

Alkaloidal Constituents of the Tubers of *Stephania cepharantha* Cultivated in Japan: Structure of 3,4-Dehydrocycleanine, a New Bisbenzylisoquinoline Alkaloid

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Received October 2, 1996; accepted November 9, 1996

Full details of the isolation and characterization of 52 alkaloids obtained from the tubers of *Stephania cepharantha* HAYATA (Menispermaceae) cultivated in Japan are presented, along with the structural determination of a new bisbenzylisoquinoline alkaloid, 3,4-dehydrocycleanine (8).

Key words 3,4-dehydrocycleanine; *Stephania cepharantha*; tuber; bisbenzylisoquinoline alkaloid; cycleanine

In previous papers,¹⁾ we have reported the isolation and structural determination of four new morphinane alkaloids, cephamonine (1),^{1a)} cephamuline (2),^{1a)} cephasamine (3),^{1b)} cephacicine (4),^{1b)} one new hasubanane alkaloid, cephatonine (5),^{1b)} and two new stephaoxocane²⁾ alkaloids, stephaoxocanine (6),^{1c)} stephaoxocanidine (7),^{1d)} from the tubers of *Stephania cepharantha* HAYATA (Menispermaceae) cultivated in Japan. In our continuing investigations of the alkaloidal constituents of the tubers of this plant, we have obtained a new bisbenzylisoquinoline alkaloid, 3,4-dehydrocycleanine (8), together with 51

known alkaloids as shown in Table 1. This paper describes the isolation and structural determination of 8 and full details of the isolation and characterization of all the alkaloids.

The methanol extract of the tubers of *S. cepharantha* was fractionated, and the alkaloid-containing fractions were repeatedly subjected to crystallization, column chromatography, and preparative TLC, to give 3,4-dehydrocycleanine (8) as colorless needles, together with 51 known alkaloids.

The molecular formula of 3,4-dehydrocycleanine (8)

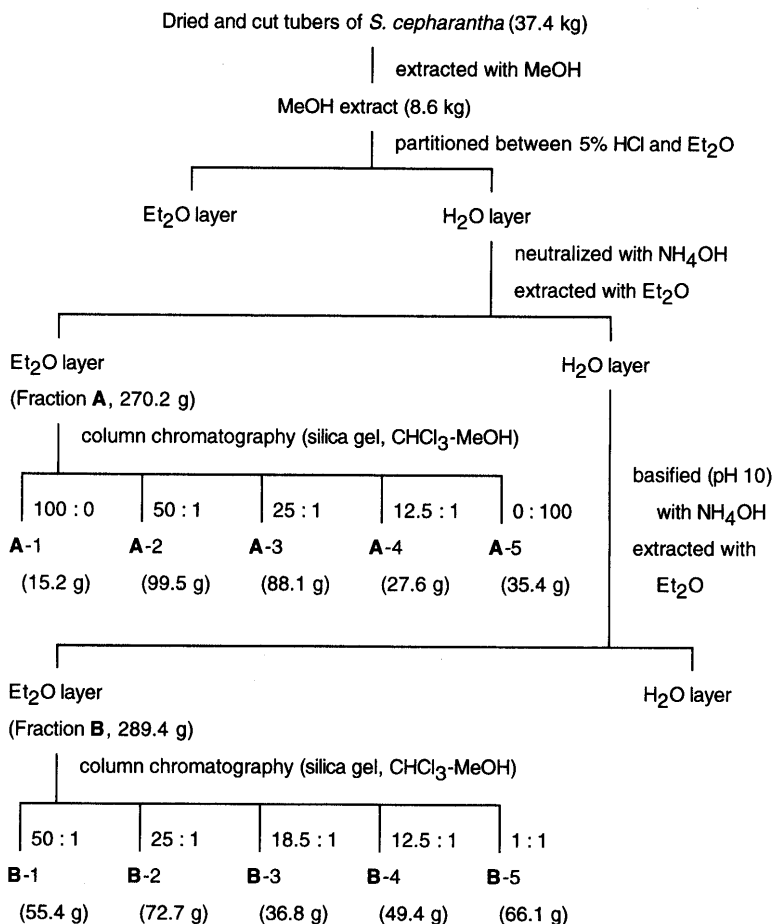


Chart 1. Fractionation of *Stephania cepharantha* HAYATA

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Table 1. Alkaloids from *Stephania cepharantha*

Fraction	Compound ^{a)}	mp (°C) ^{b)}	[α] _D ^{c)} (°)	
A-1	Cepharanthine (11, BBI)	142–143	+350	
	Cepharamine (33, Has)	187–188	–243	
A-2	Cephasamine ^{d)} (3, Mor)	142–144	+105	
	Cephakicine ^{d)} (4, Mor)	Amor. powder	–161	
A-3	Cephatonine ^{d)} (5, Has)	Amor. powder	–264	
	Stephaoxocanidine ^{d)} (7, Steph)	188–191	+30	
	(–)-Cycleanine (9, BBI)	277–280 (d)	–13	
	Cepharanthine (11, BBI)	142–143	+350	
	Isotetrandrine (20, BBI)	185–187	+146	
	14-Epispinomenine (30, Mor)	101–103	–55	
	Sinoacutine (32, Mor)	190–192	–76	
	Cepharamine (33, Has)	187–188	–243	
	Aknadinine (34, Has)	Amor. powder	–290	
	Aknadicine (35, Has)	153–155	–231	
	Aknadilactam (36, Has)	Amor. powder	–152	
	Corydine (37, Apo)	145–147	+208	
	Isocorydine (38, Apo)	184–185	+197	
	Isocorytuberine (39, Apo)	Amor. powder	+203	
	N-Methylaurotetanine (40, Apo)	Amor. powder	+121	
	(–)-Anonaine (42, Apo)	Gum	–60	
	(–)-Scoulerine (51, Pro-ber)	193–194	–269	
	A-3	Stephaoxocanine ^{d)} (6, Steph)	160–162	+60
		(–)-Cycleanine (9, BBI)	277–280 (d)	–13
	A-4	Cepharanoline (13, BBI)	272–273 (d)	+273 ^{e)}
		Homooaromoline (18, BBI)	241–243 (d)	+268 ^{e)}
	A-4	Isotetrandrine (20, BBI)	185–187	+146
		<i>trans</i> -N-Feruloyltyramine (52, Tyr)	Amor. powder	–
	A-4	Cepharanoline (13, BBI)	272–273 (d)	+273 ^{e)}
		Homooaromoline (18, BBI)	241–243 (d)	+268 ^{e)}
	A-5	Berbamine (21, BBI)	148–150	+124
		(–)-Cycleanine (9, BBI)	277–280 (d)	–13
B-1	Cepharanthine (11, BBI)	142–143	+350	
	Obaberine (15, BBI)	Amor. powder	+308	
B-1	Isotetrandrine (20, BBI)	185–187	+146	
	Secocepharanthine (26, BBI)	Amor. powder	–14	
B-2	(+)-Reticuline (46, BI)	Amor. powder	+45	
	Cephamonine ^{d)} (1, Mor)	Amor. powder ^{f)}	–36	
B-2	Cephamuline ^{d)} (2, Mor)	Amor. powder	–63	
	3,4-Dehydrocycleanine ^{d)} (8, BBI)	259–261 (d)	+79	
B-2	(–)-Cycleanine (9, BBI)	277–280 (d)	–13	
	2-Norcepharanthine (12, BBI)	Amor. powder	+345	
B-2	Isotetrandrine (20, BBI)	185–187	+146	
	Tannagine (29, Mor)	Amor. powder	+23	
B-2	FK-3000 (31, Mor)	160–161	–142	
	(+)-Isoboldine (41, Apo)	122–123	+39	
B-2	(+)-Laudanidine (48, BI)	184–186	+265	
	Stepharine (49, Proapo)	181–184	+142	
B-2	N-Methylcrotsparine (50, Proapo)	219–221	–32	
	Cepharanoline (13, BBI)	272–273 (d)	+273 ^{e)}	
B-3	Oxyacanthine (16, BBI)	Amor. powder	+297	
	Stephibaberine (17, BBI)	Amor. powder	+254	
B-3	Homooaromoline (18, BBI)	241–243 (d)	+268 ^{e)}	
	Thalrugosine (22, BBI)	Amor. powder	+297	
B-3	2-Norisotetrandrine (24, BBI)	Amor. powder	+136	
	Sinomenine (28, Mor)	164–166	–54	
B-4	14-Epispinomenine (30, Mor)	101–103	–55	
	(–)-Norcycleanine (10, BBI)	251–252 (d)	–27	
B-4	Cepharanoline (13, BBI)	272–273 (d)	+273 ^{e)}	
	Homooaromoline (18, BBI)	241–243 (d)	+268 ^{e)}	
B-4	Berbamine (21, BBI)	148–150	+124	
	Sinomenine (28, Mor)	164–166	–54	
B-4	Protosinomenine (43, BI)	Amor. powder	+53	
	(+)-N-Methylcoclaurine (44, BI)	Amor. powder	±0 ^{g)}	
B-5	2-Norcepharanoline (14, BBI)	280–282 (d)	+283	
	Aromoline (19, BBI)	217–220 (d)	+343	
B-5	Berbamine (21, BBI)	148–150	+124	
	Obamegine (23, BBI)	Amor. powder	+297	
B-5	2-Norberbamine (25, BBI)	184–187	+77	
	3',4'-Dihydrostephasubine (27, BBI)	Amor. powder	+171	
B-5	(+)-Coclaurine (45, BI)	210–212	+23	

a) BBI: bisbenzylisoquinoline, Has: hasubanane, Mor: morphinane, Steph: stephaoxocane, Apo: aporphine, Pro-ber: protoberberine, Tyr: tyramine derivative, BI: benzylisoquinoline, Proapo: proaporphine. b) Amor. powder: amorphous powder, (d): decomposition. c) Measured in CHCl₃, except for 13 and 18. d) New alkaloid. e) Measured in 0.1N HCl. f) HCl salt; mp 185–187°C. g) CD (MeOH) Δε (nm): +0.3 (290), ±0 (271), +1.5 (232), –0.5 (216).

Table 2. ¹H- and ¹³C-NMR Data for 8 and 9

Position	¹ H		¹³ C	
	8	9	8	9
1	4.70 d (10.4)	4.26 d (10.4)	58.04	59.48
3	6.15 d (7.0)	2.90 m	136.87	44.62
4	5.44 d (7.0)	3.25 m	98.20	24.79
		2.91 m		
4a	6.45 s	3.02 m	129.81	129.73
		6.57 s		
5	6.45 s	6.57 s	103.10	109.18
6			152.19	151.80
7			138.95	138.87
8			142.34	143.64
8a			114.98	125.59
α	2.81 d (13.1)	2.52 dd (12.8, 10.4)	33.67	37.72
9	2.96 dd (13.1, 10.4)	3.22 d (12.8)	129.35	130.43
10	6.26 dd (8.5, 2.1)	6.28 dd (8.2, 2.1)	128.97	128.68
11	5.89 dd (8.5, 2.8)	5.83 dd (8.2, 2.8)	114.23	113.98
12			154.02	154.10
13	6.57 dd (8.2, 2.8)	6.60 dd (8.5, 2.8)	117.26	117.36
14	6.95 dd (8.2, 2.1)	7.04 dd (8.5, 2.1)	128.46	128.10
N-CH ₃	3.12 s	2.53 s	40.10	42.37
6-OCH ₃	3.82 s	3.81 s	56.04	55.99
7-OCH ₃	3.39 s	3.40 s	60.33	60.01
1'	4.23 d (10.1)	4.26 d (10.4)	59.59	59.48
3'	2.92 m	2.90 m	44.67	44.62
4'	2.90 m	3.26 m	24.81	24.79
		3.02 m		
4a'			129.78	129.73
5'	6.58 s	6.57 s	109.24	109.18
6'			151.84	151.80
7'			138.97	138.87
8'			143.55	143.64
8a'			125.51	125.59
α'	2.52 dd (12.8, 10.1)	2.52 dd (12.8, 10.4)	37.73	37.72
9'	3.19 dd (12.8)	3.22 d (12.8)	130.57	130.43
10'	6.25 dd (8.2, 2.1)	6.28 dd (8.2, 2.1)	128.95	128.10
11'	5.81 dd (8.2, 2.8)	5.83 dd (8.2, 2.8)	114.23	113.98
12'			153.84	154.10
13'	6.62 dd (8.5, 2.8)	6.60 dd (8.5, 2.8)	117.03	117.36
14'	7.02 dd (8.5, 2.1)	7.04 dd (8.5, 2.1)	128.09	128.10
N'-CH ₃	2.52 s	2.53 s	42.44	42.37
6'-OCH ₃	3.82 s	3.81 s	55.98	55.99
7'-OCH ₃	3.41 s	3.40 s	60.05	60.01

Values in parentheses are coupling constants (Hz).

was established by the high-resolution mass spectrum (HR-MS) as C₃₈H₄₀N₂O₆, and the electron impact mass spectrum (EI-MS) showed the molecular ion peak at *m/z* 620 (100%) and strong peaks at *m/z* 312 (29%), 311 (26%), 310 (54%), and 309 (79%), indicating that 8 is a bisbenzylisoquinoline alkaloid having two “head-to-tail” diphenyl ether linkages.³⁾ The IR spectrum suggested the absence of hydroxy and primary and secondary amino groups (no absorption from 3500 to 3200 cm⁻¹). The UV spectrum showed the presence of an olefin conjugated to an aromatic ring (absorption maximum at 340 nm). The ¹H- and ¹³C-NMR spectra were similar to those of (–)-cycleanine (9), which is an alkaloid possessing two “head-to-tail” diphenyl ether linkages, and the molecular formula has 2H more than that of 8. The ¹H-NMR spectrum of 8 showed two coupled olefinic proton signals at δ_H 5.44 and 6.15, and the ¹³C-NMR spectrum

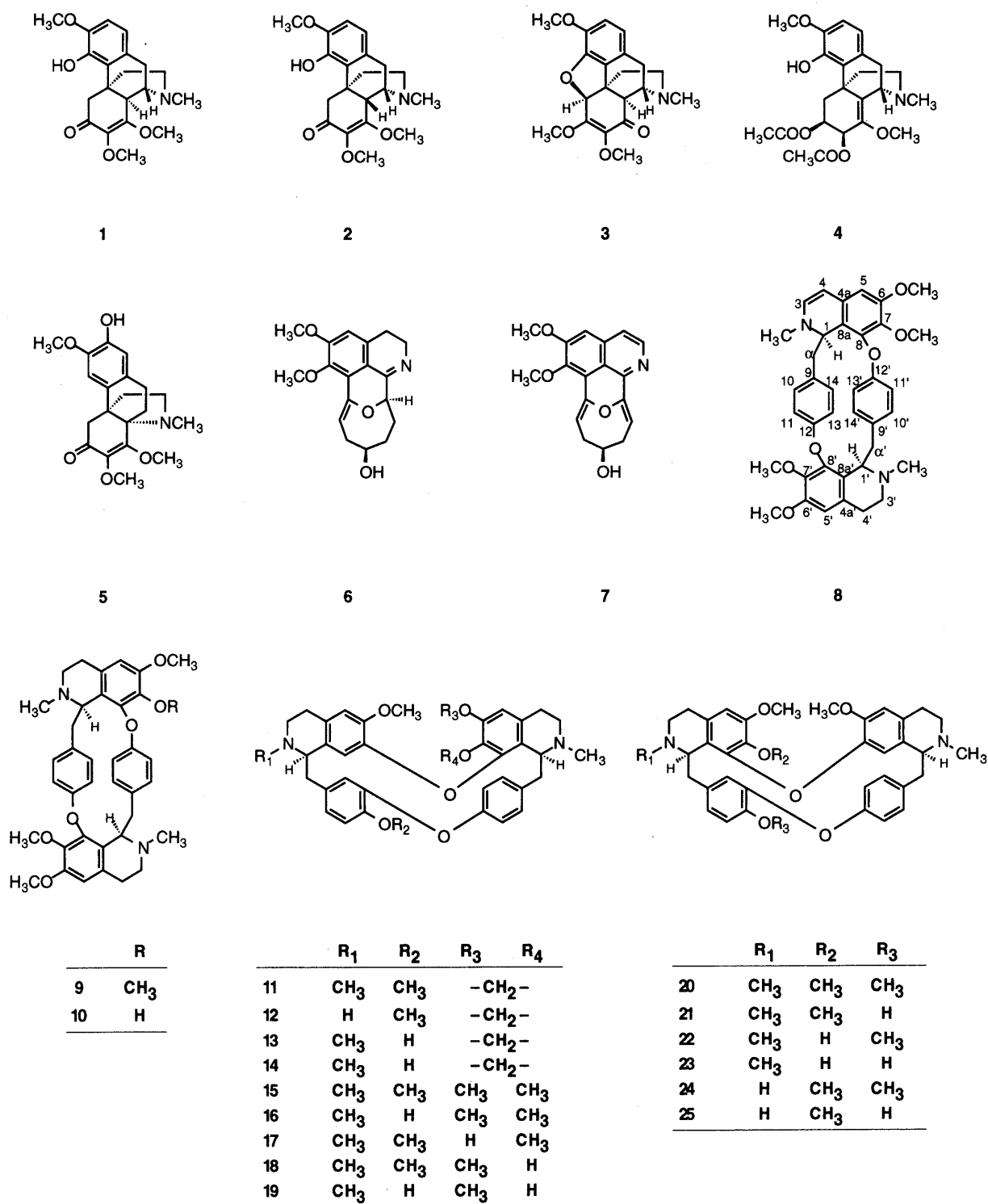


Chart 2

exhibited two sp^2 -tertiary carbon signals at δ_C 98.20 and 136.87 instead of the two signals due to C-3 (δ_C 44.62) and C-4 (δ_C 24.79) of **9** (Table 2). These data indicated that **8** should be the 3,4-dehydro derivative of **9**. The heteronuclear multiple-bond connectivity (HMBC) spectrum also supported the 3,4-dehydro structure of **9**, showing correlations between the N -CH₃ (δ_H 3.12) and C-3 (δ_C 136.87) signals and between the H-5 (δ_H 6.45) and C-4 (δ_C 98.20) signals.

Hydrogenation of **8** in the presence of 10% palla-

dium-carbon in ethanol gave a saturated compound that was identified by direct comparison with an authentic sample of **9**. Thus, the structure of **8** was determined as 1*R*,1'*R*-3,4-dehydrocycleanine.

Finally, from the tubers of *Stephania cepharantha* HAYATA (Menispermaceae) cultivated in Japan, the following 52 alkaloids were isolated: 20 bisbenzylisoquinoline alkaloids, 3,4-dehydrocycleanine (**8**), (-)-cycleanine (**9**),^{4,5} (-)-norcycleanine (**10**),⁵ cepharanthine (**11**),⁶ 2-norcepharanthine (**12**),⁶ cepharanoline (**13**),⁷ 2-norceph-

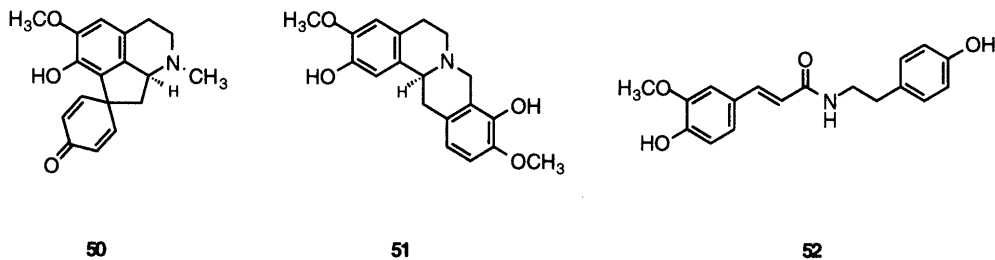
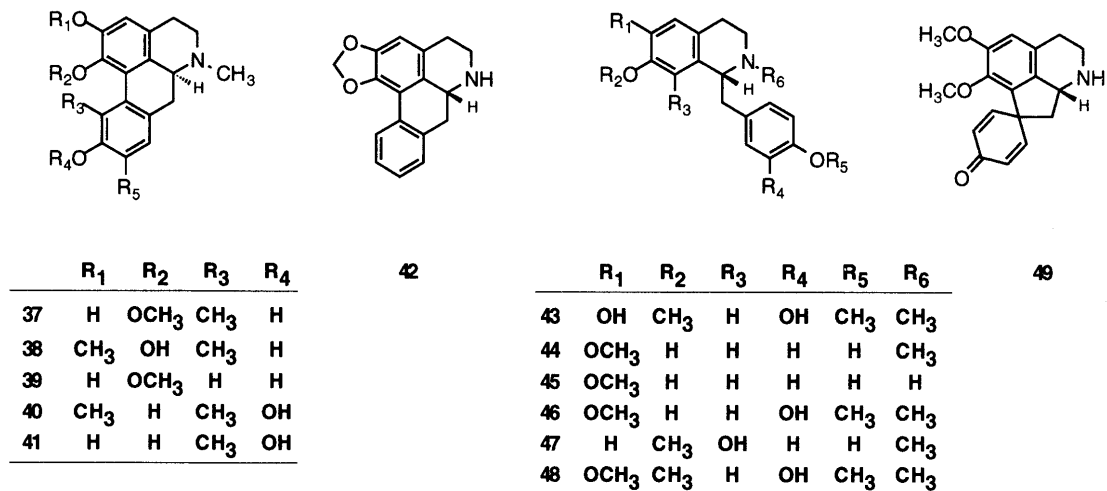
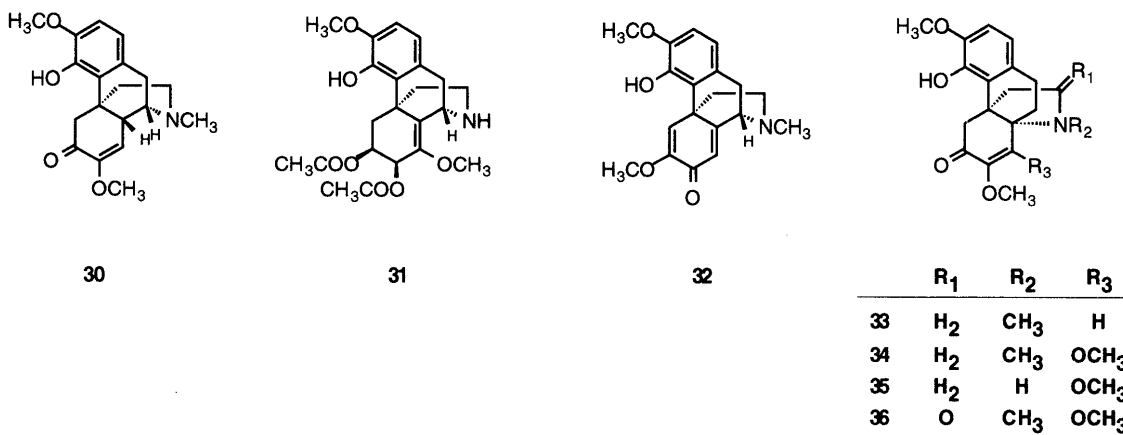
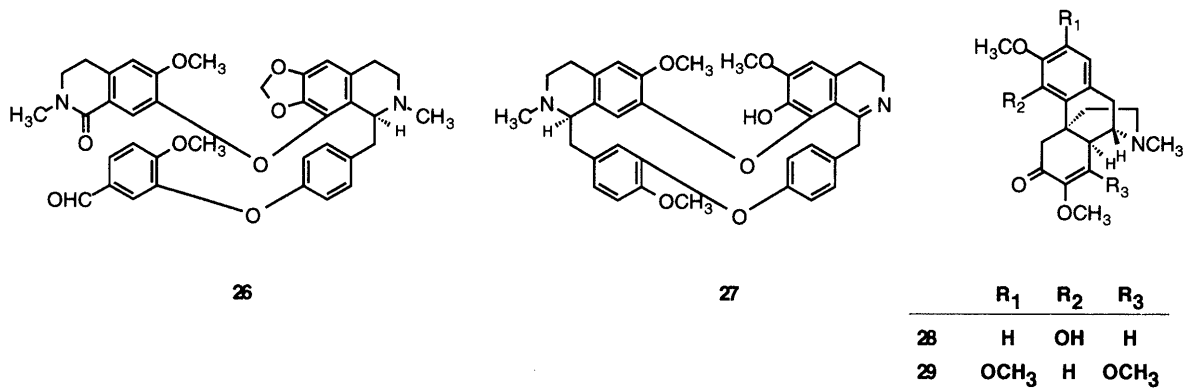


Chart 2

aranoline (14),⁸⁾ obaberine (15),⁹⁾ oxyacanthine (16),¹⁰⁾ stephibaberine (17),⁸⁾ homoaromoline (18),^{9,11)} aromoline (19),⁹⁾ isotetrandrine (20),¹²⁾ berbamine (21),¹³⁾ thalrugosine (22),^{11,14)} obamegine (23),¹⁵⁾ 2-norisotetrandrine (24),⁸⁾ 2-norberbamine (25),¹⁶⁾ secocepharanthine (26),¹⁷⁾ and 3',4'-dihydrostephasubine (27)¹⁸⁾; nine morphinane alkaloids, cephamonine (1), cephamuline (2), cephasamine (3), cephacicine (4), sinomenine (28),¹⁹⁾ tannagine (29),²⁰⁾

14-episinomenine (30),²¹ FK-3000 (31),²² and sinoacutine (32)²³; five hasubanane alkaloids, cephatonine (5), cepharamine (33),²⁴ aknadine (34),^{25,26} aknadine (35),²⁶ and aknadilactam (36)^{26,27}; two stephaoxocane alkaloids, stephaoxocanine (6) and stephaoxocanidine (7); six aporphine alkaloids, corydine (37),²⁸ isocorydine (38),²⁹ isocorytuberine (39),³⁰ *N*-methyllaurotetanine (40),³¹ (+)-isoboldine (41),³² and (–)-anonaine (42)³³; six benzylisoquinoline alkaloids, protosinomenine (43),³⁴ (+)-*N*-methylcoclaurine (44),³¹ (+)-coclaurine (45),³⁵ (+)-reticuline (46),³⁶ juziphine (47),³⁷ and (+)-laudandine (48)³¹; two proaporphine alkaloids, stepharine (49)³⁸ and *N*-methylcrotosparine (50)³⁹; one protoberberine alkaloid, (–)-scoulerine (51),²³ and one tyramine derivative, *trans*-*N*-feruloyltyramine (52).⁴⁰

The structures of the known alkaloids were identified by direct comparison with authentic samples or by comparison of the spectroscopic data with the literature values.

Experimental

Melting points were measured on a Yanagimoto hot-stage melting point apparatus without correction. IR spectra were recorded on an FT/IR-5000 (JASCO) spectrometer as KBr pellets. UV spectra were measured on a Ubest-35 (JASCO) spectrometer in MeOH. CD spectra were measured on a J-600 (JASCO) spectrometer in dioxane. NMR spectra were taken on a JNM- α 500 (JEOL) (500 MHz for ¹H and 125 MHz for ¹³C) spectrometer in CDCl₃ with tetramethylsilane (TMS) as an internal standard. Optical rotations were determined on a DIP-140 (JASCO) instrument in CHCl₃. MS were taken on a JMS-D300 (JEOL) spectrometer at 30 eV. Column chromatography was performed on Wakogel C-200 (Wako Pure Chemical Industries, Ltd.). Preparative TLC was done on precoated Silica gel 60 F₂₅₄ (0.25 mm thick) plates (Merck).

Plant Material *Stephania cepharantha* HAYATA was cultivated at Yasato-machi, Ibaraki prefecture, Japan and collected in October 1987. The plants were kept at the Yasato factory of Kaken Shoyaku Co., Ltd.

Extraction and Isolation Dried and cut tubers of *S. cepharantha* (37.4 kg) were extracted twice with hot MeOH. The extract (8.6 kg) was evaporated *in vacuo*, and the residue was treated with 5% HCl. The mixture was filtered, and the filtrate was extracted with Et₂O. The aqueous layer was adjusted to pH 7 with NH₄OH and extracted with Et₂O to yield fraction A (270.2 g). Then, the aqueous layer was basified with NH₄OH to pH 10 and extracted with Et₂O to yield fraction B (289.4 g). Fraction A was subjected to silica gel column chromatography using CHCl₃, 2%, 4%, and 8% MeOH–CHCl₃, and MeOH as eluents to afford fractions A-1 (15.2 g), A-2 (99.5 g), A-3 (88.1 g), A-4 (27.6 g), and A-5 (35.4 g). Fraction B was also chromatographed on silica gel using 2%, 4%, 6%, 8%, and 50% MeOH–CHCl₃ as eluents to give fractions B-1 (55.4 g), B-2 (72.7 g), B-3 (36.8 g), B-4 (49.4 g), and B-5 (66.1 g). Each fraction (A-1-5 and B-1-5) was further subjected to a combination of crystallization, column chromatography, and preparative TLC, to afford 52 alkaloids.

From fraction A-1; cepharanthine (11, 8.36 g), cepharamine (33, 0.110 g). From fraction A-2; cephasamine (3, 0.034 g), cephacicine (4, 0.217 g), cephatonine (5, 0.015 g), stephaoxocanidine (7, 0.022 g), (–)-cycleanine (9, 1.25 g), cepharanthine (11, 68.20 g), isotetrandrine (20, 12.37 g), 14-episinomenine (30, 0.015 g), sinoacutine (32, 0.22 g), cepharamine (33, 0.192 g), aknadine (34, 0.478 g), aknadine (35, 0.057 g), aknadilactam (36, 0.032 g), corydine (37, 0.098 g), isocorydine (38, 0.275 g), isocorytuberine (39, 0.178 g), *N*-methyllaurotetanine (40, 0.009 g), (–)-anonaine (42, 0.016 g), (–)-scoulerine (51, 0.101 g). From fraction A-3; stephaoxocanine (6, 0.058 g), (–)-cycleanine (9, 5.03 g), cepharanoline (13, 7.72 g), homoaromoline (18, 1.29 g), isotetrandrine (20, 54.66 g), *trans*-*N*-feruloyltyramine (52, 0.048 g). From fraction A-4; cepharanoline (13, 4.49 g), homoaromoline (18, 0.970 g), berbamine (21, 11.24 g), juziphine (47, 0.128 g). From fraction A-5; berbamine (21, 27.03 g). From fraction B-1; (–)-cycleanine (9, 4.22 g), cepharanthine (11, 3.96 g), obaberine (15, 0.072 g), isotetrandrine (20, 20.31 g), secocepharanthine (26, 0.050 g), (+)-reticuline (46, 0.359 g). From fraction B-2; cephamonine (1, 2.65 g), cephamuline (2, 0.047 g), 3,4-de-

hydrocycleanine (8, 0.034 g), (–)-cycleanine (9, 12.38 g), 2-norcepharanthine (12, 0.102 g), isotetrandrine (20, 37.33 g), tannagine (29, 0.038 g), FK-3000 (31, 11.17 g), (+)-isoboldine (41, 0.153 g), (+)-laudandine (48, 0.125 g), stepharine (49, 0.398 g), *N*-methylcrotosparine (50, 0.083 g). From fraction B-3; cepharanoline (13, 0.880 g), oxyacanthine (16, 0.041 g), stephibaberine (17, 0.102 g), homoaromoline (18, 6.32 g), thalrugosine (22, 0.099 g), 2-norisotetrandrine (24, 0.030 g), sinomenine (28, 1.06 g), 14-episinomenine (30, 0.065 g). From fraction B-4; (–)-norcycleanine (10, 5.53 g), cepharanoline (13, 0.325 g), homoaromoline (18, 3.36 g), berbamine (21, 20.35 g), sinomenine (28, 0.580 g), protosinomenine (43, 0.150 g), (+)-*N*-methylcoclaurine (44, 0.072 g). From fraction B-5; 2-norcepharanoline (14, 0.152 g), aromoline (19, 14.73 g), berbamine (21, 33.96 g), obamegine (23, 3.82 g), 2-norberbamine (25, 0.077 g), 3',4'-dihydrostephasubine (27, 0.022 g), (+)-coclaurine (45, 2.43 g).

3,4-Dehydrocycleanine (8) mp 259–261 °C (dec.) (acetone). [α]_D²⁴ +79° (c=0.65). IR: 1609, 1508, 1491, 1421, 1342, 1321, 1220, 1172, 1118 cm⁻¹. UV λ_{max} nm (log ϵ): 340 (3.97). CD $\Delta\epsilon$ (nm): +15.1 (339), +2.4 (306), +7.2 (290), +7.1 (287), +8.7 (279), –9.2 (257). EI-MS *m/z* (%): 620 (M⁺, 100), 312 (29), 311 (26), 310 (54), 309 (79), 204 (15), 202 (27), 174 (15), 157 (16). HR-MS *m/z*: 620.2908 (C₃₈H₄₀N₂O₆ requires 620.2887).

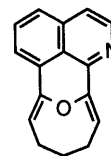
Hydrogenation of 8 A mixture of 8 (10 mg) and 10% Pd–C (5 mg) in EtOH (20 ml) was stirred for 4 h at room temperature under an H₂ atmosphere. Work-up of the product was done in a usual manner and was followed by preparative TLC [with EtOAc–Et₂NH (9:1)] to afford 9 (2 mg) and 8 (4 mg). The identification of 9 was accomplished by comparison of its TLC behavior and CD, IR, and ¹H-NMR spectra with those of an authentic sample of 9.

(–)-Cycleanine (9) mp 277–280 °C (dec.) (MeOH) [mp 268–271 °C⁴]. [α]_D²⁵ –13° (c=1.00) [[α]_D –20° (c=1.00, CHCl₃)⁴]. IR: 1607, 1580, 1508, 1454, 1417, 1344, 1296, 1220, 1118 cm⁻¹. UV λ_{max} nm (log ϵ): 277 (3.68). CD $\Delta\epsilon$ (nm): +14.7 (276), +9.4 (265), +25.3 (255), –1.2 (246). EI-MS *m/z* (%): 622 (M⁺, 88), 621 (36), 313 (22), 312 (100), 311 (32), 309 (8), 204 (6), 190 (6). HR-MS *m/z*: 622.3005 (C₃₈H₄₂N₂O₆ requires 622.3040).

Acknowledgments The authors are grateful to Prof. K. Isobe and Dr. K. Mohri (Showa College of Pharmaceutical Sciences) for valuable suggestions, Mr. T. Shinohara (Racing Chemistry Laboratories) and Mr. Y. Takase (Showa College of Pharmaceutical Sciences) for MS measurements and useful discussions, and Mr. Y. Mochizuki (Kaken Shoyaku Co., Ltd.) for the cultivation and extraction of *S. cepharantha*.

References and Notes

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