Meisenheimer Rearrangement of Azetopyridoindoles. Part 4.[1] Ring Expansion of 2-Vinyl-1,2,4,5,10,10b-hexahydroazeto[1',2':1,2]pyrido[3,4-*b*]indole *N*-Oxides

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Oxidation of 1,2-*cis*-1,2,4,5,10,10b-hexahydroazeto[1',2':1,2]pyrido[3,4-*b*]indole-1-carboxylate derivatives **1a–d** and **5** with *m*-chloroperbenzoic acid in methylene dichloride gave hexahydro[1',2']oxazepino[2',3':1,2]pyrido[3,4-*b*]indole-1-carboxylates **2a–d** and **6**, which have a 12-carbaeudistomin skeleton, *via* the [2,3]-Meisenheimer rearrangement of the *N*-oxides. On the other hand, peracid oxidation of the corresponding 1,2-*trans* derivative **7** gave the hexahydroisoxazolo[2',3':1,2]pyrido[3,4-*b*]indole **8** *via* the [1,2]-Meisenheimer rearrangement of the corresponding *N*-oxide. Stereoscopic X-ray molecular structures for (13-methyl-1,4,7,8,13,13b-hexahydro[1',2']oxazepino[2',3':1,2]pyrido[3,4-*b*]indol-1-yl)methanol **3** and (11-methyl-2-vinyl-1,2,5,6,11,11b-hexahydro isoxazolo[2',3':1,2]pyrido[3,4-*b*]indol-1-yl)methanol **12** are presented.

The thermal [1,2]- and [2,3]-rearrangements of tertiary amine *N*-oxides bearing benzyl or allyl groups are known as the Meisenheimer rearrangement.[2] Bremner *et al.*[3] reported the preparation of 1,2-oxaza heterocycles, such as 2,3-benzoxazepine, 2,3-benzoxazocine, and 2,3-benzoxazonine, *via* the [1,2]-Meisenheimer rearrangement under neat or refluxing conditions. However, the preparation of fused 1,2-oxaza heterocyclic compounds *via* the [2,3]-Meisenheimer rearrangement has hitherto been unknown. We recently[4] reported the novel transformation of tetrahydro-β-carboline-1-acetate to give azetopyridoindoles **1a**, **1b** and **7**. We now report[1c] the ring expansion of azetopyridoindoles **1a–d**, **5** and **7** by either [1,2]- or [2,3]-Meisenheimer rearrangement of the corresponding *N*-oxides under very mild reaction conditions.

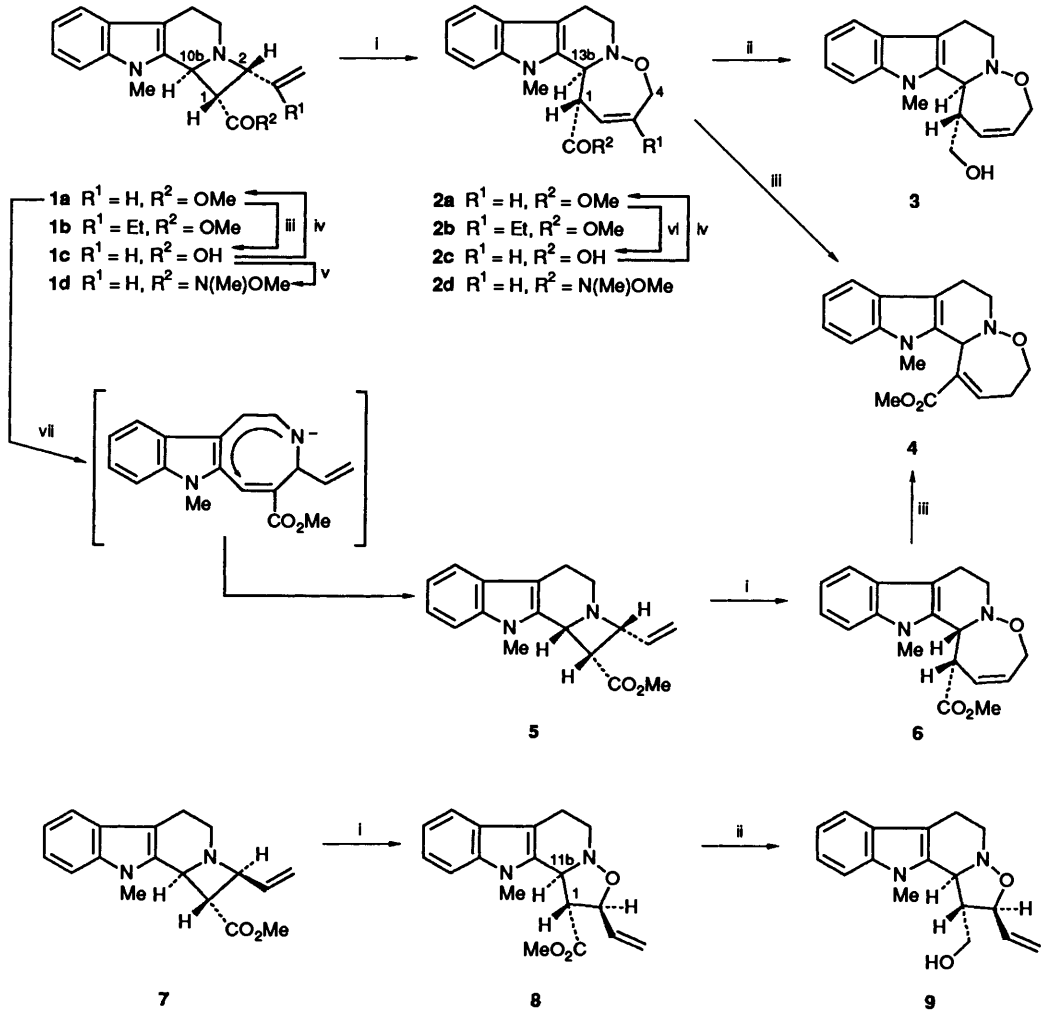
Results and Discussion

When a methylene dichloride (CH_2Cl_2) solution of *m*-chloroperbenzoic acid (MCPBA) (1.2 mol equiv.) was added to a CH_2Cl_2 solution of the 1,2-*cis* azetidine **1a** at room temperature, the reaction went to completion immediately, and after usual work-up the product **2a** (m.p. 111–112 °C) was isolated in 81% yield (Scheme 1). The ^1H NMR spectrum of compound **2a** showed the signals of a one-proton doublet (*J* 6.0 Hz) at δ 5.05 and two vinyl protons as a multiplet at δ 5.61–5.79. Incorporation of an oxygen atom into the substrate **1a** was indicated by examination of the mass spectrum of the product, which exhibited a molecular ion peak at *m/z* 312. The ester moiety of the product **2a** was easily reduced by lithium aluminium hydride in tetrahydrofuran (THF) to give a crystalline alcohol **3** in 89% yield. However, since the structure and stereochemistry of compounds **2a** and **3** could not be determined spectroscopically, an X-ray crystallographic analysis of the alcohol **3** was carried out and the structure was unambiguously established as (1,13b-*trans*-13-methyl-1,4,7,8,-13,13b-hexahydro[1',2']oxazepino[2',3':1,2]pyrido[3,4-*b*]indol-1-yl)methanol, whose stereoscopic view is drawn in Fig. 1. Hence, the structure of compound **2a** was determined to be methyl 1,13b-*trans*-13-methyl-1,4,7,8,13,13b-hexahydro[1',2']-oxazepino[2',3':1,2]pyrido[3,4-*b*]indole-1-carboxylate. A plausible mechanism for the ring expansion of **1a** to **2a** could be the [2,3]-Meisenheimer rearrangement of the intermediate *N*-oxide of compound **1a**, as shown in Scheme 2. To demonstrate the applicability of the ring expansion by [2,3]-Meisenheimer rearrangement as an efficient entry to oxazepines, the MCPBA oxidation of some 1,2-*cis* azetopyridoindole-1-carboxyl derivatives was examined. The required substrates **1b–d** and **5** were prepared as follows. But-1-en-2-yl derivative **1b** was provided by our reported method.[4] The carboxylic acid **1c** was obtained quantitatively by hydrolysis of its methyl ester **1a** with 1 mol dm^{-3} NaOH in methanol at room temperature. Esterification of acid **1c** with diazomethane gave the starting ester **1a**, which showed no change in the configuration at C-1 during hydrolysis. Condensation of acid **1c** with *N*,*O*-dimethylhydroxylamine in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 gave amide **1d** in 98% yield. In the preceding paper,[1a] we reported an interesting isomerisation of 1,10b-*trans*-1-methoxycarbonyl-2-ethylazetopyridoindole[1] by treatment with sodium methoxide in refluxing methanol to the 1,10b-*cis* isomer which is epimeric at C-10b. Hence, when ester **1a** was similarly treated with NaOMe in refluxing methanol, compound **5** was obtained in 45% yield with recovery of the starting material **1a** in 19% yield; the epimers could be separated by column chromatography. The ^1H NMR spectral data ($J_{1,2} = J_{1,10b}$ = 8.0 Hz)[5] of compound **5** clearly showed that the three neighbouring methine protons were all *cis*. It can be assumed that compound **1a** isomerises to compound **5** by a retro-Michael–Michael process as shown in Scheme 1.

The MCPBA oxidation of the azetidine **1b** under the same reaction conditions as described above gave the oxazepine **2b** (51%), whose structure was determined mainly by comparison of its spectral data with those of compound **2a**.

Oxidation of carboxylic acid **1c** with MCPBA was also found to proceed smoothly by TLC analysis, but it was difficult to isolate product **2c**, only a 10% yield being attained. Thus, the reaction product, without isolation, was subjected to esterification by diazomethane followed by purification by column chromatography to give methyl ester **2a** in 52% overall yield. Carboxylic acid **2c** was alternatively obtained by treatment of ester **2a** with the ethanethiol–aluminium tribromide system developed by Fujita and co-workers.[6]

MCPBA oxidation of amide **1d** was rather slow at room temperature and a better yield (59%) of oxazepine **2d** was obtained under reflux conditions in CH_2Cl_2. Oxidation of compound **5** with MCPBA in CH_2Cl_2 at room temperature afforded the oxazepine **6** as a single product [86% yield; oil; *m/z* 312 (M^+)], whose signal pattern of the olefinic protons in the ^1H NMR spectrum was different from that of oxazepine **2a**. By an irradiation technique a broad singlet assignable to 13b-H was observed at δ 4.67. The two compounds **2a** and **6** were



Scheme 1 *Reagents:* i, MCPBA; ii, $LiAlH_4$; iii, 1 mol dm^{-3} NaOH, MeOH; iv, CH_2N_2; v, MeNH(OMe), DCC; vi, EtSH–$AiBr_3$; vii, NaOMe, MeOH, reflux

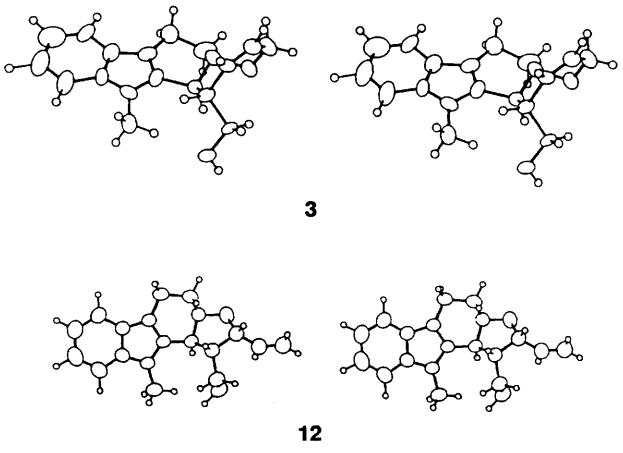
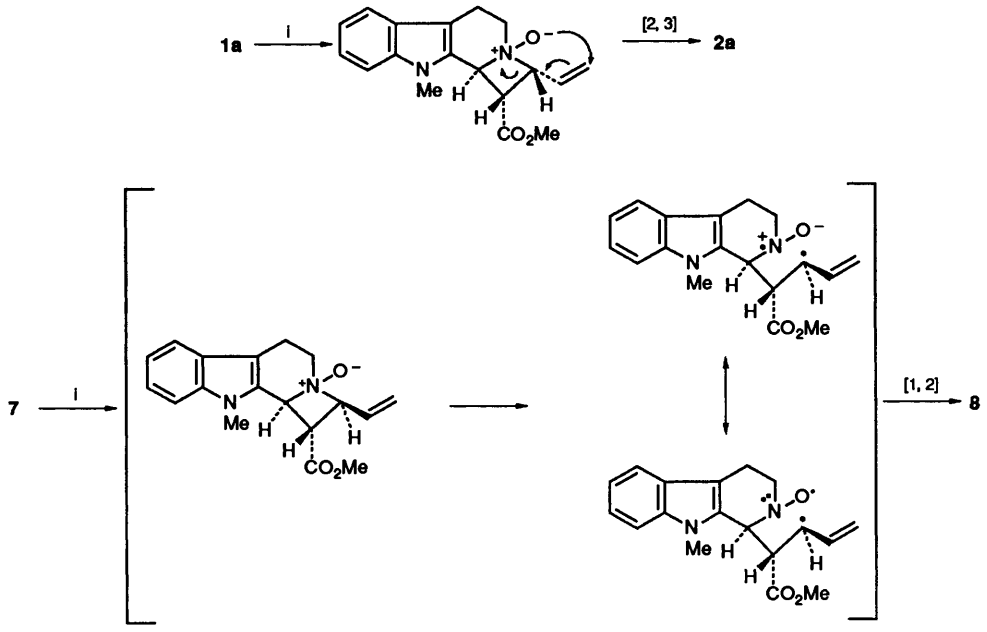


Fig. 1 Stereoscopic views of the oxazepine **3** and the isoxazolidine **12**

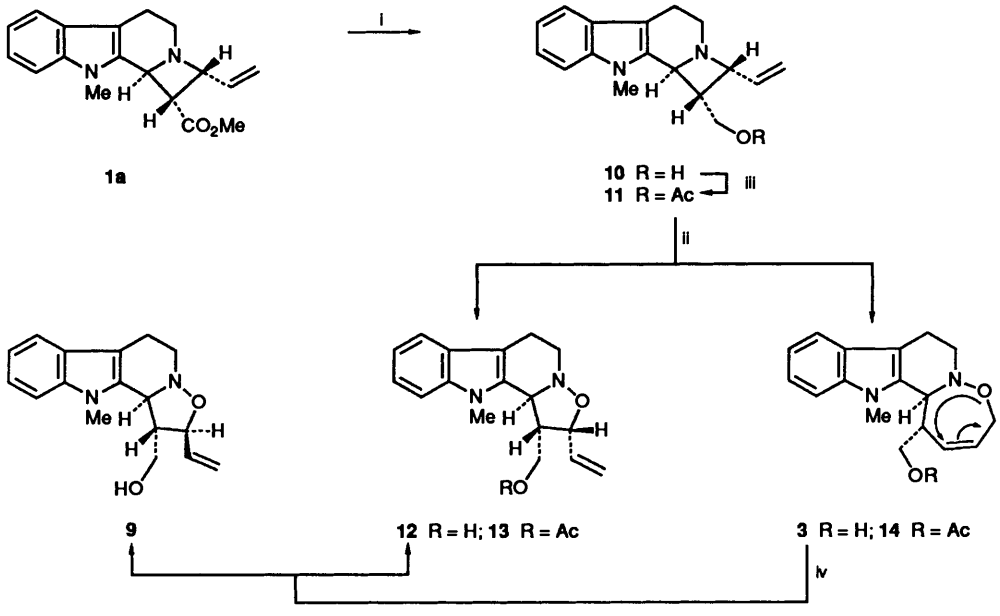
therefore considered to be epimeric at C-13b. The structural assignment was finally confirmed by conversions of compounds **2a** and **6**, respectively, into α,β-unsaturated ester **4** by treatment with 1 mol dm^{-3} NaOH in methanol at room temperature.

On the other hand, a different result was obtained in the case of the 1,2-*trans* azetidine **7**. Treatment of compound **7** with MCPBA under ordinary conditions afforded a crystalline product **8** in 42% yield. Though MS indicated the same molecular ion peak (*m*/*z* 312) as that of oxazepines **2a** and **6**, the ^1H NMR spectrum showed the presence of vinyl protons [δ 5.19 (d, *J* 10.0 Hz), 5.35 (d, *J* 17.0 Hz), and 5.78 (ddd, *J* 17.0, 10.0 and 7.5 Hz)]. The structure of compound **8** was therefore assigned to be methyl 1,13b-*trans*-2-vinylhexahydroisoxazolo[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carboxylate, which would be formed by the Meisenheimer [1,2]-rearrangement of the resulting *N*-oxide of compound **7** *via* a homolytic dissociation–recombination mechanism,[3a] as shown in Scheme 2.* Examination of the ^1H NMR spectrum, and TLC analysis, for the crude product of this reaction did not reveal the existence of any [2,3]-rearrangement product. Stereochemistry of the isoxazolidine **8** will be discussed later. An interesting feature of the results mentioned above is that 1,2-*cis* azetidines **1** and **5** give oxazepines **2** and **6** *via* the [2,3]-rearrangement, while the 1,2-*trans* azetidine **7** gives the isoxazolidine **8** *via* the [1,2]-rearrangement. The distinct difference in reaction routes can possibly be explained by postulating the *cis*-fused *N*-oxides for compounds **1** and **7** and the *trans*-fused *N*-oxide for compound **5** as intermediates, respectively. Since the *N*-oxide of compound **7** does not have a favourable configuration for the [2,3]-rearrangement, the isoxazoline **8** is obtained. However, we have not definitely confirmed this, since the *N*-oxide intermediates are too thermally unstable to be isolated.

* The mechanism of the Meisenheimer [1,2]-rearrangement of azetopyridoindoles has been discussed in ref. 1 by use of the isolable *N*-oxides of the corresponding 2-ethyl analogues.



Scheme 2 Reaction pathways from azetidine *N*-oxides. *Reagents:* i, MCPBA



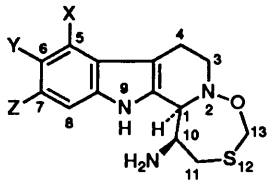
Scheme 3 *Reagents:* i, $LiAlH_4$; ii, MCPBA; iii, Ac_2O, pyridine; iv, reflux in xylene

Reduction of ester **1a** with $LiAlH_4$ in THF gave the alcohol **10**, which was treated with acetic anhydride to give acetate **11** (Scheme 3). Contrary to the previous results, oxidation of the alcohol **10** with MCPBA at room temperature gave a mixture of the oxazepine **3** (23%), which was identical with an authentic sample prepared from ester **2a**, and the isoxazolidine **12** (32%) *via* competitive [2,3]- and [1,2]-rearrangement. Compound **12** was believed to be a stereoisomer of compound **9**, obtained by $LiAlH_4$ reduction of ester **8**, with respect to the C-2 position by comparison of their ^1H NMR spectra. Thus, the ^1H NMR spectrum of the alcohol **9** was very similar to that of the alcohol **12**, except for the chemical shifts of the three neighbouring methine protons. Upon irradiation of 11b-H of compound **9**, a nuclear Overhauser effect (NOE) enhancement was observed at 2-H (4%), although there was no NOE enhancement between 2-H and 11b-H in compound **12**. Therefore, the relative configuration between 2-H and 11b-H was deduced to be *cis* in compound **8**, indicating that the Meisenheimer [1,2]-rearrangement proceeds with retention of configuration. The definitive evidence for the structure of compound **12** was obtained by an X-ray crystallographic analysis, as shown in Fig. 1. Oxidation of acetate **11** with MCPBA in the usual manner gave a mixture of the isoxazolidine **13** (33%) and the oxazepine **14** (42%). Although we cannot explain exactly why reaction of compounds **10** and **11** with MCPBA gives two reaction products, it seems likely that isoxazolidines are obtained from oxazepines *via* a [1,3]-shift under the reaction conditions. Thus, when the oxazepine **3** was refluxed in xylene for 2 h, a mixture of isoxazolidines **9** and **12** in the ratio ~1:2 was obtained in 55% combined yield, although there was no reaction under reflux in toluene.* These observations supported our contention that isoxazolidines **12** and **13** might be obtained directly from azetidines **10** and **11**, respectively, *via* [1,2]-rearrangement with

* Refluxing of a solution of oxazepino ester **2a** in xylene gave a complex mixture with decomposition, though no change was observed upon refluxing in toluene.

retention of configuration. The [1,3]-shift products obtained upon heating may be explained by product stability considerations.

The framework of oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indoles **2** and **6** corresponds to that of a 12-carba-analogue of eudistomins.[7] Eudistomins are antiviral marine natural products. This work will hopefully provide a promising route for the synthesis of carbaeudistomins[8] having an amino group at the C-1 position.



Eudistomin analogues, with eudistomin trivial numbering scheme (see the summary)

Experimental

M.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR 435 spectrophotometer. ^1H and ^{13}C NMR spectra were determined with a Varian Gemini-200 spectrometer for solutions in deuteriochloroform, with *J*-values given in Hz; and mass spectra were obtained with an Hitachi M-80 instrument. All reactions were carried out under nitrogen. For column chromatography, SiO_2 (Merck Art 9385) was used. Xylene refers to the commercial mixture.

10-*Methyl*-2-*vinyl*-1,2,4,5,10,10b-*hexahydroazeto*[1′,2′:1,2]-*pyrido*[3,4-b]*indole*-1-*carboxylic Acid* **1c**.—Aq. NaOH (1 mol dm^{-3}; 4.5 cm^3, 4.5 mmol) was added to a solution of compound **1a** (939 mg, 3.2 mmol) in MeOH (20 cm^3) and the mixture was stirred for 5 h at room temperature, then concentrated under reduced pressure. The resulting residue was neutralised by the addition of 10% aq. HCl and extracted with $CHCl_3$ (100 cm^3 × 5). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was agitated with EtOH and the resulting precipitate was collected by filtration to give pure *carboxylic acid* **1c** (826 mg, 92%), which failed to crystallise. It showed ν_{max}(KBr)/cm^{-1} 1600 (CO); δ_H($CDCl_3$) 3.0–3.35 (5 H, m, NCH_2CH_2 and 1-H), 3.65 (3 H, s, NMe), 4.57 (1 H, t, *J* 9.0, 2-H), 5.41 (1 H, d, *J* 9.0, H^c),* 5.45 (1 H, d, *J* 16.0, H^t), 5.64 (1 H br s, 10b-H), 6.44 (1 H, dt, *J* 9.0 and 16.0, =CH), 7.10–7.30 (3 H, m, ArH) and 7.55 (1 H, d, *J* 7.0, 9-H); *m*/*z* 282 (M^+) (Found: M^+, 282.1367. $C_{17}H_{18}N_2O_2$ requires *M*, 282.1367). This was used for the following reaction without purification.

To a suspension of acid **1c** (13 mg, 0.046 mmol) in CH_2Cl_2 (5 cm^3) was added a solution of ethereal CH_2N_2 until a yellow colour persisted. After being stirred for 10 min, the mixture was concentrated under reduced pressure to give almost pure ester **1a** (13 mg, 95%), which was identical with an authentic sample of **1a**, based on comparison of their ^1H NMR spectra.

N-*Methoxy*-N,2-*dimethyl*-2-*vinyl*-1,2,4,5,10,10b-*hexahydro-azeto*[1′,2′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxamide* **1d**.—To a suspension of compound **1c** (760 mg, 2.7 mmol) in CH_2Cl_2 (10 cm^3) was added MeNH(OMe) (263 mg, 2.7 mmol) followed by DCC (556 mg, 2.7 mmol) at room temperature. After being stirred for 2 h, the mixture was condensed under reduced pressure. Benzene (10 cm^3) was added to the residue, and the insoluble precipitate was removed by filtration. The filtrate was diluted with EtOAc (50 cm^3), then washed successively with saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was subjected to column chromatography (elution with $CHCl_3$) to give *compound* **1d** (862 mg, 98%) as an oil; ν_{max}(film)/cm^{-1} 1650 (CO); δ_H($CDCl_3$) 2.80–3.10 (4 H, m, NCH_2CH_2), 3.22 (3 H, s, NMe or OMe), 3.52 (6 H, s, NMe and OMe or NMe), 3.55 (1 H, m, 1-H), 4.36 (1 H, t, *J* 8.0, 2-H), 5.29 (1 H, br s, 10b-H), 5.30 (1 H, d, *J* 10.0, H^c), 5.39 (1 H, d, *J* 18.0, H^t), 5.91 (1 H, ddd, *J* 18.0, 10.0 and 8.0, =CH), 7.10–7.35 (3 H, m, ArH) and 7.57 (1 H, d, *J* 7.0, 9-H); *m*/*z* 325 (M^+) (Found: M^+, 325.1787. $C_{19}H_{23}N_3O_2$ requires *M*, 325.1788).

Methyl 13-*Methyl*-1,4,7,8,13,13b-*hexahydro*[1′,2′]*oxaze-pino*[2′,3′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxylate* **2a**.—A solution of 80% MCPBA (129 mg, 0.6 mmol) in CH_2Cl_2 (1 cm^3) was added to a solution of compound **1a** (148 mg, 0.5 mmol) in CH_2Cl_2 (2.5 cm^3) at room temperature. After being stirred for 1 h, the mixture was diluted with CH_2Cl_2 (30 cm^3), washed successively with 5% aq. Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. The residue was subjected to column chromatography (elution with 15% EtOAc in hexane) to give *compound* **2a** (126 mg, 81%). Recrystallisation from EtOH gave crystals, m.p. 111–112 °C; ν_{max}(KBr)/cm^{-1} 1720 (CO); δ_H($CDCl_3$) 2.70–3.22 (3 H, m, NC*H*HCH_2), 3.52–3.63 (4 H, m, NCH*H* and CO_2Me), 3.72 (3 H, s, NMe), 3.90 (1 H, t, *J* 6.0, 1-H), 4.39 and 4.53 (each 1 H, each d, *J* 16.0, OCH_2), 5.05 (1 H, d, *J* 6.0, 13b-H), 5.61–5.79 (2 H, m, CH=CH), 7.02–7.27 (3 H, m, ArH) and 7.45 (1 H, d, *J* 7.5, 12-H); δ_C($CDCl_3$) 21.5 (t), 31.5 (q), 49.5 (d), 52.9 (q), 53.0 (t), 65.5 (d), 72.0 (t), 109.5 (s), 109.7 (d), 118.8 (d), 120.0 (d), 122.2 (d), 123.5 (d), 126.7 (s), 131.0 (d), 135.7 (s), 139.5 (s) and 174.5 (s); *m*/*z* 312 (M^+) (Found: C, 69.3; H, 6.45; N, 8.95. $C_{18}H_{20}N_2O_3$ requires C, 69.21; H, 6.45; N, 8.95%).

Methyl 3-*Ethyl*-13-*methyl*-1,4,7,8,13,13b-*hexahydro*[1′,2′]-*oxazepino*[2′,3′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxylate* **2b**.—By the same procedure as that described for the preparation of compound **2a**, the crude product which was obtained from compound **1b** (30 mg, 0.09 mmol) and 80% MCPBA (32 mg, 0.18 mmol) was purified by columm chromatography (elution with 10% EtOAc in hexane) to give *compound* **2b** (16 mg, 51%). Recrystallisation from EtOH gave crystals, m.p. 109–111 °C; ν_{max}(KBr)/cm^{-1} 1720 (CO); δ_H($CDCl_3$) 1.55 (3 H, t, *J* 8.0, CH_2*Me*), 1.98 (2 H, q, *J* 8.0, CH_2Me), 3.20–3.69 (4 H, m, NCH_2CH_2), 3.52 and 3.62 (each 3 H, each s, NMe and OMe), 3.92 (1 H, dd, *J* 6.7 and 5.0, 1-H), 4.39 (2 H, s, OCH_2), 5.0 (1 H, d, *J* 5.0, 13b-H), 5.49 (1 H, d, *J* 6.7, 2-H), 7.0–7.29 (3 H, m, ArH) and 7.42 (1 H, d, *J* 7.5, 12-H); *m*/*z* 340 (M^+) (Found: C, 70.8; H, 7.2; N, 8.2. $C_{20}H_{24}N_2O_3$ requires C, 70.56; H, 7.11; N, 8.23%).

13-*Methyl*-1,4,7,8,13,13b-*hexahydro*[1′,2′]*oxazepino*[2′,3′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxylic Acid* **2c**.—A solution of compound **2a** (312 mg, 1 mmol) in CH_2Cl_2 (3 cm^3) was added to a stirred, ice-cooled solution of aluminium tribromide (2.67 g, 10 mmol) in ethanethiol (7 cm^3). After being stirred for 30 min, the reaction mixture was quenched by the addition of water (30 cm^3) followed by 10% aq. HCl (5 cm^3), and the mixture was vigorously stirred for an additional 30 min. The insoluble material was collected by filtration and recrystallised from MeOH to give *compound* **2c** (102 mg, 35%) as crystals, m.p. 191–192 °C; ν_{max}(KBr)/cm^{-1} 1705 (CO); δ_H[$CDCl_3$ + trace of $(CD_3)_2SO$] 2.60–3.0 (3 H, m, NC*H*HCH_2), 3.47 (1 H, m,

* Throughout this section, ^1H NMR data for the vinyl terminal hydrogens are given as follows:

NCH*H*), 3.53 (1 H, s, NMe), 3.74 (1 H, t, *J* 5.0, 1-H), 4.32 (2 H, m, OCH_2), 4.95 (1 H, d, *J* 5.0, 13b-H), 5.60 (2 H, m, CH=CH), 6.90–7.20 (3 H, m, ArH) and 7.30 (1 H, d, *J* 7.5, 12-H); *m/z* 298 (M^+) (Found: C, 68.1; H, 6.1; N, 9.4. $C_{17}H_{18}N_2O_3 \cdot 1/10H_2O$ requires C, 68.03; H, 6.11; N, 9.34%).

Reaction of Compound **1c** *with MCPBA.*—A solution of 80% MCPBA (35 mg, 0.16 mmol) in CH_2Cl_2 (1 cm^3) was added to a stirred solution of compound **1c** (28 mg, 0.1 mmol) in CH_2Cl_2 (5 cm^3) at room temperature. After disappearance of the starting material as shown by TLC (*ca.* 30 min), the mixture was concentrated under reduced pressure. The resulting precipitate was vigorously stirred in MeOH (30 cm^3) for several hours. The insoluble material was collected by filtration and recrystallised from MeOH to give compound **2c** (3 mg, 10%), which was identical with authentic acid **2c**, based on comparison of their ^1H NMR spectra. On the other hand, after disappearance of the starting material as mentioned above, an ethereal solution of CH_2N_2 was added until a yellow colour persisted. After being stirred at room temperature for 10 min, the mixture was concentrated under reduced pressure. The residue was subjected to column chromatography (elution with 15% EtOAc in hexane) to give compound **2a** (16 mg, 52%), which was identical with an authentic sample, based on comparison of their IR and ^1H NMR spectra.

N-*Methoxy*-N,13-*dimethyl*-1,4,7,8,13,13b-*hexahydro*[1′,2′]-*oxazepino*[2′,3′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxamide* **2d**.—A solution of compound **1d** (33 mg, 0.1 mmol) and 80% MCPBA (35 mg, 0.16 mmol) in CH_2Cl_2 (5 cm^3) was refluxed for 2 h. The mixture was diluted with CH_2Cl_2 (30 cm^3), washed successively with 5% aq. Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. The residue was subjected to column chromatography (elution with $CHCl_3$) to give *compound* **2d** (20 mg, 59%) as an oil; ν_{max}(film)/cm^{-1} 1650 (CO); δ_H($CDCl_3$) 2.70–3.10 (3 H, m, NC*H*HCH_2), 3.14, 3.49 and 3.52 (each 3 H, each s, 2 × NMe and OMe), 3.58 (1 H, m, NCH*H*), 4.30 (1 H, br m, 1-H), 4.49 (2 H, m, OCH_2), 5.10 (1 H, d, *J* 6.0, 13b-H), 5.67 (2 H, m, CH=CH), 7.0–7.30 (3 H, m, ArH) and 7.45 (1 H, d, *J* 7.5, 12-H); *m/z* 341 (M^+) (Found: M^+, 341.1744. $C_{19}H_{23}N_3O_3$ requires *M*, 341.1738).

(13-*Methyl*-1,4,7,8,13,13b-*hexahydro*[1′,2′]*oxazepino*[2′,3′:1,2]*pyrido*[3,4-b]*indol*-1-*yl*)*methanol* **3**.—A solution of compound **2a** (60 mg, 0.19 mmol) in THF (4 cm^3) was added to an ice-cooled suspension of $LiAlH_4$ (10 mg, 0.29 mmol) in THF (5 cm^3) and the mixture was stirred for 20 min, quenched by the addition of water, and extracted with benzene–EtOAc (1:1) (30 cm^3). The extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallised from EtOH to give *compound* **3** (48 mg, 89%), m.p. 141–143 °C; ν_{max}($CHCl_3$)/cm^{-1} 3350 (OH); δ_H($CDCl_3$) 2.27 (1 H, br s, OH), 2.63–3.10 (3 H, m, NC*H*HCH_2), 3.23 (1 H, m, 1-H), 3.52 (1 H, m, NCH*H*), 3.67 (3 H, s, NMe), 3.89 (2 H, br s, CH_2OH), 4.37 (3 H, m, OCH_2 and 13b-H), 5.60 (2 H, m, CH=CH), 6.95–7.23 (3 H, m, ArH) and 7.36 (1 H, d, *J* 7.5, 12-H); *m/z* 284 (M^+) (Found: C, 71.8; H, 7.1; N, 9.8. $C_{17}H_{20}N_2O_2$ requires C, 71.80; H, 7.09; N, 9.85%).

Methyl 13-*Methyl*-3,4,7,8,13,13b-*hexahydro*[1′,2′]*oxazepino*-[2′,3′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxylate* **4**.—Aq. NaOH (1 mol dm^{-3}; 0.3 cm^3, 0.3 mmol) was added to a solution of compound **2a** (94 mg, 0.3 mmol) in MeOH (3 cm^3). After being stirred for 2 h, the mixture was concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (50 cm^3) and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was recrystallised from EtOH to give *compound* **4** (85 mg, 95%), m.p. 143–144 °C; ν_{max}(KBr)/cm^{-1} 1710 (CO); δ_H($CDCl_3$) 2.20–2.80 (3 H, m, =CHCH_2 and NCH_2C*H*H), 3.25 (2 H, m, NC*H*HCH*H*), 3.51 (3 H, s, NMe), 3.77 (3 H, s, CO_2Me), 3.79 (1 H, m, NCH*H*), 4.02 (2 H, m, OCH_2), 5.72 (1 H, s, 13b-H), 7.0–7.30 (3 H, m, ArH) and 7.53 (2 H, m, 2- and 12-H); *m/z* 312 (M^+) (Found: C, 69.2; H, 6.5; N, 9.0. $C_{18}H_{20}N_2O_3$ requires C, 69.21; H, 6.45; N, 8.97%).

Methyl (1,10b-cis)-10-*Methyl*-2-*vinyl*-1,2,4,5,10,10b-*hexahydroazeto*[1′,2′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxylate* **5**.—A solution of compound **1a** (142 mg, 0.5 mmol) and NaOMe (95% purity) (55 mg, 1 mmol) in dry MeOH (5 cm^3) was refluxed for 3 h. After evaporation of the solvent, the residue was extracted with EtOAc (50 cm^3). The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was subjected to column chromatography (elution with 15% EtOAc in hexane) to give starting material **1a** (27 mg, 19% recovery) from the first fraction. The second eluate (50% EtOAc in hexane) gave *compound* **5** (64 mg, 45%), which was recrystallised from EtOH to give crystals, m.p. 123–125 °C; ν_{max}($CHCl_3$)/cm^{-1} 1725 (CO); δ_H($CDCl_3$) 2.50–3.10 (4 H, m, NCH_2CH_2), 3.43 and 3.56 (each 3 H, each s, NMe and CO_2Me), 3.65 (1 H, t, *J* 8.0, 1-H), 4.34 (1 H, t, *J* 8.0, 2-H), 5.14 (1 H, d, *J* 8.0, 10b-H), 5.19 (1 H, d, *J* 10.0, H^c), 5.35 (1 H, d, *J* 17.0, H^t), 5.99 (1 H, ddd, *J* 17.0, 10.0 and 8.0, =CH), 7.18 (3 H, m, ArH) and 7.55 (1 H, d, *J* 7.5, 9-H); *m/z* 296 (M^+) (Found: C, 72.8; H, 6.85; N, 9.5. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.45%).

Methyl (1,13b-cis)-13-*Methyl*-1,4,7,8,13,13b-*hexahydro*[1′,2′]*oxazepino*[2′,3′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxylate* **6**.—By the same procedure as that described for the preparation of compound **2a**, the crude product which was obtained from compound **5** (296 mg, 1 mmol) and 80% MCPBA (257 mg, 1.2 mmol) was purified by column chromatography (elution with 40% EtOAc in hexane) to give *compound* **6** (269 mg, 86%) as an oil; ν_{max}(film)/cm^{-1} 1720 (CO); δ_H($CDCl_3$) 2.70–3.10 (3 H, m, NC*H*HCH_2), 3.20 (3 H, s, CO_2Me), 3.65 (1 H, m, NCH*H*), 3.70 (3 H, s, NMe), 3.95 (1 H, br s, 1-H), 4.34 (1 H, dd, *J* 17.0 and 3.0, OC*H*H), 4.67 (1 H, br s, 13b-H), 4.72 (1 H, d, *J* 17, OCH*H*), 5.75 (1 H, m, 2-H), 5.96 (1 H, m, 3-H), 7.0–7.30 (3 H, m, ArH) and 7.47 (1 H, d, *J* 7.5, 12-H); *m/z* 312 (M^+) (Found: M^+, 312.1468. $C_{18}H_{20}N_2O_3$ requires *M*, 312.1472). This was treated with 1 mol dm^{-3} NaOH in MeOH to give compound **4** in quantitative yield.

Methyl 2-*Ethyl*-11-*methyl*-1,2,5,6,11,11b-*hexahydroisoxazolo*[2′,3′:1,2]*pyrido*[3,4-b]*indole*-1-*carboxylate* **8**.—By the same procedure as that described for the preparation of compound **2a**, the crude product which was obtained from compound **7** (148 mg, 0.5 mmol) and 80% MCPBA (120 mg, 0.6 mmol) was purified by column chromatography (elution with 15% EtOAc in hexane) to give *compound* **8** (66 mg, 42%). Recrystallisation from diisopropyl ether gave crystals, m.p. 106–108 °C; ν_{max}($CHCl_3$)/cm^{-1} 1725 (CO); δ_H($CDCl_3$) 2.60–3.30 (3 H, m, NC*H*HCH_2), 3.20 (1 H, dd, *J* 7.5 and 5.0, 1-H), 3.59 and 3.82 (each 3 H, each s, NMe and CO_2Me), 3.65 (1 H, m, NCH*H*), 4.76 (1 H, t, *J* 7.5, 2-H), 5.10 (1 H, d, *J* 5.0, 11b-H), 5.19 (1 H, d, *J* 10.0, H^c), 5.35 (1 H, d, *J* 17.0, H^t), 5.78 (1 H, ddd, *J* 17.0, 10.0 and 7.5, =CH), 7.19 (3 H, m, ArH) and 7.51 (1 H, d, *J* 7.5, 11-H); δ_C($CDCl_3$) 17.8 (t), 30.4 (q), 50.4 (t), 53.0 (q), 59.8 (d), 62.2 (d), 83.5 (d), 108.2 (s), 109.4 (d), 119.0 (d), 119.6 (t), 119.9 (d), 122.2 (d), 126.7 (s), 132.8 (s), 135.8 (d), 138.1 (s) and 172.3 (s); *m/z* 312 (M^+) (Found: C, 69.1; H, 6.5; N, 9.1. $C_{18}H_{20}N_2O_3$ requires C, 69.21; H, 6.45; N, 8.97%).

{(1,2-trans)-11-*Methyl*-2-*vinyl*-1,2,5,6,11,11b-*hexahydroisoxazolo*[2′,3′:1,2]*pyrido*[3,4-b]*indol*-1-*yl*}*methanol* **9**.—A solution of compound **8** (30 mg, 0.1 mmol) in THF (2 cm^3) was added to an ice-cooled suspension of $LiAlH_4$ (6 mg, 0.16 mmol)

Table 1 Crystal data for the oxazepine **3** and the isoxazolidine **12**

	3	**12**
Molecular formula	$C_{17}H_{20}N_2O_2$	$C_{17}H_{20}N_2O_2$
Molecular weight	284.358	284.358
Crystal System	Monoclinic	Monoclinic
Space group	*Pc*	$P2_1/n$
Cell constants (Å)		
a	18.499(4)	12.32(3)
b	6.2149(9)	11.00(4)
c	26.45(1)	10.91(3)
β (°)	103.16(3)	94.5(2)
Volume (Å^3)	2962(1)	1474(7)
Z	4	4
D_c (g cm^{-3})	1.2757	1.2814

in THF (3 cm^3). After being stirred for 10 min, the mixture was quenched by the addition of water, and extracted with benzene–EtOAc (1:1) (30 cm^3). The extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography (elution with 50% EtOAc in hexane) to give *compound* **9** (24 mg, 85%) as an oil; ν_{max}(film)/cm^{-1} 3320 (OH); δ_H($CDCl_3$) 2.54–2.76 (3 H, m, NC*H*HCH_2), 3.09 (1 H, m, NCH*H*), 3.72 (3 H, s, NMe), 3.76 (1 H, m, 1-H), 3.98 (2 H, m, CH_2OH), 4.27 (1 H, dd, *J* 7.2 and 2.8, 2-H), 4.71 (1 H, d, *J* 2.8, 11b-H), 5.05 (1 H, d, *J* 10.0, H^c), 5.22 (1 H, d, *J* 18.0, H^t), 5.60 (1 H, dd, *J* 18.0, 10.0 and 7.2, =CH), 7.08–7.31 (3 H, m, ArH) and 7.56 (1 H, d, *J* 7.5, 10-H); *m/z* 284 (M$^+$) (Found: M$^+$, 284.1525. $C_{17}H_{20}N_2O_2$ requires *M*, 284.1523).

(10-*Methyl*-2-*vinyl*-1,2,4,5,10b,10b-*hexahydroazeto*-[1′,2′:1,2]*pyrido*[3,4-b]*indol*-1-*yl*)*methanol* **10**.—By the same procedure as that described for the preparation of compound **3**, the crude product which was obtained from compound **1a** (592 mg, 2 mmol) and $LiAlH_4$ (76 mg, 2 mmol) was recrystallised from EtOH to give *compound* **10** (513 mg, 99%), m.p. 147–149 °C; ν_{max}($CHCl_3$)/cm^{-1} 3350 (OH); δ_H($CDCl_3$) 2.48 (1 H, m, 1-H), 2.65–3.16 (4 H, m, NCH_2CH_2), 3.22 (1 H, br s, OH), 3.63 (3 H, s, NMe), 4.02 (1 H, dd, *J* 10.0 and 7.0, C*H*HOH), 4.19 (2 H, m, CH*H*OH and 2-H), 4.66 (1 H, br s, 10b-H), 5.27 (1 H, d, *J* 10.0, H^c), 5.38 (1 H, d, *J* 17.0, H^t), 5.99 (1 H, ddd, *J* 17.0, 10.0 and 6.0, =CH), 7.08–7.36 (3 H, m, ArH) and 7.59 (1 H, d, *J* 7.5, 9-H); *m/z* 268 (M$^+$) (Found: C, 75.0; H, 7.35; N, 10.3. $C_{17}H_{20}N_2O$·1/4H_2O requires C, 75.15; H, 7.56; N, 10.07%).

1-*Acetoxymethyl*-10-*methyl*-2-*vinyl*-1,2,4,5,10,10b-*hexahydroazeto*[1′,2′:1,2]*pyrido*[3,4-b]*indole* **11**.—A mixture of compound **10** (134 mg, 0.5 mmol) and acetic anhydride (0.47 cm^3, 5 mmol) in the presence of a drop of pyridine was stored for 2 h. The mixture was then poured into ice–water, made alkaline with $NaHCO_3$, and then extracted with EtOAc (50 cm^3). The extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to column chromatography (elution with 40% EtOAc in hexane) to give *compound* **11** (146 mg, 94%) as an oil; ν_{max}(film)/cm^{-1} 1740 (CO); δ_H($CDCl_3$) 2.10 (3 H, s, Ac), 2.58 (1 H, m, 1-H), 2.65–3.12 (4 H, m, NCH_2CH_2), 3.62 (3 H, s, NMe), 4.19 (1 H, t, *J* 7.5, 2-H), 4.38–4.64 (2 H, m, OCH_2), 4.55 (1 H, br s, 10b-H), 5.23 (1 H, d, *J* 10.0, H^c), 5.39 (1 H, d, *J* 17, H^t), 5.89 (1 H, ddd, *J* 17.0, 10.0 and 7.5, =CH), 7.10–7.30 (3 H, m, ArH) and 7.59 (1 H, d, *J* 7.5, 9-H); *m/z* 310 (M$^+$, 310.1684. $C_{19}H_{22}N_2O_2$ requires *M*, 310.1680).

Reaction of Compound **10** *with MCPBA*.—By the same procedure as that described for the preparation of compound **2a**, the crude product which was obtained from compound **10** (531 mg, 2 mmol) and 80% MCPBA (700 mg, 3.2 mmol) was subjected to column chromatography (elution with 40% EtOAc in hexane) to give, in order of elution, compound **3** (132 mg, 23%), which was identical with an authentic sample based on comparison of their ^{1}H NMR spectra, and {(1,2-cis)-11-*methyl*-2-*vinyl*-1,2,5,6,11,11b-*hexahydroisoxazolo*[2′,3′:1,2]*pyrido*[3,4-b]*indol*-1-*yl*}*methanol* **12** (190 mg, 32%). Recrystallisation from EtOH gave crystals, m.p. 182–184 °C; ν_{max}(KBr)/cm^{-1} 3180 (OH); δ_H($CDCl_3$) 2.60–2.80 (2 H, m, 5- or 6-H_2), 2.86 (1 H, m, 1-H), 2.93–3.23 (2 H, m, 6- or 5-H_2), 3.71 (3 H, s, NMe), 3.98 (2 H, d, *J* 5.0, CH_2OH), 4.53 (1 H, t, *J* 6.0, 2-H), 4.92 (1 H, br s, 11b-H), 5.24 (1 H, d, *J* 10.0, H^c), 5.31 (1 H, d, *J* 18.0, H^t), 5.92 (1 H, ddd, *J* 18.0, 10.0 and 6.0, =CH), 7.05–7.32 (3 H, m, ArH) and 7.52 (1 H, d, *J* 7.5, 10-H); *m/z* 284 (M$^+$) (Found: C, 71.7; H, 7.1; N, 9.7. $C_{17}H_{20}N_2O_2$ requires C, 71.80; H, 7.09; N, 9.85%).

Reaction of Compound **11** *with MCPBA*.—By the same procedure as that described for the preparation of compound **2a**, the crude product which was obtained from compound **11** (146 mg, 0.47 mmol) and 80% MCPBA (122 mg, 0.56 mmol) was purified by column chromatography (20% EtOAc in hexane) to give, in order of elution, 1-*acetoxymethyl*-13-*methyl*-1,4,7,8,13,13b-*hexahydro*[1′,2′]*oxazepino*[2′,3′:1,2]*pyrido*[3,4-b]*indole* **14** (65 mg, 42%) as an oil, and 1-*acetoxymethyl*-11-*methyl*-2-*vinyl*-1,2,5,6,11,11b-*hexahydroisoxazolo*-[2′,3′:1,2]*pyrido*[3,4-b]*indole* **13** (50 mg, 33%) as an oil.

For compound **14**: ν_{max}(film)/cm^{-1} 1740 (CO); δ_H($CDCl_3$) 2.08 (3 H, s, Ac), 2.65–3.35 (3 H, m, NC*H*HCH_2), 3.40 (1 H, m, 1-H), 3.56 (1 H, m, NCH*H*), 3.76 (3 H, s, NMe), 4.22–4.68 (5 H, m, 4-H_2, AcOCH_2, and 13b-H), 5.62 (2 H, m, CH=CH), 7.0–7.30 (3 H, m, ArH) and 7.41 (1 H, d, *J* 7.5, 12-H); *m/z* 326 (M$^+$) (Found: M$^+$, 326.1637. $C_{19}H_{22}N_2O_3$ requires *M*, 326.1629).

For compound **13**: ν_{max}(film)/cm^{-1} 1740 (CO); δ_H($CDCl_3$) 2.10 (3 H, s, Ac), 2.60–3.10 (4 H, m, 1-H and NC*H*HCH_2), 3.69 (3 H, s, NMe), 3.73 (1 H, m, NCH*H*), 4.37 (2 H, m, AcOCH_2), 4.55 (1 H, m, 2-H), 4.80 (1 H, br s, 11b-H), 5.24 (1 H, d, *J* 10.0, H^c), 5.32 (1 H, d, *J* 16.0, H^t), 5.83 (1 H, ddd, *J* 16.0, 10.0 and 8.0, =CH), 7.05–7.30 (3 H, m, ArH) and 7.52 (1 H, d, *J* 7.5, 10-H); *m/z* 326 (M$^+$) (Found: M$^+$, 326.1618. $C_{19}H_{22}N_2O_3$ requires *M*, 326.1629).

Pyrolysis of Compound **3**.—A solution of compound **3** (23 mg, 0.08 mmol) in dry xylene (3 cm^3) was refluxed for 2 h. After removal of the solvent by evaporation, the residue was subjected to column chromatography (elution with 60% EtOAc in hexane) to give an oil (13 mg, 55%), which was found to be a mixture of compounds **9** and **12** (in the ratio ~1:2), which were identical with authentic samples, based on comparison of their ^{1}H spectra.

X-Ray Determinations of Compounds **3** *and* **12**.—A single crystal (needles) each of compounds **3** and **12**, recrystallised from EtOH, was used for the X-ray studies. The crystal data are summarized in Table 1. Unit-cell dimensions were determined on a Rigaku four-circle diffractometer using high-angle reflections (2*θ*) by employing graphite-monochromated Cu-Kα radiation, and were refined by the least-squares method. A total of 4574 (for compound **3**) and 2458 (for compound **12**) independent reflections ($2\theta_{max}$ < 130°) was measured using the ω–2*θ* scan mode and a scan rate of 4°/min. Both structures were solved by direct methods using the MULTAN program[9] and refined by least squares to R = 0.0443 (compound **3**) and 0.0661 (compound **12**). Tables of fractional coordinates, bond lengths and angles, thermal parameters and hydrogen atom coordinates for compounds **3** and **12** have been deposited with the Cambridge Crystallographic Database.*

* For full details of the CCDC deposition scheme see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1993, issue 1.

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