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Quinolizidines. X.[1] Stereospecific Syntheses of (±)-9-Demethylpsychotrine and (±)-10-Demethylpsychotrine

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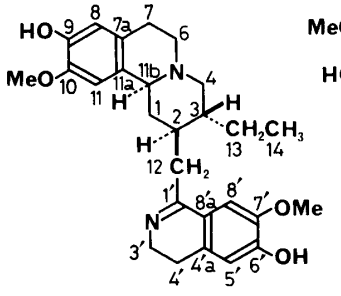
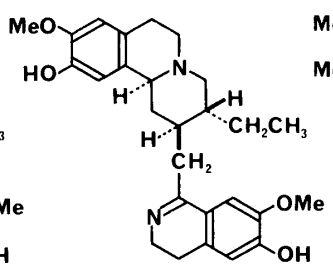
With the aim of establishing the structure of the *Alangium* alkaloid desmethylpsychotrine, stereospecific syntheses of two alternative structures, (±)-9-demethylpsychotrine (**1**) and (±)-10-demethylpsychotrine (**2**), have been achieved through a "lactim ether route." The synthesis of (±)-**1** started with an initial condensation of the lactim ether **6**, derived from the *trans*-lactam ester **5**, with 3-benzyloxy-4-methoxyphenacyl bromide (**7a**) and proceeded through the intermediates **8a**, **9a**, **10c**, **10a**, **11a**, **12a**, **13a**, **14a**, and **15a**. A parallel sequence of conversions starting with **6** and 4-benzyloxy-3-methoxyphenacyl bromide (**7b**) produced (±)-**2**. The ^{13}C nuclear magnetic resonance spectra of (±)-**1** and (±)-**2** confirmed their endocyclic double bond structure in the dihydroisoquinoline moiety. Spectral comparison of (±)-**1** and (±)-**2** with natural desmethylpsychotrine suggested formula **1** to be the most likely structure of this alkaloid.

Keywords——*Alangium* alkaloid desmethylpsychotrine; stereospecific synthesis; lactim ether alkylation; sodium borohydride reduction; catalytic hydrogenolysis; benzyl ether cleavage; diethyl phosphorocyanidate amide formation; Bischler–Napieralski cyclization; ^{13}C-NMR dihydroisoquinoline structure determination

Desmethylpsychotrine is a phenolic base found among a number of benzoquinolizidine alkaloids isolated from *Alangium lamarckii* THWAITES (family Alangiaceae).[2] In the early work of Pakrashi and Ali,[3] the alternative structures **1** and **2** were considered for this alkaloid on the basis of the mass spectral evidence and a chemical correlation with psychotrine (**3**) as well as *O*-methylpsychotrine (**4**). Its structure has now been established as 9-demethylpsychotrine (**1**) as a result of the syntheses of (±)-**1**, (±)-10-demethylpsychotrine (**2**), and (+)-**1** by our group.[2,4] This paper presents the details of the syntheses of (±)-**1** and (±)-**2**, which



1



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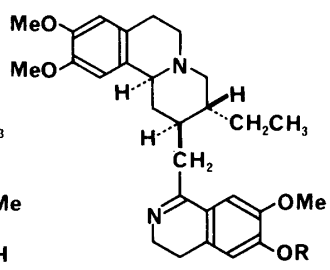


3: R=H
4: R=Me

were achieved through a "lactim ether route."[5] A brief account of the results reported here has been published in a preliminary form.[4a]

The racemic synthesis of the first alternative structure **1** started with the preparation of the lactim ether **6** from the (±)-*trans*-lactam ester **5**[6] according to the previously reported

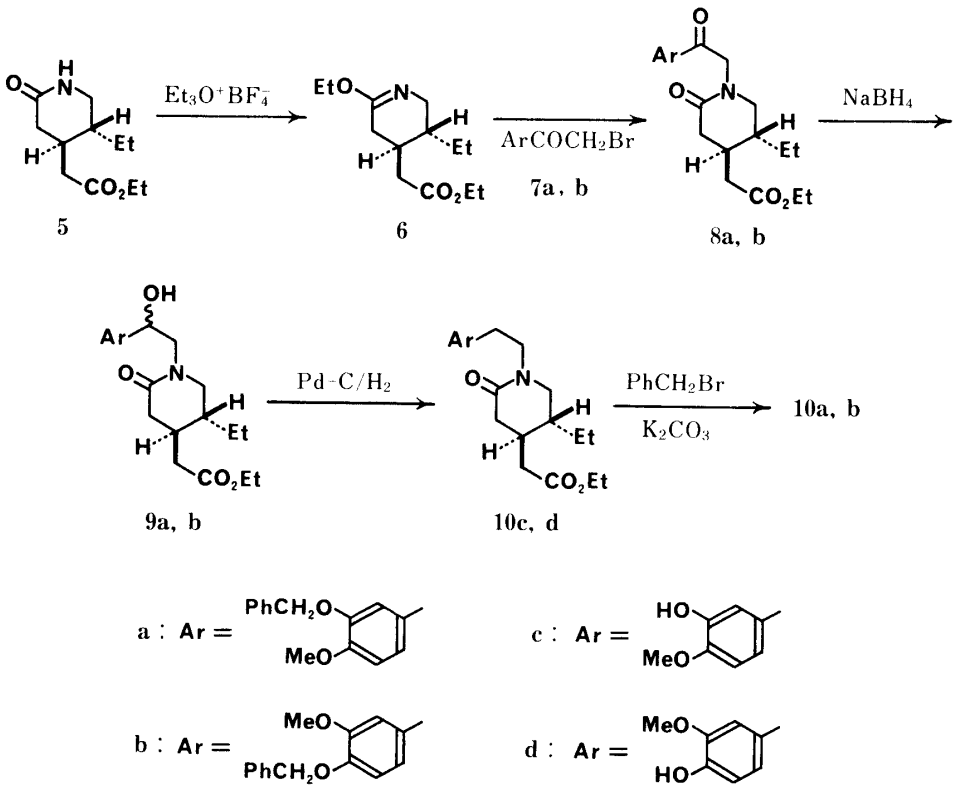
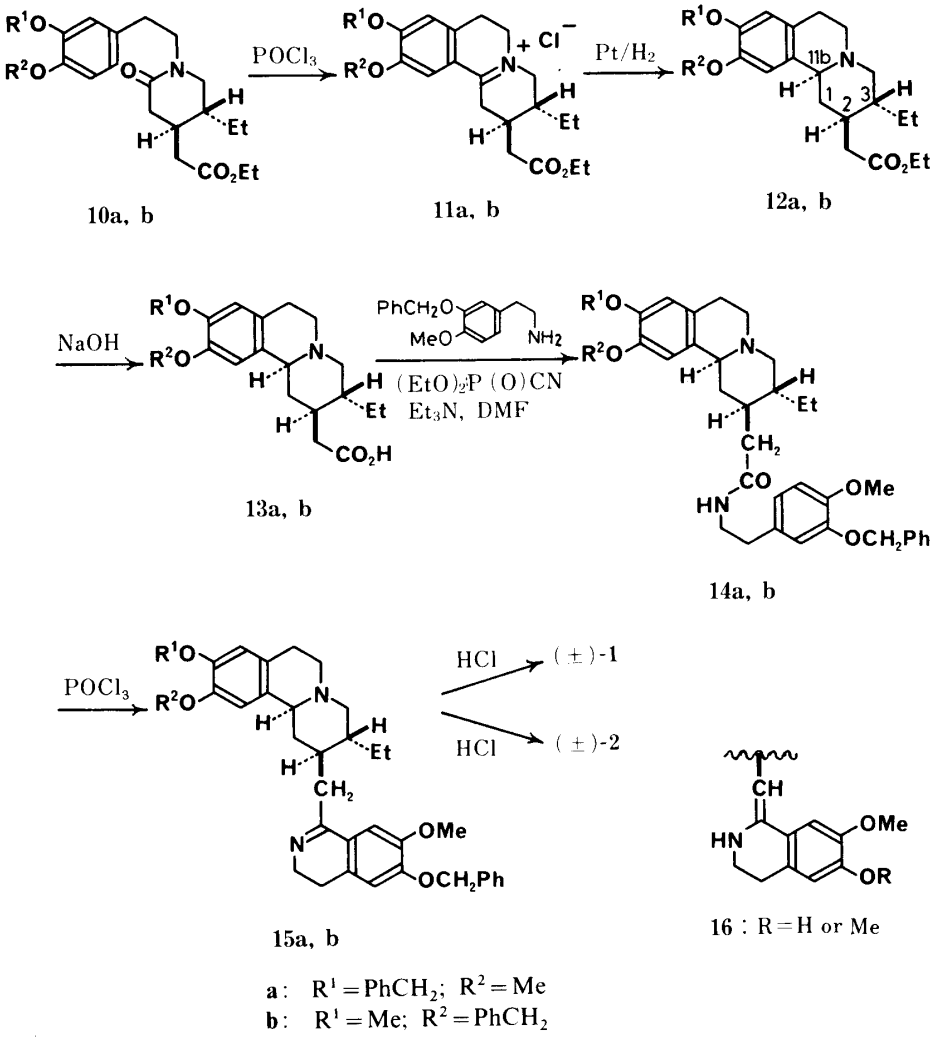


Chart 1

procedure.[5b] Treatment of **6** with 3-benzyloxy-4-methoxyphenacyl bromide (**7a**) in *N*,*N*-dimethylformamide (DMF) at 60 °C for 8 h gave the lactam ketone **8a** in 64% overall yield from **5**. The $NaBH_4$ reduction of **8a** in EtOH and catalytic hydrogenolysis of the resulting diastereomeric mixture of the lactam alcohol **9a** using hydrogen and Pd–C as a catalyst furnished the phenolic lactam **10c** in 92% overall yield from **8a**. Compound **10c** was then benzylated with benzyl bromide and K_2CO_3 in boiling acetone to produce the *O*-benzyl derivative **10a** in 74% yield. Conversion of **10a** into the tricyclic ester **12a** through the quaternary salt **11a** was effected in 71% overall yield by Bischler–Napieralski cyclization using $POCl_3$ in boiling toluene and subsequent hydrogenation using hydrogen and Adams catalyst. That all the chemical operations proceeding from **5** to **12a** did not affect the stereochemical relationship already established in the starting material and the correctness of the configuration at C-11b in **12a** were supported by our previous adaptation[5b] of a similar reaction sequence to a formal synthesis of emetine, the stereochemistry of which has been unequivocally established.[2]

On hydrolysis with aqueous NaOH in EtOH, **12a** provided the amino acid **13a** in 83% yield. Condensation of **13a** with 3-benzyloxy-4-methoxyphenethylamine in DMF using the coupling reagent[7] diethyl phosphorocyanidate[8] in the presence of Et_3N provided the amide **14a** in 97% yield. The amide **14a** was then subjected to Bischler–Napieralski cyclization using $POCl_3$ in boiling toluene to give the base **15a** in 82% yield. The final step was to debenzylate **15a**, and this was effected with boiling aqueous HCl–EtOH for 18 h to furnish (±)-9-demethylpsychotrine (**1**) (90% yield), which was characterized as an ethanolate [mp 224—226 °C (dec.)] after recrystallization from EtOH.

Some years ago, Schuij *et al.*[9] claimed the double bond in the dihydroisoquinoline moiety of psychotrine and *O*-methylpsychotrine to be exocyclic, as represented by the partial structure **16** (Chart 2), on the basis of their mass spectral study. However, we have recently



10a, b 11a, b 12a, b

13a, b

14a, b

15a, b

16 : R=H or Me

a: $R^1=PhCH_2$; $R^2=Me$
b: $R^1=Me$; $R^2=PhCH_2$

Chart 2

presented ^1H and ^{13}C nuclear magnetic resonance (NMR) and ultraviolet (UV) spectroscopic evidence that *O*-methylpsychotrine has the genuine 3,4-dihydroisoquinoline structure **4**, not the exocyclic double bond structure **16** (R=Me), both in its free base and protonated forms.[10] More recently, we have further presented ^{13}C-NMR spectroscopic evidence that psychotrine (**3**) and alangicine, an *Alangium* alkaloid corresponding to 8-hydroxypsychotrine, also have the genuine 3,4-dihydroisoquinoline structures.[5e] By analogy, synthetic (±)-9-demethylpsychotrine described above may be assigned the endocyclic double bond structure **1**, and this was supported by ^{13}C-NMR spectroscopic evidence. Table I lists the chemical shifts for all carbons of (±)-**1**, which have been assigned as in the cases of *O*-methylpsychotrine (**4**),[10] psychotrine (**3**),[5e] and alangicine.[5e] It may be seen that (±)-**1** has fourteen sp^3 carbons and thirteen sp^2 carbons. This differs from the exocyclic double bond structure (type **16**) in having one more sp^3 carbon and one less sp^2 carbon. Thus, these spectral data are consistent with the endocyclic double bond structure **1** of (±)-9-demethylpsychotrine.

For the racemic synthesis of the second alternative structure **2**, a parallel sequence of conversions starting from the lactim ether **6** and 4-benzyloxy-3-methoxyphenacyl bromide (**7b**) was followed through the intermediates **8b** (75% yield), **9b** (99%), **10d** (97%), **10b** (72%), **11b**, **12b** (73% from **10b**), **13b** (89%), **14b** (85%), and **15b** (81%). Debenzylation of **15b** with boiling aqueous HCl–EtOH for 18 h produced (±)-10-demethylpsychotrine (**2**) [mp 242—244 °C (dec.)] in 91% yield. As shown in Table I, the ^{13}C-NMR spectral data for synthetic

TABLE I. ^{13}C-NMR Data for (±)-9-Demethylpsychotrine (**1**) and (±)-10-Demethylpsychotrine (**2**) in Me_2SO-d_6

Carbon	Chemical shift[a]		Carbon	Chemical shift[a]	
	(±)-**1**[b]	(±)-**2**		(±)-**1**[b]	(±)-**2**
C(1)	37.3	37.0	C(13)	23.0	23.1
C(2)	39.1	39.1	C(14)	11.0	11.0
C(3)	41.9	41.6	C(1′)	165.4	165.5
C(4)	60.6	60.4	C(3′)	45.0	44.9
C(6)	51.8	51.8	C(4′)	25.7	25.8
C(7)	28.5	28.5	C(4′a)	132.5	132.6
C(7a)	126.5	124.5	C(5′)	115.3[c]	115.4
C(8)	115.2[c]	111.7[e]	C(6′)	153.8	154.3
C(9)	144.6[d]	144.5[f]	C(7′)	147.0	147.0
C(10)	145.6[d]	146.0[f]	C(8′)	110.1	110.4
C(11)	108.5	112.1[e]	C(8′a)	117.4	116.9
C(11a)	128.5	129.6	OMe	55.4	55.6
C(11b)	62.0	61.7	OMe	55.7	56.0
C(12)	38.4	38.6			

a) In ppm downfield from internal Me_4Si.
b) Since the sample of (±)-**1** contained 2.5 eq mol of EtOH of crystallization, two signals at 18.5 ppm ($\underline{C}H_3CH_2OH$) and 56.0 ppm ($CH_3\underline{C}H_2OH$) were observed besides those listed here.
c—*f*) Assignments indicated by a given superscript may be reversed.

(±)-**2** offer corroborating evidence that this isomer also has the endocyclic double bond structure in the dihydroisoquinoline moiety.

Now that the two compounds having the alternative structures considered for desmethylpsychotrine had been synthesized, we proceeded to the problem of comparison with the natural product. While the UV spectra (in EtOH, 0.1 N aqueous HCl, or 0.1 N aqueous NaOH) of both (±)-**1** and (±)-**2** were found to match those of natural (+)-desmethylpsychotrine [mp 166—168 °C (crystallized from EtOH)[3]], the mass spectrum (MS) of the latter corresponded to that of (±)-**1** rather than (±)-**2**. The solid-state infrared (IR) spectrum of the natural alkaloid was also quite different from that of (±)-**2**, but very similar to that of (±)-**1**. The small difference observed in the latter case is probably due to the sample of (±)-**1** crystallizing as a racemic compound[11] and/or as an ethanolate with a different EtOH content. The frequent difficulty of identifying an enantiomer with a racemic modification in the solid state by means of IR spectroscopy is well known.[11] Unfortunately, only insufficient natural desmethylpsychotrine was available for solution IR and/or NMR spectra, precluding unambiguous identification.

In conclusion, the above results suggest formula **1** to be the most likely structure of desmethylpsychotrine. This was subsequently confirmed by a chiral synthesis of (+)-**1** through a "cincholoipon-incorporating route";[4b] the details will be reported elsewhere shortly.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. See ref. 10 for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

(±)-*trans*-1-(3-Benzyloxy-4-methoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (8a)——A solution of triethyloxonium fluoroborate[12] (4.4 g, 23 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred, ice-cooled solution of (±)-**5**[6] (2.13 g, 10 mmol) in CH_2Cl_2 (15 ml) over a period of 30 min. The resulting mixture was stirred at room temperature overnight and then poured into cold 10% aqueous K_2CO_3 (28 ml). The precipitate that resulted was removed by filtration and washed with CH_2Cl_2, and the aqueous filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 washings and extracts were united, dried, and concentrated to leave (±)-**6**[5b] (2.62 g) as a pale yellowish oil. A solution of this oil and 3-benzyloxy-4-methoxyphenacyl bromide (**7a**)[13] (3.69 g, 11 mmol) in $HCONMe_2$ (5 ml) was stirred at 60 °C for 8 h. For removal of the excess bromide, the reaction mixture was then stirred with pyridine (3 ml) at room temperature overnight and evaporated *in vacuo*. The oily residue was partitioned by extraction with a mixture of 5% aqueous HCl (20 ml) and benzene (50 ml). The benzene extracts were washed successively with 5% aqueous HCl and H_2O, dried, and evaporated to leave an orange oil (3.64 g). The oil was purified by column chromatography [alumina, AcOEt–hexane (1 : 1, v/v)] to give (±)-**8a** [3.01 g, 64% overall yield from (±)-**5**] as a pale yellowish oil, MS *m/e*: 467 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726 (ester CO), 1687 (ArCO), 1634 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.27 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.96 (3H, s, OMe), 4.16 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.70 and 4.78 (2H, AB type d's, J=17 Hz, $ArCOC\underline{H}_2$), 5.18 (2H, s, $OC\underline{H}_2Ph$), 6.92 (1H, d, J=9 Hz, $H_{(5')}$), 7.2—7.7 (7H, m, $H_{(2')}$, $H_{(6')}$, and Ph).

(±)-*trans*-1-(4-Benzyloxy-3-methoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (8b)——Crude (±)-**6** (10.5 g) was prepared from (±)-**5**[6] (8.53 g, 40 mmol) as described above and allowed to react with 4-benzyloxy-3-methoxyphenacyl bromide (**7b**)[14] (14.7 g, 44 mmol) in $HCONMe_2$ (20 ml) at 60 °C for 8 h. The reaction mixture was worked up as described above for (±)-**8a**, giving (±)-**8b** [14.1 g, 75% yield from (±)-**5**] as a yellowish solid. Recrystallization from AcOEt–hexane (1 : 1, v/v) yielded an analytical sample as colorless prisms, mp 118.5—119.5 °C; IR ν_{max}^{Nujol} cm^{-1}: 1727 (ester CO), 1684 (ArCO), 1642 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.91 (3H, s, OMe), 4.13 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.67 and 4.78 (2H, AB type d's, J=17 Hz, $ArCOC\underline{H}_2$), 5.19 (2H, s, $OC\underline{H}_2Ph$), 6.85 (1H, d, J=9 Hz, $H_{(5')}$), 7.2—7.6 (7H, m, $H_{(2')}$, $H_{(6')}$, and Ph). *Anal.* Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.26; H, 7.13; N, 3.15.

(±)-*trans*-1-[2-(3-Benzyloxy-4-methoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (9a)——A solution of (±)-**8a** (2.81 g, 6 mmol) in EtOH (30 ml) was stirred under ice-cooling, and $NaBH_4$ (228 mg, 6 mmol) was added portionwise. After stirring was continued at 0—5 °C for 30 min and then at room temperature for 3 h, acetone (1 ml) was added and the mixture was concentrated *in vacuo*. The residue was partitioned between H_2O and benzene. The benzene extracts were washed successively with 5% aqueous HCl and H_2O, dried, and concentrated to leave a diastereomeric mixture of (±)-**9a** (2.80 g, 99%) as a pale yellowish oil, MS *m/e*: 469 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1727 (ester CO), 1617 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.75 and 0.79 (3H, t each, J=7 Hz, diastereomeric $CCH_2\underline{Me}$'s), 1.25 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.1—3.3 (br, OH), 3.89 (3H, s, OMe), 4.14 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.8—5.0 [1H, m, $ArC\underline{H}(OH)$], 5.16 (2H, s, $OC\underline{H}_2Ph$), 6.8—7.1 (3H, m, $H_{(2')}$, $H_{(5')}$, and $H_{(6')}$), 7.2—7.6 (5H, m, Ph).

(±)-*trans*-1-[2-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (9b)——Reduction of (±)-**8b** was carried out as described above for (±)-**9a**, and a diastereomeric mixture of (±)-**9b** was obtained in 99% yield as a pale yellowish oil, MS *m/e*: 469 (M^+); IR ν_{max}^{film} cm^{-1}: 3380 (OH), 1728 (ester CO), 1620 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.77 and 0.81 (3H, t each, J=7 Hz, diastereomeric $CCH_2\underline{Me}$'s), 1.25 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.1—3.3 (br, OH), 3.89 (3H, s, OMe), 4.11 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.8—5.0 [1H, m, $ArC\underline{H}(OH)$], 5.10 (2H, s, $OC\underline{H}_2Ph$), 6.7—7.0 (3H, m, $H_{(2')}$, $H_{(5')}$, and $H_{(6')}$), 7.15—7.5 (5H, m, Ph).

(±)-*trans*-5-Ethyl-1-(3-hydroxy-4-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester (10c)——A solution of (±)-**9a** (2.68 g, 5.7 mmol) in EtOH (60 ml) containing 70% aqueous $HClO_4$ (0.6 ml) was hydrogenated over 10% Pd–C (1.2 g) at atmospheric pressure and room temperature for 12 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ extracts were washed successively with H_2O, saturated aqueous $NaHCO_3$, and H_2O, dried, and concentrated to leave (±)-**10c** (1.92 g, 93%) as a pale yellowish solid. Recrystallization from AcOEt–hexane (2 : 1, v/v) gave an analytical sample as colorless needles, mp 109—110 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH), 1726 (ester CO), 1627 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 1.25 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.82 (3H, s, OMe), 4.11 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.3—5.1 (1H, br, OH), 6.45—7.0 (3H, m, aromatic protons). *Anal.* Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.95; H, 8.15; N, 3.78.

(±)-*trans*-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester (10d)——Catalytic hydrogenolysis of (±)-**9b** was effected in a manner similar to that described above for (±)-**10c**, giving (±)-**10d** in 97% yield as a pale yellowish oil, MS *m/e*: 363 (M^+); IR ν_{max}^{film} cm^{-1}: 3300 (OH), 1728 (ester CO), 1624 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 1727 (ester CO), 1627 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.87 (3H, s, OMe), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.3—5.0 (1H, br, OH), 6.55—7.0 (3H, m, aromatic protons).

(±)-*trans*-1-(3-Benzyloxy-4-methoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (10a)——A stirred mixture of (±)-**10c** (1.82 g, 5 mmol) and benzyl bromide (1.03 g, 6 mmol) in acetone (25 ml) containing anhydrous K_2CO_3 (830 mg, 6 mmol) was heated under reflux for 48 h. The solvent was removed by vacuum

distillation, and the residue was partitioned by extraction with a mixture of benzene and H_2O. The benzene extracts were washed successively with 5% aqueous NaOH and H_2O, dried, and evaporated to leave a yellow oil. For removal of the unaltered benzyl bromide, a solution of the oil and pyridine (5 ml) in benzene (5 ml) was stirred at room temperature overnight. Evaporation of the solvents from the reaction mixture left an oil, which was partitioned between benzene and H_2O. The benzene extracts were washed successively with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and H_2O, dried, and concentrated to give an orange oil (2.14 g). The oil was purified by column chromatography [alumina, AcOEt–hexane (1 : 2, v/v)] to afford (±)-**10a** (1.67 g, 74%) as a pale yellowish oil, MS *m/e*: 453 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726 (ester CO), 1627 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.86 (3H, s, OMe), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.13 (2H, s, $OC\underline{H}_2Ph$), 6.7—6.9 (3H, m, $H_{(2')}$, $H_{(5')}$, and $H_{(6')}$), 7.2—7.6 (5H, m, Ph).

(±)-*trans*-1-(4-Benzyloxy-3-methoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (10b)——Benzylation of (±)-**10d** as described above for (±)-**10a** furnished (±)-**10b** in 72% yield as a pale yellowish oil, MS *m/e*: 453 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1627 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.88 (3H, s, OMe), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.09 (2H, s, $OC\underline{H}_2Ph$), 6.55—6.9 (3H, m, $H_{(2')}$, $H_{(5')}$, and $H_{(6')}$), 7.15—7.5 (5H, m, Ph).

(±)-*trans*-9-Benzyloxy-2-ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-10-methoxybenzo[*a*]quinolizinium Chloride (11a)——A solution of (±)-**10a** (1.50 g, 3.3 mmol) and $POCl_3$ (2.53 g, 16.5 mmol) in dry toluene (12 ml) was heated under reflux for 1.5 h. The solvent and $POCl_3$ were removed by vacuum distillation, and the residue was partitioned by extraction with a mixture of $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and evaporated to leave crude (±)-**11a** (1.72 g) as an orange oil. The oil was used directly in the next hydrogenation step without further purification.

(±)-*trans*-10-Benzyloxy-2-ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9-methoxybenzo[*a*]quinolizinium Chloride (11b)——Crude (±)-**11b** (1.39 g) was obtained as an orange oil from (±)-**10b** (1.18 g, 2.6 mmol) in a manner similar to that described above for (±)-**11a**.

(±)-9-Benzyloxy-3α-ethyl-1,3,4,6,7,11bα-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine-2β-acetic Acid Ethyl Ester (12a)——The total amount of crude (±)-**11a** obtained above was dissolved in EtOH (35 ml), and the solution was hydrogenated over Adams catalyst (100 mg) at atmospheric pressure and room temperature for 50 min. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to leave an orange oil, to which cold 5% aqueous NaOH (15 ml) was added. The mixture was extracted with benzene, and the benzene extracts were washed with H_2O, dried over anhydrous K_2CO_3, and concentrated to leave a pale brownish solid (1.18 g), mp 80—82 °C. Recrystallization of the solid from hexane gave (±)-**12a** (1.03 g, 71% yield from **10a**) as colorless pillars, mp 89.5—90.5 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2815, 2760 (*trans*-quinolizidine ring),[15] 1725 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 1.29 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.88 (3H, s, OMe), 4.22 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.14 (2H, s, $OC\underline{H}_2Ph$), 6.68 (1H, s, $H_{(8)}$ or $H_{(11)}$), 6.76 (1H, s, $H_{(11)}$ or $H_{(8)}$), 7.25—7.6 (5H, m, Ph). *Anal.* Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 73.98; H, 8.09; N, 3.29.

(±)-10-Benzyloxy-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine-2β-acetic Acid Ethyl Ester (12b)——The total amount of crude (±)-**11b** described above was hydrogenated as in the case of the above hydrogenation of (±)-**11a**, producing crude (±)-**12b** (1.01 g) as an orange oil. Purification of the oil by column chromatography [alumina, AcOEt–hexane (1 : 4, v/v)] provided a pale yellow solid [828 mg, 73% yield from (±)-**10b**], which was recrystallized from hexane to give colorless needles, mp 72—73 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2815, 2760 (*trans*-quinolizidine ring),[15] 1725 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.83 (3H, s, OMe), 4.16 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.04 (2H, s, $OC\underline{H}_2Ph$), 6.56 (1H, s, $H_{(8)}$ or $H_{(11)}$), 6.67 (1H, s, $H_{(11)}$ or $H_{(8)}$), 7.2—7.5 (5H, m, Ph). *Anal.* Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.19; H, 8.22; N, 3.25.

(±)-9-Benzyloxy-3α-ethyl-1,3,4,6,7,11bα-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine-2β-acetic Acid (13a)——A solution of (±)-**12a** (875 mg, 2 mmol) and 2 N aqueous NaOH (2 ml) in EtOH (15 ml) was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, and H_2O (15 ml) was added to the residue. The resulting solution was neutralized with 2 N aqueous HCl (2 ml) and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellowish solid. Recrystallization of the solid from EtOH–AcOEt (1 : 1, v/v) and drying over P_2O_5 at 2 mmHg and room temperature for 20 h yielded (±)-**13a**·1/3EtOH (705 mg, 83%) as colorless prisms, mp 182—184 °C (dec.); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2460 (N^+H), 1693 (br, CO_2H and CO_2^-); ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.22 (t, J=7 Hz, $\underline{Me}CH_2OH$), 3.68 (q, J=7 Hz, $MeC\underline{H}_2OH$), 3.82 (3H, s, OMe), 5.06 (2H, s, $OC\underline{H}_2Ph$), 6.60 (1H, s, $H_{(8)}$ or $H_{(11)}$), 6.69 (1H, s, $H_{(11)}$ or $H_{(8)}$), 7.3—7.55 (5H, m, Ph), 9.35 (1H, br, CO_2H). *Anal.* Calcd for $C_{25}H_{31}NO_4 \cdot 1/3C_2H_5OH$: C, 72.56; H, 7.83; N, 3.30. Found: C, 72.60; H, 7.62; N, 3.40.

(±)-10-Benzyloxy-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine-2β-acetic Acid (13b)——The tricyclic ester (±)-**12b** (2.10 g, 4.8 mmol) was hydrolyzed as described above for (±)-**13a**, and the resulting crude acid was recrystallized from EtOH to furnish (±)-**13b**·H_2O (1.82 g, 89%, after being dried over P_2O_5 at 2 mmHg and room temperature for 20 h) as colorless scales, mp 78—79 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2460 (N^+H), 1695 (br, CO_2H and CO_2^-); ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 3.81 (3H, s, OMe), 5.01 and 5.07 (2H,

AB type d's, $J=12$ Hz, OCH_2Ph), 6.58 (1H, s, $H_{(8)}$ or $H_{(11)}$), 6.68 (1H, s, $H_{(11)}$ or $H_{(8)}$), 7.1—7.5 (5H, m, Ph), 10.1 (br, CO_2H). *Anal.* Calcd for $C_{25}H_{31}NO_4 \cdot H_2O$: C, 70.23; H, 7.78; N, 3.28. Found: C, 70.24; H, 7.77; N, 3.41.

(±)-9-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-3α-ethyl-1,3,4,6,7,11bα-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine-2β-acetamide (14a)——To a chilled, stirred solution of (±)-**13a**·1/3EtOH (491 mg, 1.16 mmol) and 3-benzyloxy-4-methoxyphenethylamine[16] (463 mg, 1.8 mmol) in $HCONMe_2$ (5 ml) were added successively diethyl phosphorocyanidate[8] (391 mg, 2.4 mmol) and Et_3N (243 mg, 2.4 mmol). The mixture was stirred at room temperature for 6 h and extracted with $CHCl_3$ after addition of H_2O (15 ml). The $CHCl_3$ extracts were washed with H_2O, dried, and concentrated to leave a pinkish solid. The solid was recrystallized from EtOH to give (±)-**14a** (728 mg, 97%) as colorless minute needles. Further recrystallization from EtOH produced an analytical sample as colorless needles, mp 178—180 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 2810, 2760 (*trans*-quinolizidine ring),[15] 1660 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 3.77 and 3.84 (3H each, s, two OMe's), 5.05 (4H, s, two OCH_2Ph's), 5.35—5.55 (1H, m, CONH), 6.57 (1H, s, aromatic proton), 6.6—6.8 (4H, m, aromatic protons), 7.2—7.5 (10H, m, two Ph's). *Anal.* Calcd for $C_{41}H_{48}N_2O_5$: C, 75.90; H, 7.46; N, 4.32. Found: C, 75.82; H, 7.39; N, 4.27.

(±)-10-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine-2β-acetamide (14b)——The tricyclic acid (±)-**13b**·H_2O was allowed to react with 3-benzyloxy-4-methoxyphenethylamine[16] as described above for (±)-**14a**, giving (±)-**14b** in 85% yield. Recrystallization of crude (±)-**14b** from EtOH afforded an analytical sample as colorless needles, mp 145—147 °C; IR ν_{max}^{KBr} cm^{-1}: 3310 (NH), 2790, 2745 (*trans*-quinolizidine ring),[15] 1638 (amide CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 2820, 2760 (*trans*-quinolizidine ring),[15] 1661 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 3.85 and 3.87 (3H each, s, two OMe's), 5.04 and 5.09 (2H each, s, two OCH_2Ph's), 5.4—5.6 (1H, m, CONH), 6.63 (1H, s, aromatic proton), 6.75—6.9 (4H, m, aromatic protons), 7.25—7.6 (10H, m, two Ph's). *Anal.* Calcd for $C_{41}H_{48}N_2O_5$: C, 75.90; H, 7.46; N, 4.32. Found: C, 75.63; H, 7.26; N, 4.46.

(±)-9-Benzyloxy-2β-(6-benzyloxy-3,4-dihydro-7-methoxy-1-isoquinolyl)methyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine (15a)——A solution of (±)-**14a** (130 mg, 0.2 mmol) and $POCl_3$ (153 mg, 1 mmol) in dry toluene (8 ml) was heated under reflux for 1.5 h. The reaction mixture was concentrated *in vacuo*, and H_2O (5 ml) and $CHCl_3$ (15 ml) were added to the oily residue under ice-cooling. After being stirred for 10 min, the mixture was made alkaline with 10% aqueous NaOH, and stirring was continued for 5 min. The $CHCl_3$ layer was separated from the aqueous layer, which was further extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a reddish-brown oil. The oil was chromatographed on a silica gel column [$CHCl_3$–EtOH (20:1, v/v)] to furnish (±)-**15a** (103 mg, 82%) as an orange glassy gum, MS *m/e*: 630 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2760 (*trans*-quinolizidine ring),[15] 1620 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 3.72 and 3.88 (3H each, s, two OMe's), 5.05 and 5.16 (2H each, s, two OCH_2Ph's), 6.49, 6.55, 6.73, and 7.03 (1H each, s, aromatic protons), 7.1—7.5 (10H, m, two Ph's).

(±)-10-Benzyloxy-2β-(6-benzyloxy-3,4-dihydro-7-methoxy-1-isoquinolyl)methyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine (15b)——The amide (±)-**14b** was cyclized as described above for (±)-**15a**, and the resulting crude (±)-**15b** was purified by column chromatography [silica gel, $CHCl_3$–EtOH (10:1, v/v)] to provide a pale yellowish glassy gum (81% yield), MS *m/e*: 630 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2760 (*trans*-quinolizidine ring),[15] 1621 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 3.82 and 3.88 (3H each, s, two OMe's), 4.96 and 5.12 (2H each, s, two OCH_2Ph's), 6.54 (2H, s, aromatic protons), 6.72 and 7.02 (1H each, s, aromatic protons), 7.1—7.5 (10H, m, two Ph's).

(±)-2β-(3,4-Dihydro-6-hydroxy-7-methoxy-1-isoquinolyl)methyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9-hydroxy-10-methoxy-2*H*-benzo[*a*]quinolizine [(±)-9-Demethylpsychotrine] (1)——A solution of (±)-**15a** (209 mg, 0.33 mmol) in a mixture of 10% aqueous HCl (10 ml) and 10% ethanolic HCl (4 ml) was heated under reflux for 18 h. After cooling, the reaction mixture was washed with benzene and neutralized with saturated aqueous $NaHCO_3$. The precipitate that resulted was filtered off, washed with H_2O, and dried to give (±)-**1** (126 mg). The filtrate and washings were united and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated to leave a brown glass. Purification of the glassy substance by preparative thin-layer chromatography [silica gel, $CHCl_3$–MeOH (4:1, v/v)] yielded a second crop (8 mg) of (±)-**1**. The total yield was 90%. For analysis, crude (±)-**1** was recrystallized from EtOH and dried over P_2O_5 at 2 mmHg and room temperature for 40 h to give an ethanolate as yellowish minute needles, mp 224—226 °C (dec.); MS *m/e* (relative intensity): 450 (M^+) (56), 435 ($M^+ - Me$) (3.3), 421 ($M^+ - Et$) (1.8), 272 (28), 260 (28), 259 (85), 258 (73), 257 (18), 256 (32), 244 (23), 231 (19), 230 (100), 228 (16), 225 (18), 216 (26), 192 (43), 191 (63), 190 (33), 178 (24), 177 (34), 176 (28); UV λ_{max} (99% aqueous EtOH) 226.5 nm (ε 17700), 277 (11500), 312.5 (4400), 409 (19500); UV λ_{max} (0.1 N aqueous HCl) 244.5 (15700), 291.5 (8200), 307 (9100), 356 (9400); UV λ_{max} (0.1 N aqueous NaOH) 243 (19800), 305 (sh) (14500), 327 (16300); ^{1}H-NMR (Me_2SO-d_6) δ: 1.05 (t, $J=7$ Hz, $MeCH_2OH$), 3.43 (q, $J=7$ Hz, $MeCH_2OH$), 3.62 and 3.75 (3H each, s, two OMe's), 6.39, 6.41, 6.53, and 6.99 (1H each, s, aromatic protons); ^{13}C-NMR (Table I). *Anal.* Calcd for $C_{27}H_{34}N_2O_4 \cdot 5/2C_2H_5OH$: C, 67.94; H, 8.73; N, 4.95. Found: C, 68.04; H, 8.52; N, 5.21.

(±)-2β-(3,4-Dihydro-6-hydroxy-7-methoxy-1-isoquinolyl)methyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-10-hydroxy-9-methoxy-2*H*-benzo[*a*]quinolizine [(±)-10-Demethylpsychotrine] (2)——The *O*,*O*-dibenzyl derivative (±)-**15b** was hydrolyzed as described above for (±)-**1**. The resulting (±)-**2** (91% yield) was recrystallized from MeOH to produce

an analytical sample as yellowish minute needles, mp 242—244 °C (dec.); MS *m/e* (relative intensity): 450 (M^+) (50), 368 (29), 284 (21), 272 (32), 260 (32), 259 (77), 258 (69), 257 (29), 256 (61), 244 (25), 236 (20), 231 (21), 230 (100), 228 (20), 225 (21), 216 (24), 192 (39), 191 (75), 190 (46), 185 (20), 178 (27), 177 (27), 176 (28); UV λ_{max} (99% aqueous EtOH) 226 nm (sh) (ε 16400), 277 (10900), 312.5 (4000), 408 (20100); UV λ_{max} (0.1 N aqueous HCl) 244.5 (14900), 292 (8200), 307 (9000), 356 (9200); UV λ_{max} (0.1 N aqueous NaOH) 243 (17200), 307 (sh) (14400), 326 (15300); ^{1}H-NMR (Me_2SO-d_6) δ: 0.90 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 3.69 and 3.76 (3H each, s, two OMe's), 6.38, 6.53, 6.55, and 6.99 (1H each, s, aromatic protons); ^{13}C-NMR (Table I). *Anal.* Calcd for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.61; N, 6.22. Found: C, 71.80; H, 7.57; N, 6.40.

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