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).

The author expresses his deep gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo, Dr. K. Takeda, the Director of this Laboratory, and to Dr. K. Hamamoto of this Laboratory for their unfailing guidance throughout the course of the present work. He is indebted to Messrs. K. Ishitobi and T. Shinno for technical cooperation, to Dr. Y. Matsui for infrared spectral measurements, and to the members of this Laboratory who undertook measurement of optical rotation and elemental analyses.

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.

(Received March 22, 1961)

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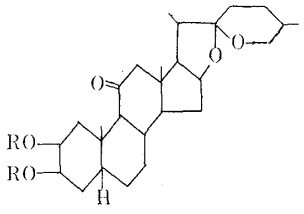
68. Hiroshi Ōsaka : On Steroidal Sapogenins. VII.*1. Huang-Minlon Reduction of 11-Oxospirostanol Derivatives.

(*Research Laboratory, Shionogi & Co., Ltd.**2)

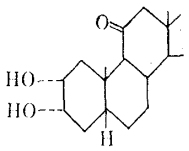
Takeda and Hamamoto[1] reported earlier that metagenone (Ia) and its diacetate (Ib) undergo Huang-Minlon reduction.[2] In general, the ketone group in 11-position of steroids is under steric hindrance to a great extent and hardly reacts with carbonyl reagents and Huang-Minlon reduction does not progress.[3]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

*1 Part VI : This Bulletin, **10**, 413 (1962).
*2 Sagisu, Fukushima-ku, Osaka (大坂 弘).
1) K. Takeda, K. Hamamoto : Tetrahedron Letters, **3**, 1 (1960); This Bulletin, 8, 1004 (1960).
2) Huang-Minlon : J. Am. Chem. Soc., **68**, 2487 (1946).
3) (a) L.F. Fieser, M. Fieser : "Natural Products related to Phenanthrene," 3rd Ed., 409 (1949), Reinhold Publ. Corp., New York. (b) Huang-Minlon : J. Am. Chem. Soc., **71**, 3301 (1949).

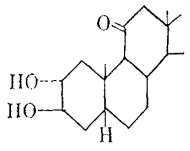
reduction of ketones leaving the ketone in 11-position intact, such as the partial reduction of 11,20-diketone[3b] and 7,11-diketone.[4] Reduction of 11-ketone group to form the corresponding 11-deoxo derivatives has been effected only under drastic conditions[5] irre-



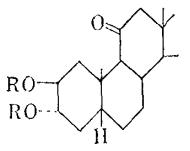
(Ia) R=H
(Ib) R=Ac
(Ic) R,R=$>C<^{CH_3}_{CH_3}$



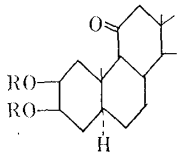
(II)



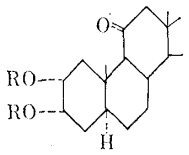
(III)



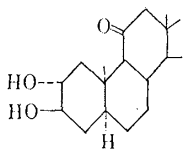
(IVa) R=H
(IVb) R=Ac



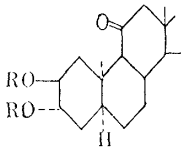
(Va) R=H
(Vb) R=Ac



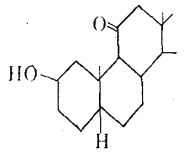
(VIa) R=H
(VIb) R=Ac



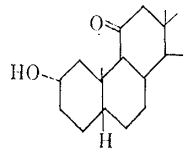
(VII)



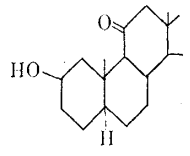
(VIIIa) R=H
(VIIIb) R=Ac



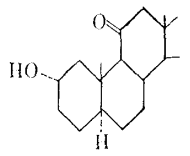
(IX)



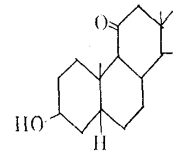
(X)



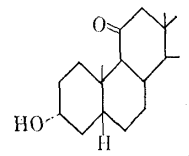
(XI)



(XII)



(XIII)



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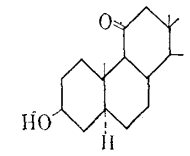
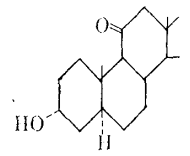
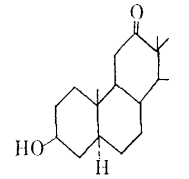


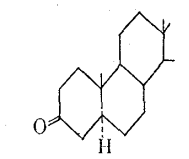
(XV)



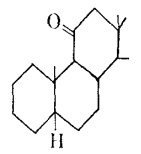
(XVI)



(XVII)



(XVIII)



(XXXI)

Chart 1.

4) (a) E.M. Chamberlin, W.V. Ruyle, *et al.*: J. Am. Chem. Soc., **75**, 3477 (1953). (b) H. Heusser, *et al.*: Helv. Chim. Acta, **34**, 2106 (1951). (c) L.F. Fiessr, J.E. Herz, W-Y. Huang: J. Am. Chem. Soc., **73**, 2397 (1951); **75**, 121 (1953). (d) L.F. Fieser, W-Y. Huang, J.C. Babcock: *Ibid.*, **75**, 116 (1953). (e) J. Elks, G.H. Phillips: J. Chem. Soc., **1956**, 4326.

5) (a) R.B. Moffett, T.H. Hunter: J. Am. Chem. Soc., **73**, 1973 (1951). (b) D.G.R. Barton, D.A. J. Ives, B.R. Thoms: J. Chem. Soc., **1955**, 2056. (c) C. Djerassi, G.H. Thomas: Chem. & Ind. (London), **1954**, 1228. (d) C. Djerassi, A.J. Manson, A. Segaloff: J. Org. Chem., **21**, 490 (1959).

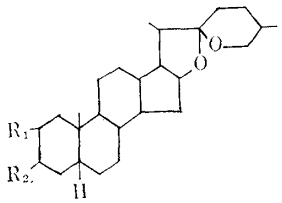
spective of 5α-H or 5β-H configuration, or of the side chain, such as cholestanol, ergostanol, cholic acid, or spirostanol.

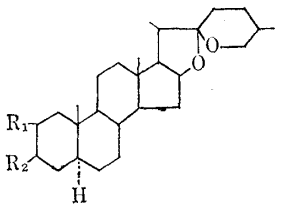
Failure of this type of reduction with metagenone acetonide[1] (Ic) and 25D,5β-spirostan-11-one[6] (XXXI) has already been reported but in order to clarify the mechanism of the Huang-Minlon reduction of metagenone, present series of experiments were carried out.

It was assumed that the Huang-Minlon reduction of metagenone was effected due to the presence of 2,3-dihydroxy or 2-hydroxy group and the reduction was therefore carried out on such compounds, using 11 kinds of derivatives of different configurations of new substances synthesized to date; 2,3-dihydroxy-25D,5β-spirostan-11-one[7] (II, III, IVa), 2,3-dihydroxy-25D,5α-spirostan-11-one[8] (Va, VIa, VII, VIIIa), 2-hydroxy-25D,5β-spirostan-11-one[9] (IX, X), and 2-hydroxy-25D,5α-spirostan-11-one[9] (XI, XII).

It was found from these experiments that the reduction proceeded irrespective of the starting material, whether 2,3-dihydroxy, 2,3-diacetoxy, or 2-hydroxy compound, 5β-H or 5α-H, and whether the hydroxyl group is axial or equatorial. As shown in Chart 2, all these compounds formed the corresponding 11-deoxo derivatives.

Of these products of the Huang-Minlon reduction, the 2,3-dihydroxy and 3-hydroxy compounds are known in the past literature and were confirmed through mixed fusion,





(XIX) $R_1=R_2=<^{H}_{OH}$

(XX) $R_1=R_2=<^{H}_{OAc}$

(XXIa) $R_1=<^{H}_{OAc}$, $R_2=<^{H}_{OAc}$

(XXIIa) $R_1=<^{H}_{OH}$, $R_2=<^{H}_{OH}$

(XXIIb) $R_1=<^{H}_{OAc}$, $R_2=<^{H}_{OAc}$

(XXIIIa) $R_1=<^{H}_{OH}$, $R_2=H_2$

(XXIIIb) $R_1=<^{H}_{OAc}$, $R_2=H_2$

(XXIVa) $R_1=<^{H}_{OH}$, $R_2=H_2$

(XXIVb) $R_1=<^{H}_{OAc}$, $R_2=H_2$

(XXVa) $R_1=R_2=<^{H}_{OH}$

(XXVb) $R_1=R_2=<^{H}_{OAc}$

(XXVc) $R_1, R_2=>C<^{CH_3}_{CH_3}$

(XXVIa) $R_1=R_2=<^{H}_{OH}$

(XXVIb) $R_1=R_2=<^{H}_{OAc}$

(XXVII) $R_1=<^{H}_{OAc}$, $R_2=<^{H}_{OAc}$

(XXVIIIa) $R_1=<^{H}_{OH}$, $R_2=<^{H}_{OH}$

(XXVIIIb) $R_1=<^{H}_{OAc}$, $R_2=<^{H}_{OAc}$

(XXIXa) $R_1=<^{H}_{OH}$, $R_2=H_2$

(XXIXb) $R_1=<^{H}_{OAc}$, $R_2=H_2$

(XXXa) $R_1=<^{H}_{OH}$, $R_2=H_2$

(XXXb) $R_1=<^{H}_{OAc}$, $R_2=H_2$

Chart 2. Huang-Minlon Reduction Products

6) K. Hamamoto : This Bulletin **9**, 32 (1961).
7) Part III : Yakugaku Zasshi, **81**, 1658 (1961).
8) Part IV : *Ibid.*, **81**, 1662 (1961).
9) Part V : This Bulletin, **10**, 404 (1962).

infrared spectra, and analytical values. The 2-hydroxyl compounds (XXIIIa and XXIVa) of 5β-series and 2α-hydroxyl compound (XXXa) of 5α-series are new substances and were confirmed by the following way.

For the confirmation of 5β-2α-hydroxy acetate (XXIVb), 2β,3β-epoxy-25D,5β-spirostane[10] (XXXII) was derived to 2α,3α-epoxide (XXXIII), m.p. 187~189°, through (XXIb) and (XXIc) by the method of Fürst and others.[11] Reduction of (XXXIII), followed by acetylation gave 2α-acetate which was found identical with (XXIVb) by mixed fusion and comparison of infrared spectra.

Oxidation of the Huang-Minlon reduction products of 2α- and 2β-hydroxy-25D,5β-spirostan-11-one respectively afforded the same ketone (XXXIV), m.p. 204~205°, identified by mixed fusion and infrared spectra. Since this ketone showed depression of the melting point on admixture with 25D, 5β-spirostan-3-one or with -11-one, it is certain that (XXXIV) is a 2-oxo compound and the reduction product of 2β-hydroxy-11-oxo compound (IX) is 2β-hydroxy compound (XXIIIa).

The compounds in the 5α-series were confirmed by the same way. Oxidation of the products, (XXIXa),[11b] 202~204°, and (XXXa), m.p. 226~227°, of the Huang-Minlon reduction of 2β- and 2α-hydroxy-25D,5α-spirostan-11-one, afforded the same ketone (XXXV), m.p. 205~206°, identified through mixed fusion and infrared spectra. This ketone is the 2-oxo compound since its mixed fusion with 25D,5α-spirostan-3-one and -11-one showed depression of the melting point.

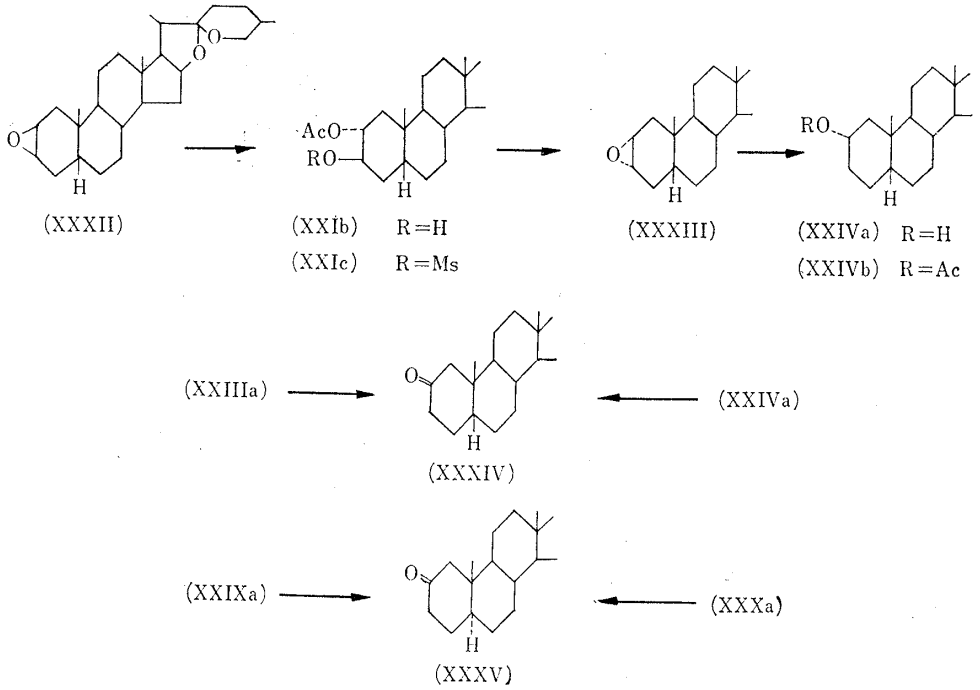


Chart 3.

As shown above, the Huang-Minlon reduction of the 11-ketone group in 2-hydroxy- and 2,3-dihydroxyspirostan-11-ones was found to progress in either of the cases. It had been believed that the ketone group in C-11 is resistant to the Huang-Minlon reduction and the past literature[3b,4] reported this reaction with compounds possessing only one hydroxyl in the A-ring, with that in 3-position. In order to compare with them, examination was carried out on four kinds of 3-hydroxy-11-oxo compounds*1 (XIII, XIV, XV, and

10) C. Djerassi, J. Fishman : J. Am. Chem. Soc., **77**, 4291 (1955).
11) (a) A. Fürst, Pl. A. Plattner : Helv. Chim. Acta, **22**, 275 (1949). (b) J. Pataki, G. Rosenkranz, C. Djerassi : J. Am. Chem. Soc., **73**, 5375 (1951).

XVI), and with ketones in positions other than C-11, hecogenin (12-ketone) (XVII) and tigogenone (3-ketone) (XVIII), as a control.

For this purpose, reaction conditions were made constant and determination was made through infrared absorption spectrum in order to avoid the loss through separation by the alumina chromatography.

Triethylene glycol was used as a solvent, in an amount 10 volumes of the starting material, the same amount of potassium hydroxide, and 2.5 volumes of 80% hydrazine hydrate were used. The reaction mixture was heated at 130~140° for 30 minutes, the temperature was raised gradually to 190° in 30 minutes, and heated at 190~200° for 2 hours.

For quantitative determination by infrared absorption spectrum, chloroform solution was used for measurement and absorbance was calculated by the base-line method. Calibration curves were obtained for the compounds (Ia) and (XV), and linearity was established, as shown in Fig. 1.

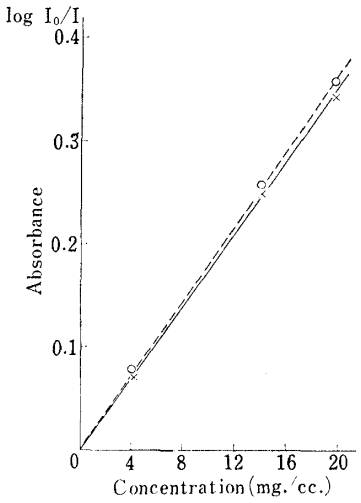


Fig. 1. Calibration Curves for Infrared Determination(1705 cm^{-1})
---o--- 2β,3β-Dihydroxy-25D,5β-spirostan-11-one (Ia)
—×— 3β-Hydroxy-25D,5α-spirostan-11-one (XV)

It was assumed from these results that other spirostanones would also show linearity and each of the starting materials was used as a standard and its infrared spectrum was measured in the same molar concentration as the amount used for the reaction. The yield was calculated from the difference in the absorbance of this standard substance and that of the reaction product.

Table I. Yield of the Huang-Minlon Reduction Product of 11-Oxospirostanol Derivatives

Starting Compd. No.	Yield of product (%) A	B	Starting Compd. No.	Yield of product (%) A	B
(Ia)	72.7	71.6	(X)	100.0	—
(II)	100.0	—	(XI)	86.6	—
(III)	100 0	—	(XII)	84.7	—
(IVa)	65.1	—	(XIII)	48.8	—
(Va)	81.7	66.8	(XIV)	49.3	49.2
(VIa)	83.3	74.2	(XV)	83.7	81.7
(VII)	78.0	—	(XVI)	36.9	—
(VIIIa)	83.0	82.7	(XVII)	100.0	—
(IX)	69.3	—	(XVIII)	100.0	—

A : The amount of triethylene glycol containing 10 (w/v)% of KOH was 10 times that of the starting material used.
B : The amount of triethylene glycol containing 10 (w/v)% of KOH was 40 times that of the starting material used.

As shown in Table I, the Huang-Minlon reduction of 3- and 12-ketone progressed 100%, as expected, and it was revealed that 11-ketone group is reduced in a fairly high yield in other compounds, except for that possessing a hydroxyl in 3-position. In the case of 3-hydroxyl compound, the yield from the reaction of 3β-hydroxy-25D,5α-spirostan-11-one (XV) was found to be fairly high. In this case, there was practically no difference in the yield between 2,3-dihydroxy and 2-hydroxy groups.

The effect of the amount of the solvent and of potassium hydroxide was examined in the compounds (V, VI, VIII, XIV. and XV) but no significant difference was found.

The foregoing experiments have shown that the Huang-Minlon reduction hardly proceeds in spirostan-11-ones possessing a hydroxyl in 3-position, excluding 3β-hydroxy-25D,5α-spirostan-11-one, and that 11-deoxo compound is obtained in a fairly good yield in the case of 2-hydroxy and 2,3-dihydroxy compounds, contrary to expectations, but no explanation can be offered at present for its reason. It is still not clear why the yield is high from 3β-hydroxy-25D,5α-spirostan-11-one compared to other compounds with 3-hydroxyl group. Further examinations are to be made on these points.

Experimental*3

Huang-Minlon Reduction of 2α,3α-Dihydroxy-25D,5β-spirostan-11-one (II)——A mixture of 52 mg. of (II), m.p. 230~230.5°, 0.3 cc. of 80% $NH_2NH_2 \cdot H_2O$, 2 cc. of triethylene glycol, and 0.1 g. of KOH was heated at 130~140° (internal temp.) for 30 min., the temperature was gradually raised, and heated at 190~200° for 2 hr. The mixture was poured into H_2O, the precipitate was taken up in Et_2O, the extract was washed with H_2O, and dried. Evaporation of Et_2O left 50 mg. of a syrupy substance.

This syrupy residue was refluxed with 2 cc. of Ac_2O to effect acetylation and usual after-treatment afforded 60 mg. of a syrupy product. This was purified through alumina chromatography and the fractions eluted with benzene-petr. ether (1:1) mixture and benzene afforded 31 mg. (51%) of crystals melting at 150~156.5°. Recrystallization from $CHCl_3$-MeOH gave prisms (XIXb), m.p. 156.5~157.5°, undepressed on admixture with an authentic specimen.[12] *Anal.* Calcd. for $C_{31}H_{48}O_6$ (2α,3α-Diacetate, XIXb): C, 72.05; H, 9.36. Found: C, 71.97; H, 9.50. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1260, 1248 (AcO).

Huang-Minlon Reduction of 2α,3β-Dihydroxy-25D,5β-spirostan-11-one (III)——A mixture of 50 mg. of (III), m.p. 224~225°, 0.3 cc. of 80% $NH_2NH_2 \cdot H_2O$, 2 cc. of triethylene glycol, and 0.1 g. of KOH was treated in the same manner as above and 50 mg. of the crude product, m.p. 168~175°, thereby obtained was acetylated by refluxing with 1 cc. of Ac_2O for 1 hr. Usual after-treatment of its product gave 57 mg. of a syrupy substance which was purified by alumina chromatography. Benzene fraction gave 35 mg. (61%) of the diacetate (XXI), m.p. 166~167.5°, which was recrystallized from MeOH to crystals of m.p. 168~169°, undepressed on admixture with an authentic specimen.[13] *Anal.* Calcd. for $C_{31}H_{48}O_6$ (2α,3β-Diacetate, XXIa): C, 72.05; H, 9.36. Found: C, 72.03; H, 9.39. IR ν_{max}^{Nujol} cm^{-1}: 1742, 1211, 1233 (AcO).

Huang-Minlon Reduction of 2β,3α-Dihydroxy-25D,5β-spirostan-11-one (IVa)——A mixture of 76 mg. of (IVa), m.p. 249~250°, 0.2 cc. of 80% $NH_2NH_2 \cdot H_2O$, 1.6 cc. of triethylene glycol, and 0.1 g. of KOH was treated as for (II) and 85 mg. of a syrupy product thereby obtained was acetylated by standing with 0.6 cc. of Ac_2O and 1.7 cc. of pyridine overnight at room temperature, forming 110 mg. of a syrupy acetate. Purification through alumina chromatography and elution with petr. ether-benzene (7:3 and 1:1) mixtures afforded 20 mg. (23%) of the diacetate (XXIIb), which recrystallized from MeOH to plates, m.p. 216~217°, and showed no depression of m.p. on admixture with yonogenin diacetate,[13] m.p. 213~214°. *Anal.* Calcd. for $C_{31}H_{48}O_6$ (2β,3α-Diacetate, XXIIb): C, 72.06; H, 9.36. Found: C, 72.35; H, 9.58.

From the fraction eluted with $CHCl_3$, 27 mg. of a syrupy substance was obtained which was considered to be a hydrazone from the presence of a strong absorption at 1680 cm^{-1} in its IR spectrum but no detailed examination was made.

Alkaline saponification of (XXIIb) afforded a gel-like substance (XXIIa) of m.p. 228~233°, which showed no depression of m.p. on admixture with yonogenin,[13] m.p. 240~243°, and IR spectra of these substances were identical.

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*3 All m.p.s are uncorrected. Optical rotation was measured in $CHCl_3$ solution.

12) K. Takeda, T. Okanishi, A. Shimaoka: This Bulletin, **7**, 942 (1959).
13) K. Takeda, T. Okanishi, A. Shimaoka, This Bulletin, **6**, 532 (1958).

Similar treatment of 114 mg. of the 2β,3α-diacetoxy-11-oxo compound (IVb), m.p. 167.5～168.5°, with 0.2 cc. of 80% $NH_2NH_2 \cdot H_2O$, 1.6 cc. of triethylene glycol, and 0.1 g. of KOH afforded 70 mg. (75%) of yonogenin.

Huang-Minlon Reduction of 2β,3β-Dihydroxy-25D,5α-spirostan-11-one (Va)——The same treatment as above of 210 mg. of (Va), m.p. 262～264°, with 1 cc. of 80% $NH_2NH_2 \cdot H_2O$, 10 cc. of triethylene glycol, and 1 g. of KOH afforded 190 mg. of yellow crystals. This was acetylated by standing with 2 cc. of Ac_2O and 2 cc. of pyridine for 48 hr. at room temperature and the product was purified by alumina chromatography. The fractions eluted with petr. ether-benzene (1:1) mixture and benzene gave 188 mg. (77%) of the diacetate (XXVb), m.p. 205～207°. *Anal.* Calcd. for $C_{31}H_{48}O_6$ (2β,3β-Diacetate): C, 72.06; H, 9.36. Found: C, 72.33; H, 9.60. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1240 (AcO).

Alkali saponification of (XXVb) and recrystallization from Me_2CO gave needles (XXVa), m.p. 232～234°. *Anal.* Calcd. for $C_{27}H_{44}O_4$ (2β,3β-Diol): C, 74.95; H, 10.25. Found: C, 75.04; H, 10.36.

A mixture of 100 mg. of this diol (XXVa), 20 cc. of Me_2CO, and 10 mg. of *p*-toluenesulfonic acid monohydrate was refluxed for 7 hr., basified with 10% Na_2CO_3, and Me_2CO was evaporated in a reduced pressure. The residue was diluted with H_2O, extracted with Et_2O, the extract was washed with H_2O, and dried over Na_2SO_4. Evaporation of Et_2O left 120 mg. of yellow crystals, which were purified by alumina chromatography. Benzene eluate afforded the acetonide (XXVc), which recrystallized from MeOH-$CHCl_3$ to 92 mg. of crystals melting at 239～242°, undepressed on admixture with an authentic specimen*4,14) of m.p. 239～241°. Their IR spectra were identical.

Similar treatment of 700 mg. of the 2β,3β-diacetoxy-11-oxo compound (Vb), m.p. 220～222°, with 3.5 cc. of 80% $NH_2NH_2 \cdot H_2O$, 14 cc. of triethylene glycol, and 3.5 cc. of KOH afforded 250 mg. (44%) of the diol (XXVa), confirmed by admixture and IR spectrum to be identical with the foregoing substance.

Huang-Minlon Reduction of 2α,3α-Dihydroxy-25D,5α-spirostan-11-one (VIa)——The same treatment of 400 mg. of (VIa), m.p. 219～220°, with 2 cc. of 80% $NH_2NH_2 \cdot H_2O$, 7 cc. of triethylene glycol, and 2 g. of KOH, and acetylation of its product by refluxing with 8 cc. of Ac_2O for 1 hr. afforded a syrupy product. This was purified through alumina chromatography and fractions eluted with petr. ether-benzene (1:1) mixture and benzene afforded 300 mg. (65%) of the diacetate (XXVIb), m.p. 235～250°. Recrystallization from hexane-$CHCl_3$ mixture raised the m.p. to 262～264°, undepressed on admixture with an authentic sample.*4,11b) *Anal.* Calcd. for $C_{31}H_{48}O_6$ (2α,3α-Diacetate): C, 72.06; H, 9.36. Found: C, 72.05; H, 9.50. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1250 (AcO).

Saponification of (XXVIb) with alkali and recrystallization of its product from MeOH-$CHCl_3$ gave the 2α,3α-diol (XXVIa), m.p. 263～266° (reported11b) m.p. 263～266°). *Anal*, Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 75.19; H, 10.43. IR ν_{max}^{Nujol} 3480 cm^{-1} (OH).

The same treatment of 300 mg. of the 2α,3α-diacetoxy-11-oxo compound (VIb), m.p. 205～206°, with 1.5 cc. of 80% $NH_2NH_2 \cdot H_2O$, 5 cc. of triethylene glycol, and 1.5 g. of KOH afforded 200 mg. (82%) of (XXVIa), which showed no depression of m.p. on admixture with the same substance obtained as above and identical IR spectrum.

Huang-Minlon Reduction of 2α,3β-Dihydroxy-25D,5α-spirostan-11-one (VII)——A mixture of 100 mg. of (VII), 1 cc. of triethylene glycol, 250 mg. of KOH, and 0.25 cc. of 80% $NH_2NH_2 \cdot H_2O$ was treated as for (II) and 92 mg. of crude product thereby obtained was acetylated with 1 cc. of Ac_2O and 3 cc. of pyridine to afford 145 mg. of a crude acetate. This was purified through alumina chromatography and the fraction eluted with benzene-petr. ether (1:1) mixture gave 67.2 mg. (58%) of a product (XXVII), m.p. 235～245°. Recrystallization from $CHCl_3$-MeOH afforded 46 mg. of needles, m.p. 245～247°, undepressed on admixture with gitogenin acetate. The IR spectra of the two were identical.

Huang-Minlon Reduction of 2β,3α-Dihydroxy-25D,5α-spirostan-11-one (VIIIa)——A mixture of 400 mg. of (VIIIa), m.p. 255～257°, 2 cc. of 80% $NH_2NH_2 \cdot H_2O$, 17 cc. of triethylene glycol, and 2 g. of KOH was treated as for (II) and the syrupy product thereby obtained was acetylated by refluxing with 8 cc. of Ac_2O. The acetate so obtained was purified through alumina chromatography and the fraction eluted with petr. ether-benzene (1 : 1) mixture afforded 350 mg. (76%) of crystals melting at 236～242°, which recrystallized from Me_2CO-E t_2O to needles (XXVIIIb), m.p. 245～247° (reported11b) m.p. 246～248°). *Anal.* Calcd. for $C_{31}H_{48}O_6$ (2β,3α-Diacetate): C, 72.06; H, 9.36. Found: C, 72.23; H, 9.50. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1250 (AcO).

Saponification of (XXVIIIb) with alkali and recrystallization of its product from Me_2CO gave the diol (XXVIIIa), m.p. 239～241° undepressed on admixture with an authentic specimen.*4,11b) The IR spectra of these substances were also identical. *Anal.* Calcd. for $C_{27}H_{44}O_4$ (2β,3α-Diol): C, 74.95; H, 10.25. Found: C, 75.04; H, 10.53. IR: ν_{max}^{Nujol} 3350 cm^{-1} (OH).

The same treatment of 200 mg. of 2β,3α-diacetoxy-11-oxo compound (VIIIb), a syrupy substance obtained by acetylation of the diol (VIIIa), with 1 cc. of 80% $NH_2NH_2 \cdot H_2O$, 3.2 cc. of triethylene glycol, and 1 g. of KOH afforded 50 mg. (31%) of the diol (XXVIIIa), whose m.p. was undepressed on admixture

*4 The sample was kindly supplied by Prof. Carl Djerassi.

14) J. Herran, G. Rosenkranz, F. Sondheimer: J. Am. Chem. Soc., **76**, 5531 (1954).

with the foregoing authentic sample and showing the same IR spectrum.

Huang-Minlon Reduction of 2β-Hydroxy-25D,5β-spirostan-11-one (IX)——A mixture of 111 mg. of (IX), 12 cc. of triethylene glycol, 1.2 g. of KOH, and 1.5 cc. of 80% $NH_2NH_2 \cdot H_2O$ was treated as for (II) and 105 mg. of the syrupy product thereby obtained was acetylated by leaving with 3 cc. of pyridine and 1.5 cc. of Ac_2O for 24 hr. at room temperature to afford 114 mg. of a syrupy product. This was purified through alumina chromatography and the fraction eluted with petr. ether-benzene (9:1 and 4:1) mixture gave 65 mg. (55%) of a syrupy product. Recrystallization from $CHCl_3$-MeOH formed needles (XXIIIb), m.p. 156~157°. $[\alpha]_D^{25}$ −62.4°(c=1.050). *Anal.* Calcd. for $C_{29}H_{46}O_4$ (2β-Acetate): C, 75.94; H, 10.11. Found: C, 76.06; H, 10.01. IR ν_{max}^{Nujol} cm^{-1}: 1737, 1250 (AcO).

Huang-Minlon Reduction of 2α-Hydroxy-25D,5β-spirostan-11-one (X)——A mixture of 66 mg. of (X). 5 cc. of triethylene glycol, 0.5 g. of KOH, and 1 cc. of 80% $NH_2NH_2 \cdot H_2O$ was treated as in the foregoing cases and the product was acetylated to give 65 mg. of a crude product This was purified through alumina chromatography and the fractions eluted petr. ether-benzene (9:1 and 4:1) mixture gave 54 mg. (77%) of a syrudy product Recrystallization from $CHCl_3$-MeOH afforded plates (XXIVb), m.p. 167.5~168°, undepressed on admixture with an authentic sample prepared by another route. $[\alpha]_D^{25}$ −68.1°(c=1.037). *Anal.* Calcd. for $C_{29}H_{46}O_4$ (2α-Acetate): C, 75.94; H, 10.11. Found: C, 75.82; H, 10.20. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1250 1230 (AcO).

25D,5β-Spirostan-2-one (XXXIV)——a) From 25D,5β-Spirostan-2β-ol Acetate (XXIIIb): A mixture of 135 mg. of crude (XXIIIb) and 15 cc. of 5% MeOH-KOH was refluxed for 1 hr. and the usual after-treatment gave 120 mg. of a syrupy substance (XXIIIa). Without purification, this was oxidized with 80 mg. of CrO_3 and 15 cc. of pyridine by leaving for 16 hr. at room temperature and the usual after-treatment afforded 116 mg. of a crude product melting at 186~195°. Purification through alumina chromatography and elution with benzene-petr. ether (1:4) gave 20 mg. of crystals melting at 161~163°, which was not further examined.

The fraction eluted with benzene-petr. ether (1:1) afforded 80 mg. of crystals melting at 200~205°, which recrystallized from $CHCl_3$-petr. ether to needles (XXXIV), m.p. 204~205°. $[\alpha]_D^{23}$ −75.4°(c=1.017). This showed depression of m.p. on admixture with 25D, 5β-spirostan-3-one and -11-one. *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.11; H, 10.30. IR: ν_{max}^{Nujol}: 1703 cm^{-1} (CO).

b) From 25D,5β-Spirostan-2α-ol Acetate (XXIVb): A mixture of 180 mg. of crude (XXIVb) and 20 cc. of 5% MeOH-KOH was refluxed for 1 hr. and treated as usual, forming 177 mg. of a crude product (XXIVa) of m.p. 173~175°. This was allowed to stand with 120 mg. of CrO_3 and 20 cc. of pyridine for 16 hr. at room temperature and the usual treatment gave 170 mg. of crude crystals melting at 200~205°. This was treated with alumina chromatography and elution with petr. ether-benzene gave crystals of 201~205°, which recrystallized from $CHCl_3$-petr. ether to 120 mg. of needles (XXXIV), m.p. 204~205°, undepressed on admixture with the sample obtained as in (a). Their IR spectra were in good agreement.

Huang-Minlon Reduction of 2β-Hydroxy-25D,5α-spirostan-11-one (XI)——A mixture of 100 mg. of (XI), 0.5 cc. of 80% $NH_2NH_2 \cdot H_2O$, 3 cc. of triethylene glycol, and 0.3 g. of KOH was treated as in foregoing examples, the product was acetylated, and 95 mg. of the product so obtained was purified through alumina chromatography. The fraction eluted with petr. ether-benzene (4:1) afforded 60 mg. of crystals melting at 190~193° and its recrystallization from MeOH gave scales (XXIXb), m.p. 196~198°(reported[11b] m.p. 187~189°). $[\alpha]_D^{26}$ −50.7°. *Anal.* Calcd. for $C_{29}H_{46}O_4$ (2β-Acetate): C, 75.94; H, 10.11. Found: C, 75.82; H, 10.11. IR ν_{max}^{Nujol} cm^{-1}: 1732, 1235 (AcO).

A mixture of 50 mg. of (XXIXb) and 2 cc. of 5% MeOH-KOH was refluxed for 1 hr. to effect saponification and recrystallization of its product from MeOH gave the 2β-hydroxy compound (XXIXa) as needles, m.p. 202~204°. $[\alpha]_D^{21}$ −55.7°(c=1.020). *Anal.* Calcd. for $C_{27}H_{42}O_3 \cdot \frac{1}{2}H_2O$ (2β-ol): C, 76.02; H, 10.62. Found: C, 76.19; H, 10.66. IR: ν_{max}^{Nujol} 3330 cm^{-1}.

Huang-Minlon Reduction of 2α-Hydroxy-25D,5α-spirostan-11-one (XII)——A mixture of 250 mg. of (XII), 7.5 cc. of triethylene glycol, 0.75 g. of KOH, and 0.8 cc. of 80% $NH_2NH_2 \cdot H_2O$ was treated as in the foregoing examples, the product was acetylated, and the resulting substance was purified through alumina chromatography. The fraction eluted with petr. ether-benzene (9:1) gave 170 mg. of crystals melting at 221~225° and recrystallized from MeOH to needles (XXXb), m.p. 224~225°. $[\alpha]_D^{28}$ −79.4°(c=1.004). *Anal.* Calcd. for $C_{29}H_{46}O_4$ (2α-Acetate): C, 75.94; H, 10.11. Found: C, 75.72; H, 10.15. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1240 (AcO).

A mixture of 50 mg. of (XXXb) and 2 cc. of 5% MeOH-KOH was refluxed for 1 hr. and the usual treatment and recrystallization from MeOH gave the 2α-ol (XXXa) as needles, m.p. 226~227°. $[\alpha]_D^{26}$ −62.5°. *Anal.* Calcd. for $C_{27}H_{42}O_3$ (2α-ol): C, 77.83; H, 10.65. Found: C, 77.53; H, 10.56. IR: ν_{max}^{Nujol} 3290~3310 cm^{-1}.

25D, α-Spirostan-2-one (XXXV)——a) From 25D,5α-Spirostan-2β-ol (XXIXa): A mixture of 30 mg. of (XXIXa), 30 mg. of CrO_3, and 1.3 cc. of pyridine was allowed to stand overnight at room temperature,

poured into H_2O, and extracted with $CHCl_3$. The extract was washed consecutively with 10% H_2SO_4, 10% Na_2CO_3, and H_2O, dried over Na_2SO_4, and $CHCl_3$ was evaporated, leaving 20 mg. of a residue. This was purified through alumina chromatography and elution with petr. ether-benzene (1:1) and benzene gave 18 mg. of the 2-oxo compound (XXXIV), which was recrystallized from $CHCl_3$-MeOH to needles (XXXIV), m.p. 205~206°. $[\alpha]_D^{23}$ −42.8° (c=0.966). *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.05; H, 10.28. IR: ν_{max}^{Nujol} 1710 cm^{-1}(CO).

b) From 25D,5α-Spirostan-2α-ol (XXXa): A mixture of 35 mg. of (XXXa), 35 mg. of CrO_3, and 1.3 cc. of pyridine was allowed to stand overnight at room temperature and the usual treatment gave 25 mg. of a product. This was purified through alumina chromatography and elution with petr. ether-benzene (1:1) and benzene afforded 20 mg. of a crude product melting at 190~192°, which was recrystallized from $CHCl_3$-MeOH to the 2-oxo compound (XXXIV) as needles, m.p. 205~206°, undepressed on admixture with the sample obtained by the foregoing method (a), but showed depression on admixture with 25D,5α-spirostan-11-one or -3-one.

2α,3α-Epoxy-25D,5β-spirostane (XXXII)——A solution of 1 g. of 2β,3β-epoxy-25D,5β-spirostane[7] (XXXII) dissolved in 400 cc. of AcOH was heated for 2 hr. on a water bath, AcOH was distilled off in a reduced pressure, and 1.1 g of 2α,3β-diol 2-acetate (XXXIb) was obtained as a brown syrupy substance. Without purification, this was dissolved in 6 cc. of pyridine, 4 cc. of mesyl chloride was added, and the mixture was allowed to stand for 44 hr. at room temperature. The mixture was treated as usual and the product was purified through alumina chromatography, from which 950 mg. of 2α,3β-diol 2-acetate 3-mesylate (XXIc) was obtained as an orange syrupy substance.

A mixture of this syrupy product, 0.7 g. of KOH, and 250 cc. of MeOH was refluxed for 2 hr. on a water bath and the usual after-treatment gave 900 mg. of an orange-yellow syrupy product. This was recrystallized from Me_2CO to 2α,3α-epoxide (XXXIII) as needles, m.p. 187~189°. *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.21; 10.21. Found: C, 78.21; H, 10.31. IR ν_{max}^{Nujol} 812 cm^{-1} (epoxide).

2α-Acetoxy-25D,5β-spirostane (XXIVb)——A solution of 400 mg. of (XXIII) dissolved in 35 cc. of dehyd. Et_2O was added to the solution of 800 mg. of $LiAlH_4$ in 42 cc. of dehyd. Et_2O and the mixture was refluxed for 4 hr. on a water bath. The usual treatment gave crude crystals, m.p. 159~170°, of the 2-hydroxy compound (XXIVa). Treatment of 210 mg. of this product (XXIVa) with 2 cc. each of Ac_2O and pyridine by warming for 1.5 hr. on a water bath afforded 200 mg. of a syrupy product, which was purified by alumina chromatography. Fractions eluted with petr. ether-benzene (1 : 1) and benzene gave 130 mg. of a syrupy substance which recrystallized from MeOH-Et_2O to needles (XXIVb), m.p. 167~168°. *Anal.* Calcd. for $C_{29}H_{46}O_4$ (2α-Acetate): C, 75.94; H, 10.11. Found: C, 75.80; H, 10.09. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1245, 1226 (Ac_2O).

Quantitative Determination through Infrared Absorption Spectra——Determination was carried out by the use of a strong absorption of carbonyl that appeared at around 1700 cm^{-1} in the IR spectra of these compounds.

(1) Preparation of Calibration Curves: As a sample, 2β,3β-dihydroxy-25D,5β-spirostan-11-one (Ia) and 3β-hydroxy-25D,5α-spirostan-11-one (XV) were used. Each of these compounds was dissolved in $CHCl_3$ to form a solution of 200, 140, or 40 mg. in 10 cc. of the solution and its absorption spectrum due to carbonyl at 1705 cm^{-1} was measured. Absorbance was calculated by the base-line method and relationship between the absorbance and concentration was plotted on a graph. As shown in Fig. 1, this showed a linear relationship and satisfied the Beer-Lambert Law in this range of concentrations. It was thereby assumed that the Beer-Lambert Law would be satisfied in other spirostanone derivatives.

(2) Method of Determination: About 200 mg. of spirostanone was weighed accurately in a flask, 2 cc. of triethylene glycol, 200 mg. of KOH, and 0.5 cc. of 80% $NH_2NH_2 \cdot H_2O$ were added, and the mixture was heated under a refiux condenser at an internal temperature of 130~140°, in an oil bath for 30 min.. The cooler was then removed, the temperature was raised gradually to 190° during 30 min., and heated at 190~200° for 2 hr.. When cooled, the reaction mixture was extracted with Et_2O, the extract was washed with H_2O, dried, and Et_2O was evaporated. The residue was dried *in vacuo*, dissolved in $CHCl_3$ to make 10 cc. of a solution, and its absorbance was measured by the base-line method.

On the other hand, ca. 200 mg. of the starting spirostanone was weighed accurately, dissolved in 10 cc. of $CHCl_3$, and this solution was measured as above as a standard. Yield of the reduction product was calculated from the difference in absorbance between this standard and the foregoing reaction product.

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Summary

In order to clarify the effect of hydroxyls in 2- and 3-position on the progress of the Huang-Minlon reduction of metagenone, the Huang-Minlon reduction was carried out on 2,3-dihydroxy-, 2-hydroxy-, and 3-hydroxy-25D,5β- and 5α-spirostan-11-one, using tigogenone and hecogenin as comparative controls. It was thereby found that (1) reduction of ketone groups in 3- and 12-positions progresses 100%, (2) the reduction progresses in fairly high yield (69~100%) in the case of 2,3-dihydroxy- and 2-hydroxy-11-oxo compounds, and (3) in the case of 3-hydroxy-11-oxo compounds, the reaction hardly progresses with the exception of 3β-hydroxy-25D,5α-spirostan-11-one.

Reason for the ease or difficulty in the reduction of these substances cannot be explained fully as yet.

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