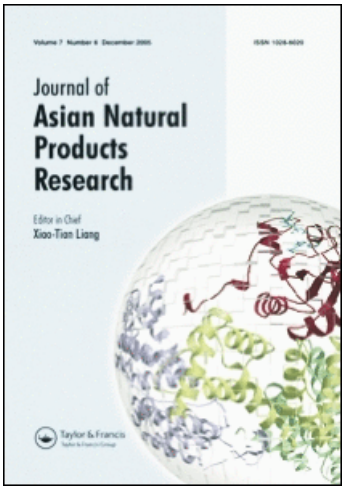


Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

Two diketopiperazines from *Acanthopanax senticosus* Harms

Zhi-Feng Li[a]; Nan Xu[b]; Bao-Min Feng[c]; Qi-Hui Zhang[a]; Yue-Hu Pei[a]
[a] School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang, China [b] College of Pharmacy, Liaoning University of Traditional Chinese Medicine, Dalian, China [c] College of Bioengineering, Dalian University, Dalian, China

Online publication date: 01 February 2010

To cite this Article Li, Zhi-Feng , Xu, Nan , Feng, Bao-Min , Zhang, Qi-Hui and Pei, Yue-Hu(2010) 'Two diketopiperazines from *Acanthopanax senticosus* Harms', Journal of Asian Natural Products Research, 12: 1, 51 — 55
To link to this Article: DOI: 10.1080/10286020903427328
URL: http://dx.doi.org/10.1080/10286020903427328

Journal of Asian Natural Products Research
Vol. 12, No. 1, January 2010, 51–55

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Two diketopiperazines from *Acanthopanax senticosus* Harms

Zhi-Feng Li[a], Nan Xu[b], Bao-Min Feng[c], Qi-Hui Zhang[a] and Yue-Hu Pei[a]*

[a]*School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang 110016, China;* [b]*College of Pharmacy, Liaoning University of Traditional Chinese Medicine, Dalian 116600, China;* [c]*College of Bioengineering, Dalian University, Dalian 116622, China*

(*Received 24 July 2009; final version received 18 October 2009*)

From the dried aerial parts of *Acanthopanax senticosus*, two new diketopiperazines, eleutherazines A (**1**) and B (**2**), were isolated. Their structures were elucidated on the basis of chemical and spectroscopic methods.

Keywords: *Acanthopanax senticosus*; diketopiperazines; eleutherazine A; eleutherazine B

1. Introduction

In the previous paper [1], we reported the isolation and structure determination of a new coumarin glycoside, eleutheroside B_2, and a new sesquiterpenoid, oplopanone B, from the dried aerial parts of *Acanthopanax senticosus* Harms. Further investigation of the aerial part led to the isolation of two diketopiperazines. This paper deals with the structure determination of the new compounds.

2. Results and discussion

Compound **1** was obtained as a yellow gummy material. The molecular formula was determined to be $C_{25}H_{30}N_2O_8$ by HR-FAB-MS at *m/z* 486.2034 $[M+H]^+$. The ^{13}C NMR spectrum revealed 14 sp^2 carbons corresponding to six carbon–carbon double bonds and two carbonyl carbons. The deshielded resonances at δ_H 7.05 (2H, d, $J = 8.4$ Hz), 6.63 (2H, d, $J = 8.4$ Hz), and δ_H 6.52 (2H, s) in the ^1H NMR spectrum were indicative of a symmetrical disubstituted and a symmetrical four-substituted aromatic rings. The direct connectivity between protons and carbons was established by the HSQC spectrum, and the tabulated ^{13}C and ^1H NMR spectral data for **1** are shown in Table 1.

According to the typical ^{13}C chemical shifts of two CONH groups (δ 168.9 and 165.2) and ^1H NMR shift protons of the two α-methine residues (δ_H 4.05 and 4.23), the presence of the diketopiperazine ring unit in compound **1** was evident [2]. The COSY experiment of **1** identified five isolated spin systems (Figure 2). Inter-residue linkages of these spin systems were established by the long-range correlation in the HMBC spectrum (Figure 2). The HMBC correlations of H-3a (δ 3.25) with C-1 and C-4; H-6 (δ 4.05) with C-5 and C-7; H-8 (δ 7.90) with C-1, C-7, C-9, and C-10; H-10 (δ 2.90) with C-1, C-9, C-11, and C-12; and H-17 (δ 3.98) with C-14, C-18, C-19, C-20, and C-21 (Table 1)

*Corresponding author. Email: peiyueh@vip.163.com

ISSN 1028-6020 print/ISSN 1477-2213 online

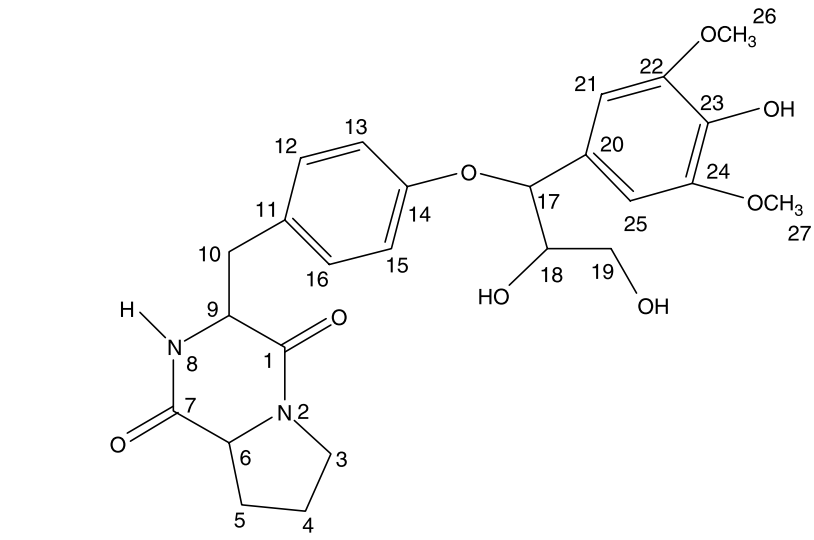
DOI: 10.1080/10286020903427328
http://www.informaworld.com

Table 1. ^{1}H and ^{13}C NMR spectroscopic data of compound **1** (600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR, DMSO-d_6).

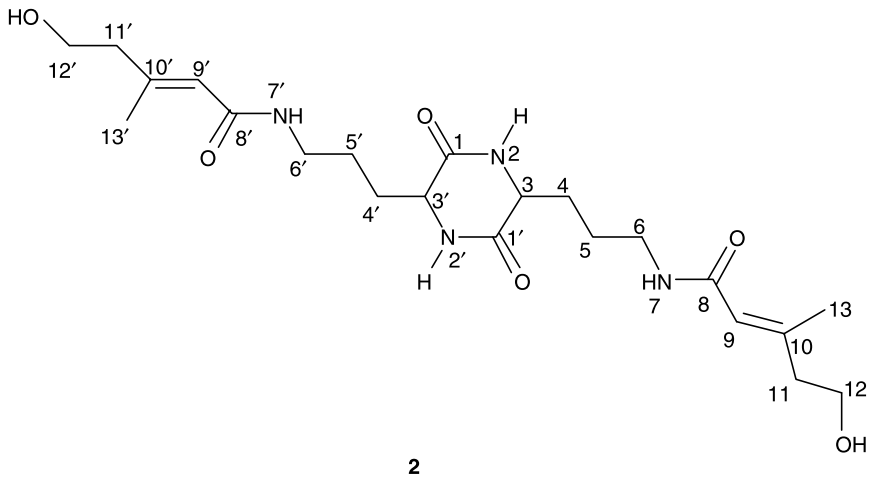
Position	^{13}C (δ)	^{1}H (δ, mult., J in Hz)	HMBC (atom number of ^{13}C)	$^{1}H-^{1}H$ COSY
1	165.2			
3	44.6	3.25 (1H, m), 3.40 (1H, m)	C-1, 4, 5, 6	H-4
4	21.9	1.75 (2H, m)	C-3, 5, 6	H-3a, 3b, 5a, 5b
5	27.9	2.00 (1H, m), 1.40 (1H, m)	C-2, 3, 4, 6, 7	H-4, 6
6	58.4	4.05 (1H, m)	C-5, 7	H-5
7	168.9			
9	56.1	4.23 (1H, m)	C-1, 7, 10, 11	H-10
10	34.8	2.90 (2H, m)	C-1, 9, 11, 12	H-9
11	127.1			
12, 16	130.9	7.05 (2H, d, 8.4 Hz)	C-10, 11, 13, 14	
13, 15	114.8	6.63 (2H, d, 8.4 Hz)	C-11, 12, 14	
14	156.0			
17	84.2	3.98 (1H, d, 6.0 Hz)	C-14, 18, 19, 20, 21	H-18
18	75.2	3.50 (1H, m)	C-17, 19	H-17, 19b
19	62.6	3.23 (1H, m), 3.09 (1H, m)	C-17, 18	H-18, OH-19
20	129.6			
21, 25	104.8	6.52 (2H, s)	C-17, 20, 22, 23	
22, 24	147.8			
23	134.9			
26, 27	56.0	3.73 (6H, s)	C-22, 24	

confirmed the presence and the linkage of the spin systems as described hereinabove. Further analysis of the HSQC and $^{1}H-^{1}H$ COSY spectra and reference to the literatures [2,3], the structure of **1** was elucidated (Figure 1) and named eleutherazine A.

Compound **2** was isolated as a colorless amorphous powder. The molecular formula was determined to be $C_{22}H_{36}N_4O_6$ by HR-FAB-MS at m/z 475.2468 $[M+Na]^+$. The ^{13}C NMR spectrum of **2** showed 11 carbon resonances, so we deduced that **2** has a completely symmetrical system. The NMR spectra of **2** also revealed the same typical ^{13}C chemical shifts of two CONH groups (δ 167.8 and 166.0) and ^{1}H NMR shift protons of the two α-methine residues (δ_H 3.80) of the diketopiperazine ring unit as compound **1**. By interpretation of the ^{13}C NMR and HSQC spectra, the assignment of 11 carbon signals including three quaternary carbons, two tertiary carbons, five secondary carbons, and one primary carbon atom was established. The $^{1}H-^{1}H$ COSY spectrum interpreted some main correlation peaks of H-2 (δ 8.14) with H-3 (δ 3.80), H-3 (δ 3.80) with H-4 (δ 1.58), H-4 (δ 1.58) with H-5 (δ 1.43), H-5 (δ 1.43) with H-6 (δ 3.03), H-6 (δ 3.03) with H-7 (δ 7.76), and H-11 (δ 2.17) with H-12 (δ 3.51), so we established the presence of two spin coupling units, namely —CONH—CH—CH_2—CH_2—CH_2—NHCO— and —CH_2—CH_2—OH. The HMBC spectrum also interpreted some main correlations of H-3 (δ 3.80) with C-1′, C-4, and C-5; H-7 (δ 7.78) with C-6 and C-8; H-9 (δ 5.62) with C-8, C-10, and C-11; H-11 (δ 2.17) with C-9, C-10, C-12, and C-13; and H-13 (δ 2.06) with C-9, C-10, and C-11. Based on the above spectroscopic analysis, inter-residue linkages of the two units were established by the HMBC experiment (Figure 2). Thus, the structure of **2** is shown in Figure 1 and named eleutherazine B.



1



2

Figure 1. Structures of compounds **1** and **2**.

3. Experimental

3.1 General experimental procedures

The NMR spectral data were recorded on Bruker AV-600 (600 MHz for ^{1}H and 150 MHz for ^{13}C) in DMSO-d_6 with TMS as an internal standard. The HR-FAB-MS data were obtained on the Micross Mass Autospec-UltimaE TOF mass spectrophotometer. Chromatography was performed on silica gel (200–300 mesh; Qingdao Haiyang Chemical Factory, Qingdao, China), Sephadex LH-20 (Pharmacia, Piscataway, NJ, USA), and reversed-phase HPLC (Shimadzu LC-10A vp, Tokyo, Japan).

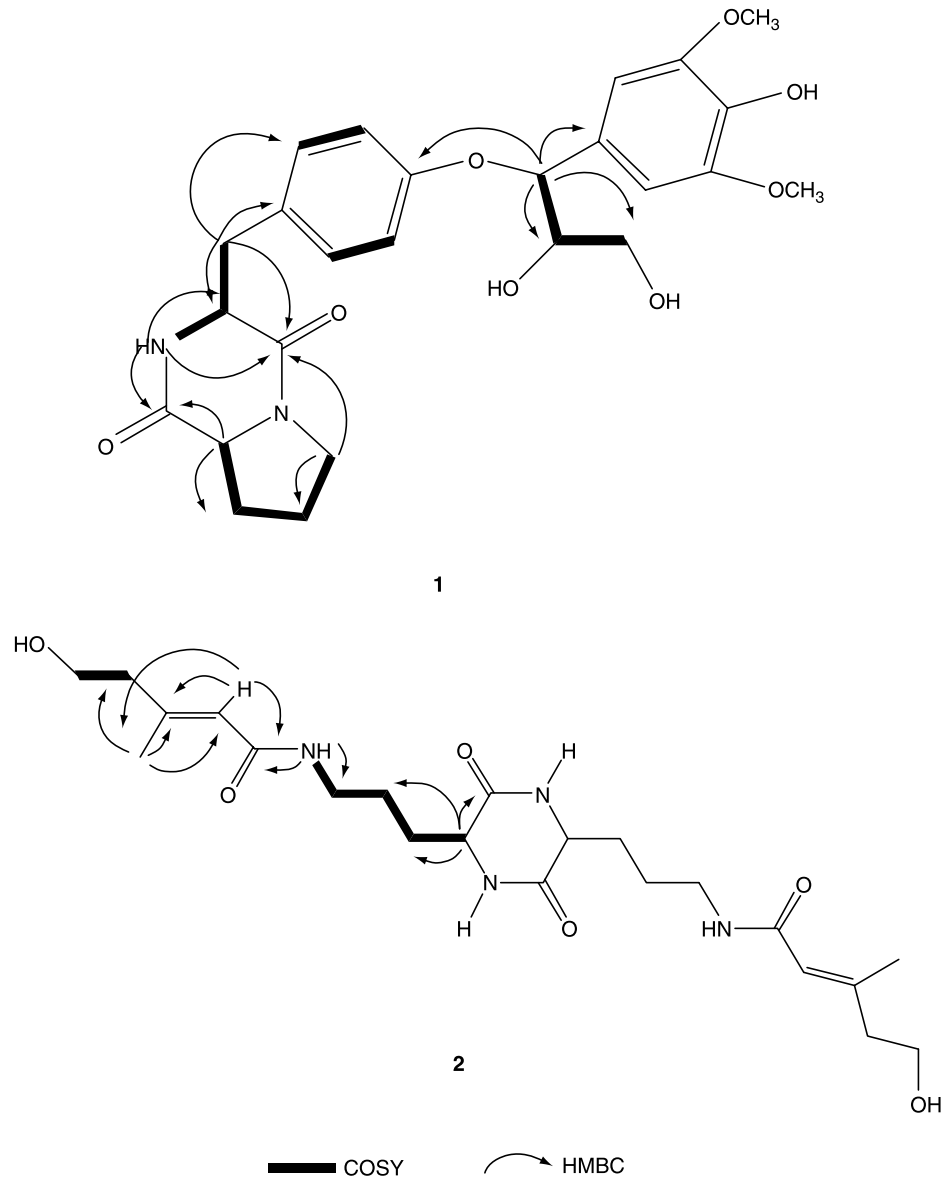


Figure 2. Key HMBC and COSY correlations observed for **1** and **2**.

3.2 Plant material

Aerial parts of *A. senticosus*, cultivated in Liaoning Province of China, were bought from the Cooperation of Traditional Chinese Medicine of Shenyang, China, in June 2005. A voucher specimen was identified by Prof. Qi-shi Sun and has been deposited in the School of Traditional Chinese Medicine of Shenyang Pharmaceutical University, China (No. 7034).

3.3 Extraction and isolation

Aerial parts (20 kg) of *A. senticosus* were extracted thrice with hot 65% EtOH, each time for 2 h, and the combined solution was

Table 2. ^{1}H and ^{13}C NMR spectroscopic data of compound **2** (600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR, DMSO-d_6).

Position	^{13}C (δ)	^{1}H (δ, mult., J in Hz)	HMBC (atom number of ^{13}C)	^{1}H–^{1}H COSY
1, 1′	167.8			
2, 2′		8.14	C-1, 1′, 3, 3′	H-3, 3′
3, 3′	54.0	3.80 (2H, m)	C-1, 1′, 4, 4′, 5, 5′	H-2, 2′, 4, 4′
4, 4′	31.0	1.58 (2H, m), 1.67 (2H, m)	C-3, 3′, 5, 5′, 6, 6′	H-3, 3′, 5, 5′
5, 5′	24.9	1.43 (4H, m)	C-4, 4′, 6, 6′	H-4, 4′, 6, 6′
6, 6′	38.0	3.03 (4H, m)	C-4, 4′, 5, 5′, 8, 8′	H-5, 5′, 7, 7′
7, 7′		7.76	C-6, 6′, 8, 8′	H-6, 6′
8, 8′	166.0			
9, 9′	120.0	5.62 (2H, s)	C-8, 8′, 10, 10′, 11, 11′, 13, 13′	
10, 10′	149.2			
11, 11′	43.6	2.17 (4H, t, 6.3 Hz)	C-9, 9′, 10, 10′, 12, 12′, 13, 13′	H-12, 12′
12, 12′	59.1	3.51 (4H, m)	C-10, 10′, 11, 11′	H-11, 11′
13, 13′	17.9	2.06 (6H, s)	C-8, 8′, 9, 9′, 10, 10′, 11, 11′	

concentrated *in vacuo* to a syrup (1000 g), followed by suspension in water. The suspension was extracted with petroleum ether, ethyl acetate, and *n*-butanol successively. The *n*-butanol fraction (150 g) was further chromatographed over a D101 macroporous resin column eluted with H_2O, and with 30, 70, and 95% EtOH gradually. The fraction (60 g) eluted with 30% EtOH was subjected to silica gel column chromatography (eluted with $CHCl_3$ and MeOH in increasing polarity) to obtain nine fractions (I–IX). Fraction II was purified by Sephadex LH-20 column chromatography (CH_3OH) and preparative HPLC (CH_3OH–H_2O 30:100, flow rate 4 ml/min, wavelength 210 nm) to obtain compound **1** (6 mg), and fraction V was purified by preparative HPLC (CH_3OH–H_2O 36:100, flow rate 4 ml/min, wavelength 210 nm) to obtain compound **2** (7.5 mg).

3.3.1 *Eleutherazine A (**1**)*

A yellow gummy material, $[\alpha]_D^{25}$ 56.6 (MeOH). IR (KBr) ν_{max} (cm^{-1}): 3460, 1670, 1640, 1600, 1510; UV λ (nm): 227, 268, 284; ^{1}H and ^{13}C NMR (DMSO-d_6) spectral data, see Table 1; HR-FAB-MS *m/z*: 487.2034 $[M]^+$ (calcd for $C_{25}H_{30}N_2O_8$, 486.2016).

3.3.2 *Eleutherazine B (**2**)*

A colorless amorphous powder. $[\alpha]_D^{25}$ 0 (MeOH). IR (KBr) ν_{max} (cm^{-1}): 3510, 1650,1620, 810; UV λ (nm): 225, 270; ^{1}H and ^{13}C NMR (DMSO-d_6) spectral data, see Table 2; HR-FAB-MS *m/z*: 475.2468 $[M+Na]^+$ (calcd for $C_{22}H_{36}N_4O_6Na$, 475.2533).

Acknowledgements

The authors thank Yi Sha and Wen Li for the measurements of NMR spectra.

References

[1] Z.F. Li, Z.H. Wu, G. Chen, Q.H. Zhang, and Y.H. Pei, *J. Asian Nat. Prod. Res.* **11**, 716 (2009).
[2] G.S. Jayatilake, M.P. Thornton, A.C. Leonard, J.E. Grimwade, and B.J. Baker, *J. Nat. Prod.* **59**, 293 (1996).
[3] H. Otsuka, M. Takeuchi, S.T. Sato, and K. Yamasaki, *Phytochemistry* **28**, 883 (1989).