Synthesis of 1,2-Dihydroisoquinoline-3-carbaldehydes

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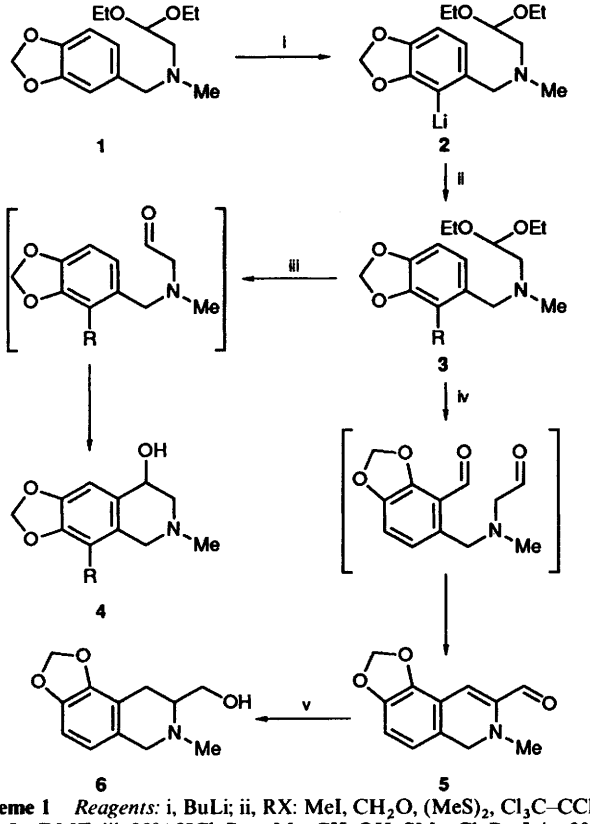
ortho-Formylation of *N*-(2,2-diethoxyethyl)benzylamines followed by acid-catalyzed cyclisation leads to 1,2-dihydroisoquinoline-3-carbaldehydes.

Lithiation of *N*-(2,2-diethoxyethyl)benzylamine **1**, followed by reactions of aryllithium **2** with electrophiles and subsequent cyclisation of intermediates **3** with 20% aqueous hydrochloric acid, afforded 1,2,3,4-tetrahydroisoquinolin-4-ols **4** having various carbo- and hetero-functional groups (*e.g.* Me, CH_2OH, SMe, Cl, Br, I) in the 8-position [1] (Scheme 1).

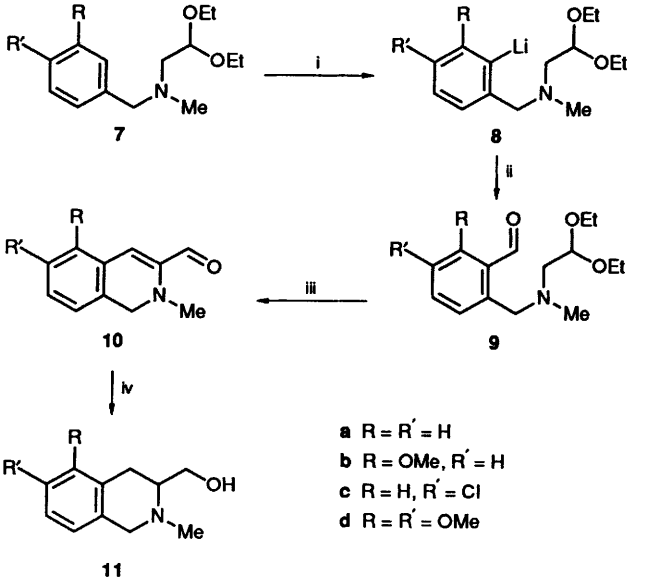


Scheme 1 *Reagents:* i, BuLi; ii, RX: MeI, CH_2O, $(MeS)_2$, $Cl_3C–CCl_3$, Br_2, I_2, DMF; iii, 20% HCl, R = Me, CH_2OH, SMe, Cl, Br, I; iv, 20% HCl, R = CHO; v, $NaBH_4$, MeOH

In the course of our work we intended to apply this procedure for the synthesis of isoquinoline-4-carbaldehyde **4** (R = CHO). However, cyclisation of the corresponding formyl derivative **3** (R = CHO) with 20% aqueous hydrochloric acid failed to give the expected product. Instead, 1,2-dihydroisoquinoline-3-carbaldehyde **5** was obtained. The structure of compound **5** was assigned on the basis of elemental analysis, IR and NMR spectroscopy and mass spectral data. Further support for the proposed structure was provided by borohydride reduction of aldehyde **5** to afford hydroxymethyl derivative **6**.

Cyclisation of type **3** acetals to isoquinolines **4** in 20% hydrochloric acid (Bobbitt's modification of the Pomeranz–Fritsch synthesis) is known to take place only if the aromatic site of the ring closure is sufficiently activated by electron-donating substituents.[2] The formyl derivative **3** (R = CHO) obviously does not fulfil this requirement. Nevertheless, it provides—under the same conditions—1,2-dihydroisoquinoline-3-carbaldehyde **5**, by acid-catalyzed intramolecular aldol condensation.

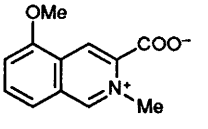
This new isoquinoline synthesis consists of bond formation between C-3 and C-4 of the resulting ring. There are few reports of isoquinoline syntheses involving the formation of this bond in the course of the cyclisation.[3] In contrast to classical (Bischler–Napieralski, Pictet–Spengler, Pomeranz–Fritsch) isoquinoline syntheses, involving ring closure between the benzene ring and a suitable side-chain, this cyclisation is not fundamentally influenced by the aromatic substitution pattern, as demonstrated by the synthesis of derivatives **10** (Scheme 2).



Scheme 2 *Reagents:* i, BuLi; ii, DMF; iii, 20% HCl; iv, $NaBH_4$, MeOH

Lithiation of the tertiary amines **7** and subsequent quenching of aryllithiums **8** with *N*,*N*-dimethylformamide afforded the aldehydes **9** and, after cyclisation with 20% aqueous hydrochloric acid, 1,2-dihydroisoquinoline-3-carbaldehydes **10** with moderate to good yields. Sodium borohydride reduction of compounds **10** in methanol furnished 3-hydroxymethyl-1,2,3,4-tetrahydroisoquinolines **11**.

Compounds **5** and **10** were found to be unstable in air.[4] The oxidation product was identified in one case: small amounts of isoquinolinium carboxylate **12** separated from stored solutions of **10b** exposed to the air.



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Experimental

M.p.s are corrected using a calibration curve which was established with authentic standards. IR spectra were recorded on a Beckmann IR 4230 spectrometer. ^{1}H NMR spectra were obtained on Bruker WH-250 FT (250 MHz) or, if marked by an asterisk, WH-360 FT (360 MHz) spectrometers. ^{13}C NMR spectra were obtained on a Bruker WH-360 FT (90.6 MHz) spectrometer. Chemical shifts refer to the signal of Me_4Si, which served as the internal reference and J values are recorded in Hz. Elementary analyses were performed by the laboratory of I. Betz, D-8640 Kronach.

Synthesis of N-*Arylmethyl*-N-*methyl*-2,2-*diethoxyethylamines*.—N-(3,4-*Methylenedioxybenzyl*)-N-*methyl*-2,2-*diethoxyethylamine* **1**. Compound **1** was prepared by the modification of a reported procedure.[5] 40% Aqueous methylamine (345 cm^3, 308 g, 4 mol) was added to a solution of 3,4-methylenedioxybenzaldehyde (300 g, 2 mol) in methanol (650 cm^3). At 0 °C, sodium borohydride (38 g, 1 mol) was added to the solution, and the mixture was stirred at room temperature for 1 h. The methanol was evaporated and the residue was extracted with dichloromethane (300 + 2 × 200 cm^3); the extract was dried (Na_2SO_4) and evaporated. Bromoacetaldehyde diethylacetal (347 cm^3, 440 g, 2.23 mol) and sodium hydrogen carbonate (458 g, 5.46 mol) was added to the residue and the mixture was stirred and heated at 130 °C for 7 h. (The reaction was monitored by TLC, eluent: methanol.) The resulting thick paste was diluted with ether (1000 cm^3) and the insoluble part was filtered off and washed with ether (2 × 500 cm^3). The ether was evaporated and the residue was distilled to give **1** (377 g, 67%), b.p. 130–135 °C at 0.4 mmHg; $\delta_H(CDCl_3)$* 1.21 (6 H, t, J 7.0), 2.27 (3 H, s), 2.55 (2 H, d, J 5.4), 3.49 (2 H, s), 3.53 (2 H, dq, J 9.3 and 7.0), 3.65 (2 H, dq, J 9.3 and 7.0), 4.64 (1 H, t, J 5.4), 5.92 (2 H, s), 6.74 (2 H, s) and 6.86 (1 H, s).

N-*Benzyl*-N-*methyl*-2,2-*diethoxyethylamine* **7a**.—A mixture of *N*-methylbenzylamine (100 cm^3, 93 g, 0.8 mol), bromoacetaldehyde diethylacetal (155 cm^3, 197 g, 1.0 mol) and sodium hydrogen carbonate (194 g, 2.3 mol) was stirred and heated at 130 °C for 8 h. The title compound **7a** (159 g, 87%) was prepared as described above for the compound **1**, b.p. 90–95 °C at 0.4 mmHg (lit.,[6] 149–150 °C at 19 mmHg); $\delta_H(CDCl_3)$ 1.19 (6 H, t, J 7.0), 2.29 (3 H, s), 2.57 (2 H, d, J 5.4), 3.49 (2 H, dq, J 9.1 and 7.0), 3.57 (2 H, s), 3.62 (2 H, dq, J 9.1 and 7.0), 4.63 (1 H, t, J 5.4) and 7.17–7.40 (5 H, m).

N-(3-*Methoxybenzyl*)-N-*methyl*-2,2-*diethoxyethylamine* **7b**.—In an analogous fashion to that described for compound **1**, 3-methoxybenzaldehyde (61 cm^3, 68 g, 0.5 mol) was converted into the title compound **7b** (101 g, 76%), b.p. 110–115 °C at 0.1 mmHg (Found: C, 67.25; H, 9.27. $C_{15}H_{25}NO_3$ requires C, 67.39, H, 9.42%); n_D^{20} 1.4920; $\delta_H(CDCl_3)$ 1.20 (6 H, t, J 7.0), 2.29 (3 H, s), 2.57 (2 H, d, J 5.3), 3.50 (2 H, dq, J 9.3 and 7.0), 3.54 (2 H, s), 3.63 (2 H, dq, J 9.3 and 7.0), 3.80 (3 H, s), 4.63 (1 H, t, J 5.3), 6.70–6.95 (3 H, m) and 7.20 (1 H, m); m/z 267 (M$^+$, 2%), 222 (9), 164 (93), 121 (100), 103 (17), 91 (14) and 75 (17).

N-(4-*Chlorobenzyl*)-N-*methyl*-2,2-*diethoxyethylamine***7c**.—In an analogous fashion to that described for the compound **1** 4-chlorobenzaldehyde (28 g, 0.2 mol) was converted into the title compound **7c** (45.1 g, 83%), b.p. 120–125 °C at 0.02 mmHg; $\delta_H(CDCl_3)$ 1.20 (6 H, t, J 7.1), 2.28 (3 H, s), 2.56 (2 H, d, J 5.5), 3.51 (2 H, dq, J 9.3 and 7.1), 3.54 (2 H, s), 3.64 (2 H, dq, J 9.3 and 7.1), 4.64 (1 H, t, J 5.5) and 7.27 (4 H, s). *Hydrochloride:* m.p. 139–140 °C (decomp., from ethyl acetate) (Found: C, 54.7; H, 7.7. $C_{14}H_{23}Cl_2NO_2$ requires C, 54.55; H, 7.52%); δ_H(250 MHz, $CDCl_3$) 1.26 (6 H, t, J 7.1 Hz), 2.80 (3 H, s), 2.82–3.05 (1 H, m), 3.10–3.30 (1 H, m), 3.60–3.90 (4 H, m), 4.33 (2 H, m), 5.29 (1 H, t, J 5.1), 7.43 (2 H, d, J 8.4) and 7.68 (2 H, d, J 8.4); m/z 271 (M$^+$, 1%), 226 (20), 170 (12), 168 (34), 127 (31), 125 (100) and 103 (93).

N-(3,4-*Dimethoxybenzyl*)-N-*methyl*-2,2-*diethoxyethylamine* **7d**. In an analogous fashion to that described for compound **1** 3,4-methoxybenzaldehyde (83 g, 0.5 mol) was converted into the title compound **7d** (109 g, 73%), b.p. 140–145 °C at 0.06 mmHg (lit.,[7] 142–146 °C at 0.08 mmHg) (Found: C, 64.75; H, 8.9. $C_{16}H_{27}NO_4$ requires C, 64.62, H, 9.15%); n_D^{20} 1.5011; $\delta_H(CDCl_3)$ 1.20 (6 H, t, J 7.0), 2.30 (3 H, s), 2.54 (2 H, d, J 5.3), 3.51 (2 H, s), 3.52 (2 H, dq, J 9.2 and 7.0), 3.63 (2 H, dq, J 9.2 and 7.0), 3.86 (3 H, s), 3.88 (3 H, s), 4.63 (1 H, t, J 5.3), 6.78 (1 H, d, J 8.2), 6.84 (1 H, dd, J 8.2 and 1.3) and 6.93 (1 H, d, J 1.3); m/z 297 (M$^+$, 1%), 252 (2), 206 (2) 194 (15) and 151 (100).

Formylation of N-*Arylmethyl*-N-*methyl*-2,2-*diethoxyethylamines* **1** *and* **7a–d**.—6-[N-(2,2-Diethoxyethyl)-N-methylaminomethyl]-2,3-methylenedioxybenzaldehyde **3** (R = CHO). At 0 °C, a solution (1.5 mol dm^{-3}; 73.3 cm^3) of butyllithium (110 mmol) in hexane was added rapidly to a solution of compound **1** (28.1 g, 100 mmol) in ether (150 cm^3). After 1 h, *N*,*N*-dimethylformamide (11.6 cm^3, 11.0 g, 150 mmol) was added to the suspension, and the mixture was stirred for 1 h at room temperature. It was then extracted with saturated aqueous ammonium chloride (50 cm^3) and saturated brine (2 × 20 cm^3), dried (Na_2SO_4) and evaporated. Trituration with light petroleum (b.p. 40–60 °C) gave **5** (20.6 g, 66%), m.p. 54–55 °C [from light petroleum (b.p. 40–60 °C)] (Found: C, 62.15; H, 7.7. $C_{16}H_{23}NO_5$ requires C, 62.11, H, 7.49%); ν_{max}(KBr)/cm^{-1} 1673; $\delta_H(CDCl_3)$* 1.17 (6 H, t, J 7.0), 2.23 (3 H, s), 2.57 (2 H, d, J 5.1), 3.49 (2 H, dq, J 9.0 and 7.0), 3.62 (2 H, dq, J 9.0 and 7.0), 3.77 (2 H, s), 4.57 (1 H, t, J 5.1), 6.12 (2 H, s), 6.81 (1 H, d, J 7.8), 6.89 (1 H, d, J 7.8) and 10.42 (1 H, s); m/z 309 (M$^+$, 6%), 264 (6), 206 (58), 163 (100), 135 (7), 103 (11) and 77 (23).

2-[N-(2,2-*Diethoxyethyl*)-N-*methylaminomethyl*]*benzaldehyde* **9a**. A solution (1.5 mol dm^{-3}; 100 cm^3) of butyllithium (150 mmol) in hexane was added to a solution of **7a** (23.7 g, 100 mmol) in ether (100 cm^3) and the mixture was kept for 48 h at 25 °C. *N*,*N*-Dimethylformamide (15.4 cm^3, 14.6 g, 200 mmol) was added at 0 °C. After 30 min at 25 °C, saturated aqueous ammonium chloride (50 cm^3) was added. The organic phase was extracted with saturated brine (2 × 20 cm^3), dried (Na_2SO_4) and evaporated. The residue was distilled at 0.03 mmHg and the fraction boiling at 120–125 °C was collected to give crude **9a** (14.6 g, 55%); ν_{max}(KBr)/cm^{-1} 1690; $\delta_H(CDCl_3)$ 1.19 (6 H, t, J 7.0). 2.25 (3 H, s), 2.60 (2 H, d, J 5.4), 3.48 (2 H, dq, J 9.1 and 7.0), 3.62 (2 H, dq, J 9.1 and 7.0), 3.88 (2 H, s), 4.59 (1 H, t, J 5.4), 6.93–7.56 (3 H, m), 7.85–7.93 (1 H, m) and 10.50 (1 H, s). The purity of the compound was judged to be *ca.* 90% by ^{1}H NMR determinations. It was used for the next reaction without further purification.

2-[N-(2,2-*Diethoxyethyl*)-N-*methylaminomethyl*]-6-*methoxybenzaldehyde* **9b**. Crude oily **9b** (28.1 g, 95%; purity > 95%, as indicated by ^{1}H NMR) was obtained starting from **7b** (26.7 g, 100 mmol) and proceeding as described for **3** (R = CHO); ν_{max}(KBr)/cm^{-1} 1687; $\delta_H(CDCl_3)$ 1.20 (6 H, t, J 7.1), 2.29 (3 H, s), 2.60 (2 H, d, J 5.3), 3.50 (2 H, dq, J 9.5 and 7.1), 3.64 (2 H, dq, J 9.5 and 7.1), 3.87 (2 H, s), 3.88 (3 H, s), 4.62 (1 H, t, J 5.3), 6.87 (1 H, d, J 7.9) 7.23 (1 H, d, J 8.2), 7.43 (1 H, t, J 8.2) and 10.57 (1 H, s).

2-[N-(2,2-*Diethoxyethyl*)-N-*methylaminomethyl*]-5-*chlorobenzaldehyde* **9c**. At 0 °C, a solution (1.5 mol dm^{-3}; 20 cm^3) of butyllithium (30 mmol) in hexane was added to a solution of **7c** (5.44 g, 20 mmol) in ether (60 cm^3). It was kept for 3 h at 0 °C, and *N*,*N*-dimethylformamide (4.62 cm^3, 4.38 g, 60 mmol) was added. After 15 min at room temperature, saturated aqueous

ammonium chloride (20 cm^3) was added, and the organic layer was extracted with saturated brine (2 × 20 cm^3), dried (Na_2SO_4) and evaporated. Oily **9c** (5.8 g, 97%, purity > 95% as shown by ^1H NMR) was obtained; ν_{max}(film)/cm^{-1} 1687; δ_H($CDCl_3$) 1.21 (6 H, t, *J* 7.0), 2.21 (3 H, s), 2.59 (2 H, d, *J* 5.4), 3.49 (2 H, dq, *J* 9.2 and 7.0), 3.63 (2 H, dq, *J* 9.2 and 7.0), 3.86 (2 H, s), 4.60 (1 H, t, *J* 5.4), 7.33 (1 H, d, *J* 8.3), 7.46 (1 H, dd, *J* 8.3 and 2.1), 7.84 (1 H, d, *J* 2.1) and 10.45 (1 H, s).

2-[N-(2,2-*Diethoxyethyl*)-N-*methylaminomethyl*]-5,6-*dimethoxybenzaldehyde* **9d**. Oily **9d** (31.1 g, 97%, purity *ca.* 90% as shown by ^1H NMR) was obtained starting from **7d** (29.7 g, 100 mmol) and proceeding as described for **3** (R = CHO), ν_{max}(film)/cm^{-1} 1690; δ_H($CDCl_3$) 1.20 (6 H, t, *J* 7.0), 2.27 (3 H, s), 2.58 (2 H, d, *J* 5.3), 3.50 (2 H, dq, *J* 9.3 and 7.0), 3.64 (2 H, dq, *J* 9.3 and 7.0), 3.77 (2 H, s), 3.88 (3 H, s), 3.91 (3 H, s), 4.61 (1 H, t, *J* 5.3), 7.02 (1 H, d, *J* 8.5), 7.23 (1 H, d, *J* 8.5) and 10.51 (1 H, s).

Compounds **9a–d** were used for the next reaction without further purification.

1,2-*Dihydroisoquinoline*-3-*carbaldehydes* **5** and **10a–d**: *General Procedure*.—Compounds **3** (R = CHO) and **9a–d** (20 mmol) were dissolved in hydrochloric acid (20%, 40 cm^3) and the solution stored for 16 h at room temperature. The solution was then treated with charcoal and its pH adjusted to 14 with 40% aqueous sodium hydroxide in such a manner that the temperature of the mixture did not rise above 40 °C.

2-*Methyl*-5,6-*methylenedioxy*-1,2-*dihydroisoquinoline*-3-*carbaldehyde* **5**. A yellow crystalline product separated, which was filtered off, washed with water and dried over potassium hydroxide to give the title compound **5** (3.8 g, 88%), m.p. 108–110 °C (decomp.). In some runs further purification was carried out by filtration through silica gel (80 g) with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:4) as the eluent. Evaporation of the solvents at ambient temperature and trituration of the residue with water gave analytically pure **5** (2.90 g, 67%), m.p. 111–112 °C [decomp., from dichloromethane–light petroleum (b.p. 40–60 °C)] (Found: C, 66.3; H, 5.2. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.10%); ν_{max}(KBr)/cm^{-1} 1670; δ_H($CDCl_3$)* 3.12 (3 H, s), 4.17 (2 H, s), 5.98 (2 H, s), 6.26 (1 H, s), 6.48 (1 H, d, *J* 7.8), 6.67 (1 H, d, *J* 7.8) and 9.20 (1 H, s); δ_C($CDCl_3$) 38.5, 55.2, 101.4, 108.3, 114.8, 115.4, 117.8, 123.3, 142.6, 144.6, 146.8 and 188.2; *m*/*z* 217 (M^+, 55%), 216 (100), 188 (3) and 130 (8).

2-*Methyl*-1,2-*dihydroisoquinoline*-3-*carbaldehyde* **10a**. The mixture was extracted with dichloromethane (50 + 2 × 20 cm^3) and the combined extracts were dried, concentrated (without heating!) and filtered through silica gel (80 g) with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:4) as the eluent. The solution was evaporated at ambient temperature. The residue was dissolved in a minimum quantity of ethyl acetate. Addition of light petroleum (b.p. 40–60 °C) gave the yellow crystalline title compound **10a** (1.80 g, 52%), m.p. 66–67 °C (Found: C, 76.0; H, 6.2. $C_{11}H_{11}NO$ requires C, 76.28, H, 6.40%); ν_{max}(KBr)/cm^{-1} 1680; δ_H($CDCl_3$) 3.12 (3 H, s), 4.28 (2 H, s), 6.24 (1 H, s), 6.98–7.30 (4 H, m) and 9.22 (1 H, s); *m*/*z* 173 (M^+, 42%), 172 (100), 149 (38), 143 (17), 128 (18) and 115 (24).

5-*Methoxy*-2-*methyl*-1,2-*dihydroisoquinoline*-3-*carbaldehyde* **10b**. The crystalline precipitate was filtered off, washed with water, dried over potassium hydroxide and dissolved in dichloromethane (5 cm^3). The solution was filtered through silica gel (80 g) with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:4) as the eluent. Evaporation of the solvents at ambient temperature and subsequent trituration of the residue with water (20 cm^3) gave the yellow product **10b** (1.46 g, 36%), m.p. 64–65 °C (Found: C, 71.2, H, 6.4. $C_{12}H_{13}NO_2$ requires C, 70.92, H, 6.45%); ν_{max}(KBr)/cm^{-1} 1665; δ_H(CD_3OD) 3.00 (3 H, s), 3.82 (3 H, s), 4.13 (2 H, s), 6.63 (1 H, s), 6.63 (1 H, d, *J* 7.1), 6.80 (1 H, d, *J* 8.5), 7.20 (1 H, t, *J* 8.3) and 9.13 (1 H, s); *m*/*z* 203 (M^+, 46%), 202 (100), 187 (18) and 173 (6).

6-*Chloro*-2-*methyl*-1,2-*dihydroisoquinoline*-3-*carbaldehyde* **10c**. The mixture was extracted with dichloromethane (50 + 2 × 20 cm^3) and the combined extracts were dried, concentrated (without heating!) and filtered through silica gel (80 g) with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:4) as the eluent. The solvents were evaporated at ambient temperature. The residue was dissolved in a minimum quantity of ethyl acetate. Addition of light petroleum (b.p. 40–60 °C) gave yellow crystalline title compound **10c** (1.91 g, 46%), m.p. 68–69 °C (Found: C, 63.85, H, 4.91. $C_{11}H_{10}ClNO$ requires C, 63.62, H, 4.85%); ν_{max}(KBR)/cm^{-1} 1668; δ_H($CDCl_3$) 3.12 (3 H, s), 4.26 (2 H, s), 6.08 (1 H, s), 6.92 (1 H, d, *J* 8.0), 7.07 (1 H, d, *J* 2.2), 7.17 (1 H, dd, *J* 8.0 and 2.2) and 9.20 (1 H, s); *m*/*z* 209 (M^+, 15%), 208 (39), 207 (41) and 206 (10).

5,6-*Dimethoxy*-2-*methyl*-1,2-*dihydroisoquinoline*-3-*carbaldehyde* **10d**. The crystalline precipitate was filtered off, washed with water, dried over potassium hydroxide and dissolved in dichloromethane (5 cm^3). The solution was filtered through silica gel (80 g) with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:4) as the eluent. Evaporation of the solvents at ambient temperature and subsequent trituration of the residue with water (20 cm^3) gave the product **10d** (1.92 g, 41%), m.p. 69–70 °C (Found: C, 67.05, H, 6.3. $C_{13}H_{15}NO_3$ requires C, 66.94, H, 6.48%); ν_{max}(KBr)/cm^{-1} 1665; δ_H($CDCl_3$) 3.11 (3 H, s), 3.84 (3 H, s), 3.85 (3 H, s), 4.18 (2 H, s), 6.53 (1 H, s), 6.72 (1 H, dd, *J* 8.2 and 0.8), 6.80 (1 H, d, *J* 8.2) and 9.25 (1 H, s); *m*/*z* 233 (M^+, 60%), 232 (100), 217 (19) and 188 (23).

3-*Hydroxymethyl*-1,2,3,4-*tetrahydroisoquinolines* **6** *and* **11a–d**: *General procedure*.—At 0 °C, sodium borohydride (0.38 g, 10 mmol) was added to a solution of the corresponding 1,2-dihydroisoquinoline-3-carbaldehyde derivative (**5** and **10a–d**, respectively; 5 mmol) in methanol (10 cm^3). The mixture was stirred for 30 min and evaporated. The residue was triturated with water (10 cm^3) and crystalline product was filtered off and washed with water (2 × 10 cm^3).

3-*Hydroxymethyl*-2-*methyl*-5,6-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline* **6** (0.99 g, 90%), m.p. 160–161 °C (from methanol) (Found: C, 65.2, H, 6.9. $C_{12}H_{15}NO_3$ requires C, 65.14, H, 6.83%); ν_{max}(KBr)/cm^{-1} 3105br; δ_H($CDCl_3$) 2.39 (3 H, s), 2.53 (1 H, dd, *J* 16.9 and 8.1), 2.70 (1 H, dd, *J* 16.9 and 5.2), 2.93 (1 H, m), 3.47 (1 H, s, br), 3.58 (1 H, dd, *J* 11.0 and 7.5), 3.64 (1 H, d, *J* 16.1), 3.70 (1 H, dd, *J* 11.0 and 4.9), 3.84 (1 H, d, *J* 16.1), 5.93 (2 H, m), 6.53 (1 H, d, *J* 8.0) and 6.67 (1 H, d, *J* 8.0); *m*/*z* 221 (M^+, 6%), 190 (100), 160 (10), 149 (17), 132 (10), 115 (8), 103 (8) and 91 (32).

3-*Hydroxymethyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* **11a**. (0.67 g, 76%), m.p. 103–104 °C (from heptane)[8] (Found: C, 74.85, H, 8.5. $C_{11}H_{15}NO$ requires C, 74.54, H, 8.52%); ν_{max}(KBr)/cm^{-1} 3140; δ_H($CDCl_3$) 2.41 (3 H, s), 2.71–2.90 (3 H, m), 2.94 (1 H, s, br), 3.52 (1 H, dd, *J* 11.1 and 5.3), 3.70 (1 H, d, *J* 16.3), 3.70 (1 H, dd, *J* 11.1 and 4.6), 3.93 (1 H, d, *J* 16.3) and 6.98–7.20 (4 H, m); *m*/*z* (chemical ionisation with ammonia) 178 (M + 1, 100%), 176 (26) and 146 (18).

3-*Hydroxymethyl*-5-*methoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* **11b**. (0.85 g, 82%), m.p. 96–97 °C (from heptane–ethyl acetate) (Found: C, 69.9; H, 8.25. $C_{12}H_{17}NO_2$ requires C, 69.54, H, 8.27%); ν_{max}(KBr)/cm^{-1} 3140br; δ_H($CDCl_3$) 2.39 (3 H, s), 2.50 (1 H, dd, *J* 17.4 and 8.6), 2.70 (1 H, dd, *J* 17.4 and 5.1), 2.88 (1 H, m), 2.95 (1 H, s, br), 3.58 (1 H, dd, *J* 11.2 and 7.1), 3.65–3.75 (2 H, s), 3.80 (3 H, s), 3.86 (1 H, d, *J* 16.2), 6.67 (1 H, d, *J* 7.0), 6.70 (1 H, d, *J* 8.0) and 7.12 (1 H, t, *J* 8.2); *m*/*z* (chemical ionisation with ammonia) 208 (M + 1, 100%) and 176 (17%).

6-*Chloro*-3-*hydroxymethyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* **11c**. (0.76 g, 72%), m.p. 75–76 °C (from ethyl acetate–light petroleum) (Found: C, 62.7, H, 6.7. $C_{11}H_{14}ClNO$ requires C, 62.41, H, 6.67%); ν_{max}(KBr)/cm^{-1} 3160; δ_H($CDCl_3$) 2.40 (3 H, s), 2.65–2.90 (4 H, m), 3.57 (1 H, dd, *J* 11.0 and 6.2), 3.63 (1 H, d,

J 16.2), 3.70 (1 H, dd, *J* 11.0 and 4.5), 3.84 (1 H, d, *J* 16.2), 6.95 (1 H, d, *J* 8.0) and 7.05–7.17 (2 H, m); *m/z* (chemical ionisation with ammonia) 214 (M + 1, 3%), 212 (9), 182 (30) and 180 (100).

3-*Hydroxymethyl*-5,6-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* **11d**. (0.84 g, 71%), m.p. 105–106 °C (from heptane) (Found: C, 65.65; H, 7.96. $C_{13}H_{19}NO_3$ requires C, 65.80, H, 8.07%); ν_{max}(KBr)/cm^{-1} 3140br; δ_H($CDCl_3$) 2.38 (3 H, s), 2.63 (1 H, dd, *J* 18.2 and 9.8), 2.70–2.90 (3 H, m), 3.58 (1 H, dd, *J* 10.8 and 6.2), 3.64 (1 H, d, *J* 15.5) 3.73 (1 H, dd, *J* 10.8 and 4.4), 3.80 (3 H, s), 3.82 (1 H, d, *J* 15.5), 3.85 (3 H, s) and 6.77 (2 H, s); *m/z* (chemical ionisation with ammonia) 238 (M + 1, 100%) and 206 (26%).

Oxidation Product: 5-*Methoxy*-2-*methylisoquinolinium*-3-*carboxylate* **12**.—In some runs small amounts of colourless crystalline compound **12** separated from the solutions of the aldehyde **11b**, m.p. 199–200 °C (from ethanol); δ_H(D_2O) 3.96 (3 H, s), 4.49 (3 H, s), 7.28 (1 H, d, *J* 7.8), 7.58 (1 H, d, *J* 7.8), 7.72 (1 H, t, *J* 7.8), 8.19 (1 H, s) and 9.30 (1 H, s). *Hydrochloride:* m.p. 199–200 °C (decomp., from ethanol) (Found: C, 56.8; H, 4.7. $C_{12}H_{12}ClNO_3$ requires C, 56.82, H, 4.77%); ν_{max}(KBr)/cm^{-1} 1747; δ_H(D_2O) 4.01 (3 H, s), 4.61 (3 H, s), 7.45 (1 H, d, *J* 8.1), 7.78 (1 H, d, *J* 8.1), 7.92 (1 H, t, *J* 8.1), 8.56 (1 H, s) and 9.55 (1 H, s).

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