tion of an isomer, which will be called neocoriamyrtin, by the hydrogenation of coriamyrtin with palladium catalyst was presumed. Neocoriamyrtin is considered to possess an isopropylidene group formed by transformation of the isopropenyl group in coriamyrtin. Unlike neopicrotoxinin, which gives aromatic picrotonol when heated in dilute mineral acid under mild conditions, the crude product which is presumed to contain neocoriamyrtin gave no aromatic derivative when heated in dilute mineral acid under various conditions. It was confirmed by chromatography and ultraviolet spectra that direct action of dilute mineral acid on coriamyrtin also gave no aromatic derivative.

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60. Ken'ichi Takeda, Hiroshi Ōsaka, and Norihide Maezono : On Steroidal Sapogenins. II.[1] Synthesis of Some 7-Oxygenated 5β,25D-Spirostanes.

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At the beginning of studies on the structure of metagenin,[2] 5β,25D-spirostane-2β,3β,11α-triol (XIV), a new steroidal sapogenin isolated from *Metanarthecium luteo-viride* MAXIM., a possibility for the position 7 for the third of the three hydroxyl groups of metagenin was not excluded. Therefore, attempt was made to synthesize 5β,25D-spirostan-7α-ol (Xa), -7β-ol (XIIIa), and -7-one (XI) from the known steroidal sapogenin.

7-Oxygenated 5β-steroids are well known in the cholic acid series, but no example is found in the 5β-spirostane series. In the 5β-cholestane series, Henbest, *et al.*[3] mentioned a formation of 7α-methoxy-5β-cholestan-3-one by catalytic hydrogenation of 7α-methoxycholest-4-en-3-one and the present authors reported[4] the synthesis of some 7-oxygenated 5β-cholestanes by hydrogenation of 7α-(tetrahydro-2'-pyranyloxy)cholest-4-en-3-one. In the present work, this method was applied to 7α-hydroxydiosgenin acetate[5] (IIa) to obtain 7-oxygenated 5β,25D-spirostanes.

7α-(Tetrahydro-2'-pyranyloxy)diosgenin acetate (IIb), obtained from 7α-hydroxydiosgenin acetate (IIa) by treatment with dihydropyran and phosphoryl chloride, was converted to 4-en-3-one (III) by saponification of the acetoxyl group to 3-ol (IIc), followed by Oppenauer oxidation. The intermediates (IIb), (IIc), and (III), did not crystallize, their formulae being assumed from infrared spectra (see Experimental). The 4-en-3-one (III), containing 4,6-dien-3-one (IV) as a by-product according to its infrared spectrum, was hydrogenated over platinum oxide in methanol solution to a saturated ketone (Va) and the latter was cleavaged to C_7-alcohol (Vb) with hydrochloric acid. The crude reaction product was purified on alumina to afford three products; substances of m.p. 191°(A) and of m.p. 210°(B) as a by-product, and substance of m.p. 240°(C) as a main product.

Substance (A) was determined as 3,3-dimethoxy-5β,25D-spirostane (VI) from its analy-

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1) A paper entitled "The Isomers of 25D-,5β-Spirostane-2,3-diol" by K. Takeda, T. Okanishi, A. Shimaoka (This Bulletin, **7**, 942 (1959)) is designated as Part I of this series.

2) *a*) K. Takeda, K. Hamamoto : Tetrahedron Letters, **3**, 1 (1960); *b*) K. Hamamoto : This Bulletin, **9**, 32 (1961).

3) H. B. Henbest, E. R. H. Jones : J. Chem. Soc., **1948**, 1798.

4) K. Takeda, H. Osaka, K. Horiki : Yakugaku Zasshi, **81**, 325 (1961).

5) H. J. Ringold, G. Rosenkranz, C. Djerassi : J. Am. Chem. Soc., **74**, 3318 (1952).

tical data, infrared spectrum, its conversion to known smilagenone[6] (VII) by acetic acid,[7] and also its regeneration from the latter with selenium dioxide and methanol.[7] Substance (B) was identified as 25D-spirosta-4,6-dien-3-one[8] (IV) by comparison with the synthesized sample.

Substance (C) and its acetate, m.p. 176.5°, were found to have a structure of hydroxyspirostanone (Vb) and its acetate (Vc) by analysis and infrared spectrum. The hydroxyketone (Vb) was oxidized with chromium trioxide and pyridine to give a diketone (VIII), m.p. 187°, which was apparently different from 5α,25D-spirostane-3,7-dione (IX), m.p. 242°, synthesized by the method reported by Marker, *et al.*[9] From this result it was assumed that the above-obtained hydroxy-ketone (Vb) must be a 5β-spirostane derivative and it was confirmed from the following experiments.

Hydroxy-ketone (Vb) was reduced to monoalcohol (Xa), m.p. 227°, or its acetate (Xb), m.p. 207°, by the Huang-Minlon method or by the Hauptmann reduction.[10] The alcohol (Xa) was oxidized to 7-ketone (XI), m.p. 157°, which was also reduced by the Huang-Minlon method to the known 5β,25D-spirostane[11] (XII), m.p. 140°, which was confirmed by the comparison of melting point and infrared spectrum with the sample synthesized from smilagenone (VII). The above 7-ketone (XI) was reduced to 7α-alcohol (Xa) by sodium borohydride[12] and to 7β-alcohol (XIIIa), m.p. 96°, and its acetate (XIIIb), m.p. 143.5°, by sodium and isopropanol.[13]

From these results it is clear that the spirostanes obtained here (Vb, VIII, Xa, XI and XIIIa) belong to 5β-spirostane series and they are the first example of 7-oxygenated 5β-spirostane derivatives.

As the monoalcohol (XV) or monoketone (XVI), derived earlier[2] from metagenin (XIV) is clearly different from either 7-alcohols (Xa, XIIIa) or 7-ketone (XI), the possibility of a C-7-hydroxyl group for metagenin is definitely excluded.

The reduction of 4-en-3-one (III) with lithium in liquid ammonia afforded another hydroxyspirostanone (XVIIb), m.p. 235°, and its acetate (XVIIc), m.p. 254°, which were distinguished from 5β-compounds (Vb and Vc) by melting point and infrared comparison. In general, the reduction of a double bond with lithium in liquid ammonia leads to the formation of a saturated compound of more stable form,[14] namely to the 5α-type in the case of

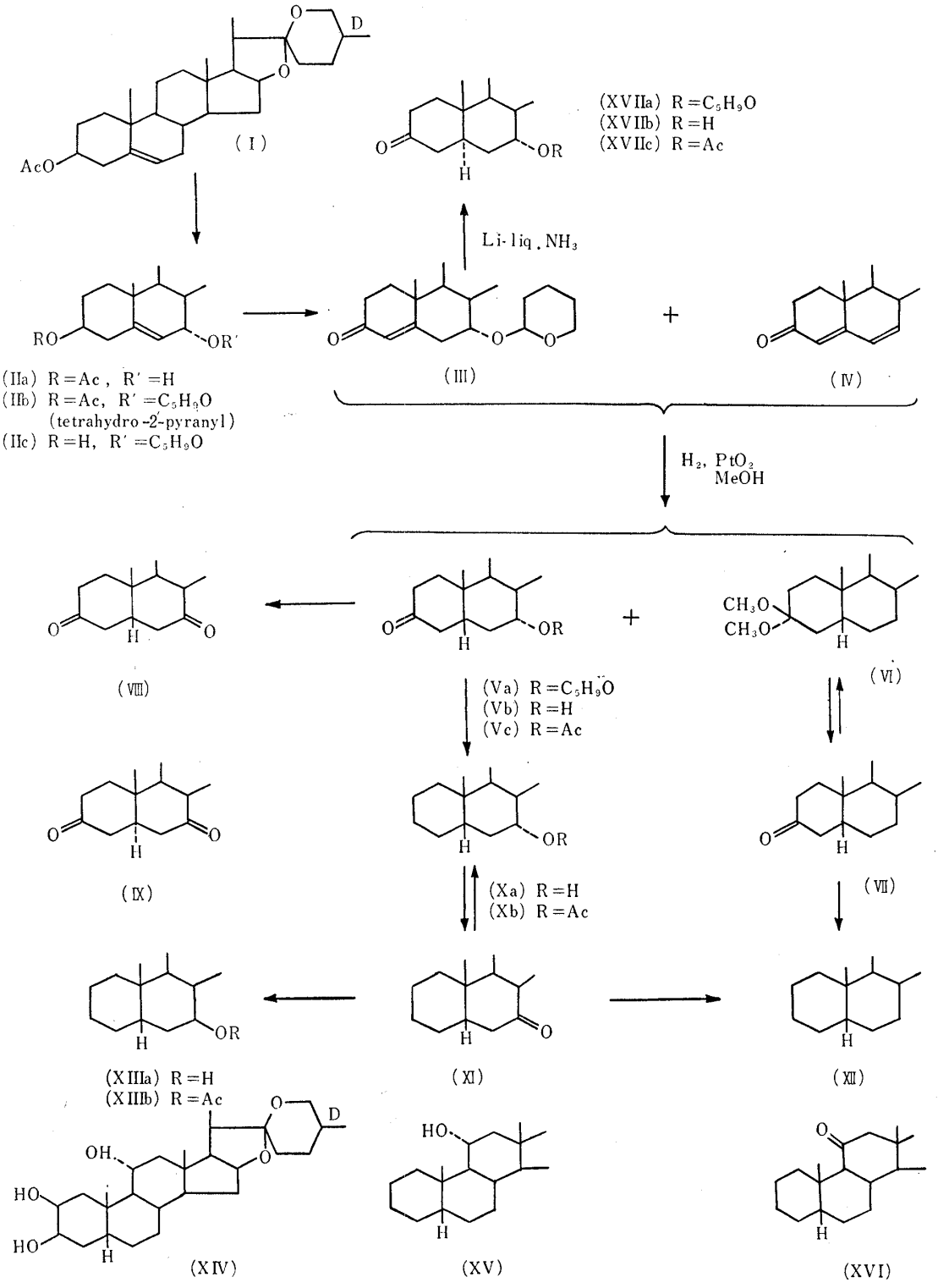
TABLE I. Molecular Rotations of 7-Oxygenated 5β,25D-Spirostanes and Contributions of Hydroxyl, Acetoxyl, and Ketone Groups in These Compounds

Compounds	Substituents	M_D	Δ		Reported
$C_{27}H_{44}O_2$ (XII)	7·H_2	−267°			
$C_{27}H_{42}O_3$ (VII)	3=O; 7·H_2	−253°			
$C_{27}H_{44}O_3$ (Xa)	7α·OH	−332°	Δ(OH, α)	−65°	−79°
$C_{27}H_{42}O_4$ (Vb)	3=O; 7α·OH	−293°	Δ(OH, α)	−40°	
$C_{29}H_{46}O_4$ (Xb)	7α·OAc	−387°	Δ(OAc, α)	−120°	−144°
$C_{29}H_{44}O_5$ (VIc)	3=O; 7α·OAc	−388°	Δ(OAc, α)	−135°	
$C_{27}H_{44}O_3\cdot\frac{1}{2}H_2O$ (XIIIa)	7β·OH	−162°	Δ(OH, β)	+105°	+95°
$C_{29}H_{46}O_4$ (XIIIb)	7β·OAc	−217°	Δ(OAc, β)	+50°	—
$C_{27}H_{42}O_3$ (XI)	7=O	−526°	Δ(C=O)	−259°	−224°
$C_{27}H_{40}O_4$ (VIII)	3=O; 7=O	−521°	Δ(C=O)	−268°	

6) cf. C. Djerassi, R. Yashin, G. Rosenkranz : J. Am. Chem. Soc., **74**, 422 (1952).
7) E. P. Oliveto, C. Gerold, E. B. Hershberg : *Ibid.*, **76**, 6113 (1954).
8) R. E. Marker, D. L. Turner : *Ibid.*, **63**, 767 (1941).
9) R. E. Marker, J. Lopez : *Ibid.*, **69**, 2401 (1947).
10) H. Hauptmann : *Ibid.*, **69**, 562 (1947).
11) cf. C. Djerassi, J. Fishman : *Ibid.*, **77**, 4291 (1955).
12) E. H. Mosbach, W. Meyer, F. H. Kendall : *Ibid.*, **76**, 5799 (1954).
13) T. Kanazawa, A. Shimazaki, T. Satō, T. Hoshino : Nippon Kagaku Zasshi, **76**, 297 (1955).
14) *a*) C. Djerassi, G. H. Thomas : J. Am. Chem. Soc., **79**, 3835 (1957); *b*) A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman, T. Wendler : *Ibid.*, **81**, 1288 (1959); *c*) P. E. Beal, M. A. Rebenstorf, J. E. Pike : *Ibid.*, **81**, 1231 (1959).

such a 4-en-3-one (III). Therefore, this product (XVIIb) must be a 5α-spirostane derivative and this is also proof of 5β-configuration for the catalytically hydrogenated product (Vb).

Molecular rotation of 7-oxygenated 5β-spirostanes and the contribution of hydroxyl, acetoxyl, and ketone groups in these compounds are indicated in Table I and are found to be analogous to those in the literature.[15]



15) W. Klyne : "Determination of Organic Structures by Physical Methods," (Braude & Nachod) 110 (1955). Academic Press Inc., New York.

Experimental*2

7α-Hydroxy-5β,25D-spirostan-3-one (Vb) and 3,3-Dimethoxy-5β,25D-spirostane (VI)——To a solution of 4 g. of 7α-hydroxydiosgenin acetate (IIa) in 70 cc. of dihydropyran, 8 drops of $POCl_3$ was added and the mixture was left for 2 hr. at 20°. The reaction mixture was basified with 10% MeOH-KOH, diluted with water, and extracted with Et_2O. The Et_2O layer was washed, dried, and evaporated to give a syrupy residue (10.7 g.) of 7α-(tetrahydro-2′-pyranyloxy)-25D-spirost-5-en-3β-ol acetate (IIb).

The above product (10.7 g.) was saponified by refluxing for 40 min. with 200 cc. of 10% MeOH-KOH. The syrupy residue, obtained by dilution with water, followed by extraction with Et_2O and evaporation, was purified on alumina and gave 4.5 g. of a syrup from Et_2O eluates. 7α-(Tetrahydro-2′-pyranyloxy)-25D-spirost-5-en-3β-ol (IIc); IR ν_{max}^{Nujol} cm^{-1} : 1115, 813 (tetrahydropyran), 3296 (OH). The same result was obtained by refluxing 3-acetate (IIb) with $LiAlH_4$ in Et_2O solution.

The above-obtained product (4.5 g.) was dissolved in a mixture of 80 cc. of Me_2CO and 130 cc. of benzene, oxidized by refluxing for 6 hr. with 30 cc. of 25% Al(*tert*-BuO)$_3$ solution in toluene, and treated in the usual manner and gave 5.9 g. of a syrup. 7α-(Tetrahydro-2′-pyranyloxy)-25D-spirost-4-en-3-one (III) and 25D-spirosta-4,6-dien-3-one (IV); IR ν_{max}^{Nujol} cm^{-1} : 1120, 815 (tetrahydropyran), 1681, 1624 (Δ^4-3-CO and $\Delta^{4,6}$-3-CO). An attempt to crystallize the above syrupy intermediates (IIb, IIc, or III) with solvent treatment was unsuccessful.

The above-obtained reaction mixture (5.9 g.) was catalytically hydrogenated with 200 mg. of PtO_2 in 150 cc. of MeOH and the reaction was stopped when H_2 absorption corresponded to 1 mole. Filtration of catalyst, followed by evaporation of the solvent furnished a syrupy residue, which was refluxed for 4 min. with 200 cc. of 80% MeOH-H_2O containing 0.25% HCl. The solution was neutralized with 10% Na_2CO_3 solution, evaporated, and the residue was extracted with Et_2O. The residue (4.4 g.), a mixture of crystals and syrup, obtained from the Et_2O layer, was chromatographed on alumina and gave the following 3 fractions :

(A) The eluate with benzene-hexane (1:1) yielded 100 mg. of crystals, m.p. 183~188°, which were purified to m.p. 190~191° from $CHCl_3$-MeOH; $[\alpha]_D^{30}$ −54.1°. IR ν_{max}^{Nujol} cm^{-1} : 1105 (MeO), no C=O band. *Anal.* Calcd. for $C_{29}H_{48}O_4$ (3,3-dimethoxy-5β,25D-spirostane (VI)) : C, 75.60; H, 10.50. Found : C, 75.42; H, 10.46.

(B) The eluate with benzene yielded 100 mg. of pale yellow crystals, m.p. 208~210° (from $CHCl_3$-MeOH); $[\alpha]_D^{30}$ −66.9°. IR ν_{max}^{Nujol} cm^{-1} : 1673 ($\Delta^{4,6}$-3-CO), 1715 (double bond). It showed no depression with the sample of (IV) on admixture. *Anal.* Calcd. for $C_{27}H_{38}O_3$ (IV) : C, 78.98; H, 9.33. Found : C, 79.00; H, 9.16.

(C) The eluate with Et_2O gave 563 mg. of crystals, m.p. 238~240° (from Me_2CO); $[\alpha]_D^{30}$ −68.1°. IR ν_{max}^{Nujol} cm^{-1} : 1722 (C=O), 3543 (OH). *Anal.* Calcd. for $C_{27}H_{42}O_4$ (7α-hydroxy-5β,25D-spirostan-3-one (Vb)): C, 75.31; H, 9.83. Found : C, 75.31; H, 9.86.

7α-Acetoxy-5β,25D-spirostan-3-one (Vc)——The hydroxy-ketone (Vb) was acetylated by refluxing with Ac_2O for 1 hr. and was processed in the usual manner to small needles of m.p. 175~175.6° (from hexane); $[\alpha]_D^{31}$ −82.0°. IR ν_{max}^{Nujol} cm^{-1} : 1727 (C=O), 1240 (AcO). *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found : C, 73.92; H, 9.50.

5β,25D-Spirostan-3-one (VII) from 3,3-Dimethoxy-5β,25D-spirostane (VI)——The above-obtained dimethoxyl derivative (VI) (100 mg.) was warmed with 4 cc. of AcOH for 1 hr. at 75° on a water bath and, after addition of 4 cc. of water, was left overnight to give 80 mg. of crude crystals, m.p. 183~184°. The m.p. was raised to 184~186° by recrystallization from $CHCl_3$-MeOH; $[\alpha]_D^{30}$ −61.0°. IR : ν_{max}^{Nujol} 1714 cm^{-1} (C=O). It showed no depression on admixture with a sample synthesized from smilagenin. *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found : C, 78.11; H, 10.10.

A solution of 47 mg. of 3-ketone (VII) and 47 mg. of SeO_2 in 23 cc. of MeOH was warmed at 50~55° for 1 hr. and cooled to room temperature. Crude crystals, m.p. 188~190°, were recrystallized from $CHCl_3$-MeOH to crystals of m.p. 190~190.5°, which showed no depression with the sample of (VI) obtained as above.

5β,25D-Spirostane-3,7-dione (VIII)——To a solution of 150 mg. of 7α-hydroxyspirostan-3-one (Vb) in 3 cc. of pyridine, a solution of 120 mg. of CrO_3 in 1.5 cc. of pyridine was added and the mixture was left for 18 hr. at room temperature. The crude crystals (130 mg., m.p. 180~186°) obtained in the usual manner from the reaction mixture were recrystallized from hexane to needles, m.p. 186.5~187°; $[\alpha]_D^{26}$ −121.6°. IR ν_{max}^{Nujol} cm^{-1} : 1712, 1729 (C=O). *Anal.* Calcd. for $C_{27}H_{40}O_4$: C, 75.43; H, 9.41. Found: C, 75.82; H, 9.44.

5β,25D-Spirostan-7α-ol (Xa)——i) Huang-Minlon Reduction of Hydroxy-ketone (Vb) : The hydroxy-ketone (Vb) (160 mg.) was refluxed with 1.6 cc. of triethylene glycol, 0.5 cc. of 80% hydrazine hydrate, and 0.5 g. of KOH at 120° for 30 min. and at 190° for 2.5 hr. By dilution of the reaction mixture with water followed by filtration, 150 mg. of crude crystals, m.p. 215~221°, were obtained which were recrystallized from Me_2CO to (Vb), m.p. 225~227°; $[\alpha]_D^{26}$ −79.6°. IR : ν_{max}^{Nujol} 3552 cm^{-1} (OH). *Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found : C, 77.75; H, 10.63.

*2 All melting points are uncorrected. Rotations were measured in $CHCl_3$ solution.

ii) Hauptmann Reduction of (Vb): To a solution of 100 mg. of hydroxy-ketone (Vb) in 2.5 cc. of AcOH ethanedithiol (0.17 cc.) and BF_3·Et_2O (0.17 cc.) were added and the mixture was left for 2 days at room temperature. Dilution with 5% NH_4OH, followed by extraction with Et_2O and evaporation yielded 118 mg. of crude mercaptal, m.p. 165~190° (decomp.).

This crude product (118 mg.) was dissolved in 40 cc. of dioxane, refluxed with 3 g. of Raney Ni for 8 hr., and was processed in the usual manner to give crude crystals, m.p. 203~209°. This was purified on alumina to give from the Et_2O-benzene (1:9) eluates 7α-alcohol (Xa) of m.p. 222~224°, identified with the sample obtained by (i) method by admixture and infrared spectral comparison.

iii) Reduction of 7-Ketone (XI) with $NaBH_4$: A solution of 20 mg. of 7-ketone (XI) and 20 mg. of $NaBH_4$ in 3 cc. of MeOH was left at 22° for 2 hr., diluted with water, filtered, and purified to 15 mg. of 7α-alcohol (Xa), m.p. 225~227°, undepressed on admixture with the sample from (i) method.

7α-Acetoxy-5β,25D-spirostane (Xb)——7α-Alcohol (Xa) was acetylated by refluxing for 1 hr. with Ac_2O. The acetate formed needles, m.p. 206~207°; $[\alpha]_D^{26}$ −84.3°. *Anal.* Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.06; H, 10.19.

5β,25D-Spirostan-7-one (XI)——7α-Alcohol (Xa) (160 mg.) in 3.2 cc. of pyridine was oxidized with 130 mg. of CrO_3 in 1.6 cc. of pyridine at 22° for 18 hr. Dilution with ice-water, filtration, extraction with Et_2O, and evaporation furnished 155 mg. of crude crystals, m.p. 145~148°. This was chromatographed on alumina and yielded from the benzene-hexane (1:1) eluted fraction, 135 mg. of needles, m.p. 156~157° (from $CHCl_3$-MeOH); $[\alpha]_D^{29}$ −126.9°. IR: ν_{max}^{Nujol} 1711 cm^{-1} (C=O). *Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.45; H, 10.15.

5β,25D-Spirostane (XII) from 7-Ketone (XI)——7-Ketone (XI) (90 mg.) was refluxed with 2 cc. of triethylene glycol, 0.5 cc. of 80% hydrazine hydrate, and 0.1 g. of KOH at 130~190° for 90 min. and at 190° for 30 min. The reaction mixture was processed in the usual Huang-Minlon reduction procedure affording crude crystals, m.p. 116~132°. Purification on alumina gave from the hexane eluates needles of pure (XII), m.p. 139~140°; $[\alpha]_D^{26}$ −66.7°. It was found to be identical with a sample synthesized from smilagenone (VII) by admixture and infrared comparison. *Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.81; H, 11.08.

5β,25D-Spirostan-7β-ol (XIIIa)——To a solution of 80 mg. of 7-ketone (XI) in 5 cc. of iso-PrOH, 200 mg. of Na was added under refluxing, which was continued until complete dissolution of Na (30 min.). Dilution with water followed by filtration furnished 81 mg. of crude product, m.p. 82~101°. It was chromatographed on alumina and the eluate with benzene yielded 9 mg. of 7α-alcohol (Xa), m.p. 220~224°, which showed no depression with the sample obtained as above. The eluates with Et_2O-benzene (1:9 and 2:8) gave 50 mg. of 7β-alcohol (XIIIa) as needles, m.p. 93~96°; $[\alpha]_D^{19}$ −38.0°. *Anal.* Calcd. for $C_{27}H_{44}O_3$·$\frac{1}{2}H_2O$: C, 76.19; H, 10.66. Found: C, 76.57; H, 10.70.

7β-Acetoxy-5β,25D-spirostane (XIIIb)——7β-Alcohol (XIIIa) was acetylated with Ac_2O and pyridine for 18 hr. at room temperature. The acetate came as tabular crystals, m.p. 143~143.5°; $[\alpha]_D^{18}$ −47.3°. *Anal.* Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.04; H, 10.22.

7α-Hydroxy-5α,25D-spirostan-3-one (XVIIb)——Crude 4-en-3-one (III) (sirupy, 1.5 g.), obtained from 1 g. of 7α-hydroxydiosgenin acetate (IIa) as in the case of 5β-derivative (Vb), was dissolved in 15 cc. of Et_2O and the solution was added to a solution of 0.2 g. of Li in 84 cc. of liquid NH_3 at −40° with stirring (ca. 5 min.), which was continued 4 min. more at this temperature. NH_4Cl was added to the solution until the blue color disappeared (NH_4Cl 1.4 g., 10 min.). After evaporation of NH_3, the reaction mixture was left overnight and refluxed for 1 hr. with 50 cc. of 5% KOH solution. This was diluted with water, extracted with Et_2O, and Et_2O was evaporated to give 1.5 g. of syrupy 7α-(tetrahydro-2′-pyranyloxy)-5α,25D-spirostan-3-one (XVIIa).

It was refluxed for 4 min. with 75 cc. of 80% MeOH containing 0.25% HCl and was processed as in the case of 5β-derivative (Vb), yielding 1.1 g. of a syrup. The crude product (1.1 g.) was chromatographed on alumina affording from the eluate with Et_2O-benzene (1:4) crystals of free 7α-alcohol (XVIIb), m.p. 233~235° (from Me_2CO); $[\alpha]_D^{30}$ −66.1°. IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O), 3556 (OH). It depressed to 210~226° upon admixture with the 5β-derivative (Vb). *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 74.92; H, 9.81.

7α-Acetoxy-5α,25D-spirostan-3-one (XVIIc)——The above 7α-alcohol (XVIIb) was acetylated by refluxing with Ac_2O. The acetate was recrystallized from hexane, m.p. 251~254°; $[\alpha]_D^{30}$ −91.8°. *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.90; H, 9.44.

The authors express their gratitude to the members of the analytical and the physicochemical sections in this laboratory for the microanalysis, measurement of infrared spectra and optical rotation.

Summary

5β,25D-Spirostan-7α-ol, -7β-ol, -7-one and some other derivatives were synthesized from 7α-hydroxydiosgenin acetate via 7α-(tetrahydro-2′-pyranyloxy)-25D-spirost-4-en-3-one. Some 5α-derivatives were also derived from the same intermediate.

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