in propylene glycol and glycerol, and the effect of propylene glycol was larger than that of glycerol. Glucose did not show any effect. The absorption decreased with concentration of the material which showed a pronounced obstructive effect.

2. Degrees of absorption from various aqueous solutions were parallel to the degree of partition between benzene and their solution.

3. Effect of viscosity and surface tension on abosorption was not shown within the region of this experiment.

(Received December 19, 1957)

UDC 547.918.02 : 582.572.2

45. **Hayao Nawa** : Studies on the Components of *Rhodea japonica* Roth. XI. Structure of Rhodeasapogenin. (4).*

(*Research Laboratories, Takeda Pharmaceutical Industries, Ltd.***)

Several years ago the author isolated rhodeasapogenin, a new steroidal sapogenin, from leaves of *Rhodea japonica* Roth. and presumed its structure to be 5β,22b-spirostane-2β,3α-diol [Chart 1(A)].[1] This presumption was drawn from the following facts: (1) Rhodeasapogenin (A) isomerizes into isorhodeasapogenin (B); (2) rhodeasapogenin is readily led to derivatives of pregnenolone; (3) oxidation of rhodeasapogenin with chromium trioxide gives rhodeasapogenic acid, a dicarboxylic acid, which has a melting point similar to that of texogenic acid (D); (4) rhodeasapogenin and its derivatives are not precipitated with digitonin and do not produce acetonide; and (5) isorhodeasapogenin agrees with neither of the homologs (C) of gitogenin but has properties akin to those of *epi*-samogenin.

Later, description about texogenic acid was found incorrect and the compound

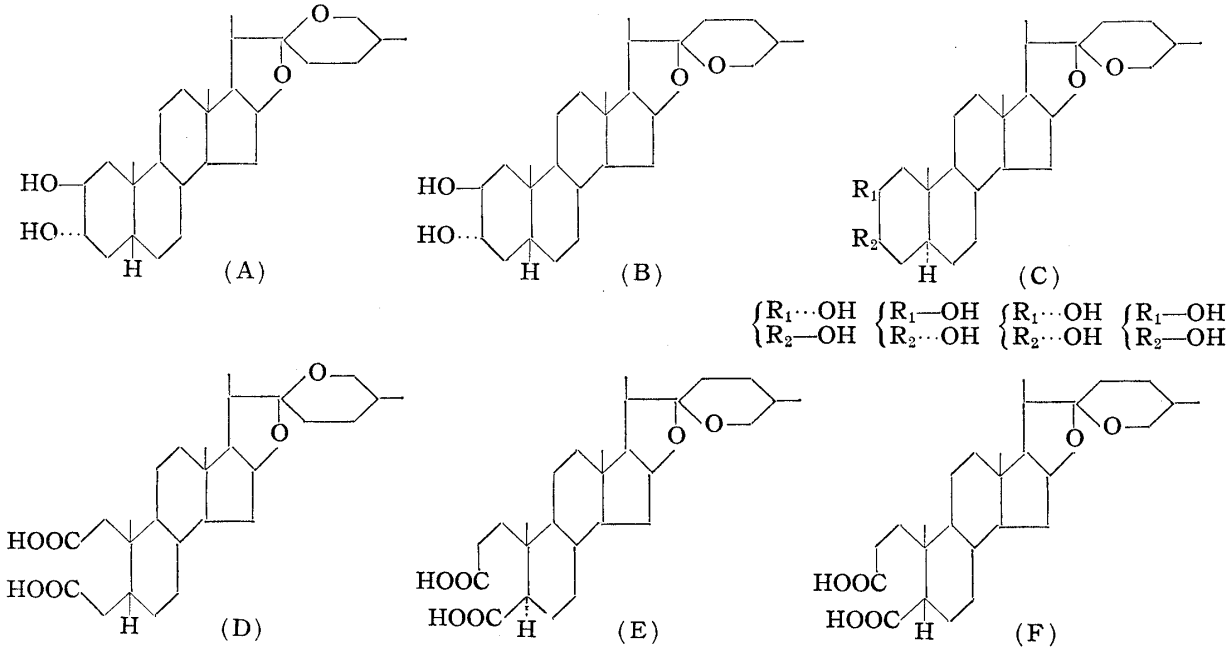
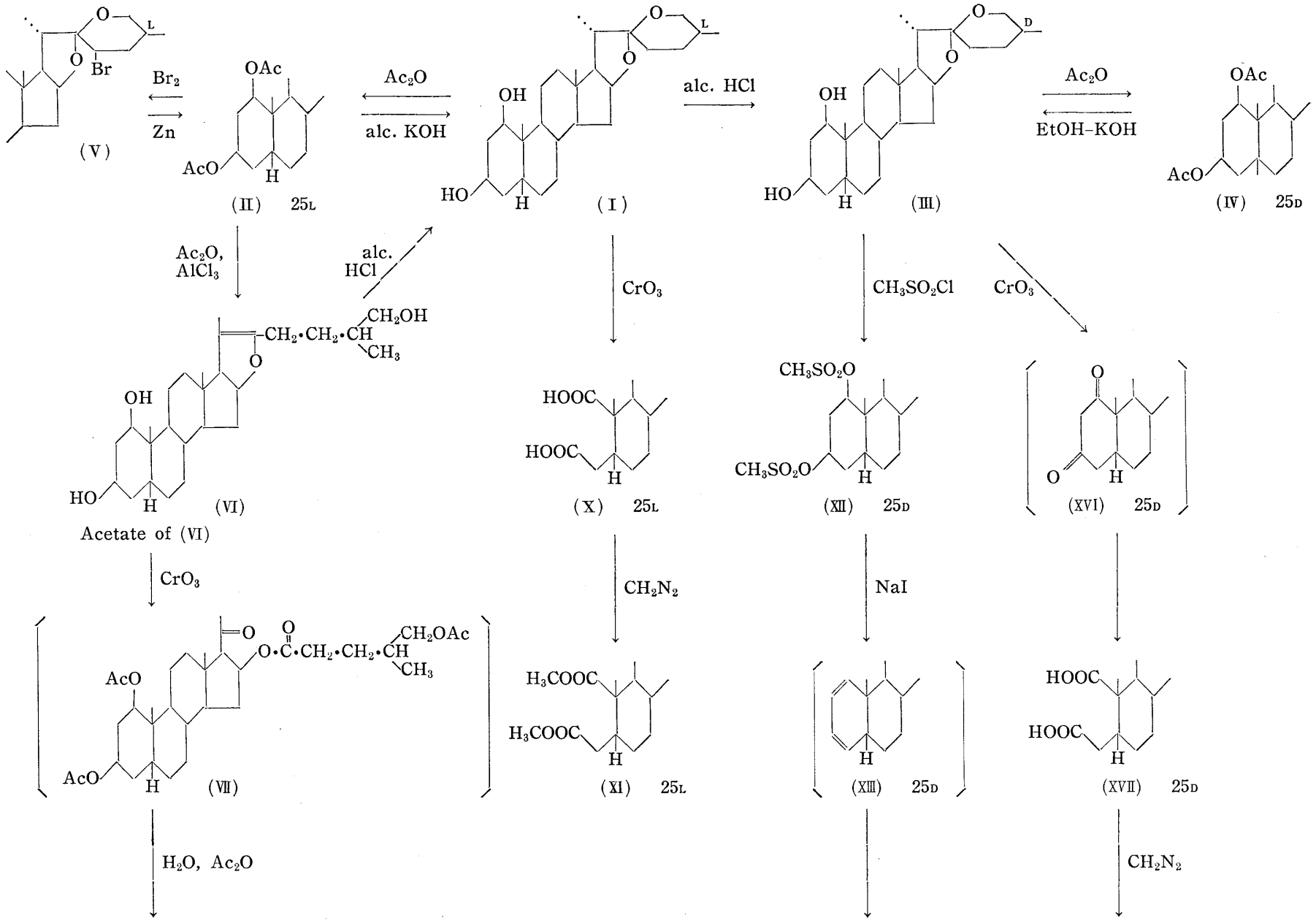


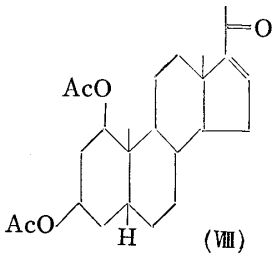
Chart 1.

* Preliminary communication, H. Nawa : Proc. Japan Acad., **33**, 570(1957).

** Juso-nishino-cho, Higashi-yodogawa-ku, Osaka (那波速男).

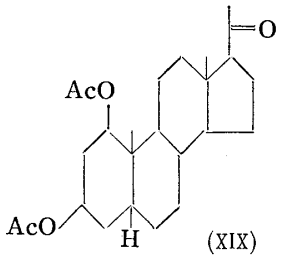
1) H. Nawa : Proc. Japan Acad., **29**, 214(1953); Yakugaku Zasshi, **73**, 1192, 1195, 1197(1953).



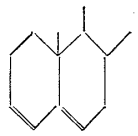


(VIII)

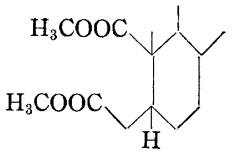
H_2, Pd



(XIX)

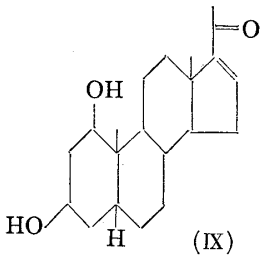


(XIV) 25_D



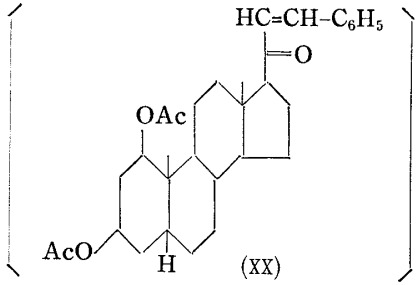
(XVIII) 25_D

↓ alc. KOH



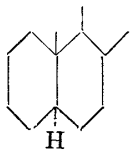
(IX)

↓ C_6H_5·CHO



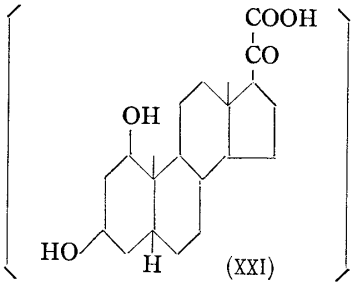
(XX)

↓ H_2, Pt



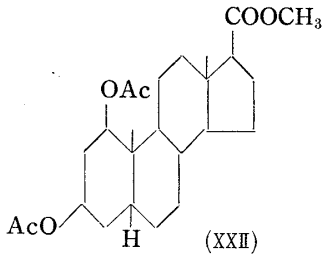
(XV) 25_D

↓ O_3 in AcOH



(XXI)

H_2O_2, CH_2N_2, Ac_2O



(XXII)

Chart 2.

corresponding to (D) was newly named markogenic acid.[2] By comparison between rhodeasapogenic acid and markogenic acid, it was found that they are quite different and hence rhodeasapogenin does not have the structure (A). After that Djerassi[3] prepared isorhodeasapogenic acid (m.p. 246~248°; dimethyl ester, m.p. 155~157°) by oxidation with chromic acid of the isorhodeasapogenin sent by the author and confirmed that the product is not in accord with any of four possible 2,3- and 3,4-*seco*-acids with either the 5α- or 5β-configuration having the side-chain of isosapogenin. Therefore, it was thought that if the two hydroxyl groups of rhodeasapogenin are in *ortho*-relation and one of them is attached to C-3, rhodeasapogenin would have an abnormal skeleton or a side-chain having a sterically peculiar configuration.

For the purpose of investigating the basic skeleton of rhodeasapogenin shown in Chart 2, isorhodeasapogenin (III) was first converted into its dimethanesulfonate (XII) and then treated with sodium iodide and acetone in a sealed tube according to the customary method for eliminating *ortho*-dihydroxyls, whereupon a product was obtained which was supposed to be 25D-spirosta-3,5-diene (XIV)[4] from its ultraviolet absorption spectrum and specific rotation. (XIV) was further led to 5α,25D-spirostane (XV) by reduction in ethanol in the presence of platinum oxide and the product was identified by the mixed melting point determination with authentic sample[5] and by comparison of their infrared absorption spectra.

The fact that isorhodeasapogenin can thus be led to 5α,25D-spirostane shows that the former has a normal steroid skeleton and its side-chain is the same as that of natural sapogenins in 25D-series. This is also supported by the fact that pseudorhodeasapogenin (VI) is recyclized to rhodeasapogenin (I) by treatment with hot ethanolic hydrogen chloride. However, if one of the two double bonds of 25D-spirosta-3,5-diene, which was unexpectedly produced from isorhodeasapogenin dimethanesulfonate, is assumed to be due to the elimination of the two methanesulfonyloxy groups, the source of the other double bond is understandable.

Recently, Morita of this Laboratories isolated, besides diosgenin, a new steroidal sapogenin, tokorogenin, from *Dioscorea tokoro* MAKINO and established its structure as 5β,25D-spirostane-1β,2β,3α-triol[6,7] [Chart 3(a)]. During his study, tokorogenic acid (b), m.p. 255°, was produced by oxidation of tokorogenin with chromic acid. As the melting points of the acid and its dimethyl ester (c), m.p. 158~159°, were similar to those of isorhodeasapogenic acid (XVII) and its dimethyl ester (XVIII), the two acids were compared and it was found that they are identical, judging from their mixed melting point determination and infrared absorption spectra.[8] Morita further obtained 5β,25D-spirostane-1β,3β-diol (e), m.p. 240~243°, by the reductive cleavage of 1β-hydroxy-2β,3β-epoxy compound (d) with lithium aluminum hydride according to the scheme shown in Chart 3. As the melting points of the product and its diacetate, m.p. 207°, also resembled those of isorhodeasapogenin (III)[9] and its diacetate (IV), they were compared

2) M. E. Wall, C. R. Eddy, S. Serota, R. F. Mininger : J. Am. Chem. Soc., **75**, 4437(1953).
3) C. Djerassi, J. Fishman : J. Am. Chem. Soc., **77**, 4291(1955).
4) 25D-Spirosta-3,5-diene was also obtained by elimination of the tosyloxy group of diosgenin tosylate. cf. M. E. Wall, S. Serota : J. Am. Chem. Soc., **78**, 1747(1956).
5) The sample cf 5α,25D-spirostane was kindly given by Dr. C. Djerassi.
6) M. Nishikawa, K. Morita, H. Hagiwara, M. Inoue : Yakugaku Zasshi, **74**, 1165(1954).
7) K. Morita : This Bulletin, **5**, 494(1957).
8) The composition of isorhodeasapogenic acid was previously reported as $C_{27}H_{42}O_6$, but it is corrected to $C_{26}H_{40}O_6$ because of its identity with tokorogenic acid.
9) The melting point of isorhodeasapogenin was reported as 245~248°, but it was found later that the substance showing this melting point was contaminated with a very small quantity of rhodeasapogenin. Complete separation of the two compounds was quite difficult. A mixture of both compounds shows no depression in melting point.

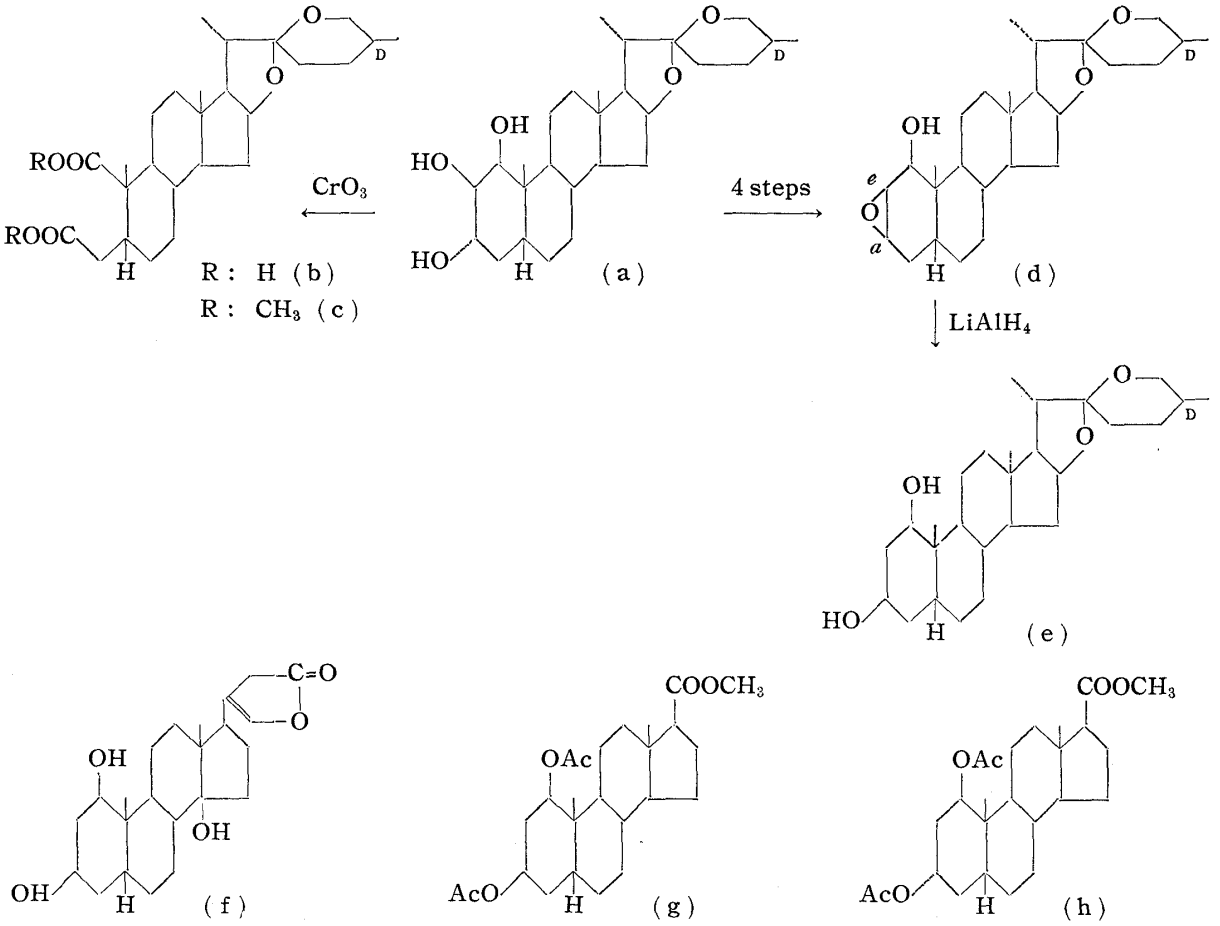


Chart 3.

and found to agree in melting point and infrared absorption spectrum.

From the general rule that cleavage with lithium aluminum hydride of an epoxy compound in a polycyclic cyclohexane system always produces an axial hydroxyl group, Morita assigned the 3β-hydroxy structure to (e). The present author also supported the structure, but as an exceptional reaction was reported most recently,[10] the structure of rhodeasapogenin was further examined by deriving the substance to known compounds.

Reichstein, *et al.*, isolated a cardioactive glycoside, acovenoside A, from *Acocanthera* of Apocynaceae family and established the structure of its aglycone, acovenosigenin A, as (f) in Chart 3.[11~13] In the course of their studies on the structure, they also obtained methyl 1β,3β-diacetoxyetiocholanate (g) and its 3α-isomer (h), which were clearly distinguishable from their melting points and specific rotations. It was considered that the structure of rhodeasapogenin could be confirmed by degradating this compound to the corresponding etiocholanic acid derivative and comparing the product with (g) and (h).

Therefore, diacetylpregnenolone compound (Ⅷ), which was derived from rhodeasapogenin as shown in the preceding paper,[1] was first converted to the pregnanolone compound (XIX) by catalytic reduction on Pd-$CaCO_3$, condensed with benzaldehyde in the presence of sodium ethoxide, and the product (XX), without being isolated, was

10) W. S. Knowles, Q. E. Thompson : J. Am. Chem. Soc., **79**, 3212(1957).
11) Ch. Tamm, T. Reichstein : Helv. Chim. Acta, **34**, 1224(1957).
12) W. Schlegel, Ch. Tamm, T. Reichstein : *Ibid.*, **38**, 1013(1955).
13) W. Schlegel, Ch. Tamm : *Ibid.*, **40**, 160(1957).

oxidized with ozone in glacial acetic acid, as shown in Chart 2. Ozone oxidation in chloroform of such a compound as (XX) generally produces a glyoxal compound,[14] but as the above oxidation in glacial acetic acid gave almost no neutral substance and as a greater part of the product was soluble in potassium hydrogen carbonate solution, the α-keto acid (XXI) was assumed to have been produced by further oxidation of the intermediate glyoxal compound. Hence, the product (XXI) dissolved in a potassium hydrogen carbonate solution was oxidized with hydrogen peroxide following the method most suitable for oxidizing an α-keto acid,[15] the acid portion of the resulting product was methylated with diazomethane, and then acetylated with acetic anhydride and pyridine. The product (XXII) thus obtained was in complete agreement with methyl 1β,3β-diacetoxyetiocholanate [Chart 3(g)] in crystal form, analytical values, melting point, and specific rotation as reported in the literature. From the above results it was established that rhodeasapogenin is 5β,25L-spirostane-1β,3β-diol and therefore isorhodeasapogenin is the 25D-isomer of the former.

In accordance with the structure of rhodeasapogenin thus made clear, the structures of its derivatives reported in the previous papers and those prepared thereafter are listed *en bloc* in Table I.

Table I.

		Formula	m.p. (°C)	$[\alpha]_D$(CHCl$_3$)
(I)	Rhodeasapogenin (5β,25L-Spirostane-1β,3β-diol)	$C_{27}H_{44}O_4$	293~295	−72°
(II)	Rhodeasapogenin diacetate (5β,25L-Spirostane-1β,3β-diol diacetate)	$C_{31}H_{48}O_6$	185~187	−71°
(III)	Isorhodeasapogenin (5β,25D-Spirostane-1β,3β-diol)	$C_{27}H_{44}O_4$	241~243	−71°
(IV)	Isorhodeasapogenin diacetate (5β,25D-Spirostane-1β,3β-diol diacetate)	$C_{31}H_{48}O_6$	205	−73°
(V)	23-Bromorhodeasapogenin diacetate	$C_{31}H_{47}O_6Br$	246	−76°
(VI)	Pseudorhodeasapogenin	$C_{27}H_{44}O_4$	188~189	+ 6°
(VII)	1β,3β-Dihydroxypregn-16-en-20-one 1,3-diacetate	$C_{25}H_{36}O_5$	205~207	0°
(IX)	1β,3β-Dihydroxypregn-16-en-20-one	$C_{21}H_{32}O_3$	236~239	+35°
(X)	Rhodeasapogenic acid (1,3-*seco*-5β,25L-Spirostane-1,3-dioic acid)	$C_{26}H_{40}O_6$	274~275	−86°
(XI)	Dimethyl ester of (X)	$C_{28}H_{44}O_6$	178~180	−54°
(XII)	Isorhodeasapogenin dimethanesulfonate (5β,25D-Spirostane-1β,3β-diol dimethanesulfonate)	$C_{29}H_{48}O_8S_2$	158	−59°
(XIV)	25D-Spirosta-3,5-diene	$C_{27}H_{40}O_2$	164	−180°
(XV)	5α,25D-Spirostane	$C_{27}H_{44}O_2$	172	−74°
(XVII)	Isorhodeasapogenic acid (1,3-*seco*-5β,25D-Spirostane-1,3-dioic acid)	$C_{26}H_{40}O_6$	254	−64°
(XVIII)	Dimethyl ester of (XVII)	$C_{28}H_{44}O_6$	156~158	−59°
(XIX)	1β,3β-Dihydroxypregnan-20-one 1,3-diacetate	$C_{25}H_{38}O_5$	163	+42°
(XXII)	Methyl 1β,3β-diacetoxyetiocholanate	$C_{25}H_{38}O_6$	173	+ 9°

When the structure (III) is assigned to isorhodeasapogenin, the reactions of this compound which appeared unusual can be readily explained. The fact that 25D-spirosta-3,5-diene (XIV) was obtained from isorhodeasapogenin dimethanesulfonate (XII) seems understandable by considering that the 1β- and 3β-methanesulfonyloxy groups, which take unstable axial configuration, are eliminated forming a double bond to give (XIII) and the product is further rearranged into the more stable 3,5-diene (XIV). Further, formation of the 1,3-*seco*-acid (XVII) from isorhodeasapogenin seems to be attributed to the oxidation of the β-diketone (XVI) which was produced first.

In fact, this assumption was supported by the separation of a β-diketone-like substance from the neutral portion of the reaction products. Although the substance showed the ultraviolet-absorption characteristics of an enolized β-diketone, its detailed examination could not be conducted because of its very small quantity.

14) W.M. Hoehn, H.L. Mason : J. Am. Chem. Soc., **60**, 1493(1938).
15) K. Meyer : Helv. Chim. Acta, **30**, 1976(1947).

Up to now, formation of a dibasic acid from a sapogenin by oxidation with chromium trioxide under mild conditions was regarded as an evidence of the presence of two hydroxyl groups in glycol-type at C-2 and C-3 of the sapogenin. However, since isorhodeasapogenin, which is a 1,3-dihydroxy compound, also gives a dibasic acid, C_{26}-acid, as mentioned above, and the acid is almost undistinguishable analytically from C_{27}-acid, the dibasic acid obtainable by oxidation of a glycol-type sapogenin, the interpretation of the experimental data in such oxidations should be made with great caution.

As the steroids having hydroxyl groups at 1 and 3, there have so far been known only acovenosigenin A and ouabagenin, which are both the genins of cardioactive glycosides, but in 1957, rusocogenin (1-hydroxydiosgenin),[16~19] tokorogenin, and rhodeasapogenin, which belong to the steroidal sapogenin, have been successively added to this group. Among these, rhodeasapogenin and ruscogenin seem useful as the material for the synthesis of valuable Δ^1-steroid hormones.

The author is grateful to Dr. Y. Asahina, Dr. S. Kuwada, and Dr. S. Tatsuoka for their encouragement throughout the present work. Thanks are also due to Mr. K. Morita for his valuable suggestions and kindness in giving samples, and to Dr. C. Djerassi for his favor toward this work.

Experimental

Pseudorhodeasapogenin (VI)—A mixture of 1 g. of rhodeasapogenin diacetate (II) (m.p. 186°), 5 cc. of Ac_2O, and 0.4 g. of pyridine hydrochloride was boiled under reflux for 5 hrs. To the cooled mixture satd. NaCl soln. was added and the resulting precipitate was filtered and washed thoroughly with water. The precipitate was hydrolyzed by heating with 50 cc. of 5% ethanolic KOH solution on a water bath for 30 mins., the reaction mixture was diluted with water, and EtOH was distilled off under reduced pressure. The product was collected, washed with water, and after drying, recrystallized from EtOH to scales, m.p. 188~189°; $[\alpha]_D^{15}$ +6.0°±0.5°(c=1, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.95; H, 10.06.

Formation of Rhodeasapogenin (I) from Pseudorhodeasapogenin (VI)—A mixture of 0.5 g. of (VI) and 40 cc. of EtOH containing 5 cc. of HCl was heated on a water bath for 1 hr. The reaction mixture was diluted with water, EtOH was distilled off, and the resulting precipitate, after washing with water and drying, was recrystallized from EtOH to prisms, m.p. 290~293°; $[\alpha]_D^{16}$ −72°(c=0.4, $CHCl_3$). The product was in accord with an authentic sample of rhodeasapogenin.

Diacetate: This was produced by acetylation of the above product with pyridine and Ac_2O and recrystallized from EtOH to prisms, m.p. 186°. The diacetate showed no depression in m.p. on admixture with an authentic sample and was in complete agreement with the latter in I.R.-spectrum.

Isorhodeasapogenin (5β,25D-Spirostane-1β,3β-diol) (III)—Isorhodeasapogenin diacetate (IV), m.p. 205°, showed no depression in m.p. on admixture with 5β,25D-spirostane-1β,3β-diol diacetate, m.p. 207°, derived from tokorogenin and they agreed in I.R.-spectrum when observed as solution in CS_2.

An amount of 1.5 g. of (IV) was hydrolyzed by heating with 100 cc. of 5% ethanolic KOH solution on a water bath for 30 mins. The reaction mixture was diluted with a little water, EtOH was distilled off, and the resulting precipitate was taken up in ether. The ethereal solution was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue was recrystallized from EtOH to 0.6 g. of needles, m.p. 241~243°.

Separation of rhodeasapogenin from isorhodeasapogenin was readily effected by recrystallization of their mixture from EtOH because the former is less soluble. When pure isorhodeasapogenin diacetate was employed as the material, it was easy to obtain pure isorhodeasapogenin. The mixed melting point determination of (III), m.p. 241~243°, with 5β,25D-spirostane-1β,3β-diol, m.p. 240~243°, showed no depression, and they also agreed in I.R.-spectrum when observed in Nujol mull.

Isorhodeasapogenin Dimesylate (5β,25D-Spirostane-1β,3β-diol Dimethanesulfonate) (XII)—A solution of 0.2 g. of isorhodeasapogenin (III), m.p. 243°, in 1 cc. of pyridine was mixed with 0.7 cc. of methanesulfonyl chloride and the mixture was left standing at room temperature for 40 hrs. The reaction mixture was poured into ice-water containing HCl and the separated oily substance was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over anhyd. Na_2SO_4, and

16) W.R. Benn, F. Colton, R. Pappo: J. Am. Chem. Soc., **79**, 3920(1957).
17) A.L. Nussbaum, F.E. Carlon, D. Gould, E.P. Oliveto, E.B. Hershberg, M.L. Gilmore, W. Charney: *Ibid.*, **79**, 4814(1957).
18) H. Lapin, M.M. Delepine: Compt. rend., **244**, 3065(1957).
19) D. Burn, B. Ellis, V. Petrow: Proc. Chem. Soc., **1957**, 119.

evaporated. The residue was recrystallized from benzene-hexane to needles, m.p. 158°(deomp.), $[\alpha]_D^{20}$ −59°(c=0.5, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{48}O_8S_2$: C, 59.15; H, 8.22. Found : C, 59.16; H, 8.19.

25D-Spirosta-3,5-diene (XIV)—A mixture of 0.4 g. of (XII) with 1.36 g. of NaI and 16 cc. of acetone was heated in a sealed tube at 100° for 24 hrs. The reaction mixture was extracted with $CHCl_3$ and the extract was washed successively with $Na_2S_2O_3$ solution and water, and evaporated after drying over anhyd. Na_2SO_4. The residue was chromatographed on Florisil and the substance obtained from the petr. ether eluate was recrystallized first from petr. ether-MeOH, then from acetone to scales, m.p. 164°; $[\alpha]_D^{18}$ −180°(c=0.3, $CHCl_3$). U. V. λ_{max}^{EtOH} mμ(log ε) : 228(4.30), 235(4.35), 243(4.14). I. R. $\nu_{max}^{CS_2}$ cm^{-1}: 979(s), 917(w), 895(s), 863(w). *Anal.* Calcd. for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found : C, 81.40; H, 10.16.

5α,25D-Spirostane (XL)—A solution of 0.1 g. of (XIV) in 40 cc. of EtOH was subjected to catalytic reduction in the presence of PtO_2. The catalyst was separated by filtration, the filtrate was evaporated *in vacuo*, and the residue was recrystallized from EtOH to plates, m.p. 172°; $[\alpha]_D^{21}$ −66° (c=0.3, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found : C, 81.07; H, 11.00.

The product showed no depression in m.p. when mixed with an authentic sample of 5α,25D-spirostane and they agreed in I. R.-spectrum when observed as solution in CS_2.

Isorhodeasapogenic Acid (1,3-*seco*-5β,25D-Spirostane-1,3-dioic Acid) (XVII)—To a solution of 0.5 g. of (III) in 80 cc. of AcOH a solution of 0.5 g. of CrO_3 in 15 cc. of 80% AcOH was added, and the mixture was allowed to stand at room temperature for 3 hrs. The excess CrO_3 was decomposed with EtOH and the mixture was evaporated under reduced pressure to remove AcOH. The residue was diluted with water, shaken with ether, and the ethereal solution, after washing with satd. NaCl solution, was extracted with 5% NaOH solution to separate the acid portion from the neutral portion.

Acid portion : 100 cc. of the alkaline solution was weakly acidified with dil. HCl and extracted with ether. The ethereal solution was washed with satd. NaCl solution, then with water, evaporated after drying over anhyd. Na_2SO_4, and the residue was recrystallized from acetone to needles, m.p. 254°; $[\alpha]_D^{20}$ −64°(c=1, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{42}O_6$: C, 70.10 H, 9.15. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found : C, 69.80; H, 9.04.

The product showed no depression in m.p. when mixed with an authentic sample of tokorogenic acid and they were also in accord in I. R.-spectrum when observed as Nujol mull.

Neutral portion : The ether solution, which had been extracted with 5% alkali solution, was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue was chromatographed on Florisil and the residue obtained by evaporating the methylene chloride eluate was recrystallized from EtOH to a very small amount of prisms. The product was not pure, showing a melting point of 220~230°, but further purification was unsuccessful. This substance, however, exhibited a sharp absorption at λ_{max}^{EtOH} 262 mμ.

Dimethyl Ester (XVIII) of (XVII)—(XVII) was dissolved in ether and methylated with CH_2N_2. The reaction mixture was worked up as usual and the product was purified by recrystallization from MeOH to scales, m.p. 156~158°; $[\alpha]_D^{20}$ −59°(c=0.5, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found : C, 70.60; H, 9.35.

The mixed m.p. determination of the product with dimethyl tokorogenate showed no depression and they were in complete agreement in I. R.-spectrum when observed as solution in $CHCl_3$.

1β,3β-Dihydroxypregnan-20-one 1,3-Diacetate (XIX)—A solution of 1.6 g. of 1β,3β-dihydroxypregn-16-en-20-one 1,3-diacetate (VIII)(m.p. 205°) in 70 cc. of EtOH was added to a suspension of 5 g. of Pd on $CaCO_3$(2% Pd) in 50 cc. of EtOH, which had been reduced in advance, and subjected to catalytic reduction. When the theoretical amount (ca. 100 cc.) of H_2 was absorbed, the catalyst was separated, the solution was concentrated, and the resulting precipitate was recrystallized from EtOH to prisms, m.p. 163°(1.3 g.); $[\alpha]_D^{20}$ +42°(c=1, $CHCl_3$), λ_{max}^{EtOH} mμ(log ε) : 285(1.67). *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found : C, 71.63; H, 9.21.

Methyl 1β,3β-Diacetoxyetiocholanate (XXII)—A solution of 0.98 g. of (XIX) dissolved in a mixture of 0.4 g. of benzaldehyde and 20 cc. of EtOH was left standing with 15 cc. of 6% ethanolic NaOEt solution at room temperature for 24 hrs. The reaction mixture was poured into ice-water containing 5 cc. of glacial AcOH, EtOH was distilled off under reduced pressure, the resulting precipitate was collected, washed with water, and dried (yield, 1 g.). The dried precipitate was boiled with 10 cc. of Ac_2O and 1 cc. of pyridine for 10 mins. and the solvent was distilled off under reduced pressure. A solution of the residue (XX) in 40 cc. of glacial AcOH was oxidized with O_3 at room temperature and the reaction mixture, after addition of 60 cc. of ether, was reduced by adding 15 g. of Zn powder and 1.5 cc. of water one after the other under stirring, and heating on a water bath until the mixture no longer colored with NaI-starch solution. The zinc acetate and Zn powder were filtered off and the filtrate, after addition of a little water, was evaporated under reduced pressure. The residue was diluted with water, the resulting precipitate was extracted with $CHCl_3$, the extract was washed successively with satd. NaCl solution and water, and dried over anhyd. Na_2SO_4. The $CHCl_3$ solu-

tion was then evaporated and the residue was heated with 100 cc. of 10% ethanolic $KHCO_3$ solution on a water bath for 30 mins. The reaction mixture was diluted with a little water and concentrated to remove EtOH, and the residue was extracted with ether. The ether solution was washed with water, dried over anhyd. Na_2SO_4, and evaporated, leaving ca. 80 mg. of crystals, m.p. 175~185°. Examination was not made on the crystals. The above-mentioned conc. $KHCO_3$ solution was slightly acidified with dil. HCl, the resulting precipitate was taken up in ether, and the ethereal solution, after successively washing with saturated NaCl solution and water, and drying over anhyd. Na_2SO_4, was evaporated to leave 760 mg. of the crude keto-acid (XXI). The crude product was dissolved in a solution of 1 g. of $KHCO_3$ in 40 cc. of water, and the solution was allowed to stand with 10 cc. of 30% H_2O_2 at room temperature for 17 hrs. The reaction mixture was weakly acidified with dil. H_2SO_4 under cooling with ice-water and the resulting precipitate was extracted with ether. The ether solution was washed with satd. NaCl soln. and water, dried over anhyd. Na_2SO_4, and evaporated.

The residue was dissolved in a small amount of MeOH and methylated with CH_2N_2 solution in ether. The reaction mixture, after addition of glacial AcOH to decompose the excess CH_2N_2, was washed with $NaHCO_3$ solution and water, dried over anhyd. Na_2SO_4, and evaporated. The residue (690 mg.) was then acetylated with 5 cc. each of pyridine and Ac_2O, the reaction mixture was evaporated under a reduced pressure, and the residue was recrystallized from ether-hexane to 310 mg. of needles, m.p. 173°; $[\alpha]_D^{20}$ +9°(c=0.5, $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.11; H, 8.52.

Summary

Several years ago the author isolated rhodeasapogenin, a new steroidal sapogenin, from the leaves of *Rhodea japonica* ROTH. and presumed its structure to be 5β,22b-spirostane-2β,3α-diol. In the present work it was found that isorhodeasapogenic acid is identical with tokorogenic acid and that isorhodeasapogenin has a structure of 1β,3b-dihydroxy-5β,25D-spirostane. Further, finding that rhodeasapogenin is degradated to methyl 1β,3β-diacetoxyetiocholanate, the author corrected the previously proposed structure of rhodeasapogenin to 1β,3β-dihydroxy-5β,25L-spirostane. The two reactions of isorhodeasapogenin which appeared unusual could be well explained by assigning the above structure to this compound.

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46. **Nobuo Ikekawa**: Studies on Naphthyridines. I. Synthesis of 1,6-Naphthyridine.

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Synthesis of 1,6-naphthyridines is generally not easy.[1] 1,6-Naphthyridine itself has not been obtained as yet and the syntheses of its alkyl derivatives have only been reported by Kato[2] and by Okuda.[3] The new synthetic process described in this paper is to build up another pyridine ring by utilizing the reactive methyl group in the 2- or 4-position of a pyridine ring and a carboxyl group adjacent to it, and is one of a general method for the synthesis of naphthyridines. In this paper, syntheses of 1,6-naphthyridine and its 7-methyl compound are described.

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