Quinolizidines. XVI. Chiral syntheses of 9-demethylcephaeline and 10-demethylcephaeline

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Quinolizidines. XVI.[1] Chiral Syntheses of 9-Demethylcephaeline and 10-Demethylcephaeline[2]

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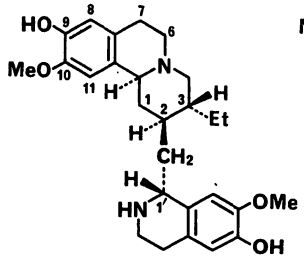
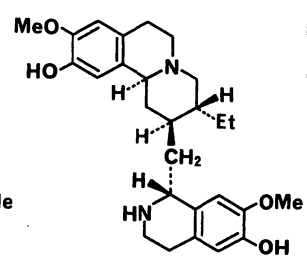
In order to establish the structure of the *Alangium* alkaloid demethylcephaeline, chiral syntheses of the two possible alternative structures, (−)-9-demethylcephaeline (**1**) and (−)-10-demethylcephaeline (**2**), have been accomplished through a "cincholoipon-incorporating route." The synthesis of (−)-**2** started with an initial condensation of the tricyclic acid (−)-**12b**, prepared from the ester (−)-**11b** by alkaline hydrolysis, with 3-benzyloxy-4-methoxyphenethylamine and proceeded through the intermediates (−)-**13b**, (+)-**15b**, and (−)-**14b**. The 1′-epimers (−)-**18b** and (−)-**17** were also produced in this reaction sequence. A parallel sequence of conversions starting with (+)-**15a** afforded (−)-**1** *via* the intermediate (−)-**14a**, together with the 1′-epimer (−)-**16** *via* (−)-**18a**. Unfortunately, however, lack of a sufficient amount of natural (−)-demethylcephaeline for a detailed and direct comparison precluded identification of either (−)-**1** or (−)-**2** with this alkaloid, leaving its chemistry incomplete.

Keywords——demethylcephaeline; demethylisocephaeline; diethyl phosphorocyanidate amide formation; Bischler–Napieralski cyclization; carbon–nitrogen double-bond catalytic reduction; benzyl ether catalytic hydrogenolysis; TLC epimer differentiation; NMR epimer differentiation

In 1970, Pakrashi and Achari[3] reported the isolation of (−)-demethylcephaeline, a new phenolic benzoquinolizidine alkaloid, from the stem bark of the Indian medicinal plant *Alangium lamarckii* THWAITES (Alangiaceae). On the basis of its chemical correlation with cephaeline (**3**) and emetine (**4**), as well as ultraviolet (UV), infrared (IR), and mass spectral evidence, they assigned either structure **1** (absolute configuration shown[4]) or **2** to the new base, with their preference for **2**.[3] However, differentiation between the 9- and the 10-demethyl structures was not possible at that time. With the aim of determining which



1



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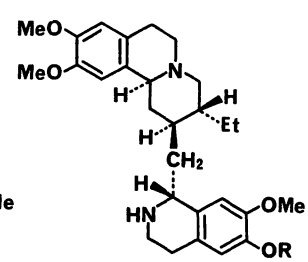
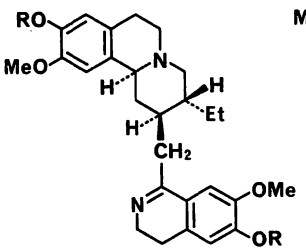


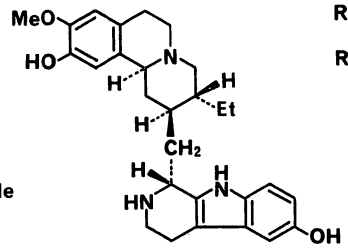
3: R=H
4: R=Me

structure is correct, we tried to synthesize both of the possible alternative structures, 9-demethylcephaeline (**1**) and 10-demethylcephaeline (**2**), through a "cincholoipon-incorporating route."[5] The simultaneous setting of the two synthetic targets is reasonable since we have recently shown that (+)-desmethylpsychotrine, another phenolic *A. lamarckii*

alkaloid,[6] has the 9-demethyl structure **5**,[7] whereas (−)-demethyltubulosine, yet another phenolic *A. lamarckii* alkaloid,[6,8] is not a 9-demethylated base,[9] but 10-demethyltubulosine (**7**).[1,10] The occurrence of both 9-demethylprotoemetinol (**8**) and 10-demethylprotoemetinol (**9**) in the seeds of *A. lamarckii* has also been reported quite recently.[11]



5: R=H
6: R=Me



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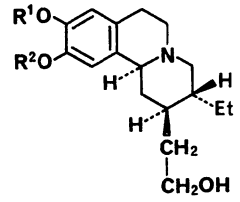

8: R^1=H; R^2=Me
9: R^1=Me; R^2=H

For the synthesis of the first target, 9-demethylcephaeline (**1**), we selected (+)-*O*,*O*-dibenzyl-9-demethylpsychotrine (**15a**) as a key intermediate. When the present work was commenced, this intermediate had already been prepared from (+)-ethyl cincholoiponate (**10**), a degradation product from the *Cinchona* alkaloid cinchonine, by a 13-step synthesis [through (−)-**11a**, (−)-**12a**, and (−)-**13a**] and utilized by us for the synthesis of (+)-9-demethylpsychotrine (**5**).[7a,c] Catalytic hydrogenation of (+)-**15a** in EtOH over Adams catalyst and chromatographic separation of the products furnished (−)-*O*,*O*-dibenzyl-9-demethylcephaeline (**14a**) and its 1′-epimer [(−)-**18a**] in 47% and 30% yields, respectively. On debenzylation using hydrogen and Pd–C catalyst, (−)-**14a** gave the first target molecule (−)-**1**

TABLE I. ^{13}C Chemical Shifts of (−)-*O*,*O*-Dibenzyl-9-demethylcephaeline (**14a**), (−)-*O*,*O*-Dibenzyl-10-demethylcephaeline (**14b**), and Their 1′α-H Isomers (−)-**18a**, **b** in $CDCl_3$

Carbon	Chemical shift[a]				Carbon	Chemical shift[a]			
	(−)-**14a**	(−)-**14b**	(−)-**18a**	(−)-**18b**		(−)-**14a**	(−)-**14b**	(−)-**18a**	(−)-**18b**
C(1)	36.9	36.7	39.4	39.2	C(4′)	29.2	29.4	29.4[b]	29.2
C(2)	36.9	36.7	38.9	39.0	C(4′a)	127.0	127.0	127.2	127.0
C(3)	41.7	41.9	42.9	42.9	C(5′)	114.8	114.8	114.8	114.8
C(4)	61.4	61.4	61.6	61.5	C(6′)	146.8[c]	146.7[d]	146.7[e]	146.7[f]
C(6)	52.3	52.4	52.5	52.5	C(7′)	148.0[c]	148.0[d]	147.8[e]	147.8[f]
C(7)	29.2	29.4	29.1[b]	29.2	C(8′)	110.0	110.1	110.4	110.4
C(7a)	127.0	127.6	126.7	127.3	C(8′a)	132.7	132.9	132.7	132.6
C(8)	114.5	112.1[g]	114.4	112.1[h]	9-OMe	—	56.0	—	56.0
C(9)	146.6[c]	148.3[d]	146.7[e]	148.2[f]	10-OMe	56.6	—	56.3	—
C(10)	147.9[c]	146.1[d]	147.8[e]	146.2[f]	7′-OMe	56.2	56.2	56.3	56.3
C(11)	109.7	112.4[g]	109.1	111.8[h]	9-OCH_2	71.0	—	71.1	—
C(11a)	131.0	130.3	130.8	130.1	10-OCH_2	—	71.7	—	71.6
C(11b)	62.4	62.3	62.8	62.6	6′-OCH_2	71.2	71.2	71.1	71.0
C(12)	40.2	40.3	40.7	40.7	Ph	137.3	137.6	137.2	137.4
C(13)	23.5	23.5	24.0	24.0		—	137.3	—	137.2
C(14)	11.2	11.2	11.3	11.3		128.4	128.5	128.4	128.3
C(1′)	51.9	51.8	55.3	55.2		127.6	127.6	127.6	127.6
C(3′)	40.7	40.7	41.1	41.0		127.2	127.3	127.2	127.2

a) In ppm downfield from internal Me_4Si. *b*—*h*) Assignments indicated by a given superscript may be interchanged.

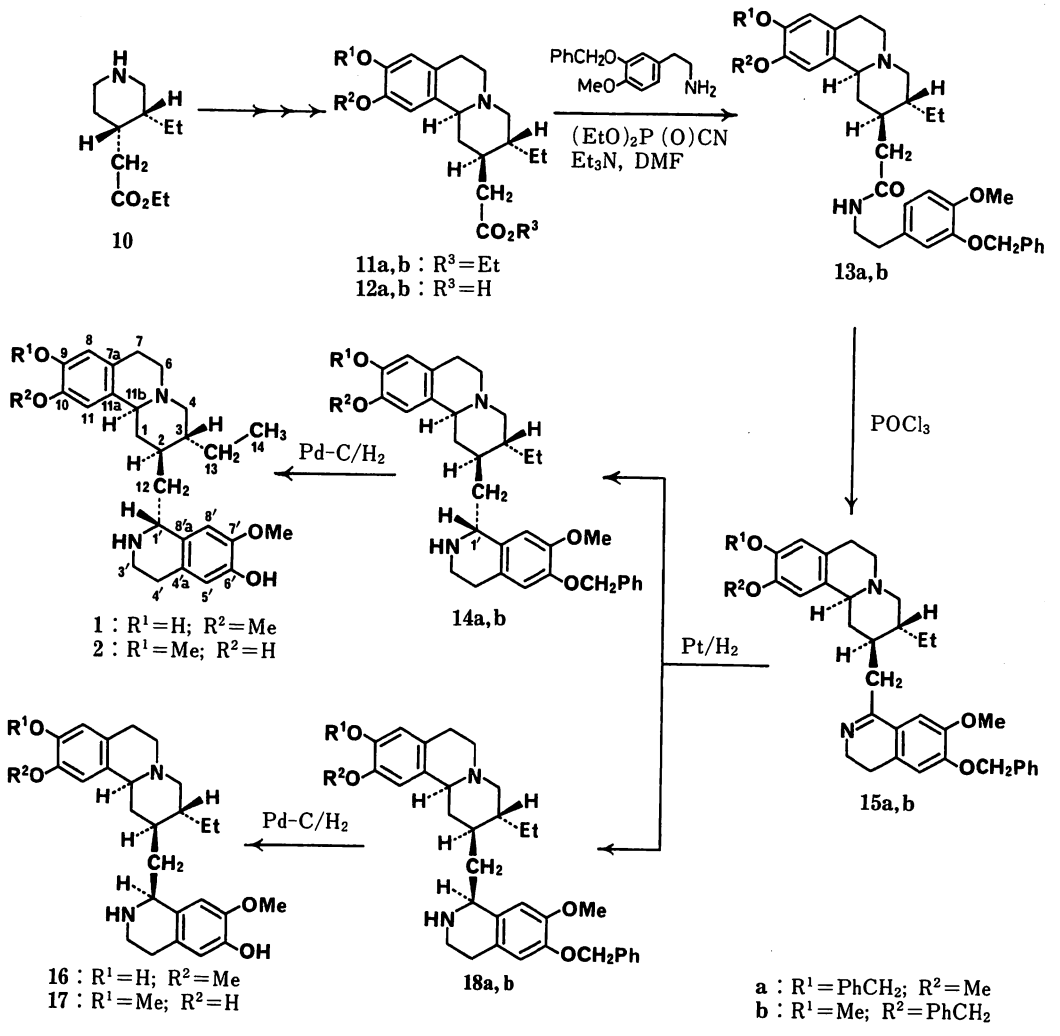

Chart 1

[mp 147 °C; $[\alpha]_D^{12}$ −55.0 ° ($CHCl_3$)] in 82% yield. A similar hydrogenolysis of the epimeric base (−)-**18a** afforded the corresponding phenolic base (−)-**16** in 73% yield.

The configurations at C-1′ of (−)-**14a** and (−)-**18a** and hence those of (−)-**1** and (−)-**16** were assigned on the basis of the following evidence. The above formation of a 1.6 : 1 mixture of (−)-**14a** and (−)-**18a** from (+)-**15a** is comparable to that[12] of a 1.7 : 1 mixture of emetine (**4**) and its 1′-epimer (isoemetine) in a similar hydrogenation of *O*-methylpsychotrine (**6**). On thin-layer chromatographic (TLC) analysis, (−)-**14a** moved faster than (−)-**18a**. In the ^{13}C nuclear magnetic resonance (^{13}C-NMR) spectra in $CDCl_3$ (see Table I), the C(1), C(2), and C(1′) carbon signals of (−)-**14a** appeared upfield from the corresponding signals of the 1′-epimer (−)-**18a** by 2.0—3.4 ppm. In the ^1H-NMR spectra in $CDCl_3$, the C(1′)H proton of (−)-**14a** resonated at δ 4.11 as a doublet with J = 10.5 Hz, whereas that of (−)-**18a** resonated at δ 4.04 as an indistinct triplet with J = 5 Hz. These chemical TLC, and NMR spectral features of (−)-**14a** and (−)-**18a** fulfilled all the recently reported criteria[1,9b,13] for distinguishing between the 1′β-H and 1′α-H isomers in such unique ring systems.

We next proceeded to the synthesis of the second target, 10-demethylcephaeline (**2**).

Alkaline hydrolysis of the tricyclic ester (−)-**11b**, prepared from (+)-**10** in 24% overall yield through the recently reported synthetic route ("cincholoipon-incorporating route"),[14] gave the amino acid (−)-**12b** in 98% yield. Condensation of (−)-**12b** with 3-benzyloxy-4-methoxyphenethylamine in *N*,*N*-dimethylformamide (DMF) by the diethyl phosphorocyanidate method[15] produced the amide (−)-**13b** (90% yield), which was then cyclized with $POCl_3$ in boiling toluene to provide (+)-*O*,*O*-dibenzyl-10-demethylpsychotrine (**15b**) in 87% yield. The correctness of the structures of (−)-**12b**, (−)-**13b**, and (+)-**15b** was verified by their spectral identity with the corresponding racemic modifications which had been obtained in the course of our recent synthesis[7b] of (±)-10-demethylpsychotrine. The subsequent steps to **2** were essentially the same as described above for the 9-demethyl series, giving an epimeric pair of (−)-**14b** [48% yield from (+)-**15b**] and (−)-**18b** (29% yield) first, and then the desired second target (−)-**2** [mp 148 °C; $[\alpha]_D^{17}$ −53.0° ($CHCl_3$); 73% yield from (−)-**14b**] and its 1′-epimer (−)-**17** [77% yield from (−)-**18b**]. The stereochemistry at C-1′ of (−)-**14b** and (−)-**18b** [and hence that of (−)-**2** and (−)-**17**] was confirmed as in the case of the above 9-demethyl congeners (see also Table I).

With the two candidate compounds (−)-**1** and (−)-**2** in hand, we now proceeded to the problem of identification with natural (−)-demethylcephaeline [mp 147—149 °C;[3] $[\alpha]_D$ −53.5° ($CHCl_3$)[3]]. The UV (in EtOH or 0.1 N ethanolic NaOH), IR (in Nujol), and mass spectra of all three were so closely similar that they were impracticable as a means of identification. Although the ^{1}H-NMR spectra (in $CDCl_3$) of (−)-**1** and (−)-**2** were clearly differentiated from one another, that of the natural alkaloid had not been measured at that time. Unfortunately, no sample of natural (−)-demethylcephaeline was available for obtaining a ^{1}H-NMR spectrum and/or for a mixture melting point test, and this precluded identification of either (−)-**1** or (−)-**2** with the *Alangium* alkaloid, thus leaving its chemistry incomplete. Since (−)-demethylcephaeline has been shown to be a constituent of an amorphous alkaloidal mixture (AL 60, isolated from *A. lamarckii*) exerting dose-dependent biphasic action on blood pressure,[3] further isolation of this alkaloid from the natural source in a sufficient quantity for a detailed and direct comparison with the synthetic samples is necessary before chemical and pharmacological investigations can continue.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise stated, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. See refs. 1 and 14*b* for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

(2*R*,3*R*,11b*S*)-10-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid [(−)-12b]——A solution of the tricyclic ester (−)-**11b**[14] (875 mg, 2 mmol) and 2 N aqueous NaOH (2 ml) in EtOH (15 ml) was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and H_2O (15 ml) was added to the residual oil. The resulting aqueous solution was neutralized with 2 N aqueous HCl (2 ml) to deposit a pale yellowish gum, which was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave (−)-**12b** (802 mg, 98%) as an almost colorless glass, $[\alpha]_D^{18}$ −56.8° (*c* = 0.50, EtOH); MS *m/e*: 409 (M^+). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were identical with those of authentic (±)-**12b**.[7b]

(2*R*,3*R*,11b*S*)-10-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine-2-acetamide [(−)-13b]——The tricyclic acid (−)-**12b** was allowed to react with 3-benzyloxy-4-methoxyphenethylamine[16] by the diethyl phosphorocyanidate method[15] in a manner similar to that carried out in the recent synthesis[7a,c] of (−)-**13a** from (−)-**12a**, giving (−)-**13b** in 90% yield as a colorless solid. Recrystallization of the solid from EtOH produced an analytical sample as colorless minute needles, mp 149—151 °C; $[\alpha]_D^{20}$ −22.2° (*c* = 0.50, EtOH). *Anal.* Calcd for $C_{41}H_{48}N_2O_5$: C, 75.90; H, 7.46; N, 4.32. Found: C, 75.79; H, 7.45; N, 4.13. The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra and TLC mobility of this sample were identical with those of authentic (±)-**13b**.[7b]

(2*R*,3*R*,11b*S*)-10-Benzyloxy-2-(6-benzyloxy-3,4-dihydro-7-methoxy-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine [(+)-15b]——Crude (+)-**15b** was obtained from (−)-**13b** and $POCl_3$ as described recently for (+)-**15a**[7a,c] and purified by column chromatography [alumina, AcOEt–hexane (1 : 1, v/v)] to give a faintly yellowish glass (87% yield), $[\alpha]_D^{26}$ +39.9° (*c* = 0.96, EtOH); MS *m/e*: 630 (M^+). The IR ($CHCl_3$) and ^1H-NMR ($CDCl_3$) spectra of this sample were superimposable on those of authentic (±)-**15b**.[7b]

[2*S*-[2α(*S),3β,11bβ]]- and [2*S*-[2α(*R**),3β,11bβ]]-9-Benzyloxy-2-(6-benzyloxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11b-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizines [(−)-14a and (−)-18a]**——A solution of (+)-**15a**[7a,c] (1.01 g, 1.6 mmol) in EtOH (30 ml) was hydrogenated over Adams catalyst (120 mg) at atmospheric pressure and 18 °C for 1 h. Removal of the catalyst by filtration and evaporation of the filtrate under reduced pressure left a yellow oil, which was dissolved in $CHCl_3$ (80 ml). The $CHCl_3$ solution was washed successively with 5% aqueous NaOH and saturated aqueous NaCl, dried, and concentrated to leave a orange glass (972 mg). This material was chromatographed successively on a Merck Lobar column (LiChroprep Si 60) and a silica gel column using $CHCl_3$–MeOH (10 : 1, v/v) as the eluent, and then on preparative TLC plate [silica gel, $CHCl_3$–MeOH (10 : 1, v/v)]. The fractions with higher TLC mobility (*Rf* 0.61) gave (−)-*O*,*O*-dibenzyl-demethylcephaeline [(−)-**14a**] (478 mg, 47%) as a faintly yellowish glass, $[\alpha]_D^{26}$ −18.7° (*c* = 0.82, EtOH); MS *m/e*: 632 (M^+); IR $\nu_{max}^{CHCl_3}$ 2760 cm^{-1} (*trans*-quinolizidine ring);[17] ^1H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J* = 6.6 Hz, $CCH_2\underline{Me}$), 3.81 and 3.85 (3H each, s, two OMe's), 4.11 (1H, d, *J* = 10.5 Hz, $H_{(1')}$), 5.10 (4H, s, two $OC\underline{H}_2Ph$'s), 6.5 and 6.80 (1H each, s, aromatic protons), 6.62 (2H, s, two aromatic protons), 7.1—7.5 (10H, m, two $OCH_2\underline{Ph}$'s); ^{13}C-NMR (Table I).

The fractions with lower TLC mobility (*Rf* 0.54) in the above chromatography afforded the 1′α-H isomer (−)-**18a** (308 mg, 30%) as a yellow glass, $[\alpha]_D^{26}$ −25.6° (*c* = 0.66, EtOH); MS *m/e*: 632 (M^+); IR $\nu_{max}^{CHCl_3}$ 2760 cm^{-1} (*trans*-quinolizidine ring);[17] ^1H-NMR ($CDCl_3$) δ: 0.94 (3H, t, *J* = 6.6 Hz, $CCH_2\underline{Me}$), 3.80 and 3.83 (3H each, s, two OMe's), 4.04 (1H, dull t, *J* = 5 Hz, $H_{(1')}$), 5.07 (4H, s, two $OC\underline{H}_2Ph$'s), 6.59 and 6.69 (1H each, s, aromatic protons), 6.61 (2H, s, two aromatic protons), 7.1—7.5 (10H, m, two $OCH_2\underline{Ph}$'s); ^{13}C-NMR (Table I).

[2*S*-[2α(*S),3β,11bβ]]- and [2*S*-[2α(*R**),3β,11bβ]]-10-Benzyloxy-2-(6-benzyloxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizines [(−)-14b and (−)-18b]**——These two isomers were prepared from (+)-**15b** by a catalytic reduction similar to that described above for (−)-**14a** and (−)-**18a**, and by subsequent chromatographic separation on an alumina column [hexane–AcOEt (2 : 1, v/v)] and on a silica gel column [$CHCl_3$–MeOH (10 : 1, v/v)].

(−)-*O*,*O*-Dibenzyl-10-demethylcephaeline [(−)-**14b**] was isolated as a faintly yellowish glass (48% yield), TLC R_f 0.55 [silica gel, $CHCl_3$–MeOH (10 : 1, v/v)] or 0.49 [alumina, hexane–AcOEt (2 : 1, v/v)]; $[\alpha]_D^{30}$ −33.2° (*c* = 0.50, EtOH); MS *m/e*: 632 (M^+); IR $\nu_{max}^{CHCl_3}$ 2760 cm^{-1} (*trans*-quinolizidine ring);[17] ^1H-NMR ($CDCl_3$) δ: 0.87 (3H, t, *J* = 6.6 Hz, $CCH_2\underline{Me}$), 3.82 and 3.85 (3H each, s, two OMe's), 3.96 (1H, d, *J* = 10.5 Hz, $H_{(1')}$), 5.05 and 5.16 (2H, AB type d's, *J* = 12 Hz, $OC\underline{H}_2Ph$), 5.10 (2H, s, $OC\underline{H}_2Ph$), 6.52, 6.60, 6.62, and 6.74 (1H each, s, aromatic protons), 7.1—7.5 (10H, m, two $OCH_2\underline{Ph}$'s); ^{13}C-NMR (Table I).

The 1′α-H isomer (−)-**18b** was obtained as a faintly orange glass (29% yield), TLC *Rf* 0.47 [silica gel, $CHCl_3$–MeOH (10 : 1, v/v)] or 0.25 [alumina, hexane–AcOEt (2 : 1, v/v)]; $[\alpha]_D^{30}$ −30.9° (*c* = 0.50, EtOH); MS *m/e*: 632 (M^+); IR $\nu_{max}^{CHCl_3}$ 2760 cm^{-1} (*trans*-quinolizidine ring);[17] ^1H-NMR ($CDCl_3$) δ: 0.93 (1H, t, *J* = 6.6 Hz, $CCH_2\underline{Me}$), 3.82 (6H, s, two OMe's), 3.99 (1H, dull t, *J* = 5.8 Hz, $H_{(1')}$), 5.05 and 5.07 (2H each, s, two $OC\underline{H}_2Ph$'s), 6.58, 6.61, 6.66, and 6.68 (1H each, s, aromatic protons), 7.1—7.5 (10H, m, two $OCH_2\underline{Ph}$'s): ^{13}C-NMR (Table I).

[2*S*-[2α(*S),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-9-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-10-methoxy-2*H*-benzo[*a*]quinolizine [(−)-9-Demethylcephaeline] [(−)-1]**——A solution of (−)-**14a** (443 mg, 0.7 mmol) in MeOH–AcOH (1 : 1, v/v) (30 ml) was hydrogenated over 10% Pd–C (350 mg) at atmospheric pressure and 18 °C for 3 h. The catalyst was filtered off and washed with MeOH (20 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a yellow oil, which was dissolved in H_2O (10 ml). The aqueous solution was made alkaline with 10% aqueous Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellowish-brown solid (306 mg). Purification of the solid by column chromatography [alumina, $CHCl_3$–EtOH (10 : 1, v/v)] gave (−)-**1** (260 mg, 82%) as a yellowish solid. The solid was then recrystallized from benzene, producing an analytical sample as faintly yellowish minute needles, mp 147 °C (sintered at 124 °C); $[\alpha]_D^{12}$ −55.0° (*c* = 0.50, $CHCl_3$); MS *m/e* (relative intensity): 453 (M^+ + 1) (19), 452 (M^+) (60), 275 (12), 274 (27), 272 (18), 261 (15), 260 (18), 259 (21), 258 (51), 232 (23), 230 (23), 192 (53), 191 (28), 179 (12), 178 (100), 177 (18); UV λ_{max} (EtOH) 225 nm (sh) (ε 14300), 284.5 (7770), 288 (7800); λ_{max} (0.1 N aqueous NaOH) 243 (17200), 299 (10100); λ_{max} (0.1 N aqueous HCl) 223.5 (13800), 284 (6980); ^1H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J* = 6.5 Hz, $CCH_2\underline{Me}$), 3.81 and 3.84 (3H each, s, two OMe's), 4.10 (1H, d, *J* = 11 Hz, $H_{(1')}$), 6.50 and 6.72 (1H each, s, aromatic protons), 6.63 (2H, s, two aromatic protons). *Anal.* Calcd for $C_{27}H_{36}N_2O_4$: C, 71.65; H, 8.02; N, 6.19. Found: C, 71.72; H, 7.89; N, 5.89.

[2*S*-[2α(*S),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-10-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-9-methoxy-2*H*-benzo[*a*]quinolizine [(−)-10-Demethylcephaeline] [(−)-2]**——Hydrogenolysis of (−)-**14b** and work-up of the reaction mixture were carried out as described above for (−)-**1**, affording (−)-**2**·H_2O (73% yield) as a yellow solid. Recrystallization of the solid from benzene and drying over P_2O_5 at 2 mmHg and

50 °C for 20 h gave an analytical sample as faintly yellowish minute needles, mp 148 °C (sintered at 129—130 °C); $[\alpha]_D^{17}$ −53.0° (c=0.50, $CHCl_3$); MS m/e (relative intensity): 453 (M^++1) (14), 452 (M^+) (46), 275 (17), 274 (29), 272 (14), 261 (12), 260 (17), 259 (17), 258 (40), 232 (21), 230 (20), 192 (32), 191 (22), 179 (12), 178 (100), 177 (12); UV λ_{max} (EtOH) 225 nm (sh) (ε 15100), 286 (7730); λ_{max} (0.1 N aqueous NaOH) 243 (15700), 299 (9940); λ_{max} (0.1 N aqueous HCl) 223.5 (13900), 284 (6650); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 3.81 and 3.85 (3H each, s, two OMe's), 4.06 (1H, d, J=11.2 Hz, $H_{(1')}$), 6.47, 6.55, 6.61, and 6.81 (1H each, s, aromatic protons). *Anal.* Calcd for $C_{27}H_{36}N_2O_4 \cdot H_2O$: C, 68.91; H, 8.14; N, 5.95. Found: C, 69.03; H, 7.88; N, 5.61.

[2*S*-[2α(*R)-3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-9-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-10-methoxy-2*H*-benzo[*a*]quinolizine [(−)-9-Demethylisocephaeline] [(−)-16]**——Debenzylation of (−)-**18a** was effected as described above for (−)-**1**, and crude (−)-**16** was obtained in 73% yield as a yellowish solid. Recrystallization of the solid from EtOH–hexane (1 : 1, v/v) and drying over P_2O_5 at 2 mmHg and 50 °C for 10 h yielded an analytical sample of (−)-**16**·1/2EtOH as colorless minute needles, mp 178—180 °C; $[\alpha]_D^{12}$ −94.0° (c=0.36, $CHCl_3$); MS m/e: 452 (M^+); UV λ_{max} (EtOH) 225 nm (sh) (ε 14000), 285 (7780), 288 (7790); λ_{max} (0.1 N aqueous NaOH) 243 (16800), 299 (10100); λ_{max} (0.1 N aqueous HCl) 223.5 (13700), 284 (6760); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 1.24 (1.5H, t, J=7.0 Hz, $\underline{Me}CH_2OH$), 3.71 (1H, q, J=7.0 Hz, $MeC\underline{H}_2OH$), 3.78 and 3.80 (3H each, s, two OMe's), 4.07 (1H, dull t, J=5.2 Hz, $H_{(1')}$), 6.45, 6.56, 6.61, and 6.63 (1H each, s, aromatic protons). *Anal.* Calcd for $C_{27}H_{36}N_2O_4 \cdot 1/2C_2H_5OH$: C, 70.71; H, 8.26; N, 5.89. Found: C, 70.79; H, 8.25; N, 5.69.

[2*S*-[2α(*R),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-10-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-9-methoxy-2*H*-benzo[*a*]quinolizine [(−)-10-Demethylisocephaeline] [(−)-17]**——The benzyl ether (−)-**18b** was debenzylated as described above for (−)-**1**, furnishing crude (−)-**17** in 77% yield as a faintly yellow solid. Recrystallization of the solid from EtOH and drying over P_2O_5 at 2 mmHg and 50 °C for 20 h gave (−)-**17**·H_2O as colorless needles, mp 114—116 °C; $[\alpha]_D^{17}$ −50.0° (c=0.34, $CHCl_3$); MS m/e: 452 (M^+); UV λ_{max} (EtOH) 225 nm (sh) (ε 14900), 286 (7770); λ_{max} (0.1 N aqueous NaOH) 243 (15700), 299.5 (10200); λ_{max} (0.1 N aqueous HCl) 224 (13800), 284 (6760); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=6.8 Hz, $CCH_2\underline{Me}$), 3.83 and 3.84 (3H each, s, two OMe's), 3.97 (1H, dull t, J=5.8 Hz, $H_{(1')}$), 6.53, 6.61, 6.64, and 6.67 (1H each, s, aromatic protons). *Anal.* Calcd for $C_{27}H_{36}N_2O_4 \cdot H_2O$: C, 68.91; H, 8.14; N, 5.95. Found: C, 68.86; H, 8.17; N, 5.67.

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