Three New Hasubanan Alkaloids from *Stephania hernandifolia* (WILLD.) WALP.

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Three new hasubanan alkaloids, hernsubanines A–C (**1**–**3**, resp.), were isolated from the whole plants of *Stephania hernandifolia*. Their structures were elucidated on the basis of physical and spectroscopic data. In *in vitro* tests for cytotoxic activity against two human cancer cell lines, A 549 and K 562, compound **1** did not exhibit any cytotoxicity.

Introduction. – The hasubanan-type alkaloids represent a group of naturally occurring minor compounds, which are distributed mainly in the plants of the genus *Stephania*, Menispermaceae [1–22]. Although they are structurally similar to the morphine alkaloids, so far, the hasubanan alkaloids isolated have not been evaluated for their analgesic activities, but some weak anti-HBV activity has been reported [22][23]. The opposite relative orientations of the N-containing rings in the hasubanan and morphinan alkaloids indicate the possibility that the hasubanan bases might also possess some interesting physiological properties.

The species *S. hernandifolia* (WILLD.) WALP. of the Menispermaceae family, a perennial twining vine distributed mainly in Southwest China, has been used as a folk medicine for the treatment of rheumatoid arthritis, heatstroke, dysentery, mumps, sore throat, stomatitis, analgesia, and paralysis [24]. Previous studies of this plant led to the isolation of some isoquinoline alkaloids, such as the hasubanan hernandine [13–15]. In the course of our investigation on the alkaloids, in the *Stephania* genus [25–27], three new hasubanan alkaloids, hernsubanines A–C (**1**–**3**, resp.; *Fig. 1*), were isolated from the whole plants of *S. hernandifolia*. In this article, we describe the isolation and structure elucidation of these new alkaloids.

Results and Discussion. – Hernsubanine **A** (**1**; *Fig. 1*), isolated as colorless crystals, had the molecular formula $C_{29}H_{31}NO_9$ on the basis of the HR-ESI-MS (*m*/*z* 560.1900 ($[M+Na]^+$; calc. 560.1896)), with fifteen degrees of unsaturation. The UV absorptions of **1** at λ_{max} 246 (3.11), 293 (3.18), and 322 nm (3.12) implied the presence of a cinnamate subunit. The IR spectrum of **1** exhibited absorption bands for OH (3452 cm^{-1}), conjugated C=O group (1634 cm^{-1}), and for an aryl group (1609 and 1484 cm^{-1}). The ^{13}C-NMR spectrum consisted 29 signals corresponding to three MeO, five CH_2 (four saturated and one O–CH_2–O), and ten CH (five aromatic, two olefinic,

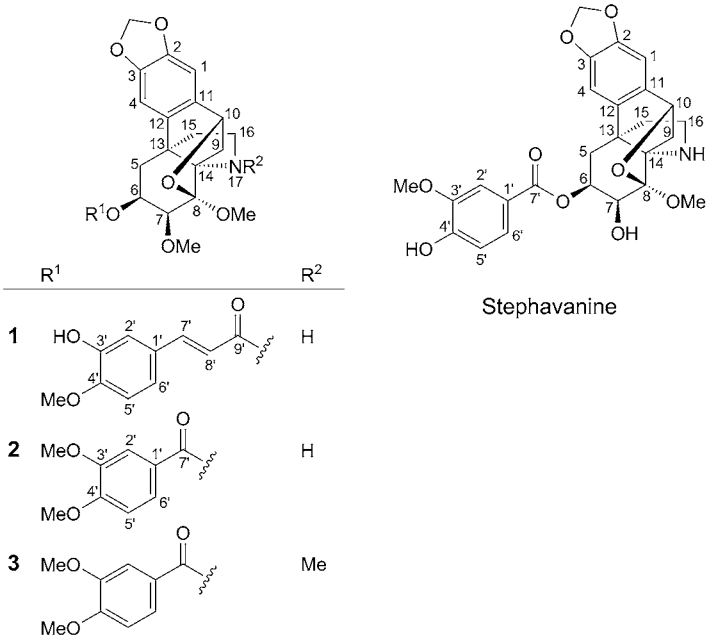

Fig. 1. *The structures of hernsubanines A – C* (**1** – **3**, resp.) *and stephavanine*

and three saturated) groups, and eleven quaternary C-atoms (one C=O, seven aromatic, and three saturated). On the basis of the typical EI-MS fragment-ion peaks at *m*/*z* 213 and 194, and the ^{13}C-NMR signals at δ(C) 101.6 (*s*) and 77.2 (*d*), compound **1** was deduced to be a hasubanan-type alkaloid with an acetal bridge between C(8) and C(10) [1].

The ^{1}H,^{1}H-COSY and HMQC spectra revealed the presence of a O–CH_2–O group, and isolated –CH_2CHORCHOR–, and –CH_2CHOR–, –CH_2CH_2– fragments (*Fig. 2*). Further examination of the ^{1}H-, ^{13}C-, and 2D-NMR data, together with the degree of molecular unsaturation, suggested that compound **1** was similar to the known alkaloid

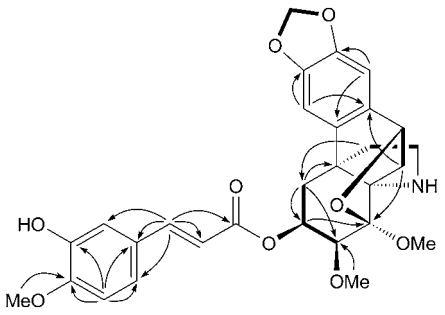

Fig. 2. *^{1}H,^{1}H-COSY* (—) *and key HMB correlations* (H → C) *of* **1**

Table 1. *^{1}H-NMR Data of Compounds* **1**–**3** *and Stephavanine* (δ in ppm, J in Hz). Atom numbering as indicated in *Fig. 1*.

H–Atom	**1**[a])	**2**[a])	**3**[b])	Stephavanine[c])
H–C(1)	6.53 (*s*)	6.48 (*s*)	6.42 (*s*)	6.46 (*s*)
H–C(4)	6.67 (*s*)	6.56 (*s*)	6.55 (*s*)	6.48 (*s*)
CH_2(5)	2.25 (*dd*, *J* = 2.4, 14.8), 2.38–2.42 (*m*[d]))	2.34 (*dd*, *J* = 3.2, 15.2), 2.41–2.46 (*m*[d]))	1.80–1.86 (*m*)	2.32 (*dd*, *J* = 3.0, 15.0), 2.53 (*dd*, *J* = 3.0, 15.0)
H–C(6)	5.33–5.36 (*m*)	5.49–5.52 (*m*)	5.49–5.50 (*m*)	5.15 (*m*)
H–C(7)	3.75 (*d*, *J* = 4.0)	3.81 (*d*, *J* = 4.4)	3.80 (br. *s*)	4.28 (*d*, *J* = 4.2)
H–C(9)	1.91 (*d*, *J* = 10.4), 2.36–2.39 (*m*[d]))	1.90 (*d*, *J* = 10.4), 2.40–2.42 (*m*[d]))	1.53 (*d*, *J* = 10.4), 2.69 (*dd*, *J* = 6.2, 10.4)	1.93 (*d*, *J* = 11.0), 2.46 (*dd*, *J* = 5.1, 11.0)
H–C(10)	4.86 (*d*, *J* = 5.6)	4.86 (*d*, *J* = 5.6)	4.90 (*d*, *J* = 6.2)	4.82 (*d*, *J* = 5.1)
CH_2(15)	1.98–2.06 (*m*)	1.95–2.06 (*m*)	2.38 (br. *s*)	2.00 (*m*)
CH_2(16)	3.14–3.18 (*m*)	3.15–3.19 (*m*)	2.51–2.53 (*m*), 3.37–3.39 (*m*)	3.15 (*m*)
Me–N(17)			2.56 (*s*)	
H–C(2′)	7.00 (*d*, *J* = 2.0)	7.33 (*d*, *J* = 2.0)	7.31 (*d*, *J* = 1.6)	7.25 (*d*, *J* = 2.0)
H–C(5′)	6.84 (*d*, *J* = 8.4)	6.63 (*d*, *J* = 8.4)	6.61 (*d*, *J* = 8.4)	6.75 (*d*, *J* = 8.5)
H–C(6′)	6.96 (*dd*, *J* = 2.0, 8.4)	6.84 (*dd*, *J* = 2.0, 8.4)	6.78 (*dd*, *J* = 1.6, 8.4)	6.92 (*dd*, *J* = 2.0, 8.5)
H–C(7′)	7.22 (*d*, *J* = 16.0)			
H–C(8′)	5.58 (*d*, *J* = 16.0)			
MeO–C(7)	3.38 (*s*)	3.40 (*s*)	3.40 (*s*)	
MeO–C(8)	3.57 (*s*)	3.58 (*s*)	3.54 (*s*)	3.60 (*s*)
MeO–C(3′)		3.89 (*s*)	3.88 (*s*)	3.92 (*s*)
MeO–C(4′)	3.92 (*s*)	3.89 (*s*)	3.88 (*s*)	
OCH_2O	5.02, 5.66 (2*d*, *J* = 1.6)	5.22, 5.72 (2*d*, *J* = 1.6)	5.23, 5.71 (2*d*, *J* = 1.4)	5.09, 5.69 (2*d*, *J* = 1.5)

[a]) Recorded in $CDCl_3$ at 400 MHz. [b]) Recorded in $CDCl_3$ at 500 MHz. [c]) Data from [5]. [d]) Overlapping signals.

stephavanine (*Fig. 1*) [5], except for the substituents at C(6) and C(7). In **1**, the presence of a 3-hydroxy-4-methoxycinnamate group was deduced from the NMR data (*Tables 1* and *2*), and confirmed by HMBCs of H–C(7′) with C(1′), C(2′), C(6′), C(8′), and C(9′), of H–C(5′) with C(1′), C(3′), C(4′), and C(6′), and MeO–C(4′)/C(4′) (*Fig. 2*). In the HMBC spectrum, one MeO group was assigned to C(7) by correlation MeO–C(7)/C(7), thus the 3-hydroxy-4-methoxycinnamate group was attached to C(6). Therefore, the structure of **1** was established as (6*β*,7*β*,8*β*,10*β*)-8,10-epoxy-7,8-dimethoxy-2,3-(methylenedioxy)hasubanan-6-yl (*Z*)-3-hydroxy-4-methoxycinnamate and was confirmed by HSQC, HMBC, ^{1}H,^{1}H-COSY, and ROESY spectra.

Hernsubanine B (**2**), obtained as colorless crystals, had the molecular formula $C_{28}H_{31}NO_9$ as determined by the HR-ESI-MS (*m*/*z* 526.2069 ($[M+H]^+$; calc. 526.2077)). The only difference between alkaloids **1** and **2** turned out to be in the ester moiety at C(6). In **2**, the ester group was determined to be a 3,4-dimethoxybenzoyl group as judged by the ^{1}H- and ^{13}C-NMR data (*Tables 1* and *2*). The assignments of the ^{1}H- and ^{13}C-NMR data were confirmed by HMQC, HMBC, and

Table 2. *^{13}C-NMR Data for Compounds* **1**–**3** *and Stephavanine* (δ in ppm). Atom numbering as indicated in *Fig. 1*.

C–Atom	**1**[a])	**2**[a])	**3**[b])	Stephavanine[c])
C(1)	106.4 (*d*)	106.5 (*d*)	106.9 (*d*)	107.2 (*d*)
C(2)	147.7 (*s*)	147.5 (*s*)	147.5 (*s*)	147.6 (*s*)
C(3)	144.9 (*s*)	144.6 (*s*)	144.5 (*s*)	144.7 (*s*)
C(4)	107.1 (*d*)	107.3 (*d*)	106.0 (*d*)	106.5 (*d*)
C(5)	36.0 (*t*)	35.9 (*t*)	37.3 (*t*)	35.4 (*t*)
C(6)	67.4 (*d*)	67.5 (*d*)	67.8 (*d*)	72.0 (*d*)
C(7)	81.1 (*d*)	81.2 (*d*)	81.4 (*d*)	73.1 (*d*)
C(8)	101.6 (*s*)	101.7 (*s*)	103.3 (*s*)	101.9 (*s*)
C(9)	38.4 (*t*)	38.4 (*t*)	29.3 (*t*)	38.9 (*t*)
C(10)	77.2 (*d*)	77.3 (*d*)	77.0 (*d*)	77.2 (*d*)
C(11)	136.8 (*s*)	136.4 (*s*)	137.1 (*s*)	136.3 (*s*)
C(12)	133.4 (*s*)	133.4 (*s*)	133.3 (*s*)	133.0 (*s*)
C(13)	47.2 (*s*)	47.1 (*s*)	49.5 (*s*)	47.0 (*s*)
C(14)	73.5 (*s*)	73.5 (*s*)	75.5 (*s*)	77.2 (*s*)
C(15)	38.9 (*t*)	39. 1 (*t*)	36.4 (*t*)	39.1 (*t*)
C(16)	41.3 (*t*)	41.3 (*t*)	53.8 (*t*)	41.3 (*t*)
Me(17)			38.6 (*q*)	
C(1′)	128.1 (*s*)	122.0 (*s*)	122.2 (*s*)	121.6 (*s*)
C(2′)	113.3 (*d*)	111.7 (*d*)	111.8 (*d*)	113.3 (*d*)
C(3′)	145. 6 (*s*)	147. 9 (*s*)	147. 9 (*s*)	149.8 (*s*)
C(4′)	148.2 (*s*)	152.5 (*s*)	152.5 (*s*)	145.6 (*s*)
C(5′)	110.4 (*d*)	109.4 (*d*)	109.4 (*d*)	111.6 (*d*)
C(6′)	121.2 (*d*)	124.5 (*d*)	124.4 (*d*)	124.2 (*d*)
C(7′)	143.2 (*d*)	166.2 (*s*)	166.2 (*s*)	165.6 (*s*)
C(8′)	116.3 (*d*)			
C(9′)	167.1 (*s*)			
*Me*O–C(7)	57.0 (*q*)	57.2 (*q*)	57.5 (*q*)	
*Me*O–C(8)	52.0 (*q*)	51.9 (*q*)	51.3 (*q*)	52.0 (*q*)
*Me*O–C(3′)		55.9 (*q*)	55.9 (*q*)	56.2 (*q*)
*Me*O–C(4′)	55.9 (*q*)	55.9 (*q*)	55.9 (*q*)	
OCH_2O	100.9 (*t*)	100.6 (*t*)	100.6 (*t*)	100.7 (*t*)

[a]) Recorded in $CDCl_3$ at 100 MHz. [b]) Recorded in $CDCl_3$ at 125 MHz. [c]) Data from [5].

^{1}H,^{1}H-COSY spectra. Therefore, **2** was identified as (6β,7β,8β,10β)-8,10-epoxy-7,8-dimethoxy-2,3-(methylenedioxy)hasubanan-6-yl 3,4-dimethoxybenzoate.

Hernsubanine C (**3**), acquired as colorless crystals, had the molecular formula $C_{29}H_{33}NO_9$ based on its HR-EI-MS (*m*/*z* 539.2146 (M^+; calc. 539.2155)). The only difference between alkaloids **2** and **3** was the presence of the Me at the N(17) in **3**, revealed by the ^{1}H- and ^{13}C-NMR data (*Tables 1* and *2*). The assignments were confirmed by HMQC, HMBC, and ^{1}H,^{1}H-COSY spectra. Therefore, **3** was identified as (6β,7β,8β,10β)-8,10-epoxy-7,8-dimethoxy-17-methyl-2,3-(methylenedioxy)hasubanan-6-yl 3,4-dimethoxybenzoate.

By *in vitro* experiments, the cytotoxicity of compound **1** was evaluated against two human cancer cell lines and found that it exhibited no cytotoxicity against A 549 and K 562 cells.

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Experimental Part

General. All solvents used for extraction and isolation were distilled prior use. Petroleum ether (PE) for chromatography had a b.p. range of 60–90°. Column chromatography (CC): silica gel (SiO_2; 300–400 mesh; *Qingdao Marine Chemical Ltd.*, Qingdao, P. R. China), SiO_2 *H* (10–40 μm; *Qingdao*), *MCI* gel *CHP20P* (75–150 *μm; Mitsubishi Chem. Co.*, Japan), *RP-18* gel (50 μm; *YMC*, Japan) and *Sephadex LH-20* (40–70 μm; *Amersham Pharmacia Biotech AB*, S-Uppsala). TLC: Glass precoated with silica gel GF_{254}; visualization with *Dragendrorff*'s reagent. M.p.: *X-4* Melting-point apparatus. Optical rotations: *Rudolph Autopol I* digital polarimeter (2.5-cm cell). UV Spectra: *Shimadzu UV-2401 PC UV/VIS* spectrophotometer; λ_{max} (log ε) in nm. CD Spectra: *JASCO-815* spectropolarimeter. IR Spectra: *Bruker Tensor 27* FT-IR spectrometer; KBr disks; $\tilde{\nu}$ in cm^{-1}. 1D- and 2D-NMR Spectra: *Varian Inova-400* and *Bruker DPX-500* NMR spectrometer; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS: *VG Auto Spec-3000 mass* spectrometer; in *m*/*z* (rel.%).

Plant Material. The plant material of *S. hernandifolia* (WILLD.) WALP. was collected at Luodian, Guizhou Province, P. R. China, in August 2008, and identified by Prof. *An-Ren Li* at the Institute of Botany, Chinese Academy of Sciences. A voucher specimen (No. Zhang20080813) has been deposited with the Key Laboratory of Chemistry for Natural Products of Guizhou Province and Chinese Academy of Sciences.

Extraction and Isolation. Dried and powdered whole plant (22.0 kg) of *S. hernandifolia* (WILLD.) WALP. was submitted to hot-circumfluence extraction with 95% EtOH four times. After removal of solvent under reduced pressure, the residue was partitioned between PE and 5% HCl soln. The pH of the aq. phase was adjusted to *ca.* 7 with sat. NH_3/H_2O soln., and it was extracted with $CHCl_3$ to give crude alkaloids (490 g). The crude alkaloids were subjected to CC (SiO_2; $CHCl_3$/MeOH 100:0 → 0:100): *Frs. A–L*. *Fr. C* (4.3 g) was further purified by CC (*MCI* gel; MeOH/H_2O 100:100 → 100:0). *Fr. C_1* (0.56 g), eluted with MeOH/H_2O 50:100, was further submitted to repeated CC (SiO_2; $CHCl_3$/MeOH 100:2; and *Sephadex LH-20*; $CHCl_3$/MeOH 1:1): **1** (58 mg). *Fr. B* (57.0 g) was subjected to CC (*MCI* gel; MeOH/H_2O 30:100 → 100:0). *Fr. B_3* (1.1 g), eluted with MeOH/H_2O 70:100, was further purified by repeated CC (SiO_2; PE/acetone 7:3; and *Sephadex LH-20*, $CHCl_3$/MeOH 1:1): **2** (71 mg). *Fr. B_4* (0.7 g), eluted with MeOH/H_2O 90:100, was further purified by repeated CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1; *RP-18*, MeOH/H_2O 70:100, and SiO_2; $CHCl_3$/AcOEt 8.5:1.5): **3** (13 mg).

Hernsubanine A (= *(6β,7β,8β,10β)-8,10-Epoxy-7,8-dimethoxy-2,3-(methylenedioxy)hasubanan-6-yl (*Z*)-3-hydroxy-4-methoxycinnamate*; *(2*S*,3*S*,4*R*,4a*S*,6*S*,11b*S*)-1,2,3,4,5,6-Hexahydro-3,4-dimethoxy-4a,11b-(epiminoethano)-4,6-epoxyphenanthro[2,3-*d*][1,3]dioxol-2-yl (2*E*)-3-(3-Hydroxy-4-methoxyphenyl)prop-2-enoate*; **1**). White crystals (MeOH). M.p. 206–208°. $[\alpha]_D^{24} = 3.7$ ($c = 1.08$, $CHCl_3$). UV ($CHCl_3$): 293 (3.18), 322 (3.12), 246 (3.11). CD (MeOH; λ_{ext} ([$\Delta\varepsilon$])): 206 (+22.86), 239.5 (−9.06), 284 (+15.15), 308 (−9.09). IR (KBr): 3452, 1634, 1509, 1484, 1263, 1035, 759. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 1*. ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 2*. EI-MS: 537 (M^+), 213, 194, 177. HR-ESI-MS: 560.1900 ([M + Na]$^+$, $C_{29}H_{31}NaNO_9^+$; calc. 560.1896).

Hernsubanine B (= *(6β,7β,8β,10β)-8,10-Epoxy-7,8-dimethoxy-2,3-(methylenedioxy)hasubanan-6-yl 3,4-dimethoxybenzoate*; *(2*S*,3*S*,4*R*,4a*S*,6*S*,11b*S*)-1,2,3,4,5,6-Hexahydro-3,4-dimethoxy-4a,11b-(epiminoethano)-4,6-epoxyphenanthro[2,3-*d*][1,3]dioxol-2-yl 3,4-Dimethoxybenzoate*; **2**). White crystals (MeOH). M.p. 182–184°. $[\alpha]_D^{24} = 7.3$ ($c = 1.09$, $CHCl_3$). UV ($CHCl_3$): 258 (3.05), 292 (2.90), 365 (2.03). IR (KBr): 2935, 1710, 1601, 1513, 1484, 1291, 1037. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 1*. ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 2*. EI-MS: 525 (M^+), 213, 182, 165. HR-ESI-MS: 526.2069 ([M + H]$^+$, $C_{28}H_{32}NO_9^+$; calc. 526.2077).

Hernsubanine C (*= (6β,7β,8β,10β)-8,10-Epoxy-7,8-dimethoxy-2,3-(methylenedioxy)-17-methylhasubanan-6-yl 3,4-dimethoxybenzoate*; *(2*S*,3*S*,4*R*,4a*S*,6*S*,11b*S*)-1,2,3,4,5,6-Hexahydro-3,4-dimethoxy-14-methyl-4a,11b-(epiminoethano)-4,6-epoxyphenanthro[2,3-*d*][1,3]dioxol-2-yl 3,4-Dimethoxybenzoate*; **3**). White crystals (MeOH). M.p. 222–224°. $[\alpha]_D^{13} = -43.1$ ($c = 1.02$, $CHCl_3$). UV ($CHCl_3$): 260 (3.10), 292 (2.99), 485 (1.13). IR (KBr): 2927, 2851, 1731, 1699, 1557, 1266, 1023. ^{1}H-NMR (500 MHz, $CDCl_3$): see *Table 1*. ^{13}C-NMR (125 MHz, $CDCl_3$): see *Table 2*. EI-MS: 539 (M^+), 227, 182, 165. HR-EI-MS: 539.2146 (M^+, $C_{29}H_{33}NO_9^+$; calc. 539.2155).

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