Tetrahydrofolate Coenzyme Models: Synthesis of Tetrahydroimidazoisoquinolines and Tetrahydroimidazoquinolines

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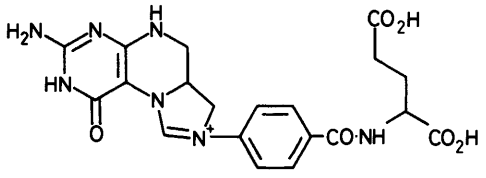
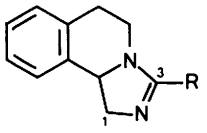
The new dihydroimidazoles 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline and 1-methyl-3,3a,4,5- tetrahydroimidazo[1,5-*a*]quinoline are efficiently and conveniently prepared from isoquinoline and quinoline, *via* 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline and 2-aminomethyl-1,2,3,4-tetrahydroquinoline, respectively. Deprotonation of the fused dihydroimidazoles at the methyl substituent leads to homologation *via* *C*-alkylation, *C*-acylation, or *C*-phosphonylation–condensation. The properties of the tetrahydroimidazo[5,1-*a*]isoquinolines and tetrahydroimidazo[1,5-*a*]quinolines towards reducing agents mirror those of monocyclic dihydroimidazoles, affording aminomethyl-isoquinolines and -quinolines, respectively.

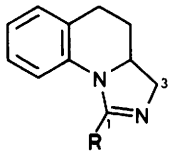
Nature uses a 4,5-dihydroimidazole (2-imidazoline) in N^5,N^{10}-methenyltetrahydrofolate (**1**) to perform the transfer of a functionalised carbon atom.[1] Whilst developing methods patterned on these biological processes, we have described various aspects of the chemistry of simple monocyclic 4,5-dihydroimidazoles.[2] The bicyclic imidazo[5,1-*a*]isoquinoline (**2**) and imidazo[1,5-*a*]quinoline (**3**) systems would be closer tetrahydrofolate models, and our wish to access and investigate these systems was strengthened by the variety of neurochemical properties reported for 1-(alkylaminomethyl)tetrahydroisoquinolines and 3-aminoimidazo[5,1-*a*]isoquinolines.[3] We report herein the preparation of new 4,5-dihydroimidazoles (**2a**) and (**3a**) *via* a convenient and improved synthesis of the diamines (**4**) and (**5**) using a common approach from isoquinoline and quinoline, respectively, and their reactions to afford derivatives of these fused systems.[4]



(**1**)



(**2**) **a**; R = Me
b; R = CH_2Me
c; R = $(CH_2)_8Me$
d; R = CH_2CHMe_2
e; R = CH=C(OH)Me
f; R = CH=CHPh
g; R = $CH{=}CMe_2$



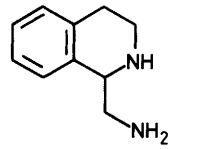
(**3**) **a**; R = Me
b; R = CH_2Me
c; R = $(CH_2)_8Me$
d; R = CH_2CHMe_2
e; R = CH=CHPh
f; R = $CH{=}CMe_2$

Results and Discussion

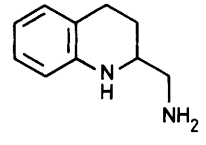
Our previous experience with the synthesis of 4,5-dihydroimidazoles[2] led us to select the diamines (**4**) and (**5**) as key intermediates in the synthesis of tetrahydroimidazo[5,1-*a*]isoquinolines and tetrahydroimidazo[1,5-*a*]quinolines. The first reported syntheses of (**4**) and (**5**) involved hydrogenation of the benzoyl Reissert compounds (**6a**) and (**7a**) at very high pressures and temperatures;[4] we were unable to complete these reductions under more accessible conditions.[5]

1-Chloromethyl-3,4-dihydroisoquinoline was prepared by Bischler–Napieralski cyclisation (P_2O_5) of the amide formed from 2-phenylethylamine and chloroacetyl chloride, but ammonolysis *en route* to (**4**) was unsuccessful under a variety of conditions.[3c] The reported approach to 1-alkylaminomethyl-1,2,3,4-tetrahydroisoquinolines *via* Bischler–Napieralski cyclisation of *N*-phenylethyl-2-phthalimidoacetamides[6] is not applicable to isoquinolines unsubstituted in the benzenoid ring. A further route to (**4**) proceeds from the less accessible 3,4-dihydroisoquinoline.[3a]

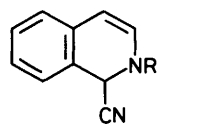
Our successful route to the diamines (**4**) and (**5**) involves the alternative arylsulphonyl Reissert compounds (**6b**) and (**7b**) and is a development of an earlier approach to (**4**).[7] Thus isoquinoline was converted into (**6b**) with benzenesulphonyl chloride and aqueous potassium cyanide, and thence into the isoquinoline nitrile (**8a**) using sodium borohydride in ethanol (65% overall).[8] Hydrolysis to the amide (**8b**) was achieved either by acidic (conc. H_2SO_4, then H_2O; 70%) or basic reagents



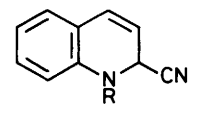
(**4**)



(**5**)



(**6**) **a**; R = COPh
b; R = SO_2Ph

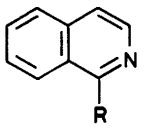


(**7**) **a**; R = COPh
b; R = $SO_2(4\text{-}MeC_6H_4)$

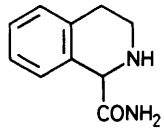
Table. Elaboration of 3-methyltetrahydroimidazo[5,1-*a*]isoquinoline (**2a**) and 1-methyltetrahydroimidazo[1,5-*a*]quinoline (**3a**).

Starting material	Product	Yield (%)
(**2a**)	(**2b**)	38
(**2a**)	(**2c**)	84
(**2a**)	(**2d**)	66
(**2a**)	(**2e**)	49
(**2a**)	(**2f**)	49
(**2a**)	(**2g**)	36
(**3a**)	(**3b**)	78
(**3a**)	(**3c**)	93
(**3a**)	(**3d**)	58
(**3a**)	(**3e**)	43
(**3a**)	(**3f**)	29

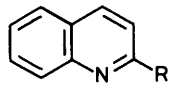
(H_2O_2, KOH aq.; 82%); the latter method is the more suitable for preparative scale. The reported conversion of (**6b**) directly into (**8b**) using aqueous sodium hydroxide[9] in our hands gave none of the amide but liberated ammonia to form the corresponding acid. The amide was reduced first by hydrogen (20 atm) over Adams' catalyst (PtO_2; EtOH, HBr aq., 20 °C) to the 1,2,3,4-tetrahydro-derivative (**9**) (95%) and then by diborane generated *in situ* ($NaBH_4$, BF_3; THF, reflux) to afford the diamine (**4**) (100%). Attempts to hydrogenate the nitrile (**8a**) directly failed; reduction of the tetrahydroamide (**9**) by lithium aluminium hydride is reported to give a low yield of the diamine (**4**)[7] but in our hands a complex mixture was obtained from which no diamine could be isolated. Condensation with ethyl acetimidate hydrochloride in ethanol at reflux (66%) completed the synthesis of 3-methyltetrahydroimidazo [5,1-*a*]isoquinoline (**2a**).



(**8**) **a**; R = CN
b; R = $CONH_2$



(**9**)

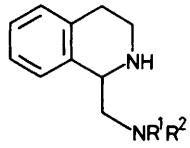


(**10**) **a**; R = CN
b; R = $CONH_2$

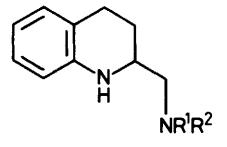
The same sequence could also be applied in the quinoline series. Quinoline-2-carbonitrile (**10a**) was thus prepared from quinoline *via* the base-labile toluene-*p*-sulphonyl Reissert adduct (**7b**) (not isolated),[10] and hydrolysed to the amide (**10b**) by the basic hydrogen peroxide method (see above) (77%). Successive reductions as before by hydrogen (30 atm) (70%) and diborane (83%) afforded the diamine (**5**) which was condensed with ethyl acetimidate hydrochloride in ethanol at reflux to provide 1-methyltetrahydroimidazo[1,5-*a*]quinoline (**3a**) (52%).

The properties of (**2a**) and (**3a**) were first assessed with respect to metallation on the methyl substituent.[2] Thus deprotonation with butyl-lithium (THF, −78 °C) followed by the appropriate alkyl iodide (−78 ⟶ 20 °C) was performed to give the homologated materials (**2b–d**) and (**3b–d**), respectively (Table). The lithio-derivative of (**2a**) was added to ethyl acetate to afford the *C*-acylated (**2e**). Our phosphonylation–condensation sequence,[2] involving treatment with lithium di-isopropylamide (2 mol equiv., −78 °C) followed by diethyl chlorophosphate (1 mol equiv.) and then an aldehyde or ketone (1 mol equiv., −78 ⟶ 20 °C), could be applied to both (**2a**) and (**3a**) to generate the unstable alkenyldihydroimidazoles (**2f, g**) and (**3e, f**) after chromatography on alumina; the moderate yields from benzaldehyde and lower recoveries from acetone (Table) reflect the stability problems. Compounds (**2f**) and (**3e**) have the *E*-geometry as expected.

Finally, we examined the effect of nucleophiles on the two new dihydroimidazole systems. Quaternisation of the 3-nonylimidazoisoquinoline (**2c**) or the 1-nonylimidazoquinoline (**3c**) with iodomethane and addition of butylmagnesium bromide led, after acid work-up, to the generation in both cases of 5-tetradecanone, albeit in only moderate yield (31 and 37%, respectively); the use of butyl-lithium in the isoquinoline series was less effective.[2] We were interested in comparing the effect of hydride on these fused dihydroimidazoles with our findings for monocyclic cases, in particular whether the production of tetrahydroimidazoles as precursors to aldehydes would be possible;[2] the chemical reduction of N^5,N^{10}-methenyltetrahydrofolate (**1**) to the N^5,N^{10}-methylene compound has been observed.[11] Treatment of the 3-alkylimidazoisoquinolines (**2a, c**) or the 1-nonylimidazoquinoline (**3c**) with lithium aluminium hydride (THF or Et_2O; reflux) instead led (as in the monocyclic case) to over-reduction to afford the 1-(alkylaminomethyl)-tetrahydroisoquinolines (**11a**) (86%) and (**11b**) (57%), and the 2-(decylaminomethyl)tetrahydroquinoline (**12a**) (58%), respectively. The same results were observed in slower reactions with sodium borohydride (EtOH, reflux), for example giving the diamine (**12a**) (92%) from (**3c**) in 5 days. The quaternary salts formed from (**2c**) and (**3c**) by reaction with iodomethane were more reactive and gave the diamines (**11c**) and (**12b**), respectively, with sodium borohydride in EtOH at −20 °C and even at −78 °C. Using sodium borohydride in dimethyl sulphoxide–pyridine (4:1 v/v), the system employed successfully in the reduction of N^5,N^{10}-methenyltetrahydrofolate,[11] reductions at 60 °C of (**2a**) (no reaction was observed at room temperature) and at 20 °C of the quaternary salt formed from (**3c**) to the corresponding diamines (**11a**) (100%) and (**11c**) (75%), respectively, were also observed, with no accumulation of the (presumed) intermediate tetrahydroimidazoles.



(**11**) **a**; R^1 = H, R^2 = CH_2Me
b; R^1 = H, R^2 = $(CH_2)_9Me$
c; R^1 = Me, R^2 = $(CH_2)_9Me$



(**12**) **a**; R^1 = H, R^2 = $(CH_2)_9Me$
b; R^1 = Me, R^2 = $(CH_2)_9Me$

We have thus devised a new route to (alkyl)aminomethyl-isoquinolines and -quinolines and to derivatives of the imidazo-isoquinoline and -quinoline systems, molecules of interest for their pharmacological potential. They behave chemically in the same way as monocyclic dihydroimidazoles.[2] The fused imidazolines offer potential for asymmetric induction in dihydroimidazole chemistry, an aspect that we have not yet explored.

Experimental

Melting points were measured on a capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 710B spectrometer. ^{1}H NMR spectra were determined in deuteriochloroform solution (tetramethylsilane as internal standard) at 90 MHz using Perkin–Elmer R32 spectrometers. ^{13}C NMR spectra were recorded in deuteriochloroform

solution at 90 MHz using a Jeol FX 90Q spectrometer. Mass spectra were obtained using an A.E.I. MS902 spectrometer. Column chromatographic separations were performed on silica gel (Merck Kieselgel 60, Art.7729) unless otherwise stated. Compounds were all homogeneous by TLC examination. 'Drying' refers to the use of magnesium sulphate. Tetrahydrofuran was distilled from lithium aluminium hydride immediately prior to use, and butyl-lithium solutions were standardised by the diphenylacetic acid method.[12] Ether refers to diethyl ether. Petroleum refers to that fraction with b.p. 40–60 °C. Unless otherwise stated, solutions of sodium hydroxide and potassium hydroxide refer to aqueous solutions and the concentrations are expressed as percentages (w/v).

2-*Phenylsulphonyl*-1,2-*dihydroisoquinoline*-1-*carbonitrile* (**6b**).—Benzenesulphonyl chloride (95 ml, 0.74 mol) was added dropwise over a period of 30 min to a vigorously stirred solution of isoquinoline (45 ml, 0.33 mol) and potassium cyanide (78 g, 1.20 mol) in water (625 ml), and stirring continued for a further 4 h. The aqueous mixture was extracted with dichloromethane. The combined organic solutions were washed with water, 10% hydrochloric acid, water, 5% potassium hydroxide, and finally with water. The organic solution was dried, filtered, and concentrated to give 2-phenylsulphonyl-1,2-dihydroisoquinoline-1-carbonitrile (**6b**) (72.57 g, 65%) as a yellow solid, m.p. 102–104 °C (lit.,[9] 109–112 °C); δ_H 6.15–6.30 (2 H, m, CHN and NC*H*=CH), 6.85 (1 H, dd, NCH=C*H*), 7.1–7.5 (4 H, m), 7.5–7.7 (3 H, m), and 7.9–8.1 (2 H, m). This was found to be suitable for use without further purification.

Isoquinoline-1-*carbonitrile* (**8a**).—Sodium borohydride (3.8 g, 0.1 mol) was added to a stirred suspension of 2-phenylsulphonyl-1,2-dihydroisoquinoline-2-carbonitrile (**6b**) (29.8 g, 0.1 ml) in ethanol (1 l). After 2 h the solvent was removed *in vacuo* and the residue partitioned between water and chloroform. The combined extracts were washed, dried, filtered, and concentrated *in vacuo* to give isoquinoline-1-carbonitrile (**8a**) (16.83 g, 100%) as a yellow solid, m.p. 86–88 °C (lit.,[9] 87–88 °C); δ_H 7.7–8.0 (4 H, m), 8.15–8.3 (1 H, m), and 8.65 (1 H, d, NCH). This was found to be suitable for use without further purification.

Isoquinoline-1-*carboxamide* (**8b**).—Potassium hydroxide (1.85 g, 25% solution) was added to a vigorously stirred suspension of the nitrile (**8a**) (1 g, 6.5 mmol) in hydrogen peroxide (33.40 g, 3% solution). The reaction mixture was heated to 40 °C, and then the heat was withdrawn. After 1.5 h, the solid was collected, dissolved in chloroform, and the solution dried, filtered, and concentrated *in vacuo* to give isoquinoline-1-carboxamide (**8b**) (0.92 g, 82%) as a white solid, m.p. 164–166 °C (lit.,[7] 168–170 °C); ν_{max}($CHCl_3$) 1 690 cm^{-1}. This was found to be suitable for use without further purification.

1,2,3,4-*Tetrahydroisoquinoline*-1-*carboxamide* (**9**).—The amide (**8b**) (8.7 g, 0.051 mol) was dissolved in 70% aqueous ethanol, which was then acidified with concentrated hydrobromic acid (12 ml). This solution was shaken over Adams' catalyst (0.45 g, 1.98 mmol) under 20 atm of hydrogen for 2 h. The catalyst was removed by filtration through Kieselguhr, and the solvent was removed *in vacuo*. The residue was dissolved in 2M sodium hydroxide, and extracted into chloroform. The combined organic extracts were dried, filtered, and concentrated to give 1,2,3,4-tetrahydroisoquinoline-1-carboxamide (**9**) (8.5 g, 95%) as a white solid, m.p. 174–176 °C (lit.,[7] 180–183 °C); δ_H(CF_3CO_2D–$CDCl_3$) 3.3 (2 H, t), 3.6–4.0 (2 H, m), 5.5 (1 H, s, CH), 7.4–7.7 (4 H, m, Ar), and 11.6 (3 H, s, 3 × NH).

1-*Aminomethyl*-1,2,3,4-*tetrahydroisoquinoline* (**4**).—Boron trifluoride–ether (4.2 ml, 34 mmol) was added dropwise *via* a syringe, over 20 min, to a stirred suspension of sodium borohydride (1.26 g, 88 mmol) and the amide (**9**) (1.0 g, 5.7 mmol) in tetrahydrofuran (10 ml), with cooling in ice. The ice bath was removed, and the mixture brought to reflux. After 12 h, the solution was allowed to cool, treated carefully with 6M hydrochloric acid (5 ml), and brought to reflux for 1 h. The solution was again allowed to cool, and the solvent removed *in vacuo*. The residue was taken up in water, basified with solid sodium hydroxide pellets, and extracted with chloroform. The combined organic extracts were dried, filtered, and concentrated *in vacuo* to give 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (**4**) (0.94 g, 100%) as an oil; δ_H($CDCl_3$) 1.75 (3 H, s, NH and NH_2), 2.05–3.15 (6 H, m, 3 × CH_2), 3.8 (1 H, t, CH), and 7.0 (4 H, s, Ph). This oil was homogeneous by TLC and was used directly (see below).

3-*Methyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinoline* (**2a**).—1-Aminomethyl-1,2,3,4-tetrahydroisoquinoline (**4**) (7.46 g, 0.046 mol) and ethyl acetimidate hydrochloride[13] (5.8 g, 0.047 mol) were dissolved in dry ethanol (45 ml) and the solution was brought to reflux. After 3 h, the reaction mixture was allowed to cool, and the solvent removed *in vacuo*. The resulting oil was dissolved in 30% sodium hydroxide solution, and extracted into chloroform. The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The crude material was columned over silica, eluting with isopropylamine–chloroform (1:99 v/v), to give 3-*methyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinoline* (**2a**) (5.8 g, 66%) as an oil (Found: M^+, 186.1149. $C_{12}H_{14}N_2$ requires M, 186.1157); ν_{max}(film) 2 930, 2 880, 1 620, 1 410, 1 240, and 750 cm^{-1}; δ_H 2.0 (3 H, s, Me), 2.5–3.0 (2 H, m, CH_2Ar), 3.15–3.55 (1 H, m, C*H*HCH_2Ar), 3.6–3.95 (2 H, m, NCH_2CHN), 4.15–4.35 (1 H, m, CH*H*CH_2Ar), 4.85 (1 H, dd, NCH_2C*H*N), and 7.0–7.4 (4 H, m, Ar); δ_C 163.1, 139.1, 133.9, 128.7, 127.0, 126.3, 125.6, 61.2, 59.6, 41.1, 28.1, and 14.0 ppm; m/z 186 (M^+). A portion of the title compound was converted into the *oxalate salt*, m.p. 177–178 °C from ethanol–ether (Found: C, 61.0; H, 6.0; N, 10.1. $C_{14}H_{16}O_4N_2$ requires C, 60.9; H, 5.8; N, 10.1%).

Quinoline-2-*carboxamide* (**10b**).—To a suspension of the nitrile (**10a**)[10] (0.89 g, 5.8 mmol) in 3% hydrogen peroxide solution (33.39 g) was added 25% potassium hydroxide solution (1.85 g). The mixture was heated to 40 °C, and then the heat was withdrawn. After 3 h, the solid was collected and dried in a vacuum desiccator over phosphorus pentaoxide to give quinoline-2-carboxamide (**10b**) (0.77 g, 77%) as a white solid, m.p. 131–132 °C (lit.,[14] 132.5–133 °C); δ_H 7.15 (2 H, br s, NH_2), 7.5–8.0 (3 H, m), and 8.0–8.5 (3 H, m).

2-*Aminomethyl*-1,2,3,4-*tetrahydroquinoline* (**5**).—A solution of the amide (**10b**) (0.74 g, 4.3 mmol) in 70% aqueous ethanol (60 ml) was acidified with concentrated hydrobromic acid (1 ml), and shaken over Adams' catalyst (0.04 g, 0.18 mmol) under 30 atm of hydrogen for 1 h. The catalyst was removed by filtration through Kieselguhr, and the solvent was removed *in vacuo*. The residue was basified with 2M potassium hydroxide solution and extracted into chloroform. The combined organic extracts were dried, filtered, and concentrated *in vacuo* to give a yellow solid. This was purified by column chromatography over silica, eluting with methanol–chloroform [5:95 v/v], to give 1,2,3,4-tetrahydroquinoline-2-carboxamide (0.53 g, 70%), as a yellow solid; δ_H 1.8–2.5 (2 H, m, CHCH_2CH_2), 2.6–2.8 (2 H, m, ArCH_2), 3.45 (1 H, s, NH), 3.95 (1 H, t, CH), 6.2 (2 H, s, NH_2), and 6.5–7.2 (4 H, m, Ar). 1,2,3,4-Tetrahydroquinoline-2-carboxamide (4.59 g, 0.026 mol) was refluxed with diborane (250 ml, 1M solution in tetrahydrofuran) for 3 days. The solution was allowed to cool, treated carefully with 5M hydrochloric acid (50 ml) and brought to reflux for 1 h. The solution was allowed

to cool, and the solvent removed *in vacuo*. The residue was basified with 2M sodium hydroxide solution, and extracted into chloroform. The combined organic extracts were dried, filtered, and concentrated *in vacuo* to give an oil (13.04 g). Some polymeric material (presumably resulting from ring opening of the tetrahydrofuran solvent in the presence of diborane) was removed by column chromatography over silica, eluting with isopropylamine–chloroform (2.5:97.5 v/v), and the remainder by acidification with 2M hydrochloric acid, and washing with ether. The ether solutions were discarded, then the aqueous solution was made basic with solid sodium hydroxide, and extracted with chloroform. The combined organic extracts were dried, filtered, and concentrated *in vacuo* to give 2-aminomethyl-1,2,3,4-tetrahydroquinoline (3.50 g, 83%), as an oil (Found: M^+, 162.1141. $C_{10}H_{14}N_2$ requires M, 162.1157); $\delta_H(CDCl_3)$ 1.45–2.05 (5 H, m, CH_2CH_2CH and 3 × NH), 2.3–3.0 (4 H, m, $ArCH_2$ and CH_2NH_2), 3.15 (1 H, m, CH), and 6.5–7.1 (4 H, m, Ar); m/z 162 (M^+), that was homogeneous by TLC and was used directly (see below).

1-*Methyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinoline* (**3a**).—2-Aminomethyl-1,2,3,4-tetrahydroquinoline (**5**) (0.0738 g, 0.45 mmol) and ethyl acetimidate hydrochloride[13] (0.06 g, 0.48 mmol) were dissolved in dry ethanol (1 ml), and the solution was brought to reflux for 4.5 h. The solution was allowed to cool, and the solvent removed *in vacuo*. The residue was basified with 2M potassium hydroxide, and extracted into chloroform. The combined extracts were dried, filtered, and concentrated under reduced pressure and the crude material was columned over silica, eluting with isopropylamine–chloroform (1:99, v/v), to afford 1-*methyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinoline* (0.0440 g, 52%) as an oil (Found: M^+, 186.1157. $C_{12}H_{14}N_2$ requires M, 186.1157); ν_{max}(film) 3 020, 2 940, 2 860, 1 630, 1 580, 1 500, and 750 cm^{-1}; δ_H 1.65–1.95 (2 H, m, CH_2CH_2Ar), 2.15 (3 H, s, Me), 2.8–3.0 (2 H, m, CH_2Ar), 3.5–4.05 (3 H, m, NCH_2CHN), and 7.05–7.35 (4 H, m, Ar); m/z 186 (M^+). A portion of the title compound was converted into the *oxalate salt*, m.p. 205–206 °C from ethanol–ether (Found: C, 60.9; H, 6.1; N, 10.2%. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.8; N, 10.1%).

General Procedure for the C-*Alkylation of* 3-*Methyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinoline* (**2a**) *and* 1-*Methyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinoline* (**3a**).—Butyl-lithium (1 ml, 1.48M solution in hexanes, 1.48 mmol) was added dropwise to a solution of the bicyclic dihydroimidazole (0.25 g, 1.34 mmol) in dry tetrahydrofuran (2.5 ml), at −78 °C under nitrogen. After 1 h, the alkyl halide (1.6 mmol) was added dropwise. The cooling bath was removed, and stirring continued for a further 18 h. The solution was poured into water and extracted with chloroform. The combined chloroform solutions were dried, filtered, and concentrated *in vacuo* to afford the crude materials. Purification by column chromatography over silica, eluting with isopropylamine–chloroform (0.5:99.5 v/v), gave the pure compounds. Where possible, the oxalate salts were prepared. This was achieved by dropwise addition of a solution of the compound in dry ethanol into ethereal oxalic acid. The mother-liquid was decanted away, and the precipitate washed with dry ether and recrystallised from ethanol–ether.

3-*Ethyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinoline* (**2b**) was prepared from (**2a**) as above using methyl iodide. Column chromatography afforded compound (**2b**) (0.98 g, 38%) as an oil (Found: M^+, 200.1307. $C_{13}H_{16}N_2$ requires M, 200.1313); ν_{max}(film) 2 940, 1 620, 1 220, and 750 cm^{-1}; δ_H 1.2 (3 H, t, Me), 2.25 (2 H, q, CH_2Me), 2.5–3.1 (2 H, m, CH_2Ar), 3.2–3.6 (1 H, m, $ArCH_2CHH$), 3.6–4.0 (2 H, m, NCH_2CHN), 4.0–4.3 (1 H, m, $ArCH_2CHH$), 4.8 (1 H, dd, CH), and 6.9–7.4 (4 H, m, Ar); m/z 200 (M^+). A portion of the title compound was converted into the *oxalate salt* and recrystallised from ethanol–ether (Found: C, 57.3; H, 6.5; N, 8.6%. $C_{15}H_{18}N_2O_4 \cdot 1.35\ H_2O$ requires C, 57.3; H, 6.6; N, 8.9%).

3-*Nonyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinoline* (**2c**) was prepared as above from (**2a**) (0.76 g, 4.09 mmol), butyl-lithium (3.45 ml, 1.42M solution in hexanes, 4.9 mmol), and 1-iodo-octane (0.81 ml, 4.5 mmol). Column chromatography over silica afforded compound (**2c**) (1.02 g, 84%) as an oil, homogeneous by TLC; ν_{max}(film) 2 950, 1 610, 1 215, 1 100, 900, and 750 cm^{-1}; δ_H 0.9 (3 H, t, Me), 1.0–1.8 [14 H, m, $(CH_2)_7Me$], 2.3 [2 H, t, $CH_2(CH_2)_7Me$], 2.6–2.9 (2 H, m, $ArCH_2$), 3.2–3.55 (1 H, m, $ArCH_2CHH$), 3.6–3.95 (2 H, m, NCH_2CH), 4.1–4.35 (1 H, m, $ArCH_2CHH$), 4.9 (1 H, dd, CH), and 7.0–7.3 (4 H, m, Ar); δ_C 166.2, 139.2, 133.9, 128.6, 126.9, 126.2, 125.6, 61.3, 59.6, 40.8, 31.9, 29.5, 29.4, 29.3, 28.0, 27.8, 26.4, and 14.0; m/z 298 (M^+).

3-*Isobutyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinoline* (**2d**) was prepared as above from (**2a**) (0.5 g, 2.7 mmol), butyl-lithium (1.75 ml, 1.6M solution in hexanes, 2.8 mmol), and 2-iodopropane (0.31 ml, 3.1 mmol). Column chromatography afforded compound (**2d**) (0.42 g, 66%) as an oil; ν_{max}(film) 2 950, 1 610, 1 215, 1 100, 1 010, 900, and 750 cm^{-1}; δ_H 1.0 (6 H, m, 2 × Me), 2.15 (3 H, m, CH_2CHMe_2), 2.6–2.9 (2 H, m, CH_2Ar), 3.2–3.5 (1 H, m, $ArCH_2CHH$), 3.6–4.0 (2 H, m, NCH_2CHN), 4.05–4.4 (1 H, m, $ArCH_2$ CHH), 4.7–4.95 (1 H, dd, CH), and 6.95–7.30 (4 H, m, Ar); m/z 228 (M^+). A portion of the title compound was converted into the *oxalate salt* and recrystallised from isopropanol–ether (Found: C, 64.1; H, 7.0; N, 8.8%. $C_{17}H_{22}N_2O_4$ requires C, 64.1; H, 7.0; N, 8.8%).

1-*Ethyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinoline* (**3b**) was prepared from (**3a**) using methyl iodide in the above procedure, followed by the usual work-up and column chromatography to afford compound (**3b**) (0.20 g, 78%) as an oil (Found: M^+, 200.1310. $C_{13}H_{16}N_2$ requires M, 200.1314); ν_{max}(film) 2 940, 1 620, 1 575, 1 490, 1 460, 1 385, 1 220, and 760 cm^{-1}; δ_H 1.2 (3 H, t, Me), 1.65–1.95 (2 H, m, CH_2CH_2Ar), 2.3–2.65 (2 H, m, CH_2Ar), 2.8–3.0 (2 H, m, CH_2Me), 3.5–4.1 (3 H, m, NCH_2CHN), and 6.95–7.3 (4 H, m, Ar); m/z 200 (M^+).

1-*Nonyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinoline* (**3c**) was prepared as above using (**3a**) (0.56 g, 3.01 mmol), butyl-lithium (2.5 ml, 1.47M solution in hexanes, 3.68 mmol), and 1-iodo-octane (0.65 ml, 3.6 mmol). The usual work-up, followed by column chromatography, afforded compound (**3c**) (0.84 g, 93%) as an oil (Found: M^+, 298.2405. $C_{20}H_{30}N_2$ requires M, 298.2409); ν_{max}(film) 2 900, 2 860, 1 620, 1 570, 1 490, 1 455, 1 390, 1 210, 1 010, and 760 cm^{-1}; δ_H 0.9 (3 H, t, Me), 1.2–1.9 [16 H, m, $(CH_2)_7Me$ and CH_2CH_2Ar], 2.3–2.6 [2 H, m, $CH_2(CH_2)_7Me$], 2.8–3.0 (2 H, m, CH_2Ar), 3.5–4.0 (3 H, m, NCH_2CHN), and 7.0–7.3 (4 H, m, Ar); m/z 298 (M^+).

1-*Isobutyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinoline* (**3d**) was prepared from (**3a**) using 2-iodopropane in the manner described above, followed by the usual work-up and column chromatography to afford compound (**3d**) (0.17 g, 58%) as an oil (Found: M^+, 228.1575. $C_{15}H_{20}N_2$ requires M, 228.1626); ν_{max}(film) 2 940, 1 610, 1 570, 1 485, 1 455, 1 375, 1 210, 1 005, and 760 cm^{-1}; δ_H 0.95 (6 H, t, 2 × Me), 1.65–2.2 (3 H, m, CH_2CH_2Ar and CH), 2.25–2.4 (2 H, m, CH_2CH), 2.75–3.0 (2 H, m, CH_2Ar), 3.5–4.1 (3 H, m, NCH_2CHN), and 7.0–7.3 (4 H, m, Ar); m/z 228 (M^+). A portion of the title compound was converted into the *oxalate salt*, m.p. 100 °C (decomp.) from ethanol–ether (Found: C, 62.3; H, 7.0; N, 8.7%. $C_{17}H_{22}N_2O_4 \cdot 0.52\ H_2O$ requires C, 62.3; H, 7.0; N, 8.5%).

3-(2-*Hydroxyprop*-1-*enyl*)-1,5,6,10b-*tetrahydroimidazo*-[5,1-a]*isoquinoline* (**2e**).—Butyl-lithium (1 ml, 1.54M solution in hexanes, 1.54 mmol) was added dropwise to a solution of 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**2a**) (0.25 g, 1.34 mmol) in tetrahydrofuran (4 ml), under nitrogen at

−78 °C. After 1 h the solution was added *via* a syringe to a solution of ethyl acetate (0.148 ml, 1.5 mmol) in tetrahydrofuran (4 ml) at −78 °C. After a further hour, the solution was allowed to warm to room temperature and stirring continued overnight. The solvent was removed *in vacuo*, and the residue partitioned between water and chloroform. The layers were separated and the aqueous layer extracted with chloroform. The combined extracts were dried, filtered, and concentrated *in vacuo* to give an oil. Column chromatography over silica, eluting with isopropylamine–chloroform (5:95 v/v), afforded the *title compound* (**2e**) (0.15 g, 49%) as an oil (Found: M^+, 228.1251. $C_{14}H_{16}N_2O$ requires M, 228.1262); ν_{max}(film) 3 280, 2 900, 1 600, 1 530, and 730 cm^{-1}; δ_H 2.05 (3 H, s, Me), 2.7–3.15 (2 H, m, CH_2Ar), 3.15–3.95 (4 H, m, $CHHCH_2Ar$, NCH_2CHN, and OH), 4.15 (1 H, m, $CHHCH_2Ar$), 4.75–5.05 (2 H, m, $NCHCH_2N$ and vinyl CH), and 7.05–7.45 (4 H, m, Ar); *m/z* 228 (M^+).

General Procedure for the Wadsworth–Emmons Condensation of 3-*Methyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinoline* (**2a**) *and* 1-*Methyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinoline* (**3a**) *with Aldehydes and Ketones*.—A solution of lithium di-isopropylamide was prepared from di-isopropylamine (0.4 ml, 2.8 mmol) in tetrahydrofuran (2.5 ml) and butyl-lithium (2 ml, 1.42M solution in hexanes, 2.8 mmol). After 0.5 h at room temperature, the solution was cooled to −78 °C and treated dropwise with a solution of the dihydroimidazole (0.25 g, 1.35 mmol) in tetrahydrofuran (2.5 ml). After a further 1 h at this temperature, freshly distilled diethyl chlorophosphate (0.2 ml, 1.4 mmol) was added dropwise, and stirring continued for a further 2 h. The aldehyde or ketone was added (1.5 mmol) and the solution was allowed to warm to room temperature and the stirring continued overnight. The mixture was poured into water and extracted into chloroform. The organic solution was dried, filtered, and concentrated *in vacuo*. Column chromatography over alumina, eluting with isopropylamine–chloroform (0.25: 99.75 v/v), afforded the pure compounds.

3-(2-*Phenylethenyl*)-1,5,6,10b-*tetrahydroimidazo*[5,1a]-*isoquinoline* (**2f**) was prepared according to the general procedure using di-isopropylamine (0.8 ml, 5.7 mmol) and butyl-lithium (4 ml, 1.42M solution in hexanes, 5.7 mmol), 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**2a**) (0.5 g, 2.7 mmol), diethyl chlorophosphate (0.4 ml, 2.8 mmol), and benzaldehyde (0.3 ml, 2.95 mmol). The usual work-up followed by column chromatography afforded compound (**2f**) (0.36 g, 49%) as an oil (Found: M^+, 274.1460. $C_{19}H_{18}N_2$ requires M, 274.1469); δ_H 2.55–2.8 (2 H, m, CH_2Ar), 3.2–3.6 (1 H, m, $CHHCH_2Ar$), 3.75–4.05 (2 H, m, NCH_2CHN), 4.2–4.5 (1 H, m, $CHHCH_2Ar$), 4.8–5.0 (1 H, dd, $CHCH_2$), 4.65 (1 H, d, *J* 17 Hz, CH=CHPh), and 6.9–7.7 (10 H, m, Ar and CH=CHPh); *m/z* 274 (M^+).

3-(2-*Methylprop*-1-*enyl*)-1,5,6,10b-*tetrahydroimidazo*-[5,1-a]*isoquinoline* (**2g**) was prepared using acetone in the above procedure from (**2a**). Usual work-up and column chromatography afforded compound (**2g**) (0.06 g, 36%) as an oil (Found: M^+, 226.1442. $C_{15}H_{18}N_2$ requires M, 226.1470); ν_{max}(film) 2 920, 1 660, 1 590, 1 450, 1 230, 1 020, 905, 830, and 750 cm^{-1}; δ_H 1.9 (3 H, s, Me), 2.0 (3 H, s, Me), 2.55–2.95 (2 H, m, CH_2Ar), 3.15–3.5 (1 H, m, $CHHCH_2Ar$), 3.60–4.05 (2 H, m, NCH_2CHN), 4.15–4.45 (1 H, m, $CHHCH_2Ar$), 4.85 (1 H, dd, $CHCH_2$), 5.75 (1 H, s, vinyl CH), and 6.95–7.3 (4 H, m, Ar); *m/z* 226 (M^+).

1-(2-*Phenylethenyl*)-3,3a,4,5-*tetrahydroimidazo*[1,5-a]-*quinoline* (**3e**) was prepared according to the general procedure from (**3a**) using benzaldehyde. The usual work-up and column chromatography afforded compound (**3e**) (1.61 g, 43%) as an oil (Found: M^+, 274.1437. $C_{19}H_{18}N_2$ requires M, 274.1470); ν_{max}(film) 3 030, 2 920, 2 860, 1 680, 1 645, 1 610, 1 595, 1 580, 1 500, 1 380, 1 220, and 750 cm^{-1}; δ_H 1.8–2.1 (2 H, m, $ArCH_2CH_2$), 2.8–3.1 (2 H, m, $ArCH_2$), 3.65–4.25 (3 H, m, NCH_2CHN), 6.9 (1 H, d, *J* 18 Hz, CH=CHPh), 7.0–7.6 (9 H, m, Ar and Ph), and 7.7 (1 H, d, *J* 18 Hz, CH=CHPh); *m/z* 274 (M^+). A portion of the title compound was converted into the *oxalate salt*, m.p. 155–156 °C from ethanol–ether (Found: C, 69.1; H, 5.7; N, 7.7%. $C_{21}H_{20}N_2O_4$ requires C, 69.2; H, 5.5; N, 7.7%).

1-(2-*Methylprop*-1-*enyl*)-3,3a,4,5-*tetrahydroimidazo*[1,5a]-*quinoline* (**3f**) was prepared using acetone in the general procedure from (**3a**). The usual work-up, followed by column chromatography, afforded compound (**3f**) (0.88 g, 29%) as an oil (Found: M^+, 226.1465. $C_{15}H_{18}N_2$ requires M, 226.1470); ν_{max}(film) 2 940, 2 840, 1 670, 1 605, 1 580, 1 500, 1 460, 1 370, 1 240, 1 180, 1 020, and 750 cm^{-1}; δ_H 1.7–2.2 (8 H, m, 2 × Me and $ArCH_2CH_2$), 2.8–3.0 (2 H, m, $ArCH_2$), 3.6–4.3 (3 H, m, NCH_2CHN), 5.75 (1 H, s, vinyl CH), and 6.9–7.2 (4 H, m, Ar); *m/z* 226 (M^+).

Reaction Between 2-*Methyl*-3-*nonyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinolinium Iodide and Butylmagnesium Bromide*.—The methiodide salt was prepared as follows. Methyl iodide (0.128 ml, 2.06 mmol) was added dropwise to 3-nonyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**2c**) (0.412 g, 1.38 mmol). After 0.5 h at room temperature, the solution was concentrated *in vacuo* to give 2-methyl-3-nonyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinolinium iodide (0.45 g, 100%) as a viscous oil; ν_{max}(film) 2 920, 1 610, 1 560, and 750 cm^{-1}; δ_H 0.85 (3 H, t, CH_2CH_3), 1.05–1.9 [14 H, m, $(CH_2)_7Me$], 2.75 [2 H, t, $CH_2(CH_2)_7Me$], 2.95–3.15 (2 H, m, CH_2Ar), 3.2 (3 H, s, NCH_3), 3.55–4.15 (3 H, m, NCH_2CHN and $CHHCH_2Ar$), 4.7 (1 H, t, $CHHCH_2Ar$), 5.65 (1 H, t, CH), and 7.0–7.4 (4 H, m, Ar); *m/z* 298 (11%, $M - CH_3I$); used without further purification. A solution of the methiodide (0.1 g, 0.23 mmol) in tetrahydrofuran (1. 5 ml) was added dropwise to butylmagnesium bromide (1.2 ml, 1.4M solution in tetrahydrofuran, 1.7 mmol), and the solution brought to reflux. After 3 h, the solution was cooled to 0 °C, and the excess Grignard reagent was destroyed with 2M hydrochloric acid (2 ml). Ether (5 ml) was added and stirring continued at 0 °C for 2 h. The layers were separated and the aqueous layer further extracted with ether. The combined extracts were dried, filtered, and concentrated. The residue was chromatographed over silica eluting with ether to give tetradecan-5-one (0.015 g, 31%) as an oil, identical to an authentic sample.

When butyl-lithium (0.5 ml, 1.5M solution in hexanes, 0.75 mmol) was added to a solution of the methiodide (1.1 g, 2.5 mmol) in tetrahydrofuran (10 ml), and stirring continued at room temperature for 3 h, work-up as above afforded a brown oil (0.8 g). Column chromatography over silica eluting with chloroform afforded tetradecan-5-one (0.12 g, 23%), identical to an authentic sample.

Reaction Between 1-*Nonyl*-2-*methyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-a]*quinolinium Iodide and Butylmagnesium Bromide*.—The methiodide salt was prepared as follows. Methyl iodide (0.5 ml, 8.03 mmol) was added cautiously to 1-nonyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinoline (**3c**) (0.0830 g, 0.28 mmol). After 30 min the solution was concentrated *in vacuo* to give the title compound (0.12 g, 100%) as a thick oil. This material was used in the following reactions without further purification. The methiodide (0.1 g, 0.23 mmol) was treated with butylmagnesium bromide in tetrahydrofuran as described above for the isoquinoline series. Work-up afforded tetradecan-5-one (0.018 g, 37%) identical to an authentic sample.

Reduction of 3-*Alkyl*-1,5,6,10b-*tetrahydroimidazo*[5,1-a]*isoquinolines* (**2a**, **c**) *and* 1-*Alkyl*-3,3a,4,5-*tetrahydroimidazo*[1,5-

a]*quinolines* (**3c**).—(i) *With lithium aluminium hydride.* Lithium aluminium hydride (0.22 g, 5.8 mmol) was added to a solution of 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**2a**) (0.52 g, 2.80 mmol) in dry tetrahydrofuran (5 ml) and the mixture brought to reflux for 0.5 h. On cooling, the excess lithium aluminium hydride was decomposed by the careful addition of water (0.22 ml), 15% sodium hydroxide (0.22 ml), and finally water (0.66 ml). The precipitate was removed by filtration and the solution dried, filtered, and concentrated *in vacuo* to give 1-*ethylaminomethyl*-1,2,3,4-*tetrahydroisoquinoline* (**11a**) (0.46 g, 86%) as an oil (Found: M^+, 190.1480. $C_{12}H_{18}N_2$ requires M, 190.1470); ν_{max}(film) 3 300, 2 930, 1 500, 1 470, 1 125, and 750 cm^{-1}; δ_H 1.1 (3 H, t, Me), 2.05 (2 H, s, 2 × NH), 2.6–3.2 (8 H, m, 4 × CH_2), 4.0 (1 H, dd, CH), and 7.0–7.2 (4 H, m, Ar); m/z 190 (M^+).

A mixture of lithium aluminium hydride (0.22 g, 0.58 mmol), 3-nonyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**2c**) (0.0863 g, 0.29 mmol) and dry ether (1 ml) was heated at reflux. After 1 h, the reaction mixture was allowed to cool, diluted with ether, and treated successively with water (0.025 ml), 15% sodium hydroxide solution (0.025 ml), and finally water (0.075 ml). The solid was removed by filtration, and the filtrate dried, filtered, and concentrated *in vacuo*. The residue was columned twice over silica, with isopropylamine–chloroform (0.5:99.5 v/v) as eluant, to afford 1-*decylaminomethyl*-1,2,3,4-*tetrahydroisoquinoline* (**11b**) (0.05 g, 57%) as an oil; ν_{max}(film) 3 300, 2 920, 2 850, 1 450, 1 120, and 740 cm^{-1}; δ_H 0.9 (3 H, t, Me), 1.3 [16 H, s, $(CH_2)_8$Me], 1.8 (2 H, s, 2 × NH), 2.5–3.3 (8 H, m, 4 × CH_2), 4.0 (1 H, t, CH), and 7.1 (4 H, s, Ar); m/z 314 (14%, M + C), 313 [57, M + (C − H)], 145 (58, $C_{10}H_{11}N$), and 132 (100, $C_9H_{10}N$). The occurrence of peaks such as (M + 11) in the mass spectrum of molecules containing ethane-1,2-diamine or propane-1,3-diamine units has been described in detail elsewhere.[15]

A mixture of 1-nonyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]-quinoline (**3c**) (0.0979 g, 0.33 mmol), lithium aluminium hydride (0.0249 g, 0.656 mmol), and dry ether (2 ml) was brought to reflux for 2 h. The reaction mixture was allowed to cool, and treated successively with water (0.025 ml), 15% sodium hydroxide (0.025 ml), and water (0.075 ml). The precipitate was removed by filtration, and the filtrate was dried, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography over silica, eluting with isopropylamine–chloroform–petroleum (0.5:50:49.5 v/v/v), to give 2-*decylaminomethyl*-1,2,3,4-*tetrahydroquinoline* (**12a**) (0.06 g, 58%) as an oil (Found: M^+, 314.2694. $C_{21}H_{34}N_2$ requires M, 314.2721); ν_{max}(film) 3 400, 2 910, 2 860, 1 605, 1 585, 1 480, 1 350, 1 310, 1 120, and 750 cm^{-1}; δ_H 0.9 (3 H, t, Me), 1.1–2.0 [20 H, m, $(CH_2)_8$Me, 2 × NH, and CH_2CH_2Ar], 2.45–3.0 (4 H, m, CH_2Ar and CH_2NH), 3.2–3.5 (1 H, m, CH), and 6.5–7.2 (4 H, m, Ar); m/z 314 (M + C), 313 [M + (C − H)], 302 (M^+).[15]

(ii) *With sodium borohydride/ethanol.* A mixture of 1-nonyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]quinoline (**3c**) (0.11 g, 0.37 mmol), sodium borohydride (0.016 g, 0.423 mmol), and dry ethanol (2 ml) was refluxed for 5 days. The solution was poured into water and extracted into chloroform. The combined extracts were dried, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography over silica, eluting with isopropylamine–chloroform (0.5:99.5 v/v), to give 2-decylaminomethyl-1,2,3,4-tetrahydroquinoline (**12a**) (0.10 g, 92%), identical by TLC examination and NMR spectroscopy to the sample prepared above.

(iii) *With sodium borohydride/dimethyl sulphoxide–pyridine.* Sodium borohydride (0.5 g, 0.013 mmol) was added to a solution of 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**2a**) (0.41 g, 2.20 mmol) in dimethyl sulphoxide–pyridine [4:1 (v/v), 5 ml], and stirring continued at room temperature overnight. The reaction mixture was poured into water, and extracted into chloroform. The combined solutions were dried, filtered, and concentrated *in vacuo* to afford unreacted 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**2a**) (0.4 g, 80%).

The experiment described above was repeated at 60 °C on a quarter scale. This afforded 1-ethylaminomethyl-1,2,3,4-tetrahydroquinoline (**11a**) (0.1 g, 100%), identical to the sample prepared earlier.

Reduction of 2-*Methyl*-3-*nonyl*-1,5,6,10b-*tetrahydroimidazo*-[5,1-a]*isoquinolinium Iodide.*—The methiodide salt was prepared from (**2c**) as outlined above. Sodium borohydride (0.12 g, 3.2 mmol) was added to a solution of the methiodide (0.08 g, 0.18 mmol) in absolute ethanol, and stirring continued for 1 h at room temperature. The solvent was removed *in vacuo*, and the residue treated with water and extracted into chloroform. The combined solutions were dried, filtered, and concentrated *in vacuo* to give an oil. Purification by column chromatography over silica in isopropylamine–chloroform (0.5:99.5 v/v) afforded 1-decylmethylaminomethyl-1,2,3,4-tetrahydroisoquinoline (**11c**) (0.35 g, 60%) as an oil; ν_{max}(film) 3 300, 2 920, 2 850, 1 490, 1 450, 755, and 740 cm^{-1}; δ_H 0.9 (3 H, t, CH_3CH_2), 1.3 [16 H, s, $(CH_2)_8$Me], 2.3 (3 H, s, NMe), 2.4–2.65 (4 H, m), 2.75–2.9 (3 H, m) 3.0–3.2 (2 H, m), 4.05 (1 H, dd, CH), and 7.2 (4 H, s, Ar); m/z 184 (100%, $C_{12}H_{26}N$) and 132 (47, $C_9H_{10}N$).

This reduction was repeated with sodium borohydride (0.01 g, 0.26 mmol) and the methiodide (0.0842 g, 0.9 mmol) in absolute ethanol but at −78 °C. After stirring for 2 h at this temperature, the reaction was quenched with 2M hydrochloric acid (1 ml), and allowed to attain room temperature. The solution was basified with 2M sodium hydroxide and extracted into chloroform. The combined extracts were dried, filtered, and concentrated *in vacuo*, and the residue purified by column chromatography over silica, eluting with isopropylamine–chloroform (0.5:99.5 v/v), to afford 1-decylmethylaminomethyl-1,2,3,4-tetrahydroisoquinoline (**11c**) (0.0332 g, 55%) as an oil, identical to the sample prepared above.

Reduction of 1-*Nonyl*-2-*methyl*-3,3a,4,5-*tetrahydroimidazo*-[1,5-a]*quinolinium Iodide.*—The methiodide salt was prepared from (**3a**) as outlined above.

(i) *With sodium borohydride/ethanol.* Sodium borohydride (0.020 g, 0.53 mmol) was added to a solution of the methiodide salt (0.12 g, 0.28 mmol) in ethanol (5 ml), and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was dissolved in water and extracted into chloroform. The combined extracts were dried, filtered, and concentrated *in vacuo* to give an oil. Column chromatography over silica, eluting with isopropylamine–chloroform–petroleum (0.5:50:49.5 v/v/v), gave a very poor separation. This was improved using isopropylamine–chloroform–petroleum (0.5:19.5:80 v/v/v), to give 2-(*decylmethylaminomethyl*)-1,2,3,4-*tetrahydroquinoline* (**12b**) (0.035 g, 40%) an oil (Found: M^+, 316.2853. $C_{21}H_{36}N_2$ requires M, 316.2878); ν_{max}(film) 3 400, 2 920, 2 860, 1 600, 1 590, 1 475, 1 350, 1 310, 1 275, and 750 cm^{-1}; δ_H 0.9 (3 H, t, Me), 1.3–2.0 [18 H, m, $(CH_2)_8$Me and CH_2CH_2Ar], 2.3 (3 H, s, NMe), 2.35–2.6 (5 H, m, 2 × NCH_2 and NH), 2.75–3.0 (2 H, m, CH_2Ar), 3.3–3.6 (1 H, m, CH), and 6.5–7.2 (4 H, m, Ar); m/z 316 (M^+).

(ii) *With sodium borohydride/dimethyl sulphoxide–pyridine.* Sodium borohydride (0.125 g, 3.30 mmol) was added to a solution of the methiodide salt (0.1127 g, 0.26 mmol) in dry dimethyl sulphoxide–pyridine (4:1 v/v, 5 ml). After 30 min, the reaction mixture was treated with 2M hydrochloric acid, and stirring continued for 30 min. The aqueous layer was basified with solid sodium hydroxide pellets and extracted with chloroform. The combined extracts were dried, filtered, and

concentrated *in vacuo* and the residue was purified by column chromatography over silica, eluting with isopropylamine–chloroform (0.5:99.5 v/v), to afford 2-decylmethylaminomethyl-1,2,3,4-tetrahydroquinoline (**12b**) (0.0613 g, 75%), identical to the sample prepared above.

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