Synthesis and oxidative behaviour of reduced indeno[1,2-*b*]quinoxalines and benzo[*b*]phenazines

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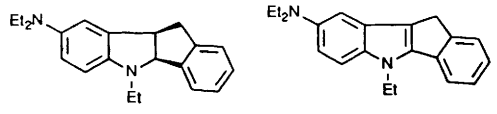
New routes to tetracyclic quinoxalines have been explored and their oxidative behaviour has been examined. Only if such compounds are devoid of benzylic hydrogen atoms are the corresponding cation radicals stable. Attempts to prepare certain polymethylated quinoxalines failed because of steric problems, and evidence is presented to show that in the case of some monohydrochloride salts proton migration between two nitrogen atoms is discernable through ^{1}H NMR spectroscopy.

We are interested in compounds which form stable radical cations on single-electron transfer since these may be of value as chain-breaking antioxidants. In previous work[1] we showed that the 8-(*N*,*N*-diethylamino)-4b,9b-dihydro-10*H*-indeno[1,2-*b*]indole **1** was readily oxidised and generated a blue radical cation which, although stable in solution for several hours, slowly decayed to the indole derivative **2** and other products. We consider that the 1,4-orientation of the nitrogen atoms is responsible for the low oxidation potential (+0.12 V *vs.* SCE) of the compound **1** and we were interested to know if the same type of conjugative effect might operate for the hexamethyl-5*H*-indeno[1,2-*b*]quinoxaline **3** where the two basic nitrogen atoms are in the same ring and have an 1,2-disposition. In this molecule the presence of methyl groups around the heterocyclic ring would be expected to prolong the life time of the corresponding radical cation by blocking the decomposition pathways which involve deprotonation.



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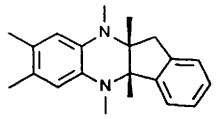


3

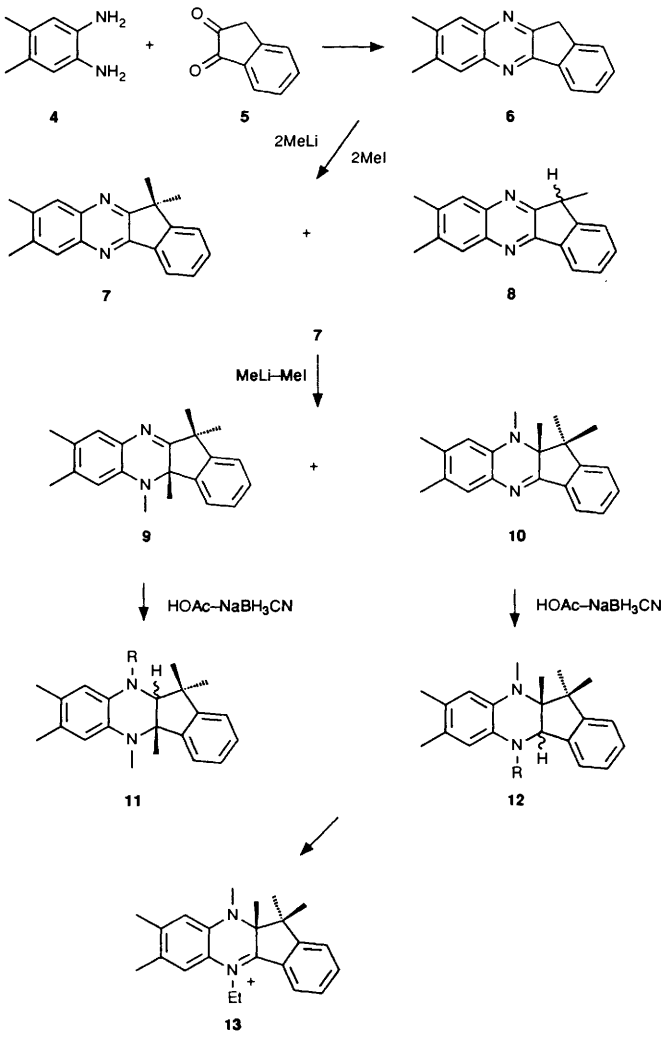
In order to synthesise **3**, dihydroindene-1,2-dione **5** and 4,5-dimethylbenzene-1,2-diamine **4**, were allowed to react to give 7,8-dimethylindenoquinoxaline **6** in 89% yield which we then planned to treat with 2 equiv. of methyllithium and of methyl iodide to give the target compound. However, this led only to alkylation at the ring methylene group and the formation of the dialkylated derivative **7**, plus a small amount of the monoalkylated analogue **8**. Further reaction of the dialkylated compound with more methyllithium, followed by methyl iodide gave the tetraalkylated isomers **9** and **10** in the ratio 10:7. These could not be separated, so the mixture was reduced with sodium cyanoboranuide in acetic acid with the expectation that **11** (R = H) and **12** (R = H) might form. Instead the *N*-ethyl tetrahydro derivatives **11** (R = Et) and **12** (R = Et) were produced and, whereas **11** (R = Et) was stable as a mixture of diastereoisomers, the isomer **12** underwent immediate oxidation to the iminium salt **13** during work-up (Scheme 1). Presumably the difference between the oxidative behaviour of the two *N*-ethyltetrahydroindenoquinoxalines is that **12** (R = Et) bears a benzylic proton.

The introduction of an *N*-ethyl group into nitrogen heterocycles during the reduction with acetic acid–sodium cyanoboranuide is not an unusual occurrence[2] and the probable mechanisms for such reactions have been discussed by Gribble.[3,4] An elegant solution to the 'problem' of reductive *N*-ethylation of diazines by sodium cyanoboranuide in acetic acid is inherent in the work of Russell *et al.*[5] who used the hydride reagent with methanol as solvent and in the presence of benzyl chloroformate. In this way, the corresponding *N*-benzyloxycarbonyl derivatives were obtained, which could be cleaved in a subsequent step. Curiously, for the benzo[*b*]phenazines described later in this paper, reductive *N*-ethylation by sodium cyanoboranuide–acetic acid was not observed, even though the reaction conditions were very similar.

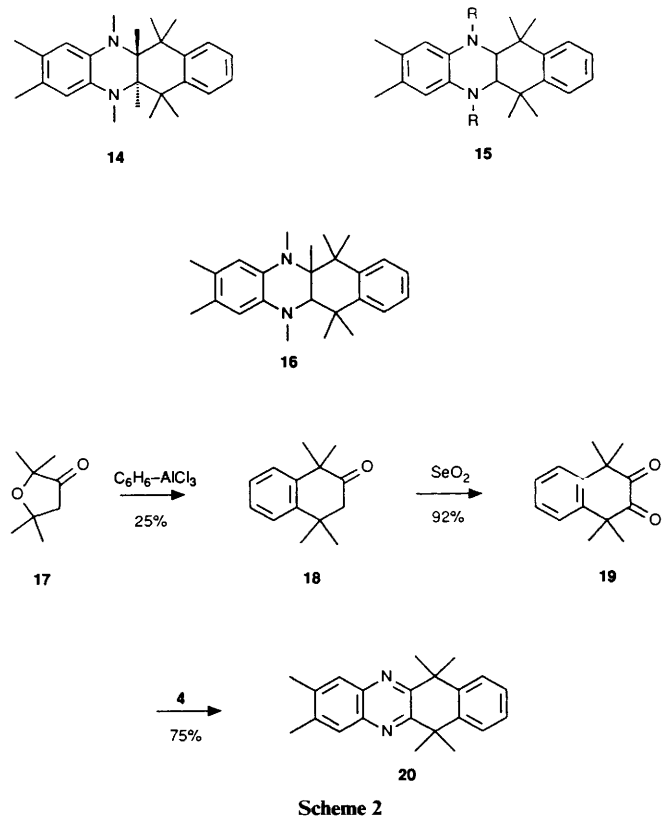
Although the full methylation of the indenoquinoxaline by a tandem dimethylation approach to give **3** was not possible, complete methylation might be possible in a less strained system and thus we selected the benzo[*b*]phenazine **14** as our next target. Even so this is still a very sterically crowded molecule, but we recognised that should the introduction of all the methyl groups prove difficult then, at least, compounds of the type **15** and **16** lacking benzylic protons should be more stable than the indenoquinoxaline **12** (R = Et).

The starting material for the synthesis of compound **14** was the corresponding benzophenazine **20** and this was obtained by the route shown in Scheme 2, the key step being a Friedel–Crafts alkylation by the tetrahydrofuranone **17** affording the ketone **18**[6] (albeit in only 25% yield). Selenium oxide oxidation of **18** then gave the diketone **19**,[7] which upon reaction with the diamine **4** yielded the desired quinoxaline **20**.

The hexahydrobenzophenazine **15** (R = H) was obtained through reduction of the parent compound **20** with sodium cyanoboranuide in acetic acid and this product was converted into the di(*N*-methyl) derivative **15** (R = Me) through successive treatment with methyllithium and methyl iodide. Both products are symmetrical so in neither case was it possible to deduce the stereochemistry of the central ring junction. Interestingly, whereas **15** (R = Me) rapidly discolours in air and forms at least four decomposition products on chromatography, its demethyl derivative **15** (R = H) is more stable and can be purified by column chromatography. In contrast to **11** (R = Et), however, this difference in reactivity cannot now be due to the presence of benzylic hydrogen atoms. Treatment of **20** with methyllithium gave the 11a-methyltetrahydro derivative **21** in quantitative yield, but attempts to introduce a second methyl group at C-5a failed, and successive reactions of either **20**, or **21**, with methyllithium and methyl



Scheme 1



Scheme 2

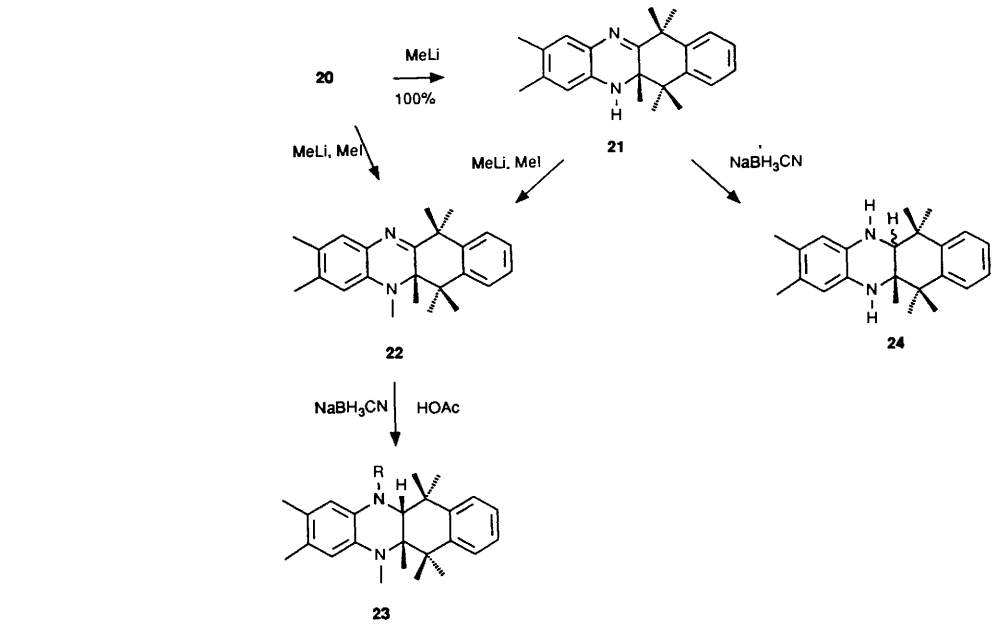
iodide gave only the *N*-methyl derivative **22**. Reduction of the imine **21** with sodium cyanoboranuide in acetic acid afforded the fully reduced derivative **23** (R = H) in 85% yield and this was then *N*-methylated by successive treatment with methyllithium and methyl iodide, affording the di(*N*-methyl) compound **23** (R = Me). Reduction of the imine **21** gave the corresponding hexahydro analogue **24**.

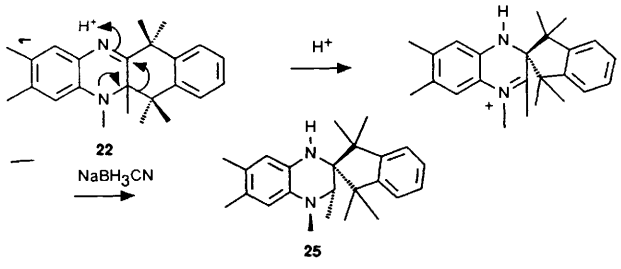
The geometry of the stable *cis*-ring fusion [8] in compound **23** (R = Me) was established by X-ray crystallography (see Fig. 1) even though, from a kinetic point of view, an approach of the reducing agent from the opposite side to the methyl group at C-11a in the parent imine might have been preferred. In addition to the expected hexahydroquinoxaline **23** (R = H), the sodium cyanoboranuide reduction of **22** led to the formation of a small amount (15%) of the spiro compound **25**. The structure of this compound was also determined by single crystal X-ray crystallography (see Fig. 2) and we assume that this product originates as shown in Scheme 3.

All the reduced benzophenazines gave rise to cyclic voltammograms with an oxidation peak at *ca.* +0.2 V (*vs.* SCE), but whereas the results for **15** (R = H), **15** (R = Me) and **23** (R = H) all showed that initial oxidation is followed by rapid chemical reactions, that of **23** (R = Me) was indicative of a slow charge-transfer irreversible oxidation, without accompanying chemical reactions. In line with this we observed that when this compound was eluted through a column of silica gel using chloroform as the eluent the corresponding radical cation was formed. It was stable and gave rise to an ESR spectrum, which consisted of a triplet broadened by further fine coupling. The ^{1}H NMR spectrum of this species showed the resonances for all of the protons attached to the reduced quinoxaline unit to be broadened, but the aromatic proton signals of the tetrahydronaphthalene ring and the methyl groups bonded to C-6 and C-11 were sharp. We consider this to reflect the distribution of electron density in the radical cation. Other compounds in this series *e.g.* **15** (R = H), **15** (R = Me), **21** and **24** when exposed to air also gave ^{1}H NMR spectra which initially showed broadened proton signals for the reduced quinoxaline unit, whereas those of the rest of each molecule were sharp. On standing, however, the spectra became complex. We are still investigating these results.

In the course of the preparation of the tetralone **18** we observed the co-production of a second compound: the acetyl compound **26**. We assume that this was formed during the Friedel–Crafts reaction between the tetrahydrofuranone **17** and benzene. Thus the IR spectrum of the residue, left after the isolation of the tetralone, indicated that a ketone was present and when this product was treated with selenium dioxide a keto aldehyde **27** was obtained. We were unable to isolate this compound, other than in the form of an acetal with ethanol, and so it was characterised as the quinoxaline **28** (this last compound was also reduced to afford its tetrahydro derivative **29**). A possible mechanism for the formation of **27** is summarised in Scheme 4. It involves a Friedel–Crafts acylation step, rather than an alkylation (as needed for the production of the tetralone), and a Lewis acid mediated migration of a methyl group.

In parallel with the work on phenazines we also selected some simpler analogues for an assessment of their ability to form stable radical cations. Thus the cyclopenta[*b*]quinoxalines **32** (R = propyl, hexyl or octyl) were synthesised by allowing 3,3,5,5-tetramethylcyclopentane-1,2-dione **30** to react with 4,5-dimethylbenzene-1,2-diamine **4** and reducing the product **31** with sodium cyanoboranuide to give **31** (R = H), which was





Scheme 3

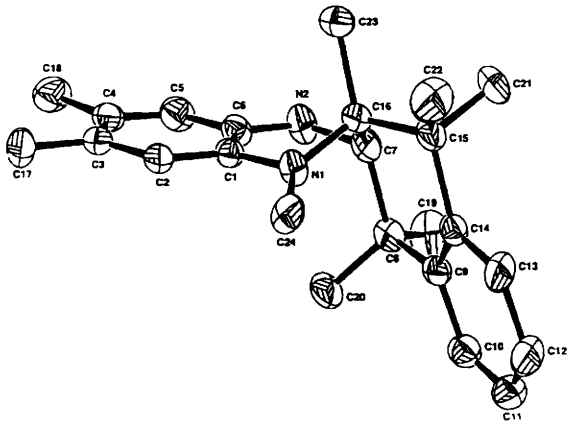


Fig. 1 ORTEP plot of **23** (R = Me)

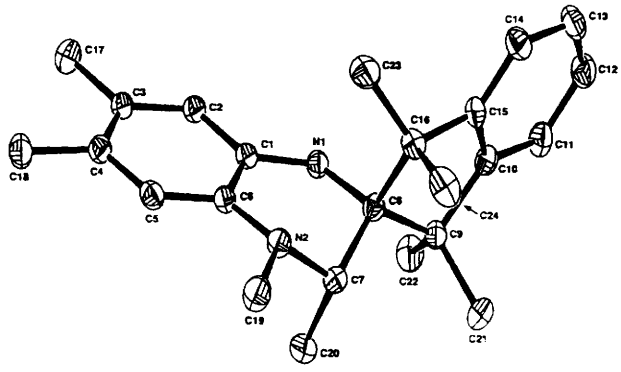
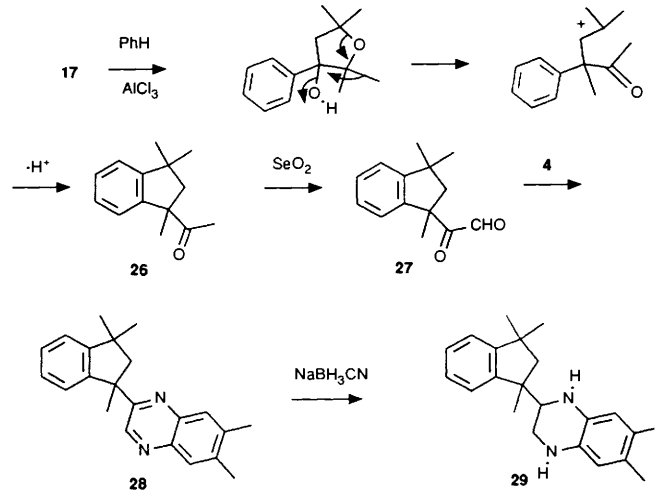


Fig. 2 ORTEP plot of **25**



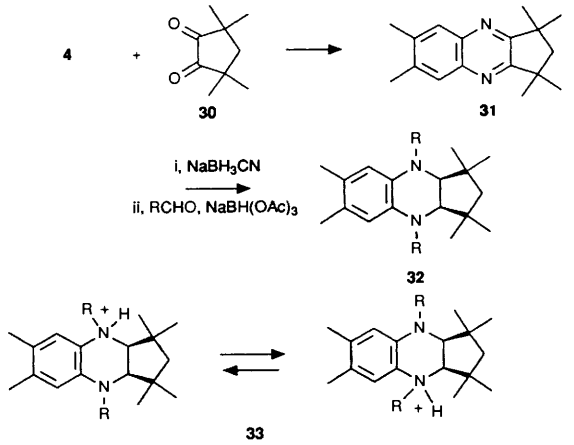
Scheme 4

reductively *N*-alkylated by the action of the appropriate alkanal and sodium triacetoxyboranuide. These products were characterised as their monohydrochloride salts **33** (R = alkyl) by treating them with a large excess of diethyl ether saturated with hydrogen chloride. It is notable that this treatment failed to give the dihydrochlorides.

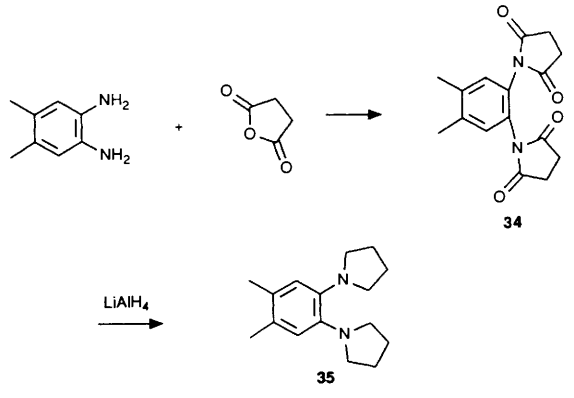
The ^{1}H NMR spectra of the monohydrochlorides **33** recorded at temperatures below *ca.* 25 °C showed that there were six chemically distinct methyl groups and two sets of non-equivalent *N*-methylene units (*e.g.* CH_2N and CH_2N^+H). However, as the temperature of the NMR sample was raised to *ca.* 50 °C, line broadening of the signals occurred and, for example, the resonances of the aromatic methyl protons coalesced into a single peak. This suggests that at temperatures below about 25 °C a proton is associated with one nitrogen atom only, but as the temperature rises there is a slow migration from one nitrogen to the other (Scheme 5). A similar effect was observed for the monohydrochloride salt of the hexahydroquinoxaline **24**.

We attempted to form the monohydrochloride salt of the dipyrrolidinylbenzene **35** to investigate whether this effect occurs in a non-heterocyclic analogue; however in this case

treatment of the free base with hydrogen chloride in diethyl ether only gave the dihydrochloride salt. The 1,2-dimethyl-4,5-di(pyrrolidin-1-yl)benzene **35** was prepared in two steps from 4,5-dimethylbenzene-1,2-diamine and succinic anhydride *via* the diimide **34** (Scheme 6). In the first step the molar ratio of succinic anhydride to diamine was 6:1, but when this was lowered then, after reduction with lithium aluminium hydride, two other products 3-(5,6-dimethylbenzoimidazol-2-yl)propan-1-ol **38** and 3-[4,5-dimethyl-2-(pyrrolidin-1-yl)phenylamino]propan-1-ol **40** were formed in significant amounts. The origins of these compounds are likely to be as shown in Scheme 7. In the first case the reaction of the diamine **4** and succinic anhydride afforded the amide **36**, which cyclised to the benzimidazole **37**, prior to reduction to **38**. In the second case the amide **36** reacted further with succinic anhydride to give the imide **39**. Reduction of this product afforded the pyrrolidine derivative **40**.



Scheme 5



Scheme 6

None of the free bases of the type **32** gave rise to a stable radical cation on oxidation and we have evidence that in the case of **32** (R = H) anodic oxidation leads, in part, to the parent quinoxaline **31**.

Experimental

Light petroleum refers to the fraction bp range 60–80 °C. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform, unless stated otherwise at 270 or 400 MHz; *J* values are given in Hz. IR spectra were obtained as Nujol mulls. All chromatographic procedures used silica gel as the solid phase. Cyclic voltammetry was performed with a Condecon™ 300 instrument, using acetonitrile as the solvent and tetrabutylammonium tetrafluoroborate as the supporting electrolyte. The anode was a platinum bead and a standard calomel electrode was used as a reference.

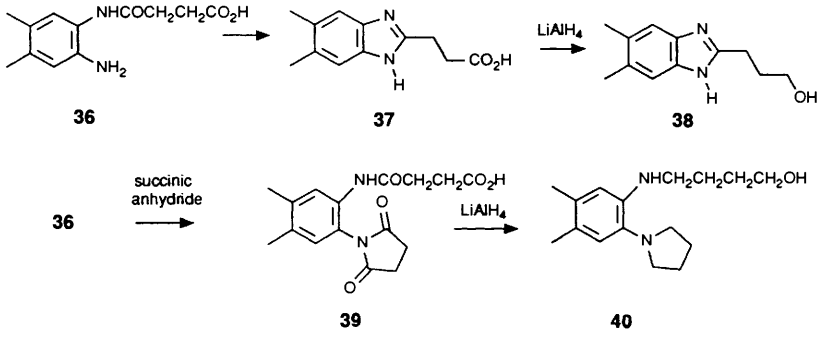
Crystallographic data for compounds 23 (R = Me) and 25

23 (R = Me). A crystal of approximate dimensions 0.2 × 0.2 × 0.4 mm was used for data collection.

Crystal data.—$C_{24}H_{32}N_2$, M = 348.5, monoclinic, a = 8.985(2), b = 8.337(2), c = 27.041(5) Å, β = 97.47(2), U = 2008.4 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.13 g cm^{-3}, μ(Mo-Kα) = 0.35 cm^{-1}, F(000) = 760. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \leqslant \theta \leqslant 24°$. 3629 Reflections were collected of which 1248 were unique with $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by Direct methods and refined using the SHELX[9,10] suite of programs. In the final least-squares cycles all non-hydrogen atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions except in the case of H2 (attached to N2) which was located in the penultimate difference Fourier and refined at a fixed distance of 1.06 Å from the parent atom. Residuals after 10 cycles of least-squares were R = 0.0490, R_w = 0.0566, for a weighting scheme of $w = 1.0000/[\sigma^2(F) + 0.007\,186(F)^2]$. Max. final shift/esd was 0.03. The max. and min. residual densities were 0.08 and −0.06 e Å^{-3} respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, together with tables of anisotropic temperature factors (for details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1995, issue 1). Also included is a figure of the asymmetric unit and the labelling scheme used.

25. A crystal of approximate dimensions 0.3 × 0.3 × 0.07 mm was used for data collection.

Crystal data.—$C_{24}H_{32}N_2 \cdot \frac{1}{2}C_2H_5OH$, M = 371.6, monoclinic, a = 11.869(1), b = 12.151(1), c = 30.105(6) Å, U =



Scheme 7

4274.3 Å^3, space group $C2/c$, $Z = 8$, $D_c = 1.15$ g cm^{-3}, μ(Mo-Kα) = 0.36 cm^{-1}, $F(000) = 1624$. Data were measured at room temperature on a CAD4 four-circle diffractometer in the range $2 \leqslant \theta \leqslant 24°$. 3728 Reflections were collected of which 1670 were unique with $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by Direct methods and refined using the SHELX[9,10] suite of programs. Four molecules of crystallisation solvent (ethanol) were found in the unit cell. The β-carbon and oxygen atoms therein were seen to be located on the 2-fold axis intrinsic in the space group symmetry and therefore had half-site occupancy. The α-carbon of the solvent moiety exhibited 50% disorder between the given position and that generated by the 2-fold axis. In the final least-squares cycles all non-hydrogen atoms were allowed to vibrate anisotropically. The hydrogens were included at calculated positions except in the case of H1 (associated with N1), which was located in an advanced Fourier and refined at a fixed distance from the parent atom. Final residuals after 9 cycles of least-squares were $R = 0.0553$, $R_w = 0.0632$ for a weighting scheme of $w = 1/[\sigma^2(F) + 0.005\,593(F)^2]$. Max. final shift/esd was 0.002. The max. and min. residual densities were 0.10 and −0.09 e Å^{-3} respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, together with tables of anisotropic temperature factors. Also included is a figure of the asymmetric unit and the labelling scheme used.

7,8-Dimethyl-11*H*-indeno[1,2-*b*]quinoxaline 6

2,3-Dihydroindene-1,2-dione (0.73 g, 5.0 mmol) and 4,5-dimethylbenzene-1,2-diamine (0.73 g, 5.4 mmol) were heated at reflux in ethanol (25 cm^3, 95%) for 1.25 h. The reaction mixture was cooled and the title compound separated as colourless needles (1.10 g, 89%), mp 200–201 °C; δ_H 2.51 (6 H, s), 4.11 (2 H, s), 7.47–7.57 (2 H, s), 7.65 (1 H, s), 7.83 (1 H, s), 7.92 (1 H, s) and 8.23 (1 H, s) (Found: C, 82.4; H, 5.7; N, 11.4. $C_{17}H_{14}N_2$ requires C, 82.9; H, 5.7; N, 11.4%).

7,8,11,11-Tetramethyl-11*H*-indeno[1,2-*b*]quinoxaline 7 and 7,8,11-trimethyl-11*H*-indeno[1,2-*b*]quinoxaline 8

To a solution of compound **6** (50 mg, 0.2 mmol) in dry tetrahydrofuran (5 cm^3) under nitrogen was added methyllithium (1.0 mol dm^{-3} in hexane; 0.5 cm^3, 0.5 mmol). After 20 min, methyl iodide (120 mg, 0.8 mmol) in tetrahydrofuran (1 cm^3) was introduced and the reaction mixture was left overnight. Two drops of 2 mol dm^{-3} aq. ammonium chloride were added and the solution was evaporated to give an oil, which was chromatographed eluting with 6% ethyl acetate–light petroleum. The first fractions contained 7,8,11,11-tetramethyl-11*H*-indeno[1,2-*b*]quinoxaline **7** (25 mg, 45%) as colourless needles, mp 113–114 °C (EtOH); δ_H 1.63 (6 H, s), 2.49 (6 H, s), 7.48 (1 H, ddd, *J* 7.0, 7.0 and 2.0), 7.51–7.60 (2 H, m), 7.89 (1 H, s), 7.91 (1 H, s) and 8.18 (1 H, d, *J* 6.5) (Found: C, 83.2; H, 6.6; N, 10.3. $C_{19}H_{18}N_2$ requires C, 83.2; H, 6.6; N, 10.2%).

Later fractions afforded 7,8,11-trimethyl-11*H*-indeno[1,2-*b*]quinoxaline **8** as a colourless oil (0.7 mg, 1.5%), δ_H 1.69 (3 H, d, *J* 7.5), 2.51 (6 H, s), 4.11 (1 H, q, *J* 7.5), 7.49–7.64 (3 H, m), 7.87 (1 H, s), 7.94 (1 H, s) and 8.23 (1 H, dd, *J* 1.0 and 6.5) (Found: M$^+$, 260.1320. $C_{18}H_{16}N_2$ requires *M*, 260.1313).

4b,5,7,8,11,11-Hexamethyl-4b,5-dihydro-11*H*-indeno[1,2-*b*]-quinoxaline 9 and 7,8,10,10a,11,11-hexamethyl-10,10a-dihydro-11*H*-indeno[1,2-*b*]quinoxaline 10

A solution of compound **7** (23 mg, 0.09 mmol) in dry tetrahydrofuran (10 cm^3) under an atmosphere of nitrogen was treated with methyllithium (1.0 mol dm^{-3}; 0.25 cm^3, 0.4 mmol). The reaction mixture became maroon coloured and, after 0.75 h, was treated with methyl iodide (0.2 g, 1.4 mmol) whereupon the colour was discharged. The solvent and excess methyl iodide were removed and the residue was chromatographed eluting with 6% ethyl acetate in light petroleum to give an oil (18 mg), which consisted of the isomeric title compounds in the ratio 10:7 respectively; these components could not be separated. 4b,5,7,8,11,11-Hexamethyl-4b,5-dihydro-11*H*-indeno[1,2-*b*]-quinoxaline **9**; δ_H 1.11 (3 H, s), 1.52 (3 H, s), 1.58 (3 H, s), 2.25 (3 H, s), 2.29 (3 H, s), 2.94 (3 H, s), 6.71 (1 H, s), 7.25 (1 H, s), 7.30–7.50 (3 H, m) and 7.58 (1 H, ddd, *J* 7.0, 1.5 and 1.5). 7,8,10,10a,11,11-Hexamethyl-10,10a-dihydro-11*H*-indeno[1,2-*b*]quinoxaline **10**; δ_H 1.04 (3 H, s), 1.37 (3 H, s), 1.63 (3 H, s), 2.21 (3 H, s), 2.26 (3 H, s), 2.86 (3 H, s), 6.49 (1 H, s), 7.16 (1 H, s), 7.30–7.50 (3 H, m) and 7.87 (1 H, br d, *J* 7.5).

10-Ethyl-4b,5,7,8,11,11-hexamethyl-4b,5,10,10a-tetrahydro-11*H*-indeno[1,2-*b*]quinoxaline 11 (R = Et) and 5-ethyl-7,8,10,10a,11,11-hexamethyl-10,10a-dihydro-11*H*-indeno-[1,2-*b*]quinoxalin-5-ium chloride 13

The mixed imines **9** and **10** (110 mg) in glacial acetic acid (3 cm^3) were treated with sodium cyanoboranuide (200 mg) in portions over a period of 2 h. The solvent was removed and the residue partitioned between 25% hydrochloric acid and chloroform. After separation and evaporation, the chloroform layer afforded a semi-solid, which was triturated with diethyl ether (5 cm^3) to give the hydrated salt **13** as a purple solid (55 mg), mp 126–128 °C (softens at 120 °C); *m/z* (CI) 334 (100%) and 305 (95); ν_{max}/cm^{-1} 3420, 1625; δ_H[(CD$_3$)$_2$SO] 1.10 (3 H, s), 1.51 (3 H, s), 1.67 (3 H, br t, *J* 7), 1.70 (3 H, s), 2.26 (3 H, s), 2.29 (3 H, s), 2.89 (3 H, s), 3.63 (2 H, s, H_2O), 4.68 (2 H, dd, *J* 10 and 7), 6.89 (1 H, s), 7.60 (1 H, s), 7.71 (1 H, t, *J* 7.5), 7.86 (1 H, d, *J* 7.5), 8.00 (1 H, t, *J* 7.5) and 8.15 (1 H, d, *J* 8) [Found: C, 71.0; H, 7.8; N, 7.3. $C_{23}H_{29}N_2Cl{\cdot}H_2O$ requires C, 71.4; H, 8.1; N, 7.2%. Found: M$^+$ (EI) 333.2287. $C_{23}H_{29}N_2$ requires *M*, 333.2331].

Basification of the aqueous acid layer gave compound **11** (R = Et) as a gum, the ^{1}H NMR spectrum of which showed it to be a mixture of diastereoisomers. Although these compounds were stable, we could not separate them by chromatography.

1,1,4,4-Tetramethyl-1,2,3,4-tetrahydronaphthalen-2-one 18 and 6,7-dimethyl-2-(1,3,3-trimethyl-2,3-dihydroinden-1-yl)-quinoxaline 28

Anhydrous aluminium trichloride (100 g) was added portionwise to a solution of the furanone **17** (50 g, 0.35 mol) in dry benzene (350 cm^3) at 0 °C. The mixture was then heated under reflux for 6 h, cooled, poured into ice (500 g) containing conc. hydrochloric acid (50 cm^3) and extracted with diethyl ether (3 × 250 cm^3). The combined organic extracts were washed with saturated aq. sodium hydrogen carbonate and water, dried and evaporated to give a dark oil. The oil was mixed with light petroleum (40–60 °C) (100 cm^3) and kept in the freezer for 2 days, after which time colourless crystals of the compound **18** had precipitated and were filtered off (17 g, 25%), mp 75 °C (lit.,[6] 75 °C).

After compound **18** had been filtered off, the filtrate was evaporated to give an oil, which was redissolved in glacial acetic acid and treated with selenium dioxide (3 g). The solvent was removed from the mixture and the residue was chromatographed, eluting with light petroleum to give 2-oxo-2-(1,3,3-trimethyl-2,3-dihydroinden-1-yl)ethanal **27** as a pale yellow oil (5.0 g). This compound was not characterised, but was redissolved in ethanol (50 cm^3) and heated under reflux with 4,5-dimethylbenzene-1,2-diamine (3.2 g, 1 equiv.) for 1 h. On cooling the reaction mixture deposited colourless crystals of the quinoxaline **28** (6.5 g, 89%), mp 96–98 °C (EtOH); δ_H 1.18 (3 H, s), 1.40 (3 H, s), 1.82 (3 H, s), 2.25 (1 H, d, *J* 13.4), 2.46 (3 H,

s), 2.48 (3 H, s), 2.81 (1 H, d, *J* 13.4), 7.18–7.20 (4 H, m), 7.78 (1 H, s), 7.82 (1 H, s) and 8.5 (1 H, s); δ_C 20.2, 29.4, 30.6, 31.0, 43.1, 52.5, 56.8, 122.7, 124.8, 127.1, 127.7, 128.0, 128.4, 139.3, 139.6, 140.1, 140.3, 143.8, 147.2, 152.4 and 160.0; *m/z* 316 (60%, M^+) (Found: C, 83.5; H, 7.6; N, 8.9. $C_{22}H_{24}N_2$ requires C, 83.5; H, 7.6; N, 8.9%).

6,7-Dimethyl-2-(1,3,3-trimethyl-2,3-dihydro-1*H*-inden-1-yl)-1,2,3,4-tetrahydroquinoxaline 29

The quinoxaline **28** (0.5 g, 1.6 mmol) in glacial acetic acid (10 cm^3) was treated with sodium cyanoboranuide (0.3 g, 3 equiv.) in small portions. The mixture was stirred for 1 h after which it was evaporated and the residue redissolved in ethyl acetate. The solution was washed with aq. sodium carbonate, dried and evaporated to afford a colourless solid which was dissolved in dry diethyl ether. Diethyl ether saturated with hydrogen chloride was added to the solution whereupon the hydrochloride salt of the title compound **29** separated out as needles (0.48 g, 86%), mp 189–192 °C (decomp.; EtOH); ν_{max}/cm^{-1} 3384, 3324, 2588, 2410 and 1624; δ_H 1.32 (3 H, s), 1.35 (3 H, s), 1.45 (3 H, s), 1.65 (1 H, d, *J* 12.8), 2.08 (3 H, s), 2.11 (3 H, s), 2.28 (1 H, d, *J* 13.2), 3.12 (1 H, t, *J* 10), 3.98 (1 H, d, *J* 10), 4.10 (1 H, d, *J* 10.2), 6.3 (1 H, s), 7.18–7.32 (5 H, m) and 11.4–11.8 (3 H, br, D_2O exchangeable); δ_C 15.2, 18.6, 27.5, 30.6, 32.5, 42.9, 43.1, 47.4, 48.7, 54.9, 113.3, 117.1, 122.6, 123.2, 123.8, 126.7, 127.5, 128.3, 137.2, 138.4, 144.9 and 152.5; *m/z* 320 (40%, M^+) (Found: C, 71.3; H, 8.4; N, 6.9. $C_{22}H_{28}N_2$·HCl·EtOH requires C, 71.6; H, 8.7; N, 7.0%).

2,3,6,6,11,11-Hexamethyl-6,11-dihydrobenzo[*b*]phenazine 20

To 4,5-dimethylbenzene-1,2-diamine (6.0 g, 4.4 mmol) in ethanol (100 cm^3) was added 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene-2,3-dione **19** (9.5 g, 4.4 mmol). The reaction mixture was heated under reflux for 30 min after which it was cooled and kept at 0 °C for several hours. After this time colourless needles of the title compound **20** which had separated were filtered off and washed with ethanol (10.4 g, 75%), mp 163–164 °C; ν_{max}/cm^{-1} 1630; δ_H 1.82 (12 H, s), 2.49 (6 H, s), 7.30–7.34 (2 H, m), 7.58–7.61 (2 H, m) and 7.83 (2 H, s); *m/z* 301 (100%, M^+ − Me) and 316 (20, M^+) (Found: C, 83.5; H, 7.7; N, 8.8. $C_{22}H_{24}N_2$ requires C, 83.5; H, 7.6; N, 8.9%).

2,3,6,6,11,11-Hexamethyl-5,5a,6,11,11a,12-hexahydrobenzo[*b*]phenazine 15 (R = H)

The phenazine **20** (11.0 g, 35 mmol) suspended in glacial acetic acid (200 cm^3) was treated with sodium cyanoboranuide (6.5 g, 100 mmol) in small portions over a period of 1 h, after which the reaction mixture was stirred for a further 1 h before being evaporated. The residue was redissolved in ethyl acetate (100 cm^3) and the solution washed with saturated aq. sodium carbonate (3 × 25 cm^3) and water (3 × 15 cm^3) and then evaporated to give the title compound **15** (10.8 g, 97%), mp 143–145 °C (EtOH); ν_{max}/cm^{-1} 3384 (NH); $\delta_H(CDCl_3–D_2O)$, 1.34 (6 H, s), 1.40 (6 H, s), 2.09 (6 H, s), 3.46 (2 H, s), 6.36 (2 H, s) and 7.17–7.34 (4 H, m); *m/z* 320 (100%, M^+) (Found: C, 82.5; H, 8.9; N, 8.7. $C_{22}H_{28}N_2$ requires C, 82.5; H, 8.75; N, 8.75%).

2,3,5,6,6,11,11,12-Octamethyl-5,5a,6,11,11a,12-hexahydrobenzo[*b*]phenazine 15 (R = Me)

The hexahydrophenazine **15** (R = H) (8.08 g, 2.5 mmol) in dry tetrahydrofuran (200 cm^3) was stirred under nitrogen at 0 °C whilst methyllithium (1.4 mol dm^{-3} solution in diethyl ether; 40 cm^3, 2.2 equiv.) was added slowly. The dark blue–green reaction mixture was allowed to stand for 30 min after which iodomethane (3.7 cm^3, 8.44 g, 2.3 equiv.) was added slowly over *ca.* 1 h, during this time the colour of the mixture changed to pale yellow. The solvent was removed from the mixture under reduced pressure and the residue dissolved in freshly redistilled and degassed light petroleum. The solution was passed through a column of basic alumina eluting with the same solvent. The fractions were combined and concentrated to give the title compound as colourless prisms and, without delay, this was dissolved in dry ether (100 cm^3) under an atmosphere of nitrogen and treated with a solution of diethyl ether saturated with hydrogen chloride to give the monohydrochloride salt of **15** (R = Me) as a colourless solid (8.5 g, 87.6%), mp 170–172 °C; δ_H 1.39 (6 H, s), 1.40 (6 H, s), 2.17 (6 H, s), 2.87 (6 H, s), 3.38 (2 H, s), 6.35 (2 H, s) and 7.18–7.35 (4 H, m); *m/z* 348 (100%, M^+), 188 (80) and 333 (60) (Found: C, 75.0; H, 8.8; N, 7.4. $C_{24}H_{32}N_2$·HCl requires C, 74.9; H, 8.6; N, 7.8%).

2,3,6,6,11,11,11a-Heptamethyl-6,11,11a,12-tetrahydrobenzo[*b*]phenazine 21

Methyllithium (0.8 mol dm^{-3} solution in diethyl ether; 3 cm^3, 2.4 equiv.) was slowly added to a solution of the phenazine **20** (0.32 g, 1 mmol) in dry tetrahydrofuran (10 cm^3) maintained at 0 °C under an atmosphere of nitrogen. After the dark blue mixture had been stirred for 30 min, it was treated with water (0.5 cm^3) at which the colour was discharged. The mixture was extracted with ethyl acetate (3 × 25 cm^3) and the combined extracts were then washed with water, dried and evaporated to give the title compound **21** (0.33 g, quantitative yield), mp 178–180 °C (EtOH); ν_{max}/cm^{-1} 3353, 2349, 1623; δ_H 1.18 (3 H, s), 1.28 (3 H, s), 1.35 (3 H, s), 1.66 (6 H, s), 2.15 (3 H, s), 2.17 (3 H, s), 6.3 (1 H, s), 7.0 (1 H, s) and 7.17–7.42 (4 H, m); *m/z* 332 (40%, M^+), 317 (100, M^+ − 15) (Found: M^+, 332.2224. $C_{23}H_{28}N_2$ requires *M*, 332.2252).

2,3,6,6,11,11,11a,12-Octamethyl-6,11,11a,12-tetrahydrobenzo[*b*]phenazine 22

The phenazine **20** (0.32 g, 1 mmol) in dry tetrahydrofuran (10 cm^3) at 0 °C under an atmosphere of nitrogen was treated with methyllithium (0.8 mol dm^{-3} solution in diethyl ether; 1.5 cm^3, 1.2 equiv.). After 30 min, iodomethane (1.2 equiv.) was added to the mixture which was then stirred for a further 30 min. Water (5 cm^3) was introduced, the mixture extracted with ethyl acetate (3 × 15 cm^3) and the combined extracts were washed, dried and evaporated to give the title compound **22** as almost colourless prisms (0.32 g, 92.5%), mp 113–115 °C (EtOH); ν_{max}/cm^{-1} 1631; δ_H 1.26 (3 H, s), 1.41 (3 H, s), 1.42 (3 H, s), 1.63 (3 H, s), 1.68 (3 H, s), 2.14 (3 H, s), 2.21 (3 H, s), 2.96 (3 H, s), 6.33 (1 H, s), 6.94 (1 H, s) and 7.17–7.37 (4 H, m); *m/z* 346 (100%, M^+) (Found: C, 83.4; H, 8.8; N, 8.1. $C_{24}H_{30}N_2$ requires C, 83.2; H, 8.7; N, 8.1%).

1,1,3,3,3′,4′,6′,7′-Octamethylspiro[2,3-dihydroindene-2,2′-(1′,2′,3′,4′-tetrahydroquinoxaline)] 25

The tetrahydrophenazine **22** (0.30 g, 0.87 mmol) in glacial acetic acid (4 cm^3) under a nitrogen atmosphere was treated with sodium cyanoboranuide (0.2 g) in small portions. The reaction mixture was then set aside for 12 h, during which time a solid separated. This was filtered off and washed with acetic acid (3 cm^3) to give the spiro compound **25** (0.045 g, 15%), mp 213–215 °C (AcOH); ν_{max}/cm^{-1} 3409; δ_H 1.10 (3 H, d, *J* 6.2), 1.21 (3 H, s), 1.34 (3 H, s), 1.36 (3 H, s), 1.40 (3 H, s), 2.07 (3 H, s), 2.15 (3 H, s), 2.89 (3 H, s), 3.48 (1 H, q, *J* 6), 6.16 (1 H, s), 6.26 (1 H, s) and 7.12–7.26 (4 H, m); $\delta_C(CDCl_3)$ 11.8, 18.9, 19.0, 24.0, 26.5, 26.9, 29.5, 36.7, 55.3, 112.9, 113, 122.0, 123.2, 124.2, 125.6, 127.1, 127.2, 132.0, 133.2, 148.8 and 149.7; *m/z* 348 (100%, M^+) and 333 (40, M^+ − 15) (Found: M^+, 348.2539. $C_{24}H_{32}N_2$ requires *M*, 348.2566).

2,3,6,6,11,11,11a,12-Octamethyl-5,5a,6,11,11a,12-hexahydrobenzo[*b*]phenazine 23 (R = H)

The filtrate from which **25** separated was concentrated under reduced pressure and partitioned between water and ethyl

acetate. The organic phase was washed with saturated aq. sodium carbonate, dried and evaporated and the residue crystallised from ethanol to give the compound **23** (R = H) (0.25 g, 83%), mp 169–172 °C; δ_H 1.22 (3 H, s), 1.28 (3 H, s), 1.30 (3 H, s), 1.47 (3 H, s), 1.60 (3 H, s), 2.13 (3 H, s), 2.15 (3 H, s), 2.76 (3 H, s), 3.37 (1 H, s), 4.10 (1 H, s), 6.33 (1 H, s), 6.35 (1 H, s) and 7.13–7.37 (4 H, m); *m/z* 348 (100%, M^+) (Found: C, 82.4; H, 9.4; N, 7.9. $C_{24}H_{32}N_2$ requires C, 82.8; H, 9.2; N, 8.05%).

2,3,5,6,6,11,11,11a,12-Nonamethyl-5,5a,6,11,11a,12-hexahydrobenzo[*b*]phenazine 23 (R = Me)

The octamethylphenazine **23** (R = H) (65 mg, 0.2 mmol) in dry tetrahydrofuran maintained at 0 °C under a nitrogen atmosphere was treated with methyllithium (1.4 mol dm^{-3} in diethyl ether; 1.5 cm^3, 1.1 equiv.) over a period of 30 min. Methyl iodide (1.2 equiv.) was added to the mixture which was then kept at 0 °C for a further 30 min, before it was evaporated. The residue was dissolved in ethyl acetate, and the solution washed, dried and evaporated to afford colourless prisms of **23** (R = Me) which were recrystallised from ethanol (50 mg, 74%), mp 179–181 °C; δ_H($CDCl_3$–D_2O) 0.98 (3 H, s), 1.02 (3 H, s), 1.27 (3 H, s), 1.48 (3 H, s), 1.75 (3 H, s), 2.12 (3 H, s), 2.19 (3 H, s), 2.49 (3 H, s), 3.23 (3 H, s), 3.48 (1 H, s), 6.22 (1 H, s), 6.24 (1 H, s) and 7.16–7.40 (4 H, m); *m/z* 362 (100%, M^+) (Found: M^+, 362.2690. $C_{25}H_{34}N_2$ requires *M*, 362.2722).

2,3,6,6,11,11,11a-Heptamethyl-5,5a,6,11,11a,12-hexahydrobenzo[*b*]phenazine 24

The tetrahydrophenazine **21** (160 mg, 0.5 mmol) in glacial acetic acid (5 cm^3) was treated with sodium cyanoboranuide (60 mg, 1 mmol). The bright orange colour of the solution rapidly disappeared after the addition of the reducing agent and the mixture was kept for 30 min before it was evaporated under reduced pressure. The residue was redissolved in ethyl acetate (20 cm^3) and the solution washed with saturated aq. sodium carbonate, dried and evaporated to afford a colourless solid. This was crystallised from ethanol to give the title compound **24** (140 mg, 87%), mp 186–187 °C; δ_H 1.13 (3 H, s), 1.22 (3 H, s), 1.26 (3 H, s), 1.39 (3 H, s), 1.58 (3 H, s), 20.6 (3 H, s), 2.12 (3 H, s), 3.25 (1 H, s), 3.3–4.4 (2 H, br, 2 × NH), 6.24 (1 H, s), 6.42 (1 H, s) and 7.15–7.38 (4 H, m); *m/z* 334 (100%, M^+) (Found: C, 82.9; H, 9.0; N, 8.2. $C_{23}H_{30}N_2$ requires C, 82.6; H, 9.0; N, 8.4%).

1,1,3,3,6,7-Hexamethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoxaline 31

4,5-Dimethylbenzene-1,2-diamine (1.1 g, 8.3 mmol) and 3,3,5,5-tetramethylcyclopentane-1,2-dione (1.1 g, 7.3 mmol) were heated in ethanol (12 cm^3, 95%) under reflux for 3 h after which the mixture was evaporated and the residue was crystallised from ethanol–water (3:7, 7 cm^3) to give the title compound **31** as pale cream prisms (1.6 g, 86%), mp 116–118 °C; δ_H 1.45 (12 H, s), 2.12 (2 H, s), 2.50 (6 H, s) and 7.90 (2 H, s) (Found: C, 80.3; H, 8.8; N, 10.9. $C_{17}H_{22}O_2$ requires C, 80.3; H, 8.7; N, 11.0%).

1,1,3,3,6,7-Hexamethyl-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]quinoxaline 32 (R = H)

To a stirred solution of the quinoxaline **31** (1.3 g, 5 mmol) in glacial acetic acid (30 cm^3) was added sodium cyanoboranuide (1.6 g, 25 mmol) in small portions over 1.5 h. The reaction mixture was poured into water (400 cm^3), neutralised with solid sodium carbonate and extracted with ethyl acetate (3 × 40 cm^3). The combined extracts were dried and evaporated to give a pale green–grey oil which was redissolved in diethyl ether (40 cm^3) and treated with diethyl ether saturated with hydrogen chloride (4 cm^3). A solid product formed and this was collected and washed with diethyl ether to give near-colourless crystals of the hydrochloride salt of the title compound **32** (1.6 g, 96%), mp 240–242 °C; *m/z* 258 (100%, M^+), 201 (70) (Found: M^+, 258.2100. $C_{17}H_{26}N_2$ requires *M*, 258.2096).

4,9-Dialkyl-1,1,3,3,6,7-hexamethyl-2,3,3a,4,9,9a-hexahydrocyclopenta[*b*]quinoxalines 32 (R = alkyl)

General method. A suspension of the hydrochloride salt of **32** (R = H) (1.0 mmol) in 1,2-dichloroethane (15 cm^3) was treated with the alkanal (6.0 mmol), triethylamine (180 mg) and sodium triacetoxyboranuide (6.0 g) over a period of 3 d. The reaction mixture was partitioned between dichloromethane and water (5:3) and the organic layer was collected and evaporated. Chromatography of the residue, eluting with light petroleum, gave an oil which was redissolved in diethyl ether (2 cm^3) previously saturated with hydrogen chloride. The monohydrochloride salt which formed was filtered off and washed with dry diethyl ether.

1,1,3,3,6,7-Hexamethyl-4,9-dipropyl-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]quinoxalinium chloride 32 (R = propyl). Yield 63%, mp 172–175 °C (diethyl ether); δ_H($CDCl_3$–D_2O) 0.84 (3 H, t, *J* 7.5), 0.91 (3 H, t, *J* 7.5), 0.98 (3 H, s), 0.99 (3 H, s), 1.19 (3 H, s), 1.18–1.30 (2 H, m), 1.44 (1 H, d, *J* 13.0), 1.54 (1 H, d, *J* 13.0), 1.52 (3 H, s), 1.35–1.63 (2 H, m), 2.17 (3 H, s), 2.21 (3 H, s), 2.98 (1 H, m), 3.40 (2 H, t, *J* 7.5), 3.67 (1 H, m), 3.69 (1 H, d, *J* 10), 4.05 (1 H, d, *J* 10), 6.62 (1 H, s) and 7.73 (1 H, s) (Found: C, 72.7; H, 10.5; N, 7.3. $C_{23}H_{38}N_2$·HCl requires C, 72.9; H, 10.3; N, 7.4%).

4,9-Dihexyl-1,1,3,3,6,7-hexamethyl-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]quinoxalinium chloride 32 (R = hexyl). Yield 52%, mp 140–142 °C (diethyl ether); δ_H 0.86 (6 H, m), 0.97 (3 H, s), 0.98 (3 H, s), 1.15–1.35 (17 H, m), 1.40–1.55 (2 H, m), 1.43 (1 H, d, *J* 13.5), 1.52 (3 H, s), 1.54 (1 H, d, *J* 13.5), 2.17 (3 H, s), 2.22 (3 H, s), 3.03 (1 H, ddd, *J* 7, 7, 14), 3.40 (2 H, m), 3.65 (1 H, ddd, *J* 7, 7, 14), 3.65 (1 H, d, *J* 10), 4.02 (1 H, d, *J* 10), 6.61 (1 H, s), 7.73 (1 H, s) and 13.08 (1 H, br s) (Found: C, 74.8; H, 11.2; N, 6.05. $C_{29}H_{50}N_2$·HCl requires C, 75.2; H, 11.0; N, 6.05%).

1,1,3,3,6,7-Hexamethyl-4,9-dioctyl-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]quinoxalinium chloride 32 (R = octyl). Yield 40%, mp 106–108 °C (light petroleum); δ_H 0.86 (6 H, m), 0.96 (3 H, s), 0.97 (3 H, s), 1.15–1.30 (25 H, m), 1.40–1.55 (2 H, m), 1.43 (1 H, d, *J* 13.5), 1.52 (3 H, s), 1.54 (1 H, d, *J* 13.5), 2.18 (3 H, s), 2.21 (3 H, s), 3.03 (1 H, dddd, *J* 7, 7, 7, 14), 3.42 (2 H, m), 3.67 (1 H, dddd, *J* 7, 7, 7, 14), 3.67 (1 H, d, *J* 10.0), 4.03 (1 H, d, *J* 10.0), 6.61 (1 H, s), 7.73 (1 H, s) and 13.05 (1 H, s) (Found: C, 75.9; H, 11.5; N, 5.4. $C_{33}H_{58}N_2$·HCl requires C, 76.3; H, 11.4; N, 5.4%).

1,2-Dimethyl-4,5-disuccinimidobenzene 34 and 1,2-dimethyl-4,5-di(pyrrolidin-1-yl)benzene 35

4,5-Dimethylbenzene-1,2-diamine (2.9 g, 21 mmol) was mixed with succinic anhydride (12.75 g, 127.5 mmol) and heated for 1.5 h under nitrogen at 200 °C after which the hot reaction mixture was poured slowly into a stirred solution of sodium carbonate (20 g) in water (400 cm^3) dichloromethane (100 cm^3) was added to the mixture and the organic layer was separated, and the aqueous phase extracted (2 × 25 cm^3) with dichloromethane. The dried, combined organic extracts were evaporated to give a resin. This was treated with diethyl ether (80 cm^3) and stirred (16 h) with a heavy magnetic stirrer bar to give the title compound **34** (3.45 g, 45%) as a pale yellow solid, mp 236–238 °C; δ_H 2.30 (6 H, s), 2.75 (8 H, s) and 7.17 (2 H, s) (Found: C, 64.2; H, 5.4; N, 9.4. $C_{16}H_{16}N_2O_4$ requires C, 64.0; H, 5.3; N, 9.3%). The product **34** (0.3 g) was suspended in dry tetrahydrofuran (40 cm^3) under an atmosphere of nitrogen and lithium aluminium hydride (0.5 g) was then added in small portions over 2 d. Excess of reagent was destroyed by the

addition of saturated aq. sodium potassium tartrate. The organic phase was collected and evaporated to give an oil. This was mixed with dichloromethane for 0.5 h, after which the mixture was filtered through Celite and the filtrate and washings were combined and evaporated to give the dipyrrolidinylbenzene as a colourless solid. This was immediately redissolved in diethyl ether and the solution treated with diethyl ether saturated with hydrogen chloride. With time the dihydrochloride salt separated and this was collected and crystallised from water as the dihydrate, mp 156–158 °C; δ_H 2.25 (8 H, br s), 2.29 (6 H, s), 3.56 (8 H, br s), 5.11 (4 H, br s, exchanged with D_2O) and 7.56 (2 H, s) (Found: C, 54.7; H, 8.1; N, 8.1. $C_{16}H_{24}N_2 \cdot 2HCl \cdot 2H_2O$ requires C, 54.3; H, 8.4; N, 7.9%).

3-(5,6-Dimethylbenzoimidazol-2-yl)propan-1-ol 38

The diamine **4** (0.41 g) and succinic anhydride (0.7 g) were heated together at 200 °C for 15 min. The residue was then triturated and heated in 95% ethanol (10 cm^3) at 80 °C and the mixture was allowed to cool overnight. The precipitated solid was filtered off, suspended in dry tetrahydrofuran (60 cm^3) and treated with portions of lithium aluminium hydride (0.9 g) under a nitrogen atmosphere. The solid gradually dissolved and after 18 h, the excess of reagent was destroyed by the addition of saturated aq. potassium ammonium tartrate (4 cm^3). The reaction mixture was then extracted with dichloromethane (2 × 25 cm^3), the aqueous phase filtered and the residual solid washed with dichloromethane (3 × 10 cm^3). The organic extracts and washings were combined and evaporated to give a semi-solid from which colourless prisms of **38** (170 mg, 28%) were obtained by trituration with dry diethyl ether (5 cm^3), mp 148–150 °C; δ_H 2.04 (2 H, quint, *J* 6.5), 2.33 (6 H, s), 3.0 (2 H, t, *J* 7.0), 3.69 (2 H, t, *J* 6.0), 7.26 (2 H, s) and 7.43 (1 H, s) (O*H* not observed); *m/z* 204 (20%, M^+), 173 (31) and 160 (100) (Found: M^+, 204.1240. $C_{12}H_{16}N_2O$ requires *M*, 204.1263).

3-[4,5-Dimethyl-2-(pyrrolidin-1-yl)anilino]propan-1-ol 40

The diethyl ether filtrate from the purification of compound **38** was evaporated to give a residue which was chromatographed on silica (eluting with 1–2% ethyl acetate in light petroleum) to give a second product as a colourless oil (100 mg, 13%); ν_{max}(liquid film)/cm^{-1} 3350, 1610; δ_H 1.71 (4 H, m), 1.89 (7 H, m), 2.15 (3 H, s), 2.19 (3 H, s), 2.96 (4 H, m), 3.13 (2 H, t, *J* 6.5), 3.67 (2 H, t, *J* 6.0), 6.45 (1 H, s) and 6.80 (1 H, s) (Found: M^+, 262.2038. $C_{16}H_{26}N_2O$ requires *M*, 262.2045).

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