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Transformation of Indole Alkaloids. VI.[1] A Novel Conversion of Oxindole Alkaloids into Indole Alkaloids *via* Indoline Derivatives

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Oxindole alkaloids chosen as starting materials were isopteropodine (**1a**) pteropodine (**1b**) isoformosanine (**7a**) and formosanine (**7b**). Reduction of the iminoethers prepared from the oxindole alkaloids with $Et_3\overset{+}{O}\overset{-}{B}F_4$, with $NaBH_3(OAc)$ or with $NaBH_4/SnCl_4\cdot 2Et_2O$ afforded the indoline derivatives (**3a**, **3b**, **9a**, **9b**). The configuration at C_7 of **3a**, **b** was determined by NMR analysis of the *N*(a)-acetyl-*N*(b)-oxides (**6a**, **b**). The signals of H-14β were observed at high field (δ 0.5—1.0) owing to the shielding effect of the aromatic ring in all A type compounds studied. Oxidative conversion of the indolines to indole alkaloids was achieved by using MnO_2 or $Me_2SO/(COCl)_2/Et_3N$ as oxidizing agents, and the latter reagent gave better results than the former. Tetrahydroalstonine (**11**) and akuammigine (**12**) were obtained from **3a**, **b**, and 19-epiajmalicine (**14**) and 3-iso-19-epiajmalicine (**15**) from **9a**, **b**. The A type compounds were more susceptible than the B type compounds to the present reduction and oxidation sequence.

Keywords——transformation; oxindole alkaloids; indole alkaloids; heteroyohimbines; reduction; oxidation; dimethyl sulfoxide–oxalyl chloride; indoline

Previously we reported[2] that reduction of an iminoether (II) with $NaBH_4$ in acetic acid (AcOH) gave mainly the 2,3-seco-2,3-dihydroindole (V) through fragmentation with the participation of the *N*(b)-lone pair electrons as shown in Chart 1. Recently it was reported[3] that reduction of II with $NaBH_4$ or $NaBH_3CN$ in CF_3CO_2H gave the indoline (VII), which was converted to the indole (VI). At that stage we thought that reduction of II with appropriate reducing agents in "aprotic media" might prevent the fragmentation (III→IV) and give the indoline (VII), which could be converted to the indole (VI) by oxidation followed by treatment with acid. The use of $NaBH_3(OAc)$ in refluxing dioxane[4] or $NaBH_4/SnCl_4\cdot 2Et_2O$ in dimeth-

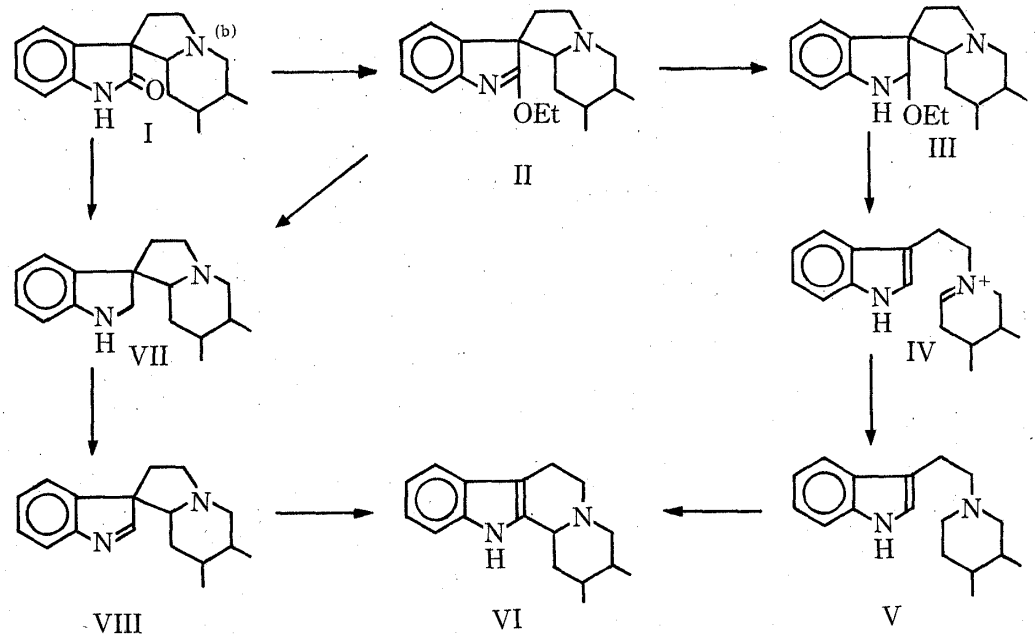


Chart 1

oxyethane (DME)[5] was found to be effective in the desired reduction of the iminoether (II) to the indoline (VII). In the present paper we describe a novel conversion of oxindole alkaloids into indole alkaloids. Oxindole alkaloids chosen as starting materials were isopteropodine (**1a**) and pteropodine (**1b**) from *Uncaria florida* Vidal[6] and isoformosanine (**7a**) and formosanine (**7b**) from *Uncaria Kawakamii* Hayata.[6]

Reduction of Iminoethers to Indolines

Isopteropodine (**1a**) and/or pteropodine (**1b**) were treated with $Et_3\overset{+}{O}\overset{-}{B}F_4$ in CH_2Cl_2 to give a mixture of the iminoethers (**2a, b**),[2] which was reduced with excess $NaBH_3(OAc)$ in refluxing dioxane[4] to give the indolines **3a** (30%, mp 156—158°C), **3b** (4%) and the seco-indole **4**[2] (11%). Although the same treatment of **1a** and **1b** with $NaBH_3(OAc)$ gave the indolines (**3a, b**), the yields were low. The indolines **3a** and **3b** showed characteristic ultraviolet (UV) spectra of an indoline having a β-alkoxyacrylate system, and mass spectra (MS) with M^+ at *m/z* 354 and the base peak at *m/z* 224. The above observations suggested that **3a** and **3b** were epimeric at C_7.

In order to determine the configuration of C_7, **3a** and **3b** were converted to the *N*(a)-acetyl-*N*(b)-oxides **6a** and **6b**, respectively. Acetylation of **3a** with acetic anhydride (Ac_2O) in pyridine followed by oxidation with *m*-chloroperbenzoic acid (MCPBA) gave the *N*-oxide (**6a**) in 58% yield. The other indoline (**3b**) gave **6b** (74%) in the same way. In the nuclear magnetic resonance (NMR) spectra of **6a** and **6b**, the signals of H-19 were observed at δ 5.12 and δ 5.05 respectively, at relatively low field owing to the deshielding effect of the *N*(b)-oxides. The signal of H-12 in **6b** was deshielded to δ 8.16 due to the *N*(a)-acetyl group. On the other hand, two aromatic protons H-12 and H-9 were observed at δ 8.0—8.3 in **6a** due to the deshielding effects of *N*(a)-acetyl and *N*(b)-oxide. The assignments of *R* configuration to C_7 of **6a** and *S* configuration to that of **6b** were made on the basis of the above observations.

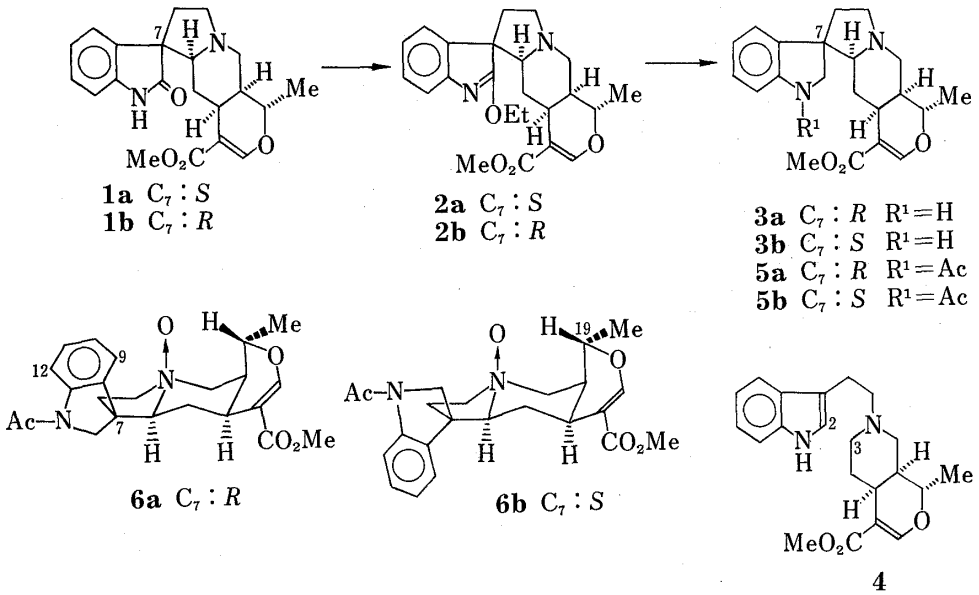
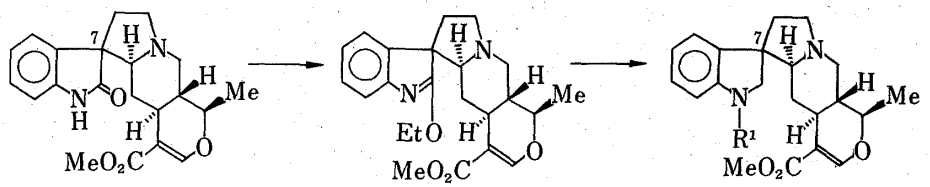


Chart 2

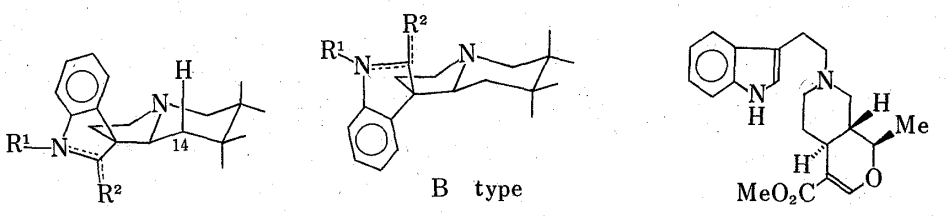
Treatment of isoformosanine (**7a**) hydrochloride with excess $Et_3\overset{+}{O}\overset{-}{B}F_4$ gave the iminoether (**8a**)[7] as the sole product in quantitative yield. The iminoether (**8a**) was reduced with $NaBH_3$-(OAc) as described above to give the indolines **9a** (19%, mp 181—182°C) and **9b** (4%, mp 130—131°C). UV and mass spectra of **9a, b** were similar to those of **3a, b**. The correctness of the assignments of C_7 configuration of **9a** (*R*) and **9b** (*S*) was confirmed by comparison of their circular dichroism (CD) and NMR spectra with those of **3a, b**. In the CD spectra, **3a** and **9a** showed a negative Cotton effect at *ca.* 300 nm while **3b** and **9b** showed a positive Cotton effect



7a C_7 : *S*
7b C_7 : *R*

8a C_7 : *S*
8b C_7 : *R*

9a C_7 : *R* R^1=H
9b C_7 : *S* R^1=H
9c C_7 : *R* R^1=Ac



A type

B type

10

Chart 3

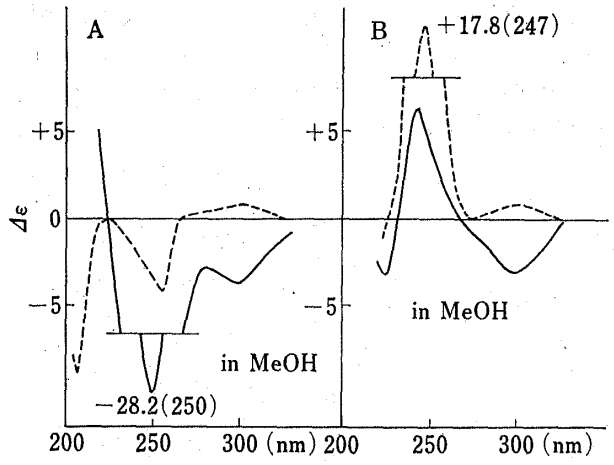


Fig. 1. CD Spectra of Indolines

A: **3a** ——, **3b** – – –.
B: **9a** ——, **9b** – – –.

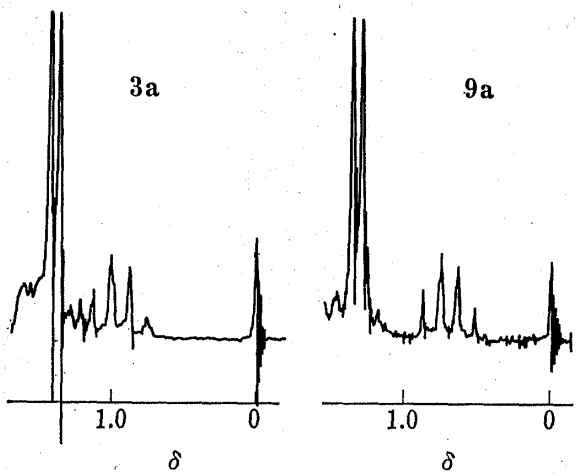


Fig. 2. NMR Spectra of Indolines (**3a** and **9a**)

TABLE I. H-14β Chemical Shifts of A Type Heteroyohimbinoid Compounds

Compounds	R^1	R^2	C_7[a]	Chemical shifts (δ)[b]
1a	H	O	*S*	0.87
2a	Iminoether		*S*	0.82
3a *allo*	H	H_2	*R*	0.93
5a	Ac	H_2	*R*	0.77
13a	MTM	H_2	*R*	0.90
7a	H	O	*S*	0.59
8a	Iminoether		*S*	0.54
9a *normal*	H	H_2	*R*	0.69
9c	Ac	H_2	*R*	0.56
16a	MTM	H_2	*R*	0.64

a) Configuration of C_7. b) Quartet, J=12 Hz.

(Fig. 1). In the NMR spectra a clear quartet assignable to H-14β was observed in the high field region for **3a** (δ 0.93) and **9a** (δ 0.69) owing to anisotropy of the aromatic ring (Fig. 2). A similar observation was reported by Finch *et al.*[8] and Le Men *et al.*[9] All A type compounds studied here (*normal* and *allo* type) exhibited a clear quartet at δ 0.5—1.0 as shown in Table I.

To improve the yield of the indoline (VII), reduction of the iminoether (II) with $NaBH_4$ in the presence of a Lewis acid was attempted. Reduction of the iminoether (**2a**)[2] with $NaBH_4$ /$SnCl_4 \cdot 2Et_2O$[5] was carried out in DME to afford the borane complex of **3a** in 96% yield (mp 180—183°C); this complex showed characteristic infrared (IR) absorption at 2380 cm^{-1} due to the BH bond. It was found that the oxidative elimination of BH_3 from amine-borane complex could be achieved with $Me_3N \rightarrow O$ in refluxing MeOH by our research group.[10] Application of this method to **3a**-BH_3 gave the indoline (**3a**) in 87% yield, but in the present case the conversion could also be achieved in refluxing MeOH without $Me_3N \rightarrow O$.

The iminoether (**2a**) afforded the indoline (**3a**) in good yield. Nevertheless, a mixture of the iminoethers (**2a, b**)[11] or the epimeric iminoether (**2b**)[11] was reduced under the same conditions to afford the indoline (**3a, b**) in low yields accompanied with by-products which were difficult to separate from **3b**.

The iminoether (**8a**) was subjected to reduction with $NaBH_4/SnCl_4 \cdot 2Et_2O$ as described above to give the indoline (**9a**, 59%) and the seco-indole (**10**, 3%). When the reduction was carried out by raising the temperature gradually from −78°C to 0°C, the yield of the indoline (**9a**) was improved as shown in Table II. The seco-indole (**10**) was positive in the Ehrlich test, and showed the characteristic UV spectrum of an indole having a β-alkoxyacrylate system and MS with M^+ at *m/z* 354 and the base peak at *m/z* 224. In addition, structural assignment was supported by the presence of the NMR signal of H-2 at δ 6.99. Racemic **10** has been synthesized by Uskoković *et al.*[12]

On the other hand, the iminoether (**8b**)[7] afforded the indolines (**9a, b**), but the yields were low (Table II).

The results indicate that while A type iminoethers (**2a, 8a**) are suitable for the preparation of indolines (**3a, 9a**), B type iminoethers (**2b, 8b**) are unsuitable.

Table II. Reduction of Iminoethers with $NaBH_4/SnCl_4 \cdot 2Et_2O$ at −78°C to 0°C

Oxindole alkaloids	Products (%)		
1a	**3a** (23)	**3b** (13)	
1b	**3a** (6)	**3b** (23)	
7a	**9a** (71)	**9b** (6)	**10** (8)
7b	**9a** (6)	**9b** (31)	**10** (7)

The Oxidative Conversion of Indolines to Indoles

The oxidative conversion of the indolines into indole alkaloids was accomplished as follows. First, the indoline (**3a**) was oxidized with active MnO_2 in CH_2Cl_2 and the product was treated with AcOH to give tetrahydroalstonine (**11**, 32%, mp 216—219°C), akuammigine (**12**, 27%) and isopteropodine (**1a**, 3%). In the case of **3b**, the alkaloids **11** and **12** were obtained in 9 and 20% yields, respectively. The same treatment of **9a** afforded 19-epiajmalicine (**14**, 35%, mp 204—206°C) and 3-iso-19-epiajmalicine (**15**, 10%). Tetrahydroalstonine (**11**) and 19-epiajmalicine (**14**) were identified by comparison with authentic samples (mixed fusion and comparison of NMR and IR spectra). The NMR and IR spectra of akuammigine (**12**) were identical with those of an authentic sample.[13] Natural 3-iso-19-epiajmalicine was not available,[14] but the ^{13}C-NMR spectrum of **15** was identical with reported data.[15] In addition, the signal pattern of the 270 MHz ^1H-NMR spectrum of **15** was identical with that of the

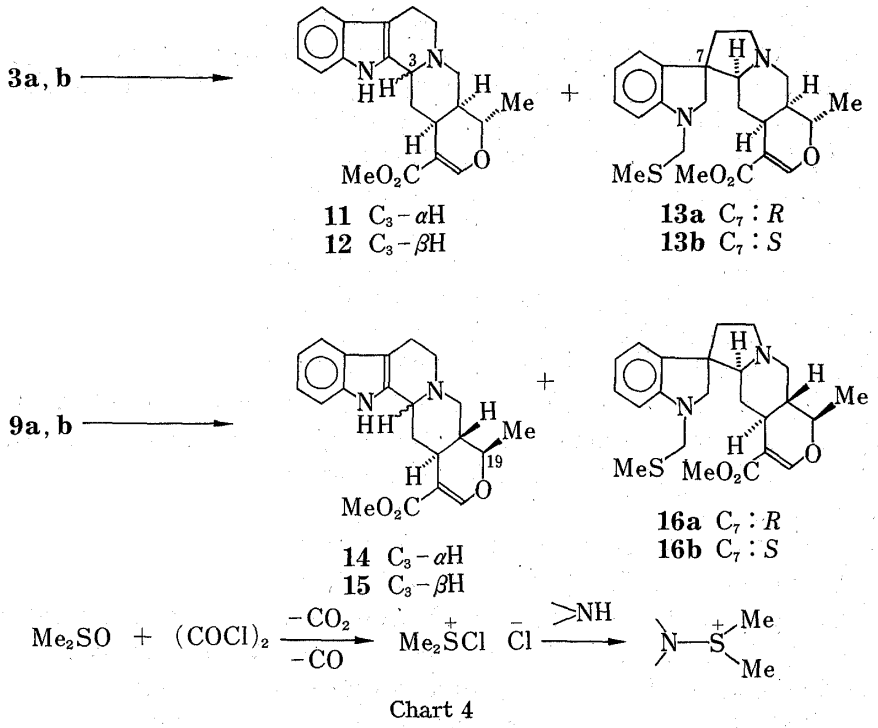


Chart 4

Table III. Oxidative Conversion of Indolines to Indoles with $Me_2SO/(COCl)_2/Et_3N$

Indolines	Products (%)		
	Indole alkaloids		*N*(a)-MTM
3a	**11**(40)	**12**(39)	**13a**(12)
3b[a]	**11**(19)	**12**(19)	**13b**(9)
9a	**14**(70)	**15**(9)	**16a**(7)
9b[b]	**14**(53)	**15**(2)	**16b**(10)

a) Recovery of **3b** (20%). *b*) Recovery of **9b** (13%).

400 MHz ^{1}H-NMR spectrum[16] of 3-iso-19-epiajmalicine.

Recently a conversion of indolines to indoles *via* azasulfonium salts using Me_2S/*tert*-BuOCl was reported.[17] Here, oxidation of indolines using Me_2SO activated with $(COCl)_2$[18] was attempted since the oxidizing agent was considered to produce the azasulfonium salt as the intermediate (Chart 4).

The indolines were treated with $Me_2SO/(COCl)_2/Et_3N$ in the same manner as for the oxidation of alcohols.[18] AcOH was added and stirring was continued to complete the rearrangement of the resulting indolenines to the indoles. The results of the one-pot reaction are summarized in Table III. Indole alkaloids were obtained in excellent yields in the cases of **3a** and **9a**, in contrast with **3b** and **9b**. Every indoline afforded the corresponding *N*(a)-methylthiomethyl (MTM)-indoline as a minor product, which showed two singlets at δ 3.60—3.61 (N–$C\underline{H}_2$–S) and δ 1.93—1.95 ($SC\underline{H}_3$) in the NMR spectra.

Results show that A type compounds are more susceptible than B type compounds to the present reduction and oxidation sequence.

Experimental

All melting points are uncorrected. IR spectra were measured with Hitachi 215 and 260 spectrometers and UV spectra with a Hitachi 340 spectrophotometer in MeOH (unless otherwise stated). NMR spectra were recorded on JEOL JNM4H-100 and FX-270 spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. MS were taken with Hitachi RMU 7M and RMU 60 mass spectrometers. A JASCO DIP 140 polarimeter was used for the measurement of optical rotations. CD spectra were measured with a JASCO J-20 spectropolarimeter in MeOH solution. Thin layer chromatography (TLC) was performed on Merck precoated silica gel 60F-254 plates. Column chromatography utilized Merck silica gel 70—230 mesh and 230—400 mesh. Organic solutions were dried with anhydrous Na_2SO_4. Abbreviations used are: singlet (s), doublet (d), quartet (q), multiplet (m), shoulder (sh), aromatic (arom).

Reduction of Iminoethers (2a, b) with $NaBH_3(OAc)$——To a suspension of $NaBH_4$ (520 mg, 10 mol eq) in dry dioxane (15 ml), a solution of AcOH (0.78 ml, 10 mol eq) in dry dioxane (2 ml) was added dropwise over 10 min with stirring in an ice bath under argon. After additional stirring for 30 min at room temperature, a solution of **2a, b**[2] (542 mg) in dry dioxane (5 ml) was added and the mixture was refluxed for 3 h. Excess reagent was decomposed with water in an ice bath and the mixture was basified with NH_4OH, and then extracted with $CHCl_3$. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel (20 g). Eluates with benzene/EtOAc (7: 3) gave 2-deoxoisopteropodine (**3a**, 147 mg, 30%). mp 156—158°C (EtOAc–hexane). $[\alpha]_D^{12}$ −152° (c=1.0 MeOH). UV λ_{max} nm (log ε): 205 (4.49), 242 (4.21), 294 (3.42). IR ν_{max}^{KBr} cm^{-1}: 3390, 2950, 2800, 1695, 1615. MS m/z (%): 354 (M^+, 30), 224 (100). NMR δ: 0.93 (1H, q, J=12 Hz, H-14β), 1.38 (3H, d, J=6 Hz, H-18), 3.63 (3H, s, OMe), 4.28 (1H, dq, J=12, 6 Hz, H-19), 6.50—7.30 (4H, m, arom H), 7.44 (1H, s, H-17). CD (c=0.0059%) $\Delta\varepsilon$ (nm): −3.83 (299), −28.2 (250). *Anal.* Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.09; H, 7.48; N, 7.86.

Polar products were subjected to flash chromatography[19] using 1%MeOH–$CHCl_3$ to give 2-deoxopteropodine (**3b**, 21 mg, 4%). $[\alpha]_D^{12}$ −36° (c=2.0, MeOH). UV λ_{max} nm (log ε): 205 (4.37), 244 (4.12), 291 (3.39). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 2930, 2800, 1690, 1620. MS m/z (%): 354 (M^+, 3), 224 (100). NMR δ: 1.37 (3H, d, J=6 Hz, H-18), 3.60 (3H, s, OMe), 4.49 (1H, dq, J=12, 6 Hz, H-19), 6.50—7.15 (4H, m, arom H), 7.48 (1H, s, H-17). CD (c=0.003%) $\Delta\varepsilon$ (nm): +0.77 (303), −4.18 (250).

Further eluates gave 2,3-seco-2,3-dihydroakuammigine (**4**, 54 mg, 11%). Its IR, UV and NMR spectra and TLC behavior were identical with those of authentic **4**.[2]

***N*(a)-Acetyl-2-deoxoisopteropodine (5a)**——A mixture of **3a** (67 mg) and Ac_2O (0.3 ml) in pyridine (0.5 ml) was allowed to stand overnight at room temperature. The mixture was poured into ice water, neutralized with 5%$NaHCO_3$, and extracted with $CHCl_3$. The organic layer was dried and concentrated. Purification of the residue by silica gel (2 g) chromatography gave **5a** (80 mg, 100%) which was eluted with benzene/EtOAc (4: 1—1: 1). UV λ_{max} nm (log ε): 210 (4.36), 247 (4.32), 279 (sh, 3.43), 288 (3.28). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 2800, 1690, 1650, 1630. MS m/z (%): 396 (M^+, 19), 224 (100). NMR δ: 0.77 (1H, q, J=12 Hz, H-14β), 1.39 (3H, d, J=6 Hz, H-18), 2.20 (3H, s, N–Ac), 3.62 (3H, s, OMe), 4.27 (1H, dq, J=12, 6 Hz, H-19), 6.90—7.38 (3H, m), 7.39 (1H, s, H-17), 8.17 (1H, d, J=7 Hz, H-12).

***N*(a)-Acetyl-2-deoxopteropodine (5b)**——Ac_2O (0.3 ml) was added to a solution of **3b** (70 mg) in pyridine (0.5 ml) at room temperature. Colorless precipitates were formed within one min, but the mixture was allowed to stand overnight. The same work-up as in the case of **3a** followed by crystallization from benzene afforded **5b** (58 mg, 74%). An analytical sample was recrystallized from $CHCl_3$–MeOH. mp 269—270°C. UV λ_{max} nm (log ε): 210 (4.42), 248 (4.36), 280 (sh, 3.51), 289 (3.40). IR ν_{max}^{KBr} cm^{-1}: 2950, 2900, 2790, 1690, 1660, 1625. MS m/z (%): 396 (M^+, 4), 224 (100). NMR δ: 1.39 (3H, d, J=6 Hz, H-18), 2.20 (3H, s, N–Ac), 3.61 (3H, s, OMe), 4.44 (1H, dq, J=12, 6 Hz, H-19) 7.00—7.30 (3H, m, arom H), 7.47 (1H, s, H-17), 8.17 (1H, d, J=7 Hz, H-12). *Anal.* Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.53; H, 7.08; N, 6.87.

***N*(a)-Acetyl-2-deoxoisopteropodine *N*(b)-Oxide (6a)**——To a solution of **5a** (63 mg) in $CHCl_3$ (1 ml), a solution of MCPBA (30 mg, 1.1 eq) in $CHCl_3$ (0.5 ml) was added in an ice bath. The mixture was stirred for 2 h at room temperature. Concentration of the mixture followed by chromatography over Al_2O_3 (2 g) gave **6a** (38 mg, 58%), which was eluted with $CHCl_3$. mp 158—159°C (acetone). UV λ_{max} nm (log ε): 208 (4.31), 249 (4.22), 279 (sh, 3.49), 289 (3.38). IR ν_{max}^{KBr} cm^{-1}: 1700, 1635. NMR δ: 1.55 (3H, d, J=6 Hz, H-18), 2.13 (3H, s, N–Ac), 3.60 (3H, s, OMe), 5.12 (1H, dq, J=12, 6 Hz, H-19), 6.90—7.30 (2H, m, H-10 and H-11), 7.51 (1H, s, H-17), 8.00—8.30 (2H, m, H-9 and H-12).

***N*(a)-Acetyl-2-deoxopteropodine *N*(b)-Oxide (6b)**——Oxidation of **5b** (44 mg) with MCPBA (21 mg) was carried out in the same manner as described above. The residue was chromatographed on Al_2O_3 (2 g). Eluates with $CHCl_3$ gave **6b** (46 mg, 100%). mp 205—209°C (acetone). UV λ_{max} nm (log ε): 209 (4.44), 250 (4.38), 280 (sh, 3.58), 289 (3.49). IR ν_{max}^{KBr} cm^{-1}: 1695, 1650, 1630. NMR δ: 1.54 (3H, d, J=6 Hz, H-18), 2.20 (3H, s, N–Ac), 3.61 (3H, s, OMe), 5.05 (1H, dq, J=12, 6 Hz, H-19), 7.00—7.30 (3H, m, arom H), 7.54 (1H, s, H-17), 8.16 (1H, d, J=7 Hz, H-12).

Reduction of Iminoether (8a) with $NaBH_3(OAc)$——To a suspension of isoformosanine (**7a**) hydrochloride

(1.18 g) in CH_2Cl_2 (15 ml), a solution of $Et_3\overset{+}{O}\overset{-}{B}F_4$ (5.60 g, 10 eq) in CH_2Cl_2 (8 ml) was added. After being stirred for 1 d at room temperature, the mixture was basified with NH_4OH, and extracted with CH_2Cl_2. The organic layer was washed with water, dried and concentrated to give the iminoether (**8a**, 1.19 g, 100%). UV λ_{max}^{EtOH} nm: 216, 243. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 2810, 1700, 1620, 1570. MS *m/z* (%): 396 (M^+, 51), 223 (100). NMR δ: 0.54 (1H, q, J=12 Hz, H-14β), 3.54 (3H, s, OMe), 3.78 (1H, dq, J=12, 6 Hz, H-19), 4.49 (2H, q, J=7 Hz, O$\underline{CH_2}CH_3$), 7.36 (1H, d, J=2 Hz, H-17).

A solution of $NaBH_3(OAc)$ was prepared from $NaBH_4$ (900 mg) and AcOH (1.34 ml) in dry dioxane (20 ml). The iminoether (**8a**, 930 mg) was reduced with $NaBH_3(OAc)$ prepared as in the case of **2a**, **b**. The same work-up gave the residue (880 mg), which was subjected to flash chromatography using $CHCl_3$/acetone (3: 2) as the solvent system. The less polar indoline was obtained as crystals. 2-Deoxoisoformosanine (**9a**, 160 mg, 19%): mp 181—182°C (EtOAc–hexane). $[\alpha]_D^{30}$ +78° (c=1.0, MeOH). UV λ_{max} nm (log ε): 206 (4.46), 240 (4.22), 295 (3.40). IR ν_{max}^{KBr} cm^{-1}: 3400, 2850, 2810, 2750, 1700, 1630. MS *m/z*(%): 354 (M^+, 9), 224 (100). NMR δ: 0.69 (1H, q, J=12 Hz, H-14β), 1.32 (3H, d, J=6 Hz, H-18), 3.60 (3H, s, OMe), 3.80 (1H, dq, J=12, 6 Hz, H-19), 6.50—7.30 (4H, m, arom H), 7.43 (1H, s, H-17). CD (c=0.0037%) $\Delta\varepsilon$ (nm): −3.20 (300), +7.10 (244). *Anal.* Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.29; H, 7.38; N, 7.84.

Further eluates gave 2-deoxoformosanine (**9b**, 37 mg, 4%). mp 130—131°C (benzene–hexane). $[\alpha]_D^{30}$ +163° (c=1.0, MeOH). UV λ_{max} nm (log ε): 205 (4.46), 241 (4.22), 297 (3.41). IR ν_{max}^{KBr} cm^{-1}: 3370, 3350, 2800, 1705, 1630. MS *m/z* (%): 354 (M^+, 21), 224 (100). NMR δ: 1.31 (3H, d, J=6 Hz, H-18), 3.56 (3H, s, OMe), 6.50—7.10 (4H, m, arom H), 7.42 (1H, s, H-17). CD (c=0.0030%) $\Delta\varepsilon$ (nm): +0.86 (302), +17.8 (247). *Anal.* Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.26; H, 7.35; N, 7.94.

***N*(a)-Acetyl-2-deoxoisoformosanine (9c)**——**9a** (100 mg) was acetylated with Ac_2O (0.5 ml) and pyridine (0.75 ml) as in the case of **3a**. The residue was chromatographed on silica gel (3 g). Eluates with 0.2—0.6% MeOH–CH_2Cl_2 gave **9c** (76 mg, 68%). mp 189—192°C (EtOAc–hexane). UV λ_{max} nm (log ε): 210 (4.42), 248 (4.36), 281 (sh, 3.58), 289 (3.48). IR ν_{max}^{KBr} cm^{-1}: 2900, 2800, 1700, 1660, 1620. MS *m/z*(%): 396 (M^+, 10), 224 (100). NMR δ: 0.56 (1H, q, J=12 Hz, H-14β), 1.32 (3H, d, J=6 Hz, H-18), 2.22 (3H, s, N–Ac), 3.60 (3H, s, OMe), 6.90—7.40 (3H, m, arom H), 7.43 (1H, s, H-17), 8.18 (1H, d, J=7 Hz, H-12). *Anal.* Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.55; H, 7.10; N, 6.95.

Reduction of 2a with $NaBH_4/SnCl_4\cdot 2Et_2O$——$NaBH_4$ (95 mg) and $SnCl_4\cdot 2Et_2O$ (210 mg) were added to a solution of **2a**[2] (250 mg) in dry DME (5 ml) in an ice bath, and the mixture was stirred for 1 h. Water was added, and the whole was basified with aq. Na_2CO_3, then $CHCl_3$ was added. After being shaken well, the mixture was filtered through celite, and the organic layer was separated from the filtrate. The aqueous layer was extracted with $CHCl_3$. The organic layers were combined, washed with water and dried. Removal of the solvent followed by crystallization from MeOH gave the borane complex of **3a** (223 mg, 96%). mp 180—183°C. IR ν_{max}^{KBr} cm^{-1}: 3400, 2380, 1695, 1640. *Anal.* Calcd for $C_{21}H_{26}N_2O_3\cdot BH_3$: C, 68.49; H, 7.94; N, 7.61. Found: C, 67.99; H, 7.84; N, 7.50.

a) A mixture of the borane complex (50 mg) and $Me_3N\rightarrow O$ (50 mg) in MeOH (1 ml) was refluxed for 1.5 h under argon. After removal of the solvent by evaporation, the residue was basified with NH_4OH and extracted with EtOAc. The extract was washed with water, dried and concentrated to give the indoline (**3a**, 41 mg, 87%).

b) A solution of the borane complex (16 mg) in MeOH (1 ml) was refluxed for 1 h. Concentration of the mixture followed by chromatography on Al_2O_3 (1 g), eluted with EtOAc, gave the indoline (**3a**, 15 mg).

Reduction of 8a with $NaBH_4/SnCl_4\cdot 2Et_2O$——To a suspension of isoformosanine (**7a**) hydrochloride (404 mg, 1 mmol) in CH_2Cl_2 (5 ml), a solution of $Et_3\overset{+}{O}\overset{-}{B}F_4$ in CH_2Cl_2 (1.25 M, 4 ml) was added. The mixture became a clear solution within a few min and was stirred overnight at room temperature. The mixture was poured into ice-NH_4OH and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to give the iminoether (**8a**, 400 mg, 100%). To a mixture of **8a** (400 mg) and $NaBH_4$ (150 mg, 4 mmol) in dry DME (5 ml), a solution of $SnCl_4\cdot 2Et_2O$ (340 mg, *ca.* 1 mmol) in dry DME (1 ml) was added in an ice bath with stirring. The mixture was stirred for 1 h and poured into ice-NH_4OH, then $CHCl_3$ was added. After being shaken well, the mixture was filtered through celite. The organic layer was separated from the filtrate and the aqueous layer was extracted with $CHCl_3$. The organic layers were combined, washed with water, dried and evaporated to give the residue (342 mg). This was taken up in MeOH (5 ml) and the solution was refluxed for 1 h under argon. Removal of the solvent gave the residue, which was chromatographed on Al_2O_3 (10 g). Eluates with benzene/EtOAc (9: 1) gave the indoline (**9a**, 208 mg, 59%).

Polar products were subjected to flash chromatography using benzene/EtOAc (1: 2) as the solvent system to give 2,3-seco-2,3-dihydro-19-epiajmalicine (**10**, 12 mg, 3%). UV λ_{max}^{EtOH} nm: 223, 243 (sh), 282, 291. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 2950, 2920, 1700, 1620. MS *m/z* (%): 354 (M^+, 9), 224 (100). NMR δ: 1.29 (3H, d, J=6 Hz, H-18) 3.70 (3H, s, OMe), 3.78 (1H, m, H-19), 6.99 (1H, d, J=2 Hz, H-2, singlet on addition of D_2O), 7.54 (1H, s, H-17), 8.42 (1H, br s, NH). High resolution (HR)-MS Calcd for $C_{21}H_{26}N_2O_3$: 354.1943. Found: 354.1939 (M^+).

Reduction of Iminoethers with $NaBH_4/SnCl_4\cdot 2Et_2O$ at—78°C to 0°C——To a suspension of hydrochloride of oxindole alkaloid (1 mmol) in CH_2Cl_2 (5 ml), a solution of $Et_3\overset{+}{O}\overset{-}{B}F_4$ (5 mmol) in CH_2Cl_2 (1.0—1.25 M) was

added. The mixture was stirred overnight at room temperature, then poured into cold NH_4OH and extracted with CH_2Cl_2. The organic layer was washed with water, dried and concentrated to give the iminoether in quantitative yield.[7,11] To a solution of the above iminoether in dry DME (5 ml) cooled with a dry ice-acetone bath, $NaBH_4$ (150 mg, 4 mmol) and a solution of $SnCl_4 \cdot 2Et_2O$ (1 mmol) in dry DME (1.5 ml) were added successively with stirring. The mixture was stirred for 2—3 h until the bath temperature reached 0°C. The same work-up followed by treatment with refluxing MeOH (5 ml) as described above gave the crude products, which were subjected to silica gel and/or flash chromatography using benzene/EtOAc or 1% MeOH–$CHCl_3$ as the solvent systems. The results are summarized in Table II.

Oxidative Conversion of Indolines to Indoles using MnO_2 as the Oxidizing Agent——a) Active MnO_2 (900 mg) was added to a solution of **3a** (300 mg) in CH_2Cl_2 (60 ml). After being stirred overnight at room temperature under argon, the mixture was filtered and the filtrate was concentrated. A solution of the residue in AcOH (3 ml) was stirred overnight at room temperature under argon. The mixture was basified with NH_4OH and extracted with $CHCl_3$. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel (10 g). The benzene/EtOAc (9: 1—4: 1) eluates gave precipitates (33 mg) on treatment with hot MeOH, and concentration of the filtrate gave tetrahydroalstonine (**11**, 96 mg, 32%), mp 216—219°C (MeOH), no depression on admixture with an authentic sample. Its IR spectrum and TLC behavior were identical with those of the authentic sample.

Elution with benzene/EtOAc (1: 1) followed by crystallization from benzene gave isopteropodine (**1a**, 8 mg, 3%, mp 193—195°C), which was shown to be identical with authentic **1a** by comparison of IR spectra and TLC behavior.

The EtOAc eluate gave akuammigine (**12**, 80 mg, 27%). Its IR and NMR spectra were identical with those of an authentic sample.[13]

b) Reaction of **3b** (144 mg) was carried out in the same manner as described above using CH_2Cl_2 (30 ml), MnO_2 (430 mg), and AcOH (1.5 ml). The residue (100 mg) was chromatographed on silica gel (20 g). The benzene/EtOAc (7: 3) eluate gave tetrahydroalstonine (**11**, 13 mg, 9%), and the EtOAc eluate afforded akuammigine (**12**, 28 mg, 20%).

c) Reaction of **9a** (200 mg) was carried out in the same manner using CH_2Cl_2 (40 ml), MnO_2 (600 mg) and AcOH (2 ml). The residue was chromatographed on silica gel (20 g). The benzene/EtOAc (7: 3) eluate gave 19-epiajmalicine (**14**, 70 mg, 35%). mp 204—206°C (acetone–benzene). $[\alpha]_D^{25}$ +59° (c=1.0, $CHCl_3$, lit.[20] +57°). $[\alpha]_D^{25}$ +75° (c=1.0, MeOH, lit.[21] +58°). Synthetic **14** was shown to be identical with an authentic sample by mixed mp determination and comparison of IR and NMR spectra.

Elution with 20%MeOH–EtOAc followed by chromatography on Al_2O_3 (2 g) gave 3-iso-19-epiajmalicine (**15**, 19 mg, 10%), eluted with benzene/EtOAc (1: 1). $[\alpha]_D^{25}$ +96° (c=1.0, MeOH, lit.[21] +76°). The ^{13}C-NMR spectrum of synthetic **15** was identical with the reported data[15] and signals of the 270 MHz ^{1}H-NMR spectrum of **15** were identical with those in the 400 MHz ^{1}H-NMR spectrum of an authentic sample.

Oxidative Conversion of Indolines to Indoles using Me_2SO activated with $(COCl)_2$ as the Oxidizing Agent—— To a solution of $(COCl)_2$ (27 μl, 1.1 eq) in dry CH_2Cl_2 (1 ml), a solution of Me_2SO (44 μl, 2.2 eq) in dry CH_2Cl_2 (0.2 ml) was added dropwise over 5 min in a dry ice-acetone bath with stirring. After 10 min, a solution of indoline (100 mg) in dry CH_2Cl_2 (1 ml) was added dropwise over 5 min. Stirring was continued for 30 min in a dry ice-acetone bath followed by addition of Et_3N (0.2 ml, 5 eq) over 5 min. The cooling bath was removed and the mixture was stirred for 1 h. Then AcOH (0.5 ml) was added and the mixture was stirred for 1 h. Basification with NH_4OH followed by extraction with CH_2Cl_2 gave crude products, which were subjected to silica gel chromatography. The results are summarized in Table III.

a) From **3a**: The benzene/EtOAc (4: 1) eluate gave tetrahydroalstonine (**11**, 40 mg) and further elution gave *N*(a)-methylthiomethyl(MTM)-2-deoxoisopteropodine (**13a**, 14 mg). UV λ_{max}^{EtOH} nm: 211, 243, 297. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 2800, 1690, 1630. NMR δ: 0.90 (1H, q, J=12 Hz, H-14β), 1.38 (3H, d, J=6 Hz, H-18), 1.95 (3H, s, SMe), 3.61 (2H, s, NCH_2S), 3.64 (3H, OMe), 4.32 (1H, dq, J=12, 6 Hz, H-19), 6.50—7.20 (4H, m, arom H), 7.40 (1H, s, H-17). HR-MS Calcd for $C_{23}H_{30}N_2O_3S$: 414.1977. Found: 414.1990.

Elution with 5%MeOH–EtOAc and MeOH followed by chromatography over Al_2O_3 (1 g) with benzene/EtOAc (4: 1) gave akuammigine (**12**, 39 mg).

b) From **3b**: The benzene/EtOAc (4: 1) eluate gave **11** (19 mg), and the benzene/EtOAc (1: 1) eluate gave *N*(a)-MTM-2-deoxopteropodine (**13b**, 11 mg). UV λ_{max}^{EtOH} nm: 208, 244, 295. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 2800, 1690, 1630. NMR δ: 1.37 (3H, d, J=6 Hz, H-18), 1.93 (3H, s, SMe), 3.60 (5H, s, OMe and NCH_2S), 4.45 (1H, m, H-19), 6.50—7.10 (4H, m, arom H), 7.44 (1H, s, H-17). HR-MS Calcd for $C_{23}H_{30}N_2O_3S$: 414.1977. Found: 414.1958.

Starting material (**3b**, 20 mg) was recovered from the EtOAc eluate. The 10%MeOH–EtOAc eluate was chromatographed over Al_2O_3 (2 g) with benzene/EtOAc (4: 1) to give **12** (19 mg).

c) From **9a** (300 mg): The quantities of all reagents and solvents were scaled up three times. The benzene/EtOAc (2: 1) eluate gave 19-epiajmalicine (**14**, 210 mg). Elution with benzene/EtOAc (2: 1—1: 1) followed by chromatography over Al_2O_3 (2 g) with benzene/$CHCl_3$ (9: 1—1: 1) gave *N*(a)-MTM-2-deoxoisoformosanine (**16a**, 24 mg). mp 103—106°C (MeOH). UV λ_{max}^{EtOH} nm: 207, 244, 298. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 2800, 1700, 1625. NMR δ: 0.64 (1H, q, J=12 Hz, H-14β), 1.31 (3H, d, J=6 Hz, H-18), 1.95 (3H, s, SMe), 3.60 (5H, s, OMe and NCH_2S), 6.50—7.30 (4H, m, arom H), 7.43 (1H, s, H-17). HR-MS Calcd for $C_{23}H_{30}N_2$-

O_3S: 414.1977. Found: 414.2012.

Elution with MeOH followed by chromatography over Al_2O_3 (2 g) with benzene/EtOAc (4: 1—1: 1) gave 3-iso-19-epiajmalicine (**15**, 26 mg).

d) From **9b**: The benzene/EtOAc (2: 1) eluate gave **14** (53 mg), and the EtOAc eluate gave *N*(a)-MTM-2-deoxoformosanine (**16b**, 12 mg). UV λ_{max}^{EtOH}nm: 210, 244, 300. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 2800, 1700, 1620. NMR δ: 1.31 (3H, d, J=6 Hz, H-18), 1.95 (3H, s, SMe), 3.56 (3H, s, OMe), 3.60 (2H, s, NCH_2S), 6.50—7.10 (4H, m, arom H), 7.43 (1H, s, H-17). HR-MS Calcd for $C_{23}H_{30}N_2O_3S$: 414.1977. Found: 414.2004.

Elution with MeOH followed by flash chromatography using $CHCl_3$/acetone (4: 1) gave the starting material (**9b**, 13 mg), and acetone elution gave **15** (2 mg), whose UV and IR spectra and TLC behavior were identical with those of authentic **15**, which was prepared as above.

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