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A NEW PROTOBERBERINE FROM THE BARK OF *Phellodendron chinense*

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*A new protoberberine, named 8,13-dioxo-14-butoxycanadine (**1**), was isolated from the bark of* Phellodendron chinense *Schneid, and its structure was elucidated by extensive spectroscopic methods, including IR, UV, HR-ESI-MS, and NMR techniques.*

Keywords: *Phellodendron chinense* Schneid, Rutaceae, protoberberine.

The plant *Phellodendron chinense* Schneid (Rutaceae), widely distributed in southwest of China, is well known as a folk medicine for immunomodulation [1] and as an antitumor [2] and antibacterial [3]. Previous phytochemical investigation on this plant revealed the presence of alkaloids, flavonoids, and coumarins [4–6]. In our continuous search for new and bioactive components from Chinese traditional medicine, we selected the bark of *P. chinense* Schneid. In this paper, we report the isolation and structural elucidation of a new compound named 8,13-dioxo-14-butoxycanadine (Fig. 1). The structure of **1** was mainly elucidated on the basis of spectroscopic analysis, including 1D and 2D NMR.

Compound **1** was obtained as a colorless oil and showed a positive reaction to modified Dragendorff reagent. Its molecular formula of $C_{24}H_{25}O_7N$ was deduced from HR-ESI-MS data at *m/z* 440.1700 $[M + H]^+$ (calcd for $C_{24}H_{26}O_7N$ 440.1704). The UV spectrum displayed maximal absorptions at 235, 265, 289, and 325 nm. The IR spectrum showed absorptions at 1665 and 1725 cm^{-1}, indicating that **1** has an 8,13-dioxo-protoberberine-type skeleton [7]. The ^1H NMR and ^{13}C NMR data of **1** are similar to those for a previously described compound, i.e., 8,13-dioxo-14-methoxycanadine [7, 8], except for a butoxy instead of a methoxy. The ^1H NMR data of **1** (Table 1) revealed four aromatic H-atoms, two of which were *para*-oriented, appearing at δ 6.98 (1H, s) and 6.61 (1H, s), and should be located at A ring of the berberine skeleton. The remaining two *ortho*-coupling aromatic protons at δ 7.11 (1H, d, J = 8.40 Hz) and 7.73 (1H, d, J = 8.40 Hz) could only be bonded with C-11 and C-12, which were confirmed by the HMBC spectrum (Fig. 1).

The ^1H NMR data of **1** (Table 1) also displayed two methoxy resonances at δ 3.95 (3H, s) and 3.97 (3H, s), as well as two methylene signals at 5.94 (2H, d, J = 7.60 Hz) and 4.96 (2H, m), characteristic of one OCH_2O group and one CH_2N group, respectively. The remaining signals, including a methyl signal, at 0.75 (3H, t, J = 7.20 Hz), two methylene signal at 1.22 (2H, m) and 1.40 (2H, m), and an oxymethylene proton signal at 3.25 (2H, t, J = 6.80 Hz), indicated that **1** should include a butoxy.

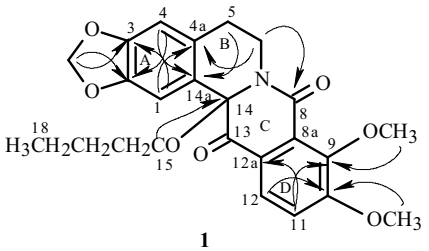

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Fig. 1. The structure and key HMBC correlations (H→C) of **1**.

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TABLE 1. NMR Data of Compound **1** (^{1}H, 400 MHz; ^{13}C 100 MHz, CD_3COCD_3, TMS, δ, ppm, J/Hz)

C atom	δ_H	δ_C	HMBC
1	6.98 (1H, s)	108.6	C-3, C-4a, C-5
2		146.2	
3		148.2	
4	6.61 (1H, s)	108.1	C-1, C-2, C-5
4a		131.6	
5	2.70 (2H, m)	29.0	C-4, C-14a
6	4.96 (2H, m)	36.4	C-4, C-4a, C-8
8		160.7	
8a		123.5	
9		149.6	
10		160.0	
11	7.11 (1H, d, J = 8.40)	115.2	C-9, C-12, C-12a
12	7.73 (1H, d, J = 8.40)	124.2	C-9, C-10, C-12a
12a		124.6	
13		189.6	
14		84.3	
14a		131.6	
15	3.25 (2H, t, J = 6.80)	63.9	C-14, C-15, C-17
16	1.40 (2H, m)	31.7	C-18
17	1.22 (2H, m)	19.3	C-15, C-16, C-18
18	0.75 (3H, t, J = 7.20)	13.7	C-16, C-17
9-OCH_3	3.95 (3H, s)	61.5	C-9
10-OCH_3	3.97 (3H, s)	56.3	C-10
-O-CH_2-O-	5.94 (1H, d, J = 7.60); 5.94 (1H, d, J = 7.60)	101.3	C-2, C-3

Information for all of the functional groups and their location in the molecule was obtained from the HMBC and ^{1}H–^{1}H COSY spectra. The butoxy is linked at the C-14 position because of the HMBC correlation between H-15 (3.25, t, J = 6.80 Hz) and C-14 (84.3). The OCH_2O group was placed in C-2 and C-3 positions of the benzene ring, as deduced from HMBC correlations between OCH_2O and C-2 and C-3 (Fig. 1). In the HMBC spectrum, correlations were found between the methoxy at δ_H 3.95 (3H, s) and C-9, and between the methoxy at 3.97 (3H, s) and C-10, indicating the two *O*-methyl groups at δ_H 3.95 and 3.97 were located at C-9 and C-10. The information obtained from the 2D NMR and ^{13}C NMR data, and comparison with previously reported data for 8,13-dioxo-14-methoxycanadine [7, 8], supported the structure of **1**. Based on the above results, compound **1** could be identified as 8,13-dioxo-14-butoxycanadine.

EXPERIMENTAL

General Procedures. IR spectra were measured on an FTS 165-IR spectrometer (Bio-Rad, USA). ^{1}H NMR (400.13 MHz), ^{13}C NMR (100.62 MHz), and 2D NMR were recorded on a Varian INOVA-400 FT-NMR spectrometer (USA) in $CDCl_3$ with TMS as an internal standard. HR-ESI-MS were recorded on a Bruker APEX II spectrometer. Separation and purification were performed by column chromatography (CC) over silica gel. Silica gel (200–300 mesh) used for CC and silica gel (GF254) for TLC were obtained from the Qingdao Marine Chemical Factory, Qingdao, China.

Plant Material. The commercial bark of *P. chinense* was obtained from Lanzhou Ltd. Co. of Fuxinghou herbal medicines, which were collected from Sichuan Province, and were authenticated by Mr. Xiao-Fei Wang of Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou. A voucher specimen (No. 2010001) is deposited at the Ion-irradiation Medicine Developing Center, Institute of Modern Physics.

Extraction and Isolation. The air-dried and powdered commercial *Phellodendron* bark (5.4 kg) was extracted three times with 95% ethanol under reflux. The extract was obtained by vacuum concentration, suspended in water, and successively extracted with petroleum ether, ethyl acetate, and *n*-butanol. The ethyl acetate fraction was subjected to silica gel column chromatography eluted with $CHCl_3$–MeOH (20:1–1:1) to afford fractions 1–9. Fraction 5 was purified by repeated column chromatography over silica gel (petroleum ether–acetone, 2:1) to provide compound **1** (30 mg).

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