A Novel Synthesis of (±)-Harmacine and (±)1,2,3,4,6,7,12,12b-Octahydroindole[2,3-*a*]quinolizine

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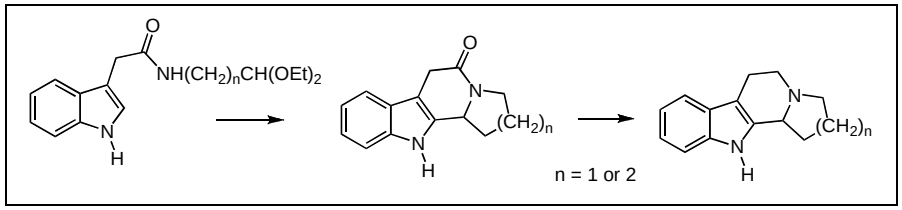
Received March 25, 2007



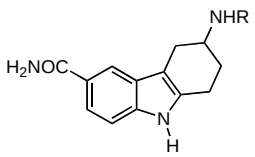
A three-step synthesis of (±)-harmacine is described from the readily available 4,4-diethoxybutan-1-amine *via* an acid-mediated acyl iminium ion cyclisation. The synthesis of the homologous (±)1,2,3,4,6,7,12,12b-octahydroindole[2,3-*a*]quinolizine from 5,5-diethoxypentan-1-amine is also described. Although similar, the two systems required very different cyclisation conditions.

J. Heterocyclic Chem., **44**, 1459 (2007).

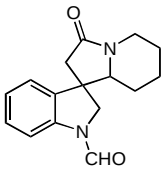
INTRODUCTION

We have had a long-standing interest in the pharmacology of conformationally restricted tryptamines, as exemplified by the identification of PU 46905 1 [1] that led to the discovery of the anti-migraine drug, Frovatriptan 2 [2].

As an alternative form of the ethylamine conformational restriction, the alkaloid harmacine 3 (Scheme I) attracted our attention. Harmacine has been used as an intermediate both for a number of indole alkaloids [3] and to a series of dopamine/serotonin receptor ligands [4]. We were particularly interested in developing a library of harmacine analogues for pharmacological evaluation. For this we wanted a facile synthesis that gave the potential for the introduction of additional functionality. The proposed methodology *via* an acid-mediated acyliminium ion cyclisation is shown in Scheme I. For library synthesis, the intermediate lactams **5** and **6** are attractive in that they contain two sites for substitution, the indole N and the indole acetate CH_2. Additional functionality can be included by using substituted indole acetic acids or by using our previously published substituted 4,4-diethoxybutan-1-amines and 5,5-diethoxypentan-1-amines [5].



1 R = H
2 R = Me



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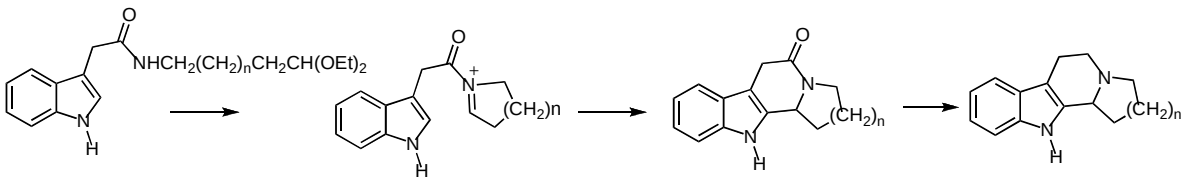
Literature precedent for the proposed cyclisations to **5** and **6** was not encouraging. The reported attempted cyclisation of **8** in formic acid gave none of the desired lactam **6**, but gave a spiro product **9**, believed to be produced by spiro-cyclisation to the indolenine followed by reduction and formylation [6]. However, cyclisations under non-reducing conditions had not been investigated and therefore this reaction warranted further investigation. The synthesis of the lactam **6** in 11 steps from quinoline has been reported, but with little exploration of its chemistry [7].

RESULTS AND DISCUSSION

Compounds **7** and **8** were prepared from indole-3-acetic acid and 4-aminobutyraldehyde diethylacetal and 5-aminovaleraldehyde diethylacetal [6,8,9] (95% yield), respectively, *via* the N-hydroxysuccinimide active ester.

Scheme I



7 n = 1
8 n = 2

5 n = 1
6 n = 2

3 n = 1
4 n = 2

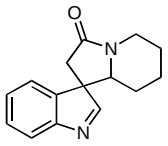
For the cyclisation of **7** to **5**, various acids in CH_2Cl_2 solution at ambient temperatures were investigated, including TFA (4 equivs., 1 h 43% yield), ethereal HCl (15 equivs, 1 h, 8% yield), $AlCl_3$ (0.5 equiv., 4 h, 55% yield; 1 equiv., 30 min, 41% yield; 1 equiv., 3 h, 71% yield; 2 equiv. 30 min, 62% yield), $TiCl_4$ (1 equiv., 4 h, 42% yield) and $BF_3.OEt_2$ (1 equiv., 2 h, 91% yield). The yields quoted are based upon an LC/MS analysis of the reaction mixtures quenched with MeOH. From these trial reactions, $BF_3.OEt_2$ appeared to be the best.

The synthesis was repeated on a preparative scale (0.01 *M*) using $BF_3.Et_2O$ (1 equiv.) to give **5** in a yield of 92%. The reduction of **5** to give the desired (±)-harmicine 3 was effected with either AlH_3 (from LAH and H_2SO_4 in THF) (81% yield) or BH_3 followed by acid hydrolysis (87% yield). Thus, the 5-membered iminium ion cyclisation gave the desired (±)-harmicine in 3 steps in an overall yield of 69%.

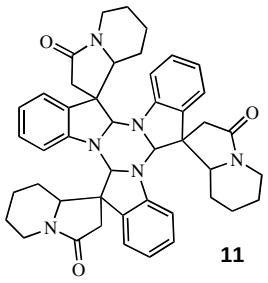
Following the above success, the cyclisation was attempted on **8**. The formic-acid mediated cyclisation was reported to give the spiro product **9** as a mixture of diastereomers [6]. Although the diastereomers were separated, no definitive assignment of stereochemistry was made. It was hoped that alternative, non-reducing conditions would result in the formation of alternative products.

The acid-induced cyclisations investigated for **7** were applied to **8**, but there was no evidence of any 2,3-fused product **6** being formed. In the majority of cases, LC/MS indicated the formation of dimers and trimers of the intermediated acyliminium ion. However, the use of TMS-triflate (5 equiv., 70% yield by LC/MS), or better TFA (6 equivs., 91% yield by LC/MS), gave a mixture of products with a molecular weight from EI MS consistent with the formation of a cyclic product. The TFA reaction was repeated on a preparative scale (6mM) and, after basification, a product was isolated as an off-white, amorphous solid (92% theoretical yield).

Reverse phase analytical LC/MS suggested that the solid was a mixture of at least two products in >98% purity and the CI HRMS was consistent with the formation of the 3,3-spiroindolenine 10. However, the ^1H NMR spectra in both $CDCl_3$ and d^6-DMSO were very complex and no meaningful ^{13}C NMR in $CDCl_3$ could be obtained. It was not possible to separate the products preparatively on either SiO_2 or Al_2O_3 using any of the normal phase solvent systems investigated. However, FAB MS of the product gave an MH^+ peak at 721, indicative that the indolenine **10** may have trimerised. 3,3-Dimethyl-indolenine has been reported to trimerise to form a hexahydro-1,3,5-triazine, which exist mainly as the triazine at room temperature in neutral solvents, but as the monomeric indolenine either at elevated temperature or in TFA [10,11]. Running the NMR of the isolated solid in TFA simplified the ^1H NMR spectrum, giving a distinctive two singlets at δ 9.26 and 9.17 in a ratio of 1:1.4, assigned as the protonated imine C-H protons of each diastereomer of **10**. The ^{13}C NMR spectrum in TFA was also simplified, showing 29 signals, most of which were closely paired signals with again a ~1:1.4 ratio, corresponding to diastereomeric mixture of the TFA salt of **10**.



10



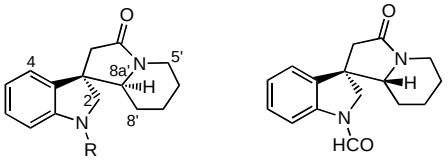
11

If the isolated solid were the trimer **11**, it would have nine stereogenic centres and would probably exist as a multitude of isomers, which could explain the complex nature of the NMR spectrum of the isolated solid. In addition, the previously reported trimer of 3,3-dimethyl-indolenine exists as approximately 15% of the indolenine in neutral solution at room temperature, presumably in equilibrium with the trimer [10]. In fact, in the DMSO spectrum of the putative solid **11**, two small imine CH peaks can be seen at δ 8.35 and δ 8.27, the comparative integration with the total aromatics suggesting 15% of **10** being present. This complex nature of **11** could also explain the failed attempts at purification and crystallization. Thus although there is no direct evidence of the solid to be the trimer **11**, the spectroscopic properties are consistent with the proposed structure.

In the reported formic acid cyclisation of **8** to **9**, the authors proposed that **10** was an intermediate, though no evidence was presented [6]. In order to investigate this, the putative trimer **11** was heated under reflux in formic acid, under which conditions **11** would be expected to revert to the monomer **10**, and then to be reduced and formylated. LC/MS indicated the formation of a new mixture of products consistent with the formation of the formamide **9** as a mixture of diastereomers. The diastereomers were readily separable by normal phase chromatography on a preparative scale to give the two isomers as oils.

The ^1H NMR of these isomers was consistent with the NMR's reported for the two isomers **9a** and **9b** [6]. A key difference between **9a** and **9b** is that the bridgehead 8a' proton of the indolizidine sits very close to one of the 2-indoline protons for **9b**, whereas for **9a** it is very close to the 4-indoline proton. From a more detailed NMR analysis of the more polar isomer **9b**, the bridgehead 8a' proton was identified as the dd at δ 3.41, coupled to both protons on position 8'. From NOE experiments, irradiation

of this 8a' proton showed a strong NOE with the 2-indoline proton at δ 4.24, together with the adjacent 8' equatorial proton on the indolizidine ring plus a weaker interaction with the axial 5' proton adjacent to the indolizidine N. There was no NOE interaction with the 4-indoline proton. Thus the more polar isomer **9b** is conclusively assigned the stereochemistry 3S,8a'R/ 3R,8a'S.



9b R = CHO
12 R = H

9a

In the original publication [6], the separated spiroindolines **9** were hydrolysed with picric acid. The less polar isomer did not give a crystalline picrate, however the more polar isomer did. In the text, it was stated that the picrate of the indoline **12** had been formed. However, in the experimental section, the calculated analytical data was presented for the picrate salt of **10**, and hence it was registered as such in the ACS registry as number 61774-69-4. The quoted CHN analysis data fitted equally well for both the picrate salt of **10** and **12**. In order to clarify which product had been formed, the more polar isomer **9b** was hydrolysed with picric acid and as reported, a highly crystalline picrate was obtained. Mass spectral (MH^+ 243 daltons) and NMR analyses confirmed that the structure is that of the picrate of the spiroindoline **12** and not that of the spiroindolenine **10**.

Assuming that the solid **11** is the hexahydro-triazine, possible conditions for its conversion to the 2,3-fused lactam **6** were investigated. It is well known that 3,3-dialkylindolenines can undergo acid-catalysed rearrangements, often under very mild conditions, to the 2,3-disubstituted indoles [12]. However, in acidic media at ambient temperatures, **11** was only converted into the indolenine **10**, which showed no evidence of rearranging. However, under the much more forcing conditions of heating with triflic acid at 100°C in dioxan for 1 h, a 58% yield of **6** was obtained. Reduction of the lactam **6** using alane, as described for **5**, gave the required quinolizidine **4** in a 71% yield.

Having converted the acetal **8** to the putative trimer **11**, and then to the lactam **6**, the direct cyclisation of **8** to **6** was investigated. Heating **8** in dioxan with triflic acid did, indeed, give the lactam **6** in a 47% isolated yield. Thus alkaloid **4** was successfully prepared from **8** in a three-step synthesis in an overall yield of 33%, or by a four-step synthesis in an overall yield of 38%.

In conclusion, this work illustrates an interesting difference between the intramolecular cyclisations of 5- and 6-membered cyclic iminium ions. Acid treatment of the acetal **7** gave directly the fused lactam **5** with no intermediate spiro-lactam being identified. Therefore, assuming the expected mechanism [11], if the spiro-lactam did form, this must have rearranged immediately to the fused product. In contrast, for acetal **8**, it was found that the spirolactam **10** was unexpectedly stable and required very much more forcing conditions to effect the rearrangement to the fused lactam **6**.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on a Bruker AM-400 spectrometer using Me_4Si as internal standard. All solvents and reagents were of commercial grade and used without purification. All evaporations of solvents were carried out under reduced pressure. All compounds and crude reaction mixtures were analysed by LC/MS using an HP1050 LC system operating under reverse phase using a 3.3cm x 4.6mm ID, 3um ABZ+PLUS column with a 5 min. run, starting with 0.1% formic acid + 10mM ammonium acetate and finishing with acetonitrile + 0.05% formic acid, with a UV detection range of 215 to 330nm. MS detection used a Waters ZQ mass spectrometer and all products were 98% pure. HRMS measurements were performed with a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer, equipped with a Z-spray interface and the elemental composition was calculated using MassLynx v4.0

Synthesis of *N*-(4,4-diethoxybutyl)-2-(3-indolyl)acetamide (7). DCC (4.1 g, 0.02 mol.) was added in one portion to a stirred solution of 3-indolylacetic acid (3.5 g, 0.02 mol.) and HOSu (2.3 g, 0.02 mol.) in EtOAc (150 mL) at ambient temperatures under Argon. After stirring for 6 h., a solution of 4,4-diethoxybutan-1-amine (ex. Aldrich, 90% pure) (3.4 mL, 0.02 mol.) in EtOAc (20 mL) was added in one portion. The reaction mixture was stirred over night. Et_2O (200 mL) was then added and the precipitated DCU collected by filtration, and washed with Et_2O (100 mL). The combined filtrate was washed with 2 *N* NaOH (50 mL), H_2O (50 mL), brine (50 mL) and then dried ($MgSO_4$), filtered and concentrated by rotary evaporation to give (**7**) as a viscous orange oil (6.4 g, 100%). LC/MS indicated 97% purity. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.2Hz, 6H), 1.40-1.60 (m, 4H), 3.17-3.22 (m, 2H), 3.34-3.40 (m, 2H), 3.50-3.57 (m, 2H), 3.73 (s, 2H), 4.37 (t, J = 5.2Hz, 1H), 5.80 (brs, 1H), 7.11-7.16 (m, 2H), 7.23 (t, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 8.50 (brs, 1H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ 15.3 (CH_3), 15.3 (CH_3), 24.6 (CH_2), 30.8 (CH_2), 33.5 (CH_2), 39.2 (CH_2), 61.2 (CH_2), 102.5 (CH) 108.7 (C), 111.5 (CH), 118.6 (CH), 119.9 (CH), 122.5 (CH), 123.9 (CH), 127.0 (C), 136.5 (C), 171.7 (C). HRMS: calcd for $C_{18}H_{29}NO_3Na$ $[M+Na]^+$, 341.1841 found 341.1840.

Synthesis of (±) 2,3,11,11b-tetrahydro-1*H*-indolizino[8,7-*b*]indol-6-one (5). $BF_3.OEt_2$ (0.9 mL, 0.007 mol) was added to a stirred solution of **7** (2.15 g, 0.007 mol) in CH_2Cl_2 (80 mL) at ambient temperatures. After 2 h, H_2O (5 mL) was added and stirring was continued for 5 min. Et_2O (100 mL) was added and the solid collected, washed with H_2O (10 mL) and Et_2O (20 mL). The organic layer from the filtrate was separated, dried ($MgSO_4$) and concentrated to give a solid. The two solid samples were combined and purified by column chromatography (SiO_2,

CH_2Cl_2 to 10% MeOH/CH_2Cl_2). Trituration of the purified product with Et_2O gave **5** as a pale yellow solid (1.41 g, 92%) m.p. 221-2° (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56-1.65 (m, 1H), 1.89-2.09 (m 2H), 2.50-2.56 (m, 1H), 3.36-3.71 (m, 4H), 4.70-4.7 (m, 1H), 6.98 (t, J = 8Hz, 1H), 7.09 (t, J = 8 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.43 (d, J = 8Hz, 1H), 11.20 (brs, 1H); ^{13}C NMR and DEPT (75 MHz, d^6-DMSO): δ 22.1 (CH_2), 29.9 (CH_2), 31.9 (CH_2), 44.2 (CH_2), 55.9 (CH), 104.0 (C), 111.2 (CH), 118.0 (CH), 118.7 (CH), 121.2 (CH), 125.4 (C), 131.8 (C), 136.7 (C), 166.5 (C).

Synthesis of (±) Harmacine (3). a) with alane: cH_2SO_4 (0.08 mL, 0.0033 mol) was added, dropwise, over 5 min. to a stirred solution of LAH (3.5 mL of a 1 *M* solution, 0.0035 mol) in dry THF (10 mL) at 0°C under argon. After stirring at 0°C for 15 min, **5** (0.5 g, 0.0022 mol) was added in one portion and the reaction heated under reflux for 1 h. The reaction mixture was then cooled to 0°C and ice (0.5 g), then 2 *N* NaOH (3 mL) in THF (20 mL) was then carefully added and the reaction mixture stirred for 15 min. CH_2Cl_2 (100 mL) was then added and the solid was collected and washed with CH_2Cl_2 (2 x 50 mL). The combined organics were then evaporated *in vacuo* and the residue purified by column chromatography (Al_2O_3, CH_2Cl_2) to give the solid product (**3**) that was collected by trituration with Et_2O and dried (0.38 g, 81%) m.p. 174-5°C (lit. 173-4° [4]). LC/MS indicated 100% purity, MS 213.2 (MH$^+$); ^{1}H NMR (400 MHz, DMSO): δ 1.78-1.84 (m, 3H), 2.14-2.22 (m 1H), 2.50-2.56 (m, 1H), 2.67-2.72 (m, 1H), 2.76- 2.90 (m, 3H) 3.15-3.3.19 (m, 1H), 3.99-4.01 (m, 1H), 6.93 (t, J = 8Hz, 1H), 7.00 (t, J = 8 Hz, 1H), 7.26 (d, J = 8 Hz, 1H), 7.35 (d, J = 8Hz, 1H), 10.76 (brs, 1H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ 17.9 (CH_2), 23.5 (CH_2), 29.5 (CH_2), 46.0 (CH_2), 49.4 (CH_2), 57.0 (CH), 107.8 (C), 110.8 (CH), 118.1 (CH), 119.4 (CH), 121.4 (CH), 127.4 (C), 135.5 (C), 136.1 (C).

Synthesis of *N*-(5,5-diethoxypentyl)-2-(3-indolyl)acetamide (8). Following the procedure described for (**7**), 5,5-diethoxy-pentan-1-amine [8,9] (1.8 g, 0.01 mol) was converted to (**8**), (3.3 g, 100%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10-1.30 (m, 8H including t, J = 7.2Hz), 1.30-1.42 (m, 2H) 1.50-60 (m, 2H), 3.17 (q, 2H, J = 6.8Hz), 3.40-3.51 (m, 2H), 3.55-3.63 (m, 2H), 3.73 (s, 2H), 4.38 (t, J = 5.2Hz, 1H), 5.73 (brs, 1H), 7.13-7.17 (m, 2H), 7.23 (t, J = 8 Hz, 1H), 7.41 (d, J = 8 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 8.52 (brs, 1H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ 15.3 (CH_3), 22.0 (CH_2), 29.3 (CH_2), 33.2 (CH_2), 33.5 (CH_2), 39.5 (CH_2), 61.1 (CH_2), 102.8 (CH) 108.8 (C), 111.5 (CH), 118.6 (CH), 119.9 (CH), 122.5 (CH), 123.9 (CH), 127.0 (C), 136.5 (C), 171.6 (C).

Synthesis of the putative trimer (11). A solution of (**8**) (2.0 g, 0.006 mol) and trifluoroacetic acid (3 ml, 0.04 mol) in CH_2Cl_2 (100 mL) was stirred at ambient temperatures for 1 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in Et_2O (100 mL) and CH_2Cl_2 (50 mL), washed with 2 *M* NaOH (2 x 30 mL), H_2O (30 mL) and brine (30 mL), and then dried ($MgSO_4$). Concentration of the filtered organic solution gave an oil that solidified on stirring with Et_2O (10 mL). The solid was filtered and dried to give what is believed to be the trimer (**11**) (1.4 g, 92%). CI MS (MH$^+$) 721; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.7 – 2.0 (m), 2.5-3.7 (m), 4.0–4.7 (series of multiplets), 5.0–6.1 (series of multiplets), 6.4 – 7.4 (m), 7.65 (d), 8.09 (s), 8.15 (s). CI HRMS: calcd. for monomer 10, $C_{15}H_{16}N_2O$ 241.1340, found 241.1345. A sample (20 mg) was dissolved in TFA to form the monomer.TFA salt: ^{1}H NMR (400 MHz, TFA): δ 0.95 – 1.67 (m, 6H), 2.76 (brt J = 12 Hz 1H), 2.85 (d, J = 18 Hz, 0.6H), 3.00 (d, J = 18 Hz 0.4H), 3.13 (d, J = 18 Hz, 0.4H), 3.38 (dd, J = 1.6, 18 Hz 0.6H), 3.97 – 4.20 (m, 2H), 7.38 – 7.56 (m, 4H), 9.17 (s, 0.6H), 9.26 (s, 0.4H). ^{13}C NMR and DEPT (100 MHz, TFA): δ 24.6 (CH_2), 24.7 (CH_2), 25.0 (CH_2), 30.1 (CH_2), 30.4 (CH_2), 38.0 (CH_2), 38.5 (CH_2), 44.9 (CH_2), 45.3 (CH_2), 62.1 (C), 62.1 (CH), 62.7 (C), 67.6 (CH), 120.4 (CH), 120.7 (CH), 125.8 (CH), 127.4 (CH), 133.4 (CH), 133.5 (CH), 133.9 (CH), 134.7 (CH), 137.6 (C), 138.5 (C), 142.1 (C), 142.4 (C), 175.6 (C), 176.0 (C), 181.8 (CH), 182.3 (CH).

Synthesis of *trans*-(±)-1-formyl-1,2,6',7',8',8'a-hexa-hydro-spiro[3H-indole-3,1'(5'*H*)-indolizin]-3'(2'*H*)-one (9a) and *cis*-(±)-1-formyl-1,2,6',7',8',8'a-hexahydro-spiro[3*H*-indole-3, 1'(5'*H*)-indolizin]-3'(2'*H*)-one (9b). A solution of 11 (0.57 g, 0.00024 mol) in formic acid (20 mL), H_2O (20 mL) and Na_2CO_3 (4 g) was heated under reflux for 1h. The cooled reaction mixture was concentrated *in vacuo* to about half the volume, carefully basified with solid K_2CO_3 and the product extracted into CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$) and concentrated. The isomers were separated by column chromatography on SiO_2, starting with EtOAc with increasing quantities of MeOH to a total of 2% to give. Fraction 1: (**9a**) as an oil (0.16 g, 25%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.44 (m, 3H), 1.57-1.75 (m, 2H), 1.90-1.95 (m, 1H), 2.57 (dd, J = 5.6, 17Hz, 1H), 2.68 (brt, J = 12.4, 1H), 2.82 (dq, J = 15.6, 1.6 Hz, 1H), 3.64-3.44 (m, 1H), 3.66 (dd, J = 0.8, 12.8, 0.8 H), 3.82 (d, J = 11.2, 0.2H), 4.12-4.19 (m, 1H), 4.40 (d, J = 10.8 Hz, 0.2H), 4.48 (d, J = 12.4 Hz, 0.8H), 7.11-7.33 (m, 3.8H), 8.07 (d, J = 8 Hz, 0.2H), 8.52 (s, 0.2H), 8.91 (s, 0.8H). HRMS: calcd. for $C_{16}H_{18}N_2O_2$ 271.1447, found 271.1451. Fraction 2: (**9b**) as an oil (0.23g, 36%) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (q, J = 13 Hz, 1H), 1.24-1.38 (m, 3H), 1.71 (d, J = 13 Hz, 1H), 1.83 (d, J = 13 Hz, 1H), 2.57 – 2.72 (m, 2H), 2.79 (d, J = 17, 0.8H), 2.88 (d, J = 17Hz, 0.2H), 3.39 – 3.44 (m, 1H), 3.91 (d, J = 13 Hz, 0.8 H), 4.04 (d, J = 11 Hz, 0.2H), 4.15 – 4.26 (m, 2H), 7.09-7.33 (m, 3.8H), 8.09 (d, J = 8 Hz, 0.2H), 8.52 (s, 0.2H), 8.92 (s, 0.8H). HRMS: calcd. for $C_{16}H_{18}N_2O_2$ 271.1447, found 271.1448.

Synthesis of *cis*-(±)-1,2,6',7',8',8'a-hexahydro-spiro[3*H*-indole-3,1'(5'*H*)-indolizin]-3'(2'*H*)-one (12). A solution of (**9b**) (0.23 g, 0.00085 mol) and picric acid (60% + 40% H_2O) (0.32 g, 0.00085 mol) in isopropanol (20 mL) was heated under gentle reflux for 1 h. On cooling, the picrate salt of (**12**) deposited as orange crystals that were collected, washed with Et_2O (2 x 20 mL) and dried m pt. 209-210° (lit. 204.5-208.5° [6]). ^{1}H NMR (300 MHz, d^6-DMSO): δ 0.73-1.34 (m, 4H), 1.57 (brd, J = 13 Hz, 1H), 1.75 (brd, J = 13 Hz, 1H), 2.49 (s, 2H), 2.58-2.69 (m, 2H), 2.83 (d, J = 17 Hz, 1H), 3.52 (dd, J = 12, 3 Hz, 1H), 3.6 (d, J = 12 Hz, 1H), 3.95 (brd, J = 13 Hz, 1H), 7.20 – 7.48 (m, 4H), 8.58 (s, 2H); ^{13}C NMR and DEPT (75 MHz, d^6-DMSO): δ 23.0 (CH_2), 23.8 (CH_2), 27.0 (CH_2), 40.2 (CH_2), 41.4 (CH_2), 48.8 (C), 57.0 (CH_2), 63.9 (CH), 118.6 (CH), 125.2 (CH), 125.3 (CH), 127.6 (CH), 129.1 (CH), 136.2 (C), 139.1 (C), 141.8 (C), 160.7 (C), 170.7 (C). MS: MH$^+$ 243.

Synthesis of 1,2,3,4,12,12b-hexahydro-indolo[2,3-*a*]quinolizin-7-one (6). Method A: A solution of (**11**) (0.6 g, 0.0008 mol) and trifluoromethanesulfonic acid (0.22 mL, 0.0025 mol) in dioxan (20 mL) was heated under reflux for 1 h. On cooling to 0°C, the solvent was decanted and the residue triturated with water. The solid was collected, dried and purified by column chromatography (SiO_2; $CHCl_3$ + 2% MeOH) to give (**6**) as an off-white solid (0.35 g, 58%). A small sample was recrystallised from EtOH to give white crystals, m.p. 253-5° (lit. 254-255° [7]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30-1.40 (m, 2H), 1.62-

1.73 (m 2H), 2.84 (brd, J = 13 Hz, 1H), 2.32 (brd, J = 12.8 Hz, 1H), 2.65 (dt, J = 2.4, 12.8 Hz, 1H), 3.54 (d, J = 2.8 Hz, 2H), 4.66 (brd, J = 11 Hz, 1H), 4.76 (brd, J = 11 Hz), 6.99 (t, J = 8 Hz, 1H), 7.09 (t, J = 8 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 7.41 (d, J = 8 Hz, 1H), 11.00 (s, 1H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$/d^6-DMSO): δ 24.1 (CH_2), 25.1 (CH_2), 29.1 (CH_2), 34.1 (CH_2), 42.9 (CH_2), 56.3 (CH), 102.8 (C), 111.0 (CH), 117.7 (CH), 118.8 (CH), 121.4 (CH), 125.4 (C), 130.7 (C), 136.7 (C), 166.5 (C). HRMS: calcd. for $C_{15}H_{16}N_2O$ 241.1340, found 241.1347

Method B: A solution of (**8**) (1.77 g, 0.005 mol) and trifluoromethanesulfonic acid (0.6 mL, 0.0068 mol) in dioxan (50 mL) was heated under reflux for 2 h. Isolation of the product as described in Method A gave the lactam (**6**) (0.56 g, 47%).

Synthesis of (±)1,2,3,4,6,7,12,12b-octahydro-indole[2,3-a]-quinolizine (4). Following the procedure, Method A, described for (**3**), (**6**) (0.30 g, 0.0013 mol) was reduced with alane prepared from LAH (2 mL of a 1M solution) to give (**4**) as a pale yellow solid (0.20 g, 71%) mpt 148-150° (lit. 147-150° [13]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 – 1.63 (m, 2H), 1.68-1.78 (m, 2H), 1.91 (brd, J = 9 Hz, 1H), 2.07 (brd, J = 9 Hz, 1H), 2.39 (dt, J = 3, 11 Hz, 1H), 2.59 – 2.75 (m, 2H), 2.97 – 3.09 (m, 3H), 3.24 (d, J = 10 Hz), 7.06 – 7.15 (m, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ 21.6 (CH_2), 24.3 (CH_2), 25.8 (CH_2), 30.0 (CH_2), 53.6 (CH_2), 55.8 (CH_2), 60.3 (CH), 108.2 (C), 110.7 (CH), 118.1 (CH), 119.4 (CH), 121.3 (CH), 127.5 (C), 135.1 (C), 136.0 (C).

Acknowledgment. I am grateful to the GSK Neurology & GI CEDD for funding this research, to J. Seaman for assistance with the NMR assignment of 9b and to Prof. S. Caddick for his support and the use of his laboratory at UCL.

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