Synthesis of 1,2-fused indoles by radical cyclisation[1]

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Treatment of the 1-(ω-iodoalkyl)indole-3-carbaldehydes 8–13 with tributyltin hydride and AIBN results in radical cyclisation to give the 1,2-fused indoles 14–19 containing five-, six- and seven-membered rings. The tetrahydropyridoindole 18 is converted into the indolequinone 23.

Free radical cyclisations find increasing application in the synthesis of mono-, bi- and poly-cyclic ring systems.[2–4] Among such reactions the intramolecular addition of radicals to an aromatic ring, followed by oxidation of the newly formed radical back to the aromatic system, constitutes a useful route to benzo-fused rings.[5–8] However the addition of radicals to heteroaromatic rings is less well described, although examples involving pyridines, quinolines, pyrroles, indoles, thiophenes, benzothiophenes, furans, benzofurans, thiazoles and isoxazoles have been reported recently.[9–23]

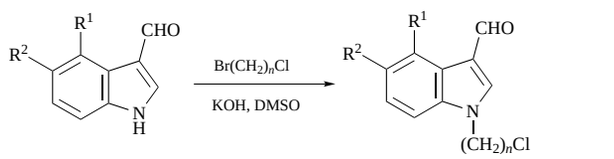
In view of our own work on the synthesis of pyrrolo[1,2-*a*]-indoles,[24–28] and the interest in these ring systems in general,[29–33] we were attracted by recent reports of radical cyclisations onto the indole 2-position. Thus Ziegler and co-workers have shown that alkyl, vinyl, oxiranyl and aziridinyl radicals cyclise onto an indole ring under photochemical or reductive conditions to give mainly 1,2-fused 2,3-dihydroindoles (or their dimers);[34–37] in contrast Caddick and co-workers have demonstrated efficient radical *ipso*-substitution of SPh, SOPh or SO_2Ar groups from the indole 2-position to give 1,2-fused indoles.[38–40] However, more directly relevant to our own work was the reported cyclisation of aryl, vinyl and alkyl radicals to the 2-position of indole-3-carbaldehydes.[12,41] We now report in detail some additional results in this area which extend and complement those referred to above.[1]

Results and discussion

The substrates for the radical cyclisation were the 1-(ω-iodoalkyl)indole-3-carbaldehydes **8**–**13**; these were prepared from commercially available indole-3-carbaldehyde **1** or the 4-benzyloxy-5-methoxy derivative **2**[42] as shown in Scheme 1. Thus alkylation of the indole with the appropriate 1-bromo-ω-chloroalkane using the Heaney–Ley method (KOH in DMSO)[43] gave the corresponding 1-(ω-chloroalkyl)indoles **3**–**7** in good yield (74–97%). Reaction of the chlorides **3**–**7** with sodium iodide in acetonitrile gave the iodides **8**–**12**. The iodopentyl derivative **13** was prepared by direct alkylation of the indole **2** with 1,5-diiodopentane.

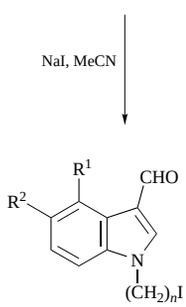
The radical cyclisation reactions were carried out by the slow addition of excess tributyltin hydride and azoisobutyronitrile (AIBN) to the iodoalkyl indoles in boiling toluene, and gave the desired 1,2-fused indoles **14**–**19** in variable yield (Scheme 2). The cyclisation leads to indoles fused with five-, six- and seven-membered rings, although the formation of the seven-membered ring, a relatively rare process in radical cyclisation methodology,[40] proceeds in significantly lower yield. The cyclisation of iodides **8** and **9** to the 1,2-pyrrolo- and 1,2-pyrido-indoles **14** and **15** has been carried out under oxidative conditions by Artis *et al.*,[12] although the yields were slightly lower (60 and 45%, respectively). In order to compare the two methods of cyclisation, we also used the oxidative conditions (H_2O_2, Fe^{II}, DMSO) to study the cyclisation of **12** to **18**, although in this case the yield was only 33%.

The formation of aromatic (*i.e.* oxidised) products in good



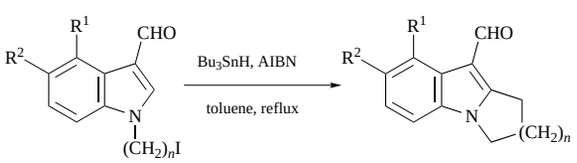
1 $R^1 = R^2 = H$
2 R^1 = OBn, R^2 = OMe

3 $R^1 = R^2 = H$, $n = 3$ (91%)
4 $R^1 = R^2 = H$, $n = 4$ (97%)
5 $R^1 = R^2 = H$, $n = 5$ (86%)
6 R^1 = OBn, R^2 = OMe, $n = 3$ (74%)
7 R^1 = OBn, R^2 = OMe, $n = 4$ (84%)



8 $R^1 = R^2 = H$, $n = 3$ (79%)
9 $R^1 = R^2 = H$, $n = 4$ (73%)
10 $R^1 = R^2 = H$, $n = 5$ (92%)
11 R^1 = OBn, R^2 = OMe, $n = 3$ (85%)
12 R^1 = OBn, R^2 = OMe, $n = 4$ (72%)
13 R^1 = OBn, R^2 = OMe, $n = 5$ (70%)
[from **2** + $I(CH_2)_5I$]

Scheme 1



8-13

14 $R^1 = R^2 = H$, $n = 1$ (64%)
15 $R^1 = R^2 = H$, $n = 2$ (75%)
16 $R^1 = R^2 = H$, $n = 3$ (43%)
17 R^1 = OBn, R^2 = OMe, $n = 1$ (47%)
18 R^1 = OBn, R^2 = OMe, $n = 2$ (73%)
19 R^1 = OBn, R^2 = OMe, $n = 3$ (29%)

Scheme 2

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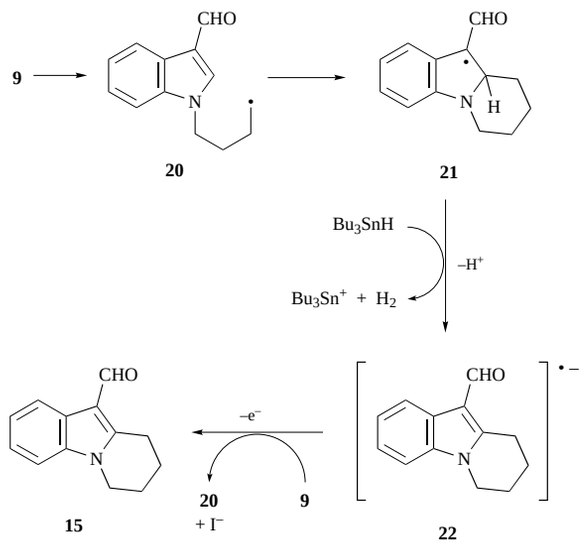
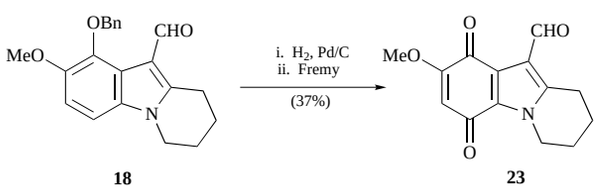
yield under reductive conditions is in direct contrast to Ziegler's results where 1,2-dihydroindoles (or their dimers) were the major products with only trace amounts of the indole themselves. The formation of aromatised (oxidised) products during reductive cyclisations using tributyltin hydride is not uncommon.[6,8] Possible explanations include disproportionation, or oxidation of an intermediate radical by AIBN,[44] although we favour the 'pseudo $S_{RN}1$' mechanism proposed by Bowman *et al.*,[6] and further exemplified by Beckwith and Storey.[45] This mechanism, as illustrated in Scheme 3 for the six-membered



Scheme 3

ring, involves as a key step the reaction of the radical **21**, formed by the addition of the initial radical **20** to the indole ring, with tributyltin hydride to give the indole radical anion **22**, the tributyltin cation and hydrogen. The highly delocalised radical anion **22** presumably subsequently undergoes single electron transfer with the (iodoalkyl)indole **9** to give the product **15** and to regenerate, after loss of iodide, the initial radical **20** to continue the chain process.

The use of these radical cyclisations in the synthesis of intermediates to biologically active indolequinones was illustrated by the conversion of **18** into the indolequinone **23** by hydrogenolytic removal of the benzyl group followed by oxidation with Fremy's salt (Scheme 4).



Scheme 4

Experimental

For general experimental details, see ref. 42. *J* values are given in Hz. Light petroleum refers to the fraction with bp 40–60 °C.

Preparation of 1-(ω-chloroalkyl)indole-3-carbaldehydes

1-(3-Chloropropyl)indole-3-carbaldehyde 3. A mixture of indole-3-carbaldehyde **1** (0.503 g, 3.47 mmol), powdered potassium hydroxide (87%; 0.254 g, 4.52 mmol) and DMSO (8 ml) was sonicated for 10 min, and then cooled to 0 °C. 1-Bromo-3-chloropropane (1.02 ml, 1.626 g, 10.33 mmol) was added at 0 °C, and the mixture was stirred at room temperature. After 4 h, water (50 ml) was added and the mixture was extracted with ethyl acetate (3 × 150 ml). The combined extracts were washed with water (6 × 100 ml), brine (2 × 75 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by column chromatography (50% light petroleum–50% diethyl ether) to give the title compound (0.696 g, 91%) as a colourless solid, mp 46 °C (lit.,[12] 47–48.5 °C); ν_{max}(Nujol)/cm^{-1} 1656, 1533 and 1401; δ_H(400 MHz; $CDCl_3$) 10.00 (1H, s, CHO), 8.31 (1H, m, H-4), 7.75 (1H, s, H-2), 7.42–7.30 (3H, m, ArH), 4.41 (2H, t, *J* 6.4, NCH_2), 3.48 (2H, t, *J* 5.6, CH_2Cl) and 2.33 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 184.5 (CHO), 138.4 (C-2), 137.0, 125.5, 124.2, 123.1, 122.3, 118.5, 109.9, 43.8 (CH_2Cl), 41.3 (NCH_2) and 32.0 (CH_2); *m/z* 221 (M^+, 51%), 158 (100), 144 (12), 130 (29) and 51 (9).

1-(4-Chlorobutyl)indole-3-carbaldehyde 4. Reaction of indole-3-carbaldehyde **1** (0.501 g, 3.45 mmol), powdered potassium hydroxide (0.256 g, 4.56 mmol) and 1-bromo-4-chlorobutane (1.19 ml, 1.771 g, 10.33 mmol) in DMSO (8 ml) as described above gave the title compound (0.785 g, 97%) as a colourless solid, mp 63 °C (lit.,[12] 62–64 °C); ν_{max}(Nujol)/cm^{-1} 1659, 1523, 1378, 1319 and 1171; δ_H(400 MHz; $CDCl_3$) 10.01 (1H, s, CHO), 8.31 (1H, m, H-4), 7.71 (1H, s, H-2), 7.39–7.30 (3H, m, ArH), 4.23 (2H, t, *J* 7.2, NCH_2), 3.55 (2H, t, *J* 6.4, CH_2Cl), 2.09 (2H, m, CH_2) and 1.82 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 184.4 (CHO), 137.8 (C-2), 137.2, 125.5, 124.1, 123.0, 122.3, 118.4, 109.9, 46.6 (CH_2Cl), 44.1 (NCH_2), 29.6 (CH_2) and 27.2 (CH_2); *m/z* 235 (M^+, 44%), 158 (100), 144 (16), 130 (24) and 51 (27).

1-(5-Chloropentyl)indole-3-carbaldehyde 5. Reaction of indole-3-carbaldehyde **1** (0.500 g, 3.44 mmol), powdered potassium hydroxide (0.300 g, 5.34 mmol) and 1-bromo-5-chloropentane (1.36 ml, 1.916 g, 10.33 mmol) in DMSO (8 ml) as described above gave the *title compound* (0.764 g, 86%) as a colourless solid, mp 64 °C (Found: M^+, 249.0920. $C_{14}H_{16}ClNO$ requires *M*, 249.0920); ν_{max}(Nujol)/cm^{-1} 1655, 1525, 1311, 1243 and 1174; δ_H(400 MHz; $CDCl_3$) 10.00 (1H, s, CHO), 8.31 (1H, m, H-4), 7.70 (1H, s, H-2), 7.38–7.29 (3H, m, ArH), 4.18 (2H, t, *J* 7.2, NCH_2), 3.51 (2H, t, *J* 6.8, CH_2Cl), 1.93 (2H, m, CH_2), 1.79 (2H, m, CH_2) and 1.51 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 184.4 (CHO), 138.0 (C-2), 137.2, 125.5, 124.0, 122.9, 122.2, 118.2, 110.0, 47.9 (CH_2Cl), 44.5 (NCH_2), 32.0 (CH_2), 29.1 (CH_2) and 24.2 (CH_2); *m/z* 249 (M^+, 39%), 186 (7), 158 (100), 144 (14), 130 (34), 77 (16) and 51 (9).

4-Benzyloxy-1-(3-chloropropyl)-5-methoxyindole-3-carbaldehyde 6. Reaction of 4-benzyloxy-5-methoxyindole-3-carbaldehyde **2**[42] (0.122 g, 0.43 mmol), powdered potassium hydroxide (0.033 g, 0.59 mmol) and 1-bromo-3-chloropropane (0.16 ml, 0.252 g, 1.60 mmol) in DMSO (3 ml) as described above gave the *title compound* (0.115 g, 74%) as a yellow oil (Found: M^+, 357.1132. $C_{20}H_{20}ClNO_3$ requires *M*, 357.1132); ν_{max}(film)/cm^{-1} 1651, 1517, 1497, 1260, 1175 and 1122; δ_H(400 MHz; $CDCl_3$) 10.35 (1H, s, CHO), 7.86 (1H, s, H-2), 7.49 (2H, m, ArH), 7.40–7.33 (3H, m, ArH), 7.15 (1H, d, *J* 8.4, H-6 or H-7), 7.06 (1H, d, *J* 8.4, H-6 or H-7), 5.26 (2H, s, OCH_2Ph), 4.35 (2H, t, *J* 6.8, NCH_2), 3.98 (3H, s, OMe), 3.50 (2H, t, *J* 6.0, CH_2Cl) and 2.32 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 188.8 (CHO), 149.8, 143.7, 139.3, 135.3, 135.0 (C-2), 130.4, 130.1, 130.0, 123.9, 119.6, 114.0 (C-6 or C-7), 107.7 (C-6 or C-7), 77.0 (OCH_2Ph), 59.7 (OMe), 45.9 (CH_2Cl), 43.2 (NCH_2) and 34.0 (CH_2); *m/z* 357 (M^+, 6%), 329 (6), 266 (38), 251 (12), 91 (100), 77 (12) and 65 (29).

4-Benzyloxy-1-(4-chlorobutyl)-5-methoxyindole-3-carbaldehyde 7. Reaction of 4-benzyloxy-5-methoxyindole-3-carbaldehyde **2** (0.357 g, 1.27 mmol), powdered potassium hydroxide (0.089 g, 1.59 mmol) and 1-bromo-4-chlorobutane (0.44 ml, 0.653 g, 4.81 mmol) in DMSO (7 ml) as described above gave the *title compound* (0.395 g, 84%) as a colourless solid, mp 82 °C (Found: C, 67.5; H, 6.0; N, 4.0. $C_{21}H_{22}ClNO_3$ requires C, 67.8; H, 6.0; N, 3.8%); ν_{max}(Nujol)/cm^{-1} 1709, 1645, 1517, 1496, 1255 and 1120; δ_H(400 MHz; $CDCl_3$) 10.33 (1H, s, CHO), 7.82 (1H, s, H-2), 7.49–7.46 (2H, m, ArH), 7.37–7.32 (3H, m, ArH), 7.06 (2H, 2 × d, *J* 8.81, H-6 and H-7), 5.24 (2H, s, OCH_2Ph), 4.15

(2H, t, *J* 6.8, NCH_2), 3.96 (3H, s, OMe), 3.54 (2H, t, *J* 6.0, CH_2Cl), 2.06 (2H, m, CH_2) and 1.80 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 186.9 (CHO), 147.8, 141.8, 137.5, 133.5, 132.8 (C-2), 128.5, 128.3, 128.1, 122.1, 117.5, 112.0 (C-6 or C-7), 105.9 (C-6 or C-7), 75.1 (OCH_2Ph), 57.9 (OMe), 46.7 (CH_2Cl), 44.1 (NCH_2), 29.6 (CH_2) and 27.0 (CH_2); *m/z* 371 (M^+, 45%), 373 (17), 280 (100), 245 (17), 190 (11) and 91 (70).

Preparation of 1-(ω-iodoalkyl)indole-3-carbaldehydes

1-(3-Iodopropyl)indole-3-carbaldehyde 8. A solution of 1-(3-chloropropyl)indole-3-carbaldehyde **3** (0.621 g, 2.80 mmol) in acetonitrile (12 ml) containing sodium iodide (0.1673 g, 11.16 mmol) was heated at reflux for 12 h. The solution was poured into water (50 ml) and extracted with dichloromethane (3 × 150 ml). The extract was washed with water (3 × 100 ml), saturated aqueous sodium sulfite (50 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by column chromatography (diethyl ether) to give the title compound (0.694 g, 79%) as a colourless oil (lit.,[12] oil) ν_{max}(film)/cm^{-1} 1647, 1530, 1261, 1217, 1166 and 1038; δ_H(400 MHz; $CDCl_3$) 10.05 (1H, s, CHO), 8.35 (1H, m, H-4), 7.81 (1H, s, H-2), 7.46–7.34 (3H, m, ArH), 4.38 (2H, t, *J* 6.4, NCH_2), 3.13 (2H, t, *J* 6.4, CH_2I) and 2.39 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 184.5 (CHO), 138.1 (C-2), 137.0, 125.6, 124.2, 123.1, 122.4, 118.5, 109.9, 47.0 (NCH_2), 32.6 (CH_2) and 1.9 (CH_2I); *m/z* 313 (M^+, 56%), 217 (9), 186 (10), 158 (100), 130 (26), 77 (15) and 51 (43).

1-(4-Iodobutyl)indole-3-carbaldehyde 9. Reaction of 1-(4-chlorobutyl)indole-3-carbaldehyde **4** (0.499 g, 2.12 mmol) in acetonitrile (12 ml) containing sodium iodide (1.306 g, 8.71 mmol) as described above gave the title compound (0.504 g, 73%) as a colourless solid, mp 57 °C (lit.,[12] 58–59 °C); ν_{max}(Nujol)/cm^+ 1645, 1533, 1468, 1401, 1135 and 752; δ_H(400 MHz; $CDCl_3$) 10.04 (1H, s, CHO), 8.34 (1H, m, H-4), 7.73 (1H, s, H-2), 7.42–7.34 (3H, m, ArH), 4.42 (2H, t, *J* 7.2, NCH_2), 3.20 (2H, t, *J* 7.2, CH_2I), 2.07 (2H, m, CH_2) and 1.88 (2H, m, CH_2); δ_H(100.6 MHz; $CDCl_3$) 186.7 (CHO), 140.0 (C-2), 139.4, 127.8, 126.4, 125.3, 124.5, 120.6, 112.2, 48.4 (NCH_2), 32.9 (CH_2), 32.6 (CH_2) and 7.2 (CH_2I); *m/z* 327 (M^+, 68%), 170 (26), 158 (91), 130 (100), 116 (45), 77 (46) and 55 (62).

1-(5-Iodopentyl)indole-3-carbaldehyde 10. Reaction of 1-(5-chloropentyl)indole-3-carbaldehyde **5** (0.545 g, 2.18 mmol) in acetonitrile (12 ml) containing sodium iodide (1.336 g, 8.91 mmol) as described above gave the *title compound* (0.683 g, 92%) as a colourless solid, mp 72–74 °C (Found: M^+, 341.0277. $C_{14}H_{16}INO$ requires *M*, 341.0277); ν_{max}(Nujol)/cm^{-1} 1646, 1531, 1260, 1234, 1169, 1137 and 1015; δ_H(400 MHz; $CDCl_3$) 10.04 (1H, s, CHO), 8.34 (1H, m, H-4), 7.74 (1H, s, H-2), 7.40–7.32 (3H, m, ArH), 4.22 (2H, t, *J* 6.8, NCH_2), 3.18 (2H, t, *J* 6.8, CH_2I), 1.97–1.84 (4H, m, 2 × CH_2) and 1.51 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 184.8 (CHO), 138.3 (C-2), 137.5, 125.9, 124.4, 123.3, 122.6, 118.6, 110.3, 47.4 (NCH_2), 33.1 (CH_2), 29.1 (CH_2), 28.1 (CH_2) and 6.3 (CH_2I); *m/z* 341 (M^+, 54%), 186 (19), 158 (100), 130 (47), 77 (16) and 51 (6).

4-Benzyloxy-1-(3-iodopropyl)-5-methoxyindole-3-carbaldehyde 11. Reaction of 4-benzyloxy-1-(3-chloropropyl)-5-methoxyindole-3-carbaldehyde **6** (0.092 g, 0.26 mmol) in acetonitrile (8 ml) containing sodium iodide (0.218 g, 1.45 mmol) as described above gave the *title compound* (0.098 g, 85%) as a yellow oil, (Found: M^+, 449.0488. $C_{20}H_{20}INO_3$ requires *M*, 449.0488); ν_{max}(film)/cm^{-1} 1652, 1515, 1497, 1260, 1123 and 1060; δ_H(400 MHz; $CDCl_3$) 10.25 (1H, s, CHO), 7.77 (1H, s, H-2), 7.39 (2H, m, ArH), 7.28–7.23 (3H, m, ArH), 7.05 (1H, d, *J* 8.8, H-6 or H-7), 6.96 (1H, d, *J* 8.8, H-6 or H-7), 5.15 (2H, s, OCH_2Ph), 4.17 (2H, t, *J* 6.4, NCH_2), 3.87 (3H, s, OMe), 3.00 (2H, t, *J* 6.4, CH_2I) and 2.25 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 186.9 (CHO), 147.8, 141.8, 137.4, 133.4, 132.9 (C-2), 128.4, 128.3, 128.1, 122.0, 117.7, 112.1 (C-6 or C-7), 105.6 (C-6 or C-7), 75.0 (OCH_2Ph), 57.8 (OMe), 47.2 (NCH_2), 32.8 (CH_2) and 1.6 (CH_2I); *m/z* 449 (M^+, 11%), 421 (8), 358 (34), 91 (100) and 51 (15).

4-Benzyloxy-1-(4-iodobutyl)-5-methoxyindole-3-carbaldehyde 12. Reaction of 4-benzyloxy-1-(4-chlorobutyl)-5-methoxyindole-3-carbaldehyde **7** (0.359 g, 0.97 mmol) in acetonitrile (12 ml) containing sodium iodide (0.599 g, 4.00 mmol) as described above gave the *title compound* (0.322 g, 72%) as a colourless solid, mp 96 °C (Found: M^+, 463.0650. $C_{21}H_{22}INO_3$ requires *M*, 463.0646); ν_{max}(Nujol)/cm^{-1} 1651, 1511, 1494, 1254, 1120 and 1052; δ_H(400 MHz; $CDCl_3$) 10.32 (1H, s, CHO), 7.79 (1H, s, H-2), 7.46 (2H, m, ArH), 7.37–7.30 (3H, m, ArH), 7.05 (2H, 2 × d, *J* 9.6, 6-H and 7-H), 5.23 (2H, s, OCH_2Ph), 4.12 (2H, t, *J* 7.2, NCH_2), 3.95 (3H, s, OMe), 3.16 (2H, t, *J* 6.8, CH_2I), 2.00 (2H, m, CH_2) and 1.82 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 186.9 (CHO), 147.8, 141.8, 137.4, 133.5, 132.7 (C-2), 128.5 (2 carbons), 128.1, 122.0, 117.5, 112.0 (C-6 or C-7), 105.9 (C-6 or C-7), 75.1 (OCH_2Ph), 57.9 (OMe), 46.4 (NCH_2), 30.5 (CH_2), 30.3 (CH_2) and 5.0 (CH_2I); *m/z* 463 (M^+, 15%), 435 (13), 372 (57), 244 (22), 202 (15), 174 (17), 155 (13), 113 (10), 91 (100), 65 (21) and 55 (31).

4-Benzyloxy-1-(5-iodopentyl)-5-methoxyindole-3-carbaldehyde 13. A mixture of 4-benzyloxy-5-methoxyindole-3-carbaldehyde **2** (0.104 g, 0.37 mmol), powdered 87% potassium hydroxide (0.046 g, 0.83 mmol) and DMSO (4 ml) was sonicated for 10 min, and then cooled to 0 °C. 1,5-Diiodopentane (0.16 ml 0.346 g, 1.07 mmol) was added at 0 °C, and the mixture was stirred at room temperature. After 4 h, water (15 ml) was added and the mixture was extracted with ethyl acetate (3 × 75 ml). The combined extracts were washed with water (6 × 50 ml), brine (2 × 25 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by column chromatography (50% light petroleum–50% diethyl ether) to give the *title compound* (0.124 g, 70%) as a yellow oil (Found: M^+, 477.0801. $C_{22}H_{24}INO_3$ requires *M*, 477.0803); ν_{max}(film)/cm^{-1} 1651, 1516, 1461, 1389, 1259, 1172, 1060 and 760; δ_H(400 MHz; $CDCl_3$) 10.33 (1H, s, CHO), 7.83 (1H, s, H-2), 7.49 (2H, m, ArH), 7.40–7.33 (3H, m, ArH), 7.07 (2H, 2 × d, *J* 8.8, H-6 and H-7), 5.25 (2H, s, OCH_2Ph), 4.13 (2H, t, *J* 7.2, NCH_2), 3.97 (3H, s, OMe), 3.16 (2H, t, *J* 7.2, CH_2I), 1.89 (4H, m, 2 × CH_2) and 1.47 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 187.1 (CHO), 148.0, 142.0, 137.7, 133.8 (C-2), 133.1, 128.7 (2 carbons), 128.4, 122.3, 117.6, 112.2 (C-6 or C-7), 106.2 (C-6 or C-7), 75.3 (OCH_2Ph), 58.1 (OMe), 47.43 (NCH_2), 33.0 (CH_2), 28.8 (CH_2), 28.6 (CH_2) and 6.0 (CH_2I); *m/z* 477 (M^+, 12%), 449 (13), 386 (71), 258 (17), 216 (28), 155 (29), 91 (100) and 51 (53).

Cyclisation reactions

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carbaldehyde 14. A solution of tri-*n*-butyltin hydride (0.29 ml, 0.314 g, 1.08 mmol) and AIBN (0.089 g, 0.54 mmol) in toluene (7 ml) was added to 1-(3-iodopropyl)indole-3-carbaldehyde **8** (0.169 g, 0.54 mmol) in toluene (5 ml) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-*n*-butyltin hydride (0.10 ml) and AIBN (0.030 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Water (0.25 ml), ethyl acetate (3 ml) and potassium fluoride (0.150 g) were added and the mixture stirred at room temperature. After 12 h, further water, ethyl acetate and potassium fluoride were added and the mixture stirred for 2 h. Potassium carbonate was added, the mixture filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography (diethyl ether) to give the title compound (0.064 g, 64%) as a colourless solid mp 136 °C (lit.,[12] 146–147 °C); ν_{max}(Nujol)/cm^{-1} 1642, 1538, 1303, 1245, 1121, 1041 and 747; δ_H(400 MHz; $CDCl_3$) 10.00 (1H, s, CHO), 8.19 (1H, m, H-4), 7.29–7.22 (3H, m, ArH), 4.12 (2H, t, *J* 6.8, NCH_2), 3.28 (2H, t, *J* 7.2, 1-CH_2) and 2.71 (2H, m, 2-CH_2); δ_C(100.6 MHz; $CDCl_3$) 183.4 (CHO), 155.4, 133.2, 130.0, 122.8, 122.7, 121.4, 110.3, 110.0, 44.5 (C-3), 26.8 (C-1)

and 24.5 (C-2); *m/z* 185 (M^+, 85%), 156 (29), 128(18), 77 (12) and 51 (11).

6,7,8,9-Tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde 15. A solution of tri-*n*-butyltin hydride (0.10 ml, 0.107 g, 0.37 mmol) and AIBN (0.030 g, 0.18 mmol) in toluene (7 ml) was added to 1-(4-iodobutyl)indole-3-carbaldehyde **9** (0.060 g, 0.18 mmol) in toluene (5 ml) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-*n*-butyltin hydride (0.03 ml) and AIBN (0.01 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Work-up as above gave the title compound (0.027 g, 75%) as a colourless solid, mp 124 °C (lit.,[12] 121–125 °C); ν_{max}(Nujol)/cm^{-1} 1640, 1519, 1313, 1249, 1169, 1061 and 748; δ_H(400 MHz; $CDCl_3$) 10.16 (1H, s, CHO), 8.20 (1H, m, ArH), 7.31–7.23 (3H, m, ArH), 4.10 (2H, t, *J* 6.0, 6-CH_2), 3.31 (2H, t, *J* 6.4, 9-CH_2), 2.15 (2H, m, 7-CH_2) and 1.98 (2H, m, 8-CH_2); δ_C(100.6 MHz; $CDCl_3$) 183.5 (CHO), 148.0, 136.5, 126.0, 123.1, 122.7, 120.6 (C-1), 112.9, 109.1, 42.4 (C-6), 22.8 (C-9), 22.5 (C-7) and 19.7 (C-8); *m/z* 199 (M^+, 100%), 170 (46), 155 (27), 113 (21) and 51 (51).

7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]indole-11-carbaldehyde 16. A solution of tri-*n*-butyltin hydride (0.36 ml, 0.388 g, 1.33 mmol) and AIBN (0.110 g, 0.67 mmol) in toluene (7 ml) was added to 1-(5-iodopentyl)indole-3-carbaldehyde **10** (0.228 g, 0.67 mmol) in toluene (5 ml) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-*n*-butyltin hydride (0.10 ml) and AIBN (0.03 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Work-up as above gave the *title compound* (0.061 g, 43%) as a colourless solid, mp 114 °C (Found: M^+, 213.1154. $C_{14}H_{15}NO$ requires *M*, 213.1154); ν_{max}(Nujol)/cm^{-1} 1645, 1576, 1533, 1376, 1203, 1047 and 743; δ_H(400 MHz; $CDCl_3$) 10.08 (1H, s, CHO), 8.24 (1H, m, ArH), 7.28–7.16 (3H, m, ArH), 4.12 (2H, t, *J* 4.8, 6-CH_2), 3.16 (2H, t, *J* 5.2, 10-CH_2), 1.84 (2H, m, 8-CH_2) and 1.73 (4H, m, 7 and 9-CH_2); δ_C(100.6 MHz; $CDCl_3$) 184.4 (CHO), 154.0, 136.7, 126.0, 123.4, 122.9, 121.6 (C-1), 113.7, 109.4, 45.2 (C-6), 31.1 (C-10), 28.5 (C-7 or C-9), 26.9 (C-7 or C-9) and 25.4 (C-8); *m/z* 213 (M^+, 100%), 184 (59), 156 (21), 77 (11) and 51 (10).

8-Benzyloxy-7-methoxy-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indole-9-carbaldehyde 17. A solution of tri-*n*-butyltin hydride (0.10 ml, 0.109 g, 0.38 mmol) and AIBN (0.038 g, 0.23 mmol) in toluene (2 ml) was added to 4-benzyloxy-1-(3-iodopropyl)-5-methoxyindole-3-carbaldehyde **11** (0.0841 g, 0.19 mmol) in toluene (1.65 ml) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-*n*-butyltin hydride (0.03 ml) and AIBN (0.013 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Work-up as above gave the *title compound* (0.028 g, 47%), mp 100–102 °C (Found: M^+, 321.1370. $C_{20}H_{19}NO_3$ requires *M*, 321.1365); ν_{max}($CHCl_3$)/cm^{-1} 1645, 1490, 1388, 1256, 1099 and 700; δ_H(400 MHz; $CDCl_3$) 10.32 (1H, s, CHO), 7.47 (2H, m, ArH), 7.38–7.30 (3H, m, ArH), 6.95 (2H, 2 × d, *J* 8.4, 5-H and 6-H), 5.20 (2H, s, OCH_2Ph), 4.07 (2H, t, *J* 7.2, NCH_2), 3.93 (3H, s, OMe), 3.31 (2H, t, *J* 7.2, 1-CH_2) and 2.66 (2H, m, 2-CH_2); δ_C(100.6 MHz; $CDCl_3$) 186.8 (CHO), 153.2, 148.0, 142.5, 137.6, 129.6 (2 carbons), 128.5, 128.1, 125.9, 111.0 (C-5 or C-6), 110.0, 105.9 (C-5 or C-6), 74.9 (OCH_2Ph), 57.8 (OMe), 44.6 (C-3), 26.7 (C-2) and 26.6 (C-1); *m/z* 321 (M^+, 18%), 230 (100) and 91 (20).

1-Benzyloxy-2-methoxy-6,7,8,9-tetrahydropyrido[1,2-*a*]-indole-10-carbaldehyde 18. (*a*) To an ultrasonically irradiated solution of iron(II) sulfate heptahydrate (0.041 g, 0.15 mmol) and 4-benzyloxy-1-(4-iodobutyl)-5-methoxyindole-3-carbaldehyde **12** (0.054 g, 0.12 mmol) in DMSO (4 ml) was added hydrogen peroxide (30%; 0.13 ml, 0.040 g, 1.16 mmol) ensuring that the reaction temperature did not exceed 40 °C. When the peroxide addition was completed, the reaction mixture was poured into water (15 ml) and extracted with dichloromethane (3 × 75 ml). The extract was washed with water (3 × 50 ml), 10% aqueous sodium sulfite (5 × 25 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a brown solid which was purified by column chromatography (diethyl ether) to give the *title compound* (0.013 g, 33%) as a colourless oil (Found: M^+, 335.1524. $C_{21}H_{21}NO_3$ requires *M*, 335.1521); ν_{max}(film)/cm^{-1} 1642, 1491, 1392, 1287, 1093 and 735; δ_H(400 MHz; $CDCl_3$) 10.49 (1H, s, CHO), 7.51–7.48 (2H, m, ArH), 7.39–7.32 (3H, m, ArH), 6.98 (2H, 2 × d, *J* 8.8, 3-H and 4-H), 5.19 (2H, s, OCH_2Ph), 4.04 (2H, t, *J* 6.0, 6-CH_2), 3.94 (3H, s, OMe), 3.35 (2H, t, *J* 6.4, 9-CH_2), 2.09 (2H, m, CH_2) and 1.94 (2H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 187.6 (CHO), 148.2, 146.4, 141.3, 137.6, 133.0, 128.5 (2 carbons), 128.0, 121.9, 112.8, 110.3 (C-3 or C-4), 105.2 (C-3 or C-4), 74.8 (OCH_2Ph), 58.0 (OMe), 42.6 (C-6), 25.3 (C-9), 22.3 (C-7) and 19.5 (C-8); *m/z* 335 (M^+, 14%), 267 (13), 244 (100), 186 (15), 155 (29), 91 (43) and 51 (50).

(*b*) A solution of tri-*n*-butyltin hydride (0.50 ml, 0.550 g, 1.19 mmol) and AIBN (0.157 g, 0.96 mmol) in toluene (16 ml) was added to 4-benzyloxy-1-(4-iodobutyl)-5-methoxyindole-3-carbaldehyde **12** (0.438 g, 0.95 mmol) in toluene (12 ml) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-*n*-butyltin hydride (0.20 ml) and AIBN (0.053 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Work-up as before gave the *title compound* (0.231 g, 73%) as a colourless oil; spectroscopic data identical to the sample prepared by the above route.

1-Benzyloxy-2-methoxy-7,8,9,10-tetrahydro-6*H*-azepino-[1,2-*a*]indole-11-carbaldehyde 19. A solution of tri-*n*-butyltin hydride (0.07 ml, 0.081 g, 0.28 mmol) and AIBN (0.029 g, 0.18 mmol) in toluene (2 ml) was added to 4-benzyloxy-1-(5-iodopentyl)-5-methoxyindole-3-carbaldehyde **13** (0.067 g, 0.14 mmol) in toluene (1.65 ml) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-*n*-butyltin hydride (0.02 ml) and AIBN (0.010 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Work-up as before gave the *title compound* (0.014 g, 29%) as a colourless solid, mp 116 °C (Found: M^+, 349.1678. $C_{22}H_{23}NO_3$ requires *M*, 349.1678); ν_{max}(Nujol)/cm^{-1} 1650, 1493, 1393, 1258, 1104 and 774; δ_H(400 MHz; $CDCl_3$) 9.69 (1H, s, CHO), 7.41 (2H, m, ArH), 7.31–7.23 (3H, m, ArH), 6.92 (2H, 2 × d, *J* 8.8, 3-H and 4-H), 5.10 (2H, s, OCH_2Ph), 4.08 (2H, t, *J* 4.8, 6-CH_2), 3.86 (3H, s, OMe), 3.46 (2H, t, *J* 4.8, 10-CH_2), 1.81 (2H, m, 8-CH_2) and 1.71 (4H, m, 7-CH_2 and 9-CH_2); δ_C(100.6 MHz; $CDCl_3$) 189.0 (CHO), 151.4, 148.0, 141.8, 137.9, 133.3, 128.8, 128.7, 128.3, 122.3, 113.1, 111.1 (C-3 or C-4), 105.3 (C-3 or C-4), 75.2 (OCH_2Ph), 58.2 (OMe), 45.3 (C-6), 31.2 (C-10), 30.2 (C-7 or C-9), 27.1 (C-7 or C-9) and 26.3 (C-8); *m/z* 349 (M^+, 25%), 321 (14), 258 (100), 243 (47), 159 (16), 130 (14), 91 (77) and 65 (18).

10-Formyl-2-methoxy-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-1,4-dione 23. To a solution of 1-benzyloxy-8-methoxy-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde **18** (0.018 g, 0.054 mmol) in ethanol (50 ml) was added 10% palladium on carbon (0.04 g). The mixture was stirred under an atmosphere of hydrogen (60 psi) for 12 h. After this time, the mixture was filtered and the spent catalyst washed with dichloromethane. The combined filtrate and washings were washed with water (3 × 25 ml), brine (20 ml) and dried (Na_2SO_4). The organic layer was evaporated to give a brown solid. Purification of the residue by column chromatography (diethyl ether) gave *hydroxy*-2-*methoxy*-6,7,8,9-*tetrahydropyrido*[1,2-a]*indole*-10-*carbaldehyde* (0.009 g, 69%) as a colourless solid, mp 110 °C (Found: M^+, 245.1044. $C_{14}H_{15}NO_3$ requires *M*, 245.1052); ν_{max}($CHCl_3$)/cm^{-1} 1597, 1579, 1506, 1434, 1314, 1254 and 1079; δ_H(250 MHz; $CDCl_3$) 11.11 (1H, s, OH), 9.61 (1H, s, CHO), 6.94 (1H, d, *J* 8.5, H-3 or H-4), 6.65 (1H, d, *J* 8.5, H-3 or H-4), 4.00 (2H,

t, *J* 6.0, 6-CH_2), 3.92 (3H, s, OMe), 3.23 (2H, t, *J* 6.25, 9-CH_2), 2.13 (2H, m, 7-CH_2 or 8-CH_2) and 1.99 (2H, m, 7-CH_2 or 8-CH_2); δ_C(100.6 MHz; $CDCl_3$) 182.9 (CHO), 150.3, 143.3, 141.4, 133.8, 115.7, 114.2, 112.5 (C-3 or C-4), 107.5 (C-3 or C-4), 57.8 (OMe), 42.6 (C-6), 29.7 (C-9), 22.3 (C-7) and 19.3 (C-8); *m/z* 245 (M^+, 10%), 149 (29), 71 (62), 57 (100) and 43 (51).

Potassium nitrosodisulfonate (0.022 g), was added to a solution of the above phenol (0.009 g, 0.037 mmol) in acetone (5 ml), aqueous sodium dihydrogen phosphate (0.167 M, 2 ml) and water (2 ml) and the resulting suspension stirred at room temperature for 12 h. The mixture was extracted with dichloromethane (3 × 10 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by column chromatography (ethyl acetate) gave the *title compound* (0.005 g, 53%) as orange needles, mp 232–233 °C (Found: M^+, 259.0845. $C_{14}H_{13}NO_4$ requires *M*, 259.0845); ν_{max}($CHCl_3$)/cm^{-1} 1638, 1591, 1228, 1147, and 1055; δ_H(400 MHz; $CDCl_3$) 10.17 (1H, s, CHO), 5.62 (1H, s, 3-H), 4.32 (2H, t, *J* 6.4, 6-CH_2), 3.77 (3H, s, OMe), 3.11 (2H, t, *J* 6.4, 9-CH_2), 1.95 (2H, m, 7-CH_2 or 8-CH_2) and 1.82 (2H, m, 7-CH_2 or 8-CH_2); δ_C(100.6 MHz; $CDCl_3$) 189.3 (CHO), 180.3 (C-1 or C-4), 179.3 (C-1 or C-4), 161.3, 144.7, 120.5, 108.1 (C-3), 58.1 (OMe), 47.8 (C-6), 26.0 (C-9), 23.7 (C-7) and 20.2 (C-8); 2 quaternary carbons not observed; *m/z* 259 (M^+, 100), 203 (47), 91 (18), 77 (19), 69 (27) and 41 (15).

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