Preparation of 2,3-Disubstituted Indoles from Indole-3-carboxylic Acids and Amides by α-Deprotonation

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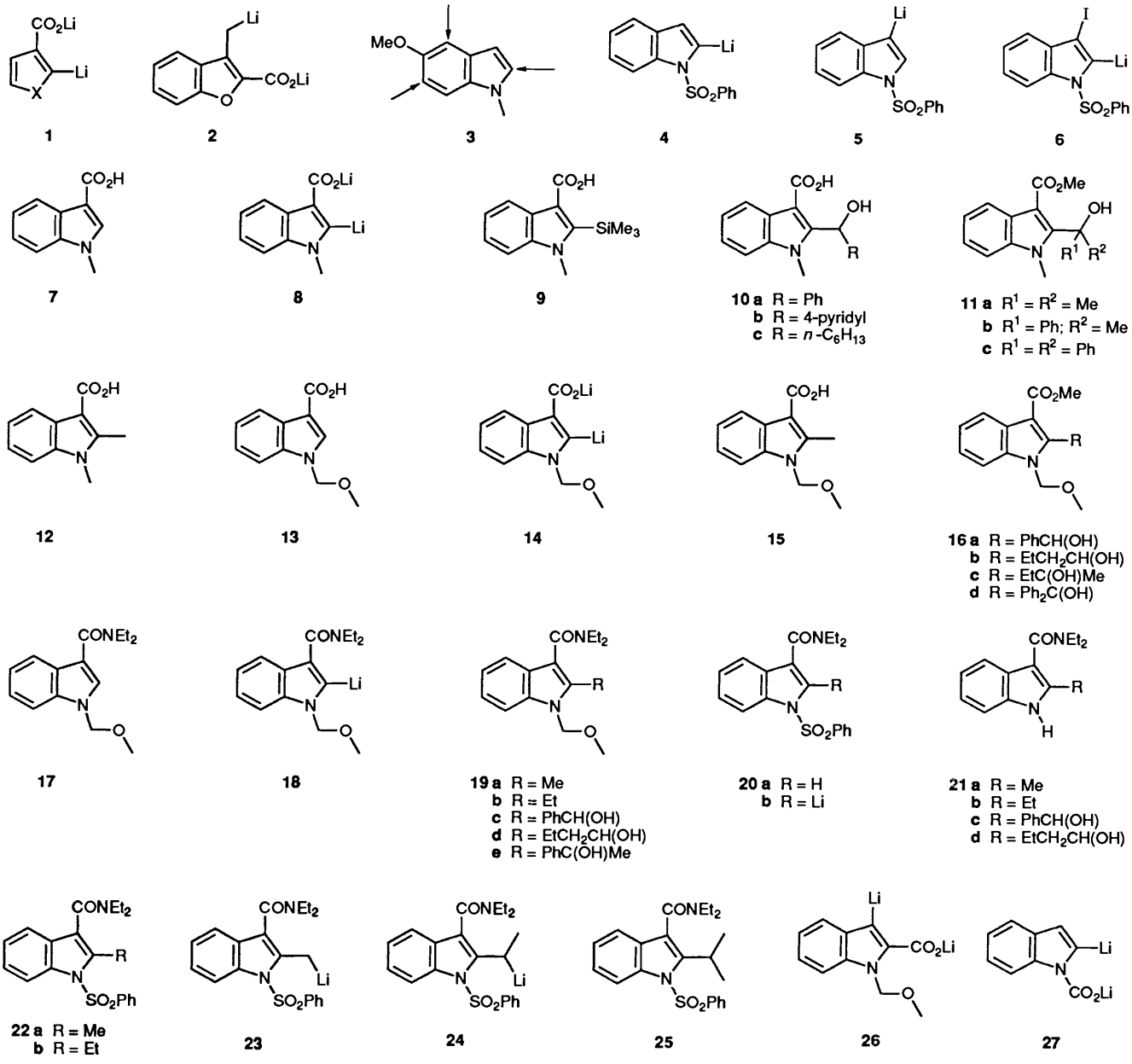
Direct deprotonations have been used to obtain the 2(α)-lithiated indole-3-carboxylate dianions **8** and **14**, together with the related 2(α)-lithiated indole-3-carboxamide monoanions **18** and **20b** from the parent compounds. These four intermediates are useful for the preparation of 2,3-disubstituted indoles, especially by condensations with aldehydes and ketones and by alkylations using primary alkyl iodides.

Metallated intermediates are amongst the most useful for the rapid and often regiospecific homologation of heteroaromatic systems.[1] When such compounds contain a single heteroatom, deprotonation almost always takes place at an adjacent site but, of course, a limitation is that deprotonation can occur at either of two vacant alpha positions. Many functional groups have been identified which are capable of directing metallations to a specific alpha site.[1] These generally contain heteroatoms which can coordinate to an incoming base, although other factors are no doubt involved in such directing effects. Our particular interest has been in the use of lithium carboxylate groups for this purpose. This turns out to be a rather good directing group as the 2-lithiated species **1** (X = O or S) are obtained exclusively from the parent heteroaryl-3-carboxylic acids and two equivalents of base.[2] In favourable circumstances, a 2-carboxylate can even direct metallation to an adjacent 3(β)-position at the expense of a free alpha site[3] and also to an adjacent and relatively unactivated methyl group, as is the case of the generation of the dianion **2** from the corresponding 3-methylbenzofuran-2-carboxylic acid.[4] We felt that this methodology could be usefully applied to the elaboration of 2,3-disubstituted indoles and herein we report in full upon our studies on the deprotonation and homologation of indole-3-carboxylic acid derivatives.

Treatment of indole itself with a strong base such as butyllithium results only in deprotonation at nitrogen.[1] *N*-Alkyl indoles can however be smoothly deprotonated at the 2(α)-position.[5] The rate of lithiation is only modest, but is enhanced by using tetrahydrofuran (THF) as the solvent.[6] The low reactivity is reflected by the lack of regioselectivity in deprotonations of 5-methoxy-1-methylindole **3**; the 4- and 6-positions are attacked as well as the 2-position, as shown, indicating that the methoxy substituent has a similar directing effect to the indolic ring nitrogen. The 2(α)-deprotonation of indoles is facilitated by the inclusion of either *N*-arylsulfonyl[6] or *N*-methoxymethyl functions[7] to such an extent that it is generally regiospecific, even when other competing directing groups are present.[6] In these first reports by Sundberg and co-workers, *tert*-butyllithium was used to obtain the intermediate **4**; subsequent results obtained by Gribble and his colleagues suggested that lithium diisopropylamide (LDA) was also suitable and indeed gave superior yields in many cases.[8] As is generally the case in this and related heteroaromatic systems, 3(β)-metallation is usually achieved by halogen–metal rather than hydrogen–metal exchange, using an alkyllithium. 1-Phenylsulfonyl-3-lithioindole **5** has been generated in just this manner; interestingly, upon warming, this intermediate rearranges to the presumably more thermodynamically stable 2-lithio species **4**.[8,9] When 3-halogenoindoles are treated with LDA, 2(α)-deprotonation occurs smoothly but the resulting lithiated species (*e.g.* **6**) rather surprisingly do not eliminate the elements of lithium iodide to give indol-2(3)-yne.[10]

Our experiments began with the readily prepared 1-methylindole-3-carboxylic acid **7**.[11] We were pleased to find that when a solution of this acid in THF was treated at −78 °C with two equivalents of LDA, a colourless suspension of the dianion **8** was obtained; quenching a sample with chlorotrimethylsilane gave a product **9**, the ^{1}H NMR spectrum of which showed no resonance due to the 2-proton of the indole nucleus. When the solution was allowed to warm slowly to ambient temperature during 1.5 h, similar treatment of small samples showed the dianion to be stable up to *ca.* 0 °C; after this, protonation began to occur. The final sample consisted of 83% of the 2-silyl acid **9**, the remainder being the starting acid **7**, according to integration of the respective *N*-methyl resonances. There was no evidence of other decomposition products. Presumably, the solvent is acting as the proton source. The dianion **8** also condensed smoothly with examples of both aromatic and aliphatic aldehydes (benzaldehyde, pyridine-4-carbaldehyde and heptanal respectively) to give the adducts **10a–c** in excellent isolated yields. Returns from condensations with ketones were somewhat lower (40–55%), presumably due to competing deprotonation in the cases of enolizable ketones (acetone, acetophenone), or to steric crowding, in the case of benzophenone. In these latter examples, it was found most convenient to isolate and characterise the products as the corresponding methyl esters **11a–c**. The material balance was made up of methyl 1-methylindole-3-carboxylate in all cases. Alkylation of the dianion **8** using iodomethane was also essentially quantitative, leading to 1,2-dimethylindole 3-carboxylic acid **12**. However, similar reactions with allyl chloride, iodoethane and benzyl bromide all failed to give more than traces of the desired products under a variety of conditions. In all cases, the starting acid **7** was recovered in high yield, suggesting that these electrophiles were acting instead as proton sources. Whatever the reason, such failures are a common phenomenon associated with many sp^2 centred carbanions[12] including the related dianions **1** derived from furan- and thiophene-carboxylic acids.[2]

A major limitation of the foregoing homologation procedure is its unsuitability for the preparation of indoles unsubstituted at nitrogen. We have therefore investigated the possibilities of generating species related to dianion **8** which contain removable nitrogen blocking groups. Likely candidates for this were the methoxymethyl and phenylsulfonyl functions. 1-Methoxymethylindole-3-carboxylic acid **13** was readily obtained from the corresponding 1-methoxymethylindole[7] by sequential treatment with trifluoroacetic anhydride and aqueous base. In the event, deprotonations of this intermediate proved only partially successful. Of a range of bases examined (LDA, BuLi,



Bu^{s}Li and Bu^{t}Li and NaH–BuLi), LDA gave the best returns while the remainder gave equivalent or lower yields. Using iodomethane as the test electrophile,[12] a maximum conversion into the required dianion **14** of 70% was achieved, according to ^{1}H NMR analysis of the resulting mixture of the desired 2-methylindole acid **15** and the starting material **13**. This was confirmed by condensation with benzaldehyde, which led to the homologue **16a** in 67% isolated yield, following esterification using diazomethane and chromatography. Condensations with enolisable aldehydes and ketones (butanal and butanone) were less efficient and led, in a similar manner, to the indole esters **16b** and **16c** in 28 and 18% yields respectively. Using benzophenone as the electrophile gave the expected derivative **16d** in 31% isolated yield. In all cases, the balance of the product was starting material, isolated as the methyl ester of acid **13**. Presumably the reasons for these poor yields are as discussed above with respect to the dianion **8**; the dianion **14** in contrast also appears to be less nucleophilic.

These relatively poor results suggested that it could be beneficial to use an alternative directing group in place of the carboxylic acid function, but at the same oxidation level. According to previous reports[1] together with our own recent success in developing related methods for oxazole and thiazole homologation,[13] an amide group appeared to be ideal. We therefore prepared the *N*,*N*-diethylamide **17** from the acid **13**, by sequential treatment with oxalyl chloride and diethylamine. Deprotonation of this amide was readily achieved using butyllithium in THF at −78 °C. The resulting monoanion **18** was formed as a white precipitate in essentially quantitative yield, according to quenching experiments using chlorotrimethylsilane and subsequent analysis by ^{1}H NMR spectroscopy and by the formation of the 2-methyl homologue **19a** in 91% isolated yield. Alkylation by iodoethane similarly gave an excellent 86% isolated yield of the 2-ethylindole amide **19b**. This extension is not trivial; many vinylic carbanions can only be efficiently alkylated using iodomethane, as is the case with the foregoing dianion **8**; although not proven, it is probable that the homologous iodides act instead as proton sources.[12] As expected from these results, condensation with benzaldehyde was also very efficient as was a similar reaction with butanal leading to the expected products **19c** and **19d** in 82 and 66% isolated yields respectively. However, reaction with the more

demanding electrophile acetophenone gave only a 26% isolated yield of the desired product **19e**. The latter compound existed as a mixture of two separate rotamers at ambient temperature.

The corresponding *N*-phenylsulfonyl carboxamide **20a**, prepared from *N*-phenylsulfonylindole[14] by reaction with oxalyl chloride under Friedel–Crafts conditions[15] followed by treatment of the resulting acid chloride with diethylamine, behaved similarly. Deprotonation was smoothly effected using butyllithium in THF at −78 °C, leading to anion **20b**. After reaction with an electrophile, it was found most convenient to directly remove the phenylsulfonyl group by base hydrolysis, prior to purification. In this manner, the free indolecarboxamides **21** were produced in ≥70% isolated yields. The reactivity profile of intermediate **20b** was very similar to that of the *N*-methoxymethyl amide anion **18**; alkylations with both iodomethane and iodoethane proceeded smoothly as did condensations with benzaldehyde and butanal. Attempted coupling to acetophenone failed.

In the cases of the alkylation reactions of anion **20b**, the intermediate *N*-phenylsulfonylindoles **22a** and **22b** have both been isolated in good yield, simply by omitting the base hydrolysis step. Further treatment of these with base indicates that there may be more applications of this type of chemistry. Thus, reaction between the 2-methyl derivative **22a** and butyllithium in THF at −78 °C resulted in the formation of a deep maroon-coloured solution, presumably containing the anion **23**, which was immediately quenched with iodomethane. An excellent yield of the 2-ethyl homologue **22b** was obtained.[16] If the electrophile was not added promptly, only desulfonylated material **21a** was isolated. In similar fashion, deprotonation of the 2-ethylindole carboxamide **22b** but using LDA, followed by treatment with iodomethane gave the 2-isopropyl derivative **25** in 47% yield, presumably by way of the anion **24**. The remainder of the product was the starting material **22b**. The reactivities of these species have not yet been further examined, although given that they are sufficiently stable, especially with respect to ring opening, they could prove to be very useful intermediates as, in general, sp^3 centred carbanions are more nucleophilic than related vinylic carbanions.[4]

This present work can be regarded as a completion of model studies which establish the potential for using carboxylate functions to control deprotonation around the pyrrole residue in indoles. While our work was in progress,[17] Japanese workers reported the successful generation of the dianion **26** in ≤64% yield from the corresponding indole-2-carboxylic acid, using *sec*-butyllithium–HMPA as the base.[18] Acylations using dimethylformamide or ethyl esters led to 40–60% yields of the 3-acylated homologues. A most appealing use of a carboxylate function in this context constitutes the final possibility in which this function is used to both temporarily block the nitrogen atom and to activate the 2(α)-position, leading to the dianionic species **27**.[19] Loss of the carboxylate group occurs upon work-up to provide the free indoles directly. These complementary series of anionic intermediates should find many applications in the elaboration of 2,3-disubstituted indoles.

Experimental

For general details, see ref. 4. Light petroleum refers to the fraction of b.p. range 40–60 °C.

1-Methylindole-3-carboxylic Acid **7**.—Indole-3-carboxylic acid (2.3 g, 14 mmol)[11] was heated under reflux with acetone (300 cm^3), iodomethane (7 cm^3, 28 mmol) and potassium carbonate (22 g, 28 mmol) for 24 h. The cooled reaction mixture was filtered and the solid washed with warm acetone. The combined filtrates were evaporated and the residue partitioned between water (30 cm^3) and chloroform (30 cm^3). The separated aqueous solution was further extracted with chloroform (2 × 30 cm^3) and the combined organic solutions washed with water (30 cm^3) and brine (30 cm^3) then dried and evaporated to furnish methyl 1-methylindole-3-carboxylate (2.4 g, 89%). This was added to a solution of potassium hydroxide (1.07 g, 1.5 equiv.) in water (50 cm^3) and the resulting mixture refluxed for 2 h. The resulting solution was cooled, washed with chloroform (30 cm^3) then acidified using 10% aqueous hydrochloric acid and finally extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with water (30 cm^3) then dried and evaporated to give the acid **7** which crystallised from benzene–ethanol (2:1 v/v) as a colourless powder (2.16 g, 82% from starting acid), m.p. 209–210 °C (decomp.) (lit.,[20] m.p. 205–206 °C), ν_{max}(KBr)/cm^{-1} 3100–2600 and 1650; δ_H-[$(CD_3)_2SO$] 3.68 (3 H, s, 1-Me), 7.03–7.43 (3 H, m, 4-, 5- and 6-H) and 7.70–8.00 (2 H, m, 2- and 7-H) (Found: C, 68.6; H, 5.3; N, 7.7. Calc. for $C_{10}H_9NO_2$: C, 68.6; H, 5.1; N, 8.0%).

Generation and Reactions of Lithium 2-Lithio-1-methylindole-3-carboxylate **8**.—*General Procedure.* Butyllithium (1.41 cm^3 of a 1.42 mol dm^{-3} solution in hexanes, 2 mmol) was added dropwise to diisopropylamine (0.3 cm^3, 2 mmol; distilled from potassium hydroxide and stored over molecular sieves) with stirring at −10 °C. After 0.25 h, the resulting viscous oil was diluted with tetrahydrofuran (THF) (4 cm^3) and the resulting solution cooled to below −70 °C (acetone–solid carbon dioxide bath) then treated dropwise with a solution of 1-methylindole-3-carboxylic acid **7** (0.17 g, 1 mmol) in THF (2.5 cm^3). The mixture was stirred at this temperature for 0.5 h and the resulting colourless suspension treated with an electrophile (1.2 mmol) which was added neat if a liquid or, if a solid, in THF solution (1 cm^3 $mmol^{-1}$). After the reaction period (see below), and unless otherwise stated, the reaction mixture was diluted with water (3–4 cm^3) and washed with diethyl ether (2 × 10 cm^3). The aqueous portion was acidified with 10% aqueous hydrochloric acid then extracted using diethyl ether (3 × 15 cm^3). The combined extracts were washed with saturated brine (30 cm^3) then dried and evaporated.

1-Methyl-2-trimethylsilylindole-3-carboxylic acid **9**. Chlorotrimethylsilane (0.28 cm^3) was added to the dianion **8** (1 mmol) prepared using the general procedure and the resulting mixture warmed to ambient temperature during 0.5 h. Following the addition of water (3 cm^3) and a solution of hydrochloric acid (2 mol dm^{-3}, 10 cm^3), the mixture was vigorously stirred for 0.5 h then diluted with water (10 cm^3) and extracted with diethyl ether (3 × 15 cm^3). The combined organic extracts were washed with brine (20 cm^3) then dried and evaporated. Crystallisation of the residue from ethanol gave the *silyl-acid* **9** (0.22 g, 88%) as colourless prisms, m.p. 190–191 °C, λ_{max}-(EtOH)/nm 230 and 298; ν_{max}(KBr)/cm^{-1} 3200–2300 and 1660; δ_H[$(CD_3)_2SO$] 0.37 (9 H, s, Me_3Si), 3.73 (3 H, s, 1-Me), 7.06–7.12 (2 H, m, 5- and 6-H), 7.25–7.43 (1 H, m, 4-H) and 7.79–7.85 (1 H, m, 7-H); *m/z* 247 (M^+, 22%), 232 (M − Me, 100), 188 (22), 158 (10), 130 (7) and 75 (18) (Found: C, 63.2; H, 6.7; N, 5.2. $C_{13}H_{17}NO_2Si$ requires C, 63.2; H, 6.9; N, 5.6%).

In another experiment on the same scale, samples of the dianion solution were withdrawn as the temperature was allowed to rise to ambient during 1.5 h and immediately quenched by addition to excess chlorotrimethylsilane. A gradual reduction in the amount of silylated product was noted, according to integration of the 1-methyl resonances of the starting acid (δ 3.68) and the product (δ 3.73); initially, the product **9** was formed in essentially quantitative yield. After 1.5 h, 83% of the silyl acid **9** was formed with the balance being the starting acid **8**.

2-(1-Hydroxy-1-phenylmethyl)-1-methylindole-3-carboxylic acid **10a**. Using the general procedure, addition of benzaldehyde (0.15 cm^3) to the dianion **8** followed by removal of the cooling

bath and stirring for a further 0.5 h and the usual work-up gave the *hydroxy-acid* **10a** which crystallised from ethanol as colourless prisms (0.25 g, 90%), m.p. 187–188 °C; λ_{max}(EtOH)/nm 231 and 289; ν_{max}(KBr)/cm^{-1} 3500–2300 and 1660; δ_H-[$(CD_3)_2SO$] 3.73 (3 H, s, 1-Me), 7.03–7.43 (8 H, m, 4-, 5- and 6-H and Ph) and 7.70–8.00 (2 H, m, 7-H and C*H*OH); *m/z* 281 (M^+, 100%), 263 (100), 248 (98), 234 (58), 218 (53), 186 (43), 158 (63) and 130 (33) (Found: C, 72.4; H, 5.6; N, 5.0. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%).

2-[1-*Hydroxy*-1-(4-*pyridyl*)*methyl*]-1-*methylindole*-3-*carboxylic acid* **10b**. Pyridine-4-carbaldehyde (0.42 cm^3) was added dropwise at −70 °C to the dianion **8** (1 mmol) according to the general procedure. After the addition, the cooling bath was removed and the solution stirred for a further 0.5 h, then worked up in the usual manner except that solid citric acid was used at the acidification step. This gave the *acid* **10b** (0.25 g, 90%) which crystallised from ethyl acetate as a colourless powder, m.p. 210–212 °C; λ_{max}(EtOH)/nm 230 and 292; ν_{max}(KBr)/cm^{-1} 3500–2200 and 1650; δ_H[$(CD_3)_2SO$] 3.58 (3 H, s, 1-Me), 6.86 (1 H, br s, OH), 7.20–7.28 (2 H, m, 5- and 6-H), 7.27 (1 H, sl. br s, 1′-H), 7.33 (2 H, d, *J* 5.5, 3- and 5-H of pyridyl), 7.44–7.47 (1 H, m, 4-H), 8.07–8.12 (1 H, m, 7-H), 8.53 (2 H, d, *J* 5.5, 2- and 6-H of pyridyl) and 12.58 (1 H, br s, CO_2H); *m/z* 282 (M^+, 100%), 264 (91), 186 (63), 158 (32) and 106 (25) (Found: C, 68.0; H, 5.2; N, 9.8. $C_{16}H_{14}N_2O_3$ requires C, 68.1; H, 5.0; N, 9.9%).

2-(1′-*Hydroxyheptyl*)-1-*methylindole*-3-*carboxylic acid* **10c**. By the general procedure, reaction between the dianion **8** (1 mmol) and heptanal (0.33 cm^3) at < −70 °C followed by warming to ambient temperature during 0.5 h and the usual work-up provided the *acid* **10c** (0.25 g, 85%) which crystallised from light petroleum as a colourless powder, m.p. 116–118 °C; λ_{max}(EtOH)/nm 230 and 290; ν_{max}(KBr)/cm^{-1} 3300–2400 and 1650; δ_H[$(CD_3)_2SO$] + 10% $CDCl_3$] 0.84 (3 H, br t, *J* *ca.* 7, 7′-Me), 1.05–1.45 (8 H, m), 1.50–2.00 (2 H, m, C*H*$_2$CHOH), 3.95 (3 H, s, 1-Me), 5.75 (1 H, t, *J* 7, C*H*OH), 7.10–7.40 (2 H, m, 5- and 6-H), 7.45–7.60 (1 H, m, 4-H) and 8.00–8.20 (1 H, m, 7-H); *m/z* 289 (M^+, 100%), 245 (57), 204 (89), 175 (86), 160 (84) and 77 (93) (Found: C, 70.9; H, 8.1; N, 4.7. $C_{17}H_{23}NO_3$ requires C, 70.6; H, 8.0; N, 4.8%).

Methyl 2-(1-*hydroxy*-1-*methylethyl*)-1-*methylindole*-3-*carboxylate* **11a**. Under the usual conditions, reaction between the dianion **8** (1 mmol) and acetone (0.21 cm^3) at −70 °C followed by warming to ambient temperature and the usual work-up gave a mixture of the starting acid **7** and the desired adduct with *ca.* 40% conversion; the mixture was esterified using diazomethane in the usual manner and separated by chromatography over silica gel eluted with hexane–ethyl acetate (2:1 v/v). The *product* **11a**, a thick oil (0.089 g, 36%), showed ν_{max}($CHCl_3$)/cm^{-1} 3490 and 1680; δ_H 1.53 (6 H, 2 × Me), 3.58 (3 H, s, 1-Me), 3.97 (3 H, s, CO_2Me) 7.06–7.12 (2 H, m, 5- and 6-H), 7.25–7.43 (1 H, m, 4-H) and 7.79–7.85 (1 H, m, 7-H) (Found: C, 68.5; H, 7.1; N, 5.6. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%).

Methyl 2-(1′-*hydroxy*-1′-*phenylethyl*)-1-*methylindole*-3-*carboxylate* **11b**. Acetophenone (0.25 cm^3) was added to a solution of the dianion **8** (1 mmol) at −70 °C; warming to ambient temperature and the usual work-up resulted in *ca.* 60% conversion to the desired adduct. The crude mixture was esterified using ethereal diazomethane in the usual way and the resulting mixture of esters separated by HPLC, using a 10μ porasil column, eluted with hexane–ethyl acetate (4:1 v/v). The *methyl ester* **11b** (0.15 g, 50%) crystallised from hexane–diethyl ether (2:1 v/v) as colourless prisms, m.p. 130–133 °C; λ_{max}(EtOH)/nm 237infl. and 292; ν_{max}(KBr)/cm^{-1} 3400–2400 and 1645; δ_H[$(CD_3)_2CO$] 2.27 (3 H, s, 1′-Me), 3.60 (3 H, s, 1-Me), 4.10 (3 H, s, OMe), 6.99 (1 H, br s, OH), 7.28–7.70 (8 H, m, 4-, 5- and 6-H and Ph) and 8.03–8.21 (1 H, m, 7-H); *m/z* 309 (M^+, 51%), 291 (49), 262 (100), 200 (37), 189 (11) and 158 (32) (Found: C, 73.6; H, 6.4; N, 4.2. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%).

Methyl 2-(*hydroxydiphenylmethyl*)-1-*methylindole*-3-*carboxylate* **11c**. By the general procedure, reaction between the dianion **8** (1 mmol) and benzophenone (0.46 g) at < −70 °C followed by warming to ambient temperature during 0.75 h and the usual work-up gave a mixture of the desired product and the starting acid **7**. A ^{1}H NMR spectrum indicated *ca.* 60% conversion. The mixture was treated with an excess of ethereal diazomethane at ambient temperature for 2 h, the resulting solution evaporated and the residue chromatographed over silica gel eluted with light petroleum (b.p. 60–80 °C)–ethyl acetate (1:1 v/v) to give the *ester* **11c** (0.20 g, 55%) as colourless prisms [from light petroleum–diethyl ether (2:1 v/v)], m.p. 173–174 °C; λ_{max}(EtOH)/nm 242; ν_{max}(KBr)/cm^{-1} 3600–2650 and 1660; δ_H[$(CD_3)_2SO$] 3.45 (3 H, s, 1-Me), 3.70 (3 H, s, OMe), 7.25–7.65 (13 H, m, 4-, 5- and 6-H and 2 × Ph) and 7.75–8.10 (1 H, m, 7-H); *m/z* 371 (M^+, 100%), 354 (7), 353 (5), 293 (34), 263 (69), 234 (28) and 189 (79) (Found: C, 77.6; H, 5.8; N, 3.4. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%).

1,2-*Dimethylindole*-3-*carboxylic acid* **12**. By the general procedure, treatment of the dianion **8** with iodomethane (0.35 cm^3) followed by warming to ambient temperature during 0.5 h, and the usual work-up gave the dimethyl acid **12** which crystallised from ethanol as colourless prisms (0.15 g, 82%), m.p. 204–205 °C (decomp.) [lit.,[21] m.p. 202–205 °C (decomp.)]; δ_H[$(CD_3)_2SO$] 2.76 (3 H, s, 2-Me), 3.73 (3 H, s, 1-Me), 7.06–7.12 (2 H, m, 5- and 6-H), 7.25–7.43 (1 H, m, 4-H) and 7.79–7.85 (1 H, m, 7-H); *m/z* 189 (M^+, 78%), 172 (96, M − Me), 158 (19), 144 (100, M − CO_2H), 128 (49), 117 (36) and 77 (78).

1-*Methoxymethylindole*-3-*carboxylic Acid* **13**.—Butyllithium (35 cm^3 of a 1.6 mol dm^{-3} solution in hexanes, 56 mmol) was added dropwise to a stirred solution of indole (5.9 g, 50 mmol) in dry THF (80 cm^3), maintained at −78 °C under nitrogen. The resulting cloudy mixture was warmed to 0 °C before re-cooling to −78 °C. Chloromethyl methyl ether (3.8 cm^3, 60 mmol) was then added dropwise, the cooling bath removed and the mixture stirred overnight.[7] Water (100 cm^3) was added and the organic phase separated. The aqueous phase was extracted with diethyl ether (2 × 50 cm^3) and the combined extracts washed with water (2 × 50 cm^3) then dried and evaporated. The residual red oil was distilled to give 1-methoxymethylindole (5.72 g, 72%) as a colourless oil, b.p. 89–91 °C at 0.1 mmHg (lit.,[7] b.p. 69–71 °C at 0.1 mmHg); δ_H 3.22 (3 H, s, OMe), 5.44 (2 H, s, C*H*$_2$OMe), 6.58 (1 H, d, *J* 4, 3-H) and 7.08–7.70 (5 H, m).

Trifluoroacetic anhydride (5.6 cm^3, 40 mmol) was added dropwise to an ice-cold, stirred solution of 1-methoxymethylindole (3.78 g, 36 mmol) in dry THF. The solution was then stirred without cooling for 1 h then evaporated. The residue was treated with a solution of sodium hydroxide (10 g) in water (200 cm^3) and the resulting mixture stirred at reflux for 8 h. The cooled mixture was filtered, washed with diethyl ether (2 × 50 cm^3), acidified using concentrated hydrochloric acid and finally extracted with ethyl acetate (3 × 50 cm^3). The combined organic extracts were washed with water (2 × 50 cm^3) then dried and evaporated. Crystallisation of the residue from ethyl acetate afforded the *acid* **13** (3.14 g, 42%) as a colourless solid, m.p. 161–163 °C (sealed capillary); λ_{max}(EtOH)/nm 281; ν_{max}($CHCl_3$)/cm^{-1} 3600–2200 and 1665; δ_H[$(CD_3)_2CO$] 3.29 (3 H, s, OMe), 5.64 (2 H, s, C*H*$_2$OCH$_3$), 7.21–7.41 (2 H, m, 5- and 6-H), 7.55–7.72 (1 H, m, 4-H) and 8.09–8.27 (2 H, m, 2- and 7-H) (Found: C, 64.2; H, 5.4; N, 6.7. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8%).

General Procedure for the Generation of Dianion **14** *from* 1-*Methoxymethylindole*-3-*carboxylic Acid* **13**.—Lithium diisopropylamide (2.2 mmol) was generated by the dropwise

addition of butyllithium (1.4 cm^3 of a 1.6 mol dm^{-3} solution in hexanes, 2.2 mmol) to a stirred solution of diisopropylamine (0.4 cm^3, 2.5 mmol) in THF (10 cm^3) cooled to *ca.* −50 °C. After 0.5 h, the resulting solution was cooled in an acetone–solid carbon dioxide bath and a solution of 1-methoxymethylindole-3-carboxylic acid **13** (0.205 g, 1 mmol) in THF (2 cm^3) was added dropwise. After 0.5 h at this temperature, the electrophile was added and the resulting mixture warmed to ambient temperature during 0.5 h then evaporated to dryness. The residue was partitioned between ethyl acetate (25 cm^3) and aqueous citric acid [0.6 g, in water (20 cm^3)] and the separated aqueous layer further extracted using ethyl acetate (2 × 25 cm^3). The combined organic extracts were washed with water (20 cm^3) then dried and evaporated and the residue purified as described below. All reactions were carried out on this scale.

Reaction between dianion **14** *and iodomethane.* Addition of iodomethane (0.5 cm^3) to the dianion **14** by the general procedure led to an inseparable mixture (0.205 g) of the starting acid **13** and 1-methoxymethyl-2-methylindole-3-carboxylic acid **15**. Integration of the signals in the ^1H NMR spectrum for the methoxy group (δ_H 3.26) and the new methyl group (δ_H 2.80) showed that a 70% conversion into the desired product had occurred. The sample was not further characterised.

Methyl 2-(1-hydroxy-1-phenylmethyl)-1-methoxymethylindole-3-carboxylate **16a**. The dianion **14** was quenched by the addition of benzaldehyde (0.5 cm^3); following the usual work-up, the residue was esterified by the addition of an excess of ethereal diazomethane and the resulting mixture of esters separated by column chromatography over silica gel eluted with dichloromethane–light petroleum (2:1) to give the *ester* **16a** as a colourless oil (0.210 g, 67%); λ_{max}(EtOH)/nm 231 and 286; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 and 1675; δ_H 3.18 (3 H, s, CH_2OMe), 3.92 (3 H, s, CO_2Me), 5.63 (2 H, s, CH_2OMe), 5.82 (1 H, d, *J* 11, CHO*H*), 6.77 (1 H, d, *J* 11, C*H*OH), 7.20–7.60 (8 H, m, 4-, 5- and 6-H and Ph) and 8.10–8.30 (1 H, m, 7-H); *m/z* 325 (M^+, 34%), 293 (27), 262 (34), 261 (100), 248 (60), 232 (27), 204 (68), 107 (35), 105 (24), 91 (39) and 77 (40) (Found: M^+, 325.1311. $C_{19}H_{19}NO_4$ requires *M*, 325.1314).

Methyl 2-(1′-hydroxybutyl)-1-methoxymethylindole-3-carboxylate **16b**. Reaction between the dianion **14** and butanal (0.5 cm^3) in the usual way led to a mixture which was esterified using diazomethane. Separation by column chromatography using dichloromethane as the eluent afforded the *ester* **16b** as a pale yellow oil (0.083 g, 28%); λ_{max}(EtOH)/nm 230, 285infl. and 289.5; ν_{max}(film)/cm^{-1} 3370 and 1665; δ_H 0.95 (3 H, t, *J* 7, 4′-CH_3), 1.18–1.78 (4 H, m, 2 × CH_2), 3.31 (3 H, s, CH_2OMe), 4.00 (3 H, s, CO_2Me), 5.05–5.31 (1 H, m, 1′-H), 5.58 (2 H, s, CH_2OMe), 5.84 (1 H, d, *J* 11, CHO*H*), 7.00–7.59 (3 H, m, 4-, 5- and 6-H) and 8.09–8.26 (1 H, m, 7-H); *m/z* 291 (M^+, 12%), 259 (11), 248 (13), 216 (90), 188 (14) and 45 (100) (Found: M^+, 291.1468. $C_{16}H_{21}NO_4$ requires *M*, 291.1471).

Methyl 2-(1′-hydroxy-1′-methylpropyl)-1-methoxymethylindole-3-carboxylate **16c**. By the general procedure, reaction between dianion **14** and butanone (0.5 cm^3) followed by esterification using diazomethane and column chromatography using diethyl ether–light petroleum (1:1.5) as eluent gave the *ester* **16c** as an oil (0.051 g, 18%); λ_{max}(EtOH)/nm 283.5 and 291; $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 1680; δ_H 1.10 (3 H, t, *J* 7, 3′-CH_3), 1.80 (3 H, s, 1′-CH_3), 2.25 (2 H, sept., *J* 7, 3′-CH_2), 3.30 (3 H, s, CH_2OMe), 3.95 (3 H, s, CO_2Me), 5.67 (2 H, s, CH_2OMe), 5.72 (1 H, br s, OH), 7.10–7.60 (3 H, m, 4-, 5- and 6-H) and 7.90–8.10 (1 H, m, 7-H); *m/z* 291 (M^+, 12%), 260 (11), 259 (37), 230 (100) and 228 (18) (Found: M^+, 291.1486).

Methyl 2-(hydroxydiphenylmethyl)-1-methoxymethylindole-3-carboxylate **16d**. A solution of benzophenone (0.275 g, 1.5 mmol) in THF (1 cm^3) was added dropwise to the dianion **14** formed in the usual manner. Work-up and esterification as described above followed by column chromatography over silica gel eluted by diethyl ether–light petroleum (1:2) separated the *ester* **16d** as a colourless gum (0.119 g, 31%); λ_{max}(EtOH)/nm 285; $\nu_{max}(CHCl_3)/cm^{-1}$ 3380 and 1675; δ_H 2.93 (3 H, s, CH_2OMe), 3.70 (3 H, s, CO_2Me), 4.86 (2 H, s, CH_2OMe), 7.27–7.53 (14 H, m, 4-, 5- and 6-H and 2 × Ph) and 8.03–8.19 (1 H, m, 7-H); *m/z* 401 (M^+, 61%), 369 (94), 338 (12), 325 (44), 294 (16), 280 (100), 167 (39), 105 (39), 91 (38) and 77 (53) (Found: M^+, 401.1611. $C_{25}H_{23}NO_4$ requires *M*, 401.1627).

N,N-Diethyl-1-methoxymethylindole-3-carboxamide **17**.—Oxalyl chloride (2.0 cm^3, 23 mmol) was added dropwise to a stirred suspension of 1-methoxymethylindole-3-carboxylic acid **13** (3.14 g, 15 mmol) in dry benzene (50 cm^3) at ambient temperature. After 4 h, the volatiles were removed under reduced pressure to leave a brown oil which was immediately dissolved in dry benzene (40 cm^3). The resulting solution was cooled in ice-water and treated dropwise with stirring with dry diethylamine (3.2 cm^3, 31 mmol). The mixture was stirred overnight at ambient temperature then diluted with diethyl ether (50 cm^3) and washed successively with a 2 mol dm^{-3} solution of hydrochloric acid (2 × 50 cm^3), a 2 mol dm^{-3} solution of sodium hydroxide (2 × 25 cm^3) and water (2 × 50 cm^3) then dried and evaporated. Trituration of the residue with light petroleum gave the *amide* **17** (2.53 g, 64%), m.p. 76–77 °C; λ_{max}(EtOH)/nm 279; $\nu_{max}(CHCl_3)/cm^{-1}$ 1610; δ_H 1.19 (6 H, t, *J* 7, 2 × CH_2CH_3), 3.15 (3 H, s, CH_2OCH_3), 3.54 (4 H, q, *J* 7, 2 × CH_2CH_3), 5.31 (2 H, s, CH_2OMe), 7.13–7.53 (4 H, m, 4-, 5- and 6-H) and 7.76–7.91 (1 H, m, 7-H); *m/z* 260 (M^+, 51%), 229 (26), 188 (100) and 129 (89) (Found: C, 69.1; H, 8.0; N, 10.8; M^+, 260.1528. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.8; N, 10.8%; *M*, 260.1527).

General Method for the Generation and Reactions of Anion **18** *from* N,N-*Diethyl-1-methoxymethylindole-3-carboxamide* **17**.—Butyllithium (0.8 cm^3 of a 1.6 mol dm^{-3} solution in hexanes, 1.3 mmol) was added dropwise to solution of the amide **17** (0.26 g, 1 mmol) in tetrahydrofuran (10 cm^3), stirred and cooled in an acetone–solid carbon dioxide bath. After 0.5 h, a white precipitate of the anion **18** had formed which was quenched as indicated. All the following reactions were carried out on this scale.

N,N-Diethyl-1-methoxymethyl-2-methylindole-3-carboxamide **19a**. Iodomethane (0.4 cm^3) was added dropwise to the anion suspension, the cooling bath removed and the mixture stirred for 0.5 h before removal of the solvents under reduced pressure. The residue was partitioned between diethyl ether (10 cm^3) and water (10 cm^3). The separated aqueous layer was further extracted with diethyl ether (3 × 15 cm^3) and the combined ethereal solutions washed with saturated aqueous sodium metabisulfite (10 cm^3) and water (2 × 10 cm^3) then dried and evaporated to leave the *amide* **19a** as a pale yellow oil (0.25 g, 91%); λ_{max}(EtOH)/nm 279; $\nu_{max}(CHCl_3)/cm^{-1}$ 1605; δ_H 1.17 (6 H, t, *J* 7, 2 × CH_2CH_3), 2.50 (3 H, s, 2-CH_3), 3.28 (3 H, s, CH_2OCH_3), 3.53 (4 H, q, *J* 7, 2 × CH_2CH_3), 5.45 (2 H, s, CH_2OMe) and 7.16–7.64 (4 H, m); *m/z* 274 (M^+, 43%), 243 (21), 202 (100) and 175 (16) (Found: M^+, 274.1663. $C_{16}H_{22}N_2O_2$ requires *M*, 274.1681). The sample was pure according to ^1H NMR and TLC analysis.

N,N,2-Triethyl-1-methoxymethylindole-3-carboxamide **19b**. Iodoethane (0.4 cm^3) was added dropwise to the anion suspension, the cooling bath removed and the mixture stirred for 0.5 h before removal of the solvents under reduced pressure. The residue was partitioned between diethyl ether (10 cm^3) and water (10 cm^3). Work-up as in the foregoing example left the 2-*ethylamide* **19b** as a pale yellow oil (0.25 g, 86%); λ_{max}(EtOH)/nm 279; $\nu_{max}(CHCl_3)/cm^{-1}$ 1605; δ_H 1.00–1.43 (9 H, m, 3 × CH_2CH_3), 2.47 (2 H, q, *J* 8.3, 2-CH_2CH_3), 3.31 (3 H, s, CH_2OCH_3), 3.36–3.75 (4 H, m, 2 × CH_2CH_3), 5.47 (2 H, s,

CH_2OMe) and 7.15–7.64 (4 H, m); *m/z* 288 (M^+, 36%), 257 (22), 216 (100), 188 (20) and 45 (71) (Found: M^+, 288.1845. $C_{17}H_{24}N_2O_2$ requires *M*, 288.1838). The sample was pure according to ^1H NMR and TLC analysis.

N,N-*Diethyl*-2-(1′-*hydroxy*-1′-*phenylmethyl*)-1-*methoxymethylindole*-3-*carboxamide* **19c**. Reaction between the anion **18** and benzaldehyde (0.25 cm^3) was carried out as described above but omitting the metabisulfite wash. The crude product, a yellow oil, was purified by column chromatography over silica gel eluted with diethyl ether–light petroleum (1:1) to give the *hydroxyamide* **19c** (0.303 g, 82%) as colourless crystals, m.p. 103–105 °C; λ_{max}(EtOH)/nm 281; $\nu_{max}(CHCl_3)/cm^{-1}$ 3310 and 1590; δ_H 0.50–1.30 (6 H, m, 2 × CH_2CH_3), 2.99–3.65 (4 H, m, 2 × CH_2CH_3), 3.24 (3 H, br s, CH_2OCH_3), 5.49 (2 H, br s, CH_2OMe), 6.18 (2 H, br s, OH and 1′-CH) and 7.03–7.65 (9 H, m); *m/z* 366 (M^+, 31%), 292 (15), 261 (75), 204 (17), 107 (22), 105 (18), 91 (25), 72 (22) and 45 (100) (Found: C, 72.2; H, 7.3; N, 7.8%; M^+, 366.1940. $C_{22}H_{26}N_2O_3$ requires C, 72.1; H, 7.2; N, 7.7%; *M*, 366.1943).

N,N-*Diethyl*-2-(1′-*hydroxybutyl*)-1-*methoxymethylindole*-3-*carboxamide* **19d**. Using butanal (0.4 cm^3) as the electrophile and following the foregoing procedure except that diethyl ether–light petroleum (1:4) was used as the chromatography solvent gave the *hydroxyamide* **19d** (0.22 g, 66%) which crystallised from light petroleum as a colouress powder, m.p. 86–87 °C; λ_{max}(EtOH)/nm 281; $\nu_{max}(CHCl_3)/cm^{-1}$ 3350 and 1595; δ_H 0.90 (3 H, t, *J* 8, 4′-Me), 1.02–1.60 (8 H, m, 3′-CH_2 and 2 × NCH_2CH_3), 1.60–2.08 (2 H, m, 2′-CH_2), 3.25 (3 H, s, CH_2OCH_3), 3.31–3.90 (4 H, m, 2 × CH_2CH_3), 4.89 (1 H, m, CHOH), 5.50 (2 H, s, CH_2OMe) and 7.09–7.56 (4 H, m); *m/z* 332 (M^+, 37%), 314 (24), 301 (13), 289 (13), 285 (12), 271 (12), 258 (17), 242 (41), 228 (30), 227 (40), 216 (60), 100 (18), 72 (17) and 45 (100) (Found: C, 68.2; H, 8.7; N, 8.5%; M^+, 332.2099. $C_{19}H_{28}N_2O_3$ requires C, 68.6; H, 8.5; N, 8.4%; *M*, 332.2100).

N,N-*Diethyl*-2-(1′-*hydroxy*-1′-*phenylethyl*)-1-*methoxymethylindole*-3-*carboxamide* **19e**. Using acetophenone (0.3 cm^3) as the electrophile and following the foregoing procedure, except that column chromatography was carried out using a solvent gradient from diethyl ether–light petroleum (4:1) up to neat diethyl ether, led to the *hydroxyamide* **19e** (0.10 g, 26%) as a colourless powder, m.p. 128–129 °C; λ_{max}(EtOH)/nm 274; $\nu_{max}(CHCl_3)/cm^{-1}$ 3390 and 1610; δ_H[$(CD_3)SO$; 400 MHz] as two rotamers (**a** and **b**, in a ratio of 7:2) at 296 K 1.03 (rot **b**, partly obscured, 3 H, *J ca.* 7, NCH_2CH_3), 1.08 (rot **a**, 3 H, *J* 7, NCH_2CH_3), 1.19 (rot **b**, partly obscured, 3 H, *J ca.* 7, NCH_2CH_3), 1.21 (rot **a**, 3 H, *J* 7, NCH_2CH_3), 1.80 (rot **a**, 3 H, sl br s, 1′-CH_3), 1.86 (rot **b**, 3 H, sl br s, 1′-CH_3), 3.28 (rot **b**, 1 H, partly obscured m, $NCH_aH_bCH_3$), 3.37 (rot **a** and **b**, 3 H, s, OCH_3), 3.42 (rot **b**, 1 H, partly obscured m, $NCH_aH_bCH_3$), 3.45 (rot **a**, 1 H, m, $NCH_aH_bCH_3$), 3.64 (rot **a**, 1 H, dq, *J* 14 and 7, $NCH_aH_bCH_3$), 5.21 (rot **b**, 2 H, AB system, $J_{A,B}$ 11, $NCH_AH_BOCH_3$), 5.37 (rot **a**, 2 H, AB system, $J_{A,B}$ 11, $NCH_AH_BOCH_3$), 6.31 (rot **b**, 1 H, s, OH), 6.38 (rot **a**, 1 H, s, OH) and 7.07–7.48 (9 H, m); *m/z* 380 (M^+, 74%), 362 (47), 333 (13), 308 (10), 290 (66), 277 (19), 276 (100), 100 (19), 91 (18), 77 (10) and 72 (16) (Found: C, 72.6; H, 7.4; N, 7.7%; M^+, 380.2117. $C_{23}H_{28}N_2O_3$ requires C, 72.6; H, 7.4; N, 7.4%; *M*, 380.2100). At higher temperatures, all the rotameric resonances began to coalesce.

N,N-*Diethyl*-1-*phenylsulfonylindole*-3-*carboxamide* **20a**.—Oxalyl chloride (11.5 cm^3, 130 mmol) was added dropwise to a stirred suspension of aluminium trichloride (17.4 g, 130 mmol) in dichloromethane (120 cm^3) cooled to 0 °C. After 0.5 h, 1-phenylsulfonylindole[14] (6.77 g, 26 mmol) in dichloromethane was added dropwise.[15] The cooling bath was removed and the mixture stirred for 2 h then poured onto crushed ice. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 50 cm^3). The combined organic solutions were washed with water (2 × 50 cm^3) then dried and evaporated. The residue was dissolved in benzene (100 cm^3) and diethylamine (10 cm^3) was carefully added. The resulting mixture was stirred at ambient temperature overnight then washed successively with aqueous solutions of hydrochloric acid (2 mol dm^{-3}) and sodium hydroxide (2 mol dm^{-3}) and water (2 × 50 cm^3 of each) then dried and evaporated. Crystallisation of the residue from diethyl ether–light petroleum gave the *amide* **20a** (3.06 g, 33% overall) as a colourless powder, m.p. 127–130 °C; λ_{max}(EtOH)/nm 249; $\nu_{max}(CHCl_3)/cm^{-1}$ 1610; δ_H 1.22 (6 H, t, *J* 7, 2 × NCH_2CH_3), 3.50 (4 H, q, *J* 7, 2 × NCH_2CH_3) and 7.32–8.21 (10 H, m); *m/z* 356 (M^+, 41%), 284 (100), 215 (83), 141 (36), 115 (14), 77 (65) and 72 (12) (Found: C, 64.3; H, 5.9; N, 7.8%; M^+, 356.1185. $C_{19}H_{20}N_2O_3S$ requires C, 64.0; H, 5.7; N, 7.9%; *M*, 356.1195).

General Method for the Preparation and Reactions of the Anion **20b** *Derived from* N,N-*Diethyl*-1-*phenysulfonylindole*-3-*carboxamide* **20a**.—Butyllithium (0.4 cm^3 of a 1.6 mol dm^{-3} solution in hexanes, 0.64 mmmol) was added dropwise to a stirred solution of the indole amide **20a** (0.178 g, 0.5 mmol) in THF (10 cm^3), maintained below −70 °C by use of an acetone–solid carbon dioxide bath. The resulting orange solution was stirred at this temperature for 0.5 h then treated with an electrophile. All subsequent reactions were performed on this scale.

N,N-*Diethyl*-2-*methylindole*-3-*carboxamide* **21a**. The solution of anion **20b** was treated with iodomethane (0.2 cm^3) and then allowed to reach ambient temperature during 3 h. The solvents were removed under reduced pressure and the residue stirred with methanol (10 cm^3) and aqueous sodium hydroxide (3 mol dm^{-3}; 5 cm^3) overnight. The bulk of the methanol was then evaporated under reduced pressure and the remaining material partitioned between ethyl acetate (15 cm^3) and water (15 cm^3). The separated aqueous layer was further extracted with ethyl acetate (2 × 15 cm^3) and the combined organic solutions washed with aqueous sodium thiosulfate (20 cm^3) and water (2 × 15 cm^3) then dried and evaporated to give the *amide* **21a** (0.085 g, 75%), m.p. 153–155 °C (diethyl ether–light petroleum); λ_{max}(EtOH)/nm 282; $\nu_{max}(CHCl_3)/cm^{-1}$ 3475 and 1600; δ_H 1.05 (6 H, t, *J* 7, 2 × NCH_2CH_3), 1.78 (3 H, s, 2-Me), 3.45 (4 H, q, *J* 7, 2 × NCH_2CH_3) and 6.90–7.55 (4 H, m); *m/z* 230 (M^+, 32%), 158 (100) and 72 (9) (Found: C, 73.4; H, 7.9; N, 12.25%; M^+, 230.1406. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%; *M*, 230.1419).

N,N,2-*Triethylindole*-3-*carboxamide* **21b**. An identical experiment to the foregoing, except that iodoethane (0.3 cm^3) was used as the electrophile, gave the *amide* **21b** (0.086 g, 70%) as a colourless powder, m.p. 150–153 °C (diethyl ether–light petroleum), λ_{max}(EtOH)/nm 282; $\nu_{max}(CHCl_3)/cm^{-1}$ 3470 and 1605; δ_H 0.93–1.33 (9 H, m, 3 × CH_2CH_3), 2.49 (2 H, q, *J* 7, 2-CH_2CH_3), 3.55 (4 H, q, *J* 7, 2 × NCH_2CH_3), 7.03–7.59 (4 H, m) and 9.89 (1 H, br s, NH); *m/z* 244 (M^+, 31%), 215 (8), 172 (100), 144 (10) and 72 (7) (Found: M^+, 244.1575. $C_{15}H_{20}N_2O$ requires *M*, 244.1575).

N,N-*Diethyl*-2-(1′-*hydroxy*-1-*phenylmethyl*)*indole*-3-*carboxamide* **21c**. In the same way as in the foregoing experiment, but omitting the thiosulfate wash, addition of benzaldehyde (0.3 cm^3, 2.86 mmol) to the anion **20b** gave the *hydroxyamide* **21c** (0.141 g, 88%) as a colourless solid, m.p. 113–117 °C (diethyl ether–light petroleum); λ_{max}(EtOH)/nm 283; $\nu_{max}(CHCl_3)/cm^{-1}$ 3445, 3290 and 1590; δ_H 0.96 (6 H, t, *J* 7, 2 × NCH_2CH_3), 3.46 (4 H, q, *J* 7, 2 × NCH_2CH_3), 6.09 (2 H, br s, OH and 1′-CH), 7.06–7.59 (4 H, m) and 9.41 (1 H, br, NH); *m/z* 332 (M^+, 55%), 250 (78), 249 (95), 248 (100), 232 (47), 204 (59), 105 (29), 89 (21), 77 (35) and 72 (29) (Found: C, 74.3; H, 7.2; N, 8.7%; M^+, 322.1679. $C_{20}H_{22}N_2O_2$ requires C, 74.5; H, 6.9; N, 8.7%; *M*, 322.1681).

N,N-*Diethyl*-2-(1'-*hydroxybutyl*)*indole*-3-*carboxamide* **21d**. By the general procedure, but omitting the thiosulfate wash, reaction of the anion **20b** with butanal (0.3 cm^3, 3.4 mmol) gave an oil which was purified by column chromatography (diethyl ether–light petroleum, gradient from 1:4 to 4:1) to give the *hydroxyamide* **21d** (0.122 g, 88%), as a colourless gum; λ_{max}(EtOH)/nm 282 and 289; ν_{max}($CHCl_3$)/cm^{-1} 3390, 3180 and 1585; δ_H 0.90 –1.90 (10 H, m, 2'-CH_2, 3'-CH_2 and 2 × NCH_2CH_3), 1.25 (3 H, t, *J* 7, 4'-Me), 3.58 (4 H, q, *J* 7, 2 × NCH_2CH_3), 4.87 (1 H, t, *J* 7, C*H*OH), 7.00–7.52 (4 H, m) and 10.10 (1 H, br s, NH); *m*/*z* 288 (M^+, 59%), 270 (11), 259 (13), 216 (32), 215 (57), 214 (71), 198 (28), 186 (23), 74 (100) and 72 (23) (Found: M^+, 288.1844. $C_{17}H_{24}N_2O_2$ requires *M*, 288.1838).

N,N-*Diethyl*-2-*methyl*-1-*phenylsulfonylindole*-3-*carboxamide* **22a**. The anion **20b** (1.44 mmol) was generated in the usual manner and treated with iodomethane (1 cm^3). The cooling bath was removed and after 0.5 h, saturated aqueous ammonium chloride (20 cm^3) was added. The organic layer was separated and the aqueous phase extracted with ethyl acetate (2 × 20 cm^3). The combined organic solutions were washed with aqueous sodium thiosulfate (20 cm^3) and water (20 cm^3) then dried and evaporated. The residual yellow oil was triturated with light petroleum to give the *sulfonylindole* **22a** (0.399 g, 75%) as a pale yellow powder, m.p. 87 °C; λ_{max}(EtOH)/nm 255 and 288infl.; ν_{max}($CHCl_3$)/cm^{-1} 1610; δ_H 0.75–1.10 (3 H, m, NCH_2CH_3), 1.10–1.47 (3 H, m, NCH_2CH_3), 2.61 (3 H, s, 2-Me), 2.97–3.38 (2 H, m, NCH_2CH_3), 3.38–3.80 (2 H, m, NCH_2CH_3), 7.27–7.70 (6 H, m), 7.83–7.99 (2 H, m) and 8.23–8.34 (1 H, m); *m*/*z* 370 (M^+, 40%), 298 (100), 229 (65), 157 (61), 129 (18), 77 (73) and 72 (40) (Found: C, 65.0; H, 5.9; N, 7.4%; M^+, 370.1388. $C_{20}H_{22}N_2O_3S$ requires C, 64.9; H, 6.0; N, 7.6%; *M*, 370.1351).

N,N,2-*Triethyl*-1-*phenylsulfonylindole*-3-*carboxamide* **22b**. By the foregoing method on a 5 mmol scale and using iodoethane (0.5 cm^3) as the electrophile, the 2-*ethylindole* **22b** was prepared. The final product crystallised from diethyl ether as yellow prisms (1.37 g, 71%), m.p. 103–105 °C; λ_{max}(EtOH)/nm 256 and 288infl.; ν_{max}($CHCl_3$)/cm^{-1} 1610; δ_H 1.19 (9 H, m, 3 × CH_2CH_3), 3.10 (2 H, br q, *J ca.* 7, 2-CH_2CH_3), 3.34–3.87 (4 H, m, NCH_2CH_3), 7.31–7.67 (6 H, m), 7.84–7.91 (2 H, m) and 8.26–8.34 (1 H, m); *m*/*z* 384 (M^+, 18%), 312 (34), 243 (100), 171 (23), 170 (50), 143 (29), 100 (19), 77 (40) and 72 (21) (Found: C, 65.5; H, 6.3; N, 7.0%; M^+, 384.1491. $C_{21}H_{24}N_2O_3S$ requires C, 65.5; H, 6.3; N, 7.3%; *M*, 384.1508).

N,N,2-*Triethyl*-1-*phenylsulfonylindole*-3-*carboxamide* **22b** *by Metallation of the* 2-*Methylindole*-3-*carboxamide* **22a**.—Butyllithium (0.1 cm^3 of a 1.6 mol dm^{-3} solution in hexanes, 0.16 mmol) was added to a stirred solution of the amide **22a** (0.045 g, 0.12 mmol) in THF (5 cm^3) cooled in an acetone–solid carbon dioxide bath. A maroon colouration developed rapidly and was immediately quenched by the addition of iodomethane (0.15 cm^3). Following the work-up procedure described above for the same compound led to a product (0.042 g) which contained > 90% of the desired homologated amide **22b**, which was identical, according to IR, MS and NMR data, with the foregoing sample. Careful integration of the ^1H NMR spectrum along with TLC data indicated the presence in the sample of *ca.* 7% of the starting 2-methylindole-3-carboxamide **22a** together with a trace of the desulfonylated starting material, *N*,*N*-diethyl-2-methylindole-3-carboxamide **21a**.

N,N-*Diethyl* 2-*isopropyl*-1-*phenylsulfonylindole*-3-*carboxamide* **25**. A solution of the 2-ethylindole **22b** (0.193 g, 0.5 mmol) in THF (5 cm^3) was added dropwise to a stirred solution of lithium diisopropylamide (0.7 mmol), prepared as described above, in THF (5 cm^3) cooled in an acetone–solid carbon dioxide bath. A deep maroon colouration developed immediately. After 0.5 h, iodomethane (0.5 cm^3) was added dropwise and the colour discharged. The resulting mixture was warmed to ambient temperature during 0.5 h then worked up as described for **22b** above. The product was purified by column chromatography (diethyl ether–light petroleum, gradient from 1:4 to 1:1) to give the *amide* **25** (0.094 g, 47%) as a colourless crystalline solid, m.p. 78–80 °C; λ_{max}(EtOH)/nm 257 and 289infl.; ν_{max}($CHCl_3$)/cm^{-1} 1615; δ_H 0.92 (6 H, t, *J* 7, 2 × NCH_2CH_3), 1.10–1.44 [6 H, m, $CH(CH_3)_2$], 3.09 (2 H, q, *J* 7, NCH_2CH_3), 3.47–4.10 [3 H, m, $CH(CH_3)_2$ and NCH_2CH_3] and 7.23–7.84 (9 H, m); *m*/*z* 398 (M^+, 10%), 326 (17), 257 (100), 184 (73), 170 (21), 100 (44), 77 (25) and 72 (11) (Found: C, 66.3; H, 6.8; N, 6.4%; M^+, 398.1672. $C_{22}H_{26}N_2O_3S$ requires C, 66.3; H, 6.6; N, 7.0%; *M*, 398.1664). Starting material **22b** (0.087 g) was also isolated.

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