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Chinese Chemical Letters 20 (2009) 823–826
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Gindarudine, a novel morphine alkaloid from *Stephania glabra*

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Received 24 November 2008

Abstract

A novel morphine alkaloid, named gindarudine **1** has been isolated from ethanol extract of *Stephania glabra* tubers, together with four known alkaloids, palmatine, dehydrocorydalmine, stepharanine, and 8-(4′-methoxybenzyl)-xylopinine. Compound **1** was elucidated as 3,6-O,N-detrimethyl-10-hydroxy-1-methoxy-thebaine by means of spectroscopic data including 2D NMR studies.
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Keywords: Stephania glabra; Menispermaceae; Gindaru; Gindarudine

Stephania glabra vern. gindaru, belonging to family Menispermaceae is a large, climbing shrub, indigenous to lower Himalaya of India. The tubers of the plant used for the treatment of variety of disorders, including asthma, tuberculosis, dysentery and fever. It is used as psycomedicine by natives in India [1,2]. More than thirty alkaloids of different classes have been isolated from the plant [3–6]. This paper reports the isolation and characterization of a novel morphine alkaloid, gindarudine (**1**) from the tubers.

Gindarudine (**1**) (Fig. 1), brown crystalline solid, mp 178–180 °C, $[\alpha]_D^{20}$ 0, deduced the molecular formula $C_{17}H_{17}NO_5$ from the molecular ion peak at *m/z* 315.1107 in its HREIMS. It was recognized as morphine alkaloid by characteristic orange-red color with dilute nitric acid, UV absorption maxima at λ_{max}^{MeOH} 276, 233 nm and IR bands at υ_{max}^{KBr} 3516 (OH) and 1454 (NH) cm^{-1}[7]. ^1H, ^{13}C NMR, COSY, HMBC and NOESY data are summarized in Table 1. The ^1H NMR spectrum exhibited the signals for three aromatic protons (*δ* 6.65, 6.83 and 6.90 all singlets), a methoxyl (*δ* 3.83 s), two aromatic hydroxyls (*δ* 11.23, OH-3 and *δ* 9.56, OH-6), an aliphatic hydroxyl (*δ* 4.26, OH-10) and a cyclic NH (*δ* 4.26). The ^{13}C NMR and DEPT spectra showed seventeen signals including one methoxyl carbon (*δ* 56.68). These data were somewhat similar to known compound thebaine [8] except the presence of hydroxyl groups and absence of N-methyl group. The HMBC experiments (Fig. 2) showed correlation of OH-3 (*δ* 11.23) to C-2 (*δ* 116.5) / C-4 (*δ* 143.3), OH-6 (9.56) to C-5 (*δ* 59.7) / C-7 (*δ* 112.0) and OH-10 (*δ* 4.26) to C-9 (*δ* 50.5), suggesting that these hydroxyl groups should be located to C-3, C-6 and C-10, respectively. The NOESY experiments showed strong correlation of OMe-1 (*δ* 3.83) to H-2 (*δ* 6.65) and H-10 (*δ* 4.42), suggested that methoxyl group located at C-1, which was further supported by the HMBC correlation of OMe-1 to C-1 (*δ* 145.4). On the basis of these findings and the most abundant ion at *m/z* 234 (100%) in MS (Fig. 3), the structure of **1** was established as 3,6-O, N-detrimethyl 10-hydroxy 1-methoxythebaine.

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doi:10.1016/j.cclet.2009.03.002

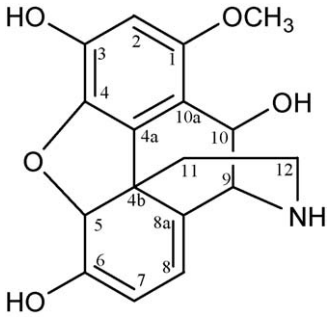


Fig. 1. Structure of **1**.

Table 1
^{13}C, ^{1}H NMR, COSY, HMBC and NOESY data of gindarudine (**1**) in DMSO-d_6.

Position	δ_C ppm	δ_H ppm (*J* Hz)	COSY	HMBC	NOESY
1	145.42	–			
2	116.51	6.65 s	3.83	143.3, 122.1	3.83
3	148.37	–			
4	143.30	–			
4 a	124.65	–			
4 b	51.28	–			
5	59.72	4.18 s			2.65, 4.67
6	147.46	–			
7	112.06	6.83 s	6.90	59.7, 122.6	
8	112.87	6.90 s	6.83	50.5, 51.2	4.67
8 a	122.64	–			
9	50.55	4.67 d (6.5)	4.42		4.18, 4.42, 6.90
10	58.32	4.42 d (8.2)	4.67	145.4	3.40, 3.83, 4.67
10 a	122.17	–			
11 α	24.62	2.65 d (2.7)			
11 β		2.91 d (3.5)	3.83		4.18
12 α	33.88	3.19 d (2.7)	3.40		
12 β		3.40 d (3.5)	3.83, 3.19		4.42
OMe-1	56.68	3.83 s	6.65, 2.91, 3.40	145.4	4.42, 6.65
NH	–	9.05 s		122.6	
OH-3	–	11.23 s		116.5, 143.3	
OH-6	–	9.56 s		59.7, 112.0	
OH-10	–	4.26 s		50.5	

^{1}H (300 MHz) and ^{13}C (125 MHz) NMR spectra were recorded in DMSO-d_6 and used TMS as the internal standard.

1. Experimental

Melting point was recorded on Perfit m.p. apparatus and uncorrected. UV spectrum on PerkinElmer, Lambda-25 spectrophotometer in MeOH. IR on PerkinElmer, Spectrum RX I FT-IR spectrophotometer (KBr discs). NMR spectra were obtained on JEOL NMR spectrophotometer (300 MHz for ^{1}H and 125 MHz for ^{13}C NMR in DMSO, TMS as internal standard). MS were recorded on Finnigan MAT spectrophotometer (CA, USA, xcalibur ver-2 software). TLC (0.5 mm thick layer) was carried out on silica gel (Merck 10–40 μ) spots were detected using UV at 254 and 365 nm and Dragendorff's reagent.

Fresh tubers (10 kg) were collected from Chaka, nearby Chandravadani temple (Tehri Garhwal) during October 2006 and identified by Prof. R.D. Gaur, Department of Botany, H.N.B. Garhwal University Srinagar. A voucher specimen (GUH- 17600) of the plant was deposited in the Departmental Herbarium.

Air dried and finely powdered tubers were extracted exhaustively with 95% ethanol at 30–50 °C (for 15 h, 3 times) on a heating mantle. The extraction mixture was filtered and solvent evaporated upto dryness under reduced pressure to yield black brown residue (200 g). It was chromatographed by pre-adsorbed onto silica gel (200 g) and then added to

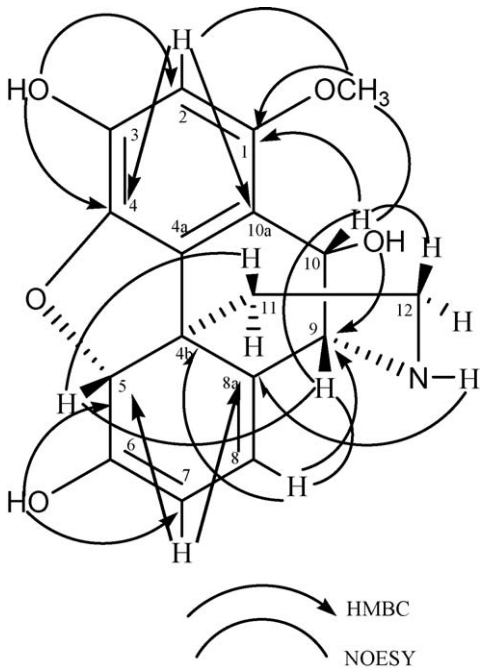
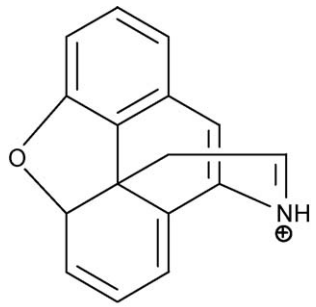


Fig. 2. Important HMBC and NOESY correlations of **1**.



m/z 234 (100%)

Fig. 3. Proposed abundant ion of **1**.

the top of the column prepared by using 500 g silica gel (Merck, 60–120 mesh) in chloroform. Elution was first started with chloroform and then with chloroform: methanol = 49:1, 24:1, 47:3, 23:2, 9:1, 22:3, 43:7, 21:4 and 41:9 (each 1000 mL) to afforded 10 fractions (SG1 to SG10). The fractions SG6 and SG7 were combined according to TLC analysis and concentrated upto dryness under reduced pressure to yield brown residue (15 g). This was further chromatographed over 150 g silica gel with $CHCl_3$:MeOH = 23:2, 91:9, 9:1, 89:11, 22:3, 87:13 and 43:7 (each 500 mL), afforded seven sub-fractions (SGa–SGg). These sub-fractions were concentrated at room temperature. After 24 h a brown amorphous solid was deposited in the bottom of SGc sub-fraction. This solid mass was filtered off and recrystallised with MeOH/$CHCl_3$ (1:1) afforded brown crystals of gindarudine (**1**) (11.26 mg).

Brown crystals; mp 178–180 °C (MeOH); $[\alpha]_D^{20}$: ± 0 (c 0.4, EtOH); UV: λ_{max}^{MeOH} 276 (log ε 3.21), 233 (2.61) nm; IR: υ_{max}^{KBr} 3516 (O–H), 3207, 2938, 1454 cm^{-1} (N–H); ^1H, ^{13}C and 2D NMR data: see Table 1; EI-MS *m/z* (rel. abun.): 316 (4) $[M + H]^+$, 315 (19) $[M]^+$, 234 (100), 208 (28), 146 (35); HREIMS *m/z*: 315.1156 [M] calcd. for $C_{17}H_{17}NO_5$ 315.1107; elemental analysis: (found C, 65.06; H, 5.21; N, 3.60; O, 25.13%; calculated for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44; O, 25.37%).

Acknowledgments

The authors are grateful to Dr. G.J.P. Singh, Punjab University for scanning NMR spectra and N.I.P.E.R., Chandigarh for measurement of mass spectrum.

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