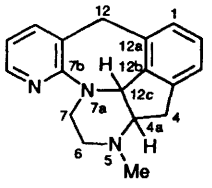
Stereoselective Construction of Vicinal Diamines. Part 2.[1] Synthesis of Indenopyrazines

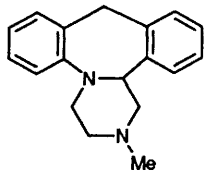
Barry S. Orlek* and Diane Lightowler
SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD, UK

The *trans*-adduct **8** derived from indene and *N,N*-dichlorourethane serves as a precursor for the *cis*-1,2-diaminoindane **6** and the *trans*-diamines **7** and **14**. Conversion of **6** and **14** into the triazabenzocycloheptafluorenes **1** and **2**, respectively, *via* the indenopyrazines **4** and **5** is described.

The synthesis of conformationally restricted analogues **1** and **2** was undertaken as part [1] of a programme to investigate the link



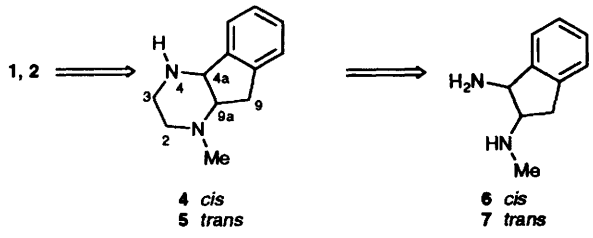
1 4a-H and 12c-H *cis*
2 4a-H and 12c-H *trans*



3

between conformation and biological activity in a series of compounds related to the antidepressant drug mianserin **3**.

The problem of constructing the target compounds may be logically reduced to that of obtaining the *cis*- and *trans*-indenopyrazines **4** and **5**, which are in principle accessible from suitably functionalised 1,2-diaminoindanes (Scheme 1). The



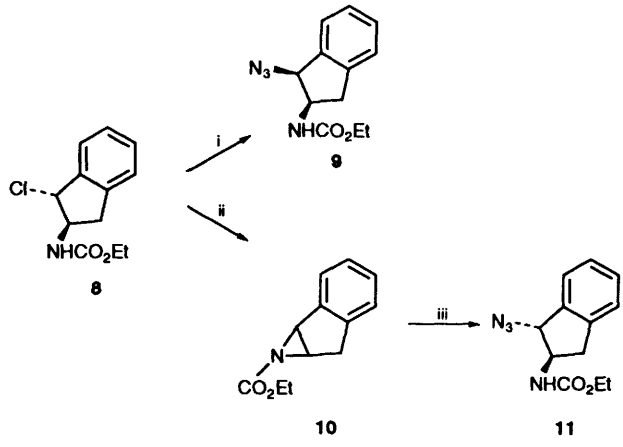
4 *cis*
5 *trans*
6 *cis*
7 *trans*

Scheme 1

initial task was therefore the stereoselective synthesis of *cis* and *trans* vicinal diamines **6** and **7**. Although methods are available for setting up vicinal diamines of this type, the most frequently used procedures, *e.g. via* epoxides, are lengthy. An alternative approach was therefore investigated.[2] The *trans*-adduct **8**[3] derived from indene and *N,N*-dichlorourethane was selected as a precursor for both *cis*- and *trans*-1,2-diaminoindanes (Scheme 2).† When adduct **8** was treated with sodium azide in *N,N*-dimethylformamide exclusive formation of the *cis*-azide **9** was observed. This stereochemical outcome is consistent with direct S_N2 displacement, and precludes neighbouring group participation under these conditions.[4]

The behaviour of azide ion in this context stands in contrast to results obtained with weakly basic poor nucleophiles. For example, the reaction of adduct **8** with aniline requires assistance from the adjacent carbamate group and leads to the *trans*-substituted product.[2] Pretreatment of the adduct **8** with sodium hydride to form the aziridine **10** followed by reaction with sodium azide produced the *trans*-isomer **11**.[5] The stereochemistry of the products was assigned by ^1H NMR

† For convenience only one stereoisomer is shown.

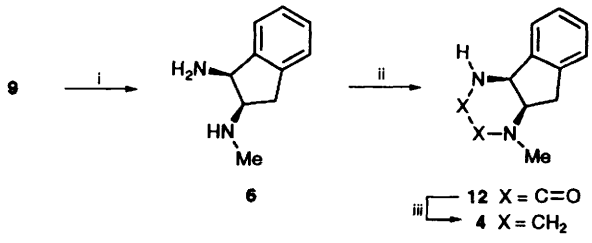


8 **9** **10** **11**

Scheme 2 *Reagents:* i, NaN_3, DMF; ii, NaH, DMF; iii, NaN_3, NH_4Cl, DMF

spectroscopy on the basis that the chemical shift difference between the protons at C-3 in 1,2-disubstituted indanes is greater for *trans*-substitution.[6] These protons appear at δ 2.80 and 3.22 in *cis*-azide **9** whereas the *trans*-isomer **11** gives signals at δ 2.70 and 3.30.

Reduction of compound **9** with lithium aluminium hydride afforded the corresponding diamine **6** (Scheme 3). Subsequent

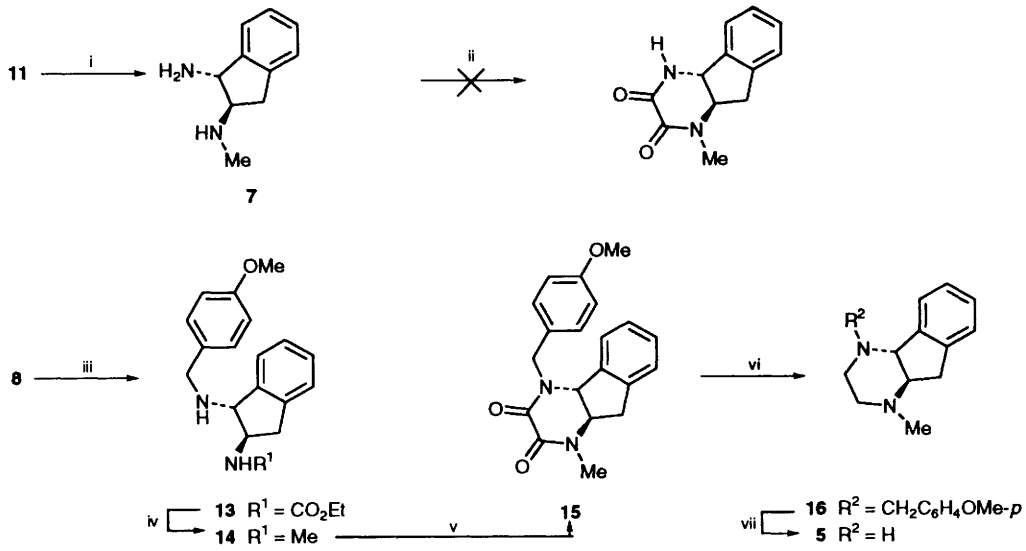


6
12 X = C=O
4 X = CH_2

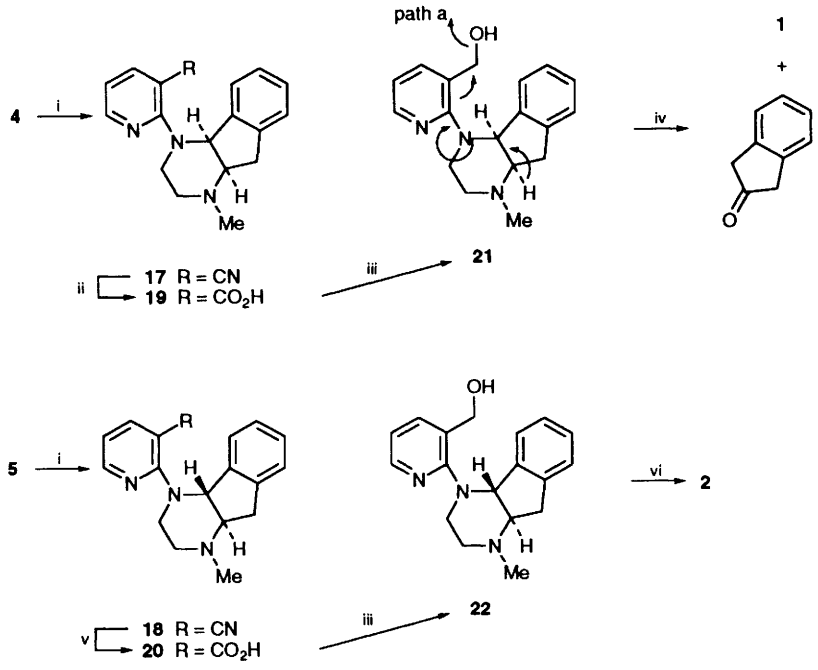
Scheme 3 *Reagents and conditions:* i, $LiAlH_4$, Et_2O; ii, diethyl oxalate, toluene, reflux; iii, alane, Et_2O

condensation with diethyl oxalate followed by reduction with alane produced the required *cis*-indenopyrazine **4**. Construction of the less favoured *trans* ring junction proved more difficult. Condensation of the *trans*-diamine **7** with diethyl oxalate failed to give the expected oxamide, presumably due to competing intermolecular reactions (Scheme 4). This problem was overcome by protection of the primary amine with a 4-methoxybenzyl group. The protected diamine precursor **13** was obtained by reaction of **8** with 4-methoxybenzylamine after *in situ* formation of the aziridine **10**. Subsequent reduction with lithium aluminium hydride afforded aminoindane **14**.

Condensation of the aminoindane **14** with diethyl oxalate produced the required oxamide **15**, although the conditions were far more vigorous than those required to form the *cis*-compound. Reduction with alane, followed by deprotection



Scheme 4 *Reagents and conditions:* i, $LiAlH_4$, Et_2O; ii, diethyl oxalate, toluene, reflux; iii, NaH, DMF then *p*-OMe–$C_6H_4CH_2NH_2$; iv, $LiAlH_4$, Et_2O; v, diethyl oxalate, mesitylene, reflux; vi, alane, Et_2O; vii, TFA, H_2SO_4, thioanisole



Scheme 5 *Reagents and conditions:* i, 2-chloronicotinonitrile, KF, DMF; ii, KOH, EtOH, 100 °C; iii, $LiAlH_4$, Et_2O; iv, PPA, 100 °C; v, KOH, EtOH, 60–80 °C; vi, $MeSO_3H$, P_2O_5

using trifluoroacetic acid–sulfuric acid–thioanisole [7] completed the synthesis of the *trans*-indenopyrazine **5**.

Condensation of the *cis*- and *trans*-indenopyrazines **4** and **5** with 2-chloronicotinonitrile produced **17** and **18** respectively (Scheme 5). Alkaline hydrolysis of compounds **17** and **18**, employing milder conditions in the case of the *trans*-isomer **18** to avoid epimerisation, afforded the acids **19** and **20**, respectively. Reduction with lithium aluminium hydride gave the alcohols **21** and **22**. The *trans*-alcohol **22** cyclised smoothly in methanesulfonic acid–phosphorous pentoxide to give the triazabenzocycloheptafluorene **2**. Under similar conditions the *cis*-precursor **21** was recovered unchanged. The desired cyclisation of compound **21** was effected using polyphosphoric acid at 100 °C although the yield was modest. The isolation of indan-2-one as a minor product from this reaction suggests that the low yield of the triazabenzocycloheptafluorene **1** is due at least in part to a competing fragmentation pathway (path a in Scheme 5 followed by hydrolysis).

^1H NMR spectra of triazabenzocycloheptafluorenes **1** and **2** revealed couplings (J) of 7 and 10 Hz, respectively, for the methine protons at C-12c and C-4a. In the case of the *cis*-isomer **1** confirmation of stereochemistry was provided by an X-ray analysis (Fig. 1).

Experimental

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Varian CFT-20, a JEOL GX-270, a Bruker WM-250 or a Bruker AM-400 spectrometer using tetramethylsilane as internal standard with coupling constants (J) given in Hz. Mass spectra were obtained on an AEI MS9 (70 ev) or a JEOL DX303 (70 ev) spectrometer and IR spectra on a Perkin-Elmer 197 spectrometer. All evaporations of solvent were carried out under reduced pressure, and organic solutions were dried over sodium sulfate. Silica gel used for column chromatography was Merck

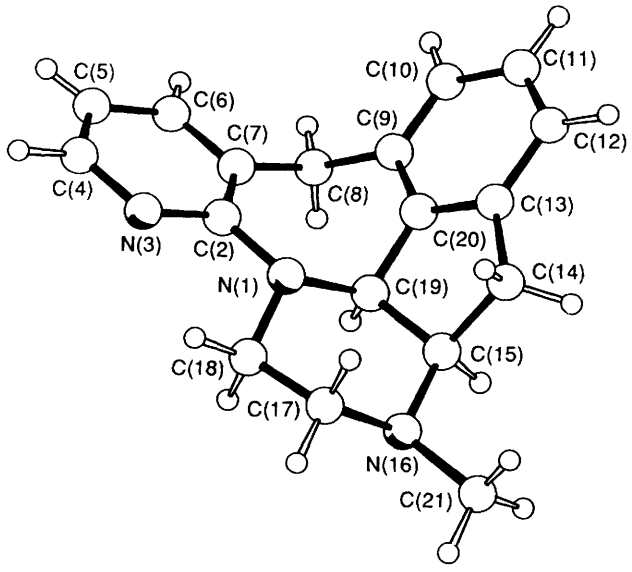


Fig. 1 Crystal structure of **1** showing crystallographic numbering

Kieselgel 60. Standard work-up for lithium aluminium hydride reductions involved quenching with wet ether followed by water, and then filtration to remove precipitated aluminium salts. Light petroleum refers to the fraction with b.p. 60–80 °C.

cis-1-*Azido*-2-*ethoxycarbonylaminoindane* **9**.—A solution of *trans*-1-chloro-2-ethoxycarbonylaminoindane **8** (6.0 g, 0.025 mol) in dry *N*,*N*-dimethylformamide (DMF) (25 cm^3) was treated with sodium azide (1.95 g, 0.03 mol) and the mixture was stirred in the dark for 48 h. The reaction was diluted with water and extracted into ether. The combined extracts were washed with water followed by brine. Concentration of the dried organic phase followed by chromatography on silica gel using a graded eluent of 5–10% ethyl acetate in light petroleum afforded the title compound **9** as a colourless oil (4.8 g, 77%), ν_{max}(film)/cm^{-1} 3320 (NH), 2090 (N_3) and 1700 (C=O); δ_H(80 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7, CH_3), 2.80 (1 H, dd, *J* 16 and 8.5, 3-H), 3.22 (1 H, dd, *J* 16 and 8, 3-H), 4.18 (2 H, q, *J* 7, OCH_2), 4.60 (1 H, m, 2-H), 4.88 (1 H, d, *J* 6, 1-H), 5.25 (1 H, br d, NH) and 7.30 (4 H, m, aromatic); *m*/*z* 218 ($M^+ - N_2$; 10%), 204 (2), 189 (5), 158 (12), 145 (20), 130 (100) and 118 (33) [Found: ($M^+ - N_2$) 218.1061. $C_{12}H_{14}N_2O_2$ requires *M*, 218.1068].

cis-2-*Methylaminoindan*-1-*amine* **6**.—A solution of the azide **9** (5.0 g, 0.02 mol) in dry ether (35 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (3.85 g, 0.10 mol) in dry ether (35 cm^3), cooled to ice temp., under nitrogen. After stirring at room temp. for 3 d, standard work-up produced a red oil (3.3 g). Bulb-to-bulb distillation (150 °C/0.1 mmHg) afforded the title compound **6** as a colourless oil (2.6 g, 81%), ν_{max}(film)/cm^{-1} 3280br (NH); δ_H(270 MHz; $CDCl_3$) 1.48 (3 H, br s, NH, exchanges with D_2O), 2.45 (3 H, s, CH_3), 2.77 (1 H, dd, *J* 15 and 7, 3-H), 2.95 (1 H, dd, *J* 15 and 7, 3-H), 3.26 (1 H, q, *J* 7, 2-H), 4.24 (1 H, d, *J* 7, 1-H), 7.18 (3 H, m, aromatic) and 7.20 (1 H, m, aromatic); δ_C(68 MHz; $CDCl_3$) 34.41, 35.54, 56.68, 63.99, 123.78, 124.70, 126.31, 127.19, 140.54 and 145.43; *m*/*z* 162 (M^+, 15%), 144 (53), 131 (63), 130 (100), 119 (74) and 103 (27). Bis hydrochloride salt m.p. 178–180 °C (from methanol–ether) (Found: C, 50.7; H, 7.1; N, 11.8. $C_{10}H_{16}Cl_2N_2$ requires C, 51.1; H, 6.9; N, 11.9%).

cis-4,4a,9,9a-*Tetrahydro*-1-*methyl*-1H-*indeno*[1,2-b]*pyrazine*-1,2-*dione* **12**.—A solution of the diamine **6** (2.7 g, 0.017 mol) in dry toluene (100 cm^3) containing diethyl oxalate (2.3 cm^3, 0.017 mol) was refluxed under nitrogen for 6 h. After cooling, the precipitate was filtered off and washed with ether to give the title compound **12** (2.2 g, 60%), m.p. 230–231.5 °C (from chloroform) (Found: C, 66.5; H, 5.3; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%); ν_{max}(KBr)/cm^{-1} 3240 (NH), 1670 and 1700 (C=O); δ_H(80 MHz; [$^2H_6$]-DMSO) 2.98 (3 H, s, CH_3), 3.0 (1 H, dd, *J* 15 and 7, 9-H), 3.38 (1 H, dd, *J* 15 and 7, 9-H), 4.33 (1 H, q, *J* 7, 9a-H), 4.97 (1 H, dd, *J* 7 and 2, collapses to a doublet *J* 7 on exchange with D_2O, 4a-H), 7.3 (4 H, m, aromatic) and 8.8 (1 H, br s, NH, exchanges with D_2O); δ_C(20 MHz; [$^2H_6$]-DMSO) 32.95, 36.21, 54.58, 59.95, 124.76, 127.03, 128.54, 139.64, 140.69, 155.50 and 156.17; *m*/*z* 216 (M^+, 22%), 188 (100), 144 (26), 130 (33) and 116 (60).

cis-2,3,4,4a,9,9a-*Hexahydro*-1-*methyl*-1H-*indeno*[1,2-b]*pyrazine* **4**.—A solution of aluminium chloride (37.3 g, 0.28 mol) in dry ether (200 cm^3) was added dropwise to a suspension of lithium aluminium hydride (10.0 g, 0.26 mol) in dry ether (200 cm^3) cooled to ice temp. under nitrogen. After stirring at room temp. for 3 h, the reaction was cooled in ice and treated portionwise with pyrazine **12** (15.0 g, 0.069 mol). The mixture was stirred overnight at room temp. and then quenched with wet ether and 10% sodium hydroxide (1 dm^3). The aqueous layer was separated and extracted with ether. The combined organic layers were washed (brine), dried and concentrated to give the title compound **4** as a yellow oil (12.7 g, 97%), ν_{max}(film)/cm^{-1} 3260 (NH); δ_H(270 MHz; $CDCl_3$) 1.80 (1 H, br s, NH, exchanges with D_2O), 2.28–2.43 (4 H, overlapping CH_3 and multiplet signals), 2.58 (1 H, m), 2.76 (1 H, dd, *J* 17 and 7, 9-H), 2.88 (2 H, m), 3.0–3.12 (2 H, overlapping, 9-H and 9a-H), 4.25 (1 H, d, *J* 5, 4a-H) and 7.15–7.38 (4 H, m, aromatic); δ_C(68 MHz; $CDCl_3$) 30.85, 42.57, 43.81, 52.35, 60.63, 65.18, 123.52, 125.60, 126.51, 127.52, 141.58 and 143.01; *m*/*z* 188 (M^+, 82%), 173 (28), 159 (10), 144 (68), 130 (38) and 116 (100). Bis hydrochloride salt m.p. 225 °C (decomp.) (from methanol–ether) (Found: C, 55.1; H, 7.2; N, 10.45. $C_{12}H_{18}Cl_2N_2$ requires C, 55.2; H, 6.95; N, 10.7%).

trans-1-*Azido*-2-*ethoxycarbonylaminoindane* **11**.—A solution of *trans*-1-chloro-2-ethoxycarbonylaminoindane **8** (5.0 g, 0.02 mol) in dry DMF (75 cm^3) was treated with sodium hydride (0.69 g of an 80% dispersion, 0.023 mol) and stirred, under nitrogen, at 40 °C for 10 h. After stirring at room temp. for a further 9 h the reaction was treated with ammonium chloride (1.24 g, 0.023 mol) followed by sodium azide (1.50 g, 0.023 mol) and heated at 50–60 °C for 50 min. The cooled mixture was poured into ice water and extracted into ether. After washing with water and brine the organic phase was dried and concentrated to give a brown oil (5.0 g). Purification on a short silica column using a graded eluent of 15–30% ethyl acetate in light petroleum afforded the title compound **11** as a pale yellow oil (3.8 g, 67%) which solidified on cooling, ν_{max}(film)/cm^{-1} 3320 (NH), 2090 (N_3) and 1690 (C=O); δ_H(60 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7, CH_3), 2.70 (1 H, dd, *J* 16 and 6, 3-H), 3.30 (1 H, dd, *J* 16 and 7, 3-H), 3.85–4.50 (3 H, overlapping, q, *J* 7, OCH_2 and m, 2-H), 4.65 (1 H, d, *J* 6, 1-H), 5.1 (1 H, br, NH) and 7.20 (4 H, m, aromatic); *m*/*z* 218 ($M^+ - N_2$; 6%), 204 (4), 189 (5), 158 (6), 145 (27), 130 (100) and 118 (46).

trans-2-*Methylaminoindan*-1-*amine* **7**.—A solution of the azide **11** (0.49 g, 2.0 mmol) in dry ether (10 cm^3) was added dropwise to a suspension of lithium aluminium hydride (0.38 g, 10.0 mmol) in dry ether (10 cm^3) under nitrogen. After 2 h at room temp. standard work-up afforded the title compound **7** as a pale brown oil (0.3 g, 92%) which was purified by bulb-to-bulb distillation (175 °C/0.1 mmHg), ν_{max}(KBr)/cm^{-1} 3320, 3210 (NH); δ_H(270 MHz, $CDCl_3$) 1.73 (3 H, s, exchanges with D_2O, NH and NH_2), 2.55 (1 H, s, CH_3), 2.58 (1 H, dd, *J* 15 and 8, 3-

H), 3.00 (1 H, q, *J* 8, 2-H), 3.21 (1 H, dd, *J* 15 and 8, 3-H), 3.98 (1 H, d, *J* 8, 1-H) and 7.15–7.33 (4 H, m, aromatic); δ_C(68 MHz; $CDCl_3$) 35.06, 36.65, 62.38, 72.18, 123.12, 124.73, 126.75, 127.37, 139.89 and 145.52; *m/z* 162 (M^+, 27%), 144 (70), 130 (60), 119 (100) and 103 (23) (Found: M^+, 162.1158. $C_{10}H_{14}N_2$ requires *M*, 162.1151).

trans-2-*Ethoxycarbonylamino*-1-(4-*methoxybenzylamino*)-*indane* **13**.—A solution of *trans*-1-chloro-2-ethoxycarbonylaminoindane **8** (5.0 g, 0.021 mol) in dry DMF (75 cm^3) was treated with sodium hydride (0.69 g, of an 80% dispersion, 0.023 mol) and stirred at 40 °C under nitrogen for 12 h. After a further 10 h at room temp., 4-methoxybenzylamine (3.0 cm^3, 0.023 mol) was added dropwise and the reaction was heated at 40 °C for 24 h, and then at 50 °C for a further 24 h. The reaction was concentrated and the residue diluted with water. After extraction into ethyl acetate the organic layers were washed (brine), dried and concentrated. Trituration with pentane followed by crystallisation from ethyl acetate–light petroleum afforded aminoindane **13** (4.2 g, 59%), m.p. 115–116.5 °C (Found: C, 70.5; H, 7.2; N, 8.1. $C_{20}H_{24}N_2O_3$ requires C, 70.6; H, 7.1; N, 8.2%); ν_{max}(KBr)/cm^{-1} 3200 (NH) and 1710 (C=O); δ_H(270 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7, CH_3), 1.66 (1 H, br, NH, exchanges with D_2O), 2.65 (1 H, dd, *J* 15 and 6, 3-H), 3.43 (1 H, dd, *J* 15 and 7, 3-H), 3.79 (3 H, s, OCH_3), 3.89 (2 H, s, CH_2N), 4.0–4.2 (3 H, overlapping signals, OCH_2 and 2-H), 4.33 (1 H, br, 1-H, collapses to a broad doublet, *J* 5 with D_2O), 4.9 (1 H, br, NH, exchanges with D_2O), 6.85 (2 H, d, *J* 8, aromatic) and 7.1–7.4 (6 H, m, aromatic); δ_C(68 MHz; $CDCl_3$) 14.66, 37.66, 50.13, 55.21, 57.89, 60.76, 68.48, 113.81, 124.47, 124.89, 126.90, 127.92, 129.30, 132.77, 140.32, 142.74, 156.41 and 158.66; *m/z* (M^+ absent) 295 (3), 251 (8), 219 (90), 136 (55), 130 (60) and 121 (100).

trans-1-(4-*Methoxybenzylamino*)-2-*methylaminoindane* **14**.—A solution of indane **13** (1.70 g, 5.0 mmol) in dry tetrahydrofuran (30 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g, 20.0 mmol) in dry tetrahydrofuran (THF) (15 cm^3) cooled in ice under nitrogen. The reaction was allowed to warm to room temp. and stirred overnight. After standard work-up, purification on silica gel, using a graded eluent of 0–30% methanol in ethyl acetate afforded the indane **14** as a pale yellow oil (0.97 g, 69%) which solidified on cooling after bulb-to-bulb distillation at 250 °C/0.1 mmHg (Found: C, 76.8; H, 8.1; N, 9.55. $C_{18}H_{22}N_2O$ requires C, 76.6; H, 7.85; N, 9.9%); ν_{max}(film)/cm^{-1} 3320 (NH); δ_H(270 MHz; $CDCl_3$) 1.72 (2 H, br s, NH), 2.48 (3 H, s, NCH_3), 2.62 (1 H, dd, *J* 17 and 8, 3-H), 3.17–3.32 (2 H, m, overlapping, 2-H and 3-H), 3.78 (3 H, s, OCH_3), 3.92 (2 H, ABq, *J* 13, CH_2N), 4.03 (1 H, d, *J* 5, 1-H), 6.87 (2 H, d, *J* 9, aromatic) and 7.16–7.40 (6 H, overlapping, aromatic); δ_C(68 MHz; $CDCl_3$) 34.78, 37.09, 50.78, 55.27, 67.58, 68.07, 113.84, 124.22, 125.15, 126.61, 127.58, 129.24, 132.96, 141.12, 143.92 and 158.67; *m/z* (M^+ absent) 161 (25), 144 (56), 136 (78), 130 (100), 121 (87) and 116 (22).

trans-4,4a,9,9a-*Tetrahydro*-4-(4-*methoxybenzyl*)-1-*methyl*-1H-*indeno*[1,2-b]*pyrazine*-2,3-*dione* **15**.—A solution of the diamine **14** (0.95 g, 3.4 mmol) in mesitylene (20 cm^3) containing diethyl oxalate (0.5 cm^3, 3.7 mmol) was refluxed under nitrogen. After 15 h, diethyl oxalate (0.5 cm^3) was added, and refluxing was continued for a further 9 h. Filtration of the cooled reaction mixture followed by washing of the precipitate with ether afforded the title compound **15** as a cream coloured solid (0.44 g, 40%), m.p. 184–185 °C (from chloroform–hexane) (Found: C, 71.1; H, 6.2; N, 8.4. $C_{20}H_{20}N_2O_3$ requires C, 71.4; H, 6.0; N, 8.3%); ν_{max}(Nujol)/cm^{-1} 1665 (C=O); δ_H(270 MHz; $CDCl_3$) 2.90 (1 H, dd, *J* 15 and 11, 9-H), 3.18 (3 H, s, NCH_3), 3.26 (1 H, dd, *J* 15 and 7, 9-H), 3.78 (1 H, s, OCH_3), 4.14 (1 H, m, 9a-H), 4.90 (1 H, d, *J* 16, CH_2N), 6.85 (2 H, d, *J* 7, aromatic) and 7.1–7.45 (6 H, overlapping signals, aromatic); δ_C(68 MHz; $CDCl_3$) 31.20, 33.07, 46.79, 55.29, 63.07, 63.85, 114.36, 124.68, 125.90, 127.76, 127.85, 127.89, 128.51, 136.46, 128.61, 158.77, 158.94 and 159.48; *m/z* 336 (M^+, 33%), 220 (25), 136 (25), 121 (100) and 116 (73) (Found: M^+, 336.1475. $C_{20}H_{20}N_2O_3$ requires *M*, 336.1474).

trans-2,3,4,4a,9,9a-*Hexahydro*-4-(4-*methoxybenzyl*)-1-*methyl*-1H-*indeno*[1,2-b]*pyrazine* **16**.—A solution of aluminium chloride (6.9 g, 0.052 mol) in dry ether (65 cm^3) was added dropwise under nitrogen to a suspension of lithium aluminium hydride (2.0 g, 0.053 mol) in dry ether (65 cm^3) cooled in ice. After stirring at room temp. for 1 h, the reaction was cooled in ice and treated portionwise with compound **15** (4.4 g, 0.013 mol). The mixture was stirred overnight at room temp. and then quenched with wet ether followed by 10% sodium hydroxide (400 cm^3). The aqueous layer was separated and extracted into ether. The combined organic layers were washed (brine), dried and concentrated to give pyrazine **16** as an oil (3.90 g, 97%). Maleate salt, m.p. 178–179.5 °C (from acetone–methanol) (Found: C, 67.8; H, 6.7; N, 6.55. $C_{24}H_{28}N_2O_5$ requires C, 67.9; H, 6.65; N, 6.6%); δ_H(270 MHz; [$^2H_6$]-DMSO) 2.85–3.15 (6 H, m, overlapping signals), 3.25–3.45 (3 H, m, overlapping signals), 3.63 (1 H, m), 3.78 (1 H, d, *J* 13, CH_2N), 3.87 (3 H, s, OCH_3), 4.10 (1 H, d, *J* 13, CH_2N), 4.41 (1 H, d, *J* 10, 4a-H), 7.05 (2 H, d, *J* 8, aromatic) and 7.35–7.65 (6 H, m, aromatic); δ_C(68 MHz; [$^2H_6$]-DMSO) 30.81, 40.42, 47.82, 49.86, 50.26, 55.07, 64.14, 68.11, 113.80, 123.34, 125.62, 127.45, 128.00, 130.21, 135.70, 137.50, 138.50 and 158.59; *m/z* (free base) 308 (M^+; 1%), 188 (29), 187 (100), 149 (20), 144 (15), 130 (18), 121 (48) and 53 (116).

trans-2,3,4,4a,9,9a-*Hexahydro*-1-*methyl*-1H-indeno[1,2-b]-*pyrazine* **5**.—A mixture of compound **16** (8.5 g, 0.0275 mol), sulfuric acid (5.5 cm^3), thioanisole (27.5 cm^3) and trifluoroacetic acid (27.5 cm^3) was refluxed under nitrogen for 75 min. The reaction was concentrated under reduced pressure and azeotropic distillation with xylene removed residual thioanisole. The resulting oil was dissolved in water and washed with ether. After the pH had been adjusted to 14 using 40% sodium hydroxide the aqueous phase was extracted into ether. The dried organic layers were concentrated and purified on silica gel using 10% methanol in ethyl acetate as eluent to give the title compound **5** (3.8 g, 74%), ν_{max}(film)/cm^{-1} 3280 (NH); δ_H(270 MHz; $CDCl_3$) 1.88 (1 H, s, NH), 2.0–2.18 (2 H, m, overlapping), 2.32 (1 H, s, NCH_3), 2.66 (1 H, dd, *J* 14 and 11 H, 9-H), 2.92 (1 H, ddd, *J* 11, 3 and 3, 2-Heq or 3-Heq), 3.02 (1 H, dd, *J* 14 and 6, 9-H), 3.12–3.24 (2 H, m, overlapping), 3.81 (1 H, d, *J* 10, 4a-H) and 7.10–7.30 (4 H, m, aromatic); δ_C(68 MHz; $CDCl_3$) 34.20, 43.86, 46.96, 57.77, 66.49, 76.25, 121.57, 125.04, 126.65, 127.13, 139.68 and 142.84; *m/z* 188 (M^+; 40%), 187 (100), 173 (7), 144 (36), 130 (39), 121 (45) and 116 (73). Maleate salt m.p. 137–139 °C (from acetone–ether) (Found: C, 63.3; H, 6.8; N, 9.2. $C_{16}H_{20}N_2O_4$ requires C, 63.1, H, 6.6; N, 9.2%).

cis-4-(3-*Cyano*-2-*pyridyl*)-2,3,4,4a,9,9a-*hexahydro*-1-*methyl*-1H-*indeno*[1,2-b]*pyrazine* **17**.—A solution of *cis*-piperazine **4** (3.77 g, 0.02 mol) in dry DMF (45 cm^3) was treated with 2-chloronicotinonitrile (3.06 g, 0.022 mol) and potassium fluoride (3.49 g, 0.06 mol). The mixture was heated at reflux, under nitrogen, for 24 h and during this period additional 2-chloronicotinonitrile (1.1 g, 0.008 mol) was added. The reaction mixture was then poured into water and extracted into chloroform. The combined organic layers were washed with water, dried and concentrated. Purification on silica gel using a graded eluent of 30–45% ethyl acetate in light petroleum afforded the nitrile **17** (4.24 g, 73%), ν_{max}(KBr)/cm^{-1} 2200 (C≡N); δ_H(270 MHz; $CDCl_3$; resolution enhanced spectrum)

2.33 (3 H, s, CH_3), 2.41 (1 H, ddd, *J* 12, 12 and 3, 2-Hax), 2.78 (1 H, ddd, *J* 12, 3 and 3, 2-Heq), 2.94 (1 H, dd, *J* 16 and 5, 9-H), 3.01 (1 H, t, *J* 5, 9a-H), 3.07 (1 H, d, *J* 16, 9-H), 3.36 (1 H, ddd, *J* 14, 12 and 3, 3-Hax), 4.34 (1 H, ddt, 14, 3, 3 and 2, 3-Heq), 6.02 (1 H, d, *J* 5, 4a-H), 6.78 (1 H, dd, *J* 7 and 5, aromatic), 7.02–7.34 (4 H, m, aromatic), 7.81 (1 H, dd, *J* 8 and 2, aromatic) and 8.36 (1 H, dd, *J* 5 and 2, aromatic); δ_C(20 MHz; $CDCl_3$) 35.52, 43.63, 43.95, 53.94, 62.60, 66.41, 93.33, 113.68, 118.14, 123.26, 125.51, 126.55, 127.66, 140.44, 141.23, 144.34, 152.04 and 159.89; *m/z* 290 (M^+; 30%), 275 (7), 233 (100), 232 (46), 158 (30), 144 (15), 130 (15), 116 (38) and 115 (36).

cis-4a,5,6,7,12,12c-*Hexahydro*-5-*methyl*-4H-5,7a,8-*triaza*-*benzo*[5,6]*cyclohepta*[1,2,3,4-def]*fluorene* **1**.—The nitrile **17** (4.0 g, 0.014 mol) was treated with a solution of potassium hydroxide (20.0 g) in ethanol (80 cm^3) and the mixture was heated at 100 °C, under nitrogen, for 30 h. After evaporation of solvent the residue was dissolved in water and washed with dichloromethane. The pH of the aqueous phase was adjusted to 6 with dilute hydrochloric acid and the solution was evaporated to dryness. Extraction of the residue into chloroform followed by evaporation of solvent afforded the acid **19** as a brown foam (5.2 g). A solution of compound **19** (4.9 g, 0.016 mol) in dry THF (100 cm^3) was added dropwise, under nitrogen, to a suspension of lithium aluminium hydride (5.0 g, 0.13 mol) in dry THF (50 cm^3). The mixture was heated under reflux for 2.5 h. Standard work-up followed by chromatography on silica gel using 2% methanol in ethyl acetate as eluent afforded alcohol **21** (2.3 g; 60% based on nitrile), ν_{max}(film)/cm^{-1} 3300 (OH); δ_H(270 MHz; $CDCl_3$) 2.40 (1 H, s, CH_3), 2.56 (1 H, m), 2.73 (1 H, m), 2.83 (1 H, dd, *J* 16 and 6, 9-H), 3.10–3.25 (2 H, m), 3.30–3.49 (2 H, m), 4.22 (1 H, d, *J* 14, C*H*OH), 4.56 (1 H, d, *J* 14, C*H*OH), 4.98 (1 H, d, *J* 5, 4a-H), 6.80–7.30 (5 H, m, aromatic), 7.54 (1 H, dd, *J* 7 and 2) and 8.36 (1 H, dd, *J* 6 and 2) (Found: M^+, 295.1687. $C_{18}H_{21}N_3O$ requires *M*, 295.1685). The alcohol **21** (2.14 g, 7.25 mmol) was added gradually to polyphosphoric acid (50 g) with stirring at 100 °C. After a further 3 h at this temperature the reaction mixture was poured into ice, washed with ether, then basified and extracted into chloroform. Concentration of the combined chloroform layers followed by purification on silica gel using 2% methanol in ethyl acetate as eluent afforded the title compound **1** (0.78 g, 39%), m.p. 118–120 °C (from ether–pentane) (Found: C, 77.6; H, 6.85; N, 15.0. $C_{18}H_{19}N_3$ requires C, 77.95; H, 6.9; N, 15.15%); δ_H(270 MHz; $CDCl_3$) 2.52 (3 H, s, CH_3), 2.75–2.98 (3 H, m), 3.03 (1 H, m), 3.22 (1 H, dd, *J* 16 and 9, 4-H), 3.35 (1 H, d, *J* 16, 12-H), 3.72 (1 H, ddd, *J* 9, 7 and 7, 4a-H), 4.82 (1 H, d, *J* 16, 12-H overlapping with 1 H, m), 5.28 (1 H, d, *J* 7, 12c-H), 6.53 (1 H, dd, *J* 7 and 5, aromatic), 7.0–7.30 (4 H, m, aromatic) and 8.0 (1 H, m, aromatic); δ_C(68 MHz; $CDCl_3$), 27.77, 39.55, 42.95, 44.41, 49.00, 58.07, 63.72, 114.28, 121.33, 123.38, 123.61, 128.90, 137.00, 138.72, 139.93, 140.16, 145.77 and 158.25; *m/z* 277 (M^+; 10%), 262 (25), 233 (11), 220 (100), 219 (46) and 204 (10) (Found: M^+, 277.1574. $C_{18}H_{19}N_3$ requires *M*, 277.1574). Concentration of the ether wash liquors afforded light brown needles (0.13 g, 13%) shown to be identical to an authentic sample of indan-2-one by ^{1}H NMR spectroscopy.

trans-4-(3-*Cyano*-2-*pyridyl*)-2,3,4,4a,9,9a-*hexahydro*-1-*methyl*-1H-*indeno*[1,2-b]*pyrazine* **18**.—A mixture of the *trans*-piperazine **5** (1.8 g, 9.8 mmol), 2-chloronicotinonitrile (2.0 g, 14.7 mmol) and potassium fluoride (1.70 g, 29.4 mmol) in dry DMF (25 cm^3) was heated under nitrogen at 140 °C for 29 h. The reaction was diluted with water, basified with sodium hydroxide and extracted into chloroform. The combined organic layers were washed with brine, dried and concentrated. Purification on silica gel using an eluent graded from 50% ethyl acetate in light petroleum to ethyl acetate afforded nitrile **18** as an oil (1.39 g, 49%) which crystallised on cooling. ν_{max}(film)/cm^{-1} 2225 (C≡N); δ_H($CDCl_3$; 270 MHz) 2.42 (3 H, s, CH_3), 2.53 (1 H, ddd, *J* 12, 12 and 3, 2-Hax), 2.65–2.90 (2 H, m, overlapping, 9-H and 9a-H), 2.98 (1 H, m, 2-Heq), 3.08 (1 H, dd, *J* 12 and 5, 9-H), 3.28 (1 H, ddd, *J* 12, 12 and 3, 3-Hax), 3.82 (1 H, ddd, *J* 12, 3 and 3, 3-Heq), 4.57 (1 H, d, *J* 11, 4a-H), 6.30 (1 H, d, *J* 9, aromatic), 6.90–7.25 (4 H, m, aromatic), 7.95 (1 H, dd, *J* 9 and 2, aromatic) and 8.48 (1 H, dd, *J* 5 and 2, aromatic); δ_C(68 MHz; $CDCl_3$) 34.22, 43.30, 56.00, 56.21, 66.97, 72.17, 104.01, 116.46, 118.46, 123.99, 124.91, 125.94, 126.71, 139.43, 141.74, 142.58, 151.61 and 164.10; *m/z* 290 (M^+, 48%), 233 (35), 232 (26), 158 (83) and 116 (100) (Found: M^+, 290.1526. $C_{18}H_{18}N_4$ requires *M*, 290.1531). Oxalate salt m.p. 210–212 °C (from methanol–acetone) (Found: C, 63.1; H, 5.3; N, 14.7. $C_{20}H_{22}N_4O_4$ requires C, 63.15; H, 5.3; N, 14.7%).

trans-4a,5,6,7,12,12c-*Hexahydro*-5-*methyl*-4H-5,7a,8-*triaza*-*benzo*[5,6]*cyclohepta*[1,2,3,4-def]*fluorene* **2**.—A stirred solution of the nitrile **18** (2.1 g, 7.2 mmol) in ethanol (50 cm^3) was treated with potassium hydroxide (4.2 g) and heated at 60 °C for 84 h. A further portion of potassium hydroxide (2.1 g) was added and heating was continued at 80 °C for 10 h. After evaporation of the solvent, the reaction was diluted with water and washed with chloroform. The pH of the aqueous phase was adjusted to 5.4 with dilute hydrochloric acid and the solution was evaporated to dryness. Extraction of the residue into chloroform afforded the acid **20** as a foam (1.3 g, 58%). The chloroform washes were concentrated and further hydrolysis afforded a second crop (0.5 g) of **20**. A solution of compound **20** (0.70 g, 2.3 mmol) in dry THF (35 cm^3) was added dropwise under nitrogen to an ice cooled suspension of lithium aluminium hydride (0.67 g, 18.4 mmol) in the dry THF (10 cm^3). After stirring at room temp. for 1 h, standard work-up followed by chromatography on silica gel using 10% methanol in ethyl acetate as eluent afforded the alcohol **22** (0.49 g, 73%), ν_{max}(KBr)/cm^{-1} 3150 (OH); δ_H(80 MHz; $CDCl_3$) 2.30–3.30 (10 H, m, overlapping), 4.56 (1 H, d, *J* 14, C*H*OH), 4.65 (1 H, d, *J* 9, 4a-H), 4.98 (1 H, d, *J* 14, C*H*OH), 5.90 (1 H, d, *J* 8, aromatic), 6.70–7.35 (4 H, m, aromatic), 7.65 (1 H, dd, *J* 7 and 2, aromatic) and 8.65 (1 H, dd, *J* 4 and 2, aromatic) (Found: M^+, 295.1690. $C_{18}H_{21}N_3O$ requires *M*, 295.1685). To a stirred solution of alcohol **22** (0.83 g, 2.8 mmol) in methanesulfonic acid (2.9 cm^3) was added phosphorous pentoxide (2.0 g) and the mixture was stirred at room temperature for 48 h. The reaction was poured into ice, basified with 40% sodium hydroxide and extracted into chloroform. Chromatography on silica gel using 5% methanol in ethyl acetate as eluent afforded the title compound **2** (0.64 g, 82%), δ_H (270 MHz; $CDCl_3$), 2.28 (1 H, m, 4a-H), 2.43 (3 H, s, CH_3), 2.60–2.86 (2 H, m, overlapping, 4-H and 6-Hax), 2.93 (1 H, dd, *J* 15 and 7, 4-H), 3.02 (1 H, m, 6-Heq), 3.38 (1 H, d, *J* 15, 12-H), 3.51 (1 H, ddd, *J* 15, 13 and 4, 7-Hax), 4.28 (1 H, d, *J* 15, 12-H), 4.55 (1 H, br d, *J* 15, 7-Heq), 4.74 (1 H, d, *J* 10, 12c-H), 6.65 (1 H, dd, *J* 9 and 5, aromatic), 7.0–7.16 (3 H, m, aromatic), 7.28 (1 H, m, aromatic) and 8.08 (1 H, dd, *J* 5 and 2, aromatic); δ_C (68 MHz; $CDCl_3$) 32.54, 37.62, 43.23, 47.05, 54.82, 66.42, 73.02, 115.69, 123.37, 124.73, 127.94, 128.80, 135.59, 136.59, 137.92, 139.93, 145.93 and 156.89; *m/z* 277 (M^+, 15%), 262 (28), 233 (16), 220 (100), 219 (40) and 204 (10) (Found: M^+, 277.1580. $C_{18}H_{19}N_3$ requires *M*, 277.1579). Maleate salt, m.p. 206–207 °C (decomp.) (from acetone–ether) (Found: C, 67.3; H, 5.8; N, 10.7. $C_{22}H_{23}N_3O_4$ requires C, 67.2; H, 5.9; N, 10.7%).

Crystal Data for Compound **1**.—$C_{18}H_{19}N_3$, *M* = 277.37. Orthorhombic, *a* = 8.644 (1), *b* = 15.179 (2), *c* = 22.204 (4) Å, *V* = 2913 $Å^3$, space group *Pnab*, *Z* = 8. The compound is a racemate. *R* = 0.054 for 1367 independent observed reflections [Fo > 3σ(Fo); $\theta \leqslant 55°$ with Cu-Kα radiation]. Tables of

fractional coordinates, bond lengths and angles, hydrogen coordinates and thermal parameters have been deposited with the Cambridge Crystallographic Database.*

Acknowledgements

The authors would like to thank Dr. D. J. Williams (Imperial College) for carrying out the X-ray determination and Mr. D. M. Smith for assistance with interpretation of NMR spectra.

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

References

1 Part 1, B. S. Orlek, G. T. Borrett and D. M. Smith, preceding paper. Paper no. 3/00733B.
2 For a preliminary account of this work see B. S. Orlek, *Tetrahedron Lett.*, 1986, 1699. References to other methods for preparing vicinal diamines are cited therein.
3 B. J. Walker and P. J. Wrobel, *J. Chem. Soc., Chem. Commun.*, 1980, 462.
4 Y. Pocker, *J. Chem. Soc.*, 1959, 2319.
5 M. Saito, Y. Kayama, T. Watanabe, H. Fukushima, T. Hara, K. Koyano, A. Takenaka and Y. Sasada, *J. Med. Chem.*, 1980, **23**, 1364.
6 C. F. Huebner, E. M. Donoghue, C. J. Novak, L. Dorfman and W. Wenkert, *J. Org. Chem.*, 1970, **35**, 1149.
7 Y. Kiso, K. Ukawa and T. Akita, *J. Chem. Soc., Chem. Commun.*, 1980, 101.

Paper 3/00734K
Received 5th *February* 1993
Accepted 25th *February* 1993