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Chemical Constituents from *Dehaasia Triandra*. II.[1] Five New Alkaloids, Secoxanthoplanine, Dehydroisocorydione, 11,8'-*O*-Bisisocorydine, (8,8'-*R*)- and (8,8'-*S*)- Bisisocorydine, isolated from the Leaves

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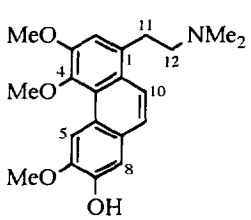
Abstract: A continuous study on the constituents from the leaves of *Dehaasia triandra* Merr. resulted in the isolation of five additional novel alkaloids– secoxanthoplanine (**1**), dehydroisocorydione (**2**), (8,8'-*R*)- (**3**) and (8,8'-*S*)-bisisocorydine (**4**), and 11,8'-*O*-bisisocorydine (**5**). Compounds **3** and **4** are the first C-C linked bisaporphines at C-8 while **5** is the first bisaporphine with a diphenyl ether-linkage at C-8 and C-11. Besides elucidation based on a spectral analysis, the structures of **1**, **3** and **4** were further confirmed by semisynthesis. Copyright © 1996 Elsevier Science Ltd

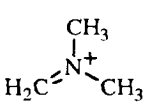
Past studies on the chemical ingredients of *Dehaasia triandra* Merr. (Lauraceae) have resulted in the isolation of five aporphines from the leaves, isocorydine, corytuberine, atheroline, nantenine and xanthoplanine, and three bisbenzylisoquinolines (BisBzlSQ), dehatridine from the leaves and obaberine and dehatrine from the stems.[2,3] Recently, we reported the isolation of three novel alkaloids, isocorydione, norisocorydione and dehatriphine, besides the most abundant aporphine isocorydine from the leaves of this plant.[1] Among these, dehatriphine, i.e. 9-*O*-(8'-isocorydinyl)-*N*-methyllaurotetanine, is the first ether-linked bisaporphine. A continuing study on the $CHCl_3$ soluble fraction yielded five additional novel alkaloids besides the five known aporphines, isoboldine, norisocorydine, *N*-methyllindcarpine, *N*-methyllaurotetanine, nantenine and two known BisBzlSQs, homoaromoline and thalrugosine. We now report the structural elucidation of these novel alkaloids.

Compound **1**, amorphous solids, showed a molecular ion peak at *m/z* 355 for a formula of $C_{21}H_{25}NO_4$ in its EIMS . Its ^{1}H NMR spectrum shows an AB system at δ 7.69 and 7.44 and three aromatic singlets at δ 9.22, 7.26 and 7.19, characteristic signals for H-5, H-8 and H-2 in a 1,3,4,6,7-substituted phenanthrene alkaloid.[4] Other ^{1}H NMR signals include four singlets for three MeO and one NMe_2 groups, and two triplets for two methylenes. The mass spectrum revealed the base peak at *m/z* 58 for which fragment **A** is responsible. These data indicated **1** to be secoxanthoplanine or its isomer. Its physical data are identical to those of the Hofmann degradation product of xanthoplanine, isolated from the same plant,[2] and confirmed **1** to be secoxanthoplanine which has been prepared [5] but is the first isolated natural product.

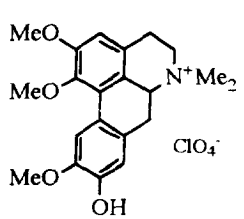
The ^{1}H NMR assignment of **1** was made by correlation with that for *N*-cyanosecoboldine.[6]



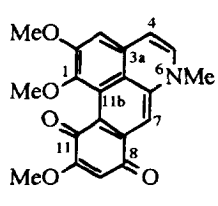
1



A



xanthoplanine (ClO_4^- salt)



2

Compound **2**, needle-like crystals, has a formula of $C_{20}H_{17}NO_5$ from HREIMS. Other than the AX signals for H-4 and H-5, both appearing as a triplet in isocorydione,[1] the ^1H NMR data of **2** are similar to that of isocorydione, including three aromatic singlets, three MeO singlets and one *N*Me singlet. Hence, **2** is the 4,5-dehydro analog of isocorydione and is named dehydroisocorydione. This structure for **2** was supported by NOE experiments. The respective irradiation at the aromatic singlets for H-3 (δ 6.66), H-7 (δ 6.73) and H-9 (δ 5.89) enhance 2-OMe (δ 3.93), H-4 (δ 6.21, d) (H-3), *N*Me (δ 3.42) (H-7) and 10-OMe (δ 3.88) (H-9). With ^1H NMR data available, the ^{13}C NMR assignment for **2** (Table 1) was also made based on an analysis of the HMQC and COLOC spectra.

Table 1. ^1H- and ^{13}C-NMR data, and COLOC data for Compound **2** in $CDCl_3$

	δ (ppm) (mult.) (*J* Hz)		COLOC[a]		δ (ppm) (mult.)		COLOC
Position	^1H	^{13}C[b]	Correlated H (#)	Position	^1H	^{13}C	Correlated H (#)
1		141.5 s	1-OMe, 3	7a		138.5 s	9
2		154.8 s	2-OMe	8		186.2 s	7, 9
3	6.66 s	103.0 d		9	5.89 s	104.7 d	
3a		131.1 s	5	10		164.3 s	9, 10-OMe
3b		125.1 s	3	11		175.7 s	9
4	6.21 d (7.4)	109.0 d		11a		116.4 s	7
5	6.63 d (7.4)	133.3 d	6-Me	11b		127.4 s	
6-Me	3.42 s	40.9 q		1-OMe	3.89 s	58.9 q	
6a		145.9 s	6-Me	2-OMe	3.93 s	56.0 q	
7	6.73 s	97.0 d		10-OMe	3.88 s	56.4 q	

[a]In COLOC, the C-H coupling constant is optimized at 8 Hz. [b]Multiplicities were obtained from DEPT experiments (s–> C, d–> CH, t–> CH_2, q–> CH_3)

Both compounds **3** and **4** have the same molecular formula, $C_{40}H_{44}N_2O_8$, as deduced from HREIMS. Their ^{13}C NMR spectra revealed signals for 20 carbons, indicating both **3** and **4** to be symmetrical dimers. Their UV spectra showed absorption maxima around 222, 267 and 305 nm, indicating 1,2,10,11-tetraoxygenated aporphine.[7] The ^1H NMR spectrum of **3** displays an *N*Me signal at δ 2.25, three MeO singlets at δ 3.91, 3.83 and 3.79, two aromatic proton singlets at δ 6.71 and 6.70, and a D_2O exchangeable singlet at δ 8.79, characteristic for 1- or 11-O<u>H</u> of a 1,2,10,11-tetraoxygenated aporphine as in corydine or isocorydine, respectively. Compound **3** showed IR absorption at 3425 cm^{-1} for hydroxyl groups but no apparent bathochromic shift in its UV spectrum under alkaline conditions, indicating a hindered phenolic OH. Subtracting the eight oxygens (6x OMe and 2x OH) from the formula left no oxygen, suggesting **3** to be a C-C linked bisaporphine which would contain 20 ring and double bond equivalents, in agreement with that calculated from the formula. Its ^{13}C NMR spectrum revealed signals for three aliphatic methylenes and one aliphatic methine as for a monomeric aporphine, suggesting a C-C linkage at the aromatic ring. The location of the substituents and the diphenyl C-C linkage was determined as follows.

Upon irradiation of a MeO singlet at δ 3.91, an aromatic singlet at δ 6.70 (H-3) and a MeO singlet at δ 3.79 were enhanced. The latter MeO signal was also enhanced upon irradiation of the phenolic signal (δ 8.79). These data established 1-OMe (δ 3.79), 2-OMe (δ 3.91) and 11-OH (δ 8.79) substitution. Therefore, the diphenyl C-C linkage is located at the ring D. That irradiation at the remaining aromatic singlet at δ 6.71 did not enhance any other signals except for the MeO singlet at δ 3.83 designated H-9 and 10-OMe at δ 6.71 and 3.83, respectively, and suggested C-8 to be the diphenyl linkage position. Accordingly, **3** is 8,8'-bisisocorydine.

This structure for **3** was confirmed by analysis of the HMBC spectrum, optimized for J = 8 Hz. The critical data are the couplings of the phenolic proton (11-OH) to C-10 (δ 148.5), C-11 (δ 143.1) and C-11a (δ 120.7); H-9 to C-7a (δ 128.0) (larger coupled), C-8 (δ 131.3) (smaller coupled), C-10 and C-11. These data and the HMQC data also allowed the complete ^{1}H and ^{13}C NMR assignments for **3** (Table 2).

Table 2. ^{1}H- and ^{13}C-NMR data (δ/ppm) for Compounds **3** and **4**, and HMBC data for Compound **3** in $CDCl_3$

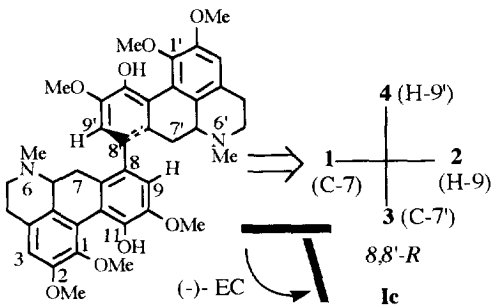
	δ_H (mult., J in Hz)		δ_C (mult.)[a]		HMBC of **3** (J = 8 Hz)	
Position	**3**	**4**	**3**	**4**	δ_H	Correlations (C#)
1			142.3 s	142.4 s		
2			151.3 s	151.1 s		
3	6.70 s	6.67 s	111.2 d	111.1 d	6.70	1, 2, 3a, 3b, 4
3a			129.3 s	129.2* s		
3b			129.7 s	129.5 s		
4	2.68 br d (16.0) (α)	2.63 br d (16.1) (α)	29.3 t	29.1 t		
	3.13 m (β)	3.04 m (β)				
5	2.39 br t (11.4) (α)	2.38 dt (2.4, 11.5) (α)	52.7 t	52.4 t		
	2.92 m (β)	2.88 m (β)				
6-Me	2.25 s	2.15 s	44.3 q	43.5 q	2.25	5, 6a
6a	2.64 dd (3.0, 12.5)	2.70 br d (13.6)	63.4 d	62.5 d		
7	2.93 dd (3.0, 12.5)(α)	2.79 dd (3.0, 13.6)(α)	33.2 t	32.3 t		
	2.18 t (12.5) (β)	1.98 t (13.6) (β)				
7a			128.0 s	129.3* s		
8			131.3 s	131.1 s		
9	6.71 s	6.94 s	113.6 d	112.6 d	6.71	7a, 8, 10, 11
10			148.5 s	148.6 s		
11			143.1 s	143.1 s		
11a			120.7 s	120.1 s		
11b			126.1 s	125.9 s		
1-OMe	3.79 s	3.69 s	62.2 q	62.0 q	3.79	1
2-OMe	3.91 s	3.89 s	55.9 q	55.9 q	3.91	2
10-OMe	3.83 s	3.95 s	56.0 q	56.2 q	3.83	10
11-OH	8.79 s	8.69 s			8.79	10, 11, 11a

[a]Multiplicities were determined by DEPT experiments (s–> C, d–> CH, t–> CH_2, q–> CH_3). *Tentatively assigned.

The bisaporphine **4** showed very similar ^{1}H- and ^{13}C- NMR spectral data to those of **3** despite the quite different optical rotation, $[\alpha]^{20}_D$ +176.0° for **4** and +14.0° for **3**. Hence, **4** could be a stereoisomer of **3** and was confirmed by NMR spectral analysis (NOE and HMBC). In comparison of their NMR data (Table 2), the larger differences appear for the chemical shifts for H-7's and C-7a. Accordingly, these two compounds could be conformational isomers due to the diphenyl chirality at C-8 and C-8'.

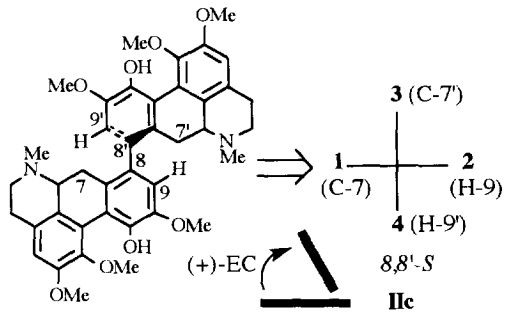
Computer-assisted molecular modeling studies of 8,8'-bisisocorydine revealed two extreme conformers I and II with minimum energy.[8] Conformers I and II, having a torsion angle (composed of C-7a, C-8, C-7'a, and C-8') of -92.7° and +72.3°, respectively, can be represented as structures **Ic** and **IIc**, each possessing *R*- and *S*-conformational chirality. In addition, conformation I will give negative exciton coupling (EC) while conformation II will possess positive EC.[9] That the CD spectrum of **4** showed two EC's, Δε +27.83 (281/264) and +145.84 (240/217 nm), that of the corresponding monomer isocorydine showing a negative Cotton effect (CE) at 268 nm and a positive CE at 233 nm, established **4** to have the structure of conformer II. By elimination, **3** has the structure of conformer I which is partially supported by the negative CE at 277 nm.

Compounds **3** and **4** are apparently produced by *para-para* oxidative coupling of two biogenetic isocorydines . The oxidative coupling of *S*-(+)-isocorydine with manganic tris(acetylacetonate)[10] yielded two products possessing identical physical data ($[\alpha]_D$, TLC and NMR) to **3** and **4** thus providing solid structural evidence for these two dimeric aporphines.



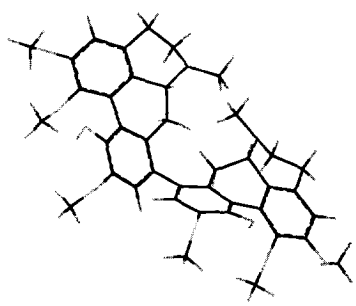
Φ (C7-C7a-C8// C8'-C7'a-C7')= -92.7°

3: one negative Cotton effect at λ 277 nm.

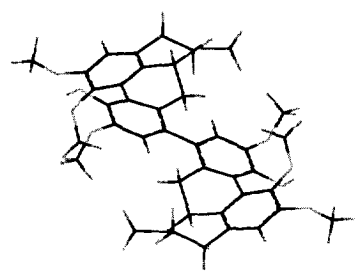


Φ (C7-C7a-C8// C8'-C7'a-C7')= +72.3°

4: two positive EC's at λ 281/264 nm and 240/217 nm.



Conformer **I**



Conformer **II**

Figure 1. Conformational analysis of Compounds **3** and **4**

Compound **5** has the same molecular formula as **3** and **4**, $C_{40}H_{44}N_2O_8$, deduced from HREIMS. Its UV spectrum showed absorption maximized around 221, 269 and 303 nm, indicating 1,2,10,11-tetraoxygenated aporphine.[6] Its ^{1}H NMR spectrum showed five aromatic proton signals including three singlets and an *ortho* coupled AB system at δ 7.07 and 6.92 (J = 8.1 Hz) for H-8 and H-9, six MeO singlets, two *N*Me singlets and an 11-OH signal (δ 8.19, D_2O exchangeable) of the aporphine. In addition, the downfield shifted H-7'α (δ 4.01, br d, J = 13.0 Hz) and upfield shifted H-7'β (δ 1.89, t, J = 13.0 Hz) relative to those of isocorydine (δ 3.04 and 2.44, respectively), and the upfield shifted C-7' (δ 27.0, t) (δ 35.6 in isocorydine), identified by the correlation in an HMQC spectrum, suggested that C-8 of an aporphine unit is oxygenated as in dehatriphine.[1,11] These messages and the absence of H-11 signals suggested **5** to likely be a bisisocorydine with the diphenyl ether linkage at C-8 and C-11 of each aporphine unit. This proposed structure was supported by the NOE difference spectral studies with results depicted in Figure 2. The critical results are the NOE of H-9' to 10'-OMe and 1-OMe, 11'-OH to 1'-OMe, 1-OMe to 6'-Me, 6'-Me to 7'α-H. The assigned ^{1}H NMR data from the NOE experiments

were correlated by an HMBC spectrum. For instance, H-3' was assigned at δ 6.65 from being coupled to C-1' which was identified from coupling to 1'-OMe (δ 3.56). Similarly, H-3 was assigned at δ 6.43. The chemical shift of C-4 and C-4' was then distinguished from their three-bond coupling to H-3 and H-3', respectively. Hence, the ^{1}H- and ^{13}C- NMR assignments of **5** were made (Table 3) mostly by analysis of NOEs, HMQC and HMBC (Table 4) spectra, and part of the quaternary carbons– C-3'a, 11'b, and 11b– were assigned by comparison with those of **3**.

Table 3. ^{1}H- and ^{13}C-NMR data (δ/ppm) for Compound **5** in $CDCl_3$

Position	δ_H (mult., J in Hz)	δ_C (mult.)[a]	Position	δ_H (mult., J in Hz)	δ_C (mult.)[a]
1		145.7 s	1'		142.2 s
2		151.2 s	2'		151.0 s
3	6.43 s	111.4 d	3'	6.65 s	111.0 d
3a		129.0 s	3'a		127.1 s
3b		128.2 s	3'b		129.7 s
4	2.49 dd (3.7, 16.5)(α)	28.8 t	4'	2.68 br d (17.0) (α)	29.4 t
	3.00 m (β)			3.21 m (β)	
5	2.30 dt (4.0, 11.6) (α)	53.2 t	5'	2.48 m (α), 3.05 m(β)	53.1 t
	2.95 dd (5.0, 11.6) (β)				
6-Me	2.48 s	44.1 q	6'-Me	2.67 s	43.7 q
6a	2.74 dd (3.2, 13.2)	63.7 d	6'a	2.86 br d (13.0)	62.1 d
7	3.02 dd (3.2, 13.2)(α)	35.8 t	7'	4.01 br d (13.0) (α)	27.0 t
	2.38 t (13.2) (β)			1.89 t (13.0) (β)	
7a		130.8 s	7'a		117.3 s
8	7.07 d (8.1)	123.0 d	8'		147.4 s
9	6.92 d (8.1)	111.8 d	9'	5.92 s	99.7 d
10		151.9 s	10'		148.3 s
11		142.7 s	11'		138.1 s
11a		126.2 s	11'a		120.7 s
11b		124.5 s	11'b		126.0 s
1-OMe	3.51 s	60.5 q	1'-OMe	3.56 s	62.0 q
2-OMe	3.68 s	55.3 q	2'-OMe	3.86 s	55.9 q
10-OMe	3.81 s	56.5 q	10'-OMe	3.54 s	56.0 q
			11'-OH	8.19 s	

[a]Multiplicities were determined by DEPT experiments (s–> C, d–> CH, t–> CH_2, q–> CH_3)

Table 4. HMBC data (J = 8 Hz) for Compound **5** in $CDCl_3$

Position	δ_H	Correlations (C#)	Position	δ_H	Correlations (C#)
3	6.43	1, 2, 3b, 4	10-OMe	3.81	10
5α	2.30	3a	3'	6.65	1', 2', 3'b, 4'
6-Me	2.48	5, 6a	6'-Me	2.67	5', 6'a
7	2.38	3b, 6a, 7a	9'	5.92	7'a, 8', 10', 11'
8	7.07	7, 10, 11a	1'-OMe	3.56	1'
9	6.92	7a, 11	2'-OMe	3.86	2'
1-OMe	3.51	1	10'-OMe	3.54	10'
2-OMe	3.68	2	11'-OH	8.19	10', 11'

The CD spectrum of **5** is similar in shape with that of isocorydine and thus is assigned to both *S*-configurations at C-6a and C-6'a. Accordingly, **5** is (6a-*S*, 6a'-*S*)-11,8'-*O*-bisisocorydine.

In correlation with the relative spatial distances deduced from the NOE results, computer-aided molecular modeling gives the favored conformation of **5** with minimum energy as shown in Figure 2.[8] This structure

reveals that an aporphine unit inserts almost perpendicularly into the groove between C-10 and C-1 of another aporphine unit.

Compounds **3** and **4** represent the first examples of a C_8-$C_{8'}$ coupled bisaporphine. Previous isolated or syn-thetic C-C linked bisaporphines such as urabaine are coupled at C-7 and C-7'.[12] Compound **5** is produced by C-1/*para* oxidative coupling of two isocorydines, and represents the first diphenyl ether linked bisaporphine at C-11 and C-8 of each unit. The presence of these rare bisaporphines in *D. triandra* is meaningful from a chemotaxonomic viewpoint. Besides, dimeric aporphines such as thalicarpine are known for their potent cytotoxic effects.[13] Whether these bisaporphines possess such biological activity is currently under investigation.

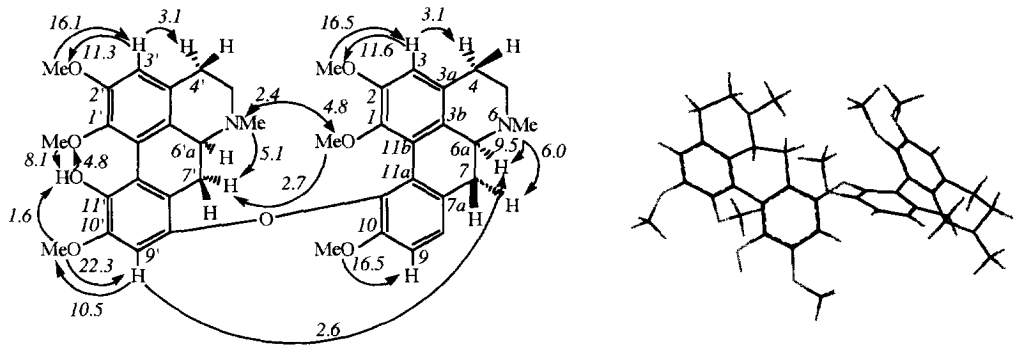


Figure 2. NOE's (%, $CDCl_3$) and stable conformation of **5**

Experimental

General.– Perkin-Elmer 1760-X Infrared FT spectrometer; Hitachi 150-20 Double Beam Spectrophotometer; Jasco J-710 Spectropolarimeter; JEOLJMX-HX110 Mass Spectrometer (70 eV); Bruker AMX-400 NMR Spectrometer in $CDCl_3$ (δ_H 7.24, δ_C 77.0). 2D NMR spectra were recorded using Bruker's standard pulse program; in the HMQC and HMBC experiments, Δ= 1 s and J =140, 8 Hz, respectively, the correlation maps consisted of 512 x 1K data points per spectrum, each composed of 16 to 64 transients. TLC solvent system A. Me_2CO-$C_6H_5CH_3$ (2:3), B. MeOH-$CHCl_3$ (1:19), both saturated with ammonia water (25%).

Isolation.– The free bases (9.04 g), obtained from the $CHCl_3$ soluble fraction (14.22 g) of the leaves of *Dehaasia triandra*, were fractionated with a Sanki CPC to give nine fractions.[1]

Fraction I (440 mg) was separated on a Si gel column (10g, SiO_2 for prep. TLC) eluted with 0.5 to 10% MeOH in $CHCl_3$ to give isoboldine [3.2 mg, R_f 0.24 (A), 0.29 (B)], **1** (9.0 mg) and homoaromoline[14] [151 mg, R_f 0.29 (A) , 0.34.(B)].

Fraction III (505 mg) was separated on a Si gel column (20 g, 230-400 mesh) eluted with 0-1.5% MeOH in $CHCl_3$, saturated with ammonia water (25%) to give norisocorydine (200 mg) and thalrugosine[14] [242 mg, R_f 0.22 (A), 0.42 (B)]. Fraction IV (554 mg) contained *N*-methyllindcarpine and *N*-methyllaurotetanine as minor and major components, respectively, identified in every respect (TLC, ^{1}H NMR) with authentic samples isolated from *Litsea cubeba*.[15] Fraction V (1.23 g) was *N*-methyllaurotetanine. From fractions VII and VIII, isocorydine and isocorydione had been isolated.[1]

Sephadex LH-20 separation of fraction IX (3.81 g) yielded isocorydine (subfraction IX-5), norisocorydione (subfraction IX-7)[1]. Separation of subfraction IX-4 (519 mg) on a Si gel column eluted with 0-5% MeOH in $CHCl_3$ yielded isocorydine (41 mg) and dehatriphine (190 mg)[1] and a mixture (68 mg) of dehatriphine

and **4**. This mixture was separated by preparative TLC (SiO_2, 1.25 mm x 2) developed twice with ^{i}PrOH-$C_6H_5CH_3$-NH_4OH (25%) (7:93:1) and once with the ratio 10:90:1 to give dehatriphine (43.6 mg) and **4** (15.6 mg). Separation of subfraction IX-3 (156 mg) on a Si gel column (6 g, 230-400 mesh) eluted with 0.5-15% MeOH in $CHCl_3$ yield **3** (6.0 mg) and **5** (33.4 mg). Separation of subfraction IX-6 (247 mg) on a Si gel column (10 g, 70-230 mesh) eluted with 5-30% Me_2CO in $C_6H_5CH_3$ yielded five fractions. Subfraction IX-6-1 was isocorydione (97 mg). PTLC separation of subfraction IX-6-2 (14.1 mg) (SiO_2, 0.5 mm, 25% $Me_2CO/C_6H_5CH_3$) yielded isocorydione (2.0 mg), norisocorydione (2.9 mg) and nantenine (4.8 mg).[16] PTLC separation of subfraction IX-6-3 (23.5 mg) (SiO_2, 1.25 mm, 2% and 3% MeOH/$CHCl_3$ each once) yielded **2** (17.0 mg) and nantenine (3.6 mg).

Secoxanthoplanine (**1**).– R_f 0.17 (A), 0.32 (B); IR (KBr) ν max 3425 (br s, OH), 2955 (m), 2850 (w), 1593 (s), 1510 (s), 1461 (s), 1280 (s), 1233 (m), 1117 (s), 1087 (m), 870 (m) cm^{-1}; UV (MeOH) λ max (log ε) 213 (4.33), 264 (4.79), 279 (sh, 4.44), 308 (4.04), 319 (4.03), 345 (3.26), 362 (3.09) nm; λ max (MeOH+NaOH) nm (log ε) 219.0 (sh, 4.35), 269.0 (sh, 4.62), 279.6 (4.66), 319.0 (sh, 4.07); ^{1}H NMR δ ($CDCl_3$) 9.22 (1H, s, H-5), 7.69 (1H, d, J = 9.1 Hz, H-10), and 7.44 (1H, d, J = 9.1 Hz, H-9), 7.26 (1H, s, H-8), 7.19 (1H, s, H-2), 4.03 (3H, s, MeO-6), 4.00 (3H, s, MeO-3), 3.88 (3H, s, MeO-4), 3.39 (2H, m, H-11), 2.83 (2H, m, H-12), 2.51 (6H, s, NMe_2); EIMS (20 eV) *m/z* $[M]^+$ 355 (69), 297 (3), 58 (100).

Hofmann degradation of xanthoplanine.– The viscous solution of xanthoplanine (ClO_4^- salt, 50 mg) in ethanolamine (1 mL) in a screw-tight sealed flask (25 mL) was heated at 142-145° C in an oil bath for 30 min. The cooled residue was diluted with H_2O (5 mL) and the solution was adjusted to pH 9 with 10% NH_4Cl (about 20 mL) and then extracted with $CHCl_3$ (25 mL x 3). The combined $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to give amorphous secoxanthoplanine (39.4 mg, quantitative yield) which was essentially pure on TLC and displayed identical spectral data with **1**.

Dehydroisocorydione (**2**).– Fine needle crystals, mp 252.5° C (Me_2CO); R_f 0.45 (A), 0.49 (B); IR (KBr) ν max 2981 (w), 2843 (w), 1651 (s), 1632 (s), 1609 (s), 1578 (m), 1555 (s), 1472 (m), 1386 (s), 1221 (s), 1096 (s), 989 (m), 908 (m), 822 (s) cm^{-1}; UV-VIS (MeOH) λ max (log ε) 214 (4.54), 266 (4.10), 341 (4.15), 398 (sh, 3.79), 416 (sh, 3.67), 693 (3.65); ^{1}H- and ^{13}C- NMR data, see Table 1; HREIMS $[M]^+$ *m/z* 351.1100 (calcd for $C_{20}H_{17}NO_5$, 351.1106); EIMS *m/z* $[M]^+$ 351 (90), 352 (18), 336 (100), 308 (10), 278 (16).

(8,8'-R)-Bisisocorydine (**3**).– Amorphous solid; R_f 0.42 (A), 0.62 (B); $[\alpha]^{20}_D$ +14.0° (*c* =0.5, MeOH); IR (KBr) ν max 3425 (br s, OH), 3230 (br m), 2931 (m), 2853 (w), 1597 (m), 1462 (s), 1427 (m), 1238 (s), 1208 (s) cm^{-1}; UV (MeOH) λ max (log ε) 222 (4.64), 267 (4.33), 276 (sh, 4.29), 305 (3.88), 322 (sh, 3.63) nm; λ max (MeOH+ NaOH) 222 (sh, 4.66), 266 (4.33), 305 (3.89) nm; CD (MeOH) (Δε) 330 (0), 316 (+2.92), 303 (0), 277 (-31.18), 259 (-11.94), 254 (-12.72), 246 (0), 235 (+50.09), 223 (+29.34), 218 (+30.48), 208 (0) nm; ^{1}H- and ^{13}C- NMR data, see Table 2; HREIMS *m/z* $[M]^+$ 680.3102 (calcd for $C_{40}H_{44}N_2O_8$ 680.3098); EIMS *m/z* 681 (23), $[M]^+$ 680 (100), 665 (18), 622 (20), 340 (41), 114 (25).

(8,8'-S)-Bisisocorydine (**4**).– Amorphous solid, R_f 0.28 (A), 0.60 (B); $[\alpha]^{20}_D$ +176.0° (*c* =0.5, MeOH); IR (KBr) ν max 3436 (br s, OH), 3220 (br m, H-bonded OH), 2941 (m), 2847 (w), 2789 (w), 1597 (m), 1462 (s), 1426 (s), 1238 (s), 1208 (s) cm^{-1} ; UV (MeOH) λ max (log ε) 220 (4.80), 266 (4.47), 276 (sh, 4.41), 304 (4.11) nm; λ max (MeOH+ NaOH) 220 (sh, 4.82), 266 (4.47), 305 (4.11) nm; CD (MeOH) (Δε) 324 (0), 304 (+4.17), 293 (sh) (+5.05), 281 (+17.4), 271 (0), 264 (-10.43), 258 (0), 240 (+58.97), 228 (0), 217 (-86.87), 206 (0) nm; ^{1}H- and ^{13}C- NMR data, see Table 2; HREIMS *m/z* $[M]^+$ 680.3127 (calcd for $C_{40}H_{44}N_2O_8$ 680.3098); EIMS *m/z* $[M]^+$ 680 (3), 355 (15), 341 (100), 340 (90), 325 (93), 310 (81), 282 (27).

(11,8')-O-Bisisocorydine (**5**).– Amorphous solid; R_f 0.30 (A), 0.52 (B); $[\alpha]^{20}_D$ +89.0° (*c* =1.0, MeOH); IR (KBr) ν max 3441 (br s, OH), 3245 (br m, H-bonded OH), 2942 (m), 2836 (w), 2786 (w), 1586 (m), 1463 (s), 1204 (s), 1139 (m) cm^{-1}; UV (MeOH) λ max (log ε) 221 (4.81), 269 (4.35), 303 (3.99) nm; λ max (MeOH+ NaOH) 221 (sh, 4.83), 269 (4.36), 303 (4.01) nm; CD (MeOH) (Δε) 365 (0), 336 (+3.44), 328 (+3.01), 320 (+3.34), 311 (0), 302 (-5.94), 292 (sh) (-10.23), 278 (-27.55), 259 (sh) (-6.68), 249 (0), 235 (+71.42), 217 (0) nm; ^1H- and ^{13}C- NMR see Table 3; HREIMS *m/z* $[M]^+$ 680.3061 (calcd for $C_{40}H_{44}N_2O_8$ 680.3098); EIMS *m/z* 681 (32), $[M]^+$ 680 (92), 665 (30), 649 (95), 340 (33), 324 (100), 309 (35).

Preparation of 3 and 4 from isocorydine via oxidative coupling.– The mixture of isocorydine (102 mg), MeCN (1mL) and manganic tris(acetylacetonate) (MTA) (373 mg, 3.5 molar ratio)[9] in a screw-tight flask (25 mL) was degassed by suction and then sealed and heated (72°C) for 18h. The reaction mixture was partitioned between H_2O (50 mL) and $CHCl_3$ (40 mL x 3). The combined organic layer was dried over $MgSO_4$ and evaporated to give a dark brown residue (142 mg) which was separated on a Si gel column (10 g, 230-400 mesh) eluted with 0.5 to 1.5% MeOH in $CHCl_3$ to give in order isocorydine (22 mg), **3** (10.2 mg), and **4** (5.2 mg).

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