67. Hiroshi Ōsaka: On Steroidal Sapogenins. VI.*1
Synthesis of 11-Oxygenated Spirostanes. (4).
(Research Laboratory, Shionogi & Co., Ltd.*2)

The preceding paper of this series*1 reported the synthesis of various 11-ketone
derivatives of 2,3-dihydroxy-25β-spirostan-11-one,17) and 2-hydroxy-25β-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*3 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.15) Synthesis of
3β-hydroxy-25β,5β-spirostan-11-one (IIa) was started from nogiragenin*6 (IIa) isolated
previously from Melanthericum luteo-viride Maxim. Formylation of (IIa) gives a diformate
(II b), m.p. 164~166°, whose partial saponification with p-toluensulfonic acid16)
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 (II c). Acetylation of (IIc) with acetic anhydride
and pyridine gives 3β-acetoxy-11α-formate (II d), 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 (II e), m.p. 201°. Oxidation of (II e)
with chromium trioxide gives the 3β-acetoxy-11-ketone compound (IIb), m.p. 176~177°, whose
saponification with alkali affords 3β-hydroxy-11-oxo compound (IIa), m.p. 211~213°.

3α-Hydroxy-25β,5β-spirostan-11-one (VIa) has already been synthesized from diosgenin
by Djerassi,17) but its synthesis from nogiragenin (IIa) was carried out. (IIa) was
oxidized to 3,11-dioxy compound (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-hydroxy*19) but the 3-ketone group is likely to give a mixture of 5β- and 3α-hydroxyl
compounds.19) Consequently, the product obtained here was considered to be a mixture of
diols (Va and VIa). 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-tolu-
encesulfonic acid.

*1 Part V. This Bulletin, 10, 404 (1962).
*2 Sagisu, Fukushima-ku, Osaka (大阪 広).
75, 116 (1953).
9) K. Hamamoto: This Bulletin, 8, 1099 (1959).
It is certain that (Vb) is 3α-monooacetate since its mixed fusion with 3β-monooacetate\(^{83}\) (Vib), m.p. 177–178\(^\circ\), synthesized by another route, showed depression of the melting point. Oxidation of (Vb) with chromium trioxide and pyridine gave (Vib), m.p. 190–191\(^\circ\). Acetylation of the mixture of crude diols (Va and Viiia) without separation, followed by oxidation and purification through alumina chromatography gave (Vib) and its isomer (Viiib), m.p. 178.5–179.5\(^\circ\). (Viiib) was identified with 3β-acetoxy-11-oxo compound through mixed fusion and comparison of infrared spectra. Saponification of (Viiia) with alkali gave 3α-hydroxy-11-oxo compound (Viiia), m.p. 206–207\(^\circ\).

Synthesis of 3α-hydroxy-25d,5α-spirostan-11-one was then carried out. Reduction of 2α,3α-epoxy-25d,5α-spirostan-11-one\(^{3}\) (Viiia) with lithium aluminium hydride gave the 3α,11β-diol (Ixa), m.p. 249.5–251\(^\circ\), 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\(^\circ\), whose oxidation affords 3α-acetoxy-11-oxo compound (Xb), m.p. 197–198\(^\circ\), which is saponified by alkali to 3α-hydroxy-11-oxo compound (Xa), m.p. 206–207\(^\circ\).

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\(^{84}\)**

25d,5β-Spirostone-3β,11α-diol Diformate (Iib)—A mixture of 903 mg. of nogiragenin (IIa), 10 cc. of HCOOH, and 4 cc. of CHCl3 was allowed to stand overnight at room temperature, poured into H2O, and the mixture was extracted with CHCl3. The extract was washed with 5% Na2CO3 solution and H2O, and CHCl3 was evaporated. The syrup residue was crystallized from MeOH to 707 mg. of needles (Iib), m.p. 164–166\(^\circ\). \([\alpha]^2_D -84.7\,^\circ\) (c=1.007). *Anal. Calcd. for C28H40O2: C, 71.28; H, 9.08. Found: C, 71.08; H, 9.00. IR ν\text{max} cm\(^{-1}\): 1713, 1210, 1187 (HCO–).*

25d,5β-Spirostone-3β,11α-diol-3-Formate (Iic)—A solution of 3.7 g. of (Iib) dissolved in 150 cc. of EtOH and added with 0.4 g. of 2-toluene sulfonic acid hydrate was warmed on a water bath for 30 min., poured into H2O, and the precipitate was filtered. The precipitate was washed with H2O 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-CHCl3(9:1) mixture afforded 2.2 g. of a monoformate (Iic), m.p. 194–226\(^\circ\), which was recrystallized from MeOH to scales, m.p. 225–226\(^\circ\). \([\alpha]^2_D -95.7\,^\circ\) (c=1.037). *Anal. Calcd. for C30H42O6: C, 73.01; H, 9.63. Found: C, 72.95; H, 9.70. IR ν\text{max} cm\(^{-1}\): 3565 (OH), 1702, 1210, 1182 (HCO–).*

From the fraction eluted with CHCl3 and CHCl3–MeOH (1:1) mixture, 0.7 g. of the diol (IIa) was obtained.

25d,5β-Spirostone-3β,11α-diol 3-Acetate 11-Formate (Iib)—A mixture of 1.4 g. of (Iic), 16 cc. of Ac2O, 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 CHCl3 and MeOH to needles (Iid), m.p. 204–206\(^\circ\). \([\alpha]^2_D -83.7\,^\circ\) (c=1.045). *Anal. Calcd. for C30H38O11: C, 71.53; H, 9.20. Found: C, 71.65; H, 9.26. IR ν\text{max} cm\(^{-1}\): 1732, 1252 (AcO), 1715, 1180 (HCO–).*

25d,5β-Spirostone-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-CHCl3(9:1) mixture, from which 0.31 g. of (Iie), m.p. 197–199\(^\circ\), formed by saponification of the formyl group, was obtained. Recrystallization from MeOH gave needles, m.p. 201\(^\circ\). \([\alpha]^2_D -67.8\,^\circ\) (c=1.023). *Anal. Calcd. for C29H36O7: C, 73.37; H, 9.78. Found: C, 73.18; H, 9.78. IR ν\text{max} cm\(^{-1}\): 3490 (OH), 1737, 1247 (AcO).*

3β-Acetoxy-25d,5β-spirostan-11-one (Iib)—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 CrO3 was added and the mixture was allowed to stand for 30 min. at room temperature. This was poured into H2O, the precipitate was collected by filtration, washed with H2O, 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

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*83 Unpublished data.*

*84 All melting points are uncorrected. Optical rotation was measured in CHCl3 solution.*

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and the fractions eluted with petr. ether-benzene (1:1) and benzene afforded 129 mg. of syrupy (Illb) which crystallized on treatment with MeOH, m.p. 166~170°. Recrystallization from MeOH gave needles, m.p. 176~177°. [α]D15 ~ -34.9° (c=0.977). Anal. Calcd. for C20H14O3: C, 73.69; H, 9.38. Found: C, 73.66; H, 9.43. IR νmax cm⁻¹: 1702 (C=O), 1735, 1255, 1238 (AcO).

3β-Hydroxy-25D,5β-spirostan-11-one (Illa) — A mixture of 124 mg. of (Illb) in MeOH~NaOH was refluxed for 1 hr., poured in to H2O, and crystals that precipitated out were collected by filtration. The crystals were washed with H2O and dried to 96 mg. of crude crystals melting at 208~211°. Recrystallization from CHCl3~MeOH gave (Illa) as spindle-shaped crystals, m.p. 211~213°. [α]D15 ~ -36.4° (c=0.917). Anal. Calcd. for C27H40O5: C, 75.31; H, 9.83. Found: C, 75.04; H, 9.84. IR νmax cm⁻¹: 3525 (OH), 1695 (C=O).

25D,5β-Spirostan-3α,11β-diol (Va) — To a solution of 300 mg. of 25α,5α-spirostan-3,11-dione (IV), m.p. 208~209°, dissolved in 2 cc. of tetrahydrofuran, 3 cc. of tetrahydrofuran, 150 mg. of NaBH4, 0.5 cc. of H2O, and 0.5 cc. of 0.1N NaOH were added and the mixture was refluxed for 20 hr. on a water bath. During this period, 100 mg. of NaBH4 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 NaBH4. The solvent was distilled off, the crystals that separated out were collected by filtration, washed with H2O, 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-CHCl3 (1:1) mixture afforded 290 mg. of (Va), m.p. 205~207°, which was recrystallized from CHCl3~petr. ether (b.p. 65~75°) to cubic crystals, m.p. 209~210°. [α]D15 ~ -46.7° (c=0.735). Anal. Calcd. for C20H32O5: C, 74.95; H, 10.25. Found: C, 74.66; H, 10.35. IR νmax cm⁻¹: 3546 (OH); νC=O absorption.

25D,5β-Spirostan-3α,11β-diol 3-Monoacetate (Vb) — A mixture of 2.1 g. of (Va) in 20 cc. of AcO and 35 cc. of pyridine was allowed to stand for 20 hr. at room temperature, poured into H2O, and crystals that precipitated out were collected by filtration. The crystals were washed with H2O and dried to 2.5 g. of a crude product which was purified through alumina chromatography. The fractions eluted with benzene-petr. ether (1:1), benzene, and benzene-Et2O (19:1) afforded 2.1 g. of crystals melting at 180~185°, which were recrystallized from MeOH to plates (Vb), m.p. 193~194°. [α]D15 ~ -25.7° (c=1.138). Anal. Calcd. for C29H34O5: C, 73.38; H, 9.77. Found: C, 73.52; H, 9.78. IR νmax cm⁻¹: 3550 (OH), 1736, 1246 (AcO).

25D,5β-Spirostan-3α,11β-diol Diacetate (Ve) — A mixture of 50 mg. of (Va), 1 cc. of AcO, and 2 cc. of β-toluenesulfonic acid monohydrate was warmed at 80° for 30 min. and allowed to stand overnight at room temperature. This was poured into H2O, extracted with CHCl3, and the extract was washed with 5% Na2CO3 and H2O. After drying, CHCl3 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 (Ve), m.p. 109~110°. Anal. Calcd. for C30H40O5: C, 72.06; H, 9.36. Found: C, 72.20; H, 9.44. IR νmax cm⁻¹: 1743, 1240 (acetate).

3α-Acetoxy-25D,5β-spirostan-11-one (Vib) — A solution of 180 mg. of CrO3 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 CHCl3~petr. ether plates, m.p. 190~191°. [α]D15 ~ -9.0° (c=1.031). Anal. Calcd. for C30H38O5: C, 73.69; H, 9.38. Found: C, 73.90; H, 9.46. IR νmax cm⁻¹: 1704 (C=O), 1740, 1257 (AcO).

The same reaction of 2.48 g. of a mixture of crude crystals (Vb and Vib) in the same manner furnished 1.29 g. of (Vib) and 100 mg. of (Illb), 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 (Vla) — 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 (Vla), m.p. 205~207°. Recrystallization from MeOH gave needles, m.p. 206~207°. [α]D15 ~ -32.0° (c=1.040). Anal. Calcd. for C20H34O5: C, 73.51; H, 9.83. Found: C, 75.44; H, 9.88. IR νmax cm⁻¹: 1710 (C=O), 3450~3370 (OH).

25D,5α-Spirostan-3α,11β-diol (IXa) — To a solution of 400 mg. of 2α,3α-epoxy-25α,5α-spirostan-11-one (Ill) dissolved in 20 cc. of dehyd. Et2O, 800 mg. of LiAlH4 suspended in 25 cc. of dehyd. Et2O and the mixture was added and refluxed for 4 hr. Usual after-treatment afforded 400 mg. of colorless crystals which were recrystallized from Me2CO to needles (IXa), m.p. 249.5~251°. [α]D15 ~ -56.0° (c=1.027). Anal. Calcd. for C20H32O5: C, 74.95; H, 10.25. Found: C, 75.21; H, 10.26. IR νmax cm⁻¹: 3500 (OH).

25D,5α-Spirostan-3,11-dione (XI) — A solution of 330 mg. of the diol (IXa) dissolved in 9 cc. of pyridine, 500 mg. of CrO3 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 (X), m.p. 239~249°, undepressed on admixture with an authentic specimen.

25α,5α-Spirostan-3α,11β-diol 3-Monoacetate (IXb)—A mixture of 1.277 g. of the diol (IXa), 10 cc. of Ac₂O, 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°. $[α]_D^{22} = -44.6°(c=1.084)$. Anal. Calcd. for C₂₉H₄₆O₃: C, 73.38; H, 9.77. Found: C, 73.32; H, 9.78. IR ν⁻¹max cm⁻¹: 1738, 1243 (AcO), 3560 (OH).

3α-Acetoxy-25α,5α-spirostan-11-one (Xb)—To a solution of 940 mg. of the monoacetate (IXb) dissolved in 20 cc. of pyridine, 700 mg. of Cr₂O₃ 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°. $[α]_D^{22} = -23.4°(c=1.021)$. Anal. Calcd. for C₂₉H₄₆O₃: C, 73.69; H, 9.38. Found: C, 73.53; H, 9.37. IR ν⁻¹max cm⁻¹: 1710 (C=O), 1735, 1240 (AcO).

3α-Hydroxy-25α,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 (Xa), m.p. 206~207°. $[α]_D^{22} = -35.6°(c=0.914)$. Yield, 300 mg. Anal. Calcd. for C₂₉H₄₆O₄: C, 75.31; H, 9.83. Found: C, 75.33; H, 9.81. IR ν⁻¹max cm⁻¹: 1798 (C=O), 5440~5370 (OH).

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Summary

3-Hydroxy-25α,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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Takeda and Hamamoto*³ reported earlier that metagenone (Ia) and its diacetate (Ib) undergo Huang–Minlon reduction. 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.*⁴ 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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