Alkaloids from the Roots of *Stemona cochinchinensis*

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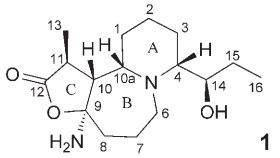
Phytochemical investigation of the roots of *Stemona cochinchinensis* led to the isolation and structure elucidation of a new pyrido[1,2-*a*]azepine-type alkaloid, stemocochinamine (**1**), and of four new pyrrolo[1,2-*a*]azepine-type alkaloids, bisdehydrostemocochinine (**2**), isobisdehydrostemocochinine (**3**), neostemocochinine (**4**), and isoneostemocochinine (**5**), together with six known alkaloids. Their structures were established on the basis of extensive 1D- and 2D-NMR analyses in combination with HR-MS experiments.

Introduction. – Plants from the genus *Stemona* (Stemonaceae) have long been used in the traditional medicine of China and Southeastern Asian countries [1][2]. Today, extracts from the roots of *Stemona* plants are still being used for the treatment of respiratory disorders, including pulmonary tuberculosis and bronchitis, or they are used externally against different insect pests [3–5]. Chemical investigations on this genus have resulted in the isolation of more than 90 different alkaloids, most of which share the common pyrrolo[1,2-*a*]azepine basic nucleus, a minor fraction also containing the pyrido[1,2-*a*]azepine skeleton [5–7].

Stemona cochinchinensis GAGNEP. is one of the three endemic *Stemona* species in Vietnam. *Greger et al.* [6] reported two protostemonine-type alkaloids and two stemofoline-type ones from this species [6]. In a preliminary investigation on this plant, *Dien et al.* [8] reported three known alkaloids and three bisbenzopyrans [8]. Subsequently, the same group investigated the minor alkaloidal constituents from the title plant; this led to the isolation of cochinchistemonine, which comprises a new alkaloidal skeleton based on a pyrido[1,2-*a*]azepine and a spiro-type α,β-unsaturated-γ-lactone moiety [9].

Herein, we describe the isolation and structural elucidation of five new metabolites of *S. cochinchinensis*, including stemocochinamine (**1**), a new pyrido[1,2-*a*]azepine-type alkaloid with an uncommon hemiaminal-type amino group, as well as four pyrrolo[1,2-*a*]azepines named bisdehydrostemocochinine (**2**), isobisdehydrostemocochinine (**3**), neostemocochinine (**4**), and isoneostemocochinine (**5**), two pairs each of the corresponding C(12)-epimers. Further, six known alkaloids were also obtained and identified as protostemonine, dehydroprotostemonine, oxyprotostemonine [6], bisdehydroprotostemonine [10], maistemonine, and isomaistemonine [11].



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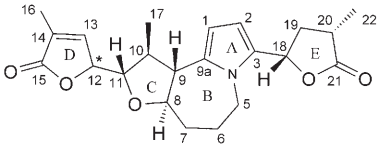
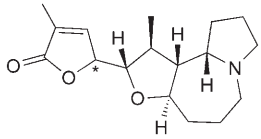


2 (12*R**)
3 (12*S**)



4 (12*R**)
5 (12*S**)

Arbitrary atom numbering and the relative configurations are shown

Results and Discussion. – 1. *Structure Elucidation*. Compound **1**, obtained as colorless needles, was assigned the molecular formula $C_{16}H_{28}N_2O_3$, based on HR-ESI-MS analysis (*m/z* 319.1989 ($[M + Na]^+$; calc. 319.1998), indicating four degrees of unsaturation. The broad and sharp IR absorption at 3390 cm^{-1} indicated the presence of a hydroxy (OH) or amino (NH or NH_2) group. The sharp absorption band at 1695 cm^{-1}, together with the resonance at δ(C) 178.9 in the ^{13}C-NMR spectrum (*Table 1*), suggested the presence of a C=O group. The EI-MS peak at *m/z* 237 ($[M - 59]^+$) pointed to a typical hydroxypropyl side chain, commonly occurring in pyrido[1,2-*a*]azepine-type alkaloids [6].

Table 1. *^{1}H- and ^{13}C-NMR (DEPT) Data of* **1**. At 400/100 MHz, resp., in $CDCl_3$ containing a small amount of CD_3OD; δ in ppm rel. to solvent signals [δ(H) $CHCl_3$: 7.26; δ(C) $CDCl_3$: 77.00], *J* in Hz. Arbitrary atom numbering.

	δ(H)	δ(C)		δ(H)	δ(C)
1	a: 1.82–1.88 (*m*)	28.3 (*t*)	9	–	97.0 (*s*)
	b: 1.64–1.70 (*m*)		10	2.16 (*dd*, *J* = 2.1, 9.3)	52.4 (*d*)
2	1.91–1.97 (*m*, 2 H)	23.3 (*t*)	10a	3.12 (*d*, *J* = 5.0)	56.6 (*d*)
3	a: 1.72–1.78 (*m*)	24.5 (*t*)	11	2.99–3.05 (*m*)	35.8 (*d*)
	b: 1.58–1.64 (*m*)		12	–	178.9 (*s*)
4	2.72 (*dt*, *J* = 3.0, 10.1)	64.0 (*d*)	13	1.21 (*d*, *J* = 7.2)	16.5 (*q*)
6	3.85–3.92 (*m*)	68.2 (*t*)	14	3.57 (*dt*, *J* = 2.8, 8.7)	71.3 (*d*)
7	a: 2.00–2.04 (*m*)	24.1 (*t*)	15	a: 1.47–1.53 (*m*)	25.8 (*t*)
	b: 1.93–1.96 (*m*)			b: 1.19–1.24 (*m*)	
8	1.98–2.05 (*m*)	35.0 (*t*)	16	0.89 (*t*, *J* = 7.2)	8.9 (*q*)

The ^{1}H-NMR spectrum of **1** (*Table 1*) displayed resonances of two Me groups (δ(H) 0.89 (*t*, *J* = 7.2 Hz), 1.21 (*d*, *J* = 7.2 Hz)). The ^{13}C-NMR spectrum showed some 15 more resonances, which were classified into one sp^3 quaternary C-atom, five sp^3 tertiary C-atoms, seven sp^3 secondary C-atoms, and two Me groups. Thus, three active H-atoms were revealed in the molecule. Because one degree of unsaturation was due to a C=O group, the remaining three degrees indicated a tricyclic skeleton.

On the basis of the HSQC and ^{1}H,^{1}H-COSY spectra of **1** (*Fig. 1,a*), a C_{11} aliphatic chain was inferred, ranging from Me(16) (*t*) to Me(13) (*d*), as well as a C_3 unit from

C(6) to C(8)[1]). The linkages of the two fragments and other atoms were determined by HMBC correlations (*Fig. 1,a*). Further, the low-field chemical shifts of C(4) (δ(H) 2.72 (*dt*, $J = 3.0, 10.1$ Hz); δ(C) 64.0), of C(6) (δ(H) 3.85–3.92 (*m*, 2 H); δ(C) 68.2), and of C(10a) (δ(H) 3.12 (*d*, $J = 5.0$ Hz); δ(C) 56.6) suggested that these positions bore a N-atom (*Table 1*).

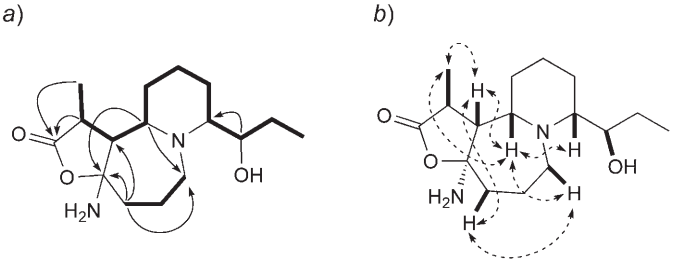


Fig. 1. a) *^{1}H,^{1}H-COSY* (—) *and key HMBC* (→) *correlations of* **1**. b) *Key ROESY correlations of* **1**.

The azepine ring of **1** was established by HMBC correlations from CH_2(8) (δ(H) 1.98–2.05 (*m*, 2 H)) to both C(10) (δ(C) 52.4) and C(9) (δ(C) 97.0), as well as from H–C(10a) to both C(6) and C(9). This structural moiety, *i.e.*, a pyrido[1,2-*a*]azepine with a 1-hydroxypropyl side chain at C(4), has been observed before in stemokerrin [6]. The additional C=O resonance was assigned to C(12), based on HMBC correlations with both H–C(11) (δ(H) 2.99–3.05 (*m*)) and Me(13). Therefore, ring *C* in **1** corresponds to an α-methylated γ-lactone, just as in stemonine [11].

The obvious low-field chemical shift of the quaternary C(9) atom (δ(C) 97.0) suggested that another electron-withdrawing functional group might be attached to it, besides the O-atom of ring *C*. According to the elemental constitution, an NH_2 group was assumed to be present at this position[2]), forming a hemiacetal-like structure. This was supported by the EI-MS peak at *m*/*z* 220, resulting from the loss of the hydroxypropyl side chain and ammonia ($[M - C_3H_7O - NH_3]^+$), as shown in the *Scheme*.

The relative configuration of **1** was derived by a ROESY experiment (*Fig. 1,b*) in combination with biogenetic considerations. The correlations of H–C(4)/H–C(10a), H_b–C(6)/H–C(10a), H–C(10)/H–C(10a), Me(13)/H–C(10), and Me(13)/H–C(10a) indicated that H–C(4), H_b–C(6), H–C(10), H–C(10a), and Me(13) were all β-orientated, the piperidine ring being in a chair conformation, with H–C(4) and H–C(10) in axial positions [6]. Therefore, H_b–C(8) also had to be axially and β-orientated, the 9-NH_2 group thus being in α-position. The relative configuration at C(14) was biogenetically assumed to be (*R*), just as in stemokerrin-type alkaloids. Accordingly, the structure of **1** was fully constructed, the detailed assignments of the ^{1}H- and ^{13}C-NMR resonances (*Table 1*) being determined by HSQC, HMBC, and ^{1}H,^{1}H-COSY experiments.

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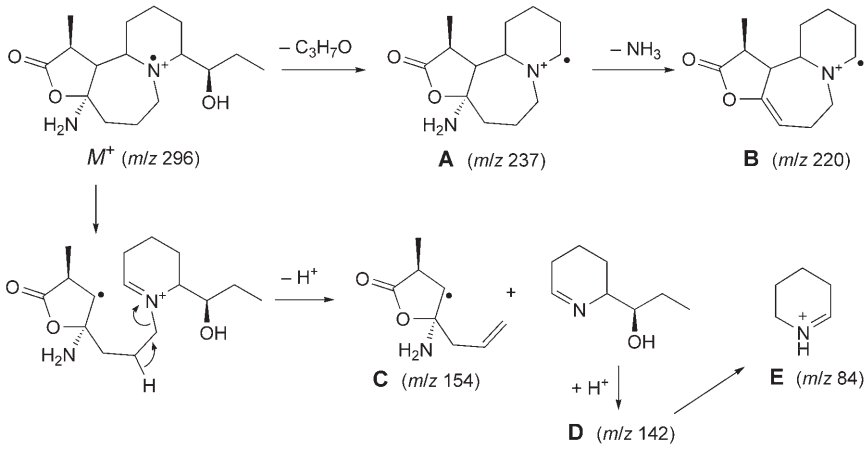
[1]) Arbitrary atom numbering. For systematic names, see *Exper. Part.*

[2]) We cannot fully exclude the possibility that **1** is an artifact formed in the presence of small amounts of aq. NH_3 during extraction.

Scheme. *Proposed EI-MS-Fragmentation Pathway of* **1**. For exact *m*/*z* values, see *Table 2*.



The proposed fragmentation pathway of **1** (*Scheme*) [12][13] can be taken as additional evidence for the above structural elucidation. The accurate masses of some key fragments are presented in *Table 2*. The molecular ion may first eliminate the hydroxypropyl group to form fragment **A**, and then looses ammonia to form fragment **B**. Alternatively, the azepine ring of the molecular ion may be subjected to α-cleavage and then to *i*-cleavage to form fragments **C** and **D**, the latter finally eliminating the hydroxypropyl group to afford fragment **E**.

Table 2. *Calculated Masses and* m/z *Values of* **1** *and Its Fragmentation Ions.* For assignments, see the *Scheme*.

Ion	Formula	$M_{calc.}$	*m*/*z*	Δ [ppm]
M^+	$C_{16}H_{28}N_2O_3$	296.2100	296.2112	– 1.2
A	$C_{13}H_{21}N_2O_2$	237.1603	237.1605	– 0.2
B	$C_{13}H_{18}NO_2$	220.1338	220.1351	– 1.3
C	$C_8H_{12}NO_2$	154.0868	154.0868	0
D	$C_8H_{16}NO$	142.1232	142.1216	1.6
E	$C_5H_{10}N$	84.0813	84.0807	0.6

Compound **2** was obtained as a yellow, amorphous powder, and HR-EI-MS suggested the molecular formula $C_{22}H_{27}NO_5$ (*m*/*z* 385.1882 (M^+; calc. 385.1887)). The strong and sharp IR band at 1763 cm^{-1} indicated a γ-lactone. The M^+ signal at *m*/*z* 385 and a fragment ion at *m*/*z* 286 ($[M - C_5H_7O_2]^+$) indicated the presence of a typical α-methyl-γ-lactone ring attached to C(3) of the azaazulene ring. The ^{1}H-NMR spectrum of **2** (*Table 3*) displayed resonances of two regular Me groups (δ(H) 1.30 (*d*, *J* = 6.5 Hz, Me(17)); 1.35 (*d*, *J* = 6.8 Hz, Me(22))), a vinylic Me group (δ(H) 1.94 (*d*, *J* = 1.6 Hz, Me(16))), an olefinic H-atom (δ(H) 7.20 (*q*, *J* = 1.6 Hz, H–C(13))), and three low-field signals (δ(H) 3.53 (*dt*, *J* = 9.8, 3.0 Hz, H–C(8)); 3.62–3.70 (*m*, H–C(11)); 4.84 (*dt*, *J* = 6.8, 1.6 Hz, H–C(12))), strongly resembling those of stemocochinine [6]. In addition,

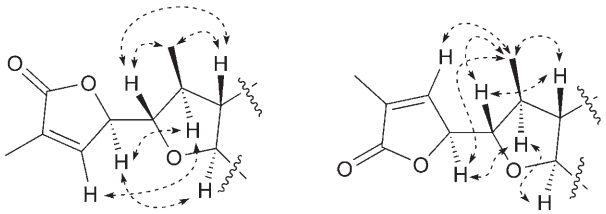
the presence of two aromatic olefinic H-atoms (δ(H) 5.96 (d, J = 3.6 Hz, H–C(1)); 6.13 (d, J = 3.6 Hz, H–C(2))) suggested a fused pyrrole ring [10], which was further supported by the downfield shifts of H_b–C(5) (δ(H) 3.70 (dd, J = 14.3, 7.0 Hz)), H_a–C(5) (δ(H) 4.30 (dd, J = 14.3, 5.8 Hz)), and H–C(18) (δ(H) 5.38 (dd, J = 11.2, 5.2 Hz)) in comparison with the corresponding data of stemocochinine. Therefore, the structural skeleton was constructed as a bisdehydro derivative of stemocochinine.

Table 3. *^{1}H- and ^{13}C-NMR (DEPT) Data of* **2** *and* **3**. At 400/100 MHz, resp., in $CDCl_3$; δ in ppm rel. to solvent signals [δ(H) $CHCl_3$: 7.26; δ(C) $CDCl_3$: 77.00], J in Hz. Arbitrary atom numbering.

	2		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)
1	5.96 (d, J = 3.6)	103.7 (d)	5.92 (d, J = 3.7)	103.6 (d)
2	6.13 (d, J = 3.6)	106.9 (d)	6.12 (d, J = 3.7)	106.9 (d)
3	–	128.4 (s)	–	128.5 (s)
5	a: 4.30 (dd, J = 5.8, 14.3)	45.5 (t)	a: 4.28 (dd, J = 6.0, 15.4)	45.5 (t)
	b: 3.70 (dd, J = 7.0, 14.3)		b: 3.67 (dd, J = 8.4, 15.4)	
6	a: 2.00–2.08 (m)	25.8 (t)	a: 1.95–2.01 (m)	25.9 (t)
	b: 1.58–1.64 (m)		b: 1.54–1.62 (m)	
7	a: 2.30–2.37 (m)	35.4 (t)	a: 2.23–2.31 (m)	35.3 (t)
	b: 1.60–1.66 (m)		b: 1.53–1.60 (m)	
8	3.53 (dt, J = 3.0, 9.8)	71.6 (d)	3.42–3.49 (m)	71.5 (d)
9	2.73–2.80 (m)	51.3 (d)	2.68–2.76 (m)	51.6 (d)
9a	–	133.2 (s)	–	133.4 (s)
10	2.55–2.61 (m)	38.9 (d)	2.63–2.68 (m)	41.4 (d)
11	3.62–3.70 (m)	83.3 (d)	3.92–3.98 (m)	83.1 (d)
12	4.84 (dt, J = 1.6, 6.8)	80.7 (d)	4.96–5.01 (m)	83.0 (d)
13	7.20 (q, J = 1.6)	145.6 (d)	7.00 (br. s)	147.0 (d)
14	–	131.5 (s)	–	130.9 (s)
15	–	174.0 (s)	–	174.0 (s)
16	1.94 (d, J = 1.6)	10.8 (q)	1.95 (s)	10.7 (q)
17	1.30 (d, J = 6.5)	16.5 (q)	1.27 (d, J = 6.1)	17.2 (q)
18	5.38 (dd, J = 5.2, 11.2)	84.0 (d)	5.46 (dd, J = 5.2, 11.0)	85.5 (d)
19	a: 2.72–2.78 (m)	34.8 (t)	a: 2.74–2.80 (m)	34.7 (t)
	b: 2.15–2.21 (m)		b: 2.22 (m)	
20	2.65–2.70 (m)	36.0 (d)	2.65–2.70 (m)	36.0 (d)
21	–	178.9 (s)	–	179.0 (s)
22	1.35 (d, J = 6.8)	14.9 (q)	1.34 (d, J = 6.8)	15.0 (q)

The skeleton of **2** was further confirmed by ^{13}C-NMR (DEPT) experiments (*Table 3*), which indicated 22 resonances, including three Me, four CH_2, and ten CH groups, as well as five quaternary C-atoms. The relative configuration of **2** was derived by a ROESY experiment (*Fig. 2*). The correlations of H–C(9)/H_b–C(5), of H–C(9)/H_b–C(7), and of H_b–C(7)/H_b–C(5) indicated that the seven-membered ring was in a stable chair conformation, H–C(9) being β-orientated. The relative correlations of H–C(11)/H–C(9), Me(17)/H–C(9), and Me(17)/H–C(11) indicated that H–C(11) and Me(17) were both β-orientated. The configuration at C(12) was determined to be (R) by comparing the J(11,12) values (6.6 Hz) with those of (11*S*,12*S*)-11,12-dihydrostemofoline [7]. The (12*R*)-configuration was further confirmed by ROESY

correlations of H–C(12)/H–C(10), H–C(13)/H–C(11), and H–C(13)/H–C(10). Thus, the full structure of **2** was established, and the detailed assignments of the ^{1}H- and ^{13}C-NMR resonances are shown in *Table 3*.



2 **3**

Fig. 2. *Key ROESY correlations of* **2** *and* **3**

Isobisdehydrostemocochinine (**3**) was obtained as a yellow, amorphous powder. The molecular formula was determined by HR-EI-MS as $C_{22}H_{27}NO_5$, the same as that of **2**. The presence of a γ-lactone was indicated by the strong and sharp IR absorption band at 1759 cm^{-1}. The ^{1}H- and ^{13}C-NMR data of **3** (*Table 3*) were similar to those of **2**. A careful analysis of these data resulted in the conclusion that both **3** and **2** shared the same structural skeleton. The major differences in their NMR data involved the chemical shifts of H–C(11), H–C(12), H–C(13), C(10), and C(12), suggesting that **3** was a stereoisomer of **2**. The relative configuration of **3** was disclosed by a ROESY experiment (*Fig. 2*). The correlations of H–C(11)/H–C(9) and H–C(11)/Me(17) revealed that H–C(9), H–C(11), and Me(17) were all β-orientated. The correlations of H–C(12)/H–C(10), H–C(13)/H–C(11), and H–C(12)/Me(17) suggested the (*S*)-configuration at C(12). The configurations at C(11) and C(12) were, thus, consistent with those of (11*S*,12*R*)-11,12-dihydrostemofoline [7].

Compounds **4** and **5** were isolated as a 1:1 mixture. Both compounds had the molecular formula $C_{17}H_{25}NO_3$, as deduced by HR-EI-MS analysis. The EI-MS base peak at *m*/*z* 194 ($[M - C_5H_5O_2]^+$) indicated the presence of an unsaturated α-methyl-γ-lactone. The ^{1}H-NMR spectra of **4** and **5** (*Table 4*) showed two sets of almost superimposable resonances: each set displayed a regular Me group (δ(H) 1.09 (*d*, *J* = 6.4 Hz) and 1.11 (*d*, *J* = 6.4 Hz), resp.), a vinylic Me group (δ(H) 1.92 (*d*, *J* = 1.8 Hz) and 1.95 (*d*, *J* = 1.6 Hz), resp.), an olefinic H-atom (δ(H) 7.18 (*dq*, *J* = 1.8, 3.2 Hz) and 7.00 (*dq*, *J* = 1.6, 3.0 Hz), resp.), and two low-field H-atoms (δ(H) 3.67 (*dd*, *J* = 6.6, 8.0 Hz) and 4.80 (*dt*, *J* = 1.9, 6.6 Hz); and δ(H) 3.79 (*dd*, *J* = 2.0, 8.8 Hz) and 4.89–4.93 (*m*), resp.).

In the ^{13}C-NMR spectra of the two compounds (*Table 4*), two sets of resonances were also observed. Upon comparing the NMR data of **4** and **5** with those of stemocochinine, we concluded that the α-methyl-γ-lactone moieties were lacking. This was supported by the fact that the molecular weights of **4** and **5** were 98 Da lower than that of stemocochinine, and only two of the three characteristic Me resonances were observed in their NMR spectra. The proposed structural skeletons were further confirmed by HSQC and HMBC experiments. Again, the ^{1}H-NMR data for H–C(11), H–C(12), and H–C(13) suggested a pair of stereoisomers, like in the case of **2** and **3**. A ROESY experiment revealed that the relative configurations of **4** and **5** were the

Table 4. *^{1}H- and ^{13}C-NMR* (DEPT) *Data of* **4** *and* **5**. At 400/100 MHz, resp., in $CDCl_3$; δ in ppm rel. to solvent signals (δ(H) $CHCl_3$: 7.26; δ(C) $CDCl_3$: 77.00), *J* in Hz. Arbitrary atom numbering.

	4		**5**	
	δ(H)	δ(C)	δ(H)	δ(C)
1	a: 1.78–1.85 (*m*) b: 1.52–1.60 (*m*)	23.2 (*t*)	a: 1.78–1.85 (*m*) b: 1.52 –1.60 (*m*)	23.2 (*t*)
2	a: 1.89–1.96 (*m*) b: 1.33–1.41 (*m*)	26.3 (*t*)	a: 1.89–1.96 (*m*) b: 1.28–1.35 (*m*)	26.3 (*t*)
3	2.65–2.75 (*m*)	52.1 (*d*)	2.65–2.75 (*m*)	52.0 (*d*)
5	a: 2.95–3.05 (*m*) b: 2.90–3.00 (*m*)	49.9 (*t*)	a: 2.95–3.05 (*m*) b: 2.90–3.00 (*m*)	49.8 (*t*)
6	a: 1.50–1.58 (*m*) b: 1.30–1.40 (*m*)	17.7 (*t*)	a: 1.50–1.58 (*m*) b: 1.30–1.40 (*m*)	17.5 (*t*)
7	a: 2.00–2.06 (*m*) b: 1.24–1.30 (*m*)	33.8 (*t*)	a: 2.00–2.06 (*m*) b: 1.24–1.30 (*m*)	33.7 (*t*)
8	4.05 (*dt*, *J* = 3.3, 10.2)	82.9 (*d*)	3.93 (*dt*, *J* = 3.3, 10.4)	82.6 (*d*)
9	2.10–2.17 (*m*)	51.8 (*d*)	2.08–2.15 (*m*)	51.4 (*d*)
9a	3.76–3.82 (*m*)	60.7 (*d*)	3.76–3.82 (*m*)	60.7 (*d*)
10	2.17–2.27 (*m*)	39.8 (*d*)	2.17–2.27 (*m*)	40.2 (*d*)
11	3.67 (*dd*, *J* = 6.6, 8.0)	80.6 (*d*)	3.79 (*dd*, *J* = 2.0, 8.8)	84.5 (*d*)
12	4.80 (*dt*, *J* = 1.9, 6.6)	78.3 (*d*)	4.89–4.93 (*m*)	78.9 (*d*)
13	7.18 (*dq*, *J* = 1.8, 3.2)	145.9 (*d*)	7.00 (*dq*, *J* = 1.6, 3.0)	146.0 (*d*)
14	–	131.1 (*s*)	–	130.9 (*s*)
15	–	173.9 (*s*)	–	174.1 (*s*)
16	1.92 (*d*, *J* = 1.8)	10.7 (*q*)	1.95 (*d*, *J* = 1.6)	10.6 (*q*)
17	1.09 (*d*, *J* = 6.4)	16.2 (*q*)	1.11 (*d*, *J* = 6.4)	14.9 (*q*)

same as of **2** and **3**, respectively, the key *J*(11,12) values of **4** and **5** being 6.6 and 2.0 Hz, respectively, in accord with the reported data [7].

2. *Biogenetic and Stereochemical Considerations.* The co-occurrence of stemokerrin-, maistemonine-, and protostemonine-type alkaloids in the same *Stemona* species supports the conclusion that alkaloids of the above three types share the same biogenetic pathway [5]. Two pairs of C(12) isomers have been discussed in this paper. Their configurations, especially that at C(12), can be elucidated from the *J*(11,12) values and ROESY experiments. *Mungkornasawakul et al.* reported in 2004 that *J*(11,12) values directly reflect the configurations at C(12) in (11*S*)-11,12-dihydrostemofoline epimers [7], the corresponding values for (11*S*,12*S*)- and (11*S*,12*R*)-dihydrostemofoline being 7 and 3 Hz, respectively. Our data are, thus, in good agreement with this conclusion.

ROESY Correlations can also be considered to confirm the configuration at C(12). According to the spatial positions in different HGS molecular models, correlations of H–C(12)/H–C(10) and of H–C(13)/H–C(11) should be observed in the ROESY spectra of both the (12*S*)- and (12*R*)-configured compounds. In contrast, the ROESY correlation of H–C(12)/Me(17) should be only observable in the (12*S*)-configured congener, whereas that of H–C(13)/H–C(10) is observed exclusively in the (12*R*)-configured model. These differences are also reflected in the above two pairs of isomers.

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Experimental Part

General. Column chromatography (CC): Silica gel (200–300 and 300–400 mesh; *QingDao Marine Chemical Industry*). TLC: Precoated silica gel *GF254* plates (*YanTai Chemical Industry*). UV Spectra: *Hewlett-Packard 8452A* diode-array spectrophotometer; λ_{max} in nm. Optical rotation: *Perkin-Elmer-341* polarimeter. IR Spectra: *Nicolet Magna-750* FT-IR spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker AM-400* and *INVOR-600* NMR spectrometers, δ in ppm rel. to Me_4Si, J in Hz; assignments based on $^1H,^1H$-COSY, HSQC, ROESY, and HMBC experiments. EI- and HR-EI-MS: *Finnigan MAT-95* mass spectrometer; in m/z. ESI-and HR-ESI-MS: *Micromass LC-MS-MS* apparatus; in m/z.

High-Performance Liquid Chromatography. Anal. HPLC was performed on a *Waters-2690* instrument with a *996* photodiode-array detector (PAD) and an *Alltech ELSD-2000* detector. Chromatographic separation was carried out on a *Waters XTerra RP18* column (4.6 × 250 mm, 5 μm), using a gradient solvent system comprised of H_2O (*A*) and MeCN (*B*) containing 0.1% ammonia, at a flow rate of 1.0 ml/min. The temp. for the *ELSD* drift tube was 105°, and the air flow was 3.2 l/min. Semi-prep. HPLC was performed on a *Waters 2690* instrument with a *996* PAD. Chromatographic separation was carried out on a *Waters XTerra RP18* column (7.8 × 150 mm, 7 μm), using a binary gradient of solvents *A* and *B* at a flow rate of 3 ml/min. Prep. HPLC was performed on a *Varian SD1* instrument with a *320* single-wave detector. Chromatographic separation was carried out on a *Merck C18* column (220 × 25 mm, 10 μm), using a binary gradient of solvents *A* and *B* at a flow rate of 15 ml/min.

Plant Material. The roots of *S. cochinchinensis* (1.52 kg) were collected in Sonla Province, Northern Vietnam, in April 2002 by *Nguyen Duc Thinh*, Director of Sonla State Farm. The plant material was identified by Prof. Dr. *Vu Ngoc Chuyen*, Hanoi University of Pharmacy, Hanoi, Vietnam.

Extraction and Isolation. The air-dried roots of *S. cochinchinensis* were ground into a powder and extracted with 95% EtOH. The crude extract was acidified with 4% aq. HCl and then partitioned between CH_2Cl_2 and H_2O. The aq. part was basified with aq. NH_3 and then extracted with CH_2Cl_2 to afford the crude alkaloidal fraction (35.52 g). Part of this material (15 g) was subjected to CC (SiO_2; 1. petroleum ether (PE)/acetone 9:1 → 1:1, 2. acetone, 3. MeOH) to afford twelve fractions (*Fr. 1 – Fr. 12*). *Fr. 4* was subjected to CC (SiO_2; PE/acetone 8:1 → 4:1) to afford bisdehydroprotostemonine, protostemonine, dehydroprotostemonine, and oxyprotostemonine. *Fr. 6* was purified by CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1) to yield a mixture of maistemonine and isomaistemonine. The residue of this fraction was further separated by CC (SiO_2; PE/acetone 4:1) and then further purified by prep. HPLC (*B*/*A* 40 → 55% over 1 h, then *B*/*A* 55 → 70% over 2 h), which afforded **2** (25 mg) and **3** (12 mg). *Fr. 8* was repeatedly subjected to CC (SiO_2 and *Sephadex LH-20*) to give five subfractions (*Fr. 8.1 – Fr. 8.5*). *Fr. 8.2* was further separated by semi-prep. HPLC (*B*/*A* 35:65) to yield the isomers **4** and **5**, which were found to be interconverted in basic solvent at r.t. *Fr. 9* was separated by repeated CC (*MCI* gel and SiO_2) to afford **1** (11 mg).

Stemocochinamine (= *(1S*,3aR*,8R*,11aS*,11bR*)-3a-Amino-8-[(1R)-1-hydroxypropyl]-1-methyldecahydrofuro[3,2-c]pyrido[1,2-a]azepin-2(1H)-one*; **1**). Colorless needles (hexane/acetone). $[\alpha]_D^{20} = 0$ ($c = 0.10$, $CHCl_3$). IR (film): 3390, 1695, 1456, 1385, 1321, 1290, 1014, 976. ^1H- and ^{13}C-NMR: see *Table 1*. ESI-MS: 297.0 ($[M+1]^+$), 319.1 ($[M+Na]^+$). EI-MS: 252 (4), 237 (65, $[M-C_3H_7O]^+$), 220 (10, $[M-C_3H_7O-NH_3]^+$), 194 (25), 154 (5), 142 (16), 124 (10), 84 (40), 82 (100). HR-EI-MS: 296.2112 (M^+, $C_{16}H_{28}N_2O_3^+$; calc. 296.2100). HR-ESI-MS: 319.1989 ($[M+Na]^+$, $C_{16}H_{28}N_2O_3Na^+$; calc. 319.1998).

Bisdehydrostemocochinine (= *(5R*)-3-Methyl-5-{(1S*,2S*,3aR*,10bR*)-1-methyl-8-[(2S*,4S*)-4-methyl-5-oxotetrahydrofuran-2-yl]-1,3a,4,5,6,10b-hexahydro-2H-furo[3,2-c]pyrrolo[1,2-a]azepin-2-yl}-furan-2(5H)-one*; **2**). Yellow, amorphous powder. $[\alpha]_D^{20} = -9$ ($c = 0.15$, $CHCl_3$). UV (MeOH): 239.4. IR (KBr): 1763, 1439, 1161, 1068, 1041, 920, 754. ^1H- and ^{13}C-NMR: see *Table 3*. ESI-MS: 386.1 ($[M+1]^+$), 408.1 ($[M+Na]^+$), 771.3 ($[2M+1]^+$), 793.2 ($[2M+Na]^+$), 769.6 ($[2M-1]^+$). EI-MS: 385 (90, M^+),

341 (61), 326 (16), 288 (100, $[M - C_5H_5O_3]^+$), 286 (24, $[M - C_5H_7O_3]^+$), 260 (44), 242 (16), 218 (22), 190 (17), 172 (25), 99 (30). HR-EI-MS: 385.1882 (M^+, $C_{22}H_{27}NO_5^+$; calc. 385.1887).

Isobisdehydrostemocochinine (=*(5S*)-3-Methyl-5-[(1S*,2S*,3aR*,10bR*)-1-methyl-8-[(2S*,4S*)-4-methyl-5-oxotetrahydrofuran-2-yl]-1,3a,4,5,6,10b-hexahydro-2H-furo[3,2-c]pyrrolo[1,2-a]azepin-2-yl}-furan-2(5H)-one*; **3**). Yellow, amorphous powder. $[\alpha]_D^{20} = -55$ ($c = 0.17$, $CHCl_3$). UV (MeOH): 240.1. IR (KBr): 1759, 1439, 1161, 1082, 1051, 922, 754. ^{1}H- and ^{13}C-NMR: see *Table 3*. ESI-MS: 386.1 ($[M + 1]^+$), 408.1 ($[M + Na]^+$). EI-MS: 385 (88, M^+), 341 (64), 326 (16), 288 (100, $[M - C_5H_5O_3]^+$), 260 (46), 244 (19), 218 (20), 190 (18), 172 (27), 149 (16), 99 (31), 85 (48), 83 (74). HR-EI-MS: 385.1889 (M^+, $C_{22}H_{27}NO_5^+$; calc. 385.1887).

Neostemocochinine and Isoneostemocochinine (=*(5R*)- and (5S*)-3-Methyl-5-[(1S*,2S*,3aR*,10aS*,10bR*)-1-methyldecahydro-2H-furo[3,2-c]pyrrolo[1,2-a]azepin-2-yl]furan-2(5H)-one*; **4**/**5**). Yellow, amorphous powder. UV (MeOH): 239.1. IR (KBr): 1755, 1664, 1618, 1458,1047. ^{1}H- and ^{13}C-NMR: see *Table 4*. ESI-MS: 292.0 ($[M + 1]^+$), 604.7 ($[2M + Na]^+$). EI-MS: 291 (20, M^+), 236 (6), 194 (100), 192 (14), 153 (12), 111 (14), 96 (24), 84 (32), 70 (36). HR-EI-MS: 291.1826 (M^+, $C_{17}H_{25}NO_3^+$; calc. 291.1835).

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