Isoindolo[2,1-*a*]indol-6-one—a new pyrolytic synthesis and some unexpected chemical properties

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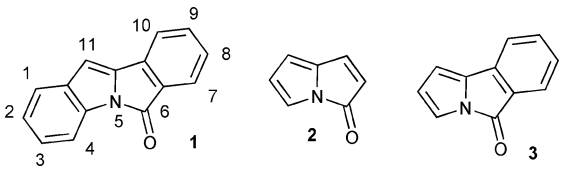
Isoindolo[2,1-*a*]indol-6-one **1** is formed by a sigmatropic shift–elimination–cyclisation cascade by flash vacuum pyrolysis (FVP) of methyl 2-(indol-1-yl)benzoate **7** at 950 °C. The dihydro compound **16** is easily obtained by catalytic reduction of **1**, but the reaction is very sensitive to steric effects at the 11-position. Attempted ring-opening of **1** in basic methanol provides an equilibrium of isoindolo[2,1-*a*]indol-6-one **1** and the ester **19**. Lithium aluminium hydride reduction of **1** provides the alcohol **22** which can be dehydrated to a mixture of **23** and **24** by FVP at 800–950 °C.

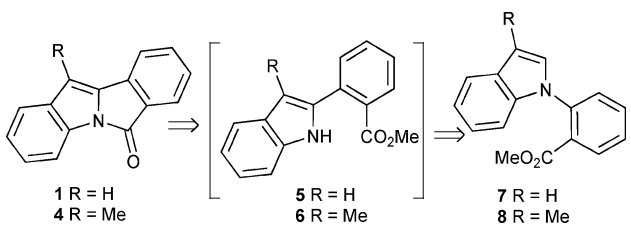
Introduction

We report a new synthetic route to isoindolo[2,1-*a*]indol-6-one derivatives **1**, from 1-arylindoles, based upon application of the sigmatropic shift–elimination–cyclisation pyrolytic cascade which we reported in 1999.[1] Derivatives of this heterocyclic system have attracted recent interest in the field of medicinal chemistry, for example as high affinity ligands for the melatonin MT3 binding site,[2] as potential anti-tumour agents,[3,4] as synthetic intermediates *en route* to bacterial NorA pump inhibitors,[5] or as conformationally-restricted model compounds for structure–activity investigation.[6]



The isoindolo[2,1-*a*]indol-6-one system **1** is a dibenzo analogue of pyrrolizin-3-one **2**[7] and we also show how the chemical properties of **1** compare and contrast with those of **2** and with the pyrroloisoindolone (benzopyrrolizinone) **3**.[1]

Our approach to **1** is summarised by the retrosynthetic analysis shown in Scheme 1. By analogy with our previous work,[1] the isoindoloindolone system **1** should be formed by thermal elimination of methanol from the 2-arylindole **5** which in turn can be generated *in situ* from the 1-arylindole **7** by thermal 1,5-sigmatropic shift.



Scheme 1

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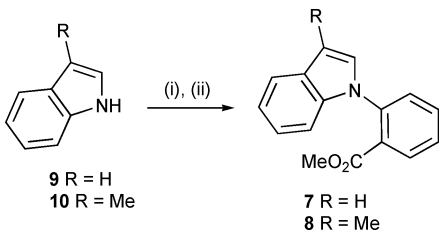
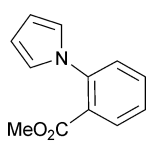
Results and discussion

The known 1-arylindole derivative **7** was made by an Ullmann-type coupling of indole **9** with 2-iodobenzoic acid, using a modification of the literature procedure.[8] The 1-arylindole carboxylic acid was then esterified to give **7** (35%, unoptimised) directly, without isolation (Scheme 2). The method was trivially extended to the 3-methyl derivative **8** (72%) using 3-methylindole as the starting material.

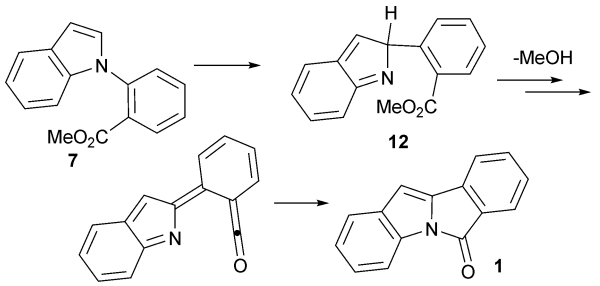


Scheme 2 *Reagents and conditions*: (i) 2-iodobenzoic acid, K_2CO_3, Cu, DMF, reflux, 48 h; (ii) MeI, K_2CO_3, DMF, 20 °C, 48 h.

FVP of **7** successfully provided **1** in reasonable yield, though the pyrolysis conditions are more vigorous than those required for the formation of **3**. Thus, the pyrrole derivative **11** is transformed exclusively to the pyrroloisoindolone **3** at 925 °C in our apparatus. However, only 84% conversion of **7** was obtained at 950 °C, even in the presence of silica tubes at the trap end of the furnace which have the effect of increasing the contact time in the hot zone of the tube.[9] Clearly the involvement of quinonoid intermediates (*e.g.* **12**, Scheme 3) in this process leads to the increase in activation energy, by comparison with the cyclisation mechanism of the pyrrole analogue (see below).



On a preparative scale (up to at least 2 g), isoindolo[2,1-*a*]indol-6-one **1** was obtained by 950 °C pyrolysis in up to 76% yield after chromatography. The 11-methyl derivative **4** was formed in similar yield, with no evidence of substituent migration to



Scheme 3

other sites at the extreme conditions of the pyrolysis. Previous routes to **1** include photochemical cyclisations,[10] intramolecular Wittig reactions[11] and various palladium-catalysed[12] and copper-catalysed[13] methods. The FVP route has the major advantage that only two synthetic steps are required from easily available starting materials, but the potential generality of the method is likely to be compromised by the very high furnace temperature required for the sigmatropic shift (see below).

An assignment of the NMR spectra of **1** is shown in Fig. 1. The two 4-spin systems were readily located by a COSY experiment and NOESY interactions with the H(11) singlet allowed assignment of H(1) and H(10). Zig-zag coupling from H(11) to H(4), well known for indole systems,[14] allowed the identification of the 'left-hand' ring and completion of the analysis. The carbon atoms due to the two overlapping signals at δ_H 7.51 were distinguished by their multiplicities in the HSQC spectrum.

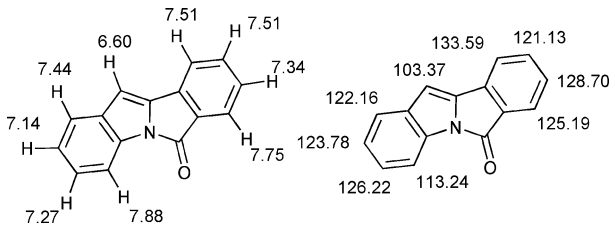


Fig. 1 ^{1}H and ^{13}C NMR parameters (δ_H and δ_C, [^{2}H]chloroform), of compound **1**.

Minor products which could be isolated from the pyrolysates include the isoindolo[1,2-*a*]indol-10-one **13** (*ca.* 3%).[15] This compound was characterised by its spectra; in particular the mass spectrum showed a strong molecular ion at *m/z* 219 and the ^{13}C NMR spectrum showed a carbonyl resonance at δ_C 181.55, very different from the lactam carbonyl resonance of **1** at δ_C 162.51. The NMR spectra of **13** were fully resolved at 360 MHz in [$^2H_6$]acetone solution and the assignments are shown in Fig 2. Zig-zag coupling from the 'indole' proton [H(11)] to H(4)[14] again provided the starting point for the analysis of the 'left-hand' ring and extrapolation to the 'right-hand' ring was possible by the NOESY interaction between H(4) and H(6). Extension to the carbon dimension was carried out by an HSQC experiment.

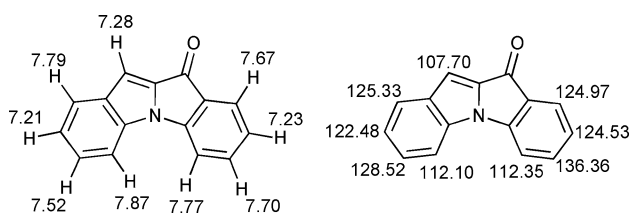
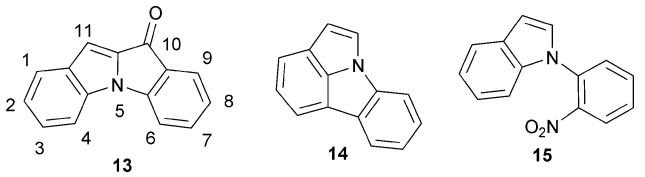


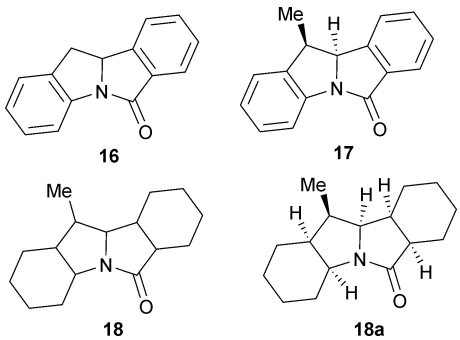
Fig. 2 ^{1}H and ^{13}C NMR parameters (δ_H and δ_C, [$^2H_6$]acetone) for **13**.



Both **1** and **13** were unchanged by FVP under the conditions of their formation showing that neither are intermediates on the route to the other. Compound **13** is therefore likely to be formed by a competitive mechanism in which cyclisation precedes the 1,5-sigmatropic aryl shift. In addition, a trace of pyrrolo[3,2,1-*jk*]indole **14** was also obtained. This compound is probably formed by cyclisation of a phenyl radical obtained by cleavage of the entire ester group; a related substituent cleavage provides **14** as the major product when the nitro compound **15** is pyrolysed.[16]

The functionality shared by compounds **1–3** include the core fused 5-membered bridgehead-nitrogen system and the lactam unit. Our study of the chemistry of **1** has focused on hydrogenation and on its reactions with nucleophiles.

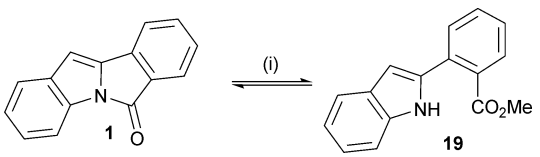
Catalytic hydrogenation of **1** at 40 psi over Pd/C gives a quantitative yield of the known[17] dihydro-compound **16** after 6 h. Analogous reduction of a 2-substituted example has been reported.[3] Under similar conditions, the 11-methyl derivative **4** is recovered unchanged, and even at 60 psi using 5% Rh/C only a trace of the dihydro derivative **17** could be identified from the NMR spectrum of the mixture. At higher pressure (400 psi), using 5% Rh–Al_2O_3 in an ethanol–acetic acid mixture (3 h, 20 °C),[18] a mixture of products was obtained from which the dihydro-compound **17** could be isolated in 80% yield.[19] The relative stereochemistry of the two asymmetric centres follows from the magnitude of the coupling constant $J_{H(11)-Me}$ (7.2 Hz) which is sensitive to the configuration of 7-methylpyrrolizidin-3-one isomers [*cis*-isomer (*c.f.* **15**) 7.4 Hz; *trans*-isomer 6.0 Hz[20]] and is consistent with a *cis*-hydrogenation mechanism.



Hydrogenation of **4** over the same catalyst but with extended reaction times (18 h), afforded a mixture of perhydro-derivatives **18** of which one isomer constituted *ca.* 80% of the mixture. Further analysis was not carried out, but our experience with pyrrolizinone hydrogenation would suggest that **18a**, formed by *cis*-hydrogenation from the least hindered face,[20b] is the most likely product. All other hydrogenation conditions attempted were ineffective.

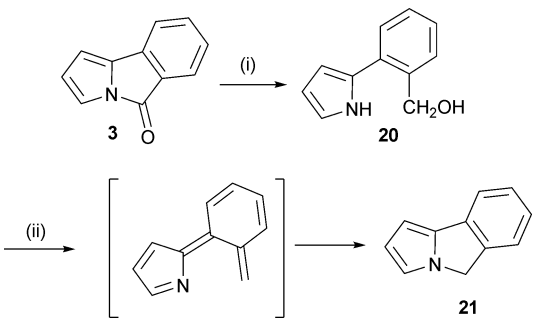
Pyrrolizin-3-one **2** and its benzo-analogues are ring-opened quantitatively in basic alcoholic solution.[7] Isoindolo[2,1-*a*]indol-6-one **1** can be ring opened to 2-(2-indolyl)benzoic acid in the

presence of potassium *tert*-butoxide.[21] In contrast, reaction of **1** with methanol in the presence of Hünig's base gave only partial conversion to the ring-opened ester **19**; in one set of conditions, equilibrium was reached at about 70% conversion after 60 min (Scheme 4). There is some indication that increasing the amount of base causes recyclisation to isoindolo[2,1-*a*]indol-6-one **1**, and this transformation may also take place during chromatography. Similarly, attempted methylation of 2-(indol-2-yl)benzoic acid (MeI, K_2CO_3, DMF) gave only isoindolo[2,1-*a*]indol-6-one **1**. The ester **19** was not obtained pure and was identified only by ^{13}C NMR spectroscopy in the presence of **1**. Joule and co-workers have also noted the tendency of 2-(indol-2-yl)benzoic acid derivatives to cyclise to isoindolo[2,1-*a*]indol-6-ones.[22] Nevertheless, this behaviour is unexpected because of the ring strain associated with the two fused 5-membered rings in **1**. The mixture of **19** and **1** was completely converted into **1** by FVP at 800 °C. This result confirms that the extreme temperatures required for the formation of **1** by FVP of **7** are due to the high energy barrier of the sigmatropic shift to give **10**, (which is the first step of the cascade sequence) rather than the ketene generation step (Scheme 3).



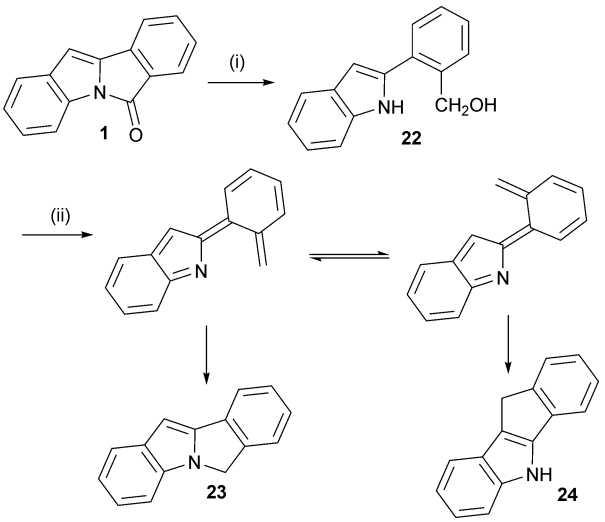
Scheme 4 *Reagents and conditions*: (i) MeOH, Hunig's base.

We have shown that reduction of the benzopyrrolizinone **3** followed by FVP of the resulting 2-(pyrrol-2-yl)benzyl alcohol **20** causes elimination of water and cyclisation to form benzopyrrolizine **21** (Scheme 5), thereby providing a two-step deoxygenation of the lactam starting material.[23]



Scheme 5 *Reagents and conditions*: (i) $LiAlH_4$; (ii) FVP (700 °C, 0.01 Torr).

Lithium aluminium hydride reduction of **1** under the conditions used for **3**,[23] gave the alcohol **22** (76%); similar ring-opening has been reported for a substituted isoindolo[2,1-*a*]indol-6-one.[3] In contrast to the behaviour of **20**, FVP of the alcohol **22** at 800–950 °C gave two products in varying ratio (Scheme 6). These were separated by chromatography and identified as the known isomers **23** and **24**. At the lower pyrolysis temperatures, **23** is the major isomer (*e.g.* 800 °C, **23** : **24** 75 : 25) and is therefore the kinetic product whereas **24** predominates at higher furnace temperatures (*e.g.* 950 °C with silica tubes in the furnace, **23** : **24** 25 : 75) and is therefore the thermodynamic product. There is significant loss of resonance energy in the formation of the xylylene intermediate, accounting for the high furnace temperatures needed for these transformations and allowing the C=C bond rotation required for the rearrangement to **24** (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) $LiAlH_4$; (ii) FVP (800–950 °C, *ca.* 0.01 Torr).

Conclusions

We conclude that the thermal cascade illustrated in Scheme 3 provides a viable synthetic route to isoindolo[2,1-*a*]indol-6-one **1**, though a high temperature is required for the initial sigmatropic migration. The chemistry of isoindolo[2,1-*a*]indol-6-one **1** shows significant differences from that of pyrrolizin-3-one **2** and its mono-benzo derivatives such as **3**. Catalytic hydrogenation of the 10b–11 site is unexpectedly sensitive to substituents and the nature of the catalyst. Isoindolo[2,1-*a*]indol-6-one **1** exists in equilibrium with the ester **19** in basic methanol, whereas both **2** and **3** are rapidly ring opened under such conditions. FVP of the benzyl alcohol **22** provides two isomeric cyclised products, whereas a single product is obtained by FVP of the pyrrole analogue **20**. Further studies of pyrrolizinones and their benzo-analogues will be reported in future publications.

Experimental

^1H and ^{13}C NMR spectra were recorded at 250 or 63 MHz respectively for solutions in [^{2}H]chloroform unless otherwise stated. ^{13}C NMR signals refer to CH resonances unless otherwise stated. Mass spectra were recorded under electron impact conditions.

Methyl 2-(indol-1-yl)benzoate 7

A suspension of indole **9** (2.93 g, 25 mmol), *o*-iodobenzoic acid (5.70 g, 23 mmol) and anhydrous potassium carbonate (6.91 g, 50 mmol) in dimethylformamide (50 cm^3) was heated under reflux, with stirring, for 48 h to give 2-(indol-1-yl)-benzoic acid. The product was not isolated but treated with iodomethane (3.55 g, 25 mmol) and anhydrous potassium carbonate (6.91 g, 50 mmol)

and the reaction left to stir at room temperature for 48 h. Upon completion of the reaction, water (120 cm^3) was added and the product was extracted into ether (3 × 40 cm^3), washed with water (3 × 50 cm^3) and dried over anhydrous $MgSO_4$. The product was purified by vacuum distillation (Kugelrohr) to give methyl 2-(indol-1-yl)benzoate **7** (2.18 g, 35%) bp 108–110 °C (0.4 Torr); δ_H 8.02 (1H, d, ^3J 8.2), 7.74–7.62 (2H, m), 7.55–7.47 (2H, m), 7.25–7.12 (4H, m), 6.71 (1H, d, ^3J 3.1) and 3.48 (3H, s); δ_C 166.58 (quat), 138.49 (quat), 137.03 (quat), 132.61, 131.09, 128.70, 128.44 (2C, quat), 128.27, 127.42, 122.09, 120.77, 119.94, 109.58, 103.04 and 52.05; *m/z* 251 (M^+, 95%), 232 (24), 231 (80), 229 (36), 228 (26), 220 (41), 203 (50), 191 (47) and 117 (100) (spectra compatible with published data[24]).

Methyl 2-(3-methylindol-1-yl)benzoate 8

3-Methylindole **10** (3.28 g, 25 mmol) was reacted under the conditions above to give methyl 2-(3-methylindol-1-yl)-benzoate **8** (4.74 g, 72%) mp 96–98 °C, bp 103–104 °C (1 Torr) (Found: M^+ 265.1094. $C_{17}H_{15}NO_2$ requires *M* 265.1103) (Found: C, 76.3; H, 5.75; N, 5.3. $C_{17}H_{15}NO_2 \cdot 0.1H_2O$ requires C, 76.45, H, 5.65, N, 5.3%); δ_H 7.85 (1H, m), 7.53–7.49 (2H, m), 7.39–7.33 (2H, m), 7.08–7.03 (3H, m), 6.90 (1H, m), 3.37 (3H, s) and 2.29 (3H, d, ^4J 1.1); δ_C 166.93 (quat), 138.73 (quat), 137.22 (quat), 132.55, 131.01, 128.54 (quat), 128.07, 126.95, 126.19, 122.12, 119.39, 118.91, 112.42 (quat), 109.49, 52.07 (CH_3) and 9.49 (CH_3) (one quaternary signal overlapping); *m/z* 265 (M^+, 100%), 264 (71), 263 (31), 262 (82), 250 (40), 232 (54), 231 (89), 204 (72) and 203 (63).

Flash vacuum pyrolysis experiments

The substrate was sublimed under vacuum into a horizontal silica furnace tube (35 × 2.5 cm) heated by an electrical furnace. For some of the high temperature pyrolyses, the contact time was increased by packing the exit end of the furnace tube with silica tubes.[9] Products were collected in a U-tube, cooled by liquid nitrogen, situated at the exit point of the furnace. When the pyrolysis was complete, the trap was allowed to warm to room temperature under an atmosphere of dry nitrogen. Pyrolysis parameters are quoted as follows: quantity of substrate, inlet temperature (T_i), furnace temperature (T_f), pressure range (P_{range}) and time of pyrolysis (*t*).

Isoindolo[2,1-*a*]indol-6-one 1

Conditions were optimised by small scale pyrolyses of methyl 2-(indol-1-yl)-benzoate **7** (*ca.* 30 mg, 0.12 mmol, T_i 100 °C, P_{range} 0.02–0.10 Torr, *t* 10 min), in the presence of silica tubes placed at the exit end of the furnace. The following conversions were observed: 800 °C, 15%; 850 °C, 23%; 900 °C, 54%; 950 °C, 84%.

A preparative pyrolysis (400 mg, 1.6 mmol, T_f 950 °C with silica tubes T_i 100 °C, P_{range} 0.01–0.12 Torr, *t* 40 min) gave a solid yellow pyrolysate that was purified by dry flash chromatography on silica (50% DCM in hexane as eluent) to give isoindolo[2,1-*a*]indol-6-one **1** (220 mg, 76%) mp 153–154 °C (lit.,[12a] 154 °C); δ_H (360 MHz) 7.88 (1H, d, ^3J 7.9), 7.75 (1H, dd, ^3J 7.9, ^4J 0.8), 7.51 (2H, m), 7.44 (1H, d, ^3J 7.8), 7.34 (1H, m), 7.27 (1H, m), 7.14 (1H, td, ^3J 7.6, ^4J 1.0) and 6.60 (1H, s); δ_C 162.54 (quat), 138.74 (quat), 134.60 (quat), 134.41 (quat), 133.80 (quat), 133.59, 133.52 (quat), 128.70, 126.22, 125.19, 123.78, 122.16, 121.13, 113.24 and 103.37; *m/z* 219 (M^+, 100%), 191 (42), 190 (80), 164 (44), 163 (46), 110 (56), 96 (48) and 82 (56).

The first fraction from the column (*ca.* 2 mg) was pyrrolo[3,2,1-*jk*]carbazole **14** δ_H 8.09 (1H, d, ^3J 7.1), 7.92 (1H, d, ^3J 7.3), 7.82 (1H, d, ^3J 7.5), 7.70 (2H, m), 7.54 (1H, m), 7.37 (2H, m) and 6.87 (1H, d, ^3J 3.1); δ_C 140.71 (quat), 139.24 (quat), 130.81 (quat), 126.41, 123.31, 123.02, 122.33, 122.03, 121.54 (quat), 120.95, 118.82 (quat), 117.25, 111.31 and 109.26; *m/z* 191 (M^+, 100%), 163 (44), 139 (23), 96 (52), 82 (45), 63 (29) and 39 (25) (spectra compatible with literature data[25]). A third fraction was shown to be isoindolo[1,2-*a*]indol-10-one **13**, (9 mg, 3%) mp 166–168 °C (lit.,[15] 169 °C) $\delta_H(C[^2H]Cl_3)$ 7.63–7.67 (2H, m), 7.48–7.55 (2H, m), 7.34–7.45 (2H, m) and 7.05–7.16 (3H, m); $\delta_C(C[^2H]Cl_3)$ 181.55 (quat), 145.43 (quat), 135.66 (quat), 135.41, 134.18 (quat), 132.49 (quat), 129.28 (quat), 128.00, 125.06, 124.94, 123.75, 121.87, 111.21 (2CH) and 107.92 (NMR spectra are better dispersed in $[^2H_6]$acetone solution—see Fig. 2); *m/z* 219 (M^+, 100%), 190 (44), 163 (18), 69 (22) and 32 (45).

11-Methylisoindolo[2,1-*a*]indol-6-one 4

FVP of methyl 2-(3-methylindol-1-yl)-benzoate **8** (265 mg, 1.0 mmol, T_f 950 °C with silica tubes, T_i 120 °C, P_{range} 0.01–0.11 Torr, *t* 40 min) using a dry ice–acetone cold-finger trap gave a solid yellow pyrolysate containing 11-methylisoindolo[2,1-*a*]indol-6-one **4** that was purified by dry flash chromatography on silica (20–50% DCM in hexane as eluent) to afford yellow needles (121 mg, 72%) mp 173–174 °C (lit.,[12c] 173–175 °C), bp 177 °C (4.5 Torr) (Found: C, 81.65; H, 4.65; N, 6.2. $C_{16}H_{11}NO \cdot 0.1H_2O$ requires C, 81.75, H, 4.7, N, 5.95%) (Found: M^+, 233.0840. $C_{16}H_{11}NO$ requires *M*, 233.0841); δ_H 7.75 (1H, dt, ^3J 7.9, ^4J 0.8), 7.63 (1H, d, ^3J 7.5, ^4J 1.0), 7.42 (1H, m), 7.38 (1H, td, ^3J 7.5, ^4J 1.0), 7.26 (1H, m), 7.22–7.14 (2H, m), 7.05 (1H, td, ^3J 7.5, ^4J 1.0) and 2.37 (3H, s); δ_C 162.15 (quat), 135.68 (quat), 134.95 (quat), 134.49 (quat), 133.87, 133.47 (quat), 133.31, 127.94, 126.39, 125.19, 123.48, 121.02 (quat), 120.05, 115.24 (quat), 113.19 and 9.35 (CH_3); *m/z* 233 (M^+, 99%), 232 (77), 219 (100), 204 (59), 203 (79) and 102 (34).

10b,11-Dihydroisoindolo[2,1-*a*]indol-6-one 16

A solution of isoindolo[2,1-*a*]indol-6-one **1** (51 mg, 0.23 mmol) in ethanol (25 cm^3) was hydrogenated over 5% Pd–C (5 mg) at 40 psi using a Parr apparatus for 6 h during which time the solution decolourised. The catalyst was removed by filtration through Celite and the filtrate was concentrated to provide 10b,11-dihydroisoindolo[2,1-*a*]indol-6-one **16** as a colourless solid (50 mg, 98%) mp 127–129 °C (lit.,[17] 136–137 °C) (Found: M^+ 221.0840. $C_{15}H_{11}NO$ requires *M* 221.0841); δ_H 7.80 (1H, m), 7.60 (1H, d, ^3J 7.8), 7.52 (1H, m), 7.44–7.38 (2H, m), 7.27–7.13 (2H, m), 6.98 (1H, t, ^3J 7.5), 5.52 (1H, apparent t, ^3J *ca.* 9.5), 3.37 (1H, dd, ^3J 15.2 and 8.7) and 2.95 (1H, dd, ^3J 15.0 and 10.4); δ_C 168.25 (quat), 145.87 (quat), 140.43 (quat), 135.82 (quat), 134.01 (quat), 132.42, 128.56, 127.83, 125.21, 124.66, 124.30, 122.70, 116.31, 65.29 and 33.61 (CH_2); *m/z* 221 (M^+, 86%), 220 (89), 219 (77), 193 (81), 192 (64), 191 (80), 190 (62), 165 (71), 130 (52), 105 (53) and 95 (100) (spectra compatible with those previously reported[17])

10b,11-Dihydro-11-methylisoindolo[2,1-*a*]indol-6-one 17

11-Methylisoindolo[2,1-*a*]indol-6-one **4** (30 mg, 0.13 mmol) was hydrogenated in a 10 : 1 mixture of ethanol and acetic acid over 5% Rh–Al_2O_3 (5 mg) at room temperature and a pressure of 400 psi for 3 h and gave a mixture of three hydrogenation products. Separation by dry flash chromatography, using a 2–40% ethyl acetate in hexane gradient as eluent, afforded one major product which was identified as 10b,11-dihydro-11-methylisoindolo[2,1-*a*]indol-6-one **17** (24 mg, 80%)[19] δ_H 7.91 (1H, m), 7.71 (1H, dd, ^3J 7.8, ^4J 0.4), 7.62 (1H, td, ^3J 7.5, ^4J 1.3), 7.54–7.49 (2H, m), 7.35–7.26 (2H, m), 7.11 (1H, td, ^3J 7.5, ^4J 0.9), 5.53 (1H, d, ^3J 7.9), 3.62 (1H, apparent quin, ^3J *ca*. 7.4) and 0.76 (3H, d, ^3J 7.2); δ_C 168.00 (quat), 142.98 (quat), 141.65 (quat), 138.82 (quat), 134.98 (quat), 132.00, 128.52, 127.99, 124.77, 124.44 (2CH), 123.55, 116.22, 68.65, 37.73 and 18.22 (CH_3).

When solutions of 11-methylisoindolo[2,1-*a*]indol-6-one **4** (30 mg, 0.13 mmol) in toluene (25 cm^3) were subjected to hydrogenation at 600, 850, 1000 Bar at room temperature and 1000 Bar with heating at 50 °C over 5% Pd–C, 10% Pd–C or 5% Rh–C for 6 h, no reaction was observed.

11-Methyltetradecahydro-isoindolo[2,1-*a*]indol-6-one 18

A hydrogenation of **4** (30 mg, 0.13 mmol) at room temperature and a pressure of 400 psi under the conditions used for **17**, but with a reaction time of 18 h, gave 11-methyltetradecahydro-isoindolo[2,1-*a*]indol-6-one **18** (29 mg, 97%) with one stereoisomer present as *ca.* 80% of the mixture (Found: M^+ 247.1939. $C_{16}H_{25}NO$ requires *M* 247.1936); δ_H 3.82 (1H, dd, ^3J 7.6 and 4.6), 3.52 (1H, m), 2.63 (1H, t, ^3J 5.3), 2.42–2.27 (2H, m), 2.22–0.87 (17H, m) and 1.11 (3H, d, ^3J 7.5); δ_C 152.52 (quat), 65.89, 52.98, 48.10, 42.60, 40.47, 37.54, 27.65 (CH_2), 25.44 (CH_2), 24.33 (CH_2), 24.11 (CH_2), 23.47 (CH_2), 23.08 (CH_2), 22.79 (CH_2), 22.07 (CH_2) and 14.08 (CH_3); *m/z* 247 (M^+, 86%), 204 (79), 190 (51), 152 (55), 138 (83), 95 (70), 81 (89), 67 (84) and 55 (100).

Reaction of isoindolo[2,1-*a*]indol-6-one 1 with Hünig's base in methanol

Isoindolo[2,1-*a*]indol-6-one **1** (0.009 g, 0.04 mmol) was dissolved in [$^2H_4$]methanol (0.5 cm^3), and its ^{1}H NMR spectrum showed a characteristic signal due to H-11 [δ_H 6.76 (1H, s)]. Hünig's base (0.013 g, 0.1 mmol) was added and the spectrum immediately showed a new peak at δ_H 6.45 due to H-3 of compound **19** (20% conversion). The following conversions were recorded: 15 min, 50%; 60 min, 70%; 150 min, 70%; showing the reaction had reached equilibrium at 70% conversion under these conditions.

The following reaction conditions allowed a sample of **19** to be isolated as a mixture with **1**. Isoindolo[2,1-*a*]indol-6-one **1** (0.022 g, 0.1 mmol) was dissolved in methanol and Hünig's base (0.026 g, 0.2 mmol) was added. The mixture was left at room temperature for 1 h and the methanol was evaporated. ^{1}H NMR analysis showed 47% conversion to **19** and elimination of the signals of the ^{13}C spectrum of **1** reported above enabled those of **19** to be identified; δ_C 169.94 (quat), 136.69 (quat), 136.41 (quat), 134.52 (quat), 131.55, 130.74, 130.06, 129.80 (quat), 128.18 (quat), 127.30, 125.15, 122.24, 120.43, 119.82, 111.17, 103.10, and 52.69 (CH_3). Attempted separation by chromatography on alumina (ethyl acetate, hexane) gave only **1**, suggesting that **19** had recyclised on the column.

2-(Indol-2-yl)benzoic acid and its attempted methylation under basic conditions

Using Itahara's method,[21] isoindolo[2,1-*a*]indol-6-one **1** (0.22 g, 1 mmol) was dissolved in *t*-butanol and water (5 cm^3) and potassium *t*-butoxide (1.12 g, 10 mmol) was added. The mixture was heated under reflux, with stirring, under nitrogen for 60 h. The solvent was removed, the mixture was diluted with water, acidified with HCl, then extracted with diethyl ether (3 × 20 cm^3). The organic extracts were dried ($MgSO_4$) and the ether was evaporated to give 2-(indol-2-yl)benzoic acid (0.23 g, 97%) after trituration with ether and hexane, mp 156–158 °C (lit.,[21] 155–157 °C); δ_H 9.25 (1H, s), 7.96 (1H, d, ^3J 8.2), 7.72 (1H, d, ^3J 7.8), 7.62 (2H, m), 7.42 (2H, m), 7.21 (2H, m) and 6.72 (1H, s); δ_C 136.48 (quat), 133.58 (quat), 132.47, 131.45, 131.03, 128.19 (quat), 127.63, 122.37, 120.53, 119.92, 111.14 and 103.46.

A solution of 2-(indol-2-yl)benzoic acid (0.23 g, 0.97 mmol) and iodomethane (0.14 g, 1 mmol) in dimethylformamide (15 cm^3) containing potassium carbonate (0.28 g, 2 mmol) was stirred at room temperature for 24 h. Water (40 cm^3) was added and the product was extracted into ether (3 × 20 cm^3). The organic extracts were washed with water (3 × 10 cm^3), dried ($MgSO_4$) then the solvent was evaporated to give **1** as the sole product.

FVP of a mixture of isoindolo[2,1-*a*]indol-6-one 1 and methyl 2-(indol-2-yl)benzoate 19

A 30 : 70 mixture of **1** and **19** (0.006 g), was subjected to FVP at 800 °C with silica tubes (T_i 90–150 °C, P_{range} 0.009–0.012 Torr, *t* 25 min). NMR analysis of the product indicated that recyclisation to **1** was complete under these conditions.

2-(2-Hydroxymethylphenyl)indole 22

Lithium aluminium hydride (0.076 g, 2 mmol) was dissolved in dry THF (10 cm^3), and a solution of isoindolo[2,1-*a*]indol-6-one **1** (0.219 g, 1 mmol) in THF (10 cm^3) was added dropwise under nitrogen. The mixture was heated under reflux, under nitrogen, with stirring, for 3 h. Wet ether was then added to quench excess $LiAlH_4$, and the inorganic residue was filtered through Celite. Water (20 cm^3) was added to the filtrate and the product was extracted into ether (3 × 10 cm^3). The organic extracts were washed with water (3 × 5 cm^3), dried ($MgSO_4$) and the solvent was removed to give a brown oil, which was distilled (Kugelrohr) to give 2-(2-hydroxymethylphenyl)indole **22** (0.17 g, 76%) as a pale orange oil, bp 160–162 °C (0.8 Torr) (lit.,[22] mp 85 °C); δ_H 10.15 (1H, s), 7.68 (1H, d, ^3J 7.3), 7.59 (1H, d, ^3J 7.7), 7.31 (4H, m), 7.09 (2H, m), 6.68 (1H, s), 4.67 (2H, s) and 2.21 (1H, s); δ_C 137.69 (quat), 136.61 (quat), 135.70 (quat), 133.88 (quat), 130.75, 130.09, 129.07, 128.45 (quat), 127.80, 121.87, 120.36, 119.72, 111.23, 101.66 and 65.13 (CH_2).

FVP of 2-(2-hydroxymethylphenyl)indole 22

The following optimisation experiments were carried out. 2-(2-Hydroxymethylphenyl)indole **22** (0.028 g, 0.13 mmol) was subjected to FVP at 800 °C (T_i 90–150 °C, P_{range} 0.008–0.013 Torr, *t*

35 min). The white solid obtained contained **22**, **23** and **24**, with an approximately 3 : 1 ratio of **23** to **24**. Repetition of this experiment at 900 °C (0.044 g, 0.2 mmol, T_i 90–120 °C, P_{range} 0.008–0.009 Torr, *t* 15 min) gave a *ca.* 1 : 1 mixture of 6*H*-isoindolo[2,1-*a*]indole **23** and 5,10-dihydroindeno[1,2-*b*]indole **24**. At 950 °C (with silica tubes inserted in the furnace tube) FVP of **22** (0.023 g, 0.1 mmol, T_i 90–120 °C, P_{range} 0.009–0.012 Torr, *t* 15 min) gave a pyrolysate which contained **23** and **24** in 1 : 3 ratio.

On a larger scale, 2-(2-hydroxymethylphenyl)indole **22** (0.104 g, 0.47 mmol) was sublimed into the FVP furnace at 900 °C (T_i 90–150 °C, P_{range} 0.011–0.017 Torr, *t* 45 min). The cream–yellow solid obtained was separated using dry flash chromatography (dichloromethane, hexane) to give 6*H*-isoindolo[2,1-*a*]indole **23** (0.03 g, 31%) mp 214–218 °C (lit.,[22] 209–211 °C); δ_H 7.78 (1H, m), 7.61 (1H, t, ^3J 8.1), 7.18 (6H, m), 6.55 (1H, s) and 5.00 (2H, s); δ_C 144.36 (quat), 141.59 (quat), 134.29 (quat), 133.48 (quat), 133.19 (quat), 130.75, 128.87, 127.45, 123.95, 122.11, 121.91, 121.34, 120.03, 109.65, 91.68 and 48.82 (CH_2); *m/z* 240 (45%), 205 (M^+, 33%), 161 (100), 129 (60), 102 (76), 76 (37) and 51 (53) (spectra compatible with literature data[22]).

The second component obtained from the column was impure 5,10-dihydroindeno[1,2-*b*]indole **24** (0.02 g, 21%) mp 230–234 °C (lit.,[26] 258–259 °C); δ_H 8.34 (1H, s), 7.63 (1H, m), 7.54 (1H, d, ^3J 6.6), 7.1–7.5 (6H, m) and 3.73 (2H, s); δ_C 147.69 (quat), 143.22 (quat), 140.51 (quat), 134.90 (quat), 126.41, 125.35, 124.63, 121.53, 120.05, 118.82, 117.21, 111.96 and 30.83 (CH_2) (2 quaternary signals overlap with impurity peaks in aromatic region); *m/z* 205 (M^+, 100%), 204 (78), 102 (24), 76 (41) and 51 (49) (spectra compatible with literature data, recorded in a different solvent[27]).

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