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The Constituents of Valerian Root. The Structures of Four New Iridoid Glycosides, Kanokoside A, B, C, and D from the Root of "Hokkaikisso"

Four new iridoid glycosides, kanokoside A, B, C and D have been isolated from valerian root cultivated in Hokkaido area under the name of "Hokkaikisso". From chemical and spectral evidence, their structures have been elucidated to be I, II, III and IV, respectively.

Keywords——iridoid glycoside; valerian root; Valerianaceae; Hokkaikisso; kanokoside A; kanokoside B; kanokoside C; kanokoside D; NMR spectrum; mass spectrum

Numerous iridoid compounds have been isolated from valerian root by several groups of workers in recent years.[1]

In the previous paper of this series, we described the structure of patrinoside,[2] isolated from the root of *Patrinia scabiosaefolia* Fischer (Valerianaceae). This paper concerns with the structures of four new iridoid glycosides, named kanokoside A (I, yield 0.28%), B (II, 0.0048%), C (III, 0.13% as the acetate) and D (IV, 0.18% as the acetate) isolated together with the known iridoid glycosides, patrinoside and valerosidate[1b] from the valerian root cultivated in Hokkaido area under the name of "Hokkaikisso.[3]

From the methanol extract of the root, I and II were obtained as the hygroscopic powders. However, III and IV were isolated as the corresponding acetates, since the isolation of two compounds was unsuccessful by column, preparative thin-layer or droplet countercurrent chromatographies. These compounds gave a dark brown colour and a strong odor of isovaleric acid by heating with mineral acids, showing that they are iridoid glycosides having an isovaleryl moiety.

The proton magnetic resonance (PMR) spectrum of I (in D_2O/DSS) showed the signals at δ 0.90 (6H, d, $J=6$ Hz) attributable to gem-dimethyl of isovaleryl group and at δ 3.55, 4.08 (each 1H, d, $J=3$ Hz) attributable to epoxy protons. Two signals at δ 6.23 (1H, broad s) and at δ 6.46 (1H, broad s) were assigned to an olefinic proton at C–3 and an acylated acetal proton at C–1 of the iridoid skeleton, respectively. Acetylation of I with acetic anhydride and pyridine afforded a pentaacetate (VI) as an amorphous powder, mp 58—62°, $C_{31}H_{42}O_{17}$,[5] [*m/e*: 670 (M^+-H_2O), 584 ($M^+-(CH_3)_2CHCH_2COOH$), 441(XIII)], $[\alpha]_D -87.5°$(MeOH). Infrared (IR) spectrum: 3450 cm^{-1} (tertiary OH), 1750 cm^{-1} (ester), 1680 cm^{-1} (enol ether). The PMR spectral data are given in Table I. Enzymatic hydrolysis of I with β-glucosidase followed by acetylation gave the aglycone acetate (V) as colourless needles, mp 87°, $C_{19}H_{26}O_9$, [*m/e*: 398 (M^+), 296 ($M^+-(CH_3)_2CHCH_2COOH$)], $[\alpha]_D$ −136.8° (MeOH). The PMR spectrum of V showed the presence of two acetyl groups at δ 2.04—2.13, two epoxy protons at δ 3.39 and 3.82 (each 1H, d, $J=3$ Hz), and two acetoxy methylene groups at δ 4.33 (2H, s) as well as at δ 4.38 and 4.88 (each 1H, d, $J=13$ Hz).

Catalytic hydrogenation of V over palladized charcoal in methanol furnished a monoacetate (VII) as colourless needles, mp 56—60°, $C_{17}H_{24}O_7$, [*m/e*: 340 (M^+), 238 ($M^+-(CH_3)_2$-

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[1] *a*) E. Stahl and W. Schild, *Tetrahedron Lett.*, **1969**, 1053; *b*) H. Inouye, S. Uesato, T. Singu and P.W. Thies, *Tetrahedron*, **30**, 2325 (1974); *c*) P.W. Thies, E. Finner and F. Rosskopf, *Tetrahedron*, **29**, 3213 (1973); *d*) S.S. Popov, N.V. Handjiva and N.L. Marekov, *Comptes rendus de l'Académie bulgare des Sciences*, **26**, 913 (1973).

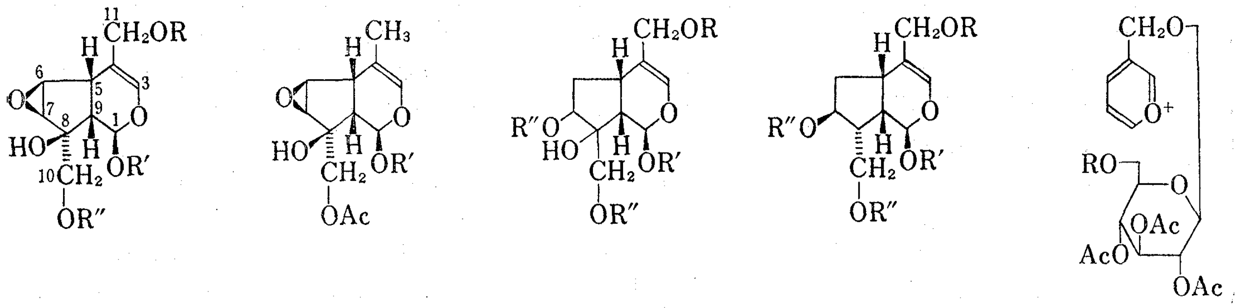
[2] H. Taguchi and T. Endo, *Chem. Pharm. Bull.* (Tokyo), **22**, 1935 (1974).

[3] H. Hikino, Y. Hikino, H. Kato, Y. Takeshita and T. Takemoto, *Yakugaku Zasshi*, **91**, 766 (1971).

Table I. The PMR Data of V—VII (δ values in $CDCl_3$, J values in Hz)

Compound	C–1	C–3	C–5	C–6	C–7	C–9	C–10	C–11	–$OCOCH_3$
V	6.50 (br. s)	6.50 (br. s)	3.08 (m)	3.82 (d, $J=3$)	3.39 (d, $J=3$)		4.33 (s)	4.38, 4.80 (d, $J=13$)	2.04—2.13 (×2)
V[a)]	7.09 (s)	6.82 (br. s)	3.42 (d, $J=9$)	4.25 (d, $J=3$)	3.96 (d, $J=3$)	2.58 (d, $J=9$)	4.76 (s)	5.12, 4.66 (d, $J=13$)	2.13—2.22 (×2)
VI	6.53 (br. s)	6.40 (br. s)	3.06 (d, $J=9$)	3.88 (d, $J=3$)	3.42 (d, $J=3$)		4.35 (s)		1.97—2.21 (×5)
VII	6.48 (s)	6.13 (m)	2.93 (d, $J=9$)	3.70 (d, $J=3$)	3.38 (d, $J=3$)		4.33 (s)	1.72 (t-like, $J=1$)	2.13 (×1)

a) Measured in pyridine-d_5.
s=singlet, d=doublet, t=triplet, m=multiplet, br=broard.



I : R=glucose,
R″=H
III : R=gentiobiose,
R″=H
V : R=R″=Ac
VI: R=gluc(OAc)$_4$,
R″=Ac
X : R=genti(OAc)$_7$,
R″=Ac

VII

II : R=glucose,
R″=H
VIII: R=gluc(OAc)$_4$,
R″=Ac
IX: R=R″=Ac

IV : R=gentiobiose,
R″=H
XI : R=genti(OAc)$_7$,
R″=Ac
XII: R=R″=Ac

XIII : R=Ac
XIV: R=gluc(OAc)$_4$

Ac=$COCH_3$ R′=$COCH_2CH(CH_3)_2$

Chart 1

$CHCH_2COOH$)], $[\alpha]_D$ −129° (MeOH), which was also given by the same reaction from VI, indicating that the sugar moiety is linked to C–11 OH group. The structure of I was clarified by the spin decoupling experiments of V (in pyridine-d_5). On irradiation at δ 3.42 (1H, d, $J=9$ Hz, C_5–H), the doublet at δ 2.58 (C_9–H) and the broad singlet at δ 6.82 (C_3–H) were changed into a broad singlet and a sharp singlet, respectively, and a broad doublet at δ 4.25 (C_6–H, $J=3/<1$Hz) was also changed into a sharp doublet. These observations are in accord with the structure (V). The coupling constant ($J=9$ Hz) between C–5 and C–9 protons indicates the *cis* relationship between these protons and that ($J<1$ Hz) between C–5 and C–6 protons indicates *trans* relationship between these protons, *i.e.*, β-orientation of epoxide ring.[4] Furthermore, the structure of I was confirmed by intermolecular nuclear Overhauser effects (NOE) in VII (in $CDCl_3$): *i.e.*, irradiation at C–10 methylene protons caused 20% and 15.7% increase in the integrated intensity of the C–7 and C–1 proton signals, respectively, indicating the α-orientation of C–1 proton and C–8 oxygenated methylene group. From the above results, the structure of kanokoside A was established to be I.

II also revealed the signals for gem-dimethyls of the isovaleryl group at δ 0.93 (6H, d, $J=6$ Hz), the olefinic proton of C–3 position at δ 6.18 (1H, d, $J=3$ Hz) and an acetal proton at δ 6.40 (1H, m) in the PMR spectrum (in D_2O/DSS). Acetylation of II with acetic anhy-

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4) *a*) T.J. Danielson, E.M. Hawes and C.A. Bliss, *Can. J. Chem.*, **51**, 760 (1973); *b*) T.A. Geissman, W. F. Knaack, Jr. and J.O. Knight, *Tetrahedron Lett.*, **1966**, 1245.

dride and pyridine afforded a pentaacetate (VIII), mp 110—111°, $C_{33}H_{46}O_{18}$,[5] $[\alpha]_D$ −27.7° (EtOH), IR ν_{max}^{KBr} cm^{-1}: 3450 (tertiary OH), 1755 (ester), 1670 (enol ether), PMR (δ in $CDCl_3$): 1.96—2.21 (18H, s, 6×OAc), 6.26 (1H, d, J=4 Hz, C_1–H), 6.40 (1H, br., s, C_3–H). The mass spectrum of VIII showed the fragment ions at m/e 628 ($M^+-(CH_3)_2CHCH_2COOH$) and 441 (XIII), indicating that the structure of VIII has the same dihydropyrane ring moiety as V.

Enzymatic hydrolysis of II with β-glucosidase followed by acetylation gave an oily substance (IX), $C_{21}H_{30}O_{10}$,[5] [m/e: 340 ($M^+-(CH_3)_2CHCH_2COOH$), 280 (340-AcOH)], whose PMR spectrum showed the presence of two acetoxy methylene groups at δ 4.20 (2H, s, C_{10}-H) as well as at δ 4.37 and 4.56 (each 1H, d-pair, J=13 Hz, C_{11}–H) and a secondary acetoxy methine at δ 5.01 (1H, t-like, J=4 Hz). The structure of II was clarified by the spin decoupling experiments of IX. On irradiation at δ 2.10 (C–6 methylene protons), the triplet at δ 5.01 was changed into a singlet. On the other hand, on irradiation at δ 2.85 (m, C_5–H), the broad singlet of C–3 proton was changed into a sharp singlet, while the signal at δ 5.01 showed no change. These observations indicate that the secondary hydroxy group is linked to C–7 position and the tertiary hydroxy group is linked to C–8 position. From the above data, the structure of kanokoside B was assumed to be II. The stereostructure of II has not yet been defined due to shortage of the material.

The fraction containing III and IV afforded, on acetylation with acetic anhydride and pyridine, corresponding octaacetate (X), mp 102—105°, $C_{43}H_{58}O_{25}$,[5] [m/e: 872 ($M^+-(CH_3)_2CHCH_2COOH$), 729 (XIV), 619, 331], $[\alpha]_D$ −51.5° (MeOH), PMR (δ in $CDCl_3$): 2.00—2.19 (24H, s, 8×OAc), 6.45 (1H, d, J=1 Hz, C_3–H), 6.54 (1H, br., s, C_1–H) and nonaacetate (XI), mp 179—181°, $C_{45}H_{62}O_{25}$,[5] [m/e: 902 ($M^+-(CH_3)_2CHCH_2COOH$), 729 (XIV), 619, 331], $[\alpha]_D$ −30.0° (MeOH), PMR (δ in $CDCl_3$): 1.96—2.13 (27H, s, 9×OAc), 5.96 (1H, d, J=5 Hz, C_1–H), 6.45 (1H, d, J=1.5 Hz, C_3–H).

The PMR spectra of X and XI closely resemble those of V and patrinoside pentaacetate, respectively, except the number of acetyl groups and the protons of secondary acetoxy methines on the sugar moiety. Enzymatic hydrolysis of the fractions containing III and IV with β-glucosidase followed by acetylation gave two corresponding aglycone acetates, V and XII, suggesting that III and IV have the same aglycone as I and patrinoside, respectively. The fragments at m/e 729 (XIV) and 619 in the mass spectra of X and XI indicate that the two moles of glucose are linked to C–11 hydroxy group of the corresponding aglycones.

Treatment of X and XI with CH_3I/DMSO/NaH (Hakomori's method) afforded the same substance, which was identified with methyl gentiobioside hepta methyl ether by gas chromatography and furthermore it gave on methanolysis methyl 2,3,4,6-tetra-*O*-methyl-glucopyranoside and methyl 2,3,4-tri-*O*-methyl-glucopyranoside in almost equal amounts on GLC. On the other hand, the PMR spectra of X or XI showed two anomeric protons of the sugar moiety at δ 4.58 (d, J=7 Hz) and 4.70 (d, J=7 Hz) or at δ 4.54 (d, J=7 Hz) and 4.58 (d, J=7 Hz) which prove the β-linkage between two glucose moieties and between the sugar moiety and aglycone. Therefore, the structure of kanokoside C and D were established to be III and IV, respectively.

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[5] Elemental analysis of the compounds gave satisfactory results.