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A new iridoid tetraester from *Valeriana jatamansi*

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A new iridoid tetraester, namely valeriotetrate A was isolated from the roots of *Valeriana jatamansi* Jones, together with the known iridoids IVHD-valtrate and valerosidate.

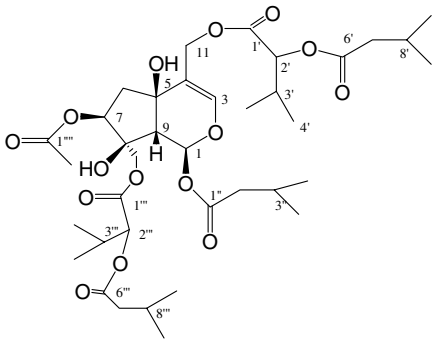
1. Introduction

The genus *Valeriana* belongs to the Valerianaceae family and contains about 250 species throughout the world. The roots and rhizomes of some *Valeriana* species have been used in traditional medicine as a sedative for centuries. A considerable number of investigations on this genus have yielded iridoids, sesquiterpenoids, lignans and alkaloids with pharmacological properties including sedative, cytotoxic, antitumor, antioxidant and vasorelaxant activities (Piccinelli et al. 2004; Ming et al. 1997; Bach et al. 1993; Thies et al. 1981; Bounthanh et al. 1981). In the search for bioactive compounds from *Valeriana* species, we investigated the dried roots of *V. jatamansi*, which is an annual herb distributed in the southwestern area of the People's Republic of China, known in Chinese folk medicine to have hypnotic, tranquilizing and antiviral activities. Previous chemical studies on *V. jatamansi* revealed the presence of iridoids, sesquiterpenoids, flavones and an essential oil (Tang et al. 2003; 2002; Ming et al. 1997; Zhang et al. 1986; Wang and Niu 1980).

2. Investigations, results and discussion

From an ethanol extract of the roots of *V. jatamansi*, we isolated a new iridoid tetraester, valeriotetrate A (**1**), together with two known iridoids IVHD-valtrate (**2**) and valerosidate (**3**). The novel structure was determined by means of spectral methods including 1D-, 2D-NMR and HR-ESIMS and the known compounds were identified on the basis of comparing their NMR data with those reported in the literature.

Valeriotetrate A (**1**) was isolated as colorless oil. The molecular formula $C_{37}H_{58}O_{15}$ was deduced by HR-ESIMS ($[M+Na]^+$ at m/z 765.3650, calcd. 765.3673). The ^1H-, ^{13}C NMR (Table) and DEPT spectra of **1** revealed the presence of eleven methyls, six methylenes, eleven methines and nine quaternary carbons. Resonance at δ_H 6.54 (1 H, d, J = 2.0, H-1), 6.61 (1 H, s, H-3), 4.77 (2 H, s, H-11), 5.01 (1 H, dd, J = 7.7, 6.1, H-7) and δ_C at 90.9 (C-1), 145.2 (C-3), 115.0 (C-4), 63.7 (C-11), 80.9 (C-7) indicated **1** has a hydroxyldihydrovaltrate-type iridoid skeleton (Tang et al. 2002; Mikhova et al. 1987). A methyl singlet, which appeared at δ_H 2.04 (3 H, s) in the ^1H NMR of **1** was assigned to the methyl protons of an acetate residue. A ^{13}C NMR signal at δ_C 171.6 was assigned to the carbonyl carbon of the acetyl group on the basis of its long-range $^{13}C-^1H$ correlation to the methyl signal, whereas the carbonyl carbon showed a three-bond correlation with H-7 in the HMBC spectrum (Fig. 1). These data revealed the presence of an acetate group at C-7. ^{13}C NMR and DEPT spectra showed five carbon signals due to two methyl carbons (δ_C 23.3 × 2), one methylene carbon (δ_C 44.2) linked to a carbonyl, one methine carbon (δ_C 27.1) and one ester carbonyl carbon (δ_C 172.2). These spectral data suggested an isovalerate group in the molecule of **1** (Tang et al. 2002; Granicher et al. 1995; Thies et al. 1981). The HMBC experiment showed a long-range correlation between H-1 and the ester carbonyl carbon of the isovalerate group (δ_C 172.2), revealing the site of attachment of the isovalerate function to be at C-1. Additionally,



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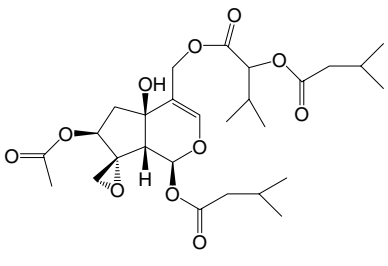

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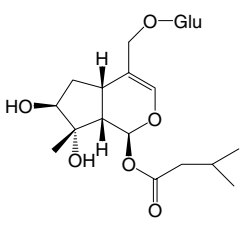

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Table: ^{1}H and ^{13}C NMR spectra data (CD_3COCD_3) for valeriotetrate A (1)*

Position	δ_H	δ_C	Position	δ_H	δ_C
1	6.54 (1 H, d, 2.0)	90.9	1″		172.2
3	6.61 (1 H, s)	145.2	2″	2.24 (2 H, m)	44.2
4		115.0	3″	2.07 (1 H, *m*)	27.1
5		71.4	4″	0.97 (3 H d, 6.0)[a]	23.3
6	2.58 (1 H, dd, 13.3, 6.1)	43.1	5″	0.96 (3 H d, 6.0)[a]	23.3
	2.08 (1 H, m)				
7	5.01 (1 H, dd, 7.7, 6.1)	80.9	1‴		170.7
8		81.0	2‴	4.86 (1 H, d, 3.3)	78.0
9	2.68 (1 H, d, 2.0)	55.6	3‴	2.08 (1 H, m)[b]	31.4
10	4.35 (1 H, d, 11.3)	69.4	4‴	1.00 (3 H, d, 6.0)	18.2
	4.30 (1 H, d, 11.3)				
11	4.77 (2 H, s)	63.7	5‴	0.94 (3 H, d, 6.0)	19.8
1′		170.9	6‴		173.6
2′	4.86 (1 H, d, 3.3)	77.8	7‴	2.26 (2 H, m)	44.1
3′	2.09 (1 H, m)[b]	31.4	8‴	2.07 (1 H, m)	27.1
4′	0.98 (3 H d, 6.0)[a]	19.8	9‴	0.96 (3 H, d, 6.0)[a]	23.3
5′	0.99 (3 H d, 6.0)[a]	18.2	10‴	0.97 (3 H, d, 6.0)[a]	23.3
6′		173.6	1⁗		171.6
7′	2.26 (2 H, m)	44.2	2⁗	2.04 (3 H, s)	21.6
8′	2.07 (1 H, m)	26.9			
9′	0.97 (3 H d, 6.0)[a]	23.3			
10′	0.96 (3 H d, 6.0)[a]	23.3			

* Coupling constants in Hz are in parentheses. [a, b] may be exchangeable

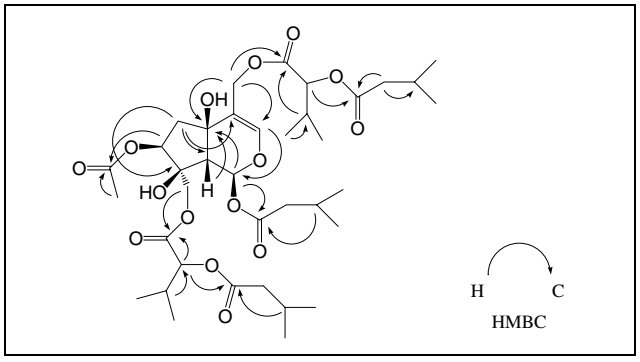

Fig. 1: HMBC correlation of valeriotetrate A (**1**)

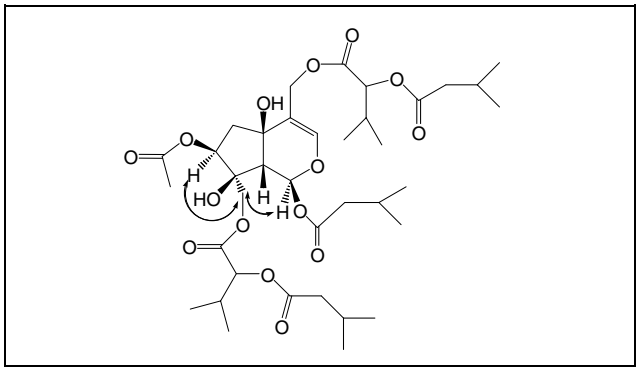

Fig. 2: Key NOE correlation of valeriotetrate A (**1**)

the ^{13}C NMR and DEPT spectra showed 20 carbon signals due to eight methyl carbons (δ_C 18.2 × 2, 19.8 × 2, 23.3 × 4), two methylene carbons (δ_C 44.2, 44.1), four methine carbons (δ_C 31.4 × 2, 26.9, 27.1), two methine carbons (δ_C 77.8, 78.0) having an oxygen function, and four ester carbonyl carbons (δ_C 170.7, 170.9, 173.6 × 2). These spectral data and long-range correlations between ester carbonyl carbons and protons at δ_H 4.86 (2 H, d, J = 3.3, H-2′, 2‴) suggested two α-isovaleroyloxyisovaleryl groups in the molecule of **1** (Mikhova et al. 1987; Bounthanh et al. 1981). The HMBC experiment showed long-range correlations between ester carbonyl carbons of α-isovaleroyloxyisovaleryl group and four hydrogens at δ_H 4.35, 4.30 (each 1 H, d, J = 11.3, H-10) and 4.77 (2 H, s, H-11), revealing the site of attachment of two α-isovaleroyloxyisovaleryl functions to be at C-10 and C-11. Thus, all the substitution positions were established. The relative configuration of **1** was determined by the 2D NOESY plot (Fig. 2). Based upon comparison of NMR data of **1** with those reported for valepotriates (Tang et al. 2002; Thies et al. 1981), the β orientation was attributed to H-9 and HO-5. The NOE between H-1 and H-10, H-10 and H-8 established the α-orientation of H-1, H-7 and H-10. Consequently, the structure of **1** was elucidated as shown in and designated as valeriotetrate A.

The known compounds IVHD-valtrate (**2**) and valerosidate (**3**) were also isolated and characterized by comparison of their spectroscopic data (NMR and MS) with literature values (Boros and Stermitz 1991; Thies et al. 1981; Stahl and Schild 1969).

3. Experimental

3.1. Equipment

MS were determined on an API Qstar Pulsa LC/TOF mass spectrometer. FAB-MS were analyzed on a VG Autospec-3000 mass spectrometer. NMR spectra were measured on a Bruker DRX-500 spectrometer with TMS as int. standard. Silica gel (200–300 mesh) was used for column chromatography and silica gel GF_{254} for TLC (Qingdao Marine Chemical Co., China). Solvents were of the industrial purity and distilled prior to use.

3.2. Plant material

The roots of *V. jatamansi* Jones were collected in July, 2003 from Gejiu of Yunnan province, China and identified by Dr. Xiao Lian, Department of Biology, Yunnan Normal University, where a voucher specimen (No. 0307013) was deposited.

3.3. Extraction and isolation

The dried and crushed roots of *V. jatamansi* Jones (4 kg) were extracted with 95% ethanol four times at room temperature. The extract was concentrated and the residue was successively extracted with petroleum ether, chloroform and acetone. The chloroform extract (50 g) was subjected to

CC on silica gel eluting with petroleum ether and an increasing ratio of acetone. The elutes were combined into thirteen fractions on the basis of TLC pattern. Fr. 12 (15 g) was further subjected to CC on silica gel eluting with petroleum ether/EtOAc 9 : 1, and then isolated on a Sephadex LH-20 column eluting with MeOH/$CHCl_3$ 95 : 5 to afford compounds **1** (40 mg) and **2** (27 mg). The acetone soluble extract (100 g) was subjected to CC on silica gel eluting with $CHCl_3$ and an increasing ratio of MeOH to afford 17 fractions. Fr. 5 (12 g) was further subjected to silica gel column chromatography eluting with $CHCl_3$/MeOH 9 : 1, and then isolated on a Sephadex LH-20 column eluting with MeOH/H_2O 9 : 1 to obtain compound **3** (20 mg).

Valeriotetrate A (**1**), colorless oils; HR-ESIMS m/z: 765.3650 $[M+Na]^+$ (calcd. for $C_{37}H_{58}O_{15}$, 765.3673); ^1H and ^{13}C NMR: See Table.

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