Synthesis of Indole Oxazolines; Novel 5-HT_3 Antagonists

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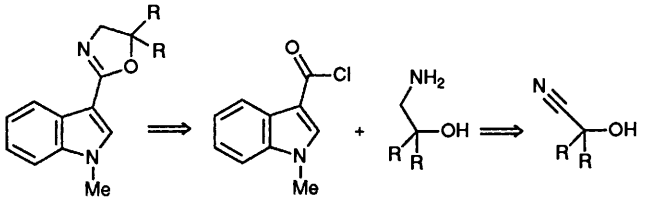
The synthesis of a novel series of spiro fused indole oxazolines is reported, the spiro centre being generated *via* addition of an azabicyclic amino alcohol to an indole imidate. The azabicyclic amino alcohol was generated from the corresponding cyanohydrin by borane reduction, which also served to protect the highly nucleophilic azabicyclic nitrogen. In the case of the unsymmetrical azabicyclic system **10**, stereocontrolled cyanohydrin formation was achieved. Selective alkylation of the indole nitrogen was facilitated by borane protection of the azabicyclic nitrogen.

Serotonin (5-HT) has been shown to be a neurotransmitter involved in a wide range of pharmacological effects, and characterisation of multiple 5-HT receptors has given impetus to the search for novel subtype selective 5-HT ligands. 5-HT receptors can be broadly classified into three types, 5-HT_1, 5-HT_2 and 5-HT_3,[1] and whilst the 5-HT_2 receptor population appears homogeneous there is ample evidence for heterogeneity within 5-HT_1 (5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c} and 5-HT_{1d}). Recent evidence suggests there may also be heterogeneity within 5-HT_3 receptors.[1] A number of 5-HT_3 antagonists have been reported and such compounds have shown activity in models thought to be predictive of therapeutic roles in the control of cancer chemotherapy induced emesis,[2] migraine,[3] schizophrenia[4] and anxiety.[5] However, to date the clinical efficacy of 5-HT_3 antagonists in all but the first indication remains unproven. As part of a programme to identify novel ligands for the 5-HT_3 receptor which would critically probe for the existence of subtypes we have prepared a series of conformationally constrained indole oxazolines **1**.[6] In this paper we report the syntheses of these compounds, encompassing a number of significant and novel features which includes stereocontrolled cyanohydrin formation and the use of borane as a protecting group for tertiary amines, allowing regioselective alkylation of the indole nitrogen.

Results and Discussions

Retrosynthetic analysis (Fig. 1) indicated that the key spirofused oxazoline **1** could be prepared from reaction of an indole acid chloride **2** with an amino alcohol **3** which could be derived from the corresponding cyanohydrin **4**. Reduction of the cyanohydrin **5**[7] derived from quinuclidin-3-one with lithium aluminium hydride gave only poor yields of the desired amino alcohol; considerable amounts of quinuclidin-3-ol were formed due to reversion of the cyanohydrin to the ketone under the basic conditions. However, the desired transformation could be achieved in high yield by reduction with three equivalents of diborane in tetrahydrofuran (THF); the product was isolated as the crystalline borane complex **6**. Formation of the adduct **6** with borane attached to the tertiary nitrogen[8] in the presence of the amino alcohol functionality is probably due to the exceptional donor properties of the quinuclidine given that the alternative bidentate adduct of borane with the amino alcohol would be expected to be very stable. The structure was initially proposed on the basis of chemical reactivity: reaction with acid chlorides yielded the amides derived from reaction with the primary amine with the borane still attached to the quinuclidine nitrogen. In addition, a detailed analysis of the ^1H and ^{13}C



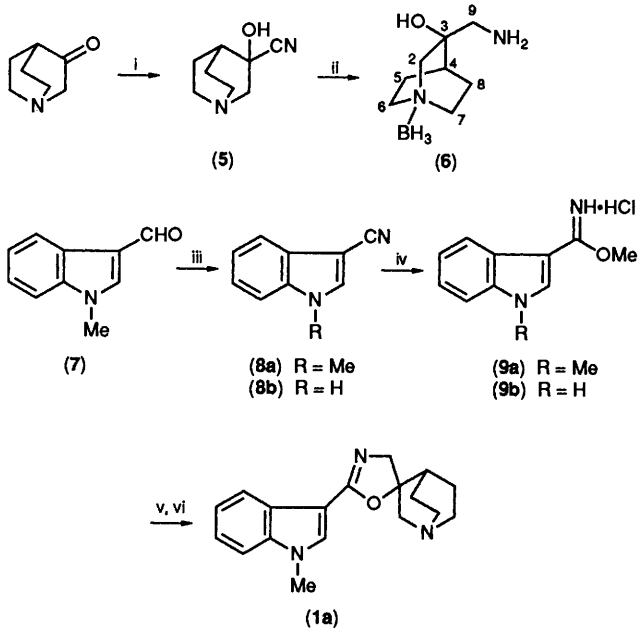
(1) (2) (3) (4)

Fig. 1.

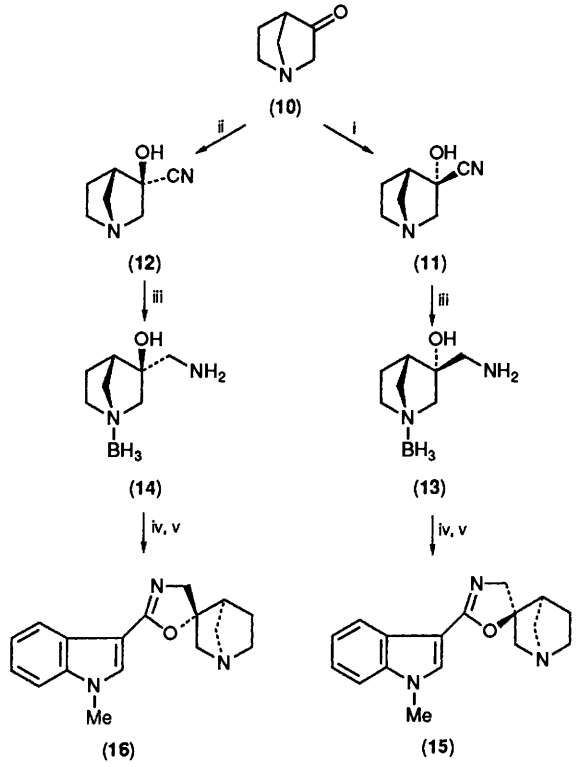
NMR data and unambiguous assignment by COSY and HCCOSY revealed that formation of the borane complex **6** caused a downfield shift of *ca.* 6 ppm for C-6 and C-7, *ca.* 4 ppm for C-2, whilst C-3 and C-9 were only slightly perturbed. This is consistent with borane complex formation with the quinuclidine nitrogen. Attempts to form the desired oxazoline ring by treating the amino alcohol **6** with 1-methylindole-3-carbonyl chloride followed by cyclisation using thionyl chloride failed to yield the desired product. Examination of the proton NMR spectrum of the crude product suggested that under the conditions employed, elimination of the tertiary alcohol had occurred to give a mixture of olefins. It was concluded that nucleophilic attack on the tertiary carbon in the cyclisation stage of the reaction was clearly disfavoured and a different strategy was investigated.

An alternative procedure involving reaction of the amino alcohols with imino ether hydrochlorides to form oxazolines was then considered since it is thought that this reaction proceeds *via* initial formation of the carbon–nitrogen bond followed by cyclisation of the alcohol onto the imino ether to form the carbon–oxygen bond.[9] Thus, commercially available 1-methylindole-3-carbaldehyde **7** was first converted into the corresponding nitrile **8a** and subsequent treatment with methanolic HCl then yielded the desired methyl imidate hydrochloride **9a**. Reaction with the amino alcohol **6** proceeded smoothly, and *in situ* removal of the borane complex with methanolic HCl gave the deprotected product **1a** as the dihydrochloride salt. The integrity of the oxazoline ring was confirmed by examination of the ^1H NMR spectra with, in particular, a pair of sharp doublets at δ 3.84 (1 H, dd, *J* 15 Hz) and δ 4.09 (1 H, d, *J* 15 Hz) corresponding to the CH_2 of the oxazoline ring.

In order to probe the stereochemical requirements for binding at the 5-HT_3 antagonist binding site, an asymmetric azabicyclic system was introduced. Treatment of an aqueous solution of the hydrochloride salt of the azabicyclic ketone **10**

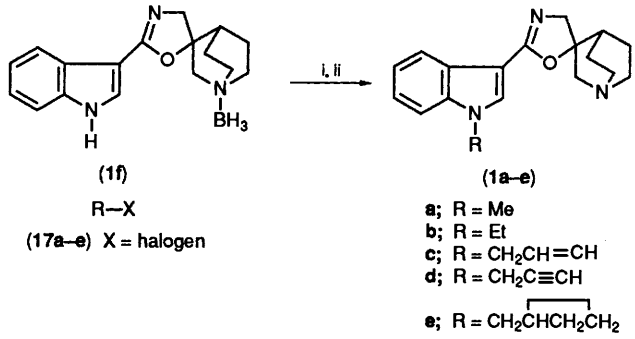


Scheme 1. *Reagents:* i, NaCN, H_2O; ii, BH_3, THF; iii, $(H_3N)_2HOP_4$, AcOH, $PrNO_2$; iv, MeOH, HCl; v, **6**, MeOH, reflux; vi, MeOH, HCl.



Scheme 2. *Reagents:* i, NaCN, H_2O, 0 °C; ii, NaCN, H_2O, 50 °C; iii, BH_3, THF; iv, **7a**, MeOH, reflux; v, MeOH, HCl.

with sodium cyanide solution whilst maintaining careful control of the temperature (< 1 °C) yielded exclusively the kinetic product, the cyanohydrin **11** (Scheme 2), in which addition of the nucleophile occurred from the less hindered face of the carbonyl group. In contrast, by allowing the temperature of the reaction to rise to 50 °C, equilibration occurred and the epimeric thermodynamic product **12** was formed exclusively (TLC analysis). These cyanohydrins were then converted to the



Scheme 3. *Reagents:* i, NaH, R-X, THF; ii, MeOH–HCl.

corresponding amino alcohols **13** and **14** by diborane reduction. The stereochemistry of the addition was confirmed by conversion into the oxazolines **15** and **16** and examination of the 1D-NOE spectra. In isomer **15** NOEs were observed from one of the oxazoline methylene protons to *endo* 4-H and 3a-H of the azabicycle, whilst in isomer **16** an NOE was only observed between *endo* 4-H of the azabicycle and 4-H of the indole.

A common advanced intermediate was required for introduction of substituents into the 1-position of the indole ring. Since direct alkylation of the indole nitrogen would be complicated by reaction with the highly nucleophilic nitrogen present in the azabicyclic system, the azabicyclic nitrogen was used as the borane complex. Indole-3-carbonitrile **8** (Scheme 3) was first converted into the imidate **9** and treated with the borane protected amino alcohol **6** to give the key intermediate indole oxazoline **1f**. The formation of the desired borane complex **1f** was confirmed by ^{13}C NMR from the expected downfield shifts of the C(6)–C(7) (*ca.* 6 ppm) and C(2) (*ca.* 4 ppm) signals of the quinuclidine. The retention of the borane results in a non-basic molecule, allowing facile purification on silica eluting with dichloromethane–methanol (9:1). Substitution on the indole nitrogen was then achieved by treatment with sodium hydride in anhydrous THF and the resulting anion was treated with a number of electrophiles **17a–e**. The borane complex was then decomposed by exposure to methanol–HCl to afford the substituted indole oxazolines **1a–e** as their dihydrochloride salts in overall yields ranging from 60–90%.

In summary a flexible and versatile methodology has been developed to allow access to a series of novel and potent 5-HT_3 antagonists. Full biological evaluation will be reported subsequently.

Experimental

General Directions.—Except where otherwise stated, the following procedures were adopted: all ^1H NMR spectra were recorded at 360 MHz on a Bruker AM 360 instrument, mass spectra with a VG 70-250 mass spectrometer using chemical ionisation (ammonia) and infrared spectra on a Perkin-Elmer 782 IR spectrophotometer. Organic solvents were purified when necessary by the methods described by D. D. Perrin, W. L. F. Armarego and D. R. Perrin, in *Purification of Laboratory Chemicals*, Pergamon, Oxford, 1986, or were purchased from the Aldrich Chemical Company (Sureseal). All solutions were dried over anhydrous sodium sulphate and evaporated on a Buchi rotary evaporator with a water bath temperature set to 40 °C or below. TLC and preparative layer chromatography were carried out on silica using plates (Merck Art No. 5719) and gravity columns (Merck Art No. 7734), or on alumina using plates (Merck Art No. 5550) and gravity columns (Woelm Alumina Act 2). M.p.s were uncorrected. Ether refers to diethyl ether.

Methyl (1-*Methylindol*-3-*yl*)*imidate Hydrochloride* **9a**.—Dry HCl gas was bubbled through a solution of 1-methylindole-3-carbonitrile **8a** (1.7 g, 11 mmol) in dry methanol (30 ml). The mixture was set aside at room temperature for 24 h and dry ether (100 ml) was added and the mixture was cooled to give **6** as colourless needles (1.8 g, 72%), m.p. 156–158 °C (Found: C, 58.9; H, 5.75; Cl, 15.7; N, 12.4. $C_{11}H_{12}N_2O$·HCl requires C, 58.80; H, 5.83; Cl, 15.78; N, 12.47%); δ_H(360 MHz; [^{2}H]$_6$-DMSO) δ 3.93 (3 H, s, NCH_3), 4.30 (3 H, s, OCH_3), 7.33 (1 H, dt, *J* 7.4 and 1.2 Hz, ArH), 7.38 (1 H, dt, *J* 8.2 and 1.6 Hz, ArH), 7.67 (1 H, d, *J* 7.8 Hz, ArH), 7.94 (1 H, dd, *J* 6.7 and 1.1 Hz, ArH) and 8.97 (1 H, s, ArH); *m*/*z* (CI) 188 (M^+).

3-*Aminomethyl*-3-*hydroxyquinuclidine–borane Complex* **6**.—A solution of borane in THF (1.0M; 266 ml, 0.26 mol) (Aldrich) was added to a stirred solution of 3-cyano-3-hydroxyquinuclidine (40 g, 0.26 mol) in THF (100 ml) under nitrogen. When the borane complex had formed (TLC monitor), further borane (2 equiv.) in THF was added (534 ml; 0.53 mol) and the reaction mixture heated at reflux for 12 h. The mixture was cooled to room temperature, ethanol (500 ml) was added slowly; the resulting solution was stirred at room temperature for 12 h. The solvent was then removed at reduced pressure and the residue was recrystallised from ethanol to afford the title compound as a white crystalline solid (32 g, 80%); m.p. 163 °C (Found: C, 56.85; H, 10.9; N, 16.65. $C_8H_{19}BN_2O$ requires C, 56.50; H, 11.26; N, 16.47; δ_H($CDCl_3$) 1–3 (6 H, br s, NH_2, OH, BH_3), 1.16–1.61 (3 H, m, CH_2, C*H*H), 1.86 (1 H, m, CH*H*), 2.05 (1 H, m, CH) and 2.4–2.97 (8 H, m, 4 × CH_2N); δ_C([^{2}H]$_6$-DMSO) 20.60 (C-5), 21.87 (C-8), 28.17 (C-4), 48.89 (C-9), 52.38 (C-7), 53.12 (C-6), 66.14 (C-2) and 70.37 (C-3); *m*/*z* (CI) 155 (M^+ − BH_3).

Treatment with HCl, then purification on basic ion-exchange resin afforded 3-aminomethyl-3-hydroxyquinuclidine; δ_C([^{2}H]$_6$-DMSO) 21.68 (C-5), 23.68 (C-8), 27.62 (C-4), 46.34 (C-7), 47.02 (C-6), 49.48 (C-9), 61.64 (m, C-2) and 70.46 (C-3).

2′-(1-*Methylindol*-3-*yl*)-*spiro*{1-*azabicyclo*[2.2.2]*octane*-3,5′(4′H)-*oxazole*} *Dihydrochloride Hydrate* **1a**.—A solution of methyl 1-methylindol-3-carboximidate hydrochloride **9a** (22.45 g, 0.1 mol) in anhydrous methanol (350 ml) was added to a stirred solution of the 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane:borane complex (20.4 g, 0.12 mol) in methanol (350 ml) under nitrogen during 75 min. The resulting solution was then heated under reflux for 12 h and allowed to cool to room temperature. Saturated methanolic HCl (50 ml) was added and the mixture heated at reflux for 12 h. The solvent was removed under reduced pressure and the residue dissolved in 2M hydrochloric acid (50 ml) and water (200 ml). The solution was washed with dichloromethane (250 ml), basified with ammonium hydroxide and extracted with dichloromethane (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and the solvent removed at reduced pressure. The residue was purified on silica and eluted with dichloromethane–methanol–NH_4OH (90:10:1) to afford the free base as a viscous oil (19.5 g, 66%); δ_H($CDCl_3$) 1.5–1.58 (3 H, m, CH_2, C*H*H), 2.01 (1 H, m, CH*H*), 2.17 (1 H, m, CH), 2.82 (2 H, m, CH_2N), 2.97 (1 H, d, *J* 15 Hz, C*H*HN), 3.0 (2 H, m, CH_2N), 3.31 (1 H, d, *J* 15 Hz, CH*H*N), 3.76 (1 H, d, *J* 12 Hz, C*H*N), 3.82 (3 H, s, NMe), 4.19 (1 H, d, *J* 12 Hz, CH*H*N), 7.22–7.35 (3 H, m, Ar), 7.63 (1 H, s, 2-H) and 8.16 (1 H, m, Ar). The oil was dissolved in methanol and a saturated solution of methanolic HCl added. The solvent was evaporated and the residue recrystallised from ethanol–ether to afford the title compound **1a**, m.p. 261–262 °C (Found: C, 56.0; H, 6.3; Cl, 18.4; N, 10.75. $C_{18}H_{21}N_3O$·2HCl·H_2O requires C, 55.96; H, 6.52; Cl, 18.35; N, 10.88%); δ_H(360 MHz, D_2O), 2.0–2.3 (3 H, m, CH_2, C*H*H), 2.46–2.56 (1 H, m, CH*H*), 2.70–2.74 (1 H, m, CH), 3.42–3.48 (2 H, m, CH_2), 3.54–3.70 (2 H, m, CH_2N), 3.84 (1 H, dd, *J* 15 and 2.1, C*H*H), 3.96 (3 H, s, NMe), 4.09 (1 H, d, *J* 15 Hz, CH*H*), 4.18 (1 H, d, *J* 12.3 Hz, C*H*HN), 4.66 (1 H, d, *J* 12.3 Hz, CH*H*N), 7.46 (1 H, dt, *J* 7.4 and 1.2 Hz, CH), 7.51 (1 H, dt, *J* 7.4 and 1.2 Hz, CH), 7.67 (1 H, dd, *J* 7.0 and 1 Hz, CH), 7.93 (1 H, dd, *J* 7.0 and 1 Hz, CH) and 8.34 (1 H, s, CH); *m*/*z* (CI) 295 (M^+, free base).

(3S*,4R*)-3-*Aminomethyl*-3-*hydroxy*-1-*azabicyclo*[2.2.1]*heptane–Borane Complex* **13**.—To a chilled solution of 1-azabicyclo[2.2.1]heptan-3-one (EP 0239309, Example 24) (2.0 g, 18 mmol) in water was added hydrochloric acid (2M, 9 ml, 18 mmol) followed by sodium cyanide (0.88 g, 18 mmol) in water. The precipitated cyanohydrin was filtered off and dried *in vacuo* (1.04 g). To a suspension of the cyano hydrin in THF (40 ml) under nitrogen, was added borane (1.0M in THF, 7.5 ml), with ice chilling, followed after 1 h by additional borane (1.0M in THF; 15 ml, 15 mmol). After 16 h under reflux, the reaction mixture was cooled, ethanol (15 ml) was added and the mixture was evaporated to dryness. Crystallisation of the residue from ethanol gave the title compound (0.85 g), m.p. 147–149 °C (Found: C, 53.8; H, 10.9; N, 17.85. $C_7H_{14}N_2O$·BH_3 requires C, 53.88; H, 10.98; N, 17.95%); δ_H(360 MHz; [^{2}H]$_6$DMSO) 1–2 (5 H, br s, BH_3, NH_2), 1.60 (3 H, br s, BH_3), 1.66–1.76 (1 H, m, C*H*H), 2.13–2.22 (1 H, m, C*H*H), 2.40 (2 H, dd, *J* 11.4 and 3.4 Hz, CH_2), 2.53 (1 H, d, *J* 13.0 Hz, C*H*H) and 2.60 (1 H, d, *J* 13.0 Hz, C*H*H), 2.61 (1 H, dd, *J* 9.8 and 3.4 Hz, C*H*HN), 2.76–2.86 (3 H, m, C*H*HN and CH_2N), 2.86–2.96 (1 H, m, CH*H*N) and 4.87 (1 H, br s, OH); *m*/*z* (CI) (155, M^+ − H).

(3R*,4R*)-3-*Aminomethyl*-3-*hydroxy*-1-*azabicyclo*[2.2.1]-*heptane–Borane Complex* **14**.—To a solution of 1-azabicyclo[2.2.1]heptan-3-one (3.15 g) in water (1.0 ml) was added, without cooling, hydrochloric acid (2M; 14 ml) followed by a solution of sodium cyanide (1.40 g) in water (4.0 ml) (temperature rose to *ca.* 50 °C). The mixture was stirred at room temperature for 30 min after which the precipitate was filtered off and dried *in vacuo* to give the cyanohydrin (3.15 g). To a chilled suspension of this cyanohydrin (3.15 g) in dry THF (50 ml) under nitrogen was added the borane–THF complex (1.0M in THF, 25 ml) dropwise. The mixture was stirred at room temperature for 1 h after which the borane–THF complex (1.0M in THF, 50 ml, 50 mmol) was added. The reaction mixture was heated at reflux for 1.5 h, cooled and ethanol (50 ml) was added. Evaporation to dryness and trituration with ether gave a colourless crystalline solid (3.47 g). Recrystallisation from ethanol gave the title compound, m.p. 130–132 °C (Found: C, 53.6; H, 10.85; N, 17.95. $C_7H_{14}N_2O$·BH_3 requires C, 53.88; H, 10.98; N, 17.95%); δ_H(360 MHz; [^{2}H]$_6$DMSO), 1.0–2.0 (5 H, br s, BH_3, NH_2), 1.56–1.66 (1 H, m, C*H*H), 1.74–1.84 (1 H, m, CH*H*), 2.39 (1 H, d, *J* 4.4 Hz, CH), 2.59 (1 H, d, *J* 8.5 Hz), 2.65 (2 H, d, *J* 8.7 Hz, CH*H*N), 2.68–2.76 (3 H, m, CH_2N, C*H*HN), 2.77–2.86 (1 H, m, CH*H*N), 3.10 (1 H, d, *J* 8.7 Hz, CH*H*N) and 4.87 (1 H, br s, OH); *m*/*z* (CI) 155 (M^+ − H).

2′-(1-*Methylindol*-3-*yl*)*spiro*{3R*,4R*)-1-*azabicyclo*[2.2.1]-*heptane*-3,5′(4′)-*oxazole*} *Dihydrochloride Hydrate* **16**.—As with the method described above, 3(R*,4R*)-3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.1]heptane–borane complex **14** (1.0 g, 6.4 mmol) was treated with methyl (1-methylindol-3-yl)imidate hydrochloride (1.2 g, 5.3 mmol), to give the title compound (1.25 g, 83%), m.p. 258–260 °C (Found: C, 54.95; H, 6.25; Cl, 19.05; N, 11.3. $C_{17}H_{19}N_3O$·2HCl·H_2O requires C, 54.85; H, 6.23; Cl, 19.05; N, 11.29%); δ_H(360 MHz; D_2O) 1.94–2.04 (1 H, m, C*H*H), 2.32–2.44 (1 H, m, C*H*H), 3.34–3.44 (2 H, m + d, *J* 5.0 Hz, C*H*HN + CH), 3.52–3.62 (2 H, m + d, *J* 10.1 Hz, 2 × C*H*HN + C*H*H), 3.75 (1 H, d, *J* 13.8 Hz, C*H*H), 3.91 (1 H, d, *J* 9.8 Hz, C*H*HN), 3.95 (3 H, s, NCH_3), 4.14 (1 H, d, *J* 13.7 Hz, C*H*HN), 4.29 (1 H, d, *J* 12.9 Hz) and 4.47 (1 H, d, *J* 12.9

Hz, CH_2N), 7.43 (1 H, dt, *J* 7.5 and 1.5 Hz, CH), 7.49 (1 H, dt, *J* 7.2 and 1.2 Hz, CH), 7.66 (1 H, d, *J* 7.8 Hz, CH), 7.98 (1 H, d, *J* 7.2 Hz, CH) and 8.26 (1 H, s, CH); *m/z* (CI) 281 (M^+, free base).

2'-(1-Methylindol-3-yl)spiro{3S,4R*)-1-azabicyclo[2.2.1]-heptane-3,5'(4'H)-oxazole} 2.1 Hydrochloride Hydrate* **15**.—As with the method described previously, 3(**S***,**4R***)-3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.1]heptane–borane complex **13** (0.35 g, 2.24 mmol) was treated with methyl(1-methylindol-3-yl)imidate hydrochloride (0.4 g, 1.8 mmol) to give the title compound (0.47 g, 92%), m.p. 215–217 °C (Found: C, 51.5; H, 6.35; Cl, 19.0; N, 10.6. $C_{17}H_{19}N_3O{\cdot}2{\cdot}1HCl{\cdot}H_2O$ requires C, 51.83; H, 6.42; Cl, 18.90; N, 10.67%); δ_H(360 MHz; D_2O) 2.20–2.32 (1 H, m) and 2.54–2.64 (1 H, m, CH_2), 3.34 (1 H, d, *J* 4.0 Hz, CH), 3.48–3.76 and 3.84–3.94 (6 H, m, CH*H*N), 3.95 (3 H, s, NCH_3), 4.17 (1 H, d, *J* 12.8 Hz, C*H*HN) 4.40 (1 H, d, *J* 12.8 Hz, CH*H*N), 7.45 (1 H, t, *J* 6.0 and 7.1 Hz, CH), 7.49 (1 H, t, *J* 6.0 and 8.2 Hz, CH), 7.66 (1 H, d, *J* 8.2 Hz, CH), 7.98 (1 H, d, *J* 7.1 Hz, CH) and 8.26 (1 H, s, CH); *m/z* (CI) 281 (M^+, free base).

2'-(1H-Indol-3-yl)spiro{1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole}–Borane Complex **1f**.—To a solution of 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane–borane complex (10.0 g, 64 mmol) in methanol (220 ml) was added dropwise a solution of methyl (1*H*-indol-3-yl)imidate hydrochloride (10.9 g, 58 mmol) in methanol (1000 ml). The reaction mixture was stirred at room temperature for 24 h under nitrogen, then stirred at 50 °C for a further 12 h. The mixture was allowed to cool and basified with ammonium hydroxide solution (*d* 0.880). The mixture was evaporated to dryness. The residue was purified by column chromatography on silica, and eluted with dichloromethane–methanol (9:1), to give the title compound (14.2 g, 50%), m.p. 262–264 °C; δ_H(360 MHz; $[^2H]_6$DMSO) 1.1–1.7 (3 H, s, BH_3), 1.69–1.75 (3 H, m) and 2.04 (1 H, s, 2 × CH_2), 2.14–2.16 (1 H, m, CH), 2.86–2.95 (2 H, m) and 3.00–3.05 (2 H, t, 2 × N-CH_2), 3.08–3.11 (1 H, d, *J* 14.2 Hz) 3.12–3.17 (1 H, d, *J* 14.2 Hz, N-CH_2), 3.80–3.84 (1 H, d, *J* 14.8 Hz) and 4.03–4.07 (1 H, d, *J* 14.7 Hz, CH_2), 7.18–7.25 (2 H, m, 2 × CH), 7.44 (1 H, dd) and 7.9 (1 H, d, 2 × CH), 8.04 (1 H, d, CH) and 11.69 (1 H, s, NH); *m/z* (CI) 281 ($M^+ - BH_3$. 20) and 271 (100%).

2'-(Prop-2-enylindol-3-yl)spiro{1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole} Dihydrochloride Dihydrate **1c**.—To a solution of 2'-(1*H*-indol-3-yl)spiro{1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole}–borane complex (0.5 g, 1.6 mmol) in THF (40 ml) under nitrogen was added sodium hydride (55% suspension in oil; 0.09 g). The mixture was stirred for 30 min and 3-bromopropane (0.24 g, 2 mmol) was added. The mixture was stirred at room temperature for a further 24 h, after which it was evaporated to dryness. The residue was dissolved in methanol and treated with anhydrous methanolic hydrogen chloride. The mixture was heated at 60 °C for 36 h and then evaporated to dryness. The residue was dissolved in water and washed with dichloromethane. The aqueous solution was basified with ammonium hydroxide solution (*d* 0.880). This solution was extracted with dichloromethane (3 × 100 ml). The organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica and elution with dichloromethane–methanol (9:1). The product was dissolved in methanol, treated with ethereal hydrogen chloride, and evaporated. Recrystallisation from propan-2-ol gave the title compound as a white crystalline solid (0.62 g, 90%), m.p. 215–217 °C (Found: C, 55.7; H, 6.55; N, 9.65. $C_{20}H_{23}N_3O{\cdot}2HCl{\cdot}2H_2O$ requires C, 55.87; H, 6.79; N, 9.76%); δ_H(360 MHz; D_2O) 2.00–2.54 (4 H, m, 2 × CH_2), 2.63 (1 H, s, CH), 3.38–3.44 (2 H, m, CH_2), 3.54–3.62 (2 H, m, CH_2), 3.75–3.79 (1 H, d), 4.00–4.04 (1 H, d, CH_2), 4.10–4.14 (1 H, d, *J* 13 Hz, C*H*H), 4.39–4.43 (1 H, d, *J* 13 Hz, CH*H*), 4.95–4.96 (2 H, d, CH_2), 5.04–5.09 (1 H, d), 5.26–5.29 (1 H, d, CH_2), 6.00–6.18 (1 H, mm, CH), 7.42–7.46 (2 H, m, 2 × CH), 7.64–7.66 (1 H, d), 7.97–7.99 (1 H, d, 2 × CH) and 8.31 (1 H, s, CH); *m/z* (CI) 329 (M^+, free base, 10%) and 96 (100).

The following compounds were also prepared using this procedure.

2'-(1-Methylindol-3-yl)spiro{1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole} dihydrochloride hydrate **1a**. Identical with material described above.

2'-(1-Ethylindol-3-yl)spiro{1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole} dihydrochloride dihydrate **1b**. M.p. 194–196 °C; δ_H(360 MHz; D_2O) 1.51–1.55 (3 H, t, *J* 7.3 Hz, CH_3), 2.08–2.27 (3 H, m), 2.78 (1 H, s, 2 × CH_2), 2.53 (1 H, m, CH), 3.44–3.46 (2 H, t), 3.61–3.66 (2 H, m, 2 × CH_2), 3.86–3.90 (1 H, d, *J* 15.1 Hz), 4.12–4.16 (1 H, d, *J* 15.1 Hz, CH_2), 4.21–4.25 (1 H, d, *J* 11.9 Hz), 4.50–4.53 (1 H, d, *J* 11.9 Hz, CH_2) and 4.36–4.42 (2 H, q 7.3 Hz, CH_2); *m/z* (CI) (M^+, free base).

2'(1-Prop-2-ynylindol-3-yl)spiro{1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole} dihydrochloride sesquihydrate **1d**. M.p. 200–220 °C (Found: C, 57.25; H, 6.1; N, 10.05. $C_{20}H_{21}N_3O{\cdot}2HCl{\cdot}1.5H_2O$ requires C, 57.27; H, 6.21; N, 10.02%); δ_H(360 MHz; D_2O) 2.09–2.28 (3 H, m), 2.50–2.52 (1 H, m, 2 × CH_2), 2.74 (1 H, m, CH), 2.97–2.99 (1 H, t, CH), 3.38–3.46 (2 H, m), 3.55–3.66 (2 H, m, 2 × N-CH_2), 3.83–3.87 (1 H, dd), 4.09–4.13 (1 H, d, N-CH_2), 4.19–4.23 (1 H, d), 4.48–4.51 (1 H, d, CH_2), 5.18–5.19 (2 H, d, N-CH_2), 7.45–7.55 (2 H, m, 2 × CH), 7.76–7.78 (1 H, dd), 7.94–7.97 (1 H, dd, 2 × CH) and 8.54 (1 H, s, CH); *m/z* (CI) 319 (M^+, free base, 15) and 225 (100).

2'-(1-Cyclopropylmethylindol-3-yl)spiro{1-azabicyclo[2.2.2]-octane-3,5'(4'H)-oxazole} dihydrochloride dihydrate **1e**. M.p. 199 °C (Found: C, 57.0; H, 7.0; N, 9.35. $C_{21}H_{31}Cl_2N_3O_3$ requires C, 56.76; H, 7.03; N, 9.46%); δ_H(360 MHz; $CDCl_3$) 0.44–0.48 (2 H, m, CH_2), 0.66–0.71 (2 H, m, CH_2), 1.39–1.43 (1 H, m, CH), 2.08–2.26 (3 H, m, CH_2 C*H*H), 2.53 (1 H, m, CH*H*), 2.77 (1 H, br s, CH), 3.43 (2 H, m, CH_2N), 3.63 (2 H, m, CH_2N), 3.87 (1 H, d, *J* 12 Hz, C*H*HN), 4.13 (1 H, d, *J* 12 Hz, CH*H*N), 4.20–4.24 (4 H, m, NCH_2, C*H*H), 4.50 (1 H, d, *J* 10 Hz, CH*H*), 7.4–7.53 (2 H, m, 5-H, 6-H), 7.75 (1 H, d, *J* 6 Hz, 7-H), 7.96 (1 H, d, *J* 6 Hz, 7-H) and 8.65 (1 H, s, 2-H); *m/z* (CI) 335 (M^+, free base).

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