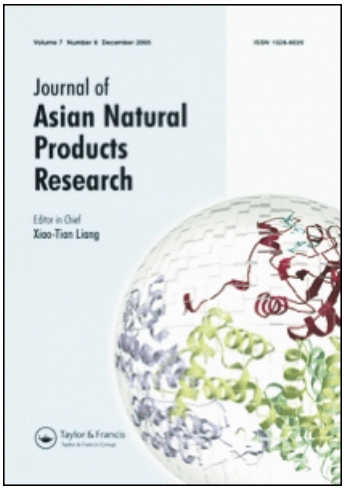

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ALKALOIDS FROM *STEMONA COLLINSAE*

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A new alkaloid, isostenine (**1**), together with two known ones neotuberostemonine (**2**) and bisdehydroneotuberostemonine (**3**) were isolated from the root of *Stemona collinsae*. Their structures were determined by various spectral methods.

Keywords: *Stemona collinsae*; Stemonaceae; Isostenine; Neotuberostemonine

INTRODUCTION

The dried roots of some *Stemona* species are used in Chinese and Vietnamese traditional and folk medicine as anti-cough agents and insecticides [1,2]. It is considered that bioactive principles of such plant roots are alkaloids, whose structures almost all contain a basic perhydroazaazulene core attaching other ring system and side-chains with different juncture and stereochemistry. Recently, the alkaloid components of all five Chinese *Stemona* species, *S. japonica*, *S. tuberosa*, *S. sessilifolia*, *S. parviflora* and *S. mairei*, among which the former three are recorded in *Chinese Pharmacopoeia* (2000 Edition), have been studied extensively by R.S. Xu *et al.* These systematic studies resulted in discovering a great diversity of alkaloid structures in *Stemona* species [3].

Vietnam has three indigenous *Stemona* species, *S. collinsae*, *S. saxorum* and *S. cochinchinensis* besides one common species *S. tuberosa*, which also distributes in China [2,4]. As part of our ongoing investigation on bioactive compounds from Vietnamese medicinal plants, we have studied the roots of *Stemona collinsae*, which are used as antitussive and anthelmintic agents in the form of decoction, and insecticide in the form of extraction solution as fumigant for flies, mosquitoes, dog fleas and lice [2]. To the best of our knowledge, no report has appeared on its chemical constituents. In this paper we describe the isolation and structural elucidation of one new alkaloid, isostenine (**1**), together with two known alkaloids neotuberostemonine (**2**) and bisdehydroneotuberostemonine (**3**).

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RESULTS AND DISCUSSION

Extraction of the roots of *S. collinsae* with 95% ethanol was followed by routine treatment to afford crude alkaloids. One new tuberostemonine-type alkaloid, isostenine (**1**), and two known alkaloids, neotuberostemonine (**2**) and bisdehydroneotuberostemonine (**3**) were obtained by repeated column chromatography on silica gel.

Isostenine (**1**), mp 215–217°C, $[\alpha]_D = +92$ ($CHCl_3$, *c* 0.6), was assigned a molecular composition of $C_{17}H_{27}NO_2$ by HREIMS. Its IR spectrum exhibited a γ-lactone carbonyl band at 1762 cm^{-1}, but no absorption for hydroxyl or N–H group. The ^1H NMR spectrum of **1** showed a doublet methyl (δ 1.23, d, $J = 7.2$ Hz), a triplet methyl (δ 1.02, t, $J = 7.4$ Hz), and a triplet oxygenated methine (δ 4.59, t, $J = 3.1$ Hz) signals. In the ^{13}C NMR spectrum, 17 carbon signals were observed, including two methyl, seven methylene, seven methine (one oxygenated), and one quaternary carbons. Above NMR feature is very similar to that of stenine [5], a known tuberostemonine-type alkaloid having a molecular formula the same as **1**. All of the ^1H and ^{13}C chemical shifts associated with the structure of **1** were determined by a series of 2D NMR experiments (^1H–^1H, ^1H–^{13}C COSY, and HMBC) (Tables I and II), which revealed the proton sequences and carbon connectivities similar to that of stenine. Previous EIMS studies showed that the presence of an ion at *m/z* 276 as base peak has been proven to be characteristic for identifying neotuberostemonine-type alkaloids, which represents fragments $[M - C_5H_7O_2$ (side-chain at C-3)$]^+$ in tuberostenine (**2**) and $[M - 1]^+$ in stenine [5,6]. The EIMS spectrum of **1** exhibited a base peak at *m/z* 276 $[M - 1]^+$, confirming its structural similarity to stenine.

Despite the similarities mentioned above, **1** was not considered as stenine but its isomer with the same planar structure due to the presence of great difference in their melting points (213–215°C for **1** and 60–63°C for stenine) and optical rotation (+92° for **1** and −30° for stenine). Previous chemical studies showed that the rings A/C, B/C, and C/D in tuberostemonine-type alkaloids might be connected in different patterns, resulting in their

TABLE I ^1H and ^{13}C NMR data of isostenine (**1**)

Position	^1H	^{13}C
1	2.65 (ddd, 10.5, 4.0, 6.0)	36.70
2	2.32 (m)	28.71
	1.82 (m)	
3	4.20 (dt, 10.0, 20.2)	56.04
	3.03 (m)	
5	3.60 (dt, 5.3, 12.4)	57.91
	2.95 (m)	
6	2.32 (m)	25.79
	1.95 (m)	
7	1.91 (m)	20.68
	1.62 (m)	
8	2.06 (m)	28.58
	1.70 (m)	
9	2.06, m	32.63
9a	3.36 (br. s)	72.17
10	2.53 (m)	37.09
11	4.59 (t, 3.1)	78.28
12	2.18 (m)	40.27
13	2.95 (m)	42.50
14		178.45
15	1.22 (3H, d, 7.2)	10.16
16	1.39 (m)	21.47
	1.70 (m)	
17	1.02 (3H, t, 7.4)	10.78

structural complexity. For stenine, the rings A/C, B/C, and C/D are in *trans*, *cis* and *cis* junction, respectively, representing H-1α, H-9aβ, H-9β, H-11β, H-12β, which were determined by X-ray crystallographic study. However, the stereochemistry of such alkaloids can be determined by vicinal $^1H-^1H$ coupling constant and NOE experiments besides X-ray analysis. The H-9a signal in ^1H NMR of **1** showed a significant line-broadening effect when a trace of DCl was added to the $CDCl_3$ solution. This suggested that H-9a is in the usual β-orientation [6,7]. In the NOESY spectrum of **1** (Table II), the correlations between H-9a/H-1, H-9a/H-9, H-1/H-15, H-11/H-12, and H-12/H-13 were observed, indicating H-1, H-9, and H-9a are all in β-orientation, while H-10, H-11, H-12, and H-13 all are in α-orientation. This was further confirmed by NOE difference spectral experiments. Irradiation of H-1 produced 4.6 and 1.9% NOE enhancement at H-9a and H-15, supporting all H-1, H-9a, and H-15 in β-orientation and H-13 in α-orientation (Fig. 1). Irradiation of H-12 produced 2.9 and 8.8% NOE enhancement at H-11 and H-13; and irradiation of H-10 produced 5.7% NOE enhancement at H-11, confirming all H-10, H-11, H-12, and H-13 in α-orientation. Thus **1** was elucidated as an isomer of stenine, having the same stereostructure except H-1 (α- for stenine, β- for **1**), H-11 and H-12 (β- for stenine and α- for **1**) orientation.

In the course of our study only three tuberostemonine-type alkaloids were obtained from the roots of *S. collinsae*, an indigenous *Stemona* species growing in northern Vietnam. Regarding the structure type of alkaloid components, the species *S. collinsae* is close to *S. tuberosa*, which distributed in southern China and contains tuberostemonine-type alkaloids predominantly. The presence of **1** in the plant is reasonable because **1** can be considered to be derived from neoturberostemonine (**2**), a major alkaloid found in the same plant, by losing the C-3 side chain.

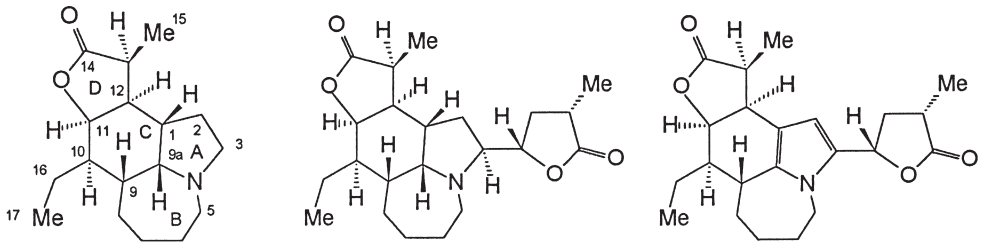
EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were measured on a Fisher–Johns apparatus and are uncorrected. Optical rotation was measure on JASCO, DIP-181 polarimeter. IR spectra were obtained on a Perkin–Elmer 599 B spectrometer. NMR spectra were recorded using a Bruker DRX 500 NMR spectrometer in $CDCl_3$. Chemical shifts are presented on the δ (ppm) scale using TMS

TABLE II HMBC and NOESY correlations of isostenine (**1**)

Position	*HMBC*	*NOESY*
1	C-3, 9, 13	H-2, 9a, 12, 15
2	C-12	H-3
3		H-2, 12
5	C-7	H-6
6	C-5, 8	H-5, 7
7	C-5, 9	H-6, 8, 9a
8	C-6, 7, 10	H-9a, 10
9	C-7	H-10
9a	C-2, 12	H-1, 2, 5, 7
10		H-8, 9, 11
11	C-1, 9	H-10, 12, 13, 17
12	C-2, 13, 14	H-1, 3, 11, 13
13	C-1, 12, 14, 15	H-11, 12, 15
15	C-12, 13, 14	H-1, 2, 13
16	C-11, 17	H-8, 10, 11
17	C-10, 16	H-10, 11, 16



1 **2** **3**

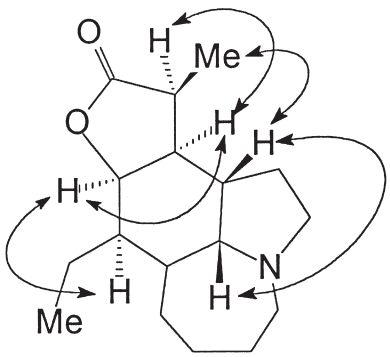


FIGURE 1 Results of NOE difference experiment of **1**

as internal standard. EIMS and HREIMS data were obtained by Finnigan-450 and MAT-711 mass pectrometers, respectively. Column chromatography was performed with Si gel 60 (Qingdao Marine chemical Qingdao, People's Republic of China), 100–200 mesh.

Plant Material

Roots of *S. collinsae* were collected in Langson province of northern Vietnam in October 1998. A voucher specimen (No. PHD981001) is deposited in the Herbarium of Institute of Natural Sources, National Center of Sciences and Technology of Vietnam.

Extraction and Isolation

The ground roots (8 kg) were percolated with 95% EtOH. After removal of solvent by evaporation, the residue was acidified with diluted HCl (4%) and filtered. The filtrate was alkalized with aq. NH_3 and extracted with $CHCl_3$. Crude alkaloids (3.0 g), obtained from $CHCl_3$ extracts, were crystallized from EtOH to yield pure **2** (2.4 g). A mixture of the mother liquor and remaining $CHCl_3$ extracts was subjected to column chromatography on silica gel eluting with $CHCl_3$–MeOH (15:1) to afford **1** (21 mg) and **3** (45 mg).

Isostenine (**1**), white crystals, mp 213–215°C; $[\alpha]_D^{25} = +92$ ($CHCl_3$, *c* 0.6); HREIMS *m/z* 276.1952 $[M - 1]^+$ (calcd for $C_{17}H_{26}NO_2$, 276.1956); IR (KBr) ν_{max} (cm^{-1}) 3421, 2910, 1762, 1463, 1164, 985, 946, 875, 553; EIMS *m/z* 277 (M^+) (30.04%), 276 $[M - 1]^+$ (base peak), 248, 204, 191, 136, 82; ^1H and ^{13}C NMR ($CDCl_3$) data: see Table I.

Neotuberostemonine (**2**) [6] obtained as white needles from EtOH, mp 160–162°C; $[\alpha]_D^{25} = +66$ (EtOH, *c* 0.6). Its IR spectrum (KBr) showed the presence of a γ-lactone (1760 cm^{-1}). EIMS *m/z* 375 (M^+), 276 (base peak, $[M - C_5H_7O_2]^+$), 232, 174, 149,128. ^1H NMR ($CDCl_3$) δ: 0.99 (3H, d, $J = 7.2$ Hz, 17-CH_3), 1.25 (3H, d, $J = 7.0$ Hz, 15-CH_3), 1.26 (3H, d, $J = 7.0$ Hz, 22-CH_3), 1.64 (2H, m, 2-H), 1.75 (1H, m, 10-H), 1.78 (1H, m, 1-H), 2.60 (1H, m, 20-H), 2.88 (1H, m, 13-H), 4,47 (1H, m, 18-H), 4.51 (1H, t, $J = 3$ Hz, 11-H).

Bisdehydroneotuberostemonine (**3**) [6] obtained as white needles from EtOH, mp 172–174°C; $[\alpha]_D^{25} = -32$ (EtOH, *c* 0.6). Its IR spectrum (KBr) showed the presence of a γ-lactone (1760 cm^{-1}). EIMS *m/z* 371 (M^+), 342, 327, 298, 272, 254, 198, 130, 99, 71. ^1H NMR ($CDCl_3$) δ: 1.03 (3H, d, $J = 7.5$ Hz, 17-CH_3), 1.30 (3H, d, $J = 7.0$ Hz, 22-CH_3), 1.90 (1H, m, 10-H), 2.80 (1H, m, 20H), 2.96 (1H, m, 13-H), 4.62 (1H, m, 11-H), 5.33 (1H, dd, $J = 10.8$ Hz, 5.0, 18-H), 5.51 (1H, dd, $J = 6.9$ Hz, 5.3, 12-H), 9.96 (1H, s, 2-H).

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