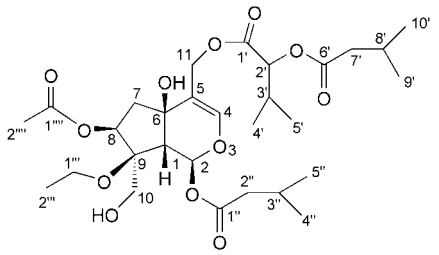
New Iridoid Triesters from *Valeriana jatamansi*

by **Lili Yu**[a]), **Rong Huang**[b]), **Changri Han**[c]), **Yuping Lv**[a]), **Yong Zhao**[a]), and **Yegao Chen***[a])

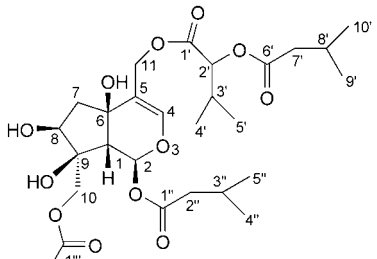
[a]) Department of Chemistry, Yunnan Normal University, Kunming 650092, Yunnan, P. R. China (phone: +86-871-5516062; fax: +86-871-5516061; e-mail: ygchen48@hotmail.com)
[b]) Experimental Center, Yunnan University, Kunming 650031, Yunnan, P. R. China
[c]) Department of Chemistry, Hainan Normal University, Haikou 571158, Hainan, P. R. China

Two new iridoid triesters, valeriotriates A (**1**) and B (**2**), were isolated from the roots of *Valeriana jatamansi* JONES. Their structures were elucidated by HR-ESI-MS and 1D- and 2D-NMR spectroscopy.

Introduction. – A considerable number of studies have been performed on plants of the *Valeriana* genus in the family of Valerianaceae. These investigations have yielded iriodoids, sesquiterpenoids, lignans, and alkaloids with pharmacological properties, including sedative, cytotoxic, antitumor, antioxidant, and vasorelaxant activities [1–5]. *Valeriana jatamansi* JONES, an annual herb distributed in the southwestern area of the People's Republic of China, was known in Chinese folk medicine to have tranquilizing hypnotic and antiviral activities [6–8]. Previous chemical investigation of *V. jatamansi* revealed the presence of iriodoids, sesquiterpenoids, and an essential oil [2][6][8]. Further investigation of the roots of this plant led now to the isolation of two new iridoid triesters, valeriotriates A (**1**) and B (**2**). It is noteworthy that few naturally occurring 6-hydroxy-substituted iridoids were found in the plants of the genus *Valeriana.* We herein report the isolation and characterization of **1** and **2**.



1 [1])



2 [1])

Result and Discussion. – Valeriotriate A (**1**) was isolated as a colorless oil. The molecular formula $C_{29}H_{46}O_{12}$ was deduced by HR-ESI-MS ($[M+Na]^+$ at m/z 609.2892), and its structure was determined as (1β,2β,6β,8β,9β)-8-(acetyloxy)-9-ethoxy-6-hydroxy-9-(hydroxymethyl)-5-{{[α-(isovaleryloxy)isovaleryl]oxy}methyl}-3-oxabicyclo[4.3.0]non-4-en-2-yl isovalerate[1]) by 1D- and 2D-NMR spectroscopy (*Table*).

[1]) Trivial name and numbering; for systematic names, see *Exper. Part.*

Table. *^{1}H- and ^{13}C-NMR Data* (CD_3COCD_3) *of Valeriotriates A*[1]) (**1**) *and B*[1]) (**2**). δ in ppm, J in Hz.

	1		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
H–C(1)	2.68 (*s*)	55.7	2.72 (*d*, *J* = 1.8)	55.6
H–C(2)	6.55 (*d*, *J* = 1.8)	91.3	6.65 (*d*, *J* = 1.8)	89.6
H–C(4)	6.59 (*s*)	144.8	6.57 (*s*)	143.4
C(5)		115.3		115.9
C(6)		71.5		69.3
CH_2(7)	2.53 (*dd*, *J* = 13.5, 7.4), 2.06 (*m*)	43.4	2.37 (*dd*, *J* = 13.2, 5.0), 2.11 (*m*)	43.4
H–C(8)	4.95 (*dd*, *J* = 7.4, 7.0)	81.1	3.82 (*dd*, *J* = 7.5, 5.1)	72.0
C(9)		82.0		79.2
CH_2(10)	3.60 (*m*)	75.2	4.14 (*d*, *J* = 11.9), 4.04 (*d*, *J* = 11.9)	66.7
CH_2(11)	4.74 (*d*, *J* = 12.9), 4.80 (*d*, *J* = 12.9)	63.8	4.74 (*d*, *J* = 12.5), 4.78 (*d*, *J* = 12.5)	62.7
C(1′)		170.8		170.2
H–C(2′)	4.86 (*d*, *J* = 4.3)	77.9	4.80 (*d*, *J* = 4.3)	77.3
H–C(3′)	2.10 (*m*)	31.4	2.09 (*m*)	30.7
CH_3(4′)	0.95 (*d*, *J* = 6.7)[a])	19.8	0.94 (*d*, *J* = 6.5)[c])	19.1
CH_3(5′)	0.97 (*d*, *J* = 6.7)[a])	17.5	0.96 (*d*, *J* = 6.5)[c])	18.2
C(6′)		173.6		173.1
CH_2(7′)	2.28 (*m*)	44.2	2.29 (*m*)	43.4
H–C(8′)	2.02 (*m*)	26.9	2.24 (*m*)	26.2
Me(9′)	0.96 (*d*, *J* = 6.7)[a])	23.3[b])	0.97 (*d*, *J* = 6.5)[c])	22.5
Me(10′)	0.99 (*d*, *J* = 6.7)[a])	23.3[b])	0.98 (*d*, *J* = 6.5)[c])	22.5
C(1″)		172.2		171.6
CH_2(2″)	2.24 (*m*)	44.3	2.28 (*m*)	43.4
H–C(3″)	2.23 (*m*)	27.1	2.08 (*m*)	26.4
Me(4″)	0.96 (*d*, *J* = 6.7)[a])	23.2[b])	0.97 (*d*, *J* = 6.5)[c])	22.6
Me(5″)	0.97 (*d*, *J* = 6.7)[a])	23.2[b])	0.99 (*d*, *J* = 6.5)[c])	22.6
CH_2(1‴) or C(1‴)	3.55 (*q*, *J* = 7.0)	68.2		171.1
Me(2‴)	1.17 (*t*, *J* = 7.0)	16.0	2.05 (*s*)	20.8
C(1⁗)		171.6		
Me(2⁗)	2.05 (*s*)	21.6		

[a]) – [c]) May be exchangeable in each column.

The ^{1}H- and ^{13}C-NMR (*Table*) and DEPT spectra of **1** revealed the presence of 8 Me, 6 CH_2, and 8 CH groups and 7 quaternary C-atoms. The resonances at δ(H) 6.55 (*d*, *J* = 1.8 Hz, 1 H), 6.59 (*s*, 1 H), 4.74 and 4.80 (each *d*, *J* = 12.9 Hz, 1 H), and 4.95 (*dd*, *J* = 7.4, 7.0 Hz, 1 H), and δ (C) 91.3 (CH), 144.8 (CH), 115.3 (C), 63.8 (CH_2), and 81.1 (CH) indicated that **1** has a hydroxydihydrovaltrate-type iriodoid skeleton [8][9]. A Me *s* at δ (H) 2.05 was assigned to an acetate residue and the signal at δ (C) 171.6 to the C=O of this acetate residue, on the basis of its long-range ^{13}C,^{1}H correlation to the Me signal (δ (H) 2.05). This C=O signal showed a three-bond correlation with H–C(8) at δ (H) 4.95 in the HMBC spectrum, revealing the presence of an acetate group at C(8)[1]). The five C-signals due to 2 Me (δ (C) 23.2 ×), 1 CH_2 (δ (C) 44.2) linked to a C=O, 1 CH (δ (C) 27.1), and 1 ester C=O (δ (C) 172.2) suggested the presence of an isovalerate group in **1** [4][8][10]. The HMBC correlation between H-C(2) at δ (H) 6.55 and the ester C=O (δ (C) 172.2) of the isovalerate group revealed the site of attachment of the isovalerate function to be at C(2). Additionally, the 10 C-signals due to 4 Me (δ (C) 18.1, 19.8, and 23.3 ×), 1 CH_2 (δ (C) 44.2), 2 CH ((δ (C) 31.4 and 26.9), 1 OCH (δ (C) 77.9), and 2 ester C=O groups (δ (C) 170.8 and 173.6) and a long-range correlation between the latter 2 ester C=O signals and δ (H) 4.86 (*d*, *J* = 4.3 Hz, 1 H) suggested the presence of an α-(isovaleryloxy)isovaleryloxy group in of **1** [5][9]. The HMBC experiments showed a long-range correlation between one ester C=O of the α-(isovaleryloxy)isovaleryloxy group (δ (C)170.8) and 2 H-atoms at δ (H) 4.74 and 4.80, reavealing the site of attachment of the α-(isovaleryloxy)isovaleryloxy function to be at C(11). The presence of an EtO group was indicated by the signals at δ (C) 68.2 (CH_2) and 16.0 (Me), and δ (H) 3.55 (*q*, *J* = 7.0 Hz, 2 H) and 1.17 (*t*, *J* = 7.0 Hz, 3 H), which was

assigned to be at C(9) by the correlation between δ (H) 3.55 and an δ (C) 82.0 of an oxygenated quaternary C-atom in the HMBC experiments. Thus, all the substitution positions were established.

The relative configuration of **1** was determined from the 2D-NOESY plot. Based upon comparison of NMR data of **1** with those reported for valepotriates [4][8], the β-orientation was attributed to H–C(1) and OH–C(6). The NOEs H–C(2)/CH_2(10) and CH_2 (10)/H–C(8) established the α-orientation of H–C(2), CH_2 (10), and H–C(8).

Valeriotriate B (**2**) was obtained as a colorless oil. The HR-ESI-MS established the molecular formula $C_{27}H_{42}O_{12}$ (($[M+Na]^+$ at m/z 581.2574) and its structure was determined as (1β,2β,6β,8β,9β)-10-(acetyloxy)-6,8,9-trihydroxy-5-{{[α-(isovaleryloxy)-isovaleryl]oxy}methyl}-3-oxabicyclo[4.3.0]non-4-en-2-yl isovalerate[1]) by 1D- and 2D-NMR spectroscopy (*Table*).

The ^{1}H-NMR, ^{13}C-NMR, and DEPT spectra of **2** revealed the presence of 7 Me, 5 CH_2, and 8 CH groups and 7 quaternary C-atoms and was very similar to that of **1**, also showing the presence of a hydroxydihydrovaltrate-type iriodoid skeleton with an α-(isovaleryloxy)isovaleryloxy residue at C(11) and an isovaleryloxy group at C(2)[1]). The acetate residue (δ (H) 2.05 (*s*, 3 H); δ (C) 171.1 (C=O and 20.8 (Me)) in **2** showed a long-range correlation between δ (C) 171.1 (C=O) and δ (H) 4.14 and 4.04 (each *d*, J = 11.9 Hz, 1 H), revealing the site of attachment of the acetate function to be at C(10). Thus, all the substitution positions of **2** were established.

The relative configuration of **2** was determined from the 2D-NOESY data. Based upon comparison of NMR data of **2** with those reported for valepotriates [4][8] and **1**, the β orientation was attributed to H–C(1) and OH–C(6). The NOEs; H–C(2)/CH_2(10) and CH_2(10)/H–C(8) established the α-orientation of H–C(2), CH_2(10), CH_2(8).

This investigation was supported by a grant (No. 30160093) from the *National Science Foundation of China*, the *Excellent Young Teachers Program* (No. 2003 192) of MOE, China, and a grant (No. 2000 C007) for international collaborative research by the *Yunnan Provincial Committee of Science and Technology*, China.

Experimental Part

General. Column chromatography (CC): silica gel (200–300 mesh) from *Qingdao Marine Chemical Factory*, Qingdao, P. R. China. TLC: silica gel GF_{254} from *Qingdao Marine Chemical Factory*. ^{1}H-, ^{13}C-, and 2D-NMR Spectra: *Bruker DRX-AV-500* spectrometer; δ in ppm, J in Hz. MS: *Applied Biosystems API-Qstar-Pulsar-LC/TOF* mass spectrometer; in m/z (rel. int.).

Plant Material. The roots of *V. jatamansi* JONES were collected at Gejiu, Yunnan Province, P. R. China, in July, 2003. The voucher specimen was deposited at the Department of Chemistry, Yunnan Normal University (No. 20030712).

Extraction and Isolation. The dried and crushed roots (4 kg) were extracted 4 × with 95% aq. EtOH at r.t. The extract was concentrated and partitioned with petroleum ether and $CHCl_3$ successively. The $CHCl_3$ extract (50 g) was subjected to CC (silica gel, petroleum ether/acetone gradient): *Fr. 1–13*. *Fr. 12* (15 g) was further subjected to CC (silica gel, petroleum ether/AcOEt 9 :1; then *Sephadex LH-20*, MeOH/$CHCl_3$ 95 :5): **1** (40 mg) and **2** (27 mg).

Valeriotriate A (*= 3-Methyl-2-(3-methyl-1-oxobutoxy)butanoic Acid [(1*S*,4a*R*,6*S*,7*S*,7a*S*)-6-Acetyloxy)-7-ethoxy-1,4a,5,6,7,7a-hexahydro-4a-hydroxy-7-(hydroxymethyl)-1-(3-methyl-1-oxobutoxy)cyclopenta[*c*]pyran-4-yl]methyl Ester*; **1**). Colorless oil. FAB-MS: 467 ($[M+1-HOOCCH_2CH(CH_3)_2-H_2O]^+$), 407, 283, 223, 177, 85 (100). HR-ESI-MS: 609.2892 ($C_{29}H_{46}NaO_{12}^+$; calc. 609.2892).

*Valeriotriate B (= 3-Methyl-2-(3-methyl-1-oxobutoxy)butanoic Acid [(1*S*,4a*R*,6*S*,7*S*,7a*S*)-7-[(Acetyloxy)-methyl]-1,4a,5,6,7,7a-hexahydro-4a,6,7-trihydroxy-1-(3-methyl-1-oxobutoxy)cyclopenta[*c*]pyran-4-yl]methyl Ester*; **2**). Colorless oil. FAB-MS: 439 (100, $[M+1-HOOCCH_2CH(CH_3)_2-H_2O]^+$), 421 ($[439-H_2O]$), 379, 321, 237, 177, 85; HR-ESI-MS: 581.2574 ($C_{27}H_{42}NaO_{12}^+$; calc. 581.2573).

REFERENCES

[1] A. L. Piccinelli, S. Arana, A. Caceres, R. E. Bianca, R. Sorrentino, L. Rastrelli, *J. Nat. Prod.* **2004**, *67*, 1135.
[2] D. S. Ming, D. Q. Yu, Y. Y. Yang, C. H. He, *Tetrahedron Lett*. **1997**, *38*, 5205
[3] K. K. Bach, F. Ghia, K. B. G. Torssell, *Planta Med.* **1993**, *59*, 478
[4] P. W. Thies, E. Finner, S. David, *Planta Med*. **1981**, *41*, 15
[5] C. Bounthanh, C. Bergmann, J. P. Beck, M. Haag-Berrurier, R. Anton, *Planta Med.* **1981**, *41*, 21
[6] Z. Y. Wang, F. D. Niu, *Acta Bot. Yunn.* **1980**, *2* , 58
[7] R. W. Zhang, H. X. Wu, Q. H., Li, *Acta Bot. Yunn.* **1986**, *8* , 107
[8] Y. P. Tang, X. Liu, B. Yu, *J. Nat. Prod.* **2002**, *65*, 1949
[9] B. P. Mikhova, N. V. Handjieva, S. S. Popov, S. L. Spassov, *J. Nat. Prod.* **1987**, *50*, 1141
[10] F. Granicher, P. Christen, P. Kamalaprija, U. Burger, *Phytochemistry* **1995**, *38*, 103

Received December 27, 2004