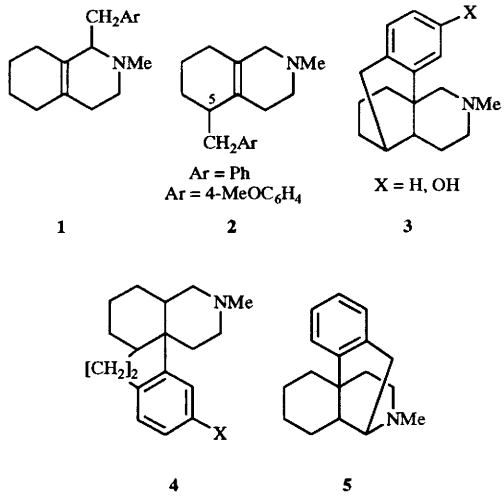
Synthesis of (±)-[4aα,4bβ,10bβ,12aβ]-9-halogeno-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho[2,1-*f*]-isoquinolines

Graham L. Patrick
Department of Chemistry and Chemical Engineering, University of Paisley, High Street, Paisley PA1 2BE, UK

Treatment of 5-(2-arylethyl)-1,2,3,4,5,6,7,8-octahydroisoquinolines with 48% HBr resulted in isomerisation of the double bond and subsequent cyclisation at position 6 of the octahydroisoquinoline ring system to give (±)-[4aα,4bβ,10bβ,12aβ]-9-halogeno-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho-[2,1-*f*]isoquinolines. The products obtained represent novel analogues of aza-D-homoestranes. No reaction was observed with the corresponding 5,5-disubstituted octahydroisoquinolines. An X-ray crystallographic study of compound **10** (X = Br) is described.

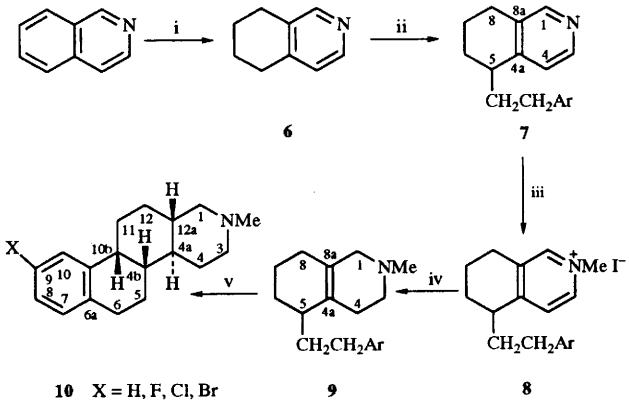
Introduction

It is well known that octahydroisoquinolines of general structure **1** cyclise under acid conditions to give morphinans.[1] However, cyclisations of octahydroisoquinolines substituted with benzyl groups at different positions of the octahydroisoquinoline ring have received less attention.[2,3] Sugimoto *et al.*[3] reported that treatment of the 5-substituted octahydroisoquinolines **2** with 48% hydrobromic acid resulted in cyclisation to give structures **3**. These compounds were tested for analgesic activity and found to be inactive. As an extension of this work, it was decided to investigate the cyclisation of 5-substituted octahydroisoquinolines of general structure **9** as a possible route to the cyclic structures **4**. Such structures could be of interest as potential analgesics since modelling studies show that the relative geometries of the aromatic ring and the basic centre are similar to those present in morphinans such as *N*-methylmorphinan **5**.



1 **2** **3** **4** **5**

Scheme 1 *Reagents:* i, Pd/C, H_2, CF_3CO_2H; ii, KNH_2, NH_3, $ArCH_2CH_2I$; iii, MeI, Et_2O; iv, $NaBH_4$, EtOH; v, HBr



6 **7** **8** **9** **10** X = H, F, Cl, Br

Results and discussion

The necessary octahydroisoquinolines **9** were synthesized as shown in Scheme 1. Isoquinoline was reduced to 5,6,7,8-tetrahydroisoquinoline **6** following a literature procedure.[4] Treatment of compound **6** with potassium amide and a series of 2-iodoethyl-substituted benzenes gave the 5-substituted tetrahydroisoquinolines **7** as well as a small yield of the 5,5-disubstituted products **11**. Purification of compounds **7** was conveniently carried out by distillation under reduced pressure while the disubstituted products **11** were purified from the distillation residue by column chromatography. Treatment of compounds **7** with iodomethane in anhydrous diethyl ether gave the methiodide salts **8** as precipitates which were treated with sodium boranuide to give compounds **9** in 60–80% yield.

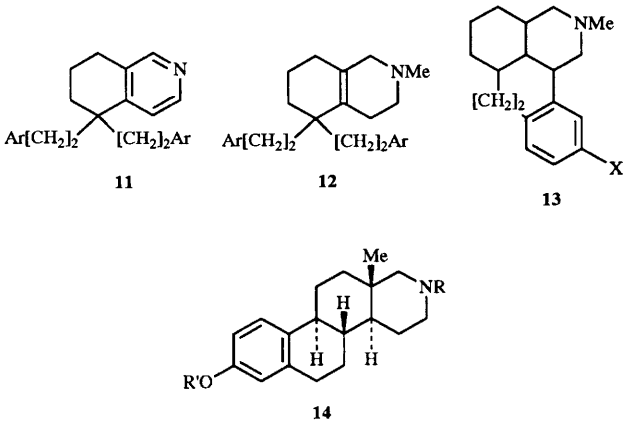
The disubstituted tetrahydroisoquinolines **11** were similarly converted into the disubstituted octahydroisoquinolines **12** in 49–72% yield.

The octahydroisoquinolines **9** were heated with 48% HBr for 16 h to give a single product as shown by TLC of the reaction mixture. Purification was carried out by distillation under reduced pressure and in certain cases by further crystallisation. Elemental analysis and mass spectra of the products obtained from these reactions showed that the products had the same relative molecular mass and elemental composition as the octahydroisoquinoline starting materials. ^1H and ^{13}C NMR analysis clearly revealed that cyclisation had taken place on the aromatic ring at a position ortho to the alkyl substituent. However, distortionless enhancement by polarisation transfer (DEPT) spectra showed the presence of three aliphatic CH signals and no aliphatic quaternary signal, thus eliminating structure **4**. The most likely compounds which would fit these results are structures **10** and **13** with the former being the more likely since cyclisation would result in a new six-membered ring compared with a seven-membered ring in structure **13**. This was

Table 1 ^{13}C, ^{1}H and 2-D NMR data for the dodecahydronaphtho[2,1-*f*]isoquinoline (**10**; X = Cl)[a]

Position	^{13}C Data	DEPT	^{1}H Data[b]	2-D COSY correlations
C-1	61.4	CH_2	1.40–1.20 m, 1-H′, 2.80–2.50 m, 1-H″	
C-3	55.8	CH_2	2.87 dm (*J* 10.0), 3-H′, 1.80–1.50 m, 3-H″	4-H′, 3-H″, 4-H″
C-4	29.0	CH_2	1.30–1.20 m, 4-H′, 1.80–1.50 m, 4-H″	
C-4a	39.6[c]	CH	1.00–0.80 m, 4a-H	
C-4b	38.7	CH	1.80–1.50 m, 4b-H	
C-5	24.1	CH_2	1.99 m, 5-H′, 1.80–1.50 m, 5-H″	6-H′, 6-H″, 5-H″, 4b-H
C-6	24.4	CH_2	2.80–2.50 m, 6-H_2	
C-6a	140.0	C		
C-7	129.9	CH	6.95 (d, *J* 8.0), 7-H	
C-8	124.9	CH	7.02 ddd (*J* 8.0, 2.0 and 1.0), 8-H	
C-9	131.0	C		
C-10	125.5	CH	7.27 br s, 10-H	
C-10a	135.0	C		
C-10b	38.0	CH	2.96 br s, 10b-H	4b-H, 11-H′
C-11	27.8	CH_2	2.41 dm (*J* 14.0), 11-H′, 1.80–1.50 m, 11–H″	10b-H, 11-H″, 12-H′
C-12	25.2	CH_2	1.40–1.20 m, 12-H′	
C-12a	41.2	CH	1.40–1.20 m, 12a-H	
NMe	45.7[c]	CH_3	2.18 s	

[a] 300 MHz, δ measured in $CDCl_3$. [b] Assignments based on chemical shifts and HETCOR experiments. [c] Tentative assignments.



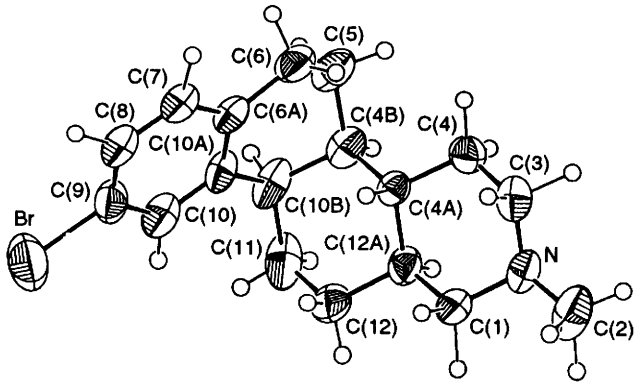


Fig. 1 X-Ray crystallographic structure of **10** (X = Br), showing the labelling of the non-H-atoms. Thermal ellipsoids are shown at 50% probability levels, except for H-atoms which are drawn as small circles

confirmed by subjecting the chloro-substituted structure (**10**; X = Cl) to 2-D homonuclear chemical-shift correlation COSY and Heteronuclear correlated (HETCOR) spectral techniques. These experiments clearly discounted structure **13** and established structure **10** as the product of the cyclisation reaction (Table 1). The bond between C-4a and C-12a was assigned as *trans*, both on the basis of the diagnostic ^{13}C chemical shifts, as well as by comparison with *trans*-*N*-methyldecahydroisoquinoline.[5] It was also argued that a *cis* stereochemistry existed between C-10b and C-4b by comparison with *cis*-decalin and other models.[6] The remaining bond between C-4a and C-4b would then have to be *trans*, as a *cis* configuration would lead to severe steric crowding.

Final confirmation for the proposed structure was provided by X-ray crystallographic analysis (Fig. 1)[7] carried out on the bromo derivative (**10**; X = Br).

The products discussed in this paper are therefore analogous to the known aza-D-homoestranes **14**,[8] having the opposite stereochemistry at C-10b. Consequently, the conformation adopted by compounds **10** is L-shaped as opposed to the flatter structure of aza-D-homoestranes (Fig. 2).

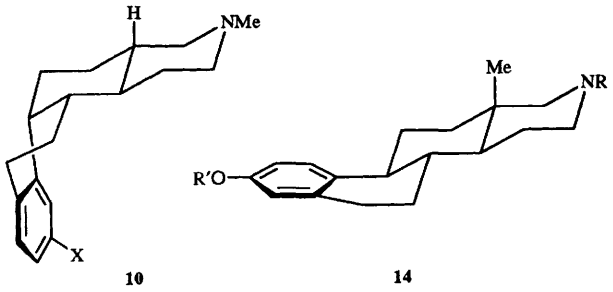
The observed product **10** could be explained by proposing an acid-catalysed isomerisation of the double bond around the isoquinoline ring to the 5,6 position as shown in Scheme 2 (**9** ⟶ **15** ⟶ **16**). One particularly interesting feature of this reaction is the absence of any cyclisation at position C-4a of the octahydroisoquinoline ring. Even when isomerisation of the double bond to C-5 is blocked by the presence of two substituents at position 5 as in structure **12**, no cyclisation was observed at C-4a and starting material was recovered. It is proposed that this direct cyclisation is inhibited by an unfavourable steric interaction arising in structure **4** between an *ortho* proton on the aromatic ring and the axial proton at position 1 of the isoquinoline ring system (Fig. 3).

It is interesting to note that the tetrahydropyridine structure **18** cyclises under the same reaction conditions to give the spiro product **19**.[9] In this case, the alternative cyclisation resulting from double-bond isomerisation is not possible. Furthermore, the lack of the second ring allows greater flexibility in the product such that the aromatic ring is less likely to interact with an axial proton in the piperidine ring.

Experimental

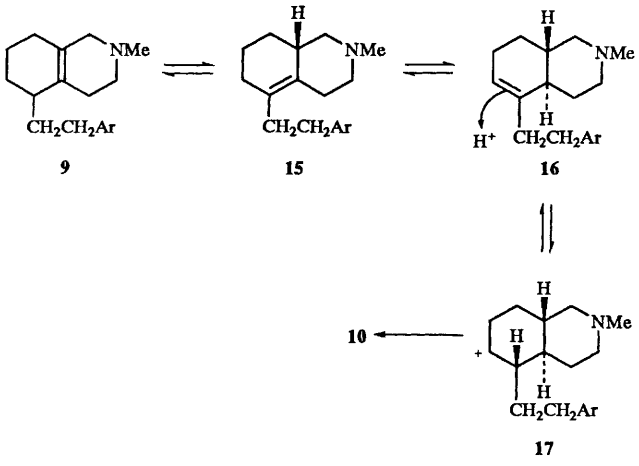
General details

Chromatography was carried out on silica gel (Merck 9385) at normal pressures. Mps (uncorrected) were obtained on a Kofler block. IR spectra were recorded as thin films or as KBr discs on a Perkin-Elmer 298 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 90, 200, 300 and 400 MHz on JEOL EX90, JEOL FX200, JEOL 300 and Bruker 400 MHz spectrometers, respectively, using $CDCl_3$ as solvent; chemical shifts are given in ppm values relative to the signal of



10 14

Fig. 2 Structural comparison of the synthetic structure **10** *versus* the azasteroid **14**



Scheme 2 Proposed mechanism for the formation of compounds **10**

Me_4Si (δ 0.00) for ^1H NMR spectra or $CDCl_3$ (δ_C 77.0) for ^{13}C NMR spectra. The number of hydrogens attached to each carbon in the ^{13}C NMR spectra was determined by DEPT techniques. *J*-Values are given in Hz to the nearest 0.5 Hz. Low-resolution and high-resolution mass spectra were recorded on a V.G. Masslab 7070F spectrometer, with only molecular ions (M^+) and major peaks being reported. The progress of all reactions was followed by TLC analysis using Kieselgel 60 F_{254} plates which were visualised by UV fluorescence (λ_{max} = 254 nm), and by staining with iodine vapour. R_f-values are quoted to the nearest 0.05. Organic solutions were dried over magnesium sulfate and concentrated under reduced pressure at not more than 40 °C. All solvents were distilled before use. Anhydrous diethyl ether was obtained by distillation from sodium/benzophenone ketal under nitrogen. Anhydrous dichloromethane was obtained by distillation from phosphorus pentaoxide and stored over molecular sieves (4 Å). Anhydrous acetone was obtained by storage of redistilled acetone over molecular sieves (4 Å). Triethylamine was distilled from potassium hydroxide pellets. Isoquinoline, (2-iodoethyl)benzene and methanesulfonyl chloride were obtained from the Aldrich Chemical Company and distilled before use. 4-Chlorophenethyl alcohol, 4-bromophenylacetic acid and 4-fluorophenethyl alcohol were obtained from the Aldrich Chemical Company and used without purification. 4-Bromophenethyl alcohol was obtained by $LiAlH_4$ reduction of 4-bromophenylacetic acid as described by Glover *et al.*,[10] using anhydrous diethyl ether as solvent rather than tetrahydrofuran (THF).

1-Fluoro-4-(2-iodoethyl)benzene

4-Fluorophenethyl alcohol (10.0 g, 71.3 mmol) was taken up in anhydrous dichloromethane (300 cm^3) containing triethylamine (14.5 cm^3), and was then treated[11] with methanesulfonyl chloride (8.97 g, 6.06 cm^3, 78 mmol) to give a quantitative yield of the mesyl ester,[12] which was used directly for the following step.

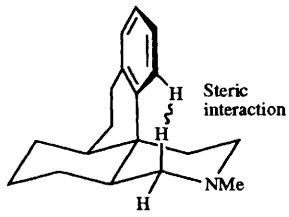
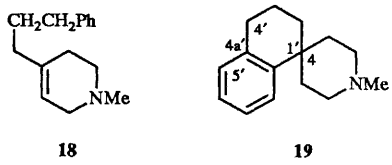


Fig. 3 Steric interaction present in structure **4**



18 19

The mesyl ester was taken up in anhydrous acetone (250 cm^3) and the stirred solution was treated[13] with sodium iodide (59.4 g, 396 mmol) for 24 h at room temperature to give a light brown oil (17.7 g). The crude oil was distilled under reduced pressure to give *1-fluoro-4-(2-iodoethyl)benzene* as a yellow oil (17.3 g, 97%), bp 76 °C/0.9 mmHg; R_f 0.85 (EtOAc) (Found: C, 38.8; H, 3.3. C_8H_8FI requires C, 38.4; H, 3.22%); ν_{max}(film)/cm^{-1} 1602m, 1510s, 1225s, 1172m, 1160m, 940m, 828m and 768m; δ_H 7.20–6.90 (4 H, m, ArH) and 3.50–3.30 (4 H, m); δ_C 161.7 (C, d, *J* 245.0, C-1), 136.2 (C, d, *J* 2.5, C-4), 129.8 (CH, d, *J* 8.0, C-2 and -6), 115.5 (CH, d, *J* 21.5, C-3 and -5), 39.3 (CH_2, CH_2Ar) and 5.6 (CH_2, CH_2I).

1-Bromo-4-(2-iodoethyl)benzene[14] and 1-chloro-4-(2-iodoethyl)benzene[15] were similarly prepared from 4-bromophenethyl alcohol and 4-chlorophenethyl alcohol, respectively.

(±)-5-Phenethyl-5,6,7,8-tetrahydroisoquinoline (7; Ar = Ph) and 5,5-bis(phenethyl)-5,6,7,8-tetrahydroisoquinoline (11; Ar = Ph)

Potassium (1.32 g, 33.8 mmol) was added in portions to a solution of ammonia (75 cm^3) containing $Fe(NO_3)_3 \cdot 9H_2O$ (35 mg) to produce a blue solution. The solution was kept and occasionally swirled for 30 min, by which time the blue colour had dissipated. 5,6,7,8-Tetrahydroisoquinoline **6** (4.55 g, 34.2 mmol) was added dropwise over a period of 10 min and the reaction mixture was kept for a further 10 min, and occasionally swirled to give a red solution. (2-Iodoethyl)benzene (7.94 g, 34.2 mmol) was added over a period of 25 min, with swirling of the mixture, to give an orange solution, which was kept overnight to give a grey residue. The residue was taken up in ice–water and diethyl ether. The aqueous solution was extracted twice with diethyl ether then the organic extracts were combined and extracted twice with 5 mol dm^{-3} hydrochloric acid. The acidic extracts were washed with diethyl ether, neutralised (pH paper) with sodium hydrogen carbonate, then was basified with 10 mol dm^{-3} aq. sodium hydroxide before extraction twice with diethyl ether. The organic extracts were dried, filtered, and concentrated to give an oil, which was distilled under reduced pressure to give 5,6,7,8-tetrahydroisoquinoline **6** (1.17 g, 26% recovery), bp 38–48 °C/0.02 mmHg; followed by the *monosubstituted tetrahydroisoquinoline* (7; Ar = Ph) (4.52 g, 56%), bp 140–142 °C/0.01 mmHg; R_f 0.38 (EtOAc) (Found: C, 86.3; H, 8.05; N, 6.05. $C_{17}H_{19}N$ requires C, 86.1; H, 8.02; N, 5.91%); ν_{max}(film)/cm^{-1} 1590m, 1487m, 830m, 750m and 700m; *m/z* 237, 146, 133, 117, 105, 92, 91, 77, 65 and 51; δ_H 8.29 (1 H, s, 1-H), 8.28 (1 H, d, *J* 5.0, 3-H), 7.32–7.15 (5 H, m, ArH), 7.00 (1 H, d, *J* 5.0, 4-H), 2.78–2.55 (5 H, m) and 2.06–1.65 (6 H, m); δ_C 150.5 (CH, C-1), 149.8 (C, C-4a), 146.7 (CH, C-3), 142.0 (C, C-1′), 133.0 (C, C-8a), 128.5 (CH, C-3′ and -5′), 128.4 (CH, C-2′ and -6′), 125.9 (CH, C-4′), 122.9 (CH, C-4), 37.7 (CH_2,

CH_2CH_2Ar), 36.6 (CH, C-5), 33.3 (CH_2, *C*H_2Ar), 27.0 (CH_2), 26.6 (CH_2) and 19.7 (CH_2, C-7).

The residue from the distillation was applied to a column of silica and eluted with ethyl acetate to give the *disubstituted tetrahydroisoquinoline* (**11**; Ar = Ph) as a solid (3.4 g, 10%), mp 78–88 °C; R_f 0.48 (EtOAc) (Found: C, 87.8; H, 8.2; N, 4.0%; M^+, 341.2145. $C_{25}H_{27}N$ requires C, 87.93; H, 7.97; N, 4.10; M, 341.2144); *m/z* 341, 250, 237, 236, 146, 132, 105 and 91; ν_{max}(film)/cm^{-1} 3020m, 2960–2920m, 2860m, 1602m, 1590m, 1490m, 1455m, 1410m, 832m, 780s, 700s; δ_H 8.4–8.3 (2 H, m, 1- and 3-H), 7.3–7.0 (11 H, m, 4-H and ArH), 2.75 (2 H, m, 8-H_2), 2.55 (2 H, m), 2.35 (2 H, m) and 2.20–1.70 (8 H, m); δ_C 151.5 (C, C-4a), 150.6 (CH, C-1), 146.9 (CH, C-3), 133.1 (C, C-8a), 142.2 (C, C-1′), 128.2 (C, C-3′ and -5′), 128.0 (CH, C-2′ and -6′), 125.6 (CH, C-4′), 121.1 (CH, C-4), 44.1 (CH_2, *C*H_2CH_2Ar), 40.0 (C, C-5), 31.2 (CH_2), 30.7 (CH_2, *C*H_2Ar), 27.1 (CH_2) and 19.2 (CH_2, C-7).

(±)-5-(4′-Fluorophenethyl)-5,6,7,8-tetrahydroisoquinoline (7; Ar = 4-FC_6H_4) and 5,5-bis(4′-fluorophenethyl)-5,6,7,8-tetrahydroisoquinoline (11; Ar = 4-FC_6H_4)

5,6,7,8-Tetrahydroisoquinoline **6** (9.18 g, 69 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (2.70 g, 69 mmol) in ammonia (400 cm^3) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (69 mg)]. The resulting carbanion was treated as above with 1-fluoro-4-(2-iodoethyl)benzene (17.26 g, 69 mmol) and worked up as previously described. Distillation under reduced pressure gave 5,6,7,8-tetrahydroisoquinoline **6** (1.55 g, 17% recovery), and the *monosubstituted tetrahydroisoquinoline* (**7**; Ar = 4-FC_6H_4) (9.42 g, 54%), bp 146–147 °C/0.05 mmHg; R_f 0.35 (EtOAc) (Found: C, 79.8; H, 7.3; F, 7.65. $C_{17}H_{18}FN$ requires C, 79.97; H, 7.10; F, 7.44%); *m/z* 255, 146, 133, 132, 123, 117 and 109; ν_{max}(film)/cm^{-1} 2935s, 2860m, 1600–1590m, 1510s, 1410m, 1220s, 1155m and 825s; δ_H 8.25 (1 H, d, *J* 2.0, 3-H), 8.23 (1 H, s, 1-H), 7.08 (2 H, m, 2′- and 6′-H), 7.0–6.8 (3 H, m, 4-, 3′- and 5′-H), 3.0–2.5 (5 H, m) and 2.1–1.5 (6 H, m); δ_C 161.1 (C, d, *J* 245.0, C-4′), 150.3 (CH, C-1), 149.3 (C, C-4a), 146.4 (CH, C-2), 137.3 (C, C-1′), 132.6 (C-8a), 129.5 (CH, d, *J* 7.0, C-2′ and -6′), 122.7 (CH, C-4), 115.0 (CH, d, *J* 20.5, C-3′ and -5′), 37.7 (CH_2, *C*H_2CH_2Ar), 36.3 (CH, C-5), 32.3 (CH_2, *C*H_2Ar), 26.7 (CH_2), 26.4 (CH_2) and 19.5 (CH_2, C-7).

A sample of the free base was converted into the *hydrochloride salt* (Found: C, 69.9; H, 6.65; N, 4.8; F, 6.5; Cl, 11.9. $C_{17}H_{18}FN \cdot HCl$ requires C, 69.98; H, 5.65; N, 4.80; F, 6.51; Cl, 12.15%); δ_H 8.60 (1 H, s, 1-H), 8.55 (1 H, d, *J* 6.5, 3-H), 7.93 (1 H, d, *J* 6.5, 4-H), 7.30 (2 H, dd, *J* 6.5 and 9.5, 2′- and 6′-H), 7.05 (2 H, br t, *J* 9.5, 3′- and 5′-H), 3.20–2.70 (m) and 2.20–1.70 (m).

The distillation residue was applied to a column of silica and eluted with ethyl acetate to give the *disubstituted tetrahydroisoquinoline* (**11**; Ar = 4-FC_6H_4) as a solid (1.78 g, 7%), mp 68–70 °C; R_f 0.49 (EtOAc) (Found: C, 79.6; H, 6.6; N, 3.6; F, 9.8. $C_{25}H_{25}F_2N$ requires C, 79.55; H, 6.68; N, 3.71; F, 10.07%); *m/z* 377, 268, 255, 254, 146, 123 and 109; ν_{max}(film)/cm^{-1} 1600m, 1590m, 1553w, 1510s, 1218s, 1158m and 820m; δ_H 8.4 (2 H, m, 1- and 3-H), 7.2–6.8 (9 H, m, 4 H and ArH), 2.85–2.65 (2 H, m), 2.52 (2 H, m), 2.32 (2 H, m) and 2.20–1.70 (8 H, m); δ_C 161.2 (C, d, *J* 245.0, C-4′), 151.3 (C, C-4a), 150.8 (CH, C-1), 147.1 (CH, C-3), 137.8 (C, d, *J* 3.0, C-1′), 133.3 (C, C-8a), 129.4 (CH, d, *J* 7.0, C-2′ and -6′), 121.0 (CH, C-4), 115.0 (CH, d, *J* 20.5, C-3′ and -5′), 44.3 (CH_2, *C*H_2CH_2Ar), 40.1 (C, C-5), 31.4 (CH_2), 29.9 (CH_2, *C*H_2Ar), 27.1 (CH_2) and 19.3 (CH_2, C-7).

(±)-5-(4′-Chlorophenethyl)-5,6,7,8-tetrahydroisoquinoline (7; Ar = 4-ClC_6H_4)

5,6,7,8-Tetrahydroisoquinoline **6** (4.16 g, 31.3 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (1.22 g, 31.3 mmol) in ammonia (200 cm^3) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (32 mg)]. The resulting carbanion was treated as above with 1-chloro-4-(2-iodoethyl)benzene (8.33 g, 31.3 mmol) and worked up as previously described. The crude reaction product was distilled under reduced pressure to give 5,6,7,8-tetrahydroisoquinoline **6** (1.22 g, 29% recovery). The distillation residue was purified by column chromatography with ethyl acetate as eluent to give an oil (4.47 g), which was distilled under reduced pressure to give the *monosubstituted tetrahydroisoquinoline* (**7**; Ar = 4-ClC_6H_4) (4.12 g, 47%), bp 160 °C/0.02 mmHg; R_f 0.38 (EtOAc) (Found: C, 74.9; H, 7.0; N, 5.2; Cl, 12.95. $C_{17}H_{18}ClN$ requires C, 75.13; H, 6.68; N, 5.15; Cl, 13.04%); *m/z* 273, 271, 146, 133, 132, 117, 103, 91 and 77; ν_{max}(film)/cm^{-1} 2920m, 1570m, 1470m, 1410m, 1090m, 1010m, 830m and 815m; δ_H 8.31 (1 H, s, 1-H), 8.29 (1 H, d, *J* 4.5, 3-H), 7.28 (2 H, d, *J* 9.0, 3′- and 5′-H), 7.16 (2 H, d, *J* 9.0, 2′- and 6′-H), 7.03 (1 H, d, *J* 4.5, 4-H), 3.00–2.50 (5 H, m) and 2.20–1.50 (6 H, m); δ_C 150.3 (CH, C-1), 149.5 (C, C-4a), 146.5 (CH, C-3), 140.3 (C, C-1′), 132.8 (C, C-4′), 131.6 (C, C-8a), 129.6 (CH, C-2′ and -6′), 128.5 (CH, C-3′ and -5′), 122.8 (CH, C-4), 37.5 (CH, C-5), 36.4 (CH_2, *C*H_2CH_2Ar), 32.5 (CH_2, *C*H_2Ar), 26.8 (CH_2), 26.5 (CH_2) and 19.6 (CH_2, C-7).

(±)-5-(4′-Bromophenethyl)-5,6,7,8-tetrahydroisoquinoline (7; Ar = 4-BrC_6H_41) and 5,5-bis(4′-bromophenethyl)-5,6,7,8-tetrahydroisoquinoline (11; Ar = 4-BrC_6H_4)

5,6,7,8-Tetrahydroisoquinoline **6** (8.55 g, 64.3 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (2.51 g, 64 mmol) in ammonia (400 cm^3) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (64 mg)]. The resulting carbanion was treated as above with 1-bromo-4-(2-iodoethyl)benzene (20.0 g, 64.3 mmol) and worked up as previously described but with ethyl acetate instead of diethyl ether for extractions. The residue obtained was distilled under reduced pressure to give 5,6,7,8-tetrahydroisoquinoline **6** (1.72 g, 20% recovery), and the *monosubstituted tetrahydroisoquinoline* (**7**; Ar = 4-BrC_6H_4) (8.67 g, 43%), bp 160 °C/0.05 mmHg; R_f 0.37 (EtOAc) (Found: C, 64.8; H, 5.7; Br, 25.2. $C_{17}H_{18}BrN$ requires C, 64.56; H, 5.74; Br, 25.27%); *m/z* 317, 315, 185, 183, 171, 169, 146, 133, 132, 117, 104, 91 and 77; ν_{max}(film)/cm^{-1} 2935s, 2860m, 1595m, 1560w, 1485s, 1070m, 1010m, 830m and 820–800m; δ_H 8.26 (1 H, s, 1-H), 8.25 (1 H, d, *J* 4.0, 3-H), 7.35 (2 H, d, *J* 10.0, 3′- and 5′-H), 7.02 (2 H, d, *J* 10.0, 2′- and 6′-H), 6.97 (1 H, d, *J* 4.0, 4-H), 2.90–2.40 (5 H, m) and 2.10–1.60 (6 H, m); δ_C 150.3 (CH, C-1), 149.2 (C, C-4a), 146.3 (CH, C-3), 140.8 (C, C-1′), 132.7 (C, C-8a), 131.3 (CH, C-3′ and -5′), 129.6 (CH, C-2′ and -6′), 122.7 (CH, C-4), 119.5 (C, C-4′), 37.3 (CH_2, *C*H_2CH_2Ar), 36.3 (CH, C-5), 32.3 (CH_2, *C*H_2Ar), 26.8 (CH_2), 26.4 (CH_2) and 19.6 (CH_2, C-7).

The distillation residue was applied to a column of silica and eluted with ethyl acetate to give the *disubstituted tetrahydroisoquinoline* (**11**; Ar = 4-BrC_6H_4) as an oil (0.57 g, 2%); R_f 0.49 (EtOAc) (Found: C, 59.9; H, 5.3; Br, 32.2. $C_{25}H_{25}Br_2N$ requires C, 60.14; H, 5.05; Br, 32.01%); *m/z* 501, 499, 330, 328, 316, 314, 171, 169, 146, 133, 132, 104, 91 and 90; ν_{max}(film)/cm^{-1} 2940m, 2860w, 1592m, 1490m, 1410m, 1070m, 1010s and 804m; δ_H 8.38 (1 H, d, *J* 5.0, 3-H), 8.35 (1 H, s, 1-H), 7.33 (4 H, d, *J* 8.0, 3′- and 5′-H), 7.15 (1 H, d, *J* 5.0, 4-H), 6.94 (4 H, d, *J* 8.0, 2′- and 6′-H), 2.75 (2 H, br s, 8-H_2), 2.48 (2 H, m), 2.27 (2 H, m) and 2.10–1.50 (8 H, m); δ_C 151.0 (C, C-4a), 150.7 (CH, C-1), 147.0 (CH, C-3), 141.0 (C, C-1′), 133.2 (C, C-8a), 131.2 (CH, C-3′ and -5′), 129.8 (CH, C-2′ and -6′) 120.9 (CH, C-4), 119.4 (C, C-4′), 43.9 (CH_2, *C*H_2CH_2Ar), 40.0 (C, C-5), 31.3 (CH_2), 30.1 (CH_2, *C*H_2Ar), 27.0 (CH_2) and 19.2 (CH_2, C-7).

(±)-2-Methyl-5-phenethyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (9; Ar = Ph)

The tetrahydroisoquinoline (**7**; Ar = Ph) (4.52 g, 19.1 mmol) was taken up in anhydrous diethyl ether (100 cm^3); the solution

was treated with iodomethane (3.0 g, 1.32 cm^3, 21.1 mmol) and stirred for one week to give the methiodide (**8**; Ar = Ph) as a precipitate (5.65 g, 78%). The methiodide was taken up in ethanol (100 cm^3), and the mixture was cooled in an ice-bath and treated with sodium boranuide (1.13 g, 30 mmol) in portions while being stirred. The solution was allowed to reach room temp. and was stirred overnight. The solvent was removed under reduced pressure and the residue was taken up in a mixture of diethyl ether and dil. aq. sodium hydroxide. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic extracts were combined and extracted twice with dil. hydrochloric acid. The acidic extracts were washed with diethyl ether, neutralised (pH paper) with sodium hydrogen carbonate, then basified with aq. sodium hydroxide and extracted twice with diethyl ether. The organic extracts were dried, filtered, and concentrated to give a residue, which was distilled under reduced pressure to give the *octahydroisoquinoline* (**9**; Ar = Ph) (2.82 g, 74%), bp 128 °C/0.03 mmHg; R_f 0.61 [MeOH–AcOH (5:1)] (Found: C, 84.65; H, 9.85; N, 5.65%; M^+, 255.198 02. $C_{18}H_{25}N$ requires C, 84.71; H, 9.80; N, 5.50%; M, 255.198 69); *m/z* 255, 164, 150, 122, 110, 108, 93, 91, 79 and 42; ν_{max}(film)/cm^{-1} 2765m, 1595w, 1490m, 1445m, 745m and 695m; δ_H (7.29–7.24 (2 H, m, ArH), 7.20–7.14 (3 H, m, ArH), 2.83 (1 H, d, *J* 16.0, 1-H′), 2.72 (1 H, ddd, *J* 5.0, 10.5 and 13.5), 2.65 (1 H, d, *J* 16.0, 1-H″), 2.58 (1 H, dd, *J* 5.0 and 10.0), 2.51 (1 H, ddd, *J* 6.5, 10.0 and 14.0), 2.41–2.35 (1 H, m), 2.33 (3 H, s, NMe), 1.97–1.80 (6 H, m), 1.80–1.66 (2 H, m) and 1.61–1.47 (3 H, m); δ_C 142.8 (C, C-1′), 129.1 (C, C-4a), 128.2 (CH, C-3′ and -5′), 128.2 (CH, C-2′ and 6′), 127.2 (C, C-8a), 125.5 (CH, C-4′), 59.0 (CH_2, C-1), 52.7 (CH_2, C-3), 45.8 (CH_3, NMe), 37.8 (CH, C-5), 34.2 (CH_2), 33.4 (CH_2), 28.7 (CH_2), 27.9 (CH_2), 27.5 (CH_2) and 20.1 (CH_2, C-7).

(±)-5-(4′-Fluorophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (9; Ar = 4-FC_6H_4)

The tetrahydroisoquinoline (**7**; Ar = 4-FC_6H_4) (8.1 g, 31.8 mmol) was treated with a solution of iodomethane (2.7 cm^3, 6.16 g, 43.5 mmol) in anhydrous diethyl ether (125 cm^3) as described above to give a precipitate (10.1 g). Further crops were obtained on longer storage. The various crops were combined to give the methiodide salt (**8**; Ar = 4-FC_6H_4) (12.1 g, 96%).

The methiodide salt was treated with sodium boranuide (2.31 g, 61 mmol) in ethanol (250 cm^3) as previously described to give an oil, which was distilled under reduced pressure to give the *octahydroisoquinoline* (**9**; Ar = 4-FC_6H_4) as an oil (7.07 g, 81%); bp 123 °C/0.05 mmHg; R_f 0.48 [MeOH–AcOH (5:1)] (Found: C, 79.1; H, 8.8; F, 7.2. $C_{18}H_{24}FN$ requires C, 79.08; H, 8.84; F, 6.95%); *m/z* 273, 164, 150, 122, 109, 108, 93, 83 and 79; ν_{max}(film)/cm^{-1} 2780w, 1600w, 1510m, 1220br m and 825br m; δ_H 7.13 (2 H, dd, *J* 6.0 and 8.0, 2′- and 6′-H), 6.95 (2 H, t, *J* 8.0, 3′- and 5′-H), 2.33 (3 H, s, NMe), 3.10–2.10 (6 H, m) and 2.10–1.40 (11 H, m); δ_C 161.0 (C, d, *J* 243.0, C-4′), 138.2 (C, C-1′), 129.4 (CH, d, *J* 7.5, C-2′ and -6′), 128.8 (C, C-4a), 127.4 (C, C-8a), 114.8 (CH, d, *J* 22.0, C-3′ and -5′), 58.6 (CH_2, C-1), 52.6 (CH_2, C-3), 45.7 (CH_3, NMe), 37.6 (CH, C-5), 34.3 (CH_2), 32.5 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 27.4 (CH_2) and 20.0 (CH_2, C-7).

(±)-5-(4′-Chlorophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (9; Ar = 4-ClC_6H_4)

The tetrahydroisoquinoline (**7**; Ar = 4-ClC_6H_4) (3.6 g, 13.2 mmol) was treated with iodomethane (1.0 cm^3, 2.28 g, 16.1 mmol) in anhydrous diethyl ether (50 cm^3) for three weeks as described above to give the methiodide (**8**; Ar = 4-ClC_6H_4) as a precipitate (4.94 g, 90%).

The methiodide salt was treated with a solution of sodium boranuide (908 mg, 24 mmol) in ethanol (150 cm^3) as previously described to give an oil, which was distilled under reduced pressure to give the *octahydroisoquinoline* (**9**; Ar = 4-ClC_6H_4) (2.94 g, 85%); bp 132–136 °C/0.01 mmHg; R_f 0.55 [MeOH–AcOH (5:1)] (Found: C, 74.4; H, 8.35; N, 4.7; Cl, 12.45. $C_{18}H_{24}ClN$ requires C, 74.59; H, 8.35; N, 4.83; Cl, 12.23%); *m/z* 291, 289, 164, 150, 122, 110, 108, 93, 91, 79 and 42; ν_{max}(film)/cm^{-1} 2960s, 2810m, 1500m, 1105m and 820m; δ_H 7.35–7.00 (4 H, m, ArH), 3.40–2.05 (6 H, m), 2.32 (3 H, s, NMe) and 2.05–1.40 (11 H, m); δ_C 141.4 (C, C-1′), 131.3 (C, C-4′), 129.7 (CH, C-2′ and -6′), 129.1 (C, C-4a), 128.4 (CH, C-3′ and -5′), 127.5 (C, C-8a), 59.0 (CH_2, C-1), 52.7 (CH_2, C-3), 45.7 (CH_3, NMe), 37.7 (CH, C-5), 34.2 (CH_2), 32.8 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 27.6 (CH_2) and 20.1 (CH_2, C-7).

(±)-5-(4′-Bromophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (9; Ar = 4-BrC_6H_4)

The tetrahydroisoquinoline (**7**; Ar = 4-BrC_6H_4) (7.62 g, 24.1 mmol) was treated with a solution of iodomethane (2.0 cm^3, 4.56 g, 32.2 mmol) in anhydrous diethyl ether (100 cm^3) as described above to give the methiodide salt as a precipitate (8.1 g). Further crops were obtained on longer treatment. The various crops were combined to give the methiodide salt (**8**; Ar = 4-BrC_6H_4) (10.92 g, 99%).

The methiodide salt was treated with a solution of sodium boranuide (1.805 g, 47.7 mmol) in ethanol (250 cm^3) as previously described to give an oil, which was distilled under reduced pressure to give the *octahydroisoquinoline* (**9**; Ar = 4-BrC_6H_4) (5.38 g, 67%), bp 159–164 °C/0.05 mmHg; R_f 0.50 [MeOH–AcOH (5:1)] (Found: C, 65.1; H, 7.2; Br, 24.1. $C_{18}H_{24}BrN$ requires C, 64.67; H, 7.24; Br, 23.90%); *m/z* 334.9, 332.9, 164, 150, 122, 110, 108 and 93; ν_{max}(film)/cm^{-1} 1485m, 1070m, 1010m and 800 br m; δ_H 7.36 (2 H, d, *J* 8.0, 3′- and 5′-H), 7.03 (2 H, d, *J* 8.0, 2′- and 6′-H), 2.31 (3 H, s, NMe), 3.00–2.10 (6 H, m) and 2.00–1.30 (11 H, m); δ_C 141.6 (C, C-1′), 131.1 (CH, C-3′ and -5′), 130.0 (CH, C-2′ and -6′), 128.8 (C, C-4a), 127.5 (C, C-8a), 119.1 (C, C-4′), 58.6 (CH_2, C-1), 52.6 (CH_2, C-3), 45.7 (CH_3, NMe), 37.6 (CH, C-5), 34.0 (CH_2), 32.8 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 27.5 (CH_2) and 20.0 (CH_2, C-7).

A sample of the free base was converted into the *hydrochloride salt*; mp 176.0–178.0 °C (Found: C, 58.1; H, 7.0; N, 3.9; Cl, 9.2. $C_{18}H_{25}BrClN$ requires C, 58.31; H, 6.80; N, 3.78; Cl, 9.56%).

2-Methyl-5,5-bis(phenethyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (12; Ar = Ph)

The disubstituted tetrahydroisoquinoline (**11**; Ar = Ph) (8.94 g, 26.2 mmol) was treated with a solution of iodomethane (2 cm^3, 4.56 g, 32.1 mmol) in anhydrous diethyl ether (125 cm^3) as described above for one week to give the methiodide salt as a gum (6.99 g). A sample of the gum (4.69 g) was treated with a solution of sodium boranuide (0.76 g, 20 mmol) in ethanol (100 cm^3) as described above. After being stirred overnight, the solution was concentrated and the residue was taken up in a mixture of diethyl ether and aq. sodium hydrogen carbonate. The diethyl ether extracts were combined and shaken with 2 mol dm^{-3} hydrochloric acid to give a precipitate (2.85 g), which was crystallised from water to give the *hydrochloride salt* of the *octahydroisoquinoline* (**12**; Ar = Ph) as plates (2.22 g, 59%), mp 208–215 °C (Found: C, 78.9; H, 8.8; N, 3.4. $C_{26}H_{34}ClN$ requires C, 78.86; H, 8.65; N, 3.54%).

A sample of the hydrochloride salt was converted into the free base; R_f 0.71 [MeOH–AcOH (5:1)]; *m/z* 359, 268, 254, 164, 162, 149, 134, 121, 110, 105 and 91; ν_{max}(film)/cm^{-1} 3085w, 3060w, 3025m, 2935s, 2780m, 1660w, 1605w, 1495m, 1455m, 750m and 700s; δ_H 7.40–7.00 (10 H, m, ArH), 2.82 (2 H, s, 1-H_2), 2.70–2.40 (6 H, m), 2.35 (3 H, s, NMe), 2.20 (2 H, br s), 1.90 (2 H, br s) and 1.80–1.55 (8 H, m); δ_C 143.3 (C, C-1′), 130.6 (C, C-4a), 129.4 (C, C-8a), 128.2 (CH, C-3′ and -5′), 128.2 (CH, C-2′ and -6′), 125.5 (CH, C-4′), 59.5 (CH_2, C-1), 53.1 (CH_2, C-3), 45.9

(CH_3, NMe), 41.5 (CH_2, CH_2CH_2Ar), 39.6 (C, C-5), 31.3 (CH_2), 31.0 (CH_2, CH_2Ar), 28.4 (CH_2), 25.0 (CH_2) and 19.4 (CH_2, C-7).

5,5-Bis(4′-fluorophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (12; Ar = 4-FC_6H_4)

The disubstituted tetrahydroisoquinoline (**11**; Ar = 4-FC_6H_4) (1.78 g, 4.71 mmol) was treated with a solution of an excess of iodomethane (0.58 cm^3, 1.33 g, 9.40 mmol) in anhydrous diethyl ether (100 cm^3) for one week as previously described to give the methiodide salt as a yellow solid (2.29 g, 93%).

The methiodide salt was treated with a solution of sodium boranuide (333 mg, 8.5 mmol) in ethanol (125 cm^3) as described above to give the *octahydroisoquinoline* (**12**; Ar = 4-FC_6H_4) as the *hydrochloride salt* (1.36 g, 72%); mp 205–208.5 °C (Found: C, 72.3; H, 7.5; N, 3.2; F, 8.8; Cl, 8.2. $C_{26}H_{32}ClF_2N$ requires C, 72.14; H, 7.65; N, 3.27; F, 8.71; Cl, 8.19%).

A sample of the hydrochloride salt was converted into the free base; R_f 0.65 [MeOH–AcOH (5:1)]; *m/z* 395.3, 286, 272, 162, 121, 110, 109, 44 and 42; ν_{max}(film)/cm^{-1} 2940m, 2780m, 1603m, 1510s, 1463m, 1220br m, 1160m, and 825br m; δ_H 6.93 (4 H, t, *J* 8.0, 3′- and 5′-H), 7.09 (4 H, dd, *J* 8.0 and 6.0, 2′- and 6′-H), 2.81 (2 H, s, 1-H_2), 2.65–2.40 (6 H, m), 2.35 (3 H, s, NMe), 2.18 (2 H, br s), 1.89 (2 H, br s) and 1.80–1.50 (8 H, m); δ_C 161.1 (C, d, *J* 243.5, C-4′), 138.8 (C, C-1′), 130.3 (C, C-4a), 129.7 (CH, d, *J* 7.5, C-2′ and -6′), 129.4 (C, C-8a), 115.0 (CH, d, *J* 22.0, C-3′ and -5′), 59.5 (CH_2, C-1), 53.1 (CH_2, C-3), 45.8 (CH_3, NMe), 41.7 (CH_2, CH_2CH_2Ar), 39.7 (C, C-5), 31.5 (CH_2), 30.3 (CH_2, CH_2Ar), 28.4 (CH_2), 25.1 (CH_2) and 19.5 (CH_2, C-7).

5,5-Bis(4′-bromophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (12; Ar = 4-BrC_6H_4)

The disubstituted tetrahydroisoquinoline (**11**; Ar = 4-BrC_6H_4) (568 mg, 1.14 mmol) was treated with a solution of an excess of iodomethane (0.14 cm^3, 0.323 g, 2.28 mmol) in anhydrous diethyl ether (40 cm^3) as previously described to give the methiodide salt as a yellow solid (592 mg, 78%).

The methiodide salt was treated with a solution of sodium boranuide (70 mg, 1.85 mmol) in ethanol (20 cm^3) as described above to give the *hydrochloride salt* of the *octahydroisoquinoline* (**12**; Ar = 4-BrC_6H_4) (246 mg, 49%), mp 208–219 °C (Found: C, 56.5; H, 5.8; N, 2.3; Cl, 6.6. $C_{26}H_{32}Br_2ClN$ requires C, 56.34; H, 5.78; N, 2.53; Cl, 6.40%).

A sample of the hydrochloride salt was converted into the free base; R_f 0.68 [MeOH–AcOH (5:1)]; ν_{max}(film)/cm^{-1} 2930m, 1487m, 1070m, 1012m and 805m; δ_H 7.36 (4 H, d, *J* 8.0, 3′- and 5′-H), 7.02 (4 H, d, *J* 8.0, 2′- and 6′-H), 2.81 (2 H, br s, 1-H_2), 2.60–2.40 (6 H, m), 2.33 (3 H, s, NMe), 2.15 (2 H, br s), 1.89 (2 H, br s) and 1.80–1.40 (8 H, m); δ_C 142.2 (C, C-1′), 131.4 (CH, C-3′ and -5′), 130.0 (CH, C-2′- and -6′), 119.3 (C, C-4′), 59.5 (CH_2, C-1), 53.1 (CH_2, C-3), 45.9 (CH_3, NMe), 41.4 (CH_2, CH_2CH_2Ar), 39.7 (C, 5-C), 31.4 (CH_2), 30.5 (CH_2, CH_2Ar), 28.4 (CH_2), 25.1 (CH_2) and 19.5 (CH_2, C-7).

(±)-(4aα,4bβ,10bβ,12aβ)-2-Methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho[2,1-*f*]isoquinoline (10; X = H)

The octahydroisoquinoline (**9**; Ar = Ph) (1.27 g, 5.0 mmol) was heated to reflux and stirred in 48% hydrobromic acid (20 cm^3) overnight. The solvent was removed under reduced pressure and the residue was taken up in water. The aqueous solution was basified with aq. sodium hydroxide and extracted three times with diethyl ether. The combined extracts were washed with brine, dried, and concentrated to give an oil, which was distilled under reduced pressure to give the *cyclised product* (**10**; X = H) as a soft solid (1.146 g, 90%), bp 120–130 °C/0.01 mmHg; R_f 0.43 [MeOH–AcOH (5:1)] (Found: C, 84.7; H, 9.95; N, 5.25%; M^+, 255.198 48. $C_{18}H_{25}N$ requires C, 84.71; H, 9.80; N, 5.50%; M, 255.198 69); *m/z* 255, 254, 240, 141, 129, 128, 110, 98, 71, 70, 58, 57 and 44; ν_{max}(film)/cm^{-1} 1490m, 1450m, 1380m, 1280m, 1170m, 1110m and 745s; δ_H 7.33 (1 H, d, *J* 7.5, 10-H), 7.18–7.06 (3 H, m, ArH), 3.06 (1 H, br s, 10b-H), 2.92 (1 H, dm, *J* 12.0, 3-H′), 2.87–2.63 (3 H, m), 2.52 (1 H, dq, *J* 3.0 and 19.0, 11-H′), 2.22 (3 H, s, NMe), 2.05–1.96 (1 H, m, 5-H′), 1.88–1.70 (5 H, m), 1.52–1.40 (2 H, m), 1.40–1.25 (1 H, m), 1.31 (1 H, dq, *J* 4.0 and 12.5, 4-H′) and 1.01–0.86 (2 H, m); δ_C 138.5 (C, C-10a), 137.3 (C, C-6a), 129.0 (CH, C-7), 126.0 (CH, C-8), 125.7 (CH, C-10), 125.1 (CH, C-9), 61.9 (CH_2, C-1), 56.3 (CH_2, C-2), 46.2 (CH_3, NMe), 41.6 (CH, C-12a), 39.5 (CH, C-4b), 38.3 (CH, C-10b), 37.2 (CH, C-4a), 29.4 (CH_2, C-4), 28.3 (CH_2, C-11), 25.7 (CH_2, C-12), 25.4 (CH_2, C-6) and 24.7 (CH_2, C-5).

(±)-(4aα,4bβ,10bβ,12aβ)-9-Fluoro-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho[2,1-*f*]isoquinoline (10; X = F)

The octahydroisoquinoline (**9**; Ar = 4-FC_6H_4) (5.97 g, 21.8 mmol) was treated with 48% hydrobromic acid (100 cm^3) as described above to give an oil, which was distilled under reduced pressure to give the *cyclised product* (**10**; X = F) (4.99 g, 84%) as a clear oil, bp 132 °C/0.25 mmHg which solidified on cooling, mp 48–60 °C; R_f 0.48 (MeOH–AcOH, 5:1) (Found: C, 79.0; H, 8.9; N, 5.2; F, 6.9%; M^+, 273.1886. $C_{18}H_{24}FN$ requires C, 79.08; H, 8.85; N, 5.12; F, 6.95%; M, 273.1893); *m/z* 273, 272, 258, 244, 214, 146, 110, 98, 58 and 44; ν_{max}(film)/cm^{-1} 2920s, 2870s, 2780m, 2740m, 1563m, 1535m, 1445s, 1414m, 1390m, 1330m, 1210m, 1103m, 1053m, 855m, 810m, 756m and 675m; δ_H 7.10–6.90 (2 H, m, ArH), 6.85–6.68 (1 H, m, ArH), 2.98 (1 H, br s, 10b-H), 2.88 (1 H, br d, *J* 11.0, 3-H′), 2.78–2.50 (3 H, m), 2.38 (1 H, br d, *J* 13.5, 11-H′), 2.18 (3 H, s, NMe), 1.97 (1 H, m, 5-H′), 1.90–1.60 (5 H, m), 1.50–1.10 (4 H, m) and 1.10–0.70 (2 H, m); δ_C 161.4 (C, d, *J* 242.0, C-9), 140.7 (C, d, *J* 6.0, C-10a), 132.7 (C, C-6a), 130.1 (CH, d, *J* 9.0, C-7), 112.5 (CH, d, *J* 19.0, C-10), 112.1 (CH, d, *J* 20.5, C-8), 62.1 (CH_2, C-1), 56.3 (CH_2, C-3), 46.3 (CH_3, NMe), 41.7 (CH, C-12a), 39.1 (CH, C-4b), 38.5 (CH, C-10b), 37.4 (CH, C-4a), 29.5 (CH_2, C-4), 28.4 (CH_2, C-11), 25.6 (CH_2, C-12), 25.6 (CH_2, C-6) and 24.6 (CH_2, C-5).

(±)-(4aα,4bβ,10bβ,12aβ)-9-Chloro-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho[2,1-*f*]isoquinoline (10; X = Cl)

The octahydroisoquinoline (**9**; Ar = 4-ClC_6H_4) (2.57 g, 8.86 mmol) was treated with 48% hydrobromic acid (40 cm^3) as described above to give a solid, which was crystallised from light petroleum (boiling range 60–80 °C) to give the *cyclised product* (**10**; X = Cl) (1.51 g, 59%), mp 99–101 °C; R_f 0.57 [MeOH–AcOH (5:1)] (Found: C, 74.75; H, 8.55; N, 4.9; Cl, 12.2%; M^+, 291.1571. $C_{18}H_{24}ClN$ requires C, 74.59; H, 8.35; N, 4.83; Cl, 12.23%; $C_{18}H_{24}{}^{37}ClN$ requires M, 291.1568); *m/z* 291, 289, 288, 163, 162, 151, 133, 112, 110, 98, 58 and 57; ν_{max}(KBr)/cm^{-1} 2920s, 1590w, 1560w, 1480m, 1460m, 1435m, 1380m, 1160m, 1100m, 864m, 845m and 825m; δ_H 7.27 (1 H, br s, 10H), 7.02 (1 H, ddd, *J* 0.9, 2.3 and 8.0, 8-H), 6.95 (1 H, d, *J* 8.0, 7-H), 2.96 (1 H, br s, 10b-H), 2.87 (1 H, dm, *J* 10.0, 3-H′), 2.80–2.50 (3 H, m, 1-H″, 6-H_2), 2.41 (1 H, dm, *J* 14.0, 11-H′), 2.18 (3 H, s, NMe), 1.99 (1 H, m, 5-H′), 1.80–1.50 (5 H, m, 3-H″, 4-H_2, 11-H″ and 5-H″), 1.40–1.20 (4 H, m, 1-, 4-, 12-H′ and 12a-H) and 1.00–0.80 (2 H, m, 4a-H and 12-H″); δ_C 140.0 (C, C-6a), 135.0 (C, C-10a), 131.0 (C, C-9), 129.9 (CH, C-7), 125.5 (CH, C-10), 124.9 (CH, C-8), 61.4 (CH_2, C-1), 55.8 (CH_2, C-3), 45.7 (CH_3, NMe), 41.2 (CH, C-12a), 38.7 (CH, C-4b), 38.0 (CH, C-10b), 36.9 (CH, C-4a), 29.0 (CH_2, C-4), 27.8 (CH_2, C-11), 25.2 (CH_2, C-12), 24.4 (CH_2, C-6) and 24.1 (CH_2, C-5).

(±)-(4aα,4bβ,10bβ,12aβ)-9-Bromo-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho[2,1-*f*]isoquinoline (10; X = Br)

The octahydroisoquinoline (**9**; Ar = 4-BrC_6H_4) (4.38 g, 13.1 mmol) was treated with 48% hydrobromic acid (60 cm^3) as described above to give a solid, which was crystallised twice from light petroleum (60–80 °C) to give the *cyclised product* (**10**; X = Br) (2.28 g, 52%), mp 121–123 °C; R_f 0.46 [MeOH–AcOH (5:1)] (Found: C, 64.9; H, 7.3; N, 4.1; Br, 24.2%; M^+, 333.1093. $C_{18}H_{24}BrN$ requires C, 64.67; H, 7.24; N, 4.19; Br, 23.91%; $C_{18}H_{24}{}^{79}BrN$ requires M, 333.1092); *m/z* 335, 333, 128, 110, 98, 70, 58 and 44; ν_{max}(KBr)/cm^{-1} 1590, 1480, 1460, 1160, 860, 840 and 810; δ_H 7.42 (1 H, s, 10-H), 7.18 (1 H, d, *J* 9.0, 8-H), 6.91 (1 H, d, *J* 10.0, 7-H), 2.98 (1 H, br s, 10b-H), 2.87 (1 H, br d, *J* 11, 3-H′), 2.74–2.50 (3 H, m), 2.40 (1 H, br d, *J* 13.5, 11-H′), 2.17 (3 H, s, NMe), 1.97 (1 H, m, 5-H′), 1.88–1.55 (5 H, m), 1.50–1.10 (4 H, m) and 1.08–0.70 (2 H, m); δ_C 141.1 (C, C-6a), 136.3 (C, C-10a), 130.6 (CH, C-7), 128.9 (CH, C-10), 128.2 (CH, C-8), 119.6 (C, C-9), 62.0 (CH_2, C-1), 56.3 (CH_2, C-3), 46.5 (CH_3, NMe), 41.7 (CH, C-12a), 39.2 (CH, C-4b), 38.4 (CH, C-10b), 37.4 (CH, C-4a), 29.5 (CH_2, C-4), 28.2 (CH_2, C-11), 25.6 (CH_2, C-12), 24.9 (CH_2, C-6) and 24.5 (CH_2, C-7).

A second crop (0.5 g, 11%) was obtained from the mother liquor.

Attempted cyclisation of 2-methyl-5,5-bis(phenethyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (12; Ar = Ph)

The hydrochloride salt of the octahydroisoquinoline (**12**; Ar = Ph) (2.0 g, 5.57 mmol) was converted into the free base, and this was heated to reflux in 48% hydrobromic acid (200 cm^3) for 48 h. No significant reaction was observed and starting material was recovered.

4-(3-Phenylpropyl)pyridine

4-Methylpyridine (4-picoline) (9.31 g, 100 mmol) was treated with potassium amide [synthesized *in situ* from potassium (3.90 g, 99.8 mmol) and $Fe(NO_3)_3{\cdot}9H_2O$ (100 mg)] in ammonia (160 cm^3) and then with phenethyl bromide (18.5 g, 100 mmol) as described above. The reaction residue was worked up as described above to give an oil, which was distilled under reduced pressure to give the *substituted pyridine* (6.13 g, 31%), bp 122–126 °C/0.02 mmHg (lit.,[9] 102–104 °C/0.06 mmHg); R_f 0.60 (EtOAc) (Found: C, 84.85; H, 7.85; N, 7.35. $C_{14}H_{15}N$ requires C, 85.24; H, 7.66; N, 7.10%); *m/z* 197, 118, 106, 93, 92, 91, 77, 65 and 51; ν_{max}(film)/cm^{-1} 1595s, 1490m, 750m and 700s; δ_H 8.48 (2 H, d, *J* 6.0, 2- and 6-H), 7.32–7.26 (2 H, m, 3′- and 5′-H), 7.23–7.15 (3 H, m, ArH), 7.11 (2 H, d, *J* 6.0, 3- and 5-H), 2.66 (2 H, t, *J* 7.5, CH_2Ar), 2.64 (2 H, t, *J* 7.5, CH_2Ar) and 1.97 (2 H, quintet, *J* 7.5, CH_2CH_2Ar); δ_C 150.9 (C, C-4), 149.5 (CH, C-2 and -6), 141.4 (C, C-1′), 128.2 (CH, C-3′ and -5′), 128.2 (CH, C-2′ and -6′), 125.8 (CH, C-4′), 123.7 (CH, C-3 and -5), 35.1 (CH_2, CH_2Ar), 34.4 (CH_2, CH_2Ar) and 31.6 (CH_2, CH_2CH_2Ar).

1-Methyl-4-(3-phenylpropyl)-1,2,3,6-tetrahydropyridine 18

4-(3-Phenylpropyl)pyridine (6.13 g, 31.1 mmol) was taken up in anhydrous diethyl ether (100 cm^3) and the stirred mixture was treated with iodomethane (5.70 g, 2.50 cm^3, 40.0 mmol) for one week at room temp. The resulting precipitate was filtered off, washed with anhydrous diethyl ether, and dried under reduced pressure over phosphorus pentaoxide to give the methiodide salt (7.02 g, 66%). A second crop (2.52 g) was obtained from the filtrate on further storage.

The methiodide salt (7.02 g, 20.7 mmol) was taken up in ethanol (150 cm^3) and treated with sodium boranuide (1.59 g, 42.0 mmol) as described above. The work-up procedure gave an oil, which was distilled under reduced pressure to give the *tetrahydropyridine* **18** (3.55 g, 80%), bp 94–96 °C/0.02 mmHg (lit.,[9] 91 °C/0.08 mmHg); R_f 0.80 [MeOH–AcOH (5:1)] (Found: C, 83.55; H, 9.9; N, 6.5. $C_{15}H_{21}N$ requires C, 83.67; H, 9.83; N, 6.50%); *m/z* 215, 122, 110, 104, 96, 91 and 42; ν_{max}(film)/cm^{-1} 2770s, 1600w, 1490m, 1450m, 820m, 745m and 695s; δ_H 7.29–7.24 (2 H, m, 3′- and 5′-H), 7.20–7.15 (3 H, m, ArH), 5.38 (1 H, m, 5-H), 2.92 (2 H, m, 6-H_2), 2.60 (2 H, t, *J* 7.5, CH_2Ar), 2.52 (2 H, t, *J* 5.5, 2-H_2), 2.35 (3 H, s, NMe), 2.13 (2 H, m, 3-H_2), 2.02 (2 H, t, *J* 7.5, =CCH_2) and 1.75 (2 H, quintet, *J* 7.5, CH_2CH_2Ar); δ_C 142.4 (C, C-1′), 135.6 (C, C-4), 128.3 (CH, C-3′ and -5′), 128.1 (CH, C-2′ and -6′), 125.5 (CH, C-4′), 118.8 (CH, C-5), 54.5 (CH_2, C-6), 52.2 (CH_2, C-2), 45.7 (CH_3, NMe), 36.4 (CH_2), 35.4 (CH_2), 29.1 (CH_2) and 29.0 (CH_2).

1-Methylspiro[piperidine-4,1′-1′,2′,3′,4′-tetrahydronaphthalene] 19.

The tetrahydropyridine **18** (1.01 g, 4.71 mmol) was taken up in 48% hydrobromic acid (5 cm^3) and the solution was heated to reflux for 16 h. The solution was worked up as described previously to give an oil, which was distilled under reduced pressure to give the *spiro compound* **19** (634 mg, 62.5%), bp 90–99 °C/0.02 mmHg (lit.,[9] 96 °C/0.08 mmHg) (Found: C, 83.8; H, 9.9; N, 6.7. $C_{15}H_{21}N$ requires C, 83.67; H, 9.83; N, 6.50%); *m/z* 215, 164, 129, 115, 96, 84, 71, 70, 57 and 44; ν_{max}(film)/cm^{-1} 3065w, 3020w, 2935s, 2795m, 1450m, 1380m and 760m; δ_H 7.49 (1 H, d, *J* 8.0, ArH), 7.17 (1 H, t, *J* 7.0, ArH), 7.08 (1 H, t, *J* 7.0, ArH), 7.05 (1 H, d, *J* 8.0, ArH), 2.79–2.71 (4 H, m), 2.35 (3 H, s, NMe), 2.27 (2 H, dt, *J* 1.5 and 12.0), 2.16 (2 H, dt, *J* 3.5 and 13.0), 1.86–1.81 (2 H, m), 1.77–1.70 (2 H, m) and 1.62 (2 H, dd, *J* 2.0 and 13.0); δ_C 144.9 (C), 137.2 (C), 128.9 (CH), 126.8 (CH), 125.9 (CH), 125.3 (CH), 51.7 (CH_2, C-2), 46.5 (CH_3, NMe), 38.4 (CH_2, C-3), 34.7 (C, C-4), 30.9 (CH_2), 30.7 (CH_2) and 18.9 (CH_2, C-3′).

Acknowledgements

I thank Dr E. Saxton, formerly of Leeds University, and Professor L. Mander of the Australian National University for providing the facilities for this research. Part of the work described in this paper was funded by an RSC grant awarded to the author.

References

1 R. Grewe and A. Mandon, *Chem. Ber.*, 1984, **81**, 279; R. Grewe, A. Mandon and E. Nolte, *Justus Liebigs Ann. Chem.*, 1949, **564**, 161; K. W. Bentley, *The Isoquinoline Alkaloids*, Pergamon Press, Oxford, 1965, p. 79.
2 N. Sugimoto and H. Kugita, *J. Pharm. Soc. Jpn.*, 1956, **76**, 169; *Chem. Pharm. Bull. Jpn.*, 1958, **6**, 429; H. Kugita, *Chem. Pharm. Bull. Jpn.*, 1956, **4**, 29; N. Sugimoto and H. Kugita, *Chem. Pharm. Bull. Jpn.*, 1957, **5**, 67.
3 N. Sugimoto, S. Ohshiro, H. Kugita and S. Saito, *Chem. Pharm. Bull. Jpn.*, 1957, **5**, 62; N. Sugimoto and S. Ohshiro, *Chem. Pharm. Bull. Jpn.*, 1957, **5**, 316.
4 F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.*, 1975, **40**, 2729.
5 J. M. Bailey, H. Booth and H. A. R. Y. Al-Shirayda, *J. Chem. Soc., Perkin Trans. 2*, 1984, 583.
6 D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, 1974, **96**, 1827.
7 G. L. Patrick and A. Willis, submitted to *Acta Crystallogr., Sect. C.*
8 B. Matkovics, B. Tarodi and L. Belaspira, *Acta Chim. Acad. Sci. Hung.*, 1974, **80**, 79.
9 E. Reimann, J. Speckbacher and H. Lotter, *Arch. Pharm. (Weinheim, Ger.)*, 1987, **320**, 385.
10 S. A. Glover, C. A. Rowbottom, A. P. Scott and J. L. Schoonraad, *Tetrahedron*, 1990, **46**, 7247.
11 R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 1970, **35**, 3195.
12 D. M. Spatz and B. Cross, *U.S. Pat.*, 4 308 213, 1981 (*Chem. Abstr.*, 1982, **96**, 122457).
13 K. Kato, Y. Hirata and S. Yamamura, *Tetrahedron*, 1971, **27**, 5987.
14 S. Nunomoto, Y. Kawakami and Y. Yamashita, *J. Org. Chem.*, 1983, **48**, 1912.
15 R. W. Bott, E. Eaborn and K. Leyshon, *J. Chem. Soc.*, 1964, 1548; C. H. DePuy and D. H. Froemsdorf, *J. Am. Chem. Soc.*, 1957, **79**, 3710.

Paper 4/07060G
Received 18*th November* 1994
Accepted 19*th December* 1994