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多刺绿绒蒿中的一个新生物碱类化合物

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摘　要:多刺绿绒蒿在藏区是一种非常重要的民间用药。该植物中已发现多种生物碱,其中很多都具有显著的生物活性。用正相硅胶、ODS 柱色谱从多刺绿绒蒿的地上部分分离得到了三个生物碱,根据其质谱、红外、核磁等波普数据鉴定结构,分别为(6a-*S*)-des-*N*-methyl-(+)-cryprochine(**1**),华紫堇碱(**2**)及原鸦片碱(**3**),其中化合物 **1** 为新化合物,化合物 **2** 为首次在该植物中分离得到。

关键词:藏药;多刺绿绒蒿;生物碱;(6a-*S*)-des-*N*-methyl-(+)-cryprochine

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A New Alkaloid from *Meconopsis horridula*

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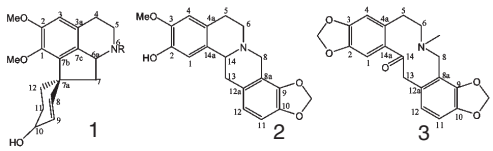
Abstract: *Meconopsis horridula* is an important traditional Tibetan folk medicine. The plant has function of clearing internal heat and promoting blood circulation for removing blood stasis. It was used to treat fractures and bruises. Many alkaloids have been isolated from this species, most of which have significant bioactivities. In this study, the 95% alcohol extract from the aerial part of *Meconopsis horridula* was fractionated using open column chromatography with silica gel and ODS. Three alkaloids were isolated from the plant. A new proaorphine alkaloid, (6a-*S*)-des-*N*-methyl-(+)-cryprochine (**1**), together with two known alkaloids, cheilanthifoline(**2**) and protopine(**3**) were isolated and identified. Compound **2** was isolated from this plant for the first time. The structures of purified compounds were determined using spectroscopic methods including IR, MS, and 1D and 2D NMR, and by comparison with literature data for known alkaloids.

Key words: Tibetan medicine; *Meconopsis horridula*; alkaloid; (6a-*S*)-des-*N*-methyl-(+)-cryprochine

Introduction

Meconopsis horridula Hook. f. et Thoms. (Papaveraceae), is an important traditional Tibetan plant medicine which has been used by Tibetan people for the treatment of fractures and bruises. Some isoquinoline alkaloids were previously isolated from plants of this genus, some of which have shown bioactivity such as anti-inflammatory and analgesic activities[1-3]. Plants of the genus have also been reported to have various alkaloids such as protopine, 8, 9-dihydroprooxocryptochine[4], Cinnamamide, *N-p*-hydroxyl-*trans*-coumaroyltyramine[5], simplicifolianine, and norsanguinarine[6]. In our recent investigation of this plant, a new proaporphine alkaloid, (6a-*S*)-des-*N*-methyl-(+)-cryprochine (**1**), together with two known alkaloids, cheilanthifoline(**2**) and protopine(**3**), were isolated and identified. Compound **2** was isolated from this plant for the first time.



R=H 6a-αH_{23}
Cryprochine R=Me 6a-βH

Fig. 1　Chemical structures of 1-3

Materials and Methods

General

Melting point was recorded on a XRC-1 Melting point detector and was uncorrected. HR-ESI-MS spectra were

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performed on an LTQ-Orbitrap XL spectrometer (Thermo Electric Finnigan Scientific Instruments Company, USA). ESI-MS spectra were recorded on a FinniganLCQ^{DECA} mass spectrometer (Thermo Electric Finnigan Scientific Instruments Company, USA). NMR spectra were recorded on a Bruker Avance-600 (Bruker Corporation, Germany) using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-IR (PerkinElmer, Inc. USA) using KBr discs. Self-packed open column chromatography was performed with silica gel (100-200 mesh, Qingdao Haiyang Chemical Group Inc. China), ODS (Nacalai Tesque, Inc. Japan).

Material

The aerial parts of *M. horridula* were collected in August 2010 in Lhasa, Tibetan Autonomous Region. A voucher specimen was authenticated by researcher Z. C. Zhao, Chengdu Institute of Biology, Chinese Academy of Sciences.

Extraction and isolation

The air-dried powdered materials (2.3 kg) were extracted with 95% EtOH (7 days ×3) at room temperature. The ethanol was evaporated in vacuumto give approx. 250 g of oily mass that was subsequently dissolved in 2% aqueous HCl (2.5 L). The aqueous phase was extracted with EtOAc (7 L), and then progressively basified with NH_4OH to pH 10 to afford a 40 g deposit. After removal of the deposit by filtration, the remaining aqueous phase was extracted with $CHCl_3$ (7 L) to afford the crude alkaloid (16 g). The crude alkaloid was chromatographed on a silica gel column (150 g) with $CHCl_3$ and $CHCl_3$/MeOH mixtures of increasing polarity, and furnished five fractions (A-E) according to TLC analysis. Fr. B (1.2 g) was further chromatographed on a silica gel column with $CHCl_3$/MeOH to give **3** (80 mg). Fr. C was purified on an ODS column with H_2O/MeOHto give **1** (10 mg) and **2** (7 mg).

Results and Discussion

Compound 1, colorless needles; m. p. 238-240 ℃; $[\alpha]_D^{24}$32° (c = 0.38, MeOH); UV (MeOH) λmax (log ε) 284.4 (3.57), 226.0 (sh) (3.85) nm; gave an orange color with Dragendorff reagent. Its ESI-MS showed a pseudo-molecular ion peak $[M + H]^+$ at m/z 302 and the molecular formula was established as $C_{18}H_{23}NO_3$ from HR-ESI-MS at m/z 302.1762 (calcd. for $C_{18}H_{24}NO_3$ 302.1751). IR (KBr) ν_{max} 3419, 2914, 2838, 1601, 1448, 1459, 1298, 1268, 1079, 991, 840, 618 cm^{-1}. ^{1}H NMR and ^{13}C NMR data (600MHz, DMSO-d_6) data; see Table 1.

Table 1 ^{1}H NMR and ^{13}C NMR Data of 1 and cryprochine (δ in ppm, J in Hz)

Position	δ_H		δ_C	
	1 (DMSO-d_6)	Cryprochine[a] ($CDCl_3$)	1 (DMSO-d_6)	Cryprochine[a] ($CDCl_3$)
1			144.3s	144.7s
2			153.8s	153.2s
3	6.69 s	6.55 s	111.4d	110.9d
3a			126.8s	126.8s
4α	3.08 dd	2.93 ddd		
	(20.5, 8.9)	(16.8, 11.4, 6.7)	25.0t	27.4t
4β	2.73 br s	2.77 brdd		
		(16.8, 5.0)		
5α	1.80 m	3.07 brdd		
		(11.4, 6.7)	45.5t	54.9t
5β	3.38 br d (12.36)	2.44 ddd		
		(11.4, 11.4, 5.0)		
6		2.32 s		43.3q
6a	4.17 t (7.74)	3.22dd (11.0, 6.4)	56.2d	65.1d

Position	δ_H		δ_C	
	1(DMSO-d_6)	Cryprochine[a](CDCl$_3$)	1(DMSO-d_6)	Cryprochine[a](CDCl$_3$)
7α	1.75 m	1.80dd(11.0,11.0)	43.8t	50.2t
7β	2.73 br s	2.39dd(11.0,6.4)		
7a			47.5s	48.3s
7b			139.8s	138.4s
7c			132.5s	134.2s
8	5.54 d (9.9)	5.83 d (10.0)	135.7s	136.0d
9	5.75dd(9.9, 3.78)	5.77dd(10.0,3.9)	129.5d	127.5d
10	4.04 d (3.78)	4.13dd(7.7,3.9)	62.6d	63.8d
11α	1.95 t (10.9)	1.90 ddd		
		(13.8,12.5,3.6)	28.8t	29.3t
11β	2.26 dd(11.5,6.1)	2.00 dddd		
		(12.5,7.7,5.6,3.8)		
12α	1.63 t (11.0)	1.55 ddd	29.9t	29.3t
		(13.7,5.6,3.6)		
12β	2.88 d(7.1)	2.72 ddd		
		(13.8,13.7,3.8)		
1 – OMe	3.64 s	3.73s	60.9q	60.8q
2 – OMe	3.76 s	3.77s	56.6q	56.3q

Note: [a]Data for this compound were from Lee, *et al*, 1993[8].

Compound **1** was isolated as colorless needles. IR spectrum absorbances at 3419 and 2914 cm^{-1} suggested the presence of reactive hydrogen. The ^{1}H NMR spectrum displayed two methoxyl signals at δ_H 3.64 and 3.76 (each 3H, s), one aromatic proton signal at δ_H 6.69 (1H, s), and two olefinic protons at δ_H 5.75(1H, dd, J = 9.9, 3.78 Hz) and 5.54(1H, d, J = 9.9 Hz). By comparing the data for epiamurolin[7], a pair of doublets at δ_H 5.75(dd, J = 9.9, 3.78 Hz) was assigned to H-9, while the H-8 signal appeared as a doublet at δ_H 5.54(d, J = 9.9 Hz) suggesting that H-10 is α-H. A broad singlet at δ_H(2.73 br s) was assigned to H-7β by comparisonwith cryprochine[8]. In its ^{13}C NMR spectrum, the presence of eight signals belonged to aromatic and olefinic carbon (δ_C > 110 ppm), of which three were protonated(CH) and five were quaternary. Of the quaternary carbons, two were oxygenated(δ_C > 140), and three nonoxygenated. It was further suggested that **1** contains an aromatic ring and a double bond. The remaining ^{13}C NMR signals revealed an aliphatic quaternary carbon(δ_C 47.5 s), two methines(δ_C 56.2, 62.6 d), five methylenes, and two methoxyl groups(δ_C 60.9, 56.6 q). The NMR spectra of **1**(Table 1) were similar to those of(+)-cryprochine except for the absence of N-CH$_3$ signals at δ_H 2.3 and δ_C 43.3, which suggested the absence of N-methyl in **1**.

NOESY correlations of **1**(Fig. 2), between the olefinic protons and 1-OCH$_3$ and 7β-H suggest that the double bond should be in β orientation. Correlations between 6a-H and 11-H and 12-H suggested that 6a-H should be in α orientation. The structure of **1** was therefore characterized as (6a-*S*)-des-*N*-methyl-(+)-cryprochine.

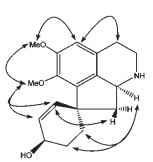

Fig. 2 Key NOESY correlations of 1

Compound **2**, colorless needles; mp. 181-183 ℃; gave an orange color with Dragendorff reagent. Its ESI-MS gave a pseudo-molecular ion peak at m/z 326.2 [M + H]$^+$. ^{1}H NMR(600 MHz, CDCl$_3$) δ: 5.94(2H, dd, J = 1.38, 1.38 Hz, -OCH$_2$O-), 5.50(1H, br s, -OH),

6.82 (1H, s, H-1), 6.68 (1H, d, J = 7.74 Hz, H-11), 6.63 (1H, d, J = 7.92 Hz, H-12), 6.60 (1H, s, H-4), 3.88 (3H, s, -OMe); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 145.1 (C-2), 144.9 (C-3), 143.3 (C-10), 144.0 (C-9), 130.4 (C-4a), 128.7 (C-12a), 126.0 (C-14a), 121.1 (C-12), 116.9 (C-8a), 111.3 (C-11), 110.6 (C-4), 106.8 (C-1), 59.4 (C-14), 53.0 (C-8), 51.5 (C-6), 36.3 (C-13), 29.2 (C-5), 101.0 (-OCH_2O-), 55.9 (-OMe). It was determined to be the known compound (±)-cheilanthifoline ($C_{19}H_{19}NO_4$) by comparison of the NMR data with literature values[9].

Compound **3**, amorphous white powder; mp. 208-210 ℃; gave an orange color with Dragendorff reagent. Its ESI-MS showed a pseudo-molecular ion peak at m/z 354.1 $[M+H]^+$. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.89 (2H, dd, J = 6.2, 1.5 Hz, -OCH_2O-), 5.95 (2H, dd, J = 6.0, 1.5 Hz, -OCH_2O-), 1.92 (3H, s, -NCH_3), 6.65 (1H, d, J = 7.5 Hz, H-12), 6.70 (1H, s, H-4), 6.78 (1H, d, J = 7.5 Hz, H-11); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 194.2 (C-14), 147.4 (C-3), 145.9 (C-2), 145.5 (C-9), 145.3 (C-10), 132.0 (C-14a), 135.8 (C-4a), 128.5 (C-12a), 124.5 (C-12), 117,6 (C-8a), 109.8 (C-4), 107.4 (C-1), 106.2 (C-11), 57.5 (C-6), 50.4 (C-8), 46.0 (C-13), 31.2 (C-5), 100.4 (-OCH_2O-), 100.3 (-OCH_2O-), 40.8 (-NCH_3). The structure proved to be that of protopine ($C_{20}H_{19}NO_5$) by comparison of the NMR data with literature values[10].

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