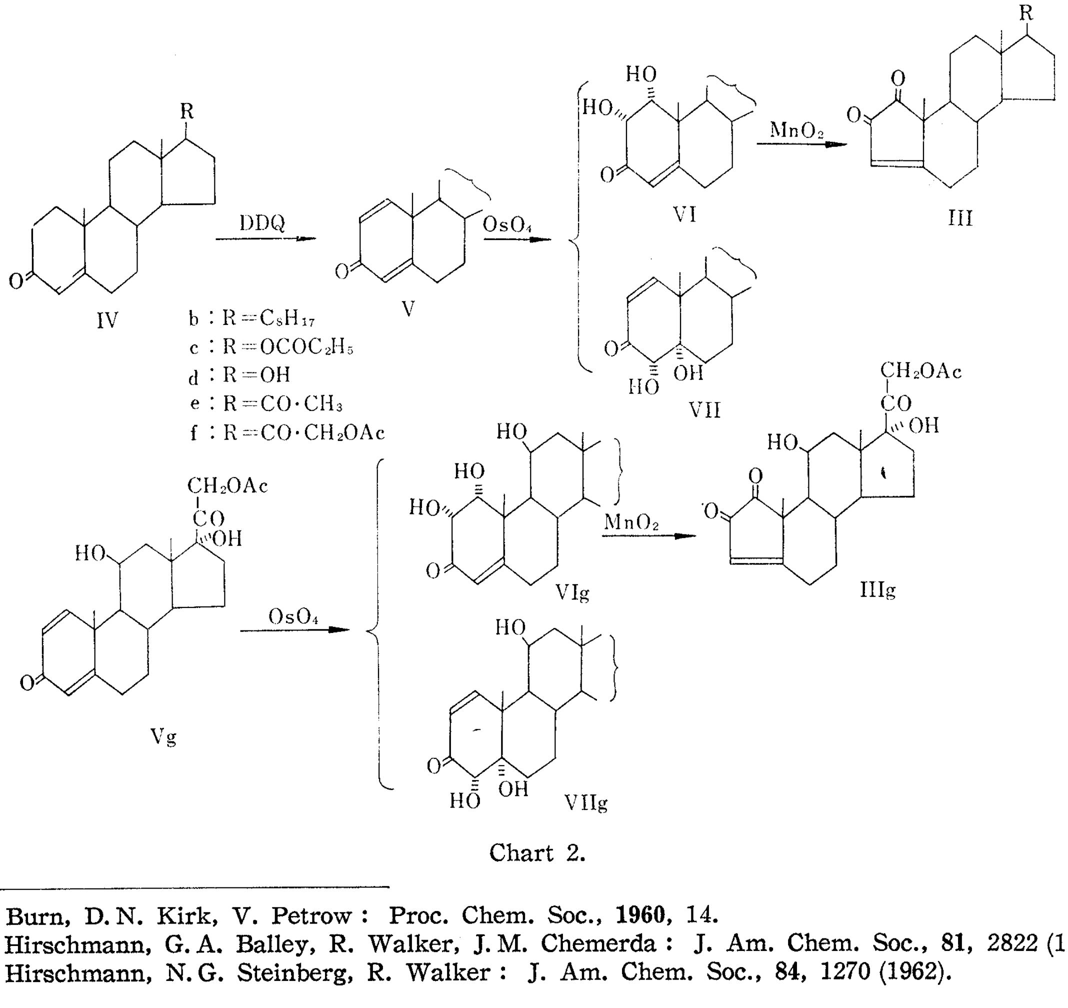

Chart 2.

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[3] D. Burn, D.N. Kirk, V. Petrow: Proc. Chem. Soc., **1960**, 14.
[4] R. Hirschmann, G.A. Bailey, R. Walker, J.M. Chemerda: J. Am. Chem. Soc., **81**, 2822 (1959).
[5] R. Hirschmann, N.G. Steinberg, R. Walker: J. Am. Chem. Soc., **84**, 1270 (1962).

thin-layer chromatographies. Separations of the mixtures, except for those from spirostadienone (Va) and cholestadienone (Vb), were performed effectively by column chromatography over silica gel to isolate the first eluted 4,5-diols (VIIc~g) and teh next eluted 1,2-diols (VIc~g). The unseparable mixtures obtained from Va and Vb were subjected to an acetonide formation. Refluxing in acetone containing a catalytic amount of *p*-toluenesulfonic acid brought on the formation of only the 1,2-diol acetonides (VIIIa, b), which could be isolated from the unreacted 4,5-diols (VIIa, b) by chromatography on silica gel. Hydrolysis of the acetonides with refluxing aqueous acetic acid regenerated the pure 1,2-diols (VIa) and (VIb). The physical constants of the 1,2- and 4,5-diols are listed in Table I. Their ultraviolet absorption data thoroughly support the assigned structures and more difinitive evidence was provided with the nuclear magnetic resonance spectra. The 1,2-dihydroxy-Δ^4-3-one (VIa) of spirostane series showed a singlet signal at 4.18 τ due to the olefinic proton at C-4, while the 4,5-dihydroxy-Δ^1-3-one (VIIa) exhibited the C-1,2 olefinic proton signals as two doublets at 3.28 τ (J=11 c.p.s.) and 3.97 τ (J=11 c.p.s.).

TABLE I.

	1α,2α-Dihydroxy-Δ^4-3-ones				4α,5α-Dihydroxy-Δ^1-3-ones		
	m.p.	$[\alpha]_D$	λ_{max} mμ (ε)		m.p.	$[\alpha]_D$	λ_{max} mμ (ε)
VIa	247~248	− 14	238 (11, 600)	VIIa	241~245	− 15	230 (8, 200)
VIb	156~157	+ 77	241 (12, 700)	VIIb	149~150	+ 82	231 (9, 000)
VIc	222~224	+ 81	240 (13, 900)	VIIc	168~170	+ 81	231 (9, 450)
VId	235~237	+ 97	241 (13, 700)	VIId	202~203	+ 80	231 (9, 150)
VIe	183~184	+183	241 (13, 800)	VIIe	222~224	+154	231 (9, 550)
VIf	195~197	+171	240 (13, 700)	VIIf	198~199	+157	231 (9, 200)
VIg	248~250	+170 (dioxane)	241 (13, 300)	VIIg	189~191	+122 (dioxane)	231 (9, 550)

The hydroxyl groups in these diols were inferred to be α-configuration on the assumption that the addition of osmium tetroxide to the double bond should occur more readily from the less hindered α-side of the steroid molecule. This conjecture was supported by the optical rotatory dispersions (ORD). The 1,2-dihydroxy-Δ^4-3-ones (VIa) and (VIb) exhibited negative Cotton curves as in 2α-hydroxy-Δ^4-3-ones but did not the reverse curve as observed in 2β-hydroxy-Δ^4-3-ones.[6] In the 4,5-dihydroxy-Δ^1-3-ones, the C_4-hydroxyl group should be equatorial, regardless of its configuration, in view of the fact that the hydroxylation of a double bond with osmium tetroxide gives a *cis* glycol. Hence the Cotton effect of the Δ^1-3-oxo moiety should not be greatly affected by the C_4-hydroxyl group but by the A/B ring juncture. The ORD of VIIa and VIIb did not exhibited a positive Cotton effect, which has been shown in the circular dichroism[7] of 17β-acetoxy-5β-androst-1-en-3-one, but were the negative Cotton curves as described[8] for cholest-1-en-3-one. Actually, the 1,2-diol obtained from the osmylation of 25D-spirosta-1,4-dien-3-one (Va) was proved to be the 1α,2α-dihydroxy-Δ^4-3-one (VIa) by correlation with the 1β,2β-dihydroxy-Δ^4-3-one (II)[1] previously derived from kogagenin. The both are entirely different from each other but on alkaline treatment yielded the identical 2-hydroxy-$\Delta^{1,4}$-3-one (X).[9] In analogy, it is most probable that all the 1,2- and 4,5-diols isolated in the other series have the same α-configuration of the hydroxyl groups.

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[6] K. Kuriyama, E. Kondo, K. Tori: Tetrahedron Letters, **1963**, 1485.
[7] L. Velluz, M. Legrand: Angew. Chem., **73**, 603 (1961).
[8] C. Djerassi, R. Riniker, B. Riniker: J. Am. Chem. Soc., **78**, 6377 (1956).
[9] K. Takeka, T. Kubota, A. Shimaoka: Tetrahedron, **7**, 62 (1959).

Although Hirschmann have described[5)] that the hydroxylation of prednisolone-BMD with osmium tetroxide was accompanied with the oxidation of the 11β-hydroxyl group to afford 1,2-dihydroxycortisone-BMD, in this experiment, osmium hydroxylation of prednisolone acetate (Vg) yielded the corresponding 1,2-diol (VIg)[*3] and 4,5-diol (VIIg) with the intact 11β-hydroxyl group, in the same way as in the other examples.

Treatment of 1α,2α-dihydroxy-25D-spirost-4-en-3-one (VIa) with manganese dioxide was carried out in the same manner as the previous experiment on the 1β,2β-dihydroxy epimer (II)[1)] and gave A-nor-25D-spirost-3(5)-ene-1,2-dione (IIIa) identical with the product from the latter. Thus all of the other 1α,2α-dihydroxy derivatives (VIb~g) were subjected to the oxidative ring contraction with manganese dioxide.

As previously described, manganese dioxide was prepared according to the direction of O. Mancera, *et al.*[10)] Although chloroform has previously been used as the reaction solvent, the reaction could be proceeded also in acetone, *tert*-butanol, benzene or carbon tetrachloride. When progresses of the reaction on VIb, d and e were followed with ultraviolet spectra,[1)] it was shown that acetone was superior as the reaction solvent to chloroform in the reaction rates. Thus, the 1,2-diols (VIb~g) were treated with manganese dioxide in acetone and smoothly converted into the corresponding A-nor-$\Delta^{3(5)}$-1,2-diones (IIIb~g), as expected. The structures were established by the satisfying analytical results and by the typical ultraviolet and infrared absorptions.[1)]

TABLE II. A-Nor-$\Delta^{3(5)}$-1,2-diones

	m.p.	$[\alpha]_D$	λ_{max} mμ (ε)	ν_{max}^{Nujol} cm^{-1}
IIIa[1)]	228~230	−118	282 (5,600)	1756, 1720, 1604
IIIb	119~120	− 26	284 (5,400)	1755, 1715, 1602
IIIc	160~162	− 26	283 (6,200)	1744, 1712, 1599
IIId	229~230	− 27	284 (5,900)	1755, 1700, 1588
IIIe	180~181	+ 75	283 (6,150)	1753, 1714, 1696, 1603
IIIf	218~220	+ 91	283 (6,200)	1753, 1746, 1730, 1710, 1600
IIIg	199~201	+100 (dioxane)	282 (5,600)	1758, 1740, 1724, 1706, 1650, 1593

On the other hand, the 4α,5α-dihydroxy-Δ^1-3-ones were found to be stable to manganese dioxide. Thus, a mixture of the isomeric diols, derived from cholestadienone (Vb), was subjected to the oxidation with manganese dioxide, without isolation of the 1,2-diol (VIb). The A-norsteroid (IIIb) arised from the oxidation of the 1,2-diol could be readily separated from the unreacted 4,5-diol (VIIb) by chromatography over silica gel.

Experimental

All melting points were uncorrected. Unless otherwise stated, optical rotations were measured in $CHCl_3$ solutions at ca. 25° with a Rudolf Photoelectric Polarimeter Model 200. UV spectra were taken in 95% EtOH solutions with a Hitachi Recording Spectrophotometer EPS-2. IR spectra were recorded on a Koken Infrared Spectrophotometer Model DS 301. NMR spectra were determined at 60 Mc. in $CDCl_3$ solutions containing tetramethylsilane as an internal standard using a Varian A-60 analytical NMR spectrometer. ORD curves were recorded in dioxane solutions with a Rudolf Recording Spectropolarimeter.

General Procedure for the Δ^1-Dehydrogenation of a Δ^4-3-Oxo Steroid——A mixture of a Δ^4-3-oxo steroid and DDQ (1.2 equiv.) in dry benzene (40~65 ml./1 g. of the steroid) was heated under reflux for 25~30 hr. The precipitated hydroquinone was removed by filtration and the filtrate was passed through a column of Al_2O_3 (10 g./1 g. of the steroid) in order to remove the excess DDQ. The Al_2O_3 was washed with $CHCl_3$ and the combined eluates were evaporated under a reduced pressure and the residue was recrystallized from a solvent.

[*3] This compound is indeed different from 1α,2α-dihydroxycortisone 21-acetate, m.p. 244.5~246°, $[\alpha]_D$ +163°, UV λ_{max}^{EtOH} mμ (ε) : 235 (13,200), obtained by osmylation of prednisone acetate. (Unpublished work in this Laboratory).

10) O. Mancera, G. Rosenkranz, F. Sondheimer : J. Chem. Soc., 1953, 2189.

Cholesta-1,4-dien-3-one (Vb)——Cholest-4-en-3-one (Ⅳb) (7.69 g.) was dehydrogenated with DDQ (5.44 g.) in dry benzene (400 ml.) by the general procedure described above. Recrystallization of the crude product (5.70 g.) from MeOH gave Vb (4.89 g.) as needles, m.p. 111∼112°, $[\alpha]_D$ +26° (c=1.01), (reported,[11] m.p. 110∼112°, $[\alpha]_D$ +31°). UV : $\lambda_{\max}$ 247 mμ (ε 15,800). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1666, 1626, 1605, 883. *Anal.* Calcd. for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found : C, 84.47; H, 11.14.

17β-Hydroxyandrosta-1,4-dien-3-one Propionate (Vc)——By the general procedure described previously, testosterone propionate (Ⅳc) (27.6 g.) was dehydrogenated with DDQ (21.8 g.) in dry benzene (1.2 L.). Recrystallization of the crude product (24.6 g.) from Me_2CO-petr. ether afforded scales of Vc (14.6 g.), m.p. 138∼140°, $[\alpha]_D$ +34° (c=1.03). UV : $\lambda_{\max}$ 245 mμ (ε 17,100). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1733, 1667, 1623, 1605, 1186, 875. *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found : C, 77.21; H, 8.86.

17β-Hydroxyandrosta-1,4-dien-3-one (Vd)——The foregoing propionate (Vc) (19.55 g.) was saponified by heating with a 1.5% KOH-MeOH solution (600 ml.) for 1 hr. The mixture was neutralized with dil. HCl and concentrated and then H_2O was added. Precipitated crystals were collected, dried (16.09 g.) and recrystallized from Me_2CO giving Vd (14.77 g.), m.p. 167∼169°, $[\alpha]_D$ +22° (c=1.06). (reported[12] m.p. 168∼170°, $[\alpha]_D$ +23°). UV : $\lambda_{\max}$ 246 mμ (ε 15,400), IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3480, 1663, 1622, 1600, 883. *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found : C, 79.93; H, 9.16.

Pregna-1,4-diene-3,20-dione (Ve)——Progesterone (Ⅳe) (4.718 g.) in dry benzene (300 ml.) was dehydrogenated with DDQ (4.08 g.) as described in the general procedure. Recrystallization of the crude product (3.658 g.) from Me_2CO gave Ve (2.833 g.) as prisms, m.p. 146∼150°. Further recrystallization from Me_2CO raised the m.p. to 150∼151°, $[\alpha]_D$ +122° (c=1.09). (reported[13] m.p. 152∼153°, $[\alpha]_D$ +120°). UV : $\lambda_{\max}$ 246 mμ (ε 16,300). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1695, 1660, 1626, 1602, 882. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found : C, 80.55; H, 9.10.

21-Hydroxypregna-1,4-diene-3,20-dione Acetate (Vf)——By the general procedure described previously, desoxycorticosterone acetate (Ⅳf) (11.18 g.) was transformed with DDQ (8.17 g.) in dry benzene (600 ml.). The crude product (9.80 g.) was recrystallized from Me_2CO yielding Vf (8.80 g.) as prisms, m.p. 201∼202°, $[\alpha]_D$ +136° (c=1.04). (reported[14] m.p. 202∼204°, $[\alpha]_D$ +143°). UV : $\lambda_{\max}$ 245 mμ (ε 16,200). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1745, 1725, 1667, 1626, 1605, 890. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74. 56; H, 8.16. Found : C, 74.89; H, 8.32.

General Procedure for the Hydroxylation of a $\Delta^{1,4}$-3-Oxo Steroid——A solution of a $\Delta^{1,4}$-3-oxo steroid in pyridine was cooled in an ice-bath and OsO_4 was added. The mixture was allowed to stand at room temperature for 7 days in a dark place and poured into a large volume of petr. ether. The precipitated crude osmate was separated from the solvent by decantation, washed with petr. ether to free from the pyridine and dissolved in a mixture of dioxane and $CHCl_3$. A stream of H_2S was bubbled through the solution kept in an ice-bath for 30 min. After standing overnight, a precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was subjected to chromatography on a column of silica gel.

Hydroxylation of 25D-Spirosta-1,4-dien-3-one (Va) with Osmium Tetroxide——A solution of Va (2.00 g.), prepared[15] by DDQ dehydrogenation of 25D-spirost-4-en-3-one, in pyridine was treated with OsO_4 (1.6 g.) by the general procedure described above. The resulting crude product (2.45 g.) was chromatographed over a column of silica gel (35 g.) to separate into two fractions, those are the eluates (220 mg.) with benzene-$CHCl_3$ (4:1 to 2:1) and the eluates (729 mg.) with benzene-$CHCl_3$ (2:1) to $CHCl_3$ alone.

Crystallization of the former fraction from MeOH gave prisms (150 mg.) of 4α,5α-dihydroxy-25D-spirost-1-en-3-one (Ⅶa), m.p. 241∼245°. Further recrystallization from MeOH did not change the m.p., $[\alpha]_D$ −15° (c=1.14). UV : $\lambda_{\max}$ 230 mμ (ε 8,200). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3510, 1695, 1610. NMR (τ) : 3.28 (doublet, J=11 c.p.s., C_1-proton), 3.97 (doublet, J=11 c.p.s., C_2-proton), 5.40 (singlet, C_4-proton), 8.73 (singlet, C_{19}-CH_3), 9.18 (singlet, C_{18}-CH_3). ORD (c=0.5878) : $[\alpha]_{348}^{\text{trough}}$ −449°, $[\alpha]_{280}$ +1565°, $[\alpha]_{260}$ +3440°. *Anal.* Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found : C, 73.25; H, 9.13.

The latter fraction of the above chromatography was dissolved in Me_2CO (80 ml.) containing *p*-toluenesulfonic acid (80 mg.). The mixture was refluxed for 5 hr., neutralized with 5% $NaHCO_3$ and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel (15 g.) and the fractions (172 mg.) eluted with benzene-$CHCl_3$ (4:1) on crystallization from hexane afforded 1α,2α-dihydroxy-25D-spirost-4-en-3-one acetonide (Ⅷa) (112 mg.) as needles, m.p. 191∼193°, $[\alpha]_D$ −35° (c=0.85, dioxane). UV : $\lambda_{\max}$ 244.5 mμ (ε 15,100). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1676, 1625. *Anal.* Calcd. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.43; H, 9.19. Elution of the chromatography with benzene-$CHCl_3$ (4:1 to 1:1) and crystallization of the eluate (160 mg.) from MeOH gave the above-mentioned 4,5-diol (Ⅶa) (55 mg.), m.p. 234∼242°. The

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11) A. L. Wilds, C. Djerassi : J. Am. Chem. Soc., **68**, 1712 (1946).

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13) F. Sondheimer, M. Velasco, G. Rosenkranz : J. Am. Chem. Soc., **77**, 5673 (1955).

14) H. L. Herzog, C. C. Payne, M. T. Hughes, M. J. Gentles, E. B. Hershberg, A. Nobile, W. Charney, C. Federbush, D. Sutter, P. L. Perlman : Tetrahedron, **18**, 581 (1962).

15) K. Takeda, T. Okanishi, K. Igarashi, A. Shimaoka : Tetrahedron, **15**, 183 (1961).

fractions (436 mg.) eluted further with $CHCl_3$ were assumed to be a mixture consisted of the unreacted 1,2-diol (Ⅵa) and 4,5-diol (Ⅶa), on the basis of the thin-layer chromatogram.

1α,2α-Dihydroxy-25D-spirost-4-en-3-one (VIa)——A mixture of the foregoing acetonide (Ⅷa) in 50% aq. AcOH (5 ml.) was heated at 70~80° for 1 hr. and then evaporated *in vacuo* to dryness. Crystallization of the residue (94 mg.) from MeOH afforded needles (67 mg.) of Ⅵa, m.p. 247~248°, $[\alpha]_D$ $-14°$ (c=1.07). UV : λ_{max} 238 mμ (ε 11,600). IR ν_{max}^{Nujol} cm^{-1} : 3566, 3472, 1680, 1620. NMR (τ) : 4.17 (singlet, C_4-proton), 5.67 (doublet, J=3 c.p.s., C_2-proton), 5.97 (doublet, J=3 c.p.s., C_1-proton), 8.72 (singlet, C_{19}-CH_3), 9.18 (singlet, C_{18}-CH_3). ORD (c=0.1158) : $[\alpha]_{700}$ $-86°$, $[\alpha]_{346}^{trough}$ $-1192°$, $[\alpha]_{300}$ $+2997°$, $[\alpha]_{281}$ $+3739°$, $[\alpha]_{275}$ $+4275°$. *Anal.* Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found : C, 73.16; H, 9.20.

Treatment of VIa with Alkali——A mixture of the above 1α,2α-diol (Ⅵa) (30 mg.) in MeOH (7 ml.) and 10% KOH (1 ml.) was refluxed for 30 min. The reaction mixture was diluted with H_2O, acidified with dil. HCl and extracted with $CHCl_3$-Et_2O (1:4). The organic layer was washed with H_2O, dried and evaporated under diminished pressure leaving an oil (30 mg.). Crystallization from Me_2CO afforded scales (17 mg.), m.p. 224~227°, which was identical with a sample of 2-hydroxy-25D-spirosta-1,4-dien-3-one (Ⅸ)[9] previously derived from kogagenin in all respects.

Treatment of VIa with Manganese Dioxide——To a solution of the 1α,2α-diol (Ⅵa) (8 mg.) in $CHCl_3$ (1 ml.), MnO_2 (100 mg.) prepared by the procedure of Mancera, *et al.*[10] was added. The mixture was stirred at 32° for 6 hr. and the MnO_2 was removed by filtration. Evaporation of the filtrate left a yellow solid, which was recrystallized from Me_2CO giving yellow prisms, m.p. 227~231°. Identity with an authentic sample of A-nor-25D-spirost-3(5)-ene-1,2-dione (Ⅲa)[1] was established by comparison of the IR spectra and a mixed melting point determination.

Hydroxylation of Cholesta-1,4-dien-3-one (Vb) with Osmium tetroxide——To a solution of Vb (5.50 g.) in pyridine (60 ml.) was added OsO_4 (4 g.). The crude product (5.0 g.), obtained after working up by the general procedure, was chromatographed on silica gel (70 g.). The elution with benzene-$CHCl_3$ (1:1) and $CHCl_3$ gave a mixture (3.69 g.) of the isomeric diols as a gelatinous solid.

a) A part (2.88 g.) of the foregoing mixture was dissolved in Me_2CO (576 ml.) and *p*-toluenesulfonic acid (288 mg.) was added. The solution was refluxed for 5 hr., neutralized with 5% $NaHCO_3$ and evaporated. The residue was taken up with Et_2O and the Et_2O solution was washed with H_2O, dried and evaporated to dryness. The residue (3.20 g.) was chromatographed over silica gel (70 g.). The fractions (1.60 g.) eluted with benzene-$CHCl_3$ (9:1) gave no crystals on attempts to crystallize it from solvents and appeared to be a mixture of the 1,2-diol acetonide and the unreacted 4,5-diol by thin-layer chromatography. The mixture was subjected to preparative thin-layer chromatography using plates (20×20 cm.) spread Merck's Silica Gel GF_{254} in thickness of 0.5 mm. After development with benzene-AcOEt (3:1), the two fractions detected by UV light were scraped, extracted with $CHCl_3$ and there were obtained the more mobile fraction (670 mg.) and the less mobile one (445 mg.). Recrystallization of the former fraction from petr. ether gave 1α,2α-dihydroxycholest-4-en-3-one acetonide (Ⅷb) (365 mg.) as plates, m.p. 134~136°. Concentration of the mother liquor afforded the second crop (60 mg.), m.p. 132~135°. The first crop showed the following constants, $[\alpha]_D$ $+51°$ (c=0.55). UV : λ_{max} 245 mμ (ε 14,600). IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1683, 1630, 1382, 1374. *Anal.* Calcd. for $C_{30}H_{40}O_3$: C, 78.89; H, 10.59. Found : C, 79.18; H, 10.73.

The less mobile fraction of the preparative thin-layer chromatography was combined with the eluates (1.23 g.) of the above column chromatography with benzene-$CHCl_3$ (9:1 to 1:1). An attempt to crystallize from abs. EtOH afforded a gelatinous solid (1.470 g.), which was acetylated by standing with Ac_2O (15 ml.) and pyridine (20 ml.) at room temperature. The crude product (1.675 g.), extracted with AcOEt in the usual manner, was chromatographed over silica gel (40 g.). Elution with benzene-$CHCl_3$ (9:1 to 4:1) gave an oily fraction (142 mg.), which resisted to crystallization. Further elution with benzene-$CHCl_3$ (4:1) to $CHCl_3$ afforded a crystalline fraction (1.476 g.), which on recrystallization from Me_2CO gave needles (977 mg.), m.p. 224~226° (decomp.). This substance was identified with an authentic sample of 4α,5α-dihydroxycholest-1-en-3-one 4-acetate described below by a mixed melting point determination and the IR spectra.

b) The remainder (810 mg.) of the mixture of the isomeric diols was dissolved in Me_2CO (81 ml.) and stirred together with MnO_2 (8.1 g.) at 30~32° for 6 hr. The mixture was filtered and the filtrate was evaporated to give the yellow crystalline residue (645 mg.), which was chromatographed on silica gel (20 g.). The yellow fractions (225 mg.) eluted with benzene to benzene-$CHCl_3$ (9:1) yielded, on recrystallization from Me_2CO, yellow plates (150 mg.), m.p. 119~120°. This substance was identical with an authentic sample of A-norcholest-3(5)-ene-1,2-dione (Ⅲb) described below in all respects.

The fractions (357 mg.) eluted the above chromatography with benzene-$CHCl_3$ (1:1) were purified further by the preparative thin-layer chromatography, in the manner as described in a). A gelatinous solid (240 mg.), obtained from the main spots, on recrystallization from abs. EtOH afforded 4α,5α-dihydroxycholest-1-en-3-one (Ⅶb) (176 mg.) as clusters of small plates, m.p. 149~150°, $[\alpha]_D$ $+82°$ (c=1.11). UV : λ_{max} 231 mμ (ε 9,000). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3576, 3490, 1685, 1618. ORD (c=0.2262) : $[\alpha]_{349}^{trough}$ $-257°$, $[\alpha]_{300}$ $+2185°$, $[\alpha]_{287}$ $+2490°$, $[\alpha]_{275}$ $+2968°$. *Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found : C, 77.64; H, 10.54.

1α,2α-Dihydroxycholest-4-en-3-one (VIb)——A mixture of the above-mentioned 1,2-diol acetonide (VIIIb) (330 mg.) and 70% AcOH (20 ml.) was heated at 80° for 1 hr. The solution was diluted with H_2O and extracted thoroughly with AcOEt. The organic layer was washed with 5% Na_2CO_3 and H_2O, dried and evaporated giving the crystalline residue (297 mg.), m.p. 149~152°. Recrystallization from Me_2CO afforded plates (158 mg.) of VIb, m.p. 156~157°. Concentration of the mother liquor gave the second crop (100 mg.), m.p. 155~156°. $[\alpha]_D$ +77° (c=1.05). UV : λ_{max} 241 mμ (ε 12,700). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3582, 3490, 1680, 1618. ORD (c=0.2926) : $[\alpha]_{470}$ +103°, $[\alpha]_{347}^{trough}$ −943°, $[\alpha]_{300}$ +3746°. *Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found : C, 77.87; H, 10.68.

4α,5α-Dihydroxycholest-1-en-3-one 4-Acetate——A mixture of the pure 4,5-diol (VIIb) (50 mg.), Ac_2O (1 ml.) and pyridine (1 ml.) was allowed to stand at room temperature overnight, The product, isolated with AcOEt in the usual manner, was recrystallized from Me_2CO to give the monoacetate (36 mg.) as needles, m.p. 224~226° (decomp.), $[\alpha]_D$ +83° (c=0.99). UV : λ_{max} 231 mμ (ε 9,950). IR ν_{max}^{Nujol} cm^{-1} : 3353, 1754, 1692, 1623, 1224. *Anal.* Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found : C, 76.21; H, 10.25. Concentration of the above mother liquor gave the second crop (13 mg.), m.p. 222~224° (decomp.).

A-Norcholest-3(5)-ene-1,2-dione (IIIb)——A mixture of VIb (100 mg.) and MnO_2 (1.0 g.) in Me_2CO (10 ml.) was stirred at 30~32° for 4 hr. The MnO_2 was filtered off and the filtrate was evaporated to dryness. The yellow crystalline residue (84 mg.) was recrystallized from Me_2CO giving IIIb (60 mg.) as yellow plates, m.p. 119~120°, $[\alpha]_D$ −26° (c=1.09). UV : λ_{max} 284 mμ (ε 5,400). IR ν_{max}^{Nujol} cm^{-1} : 1755; 1715, 1602. *Anal.* Calcd. for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48. Found : C, 81.11; H, 10.66.

Hydroxylation of 17β-Hydroxyandrosta-1,4-dien-3-one Propionate (Vc) with Osmium Tetroxide——To a solution of Vc (12.8 g.) in pyridine (125 ml.) was added OsO_4 (10.0 g.). The reaction mixture was processed by the general procedure described above. Chromatography of the crude product over silica gel (125 g.) was eluted with benzene-$CHCl_3$ (1:1) to give a fraction (3.66 g.), which on recrystallization from Me_2CO-petr. ether afforded prisms (2.55 g.) of 4α,5α,17β-trihydroxyandrost-1-en-3-one 17-propionate (VIIc), m.p. 168~170°, $[\alpha]_D$ +81° (c=1.03). UV : λ_{max} 231mμ (ε 9,450). IR ν_{max}^{Nujol} cm^{-1} : 3578, 1727, 1675, 1620, 1277, 1215. *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found : C, 70.28; H, 8.59.

The next fractions (5.19 g.) eluted the above chromatography with $CHCl_3$ gave, on recrystallization from MeOH, 1α,2α,17β-trihydroxyandrost-4-en-3-one 17-propionate (VIc) (3.93 g.), m.p. 219~222°. Further recrystallization from MeOH gave the pure sample, m.p. 222~224°, as needles, $[\alpha]_D$ +81° (c=1.06). UV : λ_{max} 240 mμ (ε 13,900). IR ν_{max}^{Nujol} cm^{-1} : 3570, 1710, 1668, 1615, 1275, 1245. *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found : C, 70.47; H, 8.61.

17β-Hydroxy-A-norandrost-3(5)-ene-1,2-dione Propionate (IIIc)——A mixture of the foregoing VIc (1.50 g.) and MnO_2 (15 g.) in Me_2CO (150 ml.) was stirred at 30~32° for 4 hr. After removals of the MnO_2 and the solvent, the yellow crystalline product (1.03 g.) was recrystallized from Me_2CO-petr. ether giving yellow scales (850 mg.) of IIIc, m.p. 160~162°, $[\alpha]_D$ −26° (c=1.06). UV : λ_{max} 283 mμ (ε 6,200). IR ν_{max}^{Nujol} cm^{-1} : 1744, 1712, 1599, 1201. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found : C, 73.07; H, 8.19.

Hydroxylation of 17β-Hydroxyandrosta-1,4-dien-3-one (Vd) with Osmium Tetroxide——A mixture of Vd (10.93 g.) and OsO_4 (10 g.) in pyridine (135 ml.) was processed by the general procedure described previously. The crude product was chromatographed on silica gel (130 g.). The fractions (3.48 g.), eluted with $CHCl_3$, were crystallized from Me_2CO-petr. ether giving prisms (2.906 g.) of 4α,5α,17β-trihydroxyandrost-1-en-3-one (VIId), m.p. 200~203° (decomp.). Further recrystallization from Me_2CO gave an analytical sample, m.p. 202~203° (decomp.), $[\alpha]_D$ +80° (c=1.02). UV : λ_{max} 231 mμ (ε 9,150). IR ν_{max}^{Nujol} cm^{-1} : 3430, 1673, 1616. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found : C, 71.47; H, 8.83.

Further elution of the chromatography with $CHCl_3$-MeOH (100:1) gave a crystalline fraction (3.39 g.). Recrystallization from MeOH afforded needles (1.945 g.) of 1α,2α,17β-trihydroxyandrost-4-en-3-one (VId), m.p. 230~232°. Concentration of the mother liquor yielded the second crop (990 mg.) m.p. 223~227°. For analysis, the first crop was recrystallized further from MeOH. m.p. 235~237°, $[\alpha]_D$ +97° (c=0.95). UV : λ_{max} 241 mμ (ε 13,700). IR ν_{max}^{Nujol} cm^{-1} : 3458, 1675, 1623. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found : C, 71.36; H, 8.82.

17β-Hydroxy-A-norandrost-3(5)-ene-1,2-dione (IIId)——A mixture of the foregoing VId (1.7 g.) and MnO_2 (17 g.) in Me_2CO (170 ml.) was stirred at 30~32° for 6 hr. The MnO_2 was filtered off and the filtrate was evaporated. The yellow crystalline residue (1.17 g.) on recrystallization from Me_2CO-petr. ether gave IIId (870mg.) as yellow needles, m.p. 229~230°, $[\alpha]_D$ −27° (c=0.98). UV : λ_{max} 284 mμ (ε 5,900). IR ν_{max}^{Nujol} cm^{-1} : 3515, 1755, 1700, 1588. NMR (τ) : 3.43 (singlet, C_3-proton), 8.72 (singlet, C_{19}-CH_3), 9.20 (singlet, C_{18}-CH_3). *Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found : C, 74.71; H, 8.36.

Hydroxylation of Pregna-1,4-diene-3,20-dione (Ve) with Osmium Tetroxide——By the general procedure described above, Ve (2.23 g.) was treated with OsO_4 (2 g.) in pyridine (30 ml.). The crude product was chromatographed on silica gel (60 g.). The fractions (609 mg.) eluted with benzene-$CHCl_3$ (1:1) were recrystallized from Me_2CO to give prisms (453 mg.) of 4α,5α-dihydroxypregn-1-ene-3,20-dione (VIIe), m.p. 222~224° (decomp.), $[\alpha]_D$ +154° (c=1.06). UV : λ_{max} 231 mμ (ε 9,550). IR ν_{max}^{Nujol} cm^{-1} : 3524, 1693, 1676, 1622. *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found : C, 72.74; H, 8.83.

The next fractions (530 mg.) eluted with benzene-$CHCl_3$ (1:1) to $CHCl_3$ were shown to be a mixture of the 1,2-diol (VIe) and the 4,5-diol (VIIe) by thin-layer chromatography. Recrystallization from Me_2CO resulted in the isolation of the 4,5-diol (VIIe) (133 mg.), m.p. 219~223° (decomp.).

Further elution with $CHCl_3$ to $CHCl_3$-MeOH (50:1) gave a fraction (588 mg.), which on crystallization from Me_2CO afforded prisms (160 mg.) of 1α,2α-dihydroxypregn-4-ene-3,20-dione (VIe), m.p. 183~184°. Concentration of the mother liquor yielded additional crystals (249 mg.), m.p. 179~181°. The first crop showed the following constants. $[\alpha]_D$ +183° (c=1.06). UV: λ_{max} 241 mμ (ε 13,800). IR ν_{max}^{Nujol} cm^{-1}: 3543, 1689, 1626. *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.74; H, 8.83.

A-Norpregn-3(5)-ene-1,2,20-trione (IIIe)——A mixture of the foregoing VIe (80 mg.), MnO_2 (800 mg.) and Me_2CO (8 ml.) was stirred at 30~32° for 4 hr. After removal of the MnO_2, the filtrate was evaporated to give the yellow crystalline residue (52 mg.), which was purified by chromatography on silica gel. The eluate (43 mg.) with benzene-$CHCl_3$ (1:1) gave, on recrystallization from Me_2CO-petr. ether, yellow needles (37 mg.), m.p. 179~181°. Further recrystallization from Me_2CO-petr. ether yielded the pure sample of IIIe, m.p. 180~181°, $[\alpha]_D$ +75° (c=1.03). UV: λ_{max} 283 mμ (ε 6,150). IR ν_{max}^{Nujol} cm^{-1}: 1753, 1714, 1696, 1603. NMR (τ): 3.43 (singlet, C_3-proton), 7.91 (singlet, C_{21}-CH_3), 8.73 (singlet, C_{19}-CH_3), 9.33 (singlet, C_{18}-CH_3). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.31; H, 8.44.

Hydroxylation of 21-Hydroxypregna-1,4-diene-3,20-dione Acetate (Vf) with Osmium Tetroxide——To a solution of Vf (2.65 g.) in a mixture of pyridine (60 ml.) and benzene (10 ml.), OsO_4 (2.0 g.) was added. Working up by the general procedure described above gave the crude product as a brittle foam, which was chromatographed over silica gel (40 g.). The fractions (865 mg.), eluted with benzene-$CHCl_3$ (1:1) and $CHCl_3$, gave plates (744 mg.) of 4α,5α,21-trihydroxypregn-1-ene-3,20-dione 21-acetate (VIIf), m.p. 194~195°, by recrystallization from Me_2CO-petr. ether. Further recrystallization from Me_2CO raised the m.p. to 198~199°. $[\alpha]_D$ +157° (c=1.08). UV: λ_{max} 231 mμ (ε 9,200). IR ν_{max}^{Nujol} cm^{-1}: 3570, 1738, 1708, 1695, 1620, 1237. *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.13; H, 8.05.

The next fractions (643 mg.), eluted the chromatography with $CHCl_3$, were recrystallized from Me_2CO yielding 1α,2α,21-trihydroxypregn-4-ene-3,20-dione 21-acetate (VIf) (408 mg.) as needles, m.p. 193~196°. Further recrystallization from the same solvent raised the m.p. to 195~197°, $[\alpha]_D$ +171° (c=1.05). UV: λ_{max} 240 mμ (ε 13,700). IR ν_{max}^{Nujol} cm^{-1}: 3585, 3525, 1743, 1724, 1693, 1630, 1235, 1218. *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.38; H, 7.99.

21-Hydroxy-A-norpregn-3(5)-ene-1,2,20-trione Acetate (IIIf)——A mixture of VIf (210 mg.) and MnO_2 (2.1 g.) in $CHCl_3$ (21 ml.) was stirred at 30~32° for 6 hr. Removals of the MnO_2 and the solvent left a yellow crystalline material (135 mg.). Recrystallization from Me_2CO-petr. ether gave IIIf (95 mg.) as yellow scales, m.p. 218~220°, $[\alpha]_D$ +91° (c=1.05). UV: λ_{max} 283 mμ (ε 6,200). IR ν_{max}^{Nujol} cm^{-1}: 1753, 1746, 1730, 1710, 1600. *Anal.* Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.00; H, 7.67.

Hydroxylation of Prednisolone Acetate (Vg) with Osmium Tetroxide——Prednisolone acetate (Vg) (2.88 g.) was hydroxylated with OsO_4 (2 g.) in pyridine (30 ml.) by the general procedure described above. The resulting crude product was chromatographed on silica gel (40 g.). The fractions (300 mg.) eluted with $CHCl_3$-MeOH (100:1 to 50:1) were recrystallized from Me_2CO-petr. ether to recover the starting material as prisms, m.p. 238~241°. The fractions (600 mg.), eluted further with $CHCl_3$-MeOH (50:1), on two recrystallization from Me_2CO gave needles (127 mg.) of 4α,5α,11β,17α,21-pentahydroxypregn-1-ene-3,20-dione 21-acetate (VIIg), m.p. 189~191°, $[\alpha]_D$ +122° (c=1.03, dioxane). UV: λ_{max} 231 mμ (ε 9,550). IR ν_{max}^{Nujol} cm^{-1}: 3500, 1723, 1695, 1676, 1616, 1268, 1246. *Anal.* Calcd. for $C_{23}H_{32}O_8 \cdot \frac{1}{2}H_2O$: C, 62.03; H, 7.46. Found: C, 62.13; H, 7.63.

The fractions (820 mg.) eluted with $CHCl_3$-MeOH (9:1) were recrystallized from Me_2CO-petr. ether giving 1α,2α,11β,17α,21-pentahydroxypregn-4-ene-3,20-dione 21-acetate (VIg) (685mg.), m.p. 246~247°, as plates. Further recrystallization from Me_2CO-petr. ether gave the pure sample with the following constants: m.p. 248~250°, $[\alpha]_D$ +170° (c=1.06, dioxane). UV: λ_{max} 241 mμ (ε 13,300). IR ν_{max}^{Nujol} cm^{-1}: 3536, 1729, 1713, 1674, 1620, 1247. *Anal.* Calcd. for $C_{23}H_{32}O_8$: C, 63.28; H, 7.39. Found: C, 63.53; H, 7.59.

11β,17α,21-Trihydroxy-A-norpregn-3(5)-ene-1,2,20-trione 21-Acetate (IIIg)——A mixture of VIg (71 mg.) and MnO_2 (710 mg.) in Me_2CO (7 ml.) was stirred for 4 hr. at 30~32°. The MnO_2 was filtered off and the filtrate was evaporated. The yellow crystalline residue (52 mg.) was chromatographed over silica gel (1 g.). The eluate with $CHCl_3$-MeOH (100:1) gave, on recrystallization from Me_2CO-petr. ether, yellow needles (25 mg.) of IIIg, m.p. 199~201°, $[\alpha]_D$ +100° (c=0.58, dioxane). UV: λ_{max} 282 mμ (ε 5,600). IR ν_{max}^{Nujol} cm^{-1}: 3604, 3576, 3465, 3354, 1758, 1740, 1724, 1706, 1650, 1593, 1279, 1270, 1245. *Anal.* Calcd. for $C_{22}H_{28}O_7 \cdot H_2O$: C, 62.54; H, 7.16. Found: C, 62.64; H, 7.19.

Summary

A number of steroidal $\Delta^{1,4}$-3-ones (Va~g) were hydroxylated with osmium tetroxide affording the 1α,2α-dihydroxy-Δ^4-3-ones (VIa~g) and the 4α,5α-dihydroxy-Δ^1-3-ones (VIIa~g). The former compounds (VIa~g) were converted into the A-norsteroids having $\Delta^{3(5)}$-1,2-dioxo structure (IIIa~g) by treatment with manganese dioxide at room temperature.

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