The mixed melting point of (XIII) with synthetic (+)-2-methylglutaric acid, m.p. 83~84°, was 83~85°, and that with synthetic (±)-2-methylglutaric acid, m.p. 80~82°, was 64~70° (see Table I).

Synthesis of (+)-2-Methylglutaric Acid——As shown in Chart 3, reduction of levulinic acid with a solution of $NaBH_4$ in 5% NaOH afforded (±)-4-hydroxyvaleric γ-lactone in 71% yield. A solution of this lactone in dehyd. EtOH was saturated with dehyd. HBr, and allowed to stand in a stoppered bottle at room temperature overnight. This operation gave ethyl (±)-4-bromovalerate in 76% yield, and refluxing with KCN in EtOH for 10 hr. led to ethyl (±)-4-cyanovalerate. Saponification of this cyanoester with KOH afforded (±)-2-methylglutaric acid, colorless prisms, m.p. 80~82° (from benzene). Resolution of this acid with strychinine by Berner's method8) gave (+)-2-methylglutaric acid, colorless prisms, m.p. 83~84°, $[\alpha]^{19}_{\mathrm{D}}$ +15.4° ±2° (c=1.075, dioxane).

The authors are indebted to Mr. S. Inaba for optical rotatory data, to Dr. T. Kubota and Mr. Y. Matsui for infrared analyses, and to the members of Analysis Room of this Laboratory for elementary microanalyses.

Summary

Attempt was made for direct determination of the absolute configuration of methyl group at C-4 and C-10 in guaiol (I) by degradation of an α,β-unsaturated ketone (IX) derived from dihydroxyguaiol (II). Since S-(+)-2-methylglutaric acid (XIII) and 4-hydroxyvaleric γ-lactone (XIV) were obtained, the C-4 methyl group in guaiol possesses the α-configuration and guaiol should be represented by (XV).

(Received November 9, 1960)

UDC 547.91.02

101. **Hitoshi Minato**: Studies on Sesquiterpenoids. II. Absolute Configuration of Guaiol. (2).[*1] Absolute Configuration of the Methyl Group at C-10 in Guaiol, and of Nepetalinic Acids and Iridolactones.

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

In the preceding paper,1),[*1] it was shown that the elucidation of the absolute configuration of guaiol was attempted and S-(+)-2-methylglutaric acid (V) and 4-hydroxyvaleric γ-lactone (VI) were obtained through (IIIa), (IIIb), and (IV) by degradation of an α,β-unsaturated ketone (II) (see Chart 1). These results led to the conclusion that the C-4 methyl group in guaiol possesses the α-configuration.[*3] In this paper will be reported the absolute configuration of the C-10 methyl group in guaiol. It was already discussed in Part I[*1] of this series that the C-10 methyl group in the ester (IV) (in Chart 1) kept its original configuration. This ester (IV), on saponification with potassium carbonate in methanol, gave S-(+)-2-methylglutaric acid (V) as well as 4-hyroxyvaleric γ-lactone (IV).

4-Hydroxyvaleric γ-lactone, b.p$_{23}$ 99~100°, thus obtained showed a negative optical rotation, $[\alpha]^{23}_{\mathrm{D}}$ −35.1°, and its infrared spectrum (film) was identical with that of the synthetic (−)-4-hydroxyvaleric γ-lactone,2) b.p$_{22}$ 97~98°, $[\alpha]^{23}_{\mathrm{D}}$ −17.2° (see Chart 2).

[*1] Prat I: This Bulletin, **9**, 619 (1961).

[*2] Fukushima-ku, Osaka (湊　均).

[*3] The terms "α" and "β" are used according to the steroidal convention.

1) K. Takeda, H. Minato: Tetrahedron Letters, No. 22, 33 (1960).

2) P.A. Levene, H.L. Haller: J. Biol. Chem., **69**, 165 (1926).

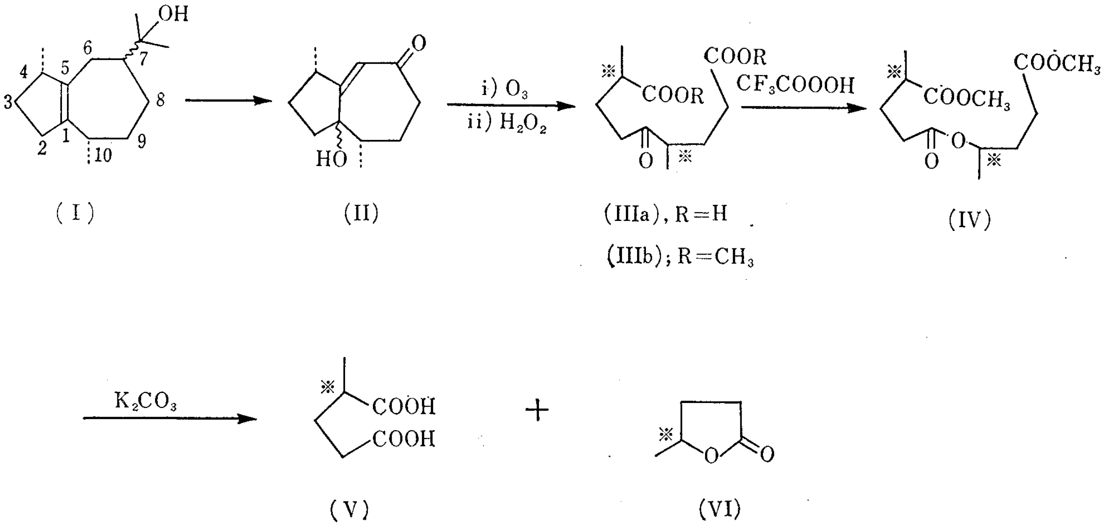

Chart 1.

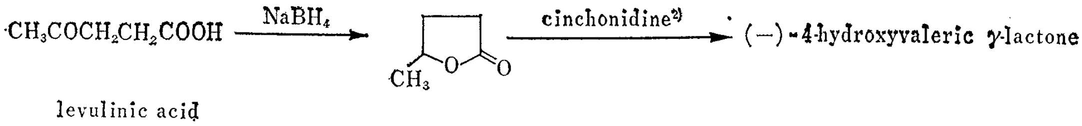

Chart 2.

The data of infrared spectra of (−)-4-hydroxybutyric γ-lactone, obtained by degradation and synthesis, and of 2- and 3-methyl-4-hydroxybutyric γ-lactone synthesized by Seidel and Stoll[3)] are cited in Table I.

Table I. Comparison of Infrared Spectra of (VI) and γ-Lactones ($\nu_{\text{max}}^{\text{film}}$ in cm^{-1})

(VI)	3570,	1773,	1461,	1421,	1387,	1345,	1300,	1279,	1223,	1199,
	1174,	1124,	1097,	1058,	1000,	940,	895,	827,	805,	—, —.
Synthetic (−)-4-hydroxyvaleric γ-lactone	3571,	1772,	1460,	1421,	1387,	1344,	1300,	1279,	1222,	1200,
	1175,	1125,	1098,	1058,	1000,	940,	896,	827,	805,	—, —.
〃 (±)-2-methyl-4-hydroxybutyric γ-lactone[3)]	3584,	1757,	1464,	—,	1383,	—,	—,	—,	—,	—,
	1176,	—,	—,	1026,	—,	915,	—,	—,	780,	708, 664.
〃 (±)-3-methyl-4-hydroxybutyric γ-lactone[3)]	3472,	1761,	1466,	—,	1385,	—,	—,	—,	—,	—.
	1175,	—,	—,	1020,	—,	938,	902,	838,	—,	—, 683.

Furthermore, the hydrazide (IX) m.p. 91.5~92.5°, $[\alpha]_D^{22}$ +16.6°, of this lactone derived from guaiol, was also identical in all respects (mixed melting point determination and infrared comparison) with that of the synthetic (−)-4-hydroxyvaleric γ-lactone, m.p. 90~91°, $[\alpha]_D^{24}$ +19.0° (see Chart 3).

In Table II, the values of the optical rotation of (VI), synthetic (−)-4-hydroxyvaleric γ-lactone, and 4-hydroxyvaleric γ-lactone obtained by Levene[2)] as well as of their hydrazides are given.

Table II.

	$[\alpha]_D$ of lactone	$[\alpha]_D$ of hydrazide
(VI)	−35.1° (in dioxane)	+16.6° (in dehyd. EtOH)
Synthetic (−)-4-hydroxyvaleric γ-lactone	−17.2° (〃)	+19.0° (〃)
〃 〃 〃[2)]	−27.75° (without solvent)	+11.6° (〃)
〃 (+) 〃 〃[2)]	+13.5° (〃)	—

---

3) C.F. Seidel, M. Stoll: Helv. Chim. Acta, **42**, 1830 (1959).

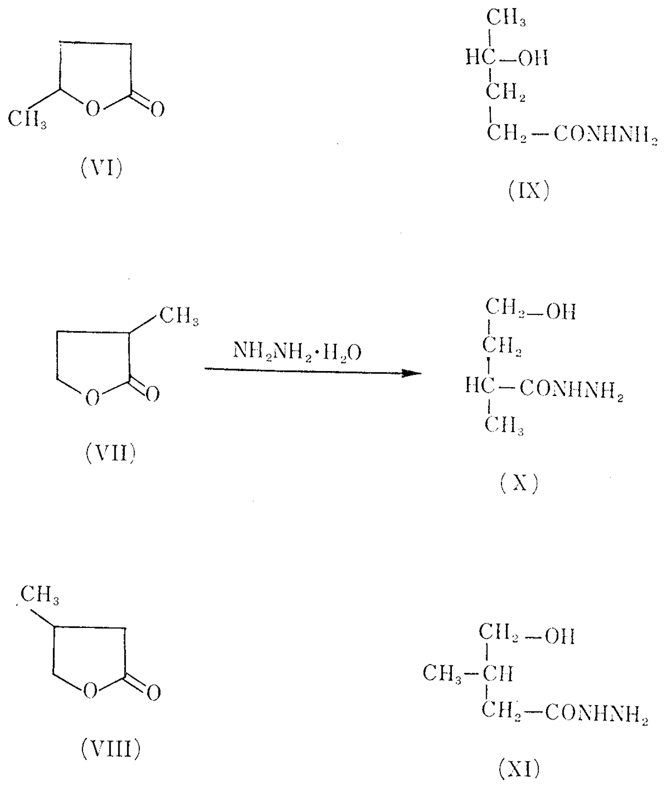

Chart 3.

In Table Ⅲ and Ⅳ, the melting points of these hydrazides and the infrared spectra of the hydrazides of (Ⅵ) and synthetic (−)-4-hydroxyvaleric γ-lactone are compared.

Table Ⅲ. Melting Point of Hydrazides

Hydrazide (Ⅸ) of (Ⅵ)		91.5~92.5°
〃	of synthetic (−)-4-hydroxyvaleric γ-lactone	90~91°, 71.5~72.5[a]
〃	〃 (+) 〃 〃	71~73°
〃	〃 (±) 〃 〃	72~74°
〃 (Ⅹ) of	〃 (±)-2-methyl-4-hydroxybutyric γ-lactone (Ⅶ)	96.5~97°[b]
〃	of (−)-2-methyl-4-hydroxybutyric γ-lactone	116~117°[b]
〃 (Ⅺ) of	synthetic (±)-3-methyl-4-hydroxybutryric γ-lactone (Ⅷ)	91~92°[b]

a) P. A. Levene : J. Biol. Chem., **69**, 170 (1926).
b) C. F. Seidel, M. Stoll : Helv. Chim. Acta, **42**, 1830 (1959).

Table Ⅳ. Infrared Spectra of the Hydrazides of (Ⅵ) and Synthetic (−)-4-Hydroxyvaleric γ-Lactone ($\nu_{\max}^{\text{CHCl}_3}$ in cm^{-1})

Hydrazide of (Ⅵ)	3510, 3349, 1670, 1627, 1485, 1456, 1426, 1379, 1357, 1318, 1274, 1147, 1123, 1095, 1070, 984, 957, 902.
〃 of synthetic (−)-4-hydroxyvaleric γ-lactone	3516, 3351, 1669, 1627, 1486, 1457, 1425, 1379, 1358, 1317, 1273, 1147, 1125, 1095, 1070, 985, 958, 903.

Since S-(−)-4-hydroxyvaleric γ-lactone was correlated with S-(+)-lactic acid by Levene[2,4] (see Chart 4), (Ⅵ) should belong to S-series. It follows, therefore, that the C-10 methyl group in guaiol possesses the α-configuration and guaiol should be represented by (Ⅻ). By the present series of experiment, all the absolute configurations of asymmetry in guaiol were established except the asymmetric center at C-7.

---

4) P.A. Levene, H.L. Haller : J. Biol. Chem., **77**, 555 (1928); P.A. Levene, T. Mori : *Ibid.*, **78**, 1 (1928); P.A. Levene : *Ibid.*, **72**, 591 (1927).

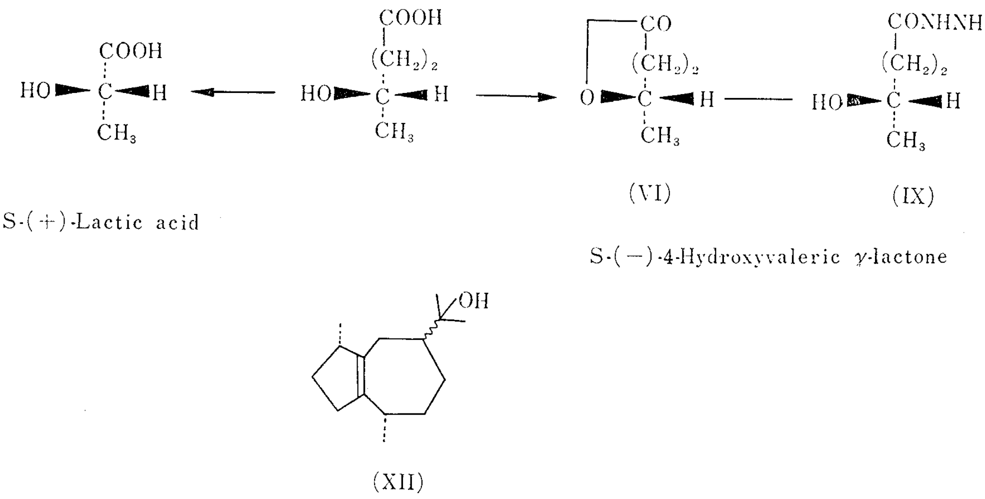

Chart 4.

As shown in Part I of this series, Djerassi's group[5),*4] reported recently that bishomonepetalinic acid (XIVa) and its acid amide (XIVb), obtained from nepetalinic acid (XVIa), m.p. 85~86°, $[\alpha]_D$ +31°, having the known configurations at C-1, C-4, and C-5 in guaiol, were identical with the degradation products of *d*-dihydroguaiol (XIII) (see Chart 5). They also assumed tentatively a β-configuration[*3] for the C-10 methyl group in guaiol from

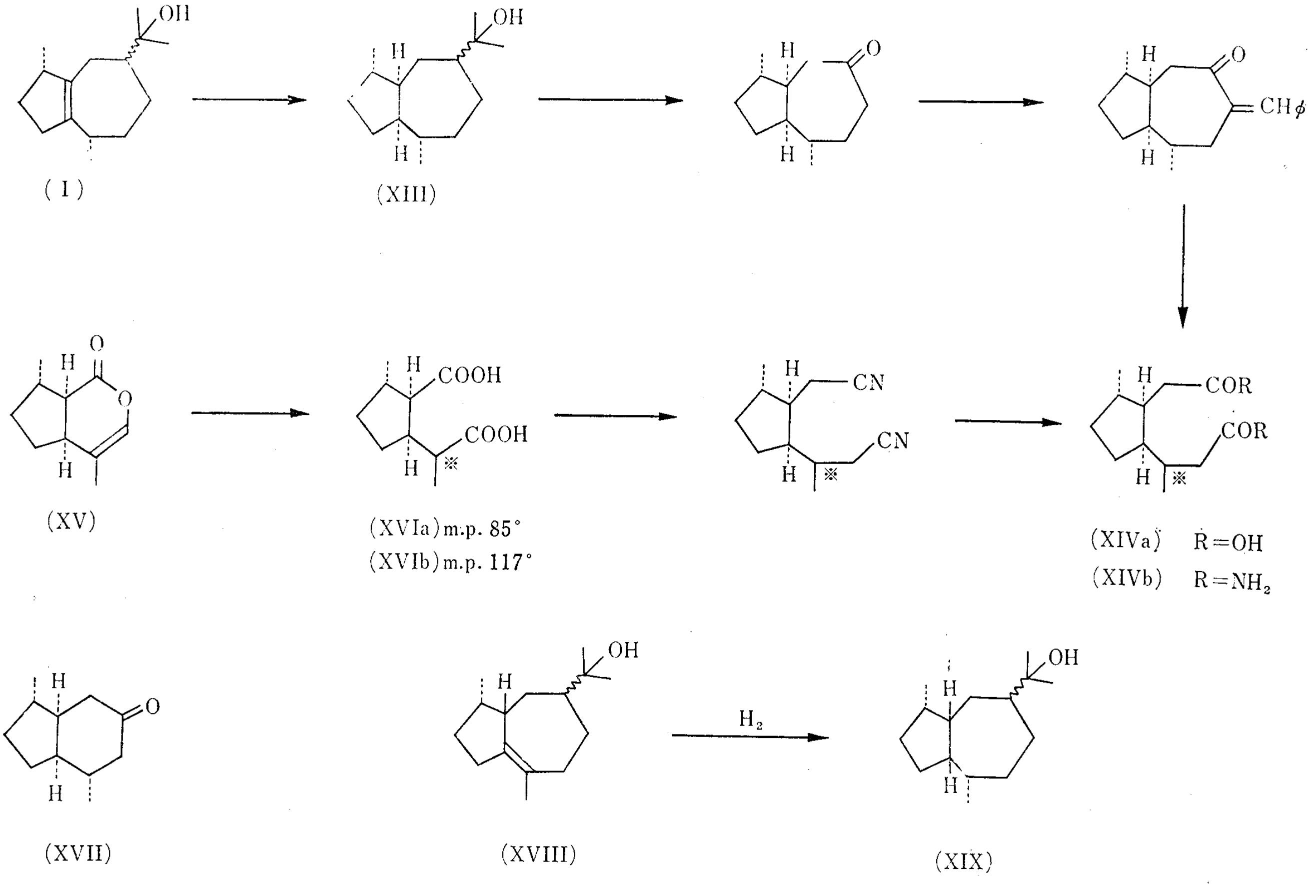

Chart 5.

[*4] The authors are very much indebted to Dr. Carl Djerassi (Stanford University) for sending them the manuscript of his paper "On the Absolute Configuration of Guaiol. Correlation with Nepetalinic Acid" before publication.

5) E. J. Eisenbraun, T. George, B. Riniker, C. Djerassi: J. Am. Chem. Soc., 82, 3648(1960).

the results of the rotatory dispersion measurement of the indanone derivative (XVII) to be derived from the above-mentioned dibasic acid (XIVa). Later, Šorm's group[6] suggested that the configuration of the C-10 methyl group in guaiol should be α-oriented from the structural elucidation of *l*-dihydroguaiol (XIX) obtained from bulnesol (XVIII).

Although the assumption on the configuration at C-10 given by Djerassi's group was found not to be correct, identity of the configurations of the methyl group at C-10 in guaiol and the methyl group at the asterisked asymmetric center in nepetalinic acid (XVIa), m.p. 85~86°, $[\alpha]_D$ +31°, had been established by them. Therefore, the configuration of the C-methyl group in (XVIa) also belongs to S-series from the results of the present experiments and the methyl group at the same position in its isomer (XVIb), m.p. 117°, $[\alpha]_D$ +16.2°, should belong to R-series. The other two isomeric nepetalinic acids, m.p. 115°, $[\alpha]_D$ +19.1°, and m.p. 111°, should be represented by (XVIc) and (XVId), respectively. Thus, the unknown configurations of four isomeric nepetalinic acids in nepetalactone (XV) series[7] were established at the same time.

Further, in iridomyrmecin series,[8] iridomyrmecin (XXb) and isoiridomyrmecin (XXa)

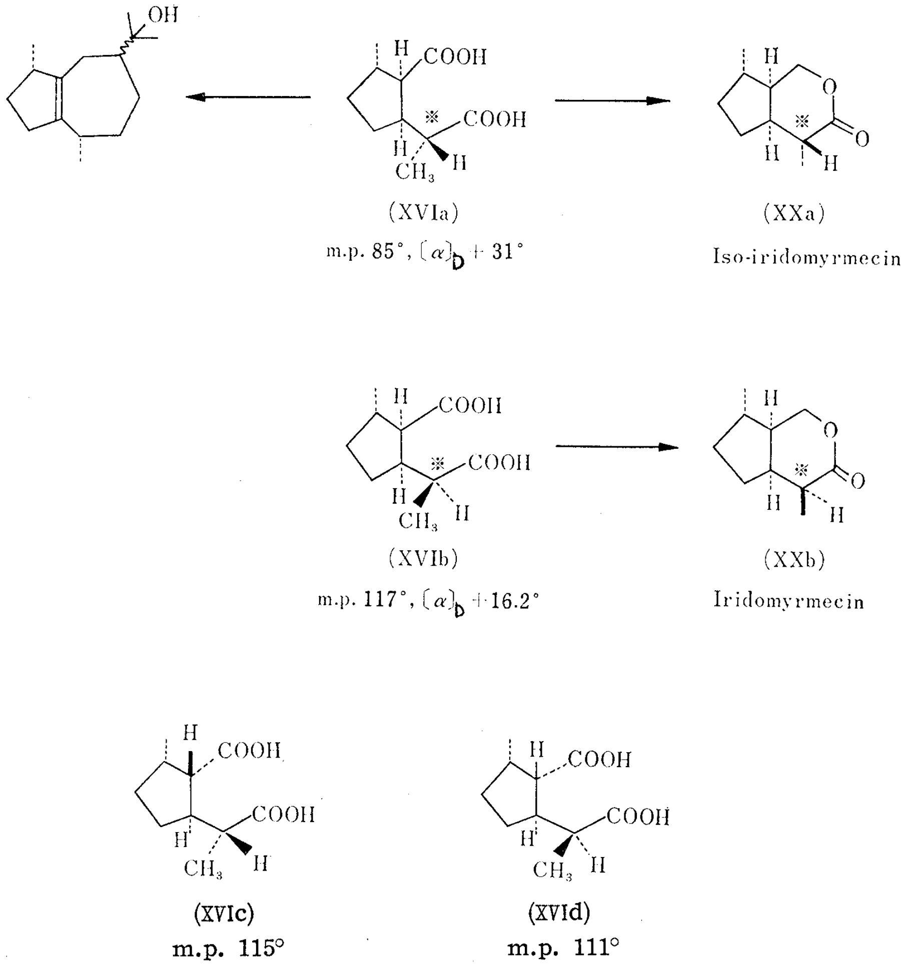

Chart 6.

---

6) L. Dolejs, A. Mironov, F. Šorm : Tetrahedron Letters, No. 11, 18 (1960).

7) S.M. McElvain, E.J. Eisenbraun : J. Am. Chem. Soc., **77**, 1599 (1955); R.B. Bates, E.J. Eisenbraun, S.M. McElvain : *Ibid.*, **80**, 3420 (1958).

8) *a*) M. Pavan : Chim. e ind. (Milan), **37**, 625, 714 (1955). *b*) R. Fusco, R. Trave, A. Vercellone : *Ibid.*, **37**, 251, 958 (1955). *c*) G.W.K. Cavill, D.L. Ford, H.D. Locksley : Chem. & Ind. (London), **1956**, 465. *d*) G.W.K. Cavill, H.D. Locksley : Austr. J. Chem., **10**, 352 (1957).

were correlated with nepetalinic acid (XVIb), m.p. 117°, [α]$_D$ +16.2°, and its isomer (XVIa), m.p. 85~86°, [α]$_D$ +31°,[8b,9] respectively. Therefore, it was concluded from the above observations that the configuration of the methyl group in asterisked asymmetric center was α-oriented in isoiridomyrmecin (XXa) and β-oriented in iridomyrmecin (XXb) (see Chart 6).

Korte, *et al.*[10] synthesized DL-iridomyrmecin (XXb) by hydrogenation of (XXI) with Raney nickel catalyst, as shown in Chart 7. Assuming that *cis*-addition of hydrogen took place during hydrogenation of (XXI), it seems that the configuration of the methyl group in asterisked asymmetric center in iridomyrmecin (XXb) is β-oriented.

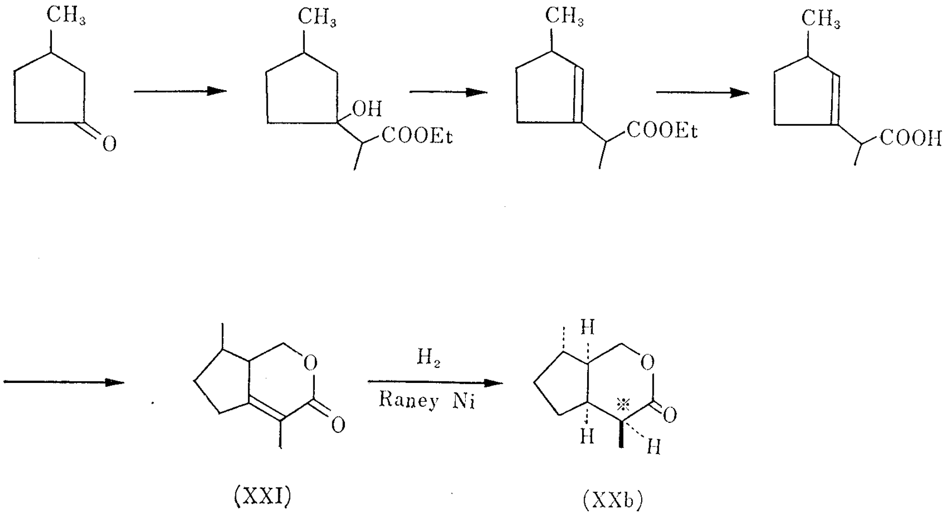

Chart 7.

Experimental[*5]

(−)-4-Hydroxyvaleric γ-Lactone (VI)——As described in Part I[*1] of this series, the ester (IV) was saponified by K_2CO_3 in MeOH to yield (+)-2-methylglutaric acid (V) and 4-hydroxyvaleric γ-lactone (VI). Distillation of (VI) gave a colorless mobile oil, b.p$_{23}$ 99~100°, [α]$^{22}_D$ −35.1°±1° (c = 4.018, dioxane). *Anal.* Calcd. for $C_5H_8C_2$: C, 59.98; H, 8.05. Found : C, 59.54; H, 8.14. IR : see Table I.

Hydrazide (IX) of (VI)——A mixture of 207 mg. of (VI) and 202 mg. of 80% $NH_2NH_2 \cdot H_2O$ was heated on a steam bath for 10 hr. The mixture was evaporated *in vacuo*, and dried over P_2O_5 in a desiccator in a reduced pressure giving colorless crystals; yield, 260 mg. Recrystallization from AcOEt gave 84 mg. of (IX), colorless micaceous crystals, m.p. 91.5~92.5°, [α]$^{22}_D$ + 16.6°±1° (c = 3.061, dehyd. EtOH). *Anal.* Calcd. for $C_5H_{12}O_2N_2$: C, 45.44; H, 9.15; N, 21.20. Found : C, 45.39; H, 9.12; N, 21.10. IR : see Table IV.

The mixed melting point of (IX) with synthetic (+)-hydrazide of 4-hydroxyvaleric γ-lactone, m.p. 90~91°, was 91~92°, and that with (±)-hydrazide of 4-hydroxyvaleric γ-lactone, m.p. 72~74°, was 50~54°.

Synthesis of (−)- and (+)-4-Hydroxyvaleric γ-Lactone——As shown in Chart 2, reduction of levulinic acid with $NaBH_4$ gave (±)-4-hydroxyvaleric γ-lactone, b.p$_{22}$ 97~98°. Resolution of this lactone with cinchonidine salt by Levene's method[2] gave (−)-lactone, [α]$^{23}_D$ − 17.2°±1° (c = 3.911, dioxane), and (+)-lactone, [α]$^{21.5}_D$ +4.2° ±2° (c=1.557, dioxone). (The cinchonidine salt of (−)-lactone was recrystallized from Me_2CO-MeOH 20 times).

Hydrazides of synthetic (−)-, (+)-, and (±)-4-hydroxyvaleric γ-lactone were respectively prepared

---

[*5] The Rudolph Photoelectric Polarimeter Model 200 was used for all determinations of optical rotations. All meting points were measured by use of Kofler block ("Monoscope" Hans Bock Co., Ltd., Frankfurt am Main, Germany) and corrected.

9) E.J. Eisenbraun, S.M. McElvain : J. Org. Chem., **22**, 976 (1957).

10) F. Korte, J. Falke, A. Zschocke : Tetrahedron, **6**, 201 (1959).

as described above : (+)-hydrazide of (−)-lactone, m.p. 90∼91°(from PrOH+AcOEt), $[\alpha]^{24}_{D}$ +19.0° ± 2° (c=1.179, dehyd. EtOH); (−)-hydrazide of (+)-lactone, m.p. 71∼73°, $[\alpha]^{21}_{D}$ −3.3° ± 2° (c = 0.924, dehyd. EtOH); (±)-hydrazide of (±)-lactone, m.p. 72∼74°.

The author expresses his deep gratitude to Dr. K. Takeda, Director of this Laboratory, for his unfailing guidance throughout the course of this work. The author is also indebted to Mr. S. Inaba for optical rotatory data, to Mr. Y. Matsui for infrared analyses, and to the members of Analysis Room of this Laboratory for elementary microanalyses.

Summary

Since S-(+)-2-methylglutaric acid (V) and S-(−)-4-hydroxyvaleric γ-lactone were obtained by degradation of an α,β-unsaturated ketone (II) derived from guaiol (I), the configurations of the methyl groups at C-4 and C-10 in guaiol are both α-oriented and guaiol should be represented by (XII). Further, from these results the stereochemistry of four isomeric nepetalinic acids and iridolactones was elucidated.

(Received November 9, 1960)

UDC 547.92 : 582.572.2

102. Ken'ichi Takeda, Tameto Okanishi, Kanzo Sasaki, and Ariyoshi Shimaoka :
Studies on the Steroidal Components of Domestic Plants. XXXI.[1)]
Constituents of *Reineckia carnea* KUNTH. (3).
Pentologenin and Kitigenin.

(*Research Laboratory, Shionogi & Co., Ltd.*[*1])

In the previous paper,[2)] it was reported that kitigenin (I), isolated together with diosgenin from the whole plant of *Reineckia carnea* KUNTH, is a new tetrahydroxy-25D-sapogenin on the basis of its analysis, formation of a triacetate, and the infrared spectra of the sapogenin and its acetate. Subsequently, β-sitosteryl *d*-glucoside and β-sitosterol[3)] were also isolated from the same source.

Recently, as a sufficient amount of the plant material was obtained, the isolation of sapogenins was further reinvestigated and two new sapogenins, m.p. 240∼245° and m.p. 320°(decomp.), were isolated. The former has not yet been studied in detail, because of the lack of material. The latter, m.p. 320°(decomp.), $[\alpha]^{25}_{D}$ −54.5° ($CHCl_3$-MeOH=1:1), corresponding to the formula $C_{27}H_{44}O_7$, present in both epigeous part and rhizome, was named pentologenin, and its infrared spectrum showed neither a ketonic band nor an isolated double bond, but a broad band of hydroxyl function. The characteristic absorption bands of the sapogenin side-chain were observed at 980, 915, 898, and 860 cm^{-1}, and the comparison of intensity of the bands at 915 and 898 cm^{-1} showed that the sapogenin belongs to a 25D-sapogenin.

Acetylation of pentologenin with acetic anhydride and pyridine followed by chromatography gave three substances of m.p. 166∼168°, 149∼153°, and 238∼241°. The analytical

---

[*1] Imafuku, Amagasaki, Hyogo-ken (武田健一, 岡西為人, 佐々木勘造, 島岡有昌).

1) Part XXX. K. Takeda, T. Okanishi, H. Ōsaka, A. Shimaoka, N. Maezono : This Bulletin, **9**, 388 (1961).

2) K. Takeda, T. Okanishi, A. Shimaoka : Yakugaku Zasshi, **75**, 560 (1955).

3) T. Okanishi, A. Shimaoka : Ann. Rept. Shionogi Research Lab., **10**, 1391 (1960).