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ON THE STEREOCHEMISTRY OF THE SOLVOLYTIC C/D RING CLEAVAGE OF THE 1,2,3,4,6,7,12,12b-OCTAHYDROINDOLO[2,3-*a*] QUINOLIZINE SYSTEM

M. J. CALVERLEY, J. HARLEY-MASON,* S. A. QUARRIE and P. D. EDWARDS
University Chemical Laboratory, Lensfield Road, Cambridge, England

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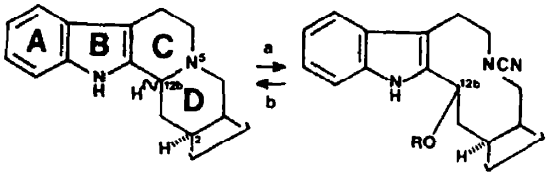
Abstract—A model sequence for the synthesis of C-mavacurine-type alkaloids is elaborated to demonstrate that substitution at C-12b in the reactions of the amines (4) with cyanogen bromide and methanol (Scheme 6) proceeds with stereospecific inversion of configuration. The same stereospecificity is observed in the analogous reactions of 4, or their O-acetates (5), with benzyl chloroformate and methanol (Scheme 8). To account for the stereospecificity an S_N1-type process at C-12b is proposed (Scheme 7).

Studies of the easy C/D ring opening of various *Corynanthe* alkaloids or their derivatives by a solvolytic von Braun-type reaction with cyanogen bromide and ethanol, methanol, or water (Scheme 1; NB indoloquinolizine numbering) have recently been made,[1,2] culminating in reports of the application of the reaction to partial syntheses of several new indole alkaloids.[2,3] Assignments of configuration in cleaved intermediates have required the assumption, supposed valid on mechanistic arguments,[1,2] of stereospecific or stereoselective inversion at the benzylic centre undergoing substitution in the ring cleavage reaction. Support for the assignment in several cases is to be found in the stereospecific C/D ring regeneration with hot acetic acid of the original alkaloidal system from the respective ethoxy-*seco*-cyanamides.[2] However, this cannot be considered to constitute a proof of the inverted configuration at C-12b[a] in the cleaved intermediate, since the reclosure reaction is manifestly *retro* ring cleavage (i.e. double retention at C-12b cannot be ruled out).



Scheme 1. (a) BrCN–ROH (R = Et, Me or H); (b) AcOH, Δ (R = Et).

The partial syntheses[3] of C-mavacurine-type alkaloids prompted us to extend our previous studies in the series, and we now report the results of a model study for the total synthesis of (±)-C-mavacurine,[4] during which we substantiate this assumption of inversion during the ring cleavage reaction by showing the stereochemical consequences for the specific case of the amines (4)[b] using a direct chemical correlation.

Partial hydrolysis of the lactam-diester (1)[5] followed by thermal decarboxylation gave the lactam-ester (2) as a mixture of diastereoisomers, in which the kinetically favoured (by protonation of the intermediate enol on the less hindered side of C-2), though less stable, *trans*-epimer (**2b**) predominated (Scheme 2). (*Cis*/*trans* notation here refers to the relative disposition of the C-2 and C-12b protons in ring D.) An alternative de-ethoxy-carbonylation of **1** using sodium cyanide in hot dimethyl sulphoxide gave a mixture from which the *cis*-**2a**- and *trans*-**2b**-epimer lactam-esters could be fractionally crystallised in yields of 50% and 18% respectively, the conditions for this reaction evidently causing equilibration. (The expected inversion of the epimeric ratio manifested in the NMR-spectrum of the kinetically favoured mixture (**2**) was observed after brief treatment with hot sodium ethoxide in ethanol). The designation of the *cis*-stereochemistry to the more stable epimer (**2a**) was made on the basis of conformational analysis and justified by subsequent transformations.

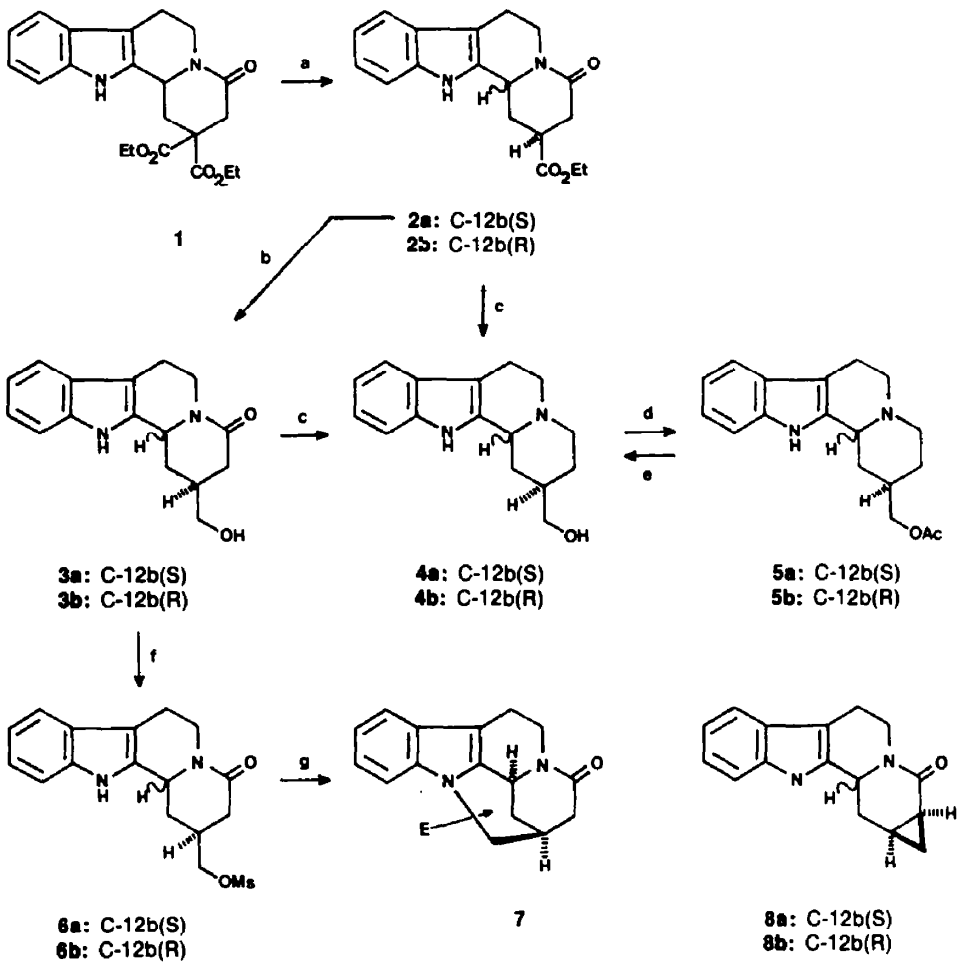
Selective reduction of the ester function of the *cis*-epimer lactam-ester (**2a**) was accomplished using sodium borohydride in methanol heated under reflux to yield an approximately 4:1 mixture of the lactam-alcohols (**3a**, **3b** respectively), separated by fractional crystallisation. The relative stereochemistries in the alcohols (**3**) were deduced from the outcome of attempted base-induced closure of ring E on their respective O-mesylates (**6**) to produce the lactam (**7**), having the C-mavacurine ring system. (Examination of molecular models clearly shows that only in the *cis*-series can this result be achieved.)

Thus, the reaction of the mesylate (**6a**) derived (methanesulphonyl chloride in pyridine) from the major alcohol (**3a**) with sodium hydride gave two products (Scheme 2). The major one (61%) was shown to be the required lactam **7** [having the perturbed indolic UV spectrum typical[6] of the strained mavacurine system and *m/e* 252 (M^+, 100%), 180[c] (84%)], while the minor product (81%) has been assigned the isomeric structure (**8a**). Similar reaction of the mesylate (**6b**) derived from the minor alcohol (**3b**) produced solely the epimeric cyclopropyl–lactam (**8b**), having very similar spectroscopic properties (a normal indolic UV spectrum, indolic

[a]The numbering of the titled system is retained for cleaved intermediates in the discussion section.

[b]All synthetic compounds are racemic. The schemes depict and the experimental section describes only the enantiomer bearing the C-2 configuration relating it to the natural series.

[c]The peaks at *m/e* 180 in the mass spectra of compounds **7**, **9**, **15** and **23** have been shown by accurate mass measurements to correspond to the formula $C_{13}H_{16}N^+$, a characteristic fragment ion for the mavacurine[6] and C/D-*seco*-mavacurine[3,6] systems.

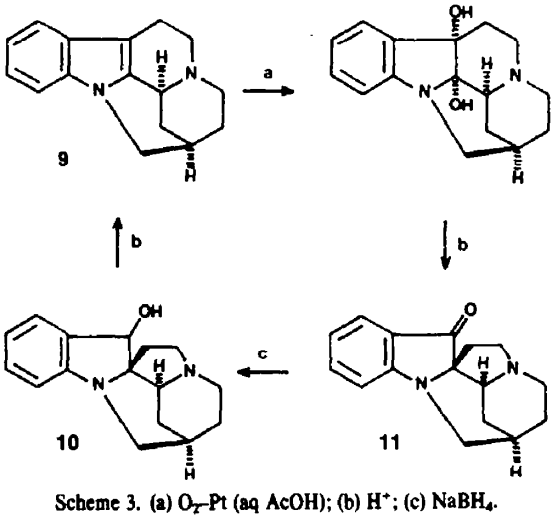


Scheme 2. (a) NaCN (DMSO) *or* (i) KOH (ii) Δ (DMF); (b) $NaBH_4$; (c) $LiAlH_4$; (d) AcCl; (e) KOH; (f) MsCl–Py; (g) NaH(THF).

NH signals in IR and NMR spectra, and *m/e* 252 (M^+)) to **8a** but being distinguishable from it on tlc.

It should be noted that the formation of the lactam (**7**) constitutes the only reported *direct* establishment of the pentacyclic C-mavacurine system by closing ring E,[4] and in view of the ambident nucleophilicity of the indole anion, confirmation for the proposed structure **7** by chemical means was required. This was achieved by submitting the amine (**9**), obtained by LAH reduction of **7**, to the cyclic reaction sequence (Scheme 3) corresponding to that used for the interelation of the *quaternary* alkaloids C-mavacurine and C-fluorocurine (a pseuduoindoxyl alkaloid) in the natural series.[7] Oxidation of the amine (**9**) with platinum and oxygen followed by treatment with methanolic hydrogen chloride gave the pseudoindoxyl amine (**11**; a nor-C-fluorocurine analogue), from which the amine **9** could be regenerated by the sequence of borohydride reduction to the benzylic alcohol (**10**) and acid catalysed rearrangement. This transformation demonstrates that the anticipated closure of ring E had occurred.

LAH reduction of the lactam-alcohols (**3a**, **3b**) generated the respective amine-alcohols (**4a**, **4b**) (Scheme 2), though these products were more conveniently prepared, now that their relative stereochemistries had been defined, by direct reduction of the "kinetic" mixture of lactam-esters (**2**) from the hydrolysis/decarboxylation



Scheme 3. (a) O_2–Pt (aq AcOH); (b) H^+; (c) $NaBH_4$.

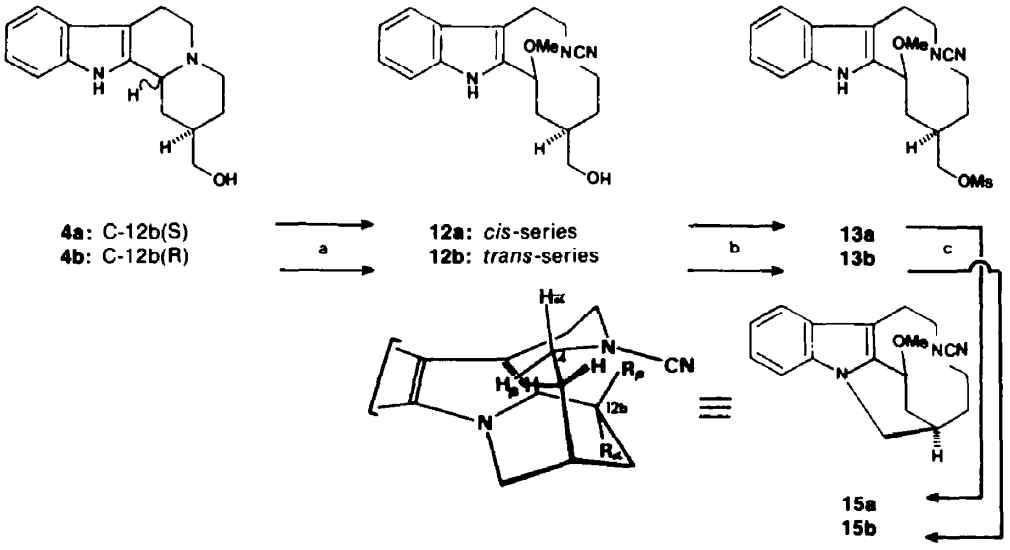
[4]Thus, the other reported synthetic entries into the system (Sakai and Shinma[3], and D. D. O'Rell, F. G. H. Lee and V. Boekelheide, *J. Am. Chem. Soc.* (1972) **94**, 3205 complete the skeleton by re-establishing ring C.

sequence described above. Separation of the amine-alcohols (**4**), predominantly the *trans*-isomer (**4b**), from the mixture thus obtained was best effected by sequential conversion to the O-acetates (**5**), chromatography and hydrolysis. The epimerically pure amine alcohols (**4a**, **4b**) were submitted to the C/D ring cleavage reaction with cyanogen bromide and excess methanol in tetrahydrofuran in the presence of anhydrous sodium carbonate at room temperature for 1 hr giving stereo-specifically and in high yield the epimeric 12b-methoxy-5, 12b-*seco*-cyanamide derivatives (**12**), easily distinguishable on tlc (Scheme 4). The high stereospecificity of the reaction is IR from our failure to detect by tlc any formation of the corresponding epimer, even in the *trans*-series, where the least degree of stereospecificity was observed in the natural systems.[1-3] The possibility of stereospecificity dependence on nucleophile concentration (also observed in the natural series[2]) was obviated by using a high methanol to substrate ratio (about 100:1), but no investigation of the effect with lower ratios was made.

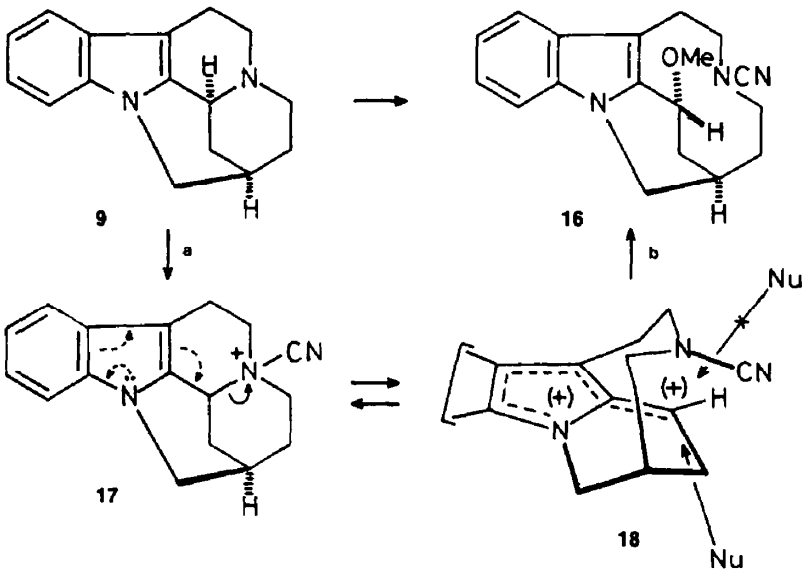
Having established the stereospecificity, though not the stereochemical consequence, of the ring cleavage reaction of this system, the sequence was simplified further by preparing the cleaved alcohols (**12**) for subsequent work directly from the mixture of amine alcohols (**4**) obtained above, deferring chromatographic separation until after ring opening. Cyclisation of the respective O-mesylates (**13**) of the alcohols (**12**) with sodium hydride in dimethyl sulphoxide gave the *seco*-mavacurine-type derivatives (**15**) (Scheme 4). The UV spectra (showing the presence of the perturbed indolic chromophore) and mass spectra [*m/e* 295 (M^+, 100%), 180[c] (*cis*-series 46%, *trans*-series 25%)] of the products (**15**) are in full accord with expectations for the system.[3] Furthermore the NMR spectra show the characteristic highfield signal [δ −0.08(*cis*-series) or −0.03(*trans*-series), 1H, td, J_{gem} 13, J_{vic} 13, 2 Hz] for the C-4 β-proton (see **14**; the observed coupling constants indicate the bridge conformation shown), which is highly shielded by the indole ring,[3,6] a feature also observed in the amine (**9**). Although the *cis*- and *trans*-series epimers of **15** were indistinguishable on tlc, ready distinction was achieved by comparison of their NMR spectra, the most helpful feature in this respect being the position of the OMe singlet [*cis*-series δ 3.21; *trans*-series, δ 3.58]. The deshielding effect observed in the *trans*-series product **15b** (the corresponding resonance appears at δ 3.19–3.23 for the alcohols (**12**) and their O-mesylates **13**) suggested the β-configuration for the OMe (in proximity to the cyanamide function) in this compound, but distinction in absolute terms could not be made on the basis of spectroscopic data alone.

Unambiguous assignment of the C-12b relative configurations in **15** came from comparison with the product of C/D ring opening in the amine (**9**). Irrespective of the mechanism operative in the cleavage reaction generally [i.e. whether bimolecular or (more likely) unimolecular fission of the benzylic C–N bond occurs], in this particular system the nucleophile can only be captured in the α-side of C-12b to give exclusively the inverted configuration here. Thus after initial quaternisation of the basic nitrogen N(b) of **9**, the intermediate cyanotrialkylammonium ion (**17**) may be attacked directly in an S_N2-type process, or alternatively ring cleave spontaneously, assisted by N(a), to give the *seco*-cation (**18**), with a delocalised carbonium ion on C-12b (Scheme 5). Assuming the *seco*-cation (**18**) to have a conformation similar to both those of the uncleaved system (**17**) and the cleaved product (**16**), it is apparent that nucleophile capture on the β-side of C-12b is severely hindered by the bridge and would not be expected to be competitive with α-attack. Accordingly, reaction of **9** with cyanogen bromide and methanol led smoothly to a product (**16**, indistinguishable on tlc from either compound **15**) the NMR spectrum of which showed only one OMe singlet (at δ 3.21) and moreover was identical to that of the *cis*-series epimer (**15a**) which consequently has the C-12b α-substituent. The *cis*-(or(a)series is therefore assigned the C-12b(R) configuration demonstrating inversion in the reactions (**4a** → **12a**) and, by inference, (**4b** → **12b**) (Scheme 6).

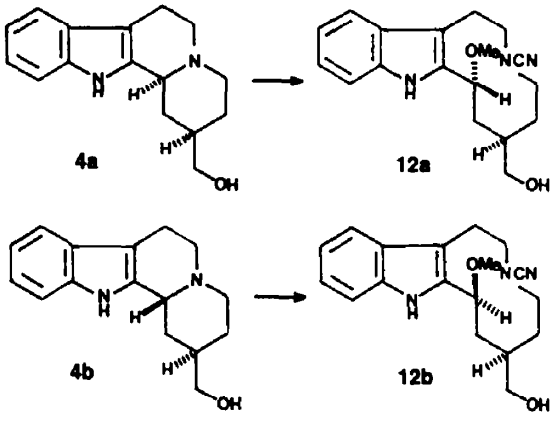
The stereochemical outcome of the reaction can be accommodated in a mechanism involving an S_N1-type process at C-12b by proposing that the "twist" about the



Scheme 4. (a) BrCN–MeOH, Na_2CO_3 (THF); (b) MsCl–Py; (c) NaH (DMSO).



Scheme 5. (a) BrCN; (b) MeOH (α-attack).



Scheme 6.

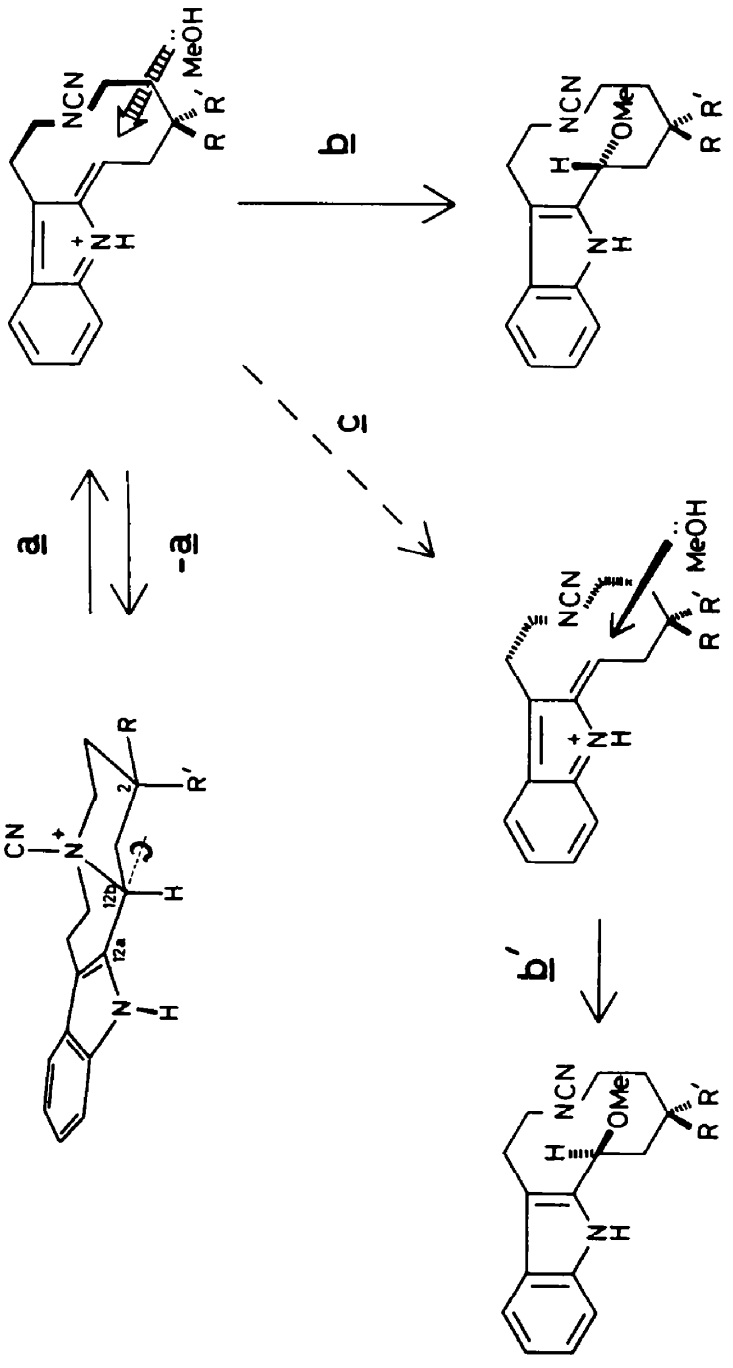
C-12a–C-12b axis concomitant with bond fission generates a delocalised carbonium ion, in which different sides of C-12b (relative to the C-2 substituent) are screened to nucleophilic attack by a "bridge" (in a system similar to that imposed in the *seco*-cation **18**) for the *cis*- and *trans*-series systems (i.e. the chiral information at C-12b is not lost in forming the *seco*-cation but rather transferred to the 10-membered ring) (Scheme 7). Although for this argument even the *trans*-series free base has been assumed to adopt the (5,12b-)*trans*-quinolizidine conformation (substantiated in the present case by the relevant IR and NMR spectroscopic features[8] on the amine-alcohols (**4**) and the O-acetates **5**[a]) prior to quarternisation, it should be noted that examination of molecular models indicates that bond fission (corresponding to step *a*) in the quaternised *cis*-fused quinolizidine (i.e. having the C-12b substituent *axial* in the ring D chair) leads to the generation of the *same* critical C-12a–C-12b (double-) bond geometry (i.e. *Z*) in the *seco*-cation, while inducing the *opposite* instantaneous conformation of the 10-membered ring, to bond fission in the system having the *trans* C/D ring fusion, and therefore the outcome is unaffected.

Furthermore, this model can be developed by invoking a reversible "inversion" of the 10-membered ring (step *c*) (resulting in a partial equilibration of the *seco*-cations to provide a plausible explanation for any observed epimerisation in the natural series[1-3] [e.g. at decreasing nucleophile concentration, when for a given system the life-time of the intermediate *seco*-cation is increasing; or in the *cis*-fused indoloquinolizidines, for which the "kinetic" *seco*-cation must be considered to be the less stable one, accounting for more rapid "inversion"] *if* step *b* is rate determining.

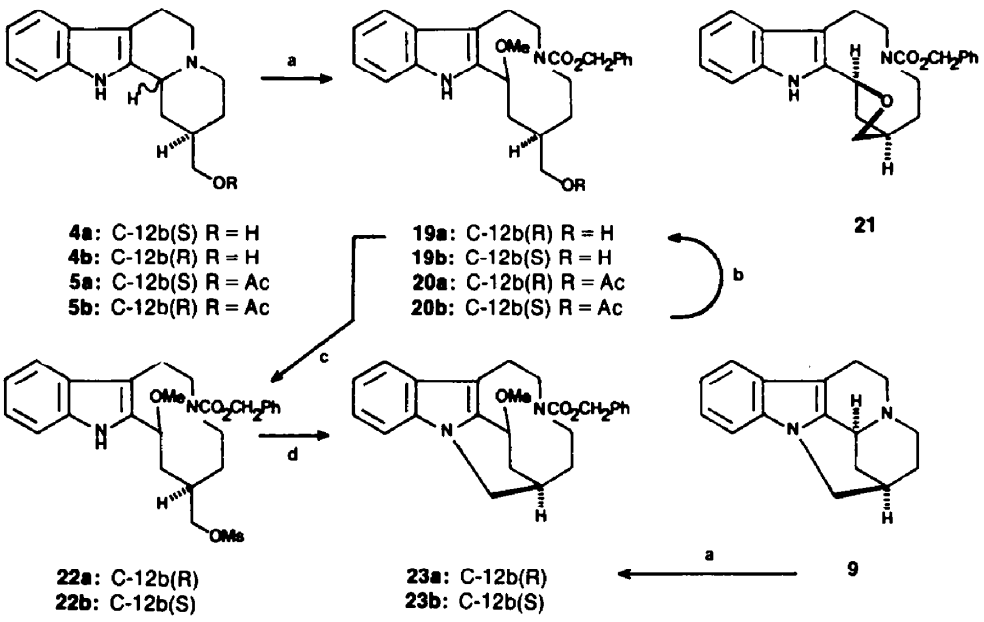
Chloroformate esters have been reported[2,9] to effect an analogous solvolytic C/D ring cleavage of the titled system, and the stereochemistry of this reaction with the amines (**4**) was investigated (Scheme 8). Thus, using benzyl chloroformate and excess methanol in tetrahydrofuran the *cis*-**4a**- and *trans*-**4b**-amine-alcohols each produced a single (as judged from tlc), different diastereoisomer of the cleaved alcohol (**19**), but the reaction was complicated by appearance of an additional minor product in the case of the *trans*-epimer (**4b**). This new product was found to be identical to the sole product of reaction of the *trans*-amine-alcohol (**4b**) with benzyl chloroformate in the *absence* of methanol and results from the capture of the internal nucleophile (the hydroxymethyl function on C-2) to give the cleaved ether (**21**). (Interestingly, the competitive capture of the internal nucleophile at high methanol concentration was not observed in the cyanogen bromide cleavages described earlier of either amine-alcohol **4**.)

Ring cleavage of the amine-acetates (**5**) followed by hydrolysis of the unisolated cleaved acetates (**20**) was again found to be an entirely stereospecific reaction yielding the respective cleaved alcohols (**19**), contamination in the *trans*-series with the cleaved ether (**21**) now being circumvented. The preparative simplification of

[a]viz. The presence of significant Bohlmann bands in the IR spectra of all four amines, and the absence of a lowfield (of δ 3.7) C-12b proton resonance in the NMR spectra of **4a**, **b** and **5a**. The value of δ 3.90 for the C-12b proton resonance in **5b** may suggest comparable amounts of *cis*- and *trans*-fused systems in equilibrium.



Scheme 7.



Scheme 8. (a) $ClCO_2CH_2Ph$–MeOH; (b) KOH; (c) MsCl–Py; (d) NaH (DMSO).

deferring chromatographic separation until after ring cleavage of the amine-acetates (**5**) and hydrolysis of the cleaved acetates (**20**) gave the cleaved alcohols (**19**) in 30% (*cis*-series) and 46% (*trans*-series) overall yields from the "kinetic" mixture of lactam-esters (**2**). Inversion of configuration at C-12b during the cleavage reactions was deduced from transformations analogous to those previously used in the cyanamide work. The *cis*-**23a**- and *trans*-**23b**-series *seco*-mavacurine-type urethane derivatives were prepared *via* the respective mesylates (**22**) and compared with the product of C/D ring opening in the amine (**9**) with benzyl chloroformate and methanol. Again the lower field position of the methoxy singlet in the NMR-spectrum of the *trans*-series product (**23b**) (δ 3.43) allowed ready distinction from the *cis*-series product **23a** (δ 3.07) which was identical with the single isomer derived from the amine (**9**).

We shall shortly be reporting the use of a novel and again highly stereospecific chloroformate ester induced cleavage reaction as a key step in the total synthesis of (±)-C-mavacurine.[4]

EXPERIMENTAL

M.ps were measured on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were carried out by Mr. D. Flory and his staff at the University Chemical Laboratory, Cambridge. IR spectra were recorded on a Perkin–Elmer 257 grating spectrometer and, unless otherwise stated, run as solns in $CHCl_3$. Absorptions are given in cm^{-1}. NMR spectra were recorded on a Varian HA 100 spectrometer and were run as solns in $CDCl_3$ except where otherwise stated, absorptions in ppm being quoted on the δ scale using, unless otherwise stated, TMS ($\delta = 0$) as internal standard. Coupling constants J are given in Hz. Mass spectra were recorded on an AEI MS 12 or MS 30 spectrometer. High resolution mass spectra were measured on an AEI MS 30 or MS 902 spectrometer. UV spectra were recorded on a Pye Unicam SP 800B (qualitative spectra) or SP 1800 spectrometer (quantitative spectra) and were run in 95% EtOH soln. Absorption data are quoted in nm and only for those spectra which differ significantly from that of a typical 2,3-disubstituted indole.[10] Preparative layer chromatography was carried out on 20 × 20 cm plates coated to a thickness of 0.3 nm in Merck Alumina F_{254} or 1 mm in Kieselgel PF_{254}. Short column chromatography[11] was carried out on Reeve Angel silica gel/CT with binder. Organic solns were dried over $MgSO_4$ unless otherwise stated. All reactions were performed under an atmosphere of N_2.

2 - *Ethoxycarbonyl* - 4 - *oxo* - 1,2,3,4,6,7,12,12*b* - *octahydroindolo*[2,3 - *a*]*quinolizine* (2)

(a) *Sodium cyanide-dimethyl sulphoxide method.* Dry NaCN (2.94 g, 60 mmol) and **1**[5] (11.55 g, 37 mmol) were dissolved in dry DMSO (180 ml), and the stirred soln heated in a preheated oil bath maintained at 150° for 3 hr. The DMSO was removed *in vacuo*, and the residue partitioned between water (300 ml) and CH_2Cl_2 (100 ml, ×3). The combined organic layers were washed with water (100 ml), dried and concentrated. Recrystallisation from benzene of the resulting solid gave pure *cis*-epimer (2*S*, 12b*S*) *lactam-ester* **2a** (4.70 g, 50%) as prisms, m.p. 224–225° (Found: C, 69.47; H, 6.71; N, 9.12. $C_{18}H_{20}N_2O_3$ (312.4) requires: C, 69.21; H, 6.45; N, 8.97%), ν_{max} 3460 (indole NH), 1725 (ester C=O) and 1630 (lactam C=O), δ 1.26 (3H, t, *J*7 CH_2–CH_3), 4.15 (2H, q, *J*7, O–CH_2–CH_3), 4.67–5.26 (2H, m, Ar–CH–N–CHH), 6.99–7.56 (4H, m, Ar–H) and 8.66 (1H, br s, indole NH), *m/e* (rel intensity) 312 (M^+, 100), 311 (18), 283 (22), 267 (12) and 239 (38).

Evaporation of the mother liquors and recrystallisation of the residue from EtOH–water (using charcoal) gave largely the *trans*-epimer (2*S*, 12b*R*) *lactam-ester* (**2b**) (1.70 g, 18%) as prisms, m.p. 223–225° dec., ν_{max} 3458 (indole NH), 1728 (ester C=O) and 1633 (amide C=O), δ 1.26 (3H, t, *J*7, CH_2–CH_3), 4.19 (2H, q, *J*7, O–CH_2–CH_3), 4.80–5.28 (2H, m, Ar–CH–N–CHH), 6.98–7.55 (4H, m, Ar–H) and 8.15 (1H, br s, indole NH), *m/e* 312.1479 (M^+; $C_{18}H_{20}N_2O_3$ requires: 312.1474).

(b) *Hydrolysis/decarboxylation method.* To a soln of **1** (6.00 g, 15.6 mmol) in abs. EtOH (300 ml) was added a soln of KOH (2.4 g) in EtOH (160 ml) and water (80 ml). After standing at room temp. for 1 hr the soln was poured into water (700 ml), acidified with 5% HCl (80 ml) and extracted with CH_2Cl_2 (100 ml, ×4). The combined organic layers were washed with sat. NaClaq (100 ml) and dried. Removal of the solvent *in vacuo* gave a solid which was dissolved in dry dimethylformamide (120 ml), and the stirred soln heated at 100° for 1.5 hr. The dimethylformamide was removed *in vacuo* and the residue partitioned between EtOAc (200 ml) and 5% $NaHCO_3$aq (70 ml). The organic layer was separated, washed with sat. NaClaq (50 ml) and dried. Removal of the EtOAc *in vacuo* gave the *lactam-ester* **2** (4.62, 95%), the kinetically favoured mixture, as a pale yellow solid.

2 - *Hydroxymethyl* - 4 - *oxo* - 1,2,3,4,6,7,12,12*b* - *octahydroindolo* - [2,3 - a]*quinolizine* (3)

$NaBH_4$ was added in *ca* 0.2 g portions to a stirred soln heated under reflux of **2a** (4.70 g, 15 mmol) in MeOH (270 ml) to which NaOH (0.5 g) had been added, until the tlc (silica, using 10% MeOH in $CHCl_3$ as eluant) indicated complete consumption of starting material (*ca* 1.5 hr). The cooled soln was then partially concentrated *in vacuo* to *ca* 150 ml before being poured into water (800 ml). After standing at 0° for 18 hr, filtration gave pure *cis*-epimer (2*S*, 12b*S*) *alcohol* **3a** (3.25 g, 75%) as a monohydrate, which was dried at 60° 0.2 mm Hg over P_2O_5 and recrystallised from acetone to give needles, m.p. 227.5–229.5° (Found: C, 71.22; H, 6.81; N, 10.30. $C_{16}H_{18}N_2O_2$ (270.3) requires: C, 71.09; H, 6.71; N, 10.36%), ν_{max} (Nujol) 3400 (indole NH), 3280 (OH) and 160.3 (C=O), δ ($(CD_3)_2SO$) 3.20–3.50 (3H, m, including CH_2–OH), 4.58–5.06 (3H, m, Ar–CH–N–CHH and OH), 6.84–7.48 (4H, m, Ar–H) and 10.88 (1H, br, s, indole NH), *m/e* 270 (M^+) and 239.

The filtrate from the separation of the *cis*-epimer was adjusted to pH 2 with 5% HCl and continuously extracted with benzene for 2 days. The benzene soln was dried and concentrated *in vacuo* to give the *trans*-epimer (2*S*, 12b*R*) *alcohol* **3b** (0.65 g, 16%) as prisms, m.p. 199–200.5° (from acetone) (Found: C, 71.09; H, 6.88; N, 10.18. $C_{16}H_{18}N_2O_2$ requires: C, 71.09; H, 6.71; N, 10.36%), ν_{max} (Nujol) 3400 (indole NH), 3280 (OH) and 1603 (C=O), δ ($(CD_3)_2SO$) 3.43 (2H, t, *J*5, CH_2OH), 4.60–5.02 (3H, m, Ar–CH–N–CHH and OH), 6.87–7.46 (4H, m, Ar–H) and 10.91 (1H, br, s, NH), *m/e* 270(M^+) and 239.

2(S) - *Methanesulphonyloxymethyl* - 4 - *oxo* - 1,2,3,4,6,7,12,12b(S) - *octahydroxindolo*[2,3 - a]*quinolizine* (**6a**)

To a soln of freshly distilled methanesulphonyl chloride (1.32 g, 11.5 mmol) in dry pyridine (30 ml) was added **3a** (1.60 g, 5.9 mmol) and the resulting soln left to stand for 2.5 hr. The pyridine soln was then partially concentrated *in vacuo* to *ca* 15 ml before adding dropwise over 5 min to crushed ice and water (150 ml). The mixture was stirred overnight, filtered, and the ppt dried to give the *mesylate* **6a** (1.98 g, 96%) as a pale yellow solid which afforded needles, m.p. 216–217.5° (from EtOAc) (Found: C, 58.16; H, 6.02; N, 7.73. $C_{17}H_{20}N_2O_4S$ (348.4) requires: C, 58.60; H, 5.79; N, 8.04%), ν_{max} (Nujol) 3380 (indole NH), 1621 (C=O), 1362 and 1183 (SO), δ ($(CD_3)_2SO$) 3.17 (3H, s, CH_3S), 3.94–4.32 (2H, m, CH_2O), 4.68–5.05 (2H, m, Ar–CH–N–CHH), 6.85–7.50 (4H, m, Ar–H) and 10.89 (1H, br, s, indole NH), *m/e* (rel intensity) 348.1140 (M^+, 100; $C_{17}H_{20}N_2O_4S$ requires: 348.1144), 347 (38), 252 (13), 251 (20), 239 (35), 169 (51), 168 (20), 156 (22), 144 (15), and 143 (14).

2,12 - *Methano* - 4 - *oxo* - 1,2,3,4,6,7,12,12b - *octahydroindolo*[2,3 - a] - *quinolizine* (7) *and* 2(S), 3 - *Methano* - 4 - *oxo* - 1,2,3,4,6,7,12,12b(S) - *octahydroindolo*[2,3 - a]*quinolizine* (**8a**)

The mesylate **6a** (696 mg, 2 mmol) was added to a stirred suspension of NaH (240 mg, 10 mmole) in dry THF and the mixture heated under reflux for 5 hr. After the careful addition of water (5 ml), the mixture was filtered through celite and the solvents removed *in vacuo*. The residue was subjected to column chromatography on alumina (Woelm, neutral, activity II, 20 g) using a 5% soln of EtOAc in benzene as eluant. The first eluted product was the *lactam* **7** (310 mg, 61%) obtained as needles, m.p. 166.5–168.5° (from benzene–petrol). (Found: C, 76.26; H, 6.33; N, 10.92. $C_{16}H_{14}N_2O$ (252.3) requires: C, 76.17; H, 6.39; N, 11.10%), ν_{max} (KBr) 1660 (C=O), δ 6.90–7.60 (m, Ar–H), *m/e* (rel intensity) 252 (M^+, 100), 195 (7), 194 (29), 181 (26) and 180.0819 (84; $C_{13}H_{10}N$ requires: 180.0813), λ_{max} (log ϵ) 231 (4.47) and 289 (3.80).

The second eluted product was the *lactam* **8a** (90 mg, 18%), m.p. 302–304° (from benzene) (Found: C, 75.96; H, 6.36; N, 10.82. $C_{16}H_{14}N_2O$ (252.3) requires: C, 76.17; H, 6.39; N, 11.10%), ν_{max} (Nujol) 3210 (indole NH) and 1608 (C=O), δ ($(CD_3)_2SO$) 0.77–1.00 (2H, m, CH_2–CH–C=O), 4.66–5.01 (2H, m, Ar–CH–N–CHH), 6.88–7.56 (4H, m, Ar–H) and 10.92 (1H, br, s, indole NH), *m/e* (rel intensity) 252 (M^+, 93), 251 (36), 170 (78) and 169 (100), λ_{max} 228, 274, 281 and 290.

2,12 - *Methano* - 1,2,3,4,6,7,12,12b - *octahydroindolo*[2,3 - a]*quinolizine* (**9**)

LAH (190 mg, 5 mmol) was added to a stirred soln of **7** (150 mg, 0.6 mmol) in dry THF (60 ml) and the mixture heated under reflux for 1 hr. After careful addition of water (5 ml) to the cooled mixture the resulting emulsion was poured into sat. potassium sodium tartrate soln (30 ml) and the organic layer separated. The aqueous phase was extracted with EtOAc (10 ml, ×2) and the combined organic layers washed with sat. NaClaq (20 ml), dried (Na_2SO_4) and the solvents removed *in vacuo*. Purification of the resulting oil by preparative layer chromatography on alumina using EtOAc as eluant gave the *amine* **9** (72 mg, 51%) as a colourless oil which solidified on standing. Trituration with ether yielded a white solid, m.p. 100–101°, from which sublimation at 78°/0.2 mm Hg gave a sample m.p. 101–102.5°, (Found: C, 80.38; H, 7.50; N, 11.95. $C_{16}H_{18}N_2$ (238.3) requires: C, 80.63; H, 7.61; N, 11.76%), δ 0.27 (1H, m, N–CHH–CH_2–CH), 3.75 (1H, m, Ar–CH–N), 3.98 (1H, dd, *J* 13,2, N(a)–CHH), 4.30 (1H, dd, *J*13,3, N(a)–CHH) and 7.01–7.66 (4H, m, Ar–H), *m/e* (rel intensity) 238 (M^+, 100), 237 (8), 195 (42), 194 (57), 182 (25), 180.0819 (83; $C_{13}H_{10}N$ requires: 180.0813), 168 (11), 167 (12), 158 (15) and 154(14), λ_{max} (log ϵ) 234 (4.51), 289 (3.85) and 294.5sh (3.83).

1,7' - *Methano* - 3 - *oxo* - 2',3',6',7',8',8a' - *hexahydrospiro*[*indoline* - 2, - 1' - (5'H) - *indolizine*] (**11**)

A soln of **9** (70 mg, 0.29 mmol) in 2% AcOH (4 ml) was added to a suspension of pre-reduced Adams catalyst (90 mg) in water (4 ml) and the mixture stirred under an *oxygen* atmosphere for 60 hr. After filtration the mixture was basified with 5% $NaHCO_3$aq (15 ml) and extracted with EtOAc (10 ml, ×3). The combined organic layers were washed with sat. NaClaq (10 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a brown solid which was immediately dissolved in sat. methanolic HCl (10 ml) and the resulting soln heated under reflux for *one* min cooled, and poured into water (25 ml). After basifying the soln with solid $NaHCO_3$ it was extracted with EtOAC (10 ml, ×3) and the combined organic extracts washed with sat. NaClaq (10 ml) and dried (Na_2SO_4). Concentration *in vacuo* gave a gum which was purified by preparative layer chromatography on alumina using EtOAc as eluant gave the *pseudoindoxylamine* **11** (33 mg, 44%) as a yellow-green gum which solidified on standing at −15°. Sublimation of a sample at 90°/0.4 mm Hg gave a green amorphous solid, m.p. 136–137°, ν_{max} 1685 (C=O), δ 6.60–7.70 (m, Ar–H), *m/e* 254.1407 (M^+; $C_{16}H_{18}N_2O$ requires: 254.1419), λ_{max} (log ϵ) 241.5 (4.38), 262(4.01) and 415 (3.56).

3 - *Hydroxy* - 1,7' - *methano* - 2',3',6',7',8',8a' - *hexahydrospiro*[*indoline* - 2,1' - (5'H) - *indolizine*] (**10**)

$NaBH_4$ (25 mg) was added to a stirred soln of **11** (30 mg, 0.12 mmol) in abs EtOH (20 ml) and the soln heated under reflux for 2 hr. The cooled mixture was poured into water (30 ml) and extracted with $CHCl_3$ (10 ml, ×3). The combined organic layers were washed with sat. NaClaq (10 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave the *benzylic alcohol* **10** (30 mg, 99%) as a gum. Preparative layer chromatography of a portion on alumina using MeOH as eluant gave a pure sample, ν_{max} 3580 (OH), δ 6.50–7.50 (m, Ar–H), *m/e* 256.1575 (M^+; $C_{16}H_{20}N_2O$ requires: 256.1575) and 239.1560 ($C_{16}H_{19}N_2$ requires: 239.1547), λ_{max} 217 and 262.

Action of dilute sulphuric acid on 3 - *hydroxy* - 1,7' - *methano* - 2',3',6',7',8',8a' - *hexahydrospiro*[*indoline* - 2,1' - (5'H) - *indolizine*] (**10**).

A soln of **10** (30 mg, 0.12 mmol) in 0.5 N H_2SO_4 (10 ml) was heated at 80° for 40 min, cooled and poured into 5% $NaHCO_3$aq (20 ml). The soln was extracted with $CHCl_3$ (10 ml, ×3) and the combined organic layers washed with sat. NaClaq (10 ml) and dried (Na_2SO_4). Removal of the $CHCl_3$ *in vacuo* gave a gum which was purified by preparative layer chromatography on alumina using EtOAc as eluant to give the *amine* **9** (10 mg, 36%)

as an oil which solidified on standing. Trituration with ether gave a white solid, m.p. 100–101°, the spectroscopic (and tlc) properties of which were identical to those obtained earlier for this compound.

2 - *Acetoxymethyl* - 1,2,3,4,6,7,12,12b - *octahydroindolo*[2,3 - a]*quinolizine* (**5**)

LAH (0.55 g, 14 mmol) was added in one portion to a stirred, ice-cooled soln of **2** ("kinetic" mixture from hydrolysis/decarboxylation sequence, 967 mg, 3.1 mmol) in dry THF (70 ml) and the mixture heated under reflux for 1 hr. The cooled mixture was carefully poured into sat. potassium sodium tartrate soln (40 ml) and extracted with EtOAc (20 ml, ×4). The combined organic layers were washed with brine (30 ml), dried (Na_2SO_4), and the solvents removed *in vacuo* to give **4** as a pale yellow solid (0.79 g). The product was dissolved in dry THF (50 ml) and Et_3N (2 ml), cooled to 0°, and acetyl chloride (0.53 ml, 7.4 mmol) added dropwise to the stirred soln. Stirring was then continued at room temp for 3 hr before the mixture was partially concentrated *in vacuo*, and the residue partitioned between water (40 ml) and EtOAc (25 ml, ×3). The combined organic layers were washed with sat. NaClaq (30 ml), dried (Na_2SO_4), and the EtOAc removed *in vacuo*. The residue (1.04 g) was subjected to short column chromatography on silica (100 g) using a 20% soln of MeOH in EtOAc as eluant to give the *amine-acetates* **5** as pale yellow foam. The first eluted product was the *cis*-epimer (2*R*, 12b*S*) (**5a**) (329 mg, 36%), ν_{max} 3470 (indole NH), 2850, 2810, 2755 (*trans*-quinolizidine) and 1726 (C=O), δ 2.08 (3H, s, CH_3), 3.97 (2H, d, *J*6, CH_2–O), 6.98–7.52 (4H, m, Ar–H) and 8.04 (1H, br, s, indole NH), *m/e* (rel intensity) 298.1682 (M^+, 100; $C_{18}H_{22}N_2O_2$ requires: 198.1681), 197.1612 (97; $C_{18}H_{21}N_2O_2$ requires: 197.1602), 225 (28), 223 (19), 197 (34), 184 (13), 170 (22), 169 (27), 156 (19), 154 (10), 144 (10) and 143 (11).

The second eluted product was the *trans*-epimer (2*R*, 12b*R*) (**5b**) (487 mg, 53%), ν_{max} 3470 (indole NH), 2850, 2810, 2760 (*trans*-quinolizidine) and 1728 (C=O), δ 2.09 (3H, s, CH_3), 3.90 (1H, m, Ar–CH–N), 4.12 (2H, d, *J*7, CH_2O), 6.98–7.52 (4H, m, Ar–H) and 8.02 (1H, br, s, indole NH), *m/e* (rel intensity) 298.1654 (M^+, 100; $C_{18}H_{22}N_2O_2$ requires: 198.1681), 297.1587 (99; $C_{18}H_{21}N_2O_2$ requires: 197.1602), 225(20), 223(26), 197(30), 184(12), 170(22), 169(23), 156(32), 154(10), 144(10) and 143(11).

2(R) - *Hydroxymethyl* - 1,2,3,4,6,7,12,12b(S) - *octahydroindolo*[2,3 - a]*quinolizine* (**4a**)

To a soln of **5a** (340 mg, 1.1 mmol) in MeOH (20 ml) was added a soln of KOH (0.5 g) in water (5 ml). After 0.5 hr the mixture was poured into water (100 ml) and extracted with EtOAc (30 ml, ×4). The combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and partially concentrated *in vacuo* to *ca* 10 ml and left to stand at 0°. Filtration gave the *amine-alcohol* **4a** (242 mg, 83%) as a very pale yellow amorphous solid, decomposing without melting above 220°, (Found on sample sublimed at 170°/0.2 mm Hg: C, 75.27; H, 7.95; N, 10.75. $C_{16}H_{20}N_2O$ (256.3) requires: C, 74.96; H, 7.87; N, 11.00%, ν_{max} (K Br) 3400 (indole NH), 3220 (OH) 2820 and 2770 (*trans*-quinolizidine), δ ($(CD_3)_2SC$) 4.51 (1H, br, s, OH (exchanged with D_2O)), 6.82–7.42 (4H, m, Ar–H) and 10.71 (1H, br, s, indole NH), *m/e* (rel intensity) 256 (m^+, 89), 255 (100), 225 (31), 223 (12), 197 (28), 184 (11), 170 (19), 169 (25), 156 (17), 154 (9), 144 (9) and 143 (11).

This epimer was found to be indistinguishable on tlc (silica, using 20% MeOH in $CHCl_3$ as eluant) from the single amine–alcohol prepared by the action of LAH on the *cis*-epimer lactam-alcohol (**3a**) (1 hr in dry THF heated under reflux followed by the usual work-up).

2(R) - *Hydroxymethyl* - 1,2,3,4,6,7,12,12b(R) - *octahydroindolo* - [2,3 - a]*quinolizine* (**4b**)

The use of **5b** as substrate in the preceding preparation gave the *amine–alcohol* **4b** (81%) as a very pale yellow amorphous solid, (Found on sample sublimed at 170°/0.2 mm Hg: C, 74.73; H, 8.10; N, 10.93. $C_{16}H_{20}N_2O$ (256.3) requires: C, 74.96; H, 7.87; N, 11.00%), ν_{max} (K BR) 3290 (indole NH and OH), 2810, 2780 and 2760 (*trans*-quinolizidine), δ ($(CD_3)_2SO$) 4.49 (1H, br, s, OH (exchanged with D_2O)), 6.80–7.41 (4H, m, Ar–H) and 10.82 (1H, br, s, indole NH), *m/e* (rel intensity) 256 (M^+, 85), 255 (100), 225 (25), 223 (14), 197 (25), 184 (9), 170 (15), 169 (17), 156 (14), 154 (9), 144 (8) and 143 (9).

This epimer was found to be indistinguishable on tlc (silica, using 20% MeOH in $CHCl_3$ as eluant) from the single amine–alcohol correspondingly prepared by the action of LAH on the *trans*-epimer lactam-alcohol (**3b**).

3 - *Cyano* - 6(R) - *hydroxymethyl* - 8(R) - *methoxy* - 1,2,3,4,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**12a**)

To a stirred soln of **4a** (122 mg, 0.48 mmole) in dry THF (10 ml) and dry MeOH (2 ml, 49 mmole) was added anhyd Na_2CO_3 (0.3 g) and then cyanogen bromide (71 mg, 0.67 mmol). The mixture was stirred for 1 hr at room temp before partitioning between water (30 ml) and EtOAc (10 ml, ×3). The combined organic extracts were washed with sat. NaClaq (15 ml) and dried. Removal of the solvents *in vacuo* gave a solid which was recrystallised from EtOAc–light petroleum b.p. 60–80° to give the *cyanamide–alcohol* **12a** (128 mg, 86%) as prisms, m.p. 182–183°, (Found: C, 68.79; H, 7.07; N, 13.12. $C_{18}H_{23}N_3O_2$ (313.4) requires: C, 68.98; H, 7.39; N, 13.41%), ν_{max} 3445 indole NH), 3300 (OH) and 2208 (NCN), δ 3.19 (3H, s, CH_3O), 3.50 (2H, d, *J*6, CH_2–O), 4.52 (1H, dd, *J*10,3, Ar–CH–O), 7.00–7.54 (4H, m, Ar–H) and 8.61 (1H, br, s, indole NH), *m/e* (rel intensity) 313 (M^+, 100), 298 (63), 282 (31), 280 (7), 250 (9), 186 (23), 173 (20), 160 (10), 158 (33), 156 (25), 154 (9), 144 26), 143 (53) and 130 (21).

3 - *Cyano* - 6(R) - *hydroxymethyl* - 8(S) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**12b**)

The use of **4b** as substrate in the immediately preceding preparation gave the *cyanamide–alcohol* **12b** in an 88% yield as prisms, m.p. 234–237° (from EtOAc–light petroleum b.p. 60–80°), (Found: C, 68.89; H, 7.26; N, 13.29. $C_{18}H_{23}N_3O_2$ (313.4) requires: C, 68.98; H, 7.39; N, 13.41%), ν_{max} 3453 (indole NH), 3300 (OH) and 2210 (NCN), δ 3.21 (3H, s, CH_3O), 3.40–3.60 (2H, m, CH_2O), 4.72 (1H, dd, *J*10,6, Ar–CH–O), 6.96–7.58 (4H, m, Ar–H) and 8.93 (1H, br, s, indole NH), *m/e* (rel intensity) 313 (M^+, 100), 298(63), 282 (35), 280 (19), 250 (10), 186 (25), 173 (29), 160 (24), 158 (48), 156 (35), 154 (14), 144 (37), 143 (79) and 130 (31).

Simplified preparation of 3 - *cyano* - 6 - *hydroxymethyl* - 8 - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**12**)

Cyanogen bromide (1.55 g, 14.6 mmol) was added to stirred soln in dry THF (200 ml) and dry MeOH (43 ml 1.06 mmol), containing suspended anhyd Na_2CO_3 (9 g), of **4**, prepared from **2** ("kinetic" mixture, 4.35 g, 13.9 mmol) as described in the preparation of **5**. After stirring for 1 hr at room temp the mixture was poured into water (200 ml) and extracted with EtOAc (70 ml, ×3). The combined organic layers were washed with brine (50 ml), dried, and the solvents removed *in vacuo*. The residue (a pale yellow foam, 4.4 g) was subjected to short column chromatography on silica (350 g) using a 2% soln of MeOH in EtOAc as eluant. The first eluted product was the *cis*-series epimer (6*R*, 8*R*) *cyanamide–alcohol* **12a** (1.33 g, 30.5%), which was followed by the *trans*-series epimer (6*R*, 8*S*) *cyanamide-alcohol* **12b** (2.03 g, 46.5%).

3 - *Cyano* - 6(R) - *methanesulphonyloxymethyl* - 8(R) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**13a**)

To an ice-cooled soln of **12a** (300 mg, 0.96 mmol) in dry pyridine (3 ml) was added methanesulphonyl chloride (0.15 ml, 1.92 mmol). After standing at room temp for 1 hr the mixture was diluted with CH_2Cl_2 (35 ml) and washed successively with 25 mls of each 5% HCl, water, 5% $NaHCO_3$aq and sat. NaClaq and dried. Removal of the CH_2Cl_2 *in vacuo* gave a white foam which was crystallised by dissolution in 95% EtOH followed by partial concentration *in vacuo*. Filtration gave the *mesylate* **13a** (318 mg, 85%) as prisms, m.p. 140–141°, (Found: C, 58.49; H, 6.61; N, 10.78; S, 8.25. $C_{19}H_{25}N_3O_4S$ (391.5) requires: C, 58.30; H, 6.39; N, 10.73; S, 8.19%), ν_{max} 3450 (indole NH), 2208 (NCN), 1370 and 1172 (SO), δ 3.02 (3H, s, CH_3S), 3.21 (3H, s, CH_3O), 4.13 (2H, d, *J*6, CH_2–O), 4.50 (1H, br, d, *J*10, Ar–CH–O), 7.00–7.62 (4H, m, Ar–H) and 8.39 (1H, br, s, indole NH), *m/e* (rel intensity) 391

(M^+, 77), 376(68), 360(21), 359(18), 296(29), 295(92), 282 (13), 280 (47), 264 (31), 250 (42), 196 (32), 194 (50), 180 (72), 168 (95), 167 (64), 160 (12), 158 (51), 156 (53), 154 (36), 144 (77), 143 (100) and 130 (45).

3 - *Cyano* - 6(R) - *methanesulphonyloxymethyl* - 8(S) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**13b**)

The use of **12b** as substrate in the immediately preceding preparation gave the *mesylate* **13b** in an 89% yield as prisms, m.p. 162–164° dec from EtOH, (Found: C, 58.31; H, 6.45; N, 10.56; S, 8.13. $C_{19}H_{25}N_3O_4S$ (391.5) requires: C, 58.30; H, 6.39; N, 10.73; S, 8.19%), ν_{max} 3450 (NH), 2205 (NCN), 1373 and 1175 (SO), δ 2.91 (3H, s, CH_3S), 3.23 (3H, s, CH_3O), 4.04 (2H, d, *J*5, CH_2–O), 4.69 (1H, dd, *J*8,9, Ar–CH–O), 7.05–7.56 (4H, m, Ar–H) and 8.08 (1H, br, s, indole NH), *m/e* (rel intensity) 391 (M^+, 100), 376(72), 360 (22), 359 (14), 296 (10), 295 (8), 282 (11), 280 (12), 264 (11), 250 (10), 196 (9), 194 (9), 180 (11), 168 (18), 167 (11), 160 (21), 158 (37), 156 (32), 154 (10), 144 (26), 143 (61) and 130 (19).

3 - *Cyano* - 6(R),9 - *methano* - 8(R) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**15a**)

NaH (prewashed, 10 mg, 0.41 mmol) was added as a suspension in dry THF (0.5 ml) to a stirred soln of **13a** (107 mg, 0.27 mmol) in dry DMSO (2.5 ml) and stirring continued at room temp for 0.5 hr before the mixture was poured into water (25 ml). The solid which separated was extracted into EtOAc (10 ml, ×3) and the combined organic layers washed with water (10 ml), sat. NaClaq (10 ml), and dried. Removal of the EtOAc *in vacuo* gave a white foam which was crystallised from ether to give the *seco-cyanamide* **15a** (67 mg, 83%) as rosettes, m.p. 157 1/2–158°, (Found: C, 73.08; H, 7.03; N, 13.96. $C_{18}H_{21}N_3O$ (295.4) requires: C, 73.19; H, 7.17; N, 14.22%), ν_{max} 2210 (NCN), δ ($CHCl_3$ internal standard) −0.08 (1H, td, *J*13,13,2, N–CHH–CH_2–CH), 3.21 (3H, s, CH_3O), 4.06 (1H, dt, *J*13,2,2, N(a)–CHH), 4.35 (1H, dd, *J*13,2, N(a)–CHH) and 4.75 (1H, dd, *J*9,2, Ar–CH–O), *m/e* (rel intensity) 295.1678 (M^+, 100; $C_{18}H_{21}N_3O$ requires: 295.1684), 280 (89), 264 (25), 241 (7), 236 (18), 226 (64), 212 (9), 210 (12), 196 (9), 194 (16), 183 (21), 182 (27), 180.0814 (46; $C_{13}H_{10}N$ requires: 180.0813), 168 (19), 167 (15), 156 (8), 154 (10), 144 (8) and 143 (10), λ_{max} (log ϵ) 229 (4.54), 280 (3.82) and 286 sh (3.81).

3 - *Cyano* - 6(R),9 - *methano* - 8(S) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**15b**)

The use of **13b** as substrate in the immediately preceding preparation with the modification that stirring was continued at 50° for 1 hr gave the *seco-cyanamide* **15b** in an 80% yield as rosettes, m.p. 141–143° from ether, (Found: C, 72.38; H, 7.41; N, 14.23. $C_{18}H_{21}N_3O$ (295.4) requires: C, 73.19; H, 7.17; N, 14.22%), ν_{max} 2210 (NCN), δ $CHCl_3$ as internal standard) −0.03 (1H, td, *J*13,13,2, N–CHH–CH_2–CH), 3.58 (3H, s, CH_3O), 4.05 (2H, d, *J*2, N(a)–CH_2) and 4.76 (1H, dd, *J*10,7, Ar–CH–O), *m/e* (rel intensity) 295.1683 (M^+, 100; $C_{18}H_{21}N_3O$ requires: 295.1684), 280 (38), 264 (23), 241 (14), 236 (28), 226 (55), 212 (16), 210 (12), 195 (9), 194 (10), 183 (28), 182 (27), 180.0816 (25; $C_{13}H_{10}N$ requires: 180.0813), 168 (16), 167 (9), 156 (6), 154 (6), 144 (7) and 143 (8), λ_{max} (log ϵ) 231 (4.51), 280 sh (3.81), 286 (3.83) and 293 sh (3.78).

Action of cyanogen bromide and methanol on 2,12 - *methano* - 1,2,3,4,6,7,12,12b - *octahydroindolo*[2,3 - a]*quinolizine* (**9**)

To a stirred soln of **9** (58 mg, 0.24 mmol) in dry THF (10 ml) and dry MeOH (1 ml, 25 mmol) was added anhyd Na_2CO_3 (0.2 g) and then cyanogen bromide (37 mg, 0.35 mmol) and stirring continued for 1 hr at room temp before the mixture was poured into water (20 ml) and extracted with EtOAc (10 ml, ×3). The combined organic layers were washed with sat. NaClaq (20 ml), dried, and the solvents removed *in vacuo* to give a gum which was purified by preparative layer chromatography on silica using a 10% soln of EtOAc in CH_2Cl_2 as eluant yielding the *seco-cyanamide* **16** (60 mg, 83%) as a white foam, the spectroscopic properties of which were identical to those previously obtained for the *cis*-series epimer *seco*-cyanamide (**15a**).

3 - *Benzyloxycarbonyl* - 6 - *hydroxymethyl* - 8 - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**19**)

To a stirred soln of the crude (pre-column) mixture **5**, prepared from **2** ("kinetic" mixture, 1.50 g, 4.8 mmol), in dry THF (70 ml) and dry MeOH (15 ml, 0.37 mmol) was added anhyd Na_2CO_3 (2 g) and then benzyl chloroformate (2.5 g, 14.6 mmol). After stirring for 2 hr at 55° a soln of KOH (2 g) in 50% aqueous MeOH (20 ml) was added and stirring continued at room temp for a further 2 hr before the mixture was poured into water (150 ml) and extracted with EtOAc (50 ml, ×3). The combined organic layers were washed with sat. NaClaq (50 ml), dried, and the solvents removed *in vacuo*. The residue was subjected to short column chromatography on silica (200 g) using a 1% soln of MeOH in EtOAc as eluant. The first eluted product was the *cis*-series epimer *urethane–alcohol* **19a** (0.61 g, 30%), obtained as a white foam, ν_{max} 3460 (indole NH), 3300 (OH) and 1670 (C=O), δ 3.18 (3H, s, CH_3O), 4.43 (1H, m, Ar–CH–O), 5.26 (2H, ABq, *J*13, CH_2Ph), 7.00–7.85 (9H, m, Ar–H) and 8.42 (1H, br, s, indole NH), *m/e* (rel intensity) 422.2206 (M^+, 51; $C_{25}H_{30}N_2O_4$ requires: 422.2205), 390 (1), 345 (2), 287 (2), 255 (49), 186 (11), 174 (7), 173 (7), 158 (14), 156 (13), 144 (14), 143 (26), 130 (9) and 91 (100).

The second eluted product was the *trans*-series epimer *urethane–alcohol* **19b** (0.93 g, 46%) obtained as prisms, m.p. 160–161° from acetone–light petroleum b.p. 40–60°, (Found: C, 71.05; H, 7.28; N, 6.49. $C_{25}H_{30}N_2O_4$ (422.5) requires: C, 71.06; H, 7.16; N, 6.63%), ν_{max} 3460 (indole NH), 3300 (OH) and 1667 (C=O), δ (CD_3OD) 3.17 (3H, s, CH_3O), 4.55–4.95 (3H, m, Ar–CH–O and CH_2Ph), 6.80–7.60 (9H, m, ArH), *m/e* (rel intensity) 422 (M^+, 52), 390 (2), 345 (3), 287 (3), 255 (40), 186 (12), 174 (8), 173 (7), 158 (15), 156 (10), 144 (17), 143 (29), 130 (9) and 91 (100).

3 - *Benzyloxycarbonyl* - 8(S)6(R) - (*epoxymethano*)1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**21**)

To a stirred soln of **4b** (164 mg, 0.64 mmol) in dry THF (30 ml) was added anhyd Na_2CO_3 (0.5 g) and then benzyl chloroformate (0.4 g, 2.3 mmol). After stirring for 2 hr at 55° the mixture was poured into 10% KOHaq (50 ml) and extracted with EtOAc (20 ml, ×3). The combined organic layers were washed with water (20 ml), brine (20 ml), and dried. Removal of the solvents *in vacuo* gave an oil which was purified by short column chromatography on silica (50 g) using a 10% soln of EtOAc in CH_2Cl_2 as eluant to give the *urethane–ether* **21** (197 mg, 79%) as prisms, m.p. 185–187° from ether, (Found: C, 73.84; H, 6.75; N, 6.99. $C_{24}H_{25}N_2O_3$ (390.5) requires: C, 73.82; H, 6.71; N, 7.18%), ν_{max} 3455 (indole NH) and 1689 (C=O), δ 3.44 (1H, dd, *J*9,1,5, Ar–CH–O–CHH), 3.99 (1H, dd, *J*9,6,5, Ar–CH–O–CHH), 4.23, 4.38 (1H, m, s, Ar–CH–O), 5.19 (2H, m, CH_2Ph), 6.92–7.50 (9H, m, Ar–H) and 8.53 (1H, br, s, indole NH), *m/e* (rel intensity) 390 (M^+, 64), 255 (22), 168 (8), 156 (9), 144 (29), 143 (100), 130 (10) and 91 (93).

Action of benzyl chloroformate and methanol on (1) 2 - *hydroxymethyl* - 1,2,3,4,6,7,12,12b - *octahydroindolo*[2,3 - a]*quinolizine* (**4**) *and on* (2) 2 - *acetoxymethyl* - 1,2,3,4,6,7,12,12b - *octahydroindolo* - [2,3 - a]*quinolizine* (**5**)

(1) Benzyl chloroformate (0.1 g) was added to a stirred soln of *cis*-**4a**- and *trans*-**4b**-epimers (in separate experiments) (30 mg, 0.12 mmol) in dry THF (10 ml) and dry MeOH (0.5 ml) containing suspended anhyd Na_2CO_3 (0.1 g). After stirring for 2 hr at 55° the mixture was pouned into 10% KOHaq (20 ml) and extracted with EtOAc (10 ml, ×3). The combined organic layers were washed with sat. NaClaq (10 ml), dried, and concentrated *in vacuo*. Examination of the residue by tlc comparison on silica using EtOAc as eluant with the urethane–alcohols (**19**) showed that the less polar isomer **19a** was present only in the product derived from the *cis*-epimer amine–alcohol (**4a**) and the more polar isomer (**19b**) was present only in that derived from the *trans*-epimer amine–alcohol (**4b**). Also present in the latter crude reaction product was a compound indistinguishable (also in the eluant systems 10% MeOH in $CHCl_3$ and 20% EtOAc in $CHCl_3$) from **21**.

(2) The *cis*-**5a**- and *trans*-**5b**-epimers (in separate experiments) were used as substrate in the immediately preceding experiment as far as the stirring at 55°, after which a soln of KOH (0.2 g) in 50% aqueous MeOH (2 ml) was added and stirring continued at room temp for 1 hr. Thereafter following of the previous experimental details was resumed, and examination of the residue by tlc showed that the less polar **19a** was present only in the

product derived from the *cis*-epimer **5a** and the more polar isomer **19b** was present only in that derived from the *trans*-epimer **5b**.

3 - *Benzyloxycarbonyl* - 6(R) - *methanesulphonyloxymethyl* - 8(R) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**22a**)

To an ice-cooled soln of **19a** (114 mg, 0.27 mmol) in dry pyridine (2 ml) was added methanesulphonyl chloride (0.05 ml, 0.74 mmol). After standing at room temp for 1 hr the mixture was diluted with CH_2Cl_2 (30 ml) and washed successively with 20 mls of each of 5% HCl, water 5% $NaHCO_3$aq and sat. NaClaq and dried. Removal of the CH_2Cl_2 *in vacuo* gave the *mesylate* **22a** (134 mg, 99%) as a white foam, ν_{max} 3455 (indole NH), 1690 (C=O), 1363 and 1180 (S–O), δ 2.80 (3H, s, CH_3S), 3.16 (3H, s, CH_3O), 4.42 (1H, m, Ar–CH–O), 5.22 (2H, m, CH_2Ph) 7.01–7.72 (9H, m, Ar–H) and 8.30 (1H, br, s, indole NH), *m/e* (rel intensity) 500.1976 (M^+, 8; $C_{26}H_{32}O_6S$ requires: 500.1981), 404 (3), 333 (4), 270 (31), 269 (35), 255 (3), 225 (14), 223 (6), 186 (12), 168 (5), 156 (8), 144 (6), 143 (9), 107 (43) and 91 (100).

3 - *Benzyloxycarbonyl* - 6(R) - *methanesulphonyloxymethyl* - 8(S) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**22b**)

The use of **19b** as substrate in the immediately preceding preparation gave the *mesylate* **22b** in a 99% yield as a white foam, ν_{max} 3455 (indole NH), 1681 (C=O), 1360 and 1177 (S–O), δ 2.76 (3H, s, CH_3S), 3.20 (3H, s, CH_3O), 4.50–4.88 (3H, m, Ar–CH–O and CH_2Ph), 6.80–7.65 (9H, m, Ar–H) and 8.22 (1H, br, s, indole NH), *m/e* (rel intensity) 500.1983 (M^+, 13; $C_{26}H_{32}N_2O_6S$ requires: 500.1981), 404 (3), 333 (5), 270 (3), 269 (3), 186 (9), 168 (4), 158 (5), 156 (4), 144 (6), 143 (12), 107 (20) and 91 (100).

3 - *Benzyloxycarbonyl* - 6(R),9 - *methano* - 8(R) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino* 5,4 - b *indole* (**23a**)

NaH (prewashed, 12 mg, 0.5 mmol) was added as a suspension in dry THF (0.5 ml) to a stirred soln of **22a** (126 mg, 0.25 mmol) in dry DMSO (3 ml) and stirring continued at room temp for 1 hr. The mixture was then diluted with water (25 ml) and extracted with EtOAc (10 ml, ×3). The combined organic layers were washed with water (10 ml), sat. NaClaq (10 ml), and dried. Removal of the EtOAc *in vacuo* gave the *seco-urethane* **23a** (91 mg, 89%) as a white foam, ν_{max} 1690 (C=O), δ −0.52 (1H, m, N–CHH–CH_2–CH), 3.07 (3H, s, CH_3O), 4.32 (1H, br, d, *J*9, Ar–CH–O), 5.25 (2H, ABq, *J*14, CH_2Ph) and 7.01–7.70 (9H, m, Ar–H), *m/e* (rel intensity) 404.2093 (M^+, 100; $C_{25}H_{28}N_2O_3$ requires: 404.2100), 389 (10), 373 (5), 372 (8), 313 (10), 281 (31), 269 (8), 237 (14), 226 (21), 196 (6), 194 (20), 182 (12), 180.0812 (32; $C_{13}H_{10}N$ requires: 180.0813), 168 (16) and 91 (98), λ_{max} (log ϵ) 231 (4.50), 279 (3.80) and 285 sh (3.79).

3 - *Benzyloxycarbonyl* - 6(R),9 - *methano* - 8(S) - *methoxy* - 1,2,3,4,5,6,7,8 - *octahydro* - 9H - *azecino*[5,4 - b]*indole* (**23b**)

The use of **22b** as substrate in the immediately preceding preparation with the modification that stirring was continued at 50° gave the *seco-urethane* **23b** in an 88% yield as a white foam, ν_{max} 1683 (C=O), δ −0.79 (1H, m, N–CHH–CH_2–CH), 3.43 (3H, s, CH_3O), 4.68 (1H, t, *J*8, Ar–CH–O), 5.22 (2H, ABq, *J*14, CH_2Ph) and 7.02–7.60 (9H, m, Ar–H), *m/e* (rel intensity) 404.2093 (M^+, 57; $C_{25}H_{28}N_2O_3$ requires: 404.2100), 389 (8), 372 (31), 313 (5), 281 (45), 269 (15), 237 (31), 226 (9), 196 (11), 194 (26), 182 (12), 180 (30), 168 (9) and 91 (100), λ_{max} 231, 281 sh, 286 and 291 sh.

Action of benzyl chloroformate and methanol on 2,12 - *methano* - 1,2,3,4,6,7,12,12b - *octahydroindolo*[2,3 - a]*quinolizine* (**9**)

Benzyl chloroformate (0.5 g) was added to a stirred soln of **9** (20 mg, 0.08 mmol) in dry THF (5 ml) and dry MeOH (0.5 ml) containing suspended anhyd Na_2CO_3 (50 mg). After stirring for 1 hr at room temp the mixture was poured into 10% KOHaq (10 ml) and extracted with EtOAc (5 ml, ×3). the combined organic layers were washed with water, sat. NaClaq (10 ml of each) and dried. Removal of the solvents *in vacuo* gave an oil which was purified by preparative layer chromatography on silica using a 10% soln of EtOAc in CH_2Cl_2 as eluant to give the (6*R*, 8*R*) *seco-urethane* **23a** (26 mg, 77%) as a white foam, the spectroscopic properties of which were identical to those previously obtained for the *cis*-series epimer *seco*-urethane **23a**.

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