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67. Hiroshi Ōsaka : On Steroidal Sapogenins. VI.*1 Synthesis of 11-Oxygenated Spirostanes. (4).

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The preceding paper of this series*1 reported the synthesis of various 11-ketone derivatives of 2,3-dihydroxy-25D-spirostan-11-one[1,2] and 2-hydroxy-25D-spirostan-11-one of 5α and 5β series in order to examine the Huang-Minlon[3] reduction of spirostan-11-one.

The ketone group at C-11 has been known to be resistant to the Huang-Minlon reduction and the past examples[4] of such reaction used the derivatives with one hydroxyl at the 3-position of the A-ring. In order to compare with these past examples, plans were made to synthesize various kinds of 3-hydroxy-11-ketone compounds of 5β-H and 5α-H series and examine their behavior to the Huang-Minlon reduction.

Synthesis of 11-oxotigogenin (I) followed the method of Chapman.[5] Synthesis of 3β-hydroxy-25D,5β-spirostan-11-one (IIIa) was started from nogiragenin[6] (IIa) isolated previously from *Metanarthecium luteo-viride* MAXIM. Formylation of (IIa) gives a diformate (IIb), m.p. 164~166°, whose partial saponification with *p*-toluenesulfonic acid[7] affords a monoformate, considered to be the 3β-hydroxy-11α-formate (IIc), m.p. 225~226°. This structure was later confirmed by the Huang-Minlon reduction of the monoketone compound obtained from this substance (IIc). Acetylation of (IIc) with acetic anhydride and pyridine gives 3β-acetoxy-11α-formate (IId), m.p. 204~206°, which, when allowed to stand overnight in an alumina column, undergoes saponification of the formate group to form the 3β-acetoxy-11α-hydroxy compound (IIe), m.p. 201°. Oxidation of (IIe) with chromium trioxide gives the 3β-acetoxy-11-ketone compound (IIIb), m.p. 176~177°, whose saponification with alkali affords 3β-hydroxy-11-oxo compound (IIIa), m.p. 211~213°.

3α-Hydroxy-25D,5β-spirostan-11-one (VIa) has already been synthesized from diosgenin by Djerassi,[8] but its synthesis from nogiragenin (IIa) was carried out. (IIa) was oxidized to 3,11-dioxo compound[6] (IV) and its reduction with sodium borohydride gave a crude product melting at 204~208°. In this case, 11-ketone is preferentially reduced to 11β-hydroxyl[9] but the 3-ketone group is likely to give a mixture of 3β- and 3α-hydroxyl compounds.[10] Consequently, the product obtained here was considered to be a mixture of diols (Va and VIIa). Its purification gave a diol (Va), m.p. 209~210°, which formed a monoacetate (Vb) of m.p. 193~194° by acetylation with acetic anhydride and pyridine, and a diacetate (Vc) of m.p. 109~110° by acetylation with acetic anhydride and *p*-toluenesulfonic acid.

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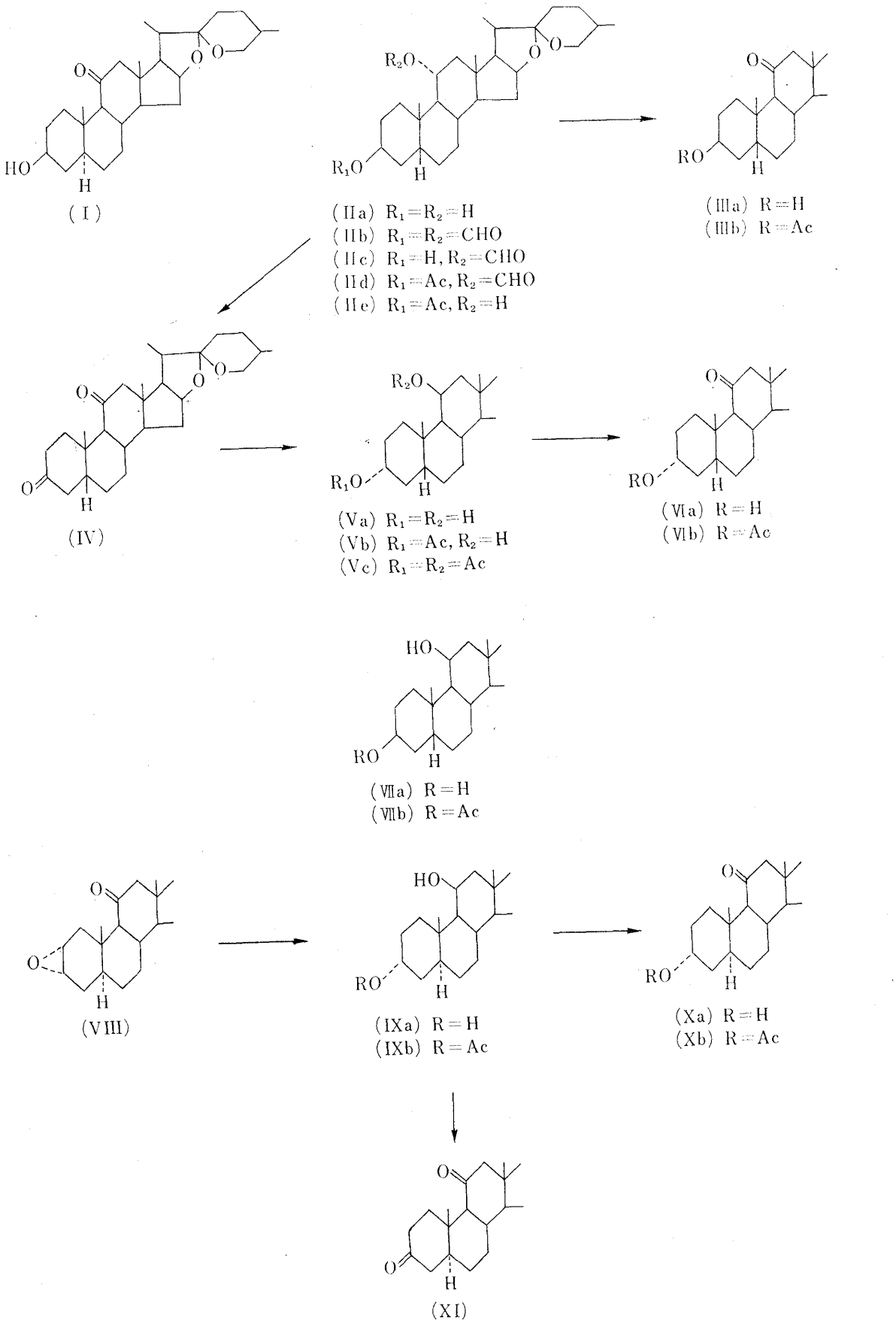

Chart 1.

It is certain that (Vb) is 3α-monoacetate since its mixed fusion with 3β-monoacetate*[3] (VIIb), m.p. 177~178°, synthesized by another route, showed depression of the melting point. Oxidation of (Vb) with chromium trioxide and pyridine gave (VIb), m.p. 190~191°.

Acetylation of the mixture of crude diols (Va and VIIa) without separation, followed by oxidation and purification through alumina chromatography gave (VIb) and its isomer (IIIb), m.p. 178.5~179.5°. (IIIb) was identified with 3β-acetoxy-11-oxo compound through mixed fusion and comparison of infrared spectra. Saponification of (VIb) with alkali gave 3α-hydroxy-11-oxo compound (VIa), m.p. 206~207°.

Synthesis of 3α-hydroxy-25D,5α-spirostan-11-one was then carried out. Reduction of 2α,3α-epoxy-25D,5α-spirostan-11-one[2] (VIII) with lithium aluminium hydride gave the 3α,11β-diol (IXa), m.p. 249.5~251°, whose oxidation with chromium trioxide-pyridine gave 3,11-dioxo compound (XI), showing that the two hydroxyls in (IXa) are at 3- and 11-positions. Acetylation of the foregoing diol (IXa) gives a monoacetate (IXb), m.p. 203~204°, whose oxidation affords 3α-acetoxy-11-oxo compound (Xb), m.p. 197~198°, which is saponified by alkali to 3α-hydroxy-11-oxo compound (Xa), m.p. 206~207°.

The Huang-Minlon reduction of the four kinds of 3-hydroxy-25D,5β- and -5α-spirostan-11-one herein synthesized will be reported in the following paper.

Experimental*[4]

25D,5β-Spirostane-3β,11α-diol Diformate (IIb)——A mixture of 903 mg. of nogiragenin (IIa), 10 cc. of HCOOH, and 4 cc. of $CHCl_3$ was allowed to stand overnight at room temperature, poured into H_2O, and the mixture was extracted with $CHCl_3$. The extract was washed with 5% Na_2CO_3 solution and H_2O, and $CHCl_3$ was evaporated. The syrupy residue was crystallized from MeOH to 707 mg. of needles (IIb), m.p. 164~166°. $[\alpha]_D^{22}$ −84.7°(c=1.007). *Anal.* Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.08; H, 9.00. IR ν_{max}^{Nujol} cm^{-1}: 1713, 1210; 1187 (HCO-).

25D,5β-Spirostane-3β,11α-diol 11-Formate (IIc)——A solution of 3.7 g. of (IIb) dissolved in 150 cc. of EtOH and added with 0.4 g. of *p*-toluenesulfonic acid hydrate was warmed on a water bath for 30 min., poured into H_2O, and the precipitate was filtered. The precipitate was washed with H_2O and extracted with benzene. The extract was dried and evaporation of benzene left 3.4 g. of crystals. Purification of this product through alumina chromatography and elution with petr. ether-benzene resulted in recovery of 0.6 g. of diformate (IIb).

Elution of the alumina column with benzene and benzene-$CHCl_3$ (9:1) mixture afforded 2.2 g. of a monoformate (IIc), m.p. 194~220°, which was recrystallized from MeOH to scales, m.p. 225~226°. $[\alpha]_D^{21}$ −95.7°(c=1.037). *Anal.* Calcd. for $C_{28}H_{44}O_5$: C, 73.01; H, 9.63. Found: C, 72.95; H, 9.70. IR ν_{max}^{Nujol} cm^{-1}: 3565 (OH), 1702, 1210, 1182 (HCO-).

From the fraction eluted with $CHCl_3$ and $CHCl_3$-MeOH (1:1) mixture, 0.7 g. of the diol (IIa) was obtained.

25D,5β-Spirostane-3β,11α-diol 3-Acetate 11-Formate (IIa)——A mixture of 1.4 g. of (IIc), 16 cc. of Ac_2O, and 16 cc. of pyridine was allowed to stand overnight at room temperature and the usual after-treatment afforded 1.4 g. of crude product which was recrystallized from $CHCl_3$ and MeOH to needles (IId), m.p. 204~206°. $[\alpha]_D^{22}$ −83.7°(c=1.045). *Anal.* Calcd. for $C_{30}H_{46}O_6$: C, 71.53; H, 9.20. Found: C, 71.65; H, 9.26. IR ν_{max}^{Nujol} cm^{-1}: 1732, 1252 (AcO), 1715, 1180 (HCO-).

25D,5β-Spirostane-3β,11α-diol 3-Monoacetate (IIe)——A chromatographic column of alumina with 0.35 g. of (IId) was allowed to stand overnight and eluted with benzene-$CHCl_3$ (9:1) mixture, from which 0.31 g. of (IIe), m.p. 197~199°, formed by saponification of the formyl group, was obtained. Recrystallization from MeOH gave needles, m.p. 201°. $[\alpha]_D^{21}$ −67.8°(c=1.023). *Anal.* Calcd. for $C_{29}H_{46}O_5$: C, 73.37; H, 9.78. Found: C, 73.18; H, 9.78. IR ν_{max}^{Nujol} cm^{-1}: 3480 (OH), 1737, 1247 (AcO).

3β-Acetoxy-25D,5β-spirostan-11-one (IIIb)——To a solution of 330 mg. of (IIe) dissolved in 10 cc. of AcOH, 2 cc. of 90% AcOH solution of 0.2 g. of CrO_3 was added and the mixture was allowed to stand for 30 min. at room temperature. This was poured into H_2O, the precipitate was collected by filtration, washed with H_2O, and extracted with benzene. The extract was dried and benzene was evaporated, leaving 260 mg. of a syrupy product. This was purified through alumina chromatography

*3 Unpublished data.

*4 All melting points are uncorrected. Optical rotation was measured in $CHCl_3$ solution.

and the fractions eluted with petr. ether-benzene (1:1) and benzene afforded 129 mg. of syrupy (IIIb) which crystallized on treatment with MeOH, m.p. 166~170°. Recrystallization from MeOH gave needles, m.p. 176~177°. $[\alpha]_D^{22}$ −34.9° (c=0.977). *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.66; H, 9.43. IR ν_{max}^{Nujol} cm^{-1}: 1702 (C=O), 1735, 1255, 1238 (AcO).

3β-Hydroxy-25D,5β-spirostan-11-one (IIIa)——A mixture of 124 mg. of (IIIb) in MeOH-NaOH was refluxed for 1 hr., poured in to H_2O, and crystals that precipitated out were collected by filtration. The crystals were washed with H_2O and dried to 96 mg. of crude crystals melting at 208~211°. Recrystallization from $CHCl_3$-MeOH gave (IIIa) as spindle-shaped crystals, m.p. 211~213°. $[\alpha]_D^{20}$ −36.4° (c=0.917). *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.04; H, 9.84. IR ν_{max}^{Nujol} cm^{-1}: 3525 (OH), 1695 (C=O).

25D,5β-Spirostane-3α,11β-diol (Va)——To a solution of 300 mg. of 25D,5β-spirostane-3,11-dione (IV), m.p. 208~209°, dissolved in 2 cc. of tetrahydrofuran, 3 cc. of tetrahydrofuran, 150 mg. of $NaBH_4$, 0.5 cc. of H_2O, and 0.5 cc. of 0.1*N* NaOH were added and the mixture was refluxed for 20 hr. on a water bath. During this period, 100 mg. of $NaBH_4$ was added after 7 hr., and 50 mg. after 15 hr., and 15 cc. of 10% AcOH was added after completion of the reaction to decompose excess $NaBH_4$. The solvent was distilled off, the crystals that separated out were collected by filtration, washed with H_2O, and dried to 294 mg. of a product melting at 204~208°. This was purified through alumina chromatography and the fractions eluted with benzene and benzene-$CHCl_3$ (1:1) mixture afforded 290 mg. of (Va), m.p. 205~207°, which was recrystallized from $CHCl_3$-petr. ether (b.p. 65~75°) to cubic crystals, m.p. 209~210°. $[\alpha]_D^{28}$ −46.7° (c=0.735). *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.66; H, 10.35. IR ν_{max}^{Nujol} 3546 cm^{-1} (OH); no C=O absorption.

25D,5β-Spirostane-3α,11β-diol 3-Monoacetate (Vb)——A mixture of 2.1 g. of (Va) in 20 cc. of Ac_2O and 35 cc. of pyridine was allowed to stand for 20 hr. at room temperature, poured into H_2O, and crystals that precipitated out were collected by filtration. The crystals were washed with H_2O and dried to 2.3 g. of a crude product which was purified through alumina chromatography. The fractions eluted with benzene-petr. ether (1:1), benzene, and benzene-Et_2O (19:1) afforded 2.1 g. of crystals melting at 180~185°, which were recrystallized from MeOH to plates (Vb), m.p. 193~194°. $[\alpha]_D^{21}$ −25.7° (c=1.138). *Anal.* Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.52; H, 9.78. IR ν_{max}^{Nujol} cm^{-1}: 3550 (OH), 1736, 1246 (AcO).

25D,5β-Spirostane-3α,11β-diol Diacetate (Vc)——A mixture of 50 mg. of (Va), 1 cc. of Ac_2O, and 2 mg. of *p*-toluenesulfonic acid monohydrate was warmed at 80° for 30 min. and allowed to stand overnight at room temperature. This was poured into H_2O, extracted with $CHCl_3$, and the extract was washed with 5% Na_2CO_3 and H_2O. After drying, $CHCl_3$ was evaporated and the syrupy residue so obtained was purified through alumina chromatography. Fractions eluted with petr. ether and petr. ether-benzene (1:1) mixture gave 40 mg. of a syrupy product which crystallized from hydr. MeOH to (Vc), m.p. 109~110°. *Anal.* Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.20; H, 9.44. IR ν_{max}^{Nujol} cm^{-1}: 1743, 1240 (acetate).

3α-Acetoxy-25D,5β-spirostan-11-one (VIb)——A solution of 180 mg. of CrO_3 in 2.5 cc. of pyridine was added to the solution of 250 mg. of the 3α,11β-diol 3-monoacetate (Vb) in 5 cc. of pyridine and the mixture was allowed to stand for 34 hr. at room temperature. Usual after-treatment gave 238 mg. of a crude product which was purified through alumina chromatography. Fractions eluted with petr. ether-benzene and benzene gave 142 mg. of (VIb), m.p. 186~188°, which was recrystallized from $CHCl_3$-petr. ether to plates, m.p. 190~191°. $[\alpha]_D^{21}$ −9.0 (c=1.031). *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.90; H, 9.46. IR ν_{max}^{Nujol} cm^{-1}: 1704 (C=O), 1740, 1257 (AcO).

The same reaction of 2.48 g. of a mixture of crude crystals (Vb and VIIb) in the same manner furnished 1.29 g. of (VIb) and 100 mg. of (IIIb), both showing no depression of the melting point on admixture with the respective specimens obtained earlier. Infrared spectra of these substances were in good agreement.

3α-Hydroxy-25D,5β-spirostan-11-one (VIa)——A mixture of 1.117 g. of (VIb) and 100 cc. of 10% MeOH-KOH was refluxed for 1 hr. and the usual after-treatment afforded 1.01 g. of (VIa), m.p. 205~207°. Recrystallization from MeOH gave needles, m.p. 206~207°. $[\alpha]_D^{21}$ −32.0° (c=1.042). *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.44; H, 9.88. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 3450~3370 (OH).

25D,5α-Spirostane-3α,11β-diol (IXa)——To a solution of 400 mg. of 2α,3α-epoxy-25D,5α-spirostan-11-one (VIII) dissolved in 20 cc. of dehyd. Et_2O, 800 mg. of $LiAlH_4$ suspended in 25 cc. of dehyd. Et_2O was added and the mixture was refluxed for 4 hr. Usual after-treatment afforded 400 mg. of colorless crystals which were recrystallized from Me_2CO to needles (IXa), m.p. 249.5~251°. $[\alpha]_D^{26}$ −56.0° (c=1.027). *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 75.21; H, 10.26. IR: ν_{max}^{Nujol} 3500 cm^{-1} (OH).

25D,5α-Spirostane-3,11-dione (XI)——To a solution of 330 mg. of the diol (IXa) dissolved in 9 cc. of pyridine, 500 mg. of CrO_3 suspended in 7 cc. of pyridine was added and the mixture was allowed to stand overnight at room temperature. The usual aftertreatment afforded 290 mg. of a powdery

product which was recrystallized from hexane-benzene to needles (XI), m.p. 239~249°, undepressed on admixture with an authentic specimen.

25D,5α-Spirostane-3α,11β-diol 3-Monoacetate (IXb)——A mixture of 1.277 g. of the diol (IXa), 10 cc. of Ac_2O, and 30 cc. of pyridine was allowed to stand for 40 hr. at room temperature and usual after-treatment gave 1.425 g. of a crude product melting at 193~195°. Recrystallization from MeOH afforded 1.02 g. of scales (IXb), m.p. 203~204°. $[\alpha]_D^{26}$ −44.6°(c=1.084). *Anal.* Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found : C, 73.32; H, 9.78. IR ν_{max}^{Nujol} cm^{-1} : 1738, 1243 (AcO), 3560 (OH).

3α-Acetoxy-25D,5α-spirostan-11-one (Xb)——To a solution of 940 mg. of the monoacetate (IXb) dissolved in 20 cc. of pyridine, 700 mg. of CrO_3 in 40 cc. of pyridine was added and the mixture was allowed to stand for 50 hr. at room temperature. Usual after-treatment gave 920 mg. of a crude product melting at 193~195°. This was purified through alumina chromatography and the fraction eluted with petr. ether-benzene (1:1) mixture afforded 680 mg. of a product melting at 194~195°, which was recrystallized from MeOH to 685 mg. of pillars (Xb), m.p. 197~198°. $[\alpha]_D^{27}$ −23.4°(c=1.021). *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found : C, 73.53; H, 9.37. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1735, 1240 (AcO).

3α-Hydroxy-25D,5α-spirostan-11-one (Xa)——A mixture of 500 mg. of (Xb), 5 g. of KOH, and 50 cc. of MeOH was refluxed for 1 hr. and the usual after-treatment afforded 450 mg. of a crude product melting at 199~202°. Recrystallization from MeOH gave needles (XIa), m.p. 206~207°. $[\alpha]_D^{21}$ −35.6°(c=0.914). Yield, 300 mg. *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found : C, 75.33; H, 9.81. IR ν_{max}^{Nujol} cm^{-1} : 1708 (C=O), 3440~3370 (OH).

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Summary

3-Hydroxy-25D,5β- and 5α-spirostan-11-ones of various configurations were synthesized in order to examine the Huang-Minlon reduction of the 11-ketone group of steroids.

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68. Hiroshi Ōsaka : On Steroidal Sapogenins. VII.*1. Huang-Minlon Reduction of 11-Oxospirostanol Derivatives.

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Takeda and Hamamoto[1] reported earlier that metagenone (Ia) and its diacetate (Ib) undergo Huang-Minlon reduction.[2] In general, the ketone group in 11-position of steroids is under steric hindrance to a great extent and hardly reacts with carbonyl reagents and Huang-Minlon reduction does not progress.[3] For that reason, the Huang-Minlon reduction is usually used for the reduction of ketones with little hindrance and often for

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