Synthesis of the Naturally Occurring Indolequinone BE 10988, an Inhibitor of Topoisomerase II[1]

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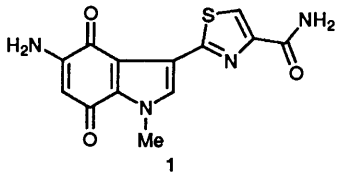
A short synthesis (28% overall yield) of the naturally occurring indolequinone BE 10988 **1** is described. The synthesis starts from 4-benzyloxy-5-methoxyindole and involves, as key steps, the use of chlorosulfonyl isocyanate to introduce the amide side-chain into the indole 3-position, followed by thioamide formation and construction of the thiazole ring using a Hantzsch reaction.

Topoisomerases, DNA-modifying enzymes, are becoming increasingly important as biological targets for potential anticancer agents,[2] and in the search for new compounds of this type, natural products have produced interesting leads.[3] One example of this is the compound designated BE 10988, a potent inhibitor of topoisomerase II, recently isolated from culture broths by Japanese workers.[4,5] The structure of BE 10988 **1**, which contains a novel thiazole substituted indolequinone, was established by spectroscopic methods. In view of our own interest in indolequinones and their anticancer properties,[6,7] we decided to investigate the synthesis of BE 10988. The details of this first synthesis of the natural product are reported herein;[1] a second synthesis has recently been published.[8]



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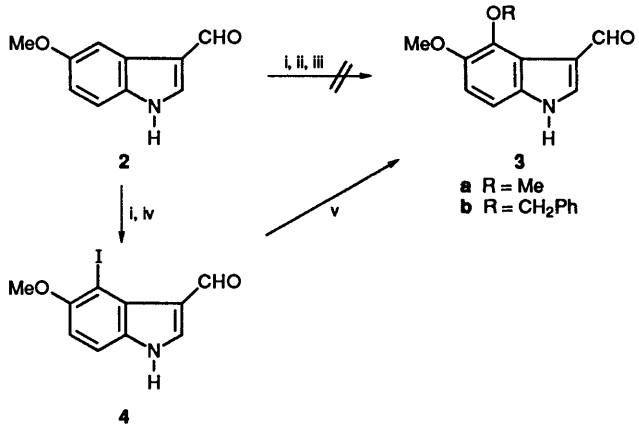
BE 10988

Results and Discusion

The overall strategy for the synthesis of BE 10988 was based on (a) the construction of the thiazole ring using a classical Hantzsch reaction and (b) the formation of the key 5-aminoindole-4,7-quinone unit from the corresponding 5-methoxyindolequinone, itself derived by oxidation of a 4- (or 7-) hydroxyindole. Therefore, we investigated several approaches to the required indole.

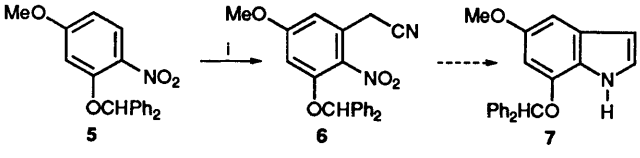
The first approach was based on the reported conversion of indole-3-carbaldehyde into 4-alkoxyindoles by reaction with thallium(III) trifluoroacetate, followed by iodine and the alkoxide.[9] Attempts to carry out a similar reaction on 5-methoxyindole-3-carbaldehyde **2**, readily prepared by formylation of commercially available 5-methoxyindole, were unsuccessful, and none of the desired product **3** was obtained. The conversion could be carried out by isolation of the intermediate iodide **4** (70% on a small scale),[10] followed by reaction with the sodium salts of methanol or benzyl alcohol in the presence of copper(I) iodide (Scheme 1). However the yields of **3** were low (R = Me, 22%; R = CH_2Ph, 19%) and the method was not considered viable on a larger scale.

Secondly, we investigated the indole synthesis described by Makosza and co-workers based on the reductive cyclisation of *ortho*-nitrophenylacetonitriles, prepared by vicarious nucleophilic substitution (VNS) of hydrogen *ortho* to the nitro group.[11] The required starting material, the protected nitrophenol **5** was readily prepared from 3-methoxyphenol by nitration,[12] followed by *O*-alkylation. Unfortunately, the key VNS step using 4-chlorophenoxyacetonitrile gave the required *ortho*-nitrophenylacetonitrile **6** in only 20% yield and, therefore,



Scheme 1 *Reagents:* i, $(CF_3CO_2)_3Tl$, CF_3CO_2H; ii, CuI, I_2; iii, NaOR (R = Me or CH_2Ph); iv, aq. KI; v, CuI, NaOR (R = Me or CH_2Ph)

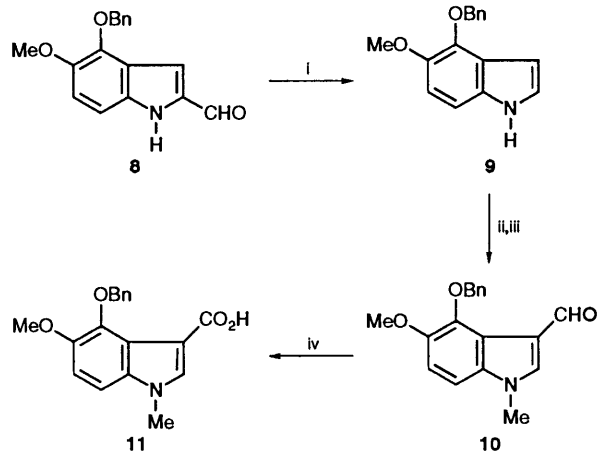
the cyclisation to the indole **7** was not investigated further (Scheme 2). We also attempted to prepare the indole **7** by reaction of the nitro compound **5** with vinylmagnesium bromide, in the so-called Bartoli reaction,[13] again without success.



Scheme 2 *Reagents:* i, 4-chlorophenoxyacetonitrile, Bu'OK, DMF

With the failure to prepare the appropriately substituted indole by the above routes, we decided to use a starting material, 4-benzyloxy-5-methoxyindole-2-carbaldehyde **8**, that was readily available to us from our work on the synthesis of mitomycin analogues.[7,14,15] This indole is easily prepared on a 10 g-scale using the route described for its 6-methyl derivative,[7] and can be decarbonylated to the indole **9** in high yield using a rhodium catalyst.[16] Decarboxylation of the corresponding carboxylic acid was unsatisfactory. Initial attempts to introduce the correct side chain into the indole 3-position were based on Vilsmeier formylation (69%) to give, after *N*-methylation (78%), the indole-3-carbaldehyde **10** (Scheme 3). However, the subsequent oxidation to the carboxylic acid **11** using potassium permanganate[17] proceeded in poor yield. This oxidation step was investigated in more detail using other reagents for conversion of aldehydes into acids (silver nitrate, pyridinium dichromate), or directly into amides (nickel peroxide/ ammonia,[18] sodium cyanide/ ammonia/manganese dioxide,[19] *N*-bromosuccinimide/ammonia[20]), although none of these methods showed any improvements over the original.

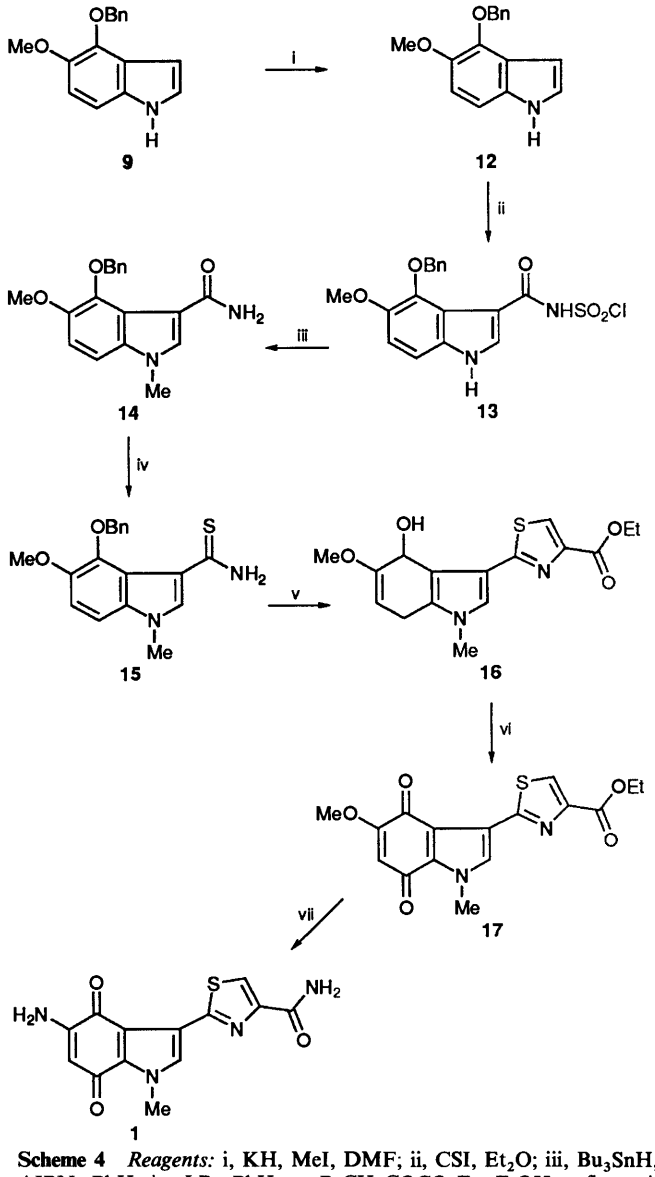
The problem was solved by use of the highly electrophilic chlorosulfonyl isocyanate (CSI) to introduce the amide side



Scheme 3 *Reagents:* i, $[Rh(Ph_3P)_2CO]Cl$, $Ph_2P(CH_2)_3PPh_2$, mesitylene; ii, $POCl_3$, DMF; iii, MeI, KH, DMF; iv, $KMnO_4$, acetone

chain directly into the indole 3-position.[21] Thus, reaction of the *N*-methylindole **12** with freshly distilled CSI in dry ether resulted in precipitation of the *N*-chlorosulfonylamide **13** in excellent yield (97%) (Scheme 4). Attempts to remove the chlorosulfonyl group under the usual reductive hydrolytic conditions (Na_2SO_3–KOH) were unsuccessful[22] and, therefore, a new procedure was developed involving treatment of the chlorosulfonylamide **13** with tributyltin hydride in benzene in the presence of AIBN as radical initiator, to give the desired amide **14** in 88% yield. As far as we are aware, this represents the first use of tributyltin hydride to cleave the chlorosulfonyl group from nitrogen; the reaction presumably involves homolytic cleavage of the S–Cl bond, followed by loss of sulfur dioxide. Subsequently, it was found that **13** can be converted into **14** simply by stirring in THF at room temperature! This reaction proceeds only in the light; when the reaction mixture is protected from daylight, little cleavage of the chlorosulfonamide is observed.

The amide **14** was converted into the thioamide **15** (94%) with Lawesson's reagent (LR). The synthesis was completed by a Hantzsch reaction of the thioamide **15** with ethyl bromopyruvate, resulting not only in formation of the thiazole ring, but also, somewhat surprisingly, in debenzylation. Although the 4-hydroxyindole **16** could be purified by chromatography, it was best oxidised directly to the quinone **17** (65% from **15**) with Fremy's salt in buffered acetone solution. Finally, reaction of the methoxy ester **17** with liquid ammonia in a sealed tube at room temperature for 3–4 days gave BE 10988 **1** in 72% yield. The overall yield of BE 10988 is 28% (from **8**), and the spectroscopic properties of the synthetic material closely matched those described in the literature for the natural product.[4,5]



Scheme 4 *Reagents:* i, KH, MeI, DMF; ii, CSI, Et_2O; iii, Bu_3SnH, AIBN, PhH; iv, LR, PhH; v, $BrCH_2COCO_2Et$, EtOH, reflux; vi, Fremy's salt, acetone, NaH_2PO_4 buffer; vii, liq. NH_3

Experimental

Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. 'Light petroleum' refers to the fraction boiling between 40 and 60 °C, and was distilled through a 36 cm Vigreux column before use. Diethyl ether, xylene, benzene and toluene were dried where necessary by storage over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane was distilled from phosphorus pentoxide. DMF was dried by stirring over calcium hydride for 15 h, decanted, and distilled under reduced pressure before storage over 4 Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from, and stored over, potassium hydroxide pellets. Methanol and ethanol were distilled from magnesium turnings and iodine, and stored over activated 4 Å molecular sieves under nitrogen.

Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with Ehrlich's reagent or phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Pressure was applied at the column head with hand bellows. Samples were applied pre-adsorbed on silica or as a saturated solution in an appropriate solvent.

IR spectra were recorded in the range 4000–600 cm^{-1} using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as solutions in chloroform, thin films or as KBr discs. UV/visible spectra were obtained using a Shimadzu UV-160 spectrophotometer. Elemental analyses were carried out on a Perkin-Elmer 2400 Elemental Analyser. ^1H and ^{13}C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick) instruments; *J* values are recorded in Hz. High- and low-resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (SERC

mass spectrometry service Swansea). M.p.s. were measured on an Electrothermal digital melting point apparatus and are uncorrected.

5-Methoxyindole-3-carbaldehyde **2**.—DMF (7.6 g, 51.7 mmol) and phosphorus oxychloride (3.5 g, 22.8 mmol) were stirred at −5 °C for 30 min after which a solution of 5-methoxyindole (3.1 g, 20.8 mmol) in DMF (3 cm^3) was added slowly dropwise, the temperature being maintained < 10 °C. After the addition was completed the mixture was stirred at 35 °C for 1 h after which ice–water (10 cm^3), followed by aqueous sodium hydroxide (37%; 10 cm^3) were added to it; the mixture was then extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated. The crude solid was recrystallized (light petroleum–dichloromethane) yielding the *aldehyde* **2** (3.3 g, 93%) as colourless crystals, m.p. 174–175 °C (lit.,[23] 177–178 °C) (Found: M^+, 175.0640. $C_{10}H_9NO_2$ requires *M*, 175.0633); $\nu_{max}(CHCl_3)/cm^{-1}$ 2936, 2832 and 1622; δ_H(250 MHz; $CDCl_3$/DMSO) 11.38 (1 H, br s, NH), 9.96 (1 H, s, CHO), 7.81 (1 H, d, *J* 3.2), 7.73 (1 H, d, *J* 2.5), 7.35 (1 H, *J* 8.5), 6.90 (1 H, dd, *J* 8.8, 2.5) and 3.88 (3 H, s, OMe); δ_C(62.9 MHz; $CDCl_3$/DMSO) 184.75 (CHO), 155.96, 137.23 (CH), 132.04, 125.09, 118.44, 113.70 (CH), 112.93 (CH), 102.83 (CH) and 55.46 (OMe); *m/z* (EI) 175 (M^+, 100%), 160 (26) and 132 (43).

4-Iodo-5-methoxyindole-3-carbaldehyde **4**.—A solution of thallium(III) trifluoroacetate (0.23 g, 0.42 mmol) in TFA (4 cm^3) was added to the carbaldehyde **2** (0.05 g, 0.28 mmol) and the mixture stirred for 2 h at 30 °C. After evaporation of excess of solvent under reduced pressure, aqueous potassium iodide (0.33 g, 2.0 mmol) was added to the residue. This blue/black suspension was stirred for 15 min after which solid sodium metabisulfate was added to it until it turned yellow. The mixture was basified with aqueous sodium hydroxide (3 mol dm^{-3}) and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (ethyl acetate elution) yielded the *iodide* **4** (0.06 g, 70%) as an off-white solid, m.p. 167–168 °C (Found: M^+, 300.9617. $C_{10}H_8INO_2$ requires *M*, 300.9600); $\nu_{max}(CHCl_3)/cm^{-1}$ 2936, 2832 and 1622; δ_H(250 MHz; $CDCl_3$/DMSO) 11.87 (1 H, br s, NH), 11.20 (1 H, s, CHO), 8.08 (1 H, d, *J* 3.3), 7.38 (1 H, d, *J* 8.7), 6.91 (1 H, d, *J* 8.7) and 3.94 (3 H, s, OMe); δ_C(62.9 MHz; $CDCl_3$/DMSO) 185.00 (CHO), 154.17, 133.53, 133.12 (CH), 130.09, 118.50, 113.64 (CH), 108.31 (CH), 74.73 (CI) and 57.74 (OMe); *m/z* (FAB) 302 (MH^+, 100%), 301 (M^+, 86) and 175 (MH^+ − I, 68).

4,5-Dimethoxyindole-3-carbaldehyde **3a**.—A solution of the carbaldehyde **4** (0.02 g, 0.07 mmol) in DMF (1 cm^3) was added to freshly prepared sodium methoxide and copper iodide (0.025 g, 0.13 mmol). The sodium methoxide was prepared by addition of sodium (0.024 g, 1.0 mmol) to methanol (1 cm^3). The mixture was heated for 45 min at 110–120 °C. The DMF was removed under reduced pressure, and water (1 cm^3) and 5% methanol in dichloromethane (10 cm^3) were added to the residue. The mixture was filtered through Celite. The layers were separated and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (ethyl acetate elution) to yield the *diether* **3a** (0.003 g, 22%) as a brown oil (Found: M^+, 205.0737. $C_{11}H_{11}NO_3$ requires *M*, 205.0739); ν_{max}(film)/cm^{-1} 3065, 2955, 2850 and 1675; δ_H(250 MHz; $CDCl_3$) 10.42 (1 H, s, CHO), 9.04 (1 H, br s, NH), 7.89 (1 H, d, *J* 3.1), 7.16 (1 H, d, *J* 8.7), 7.01 (1 H, d, *J* 8.7), 3.94 (3 H, s, OMe) and 3.89 (3 H, s, OMe); *m/z* (EI) 205 (M^+, 85%), 190 (43) and 175 (100).

4-Benzyloxy-5-methoxyindole-3-carbaldehyde **3b**.—A solution of the carbaldehyde **4** (0.023 g, 0.07 mmol) in DMF (1 cm^3) was added to freshly prepared sodium benzylate and copper iodide (0.029 g, 0.15 mmol). The sodium benzylate was prepared by addition of sodium (0.028 g, 1.2 mmol) to benzyl alcohol (0.66 g, 6.1 mmol). The mixture was heated at 100 °C for 2 h after which the DMF was removed under reduced pressure; and water (1 cm^3) and 5% methanol in dichloromethane (10 cm^3) were added to the residue. The mixture was filtered through Celite. The layers were separated and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (50% ethyl acetate/50% light petroleum–ethyl acetate, gradient elution). The desired *benzylindole* **3b** (0.004 g, 19%) was obtained as an off-white solid, m.p. 113–114 °C (Found: M^+, 281.1050. $C_{17}H_{15}NO_3$ requires *M*, 281.1052); ν_{max}(film)/cm^{-1} 3055, 2987, 1656 and 1514; δ_H(250 MHz; $CDCl_3$) 10.32 (1 H, s, CHO), 9.43 (1 H, br s, NH), 7.84 (1 H, d, *J* 3.2), 7.37 (5 H, m, Ar), 7.11 (1 H, d, *J* 8.8), 6.99 (1 H, d, *J* 8.8), 5.22 (2 H, s, CH_2Ph) and 3.94 (3 H, s, OMe); δ_C(62.9 MHz; $CDCl_3$) 187.04 (CHO), 147.83, 141.83, 141.07, 137.35, 133.39, 132.43 (CH), 128.66 (CH), 128.47 (CH), 128.20 (CH), 120.94, 118.28, 111.93 (CH), 108.28 (CH), 75.43 (CH_2Ph) and 57.62 (OMe); *m/z* (EI) 281 (M^+, 16%), 253 (13), 190 (57) and 91 (100).

2-Benzhydryloxy-4-methoxynitrobenzene **5**.—To a stirred suspension of potassium hydride (0.16 g, 6.6 mmol) in DMF (30 cm^3), at O °C was added dropwise a solution of 5-methoxy-2-nitrophenol (0.55 g, 3.3 mmol) in DMF (10 cm^3). The mixture was stirred at room temperature for 45 min after which a solution of benzhydryl bromide (0.96 g, 3.9 mmol) in DMF (10 cm^3) was added dropwise to it at 0° C; the mixture was then allowed to warm to room temperature. After 1 h saturated aqueous ammonium chloride was added to the mixture which was then extracted with ether. The ether layer was washed twice with water, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (1:1, light petroleum–ether elution) to give the *benzhydryl ether* **5** (0.47 g, 47%) as a colourless solid, m.p. 90–91 °C (Found: M^+ − $OCHPh_2$, 153.0609. $C_7H_7NO_3$ requires 153.0426); ν_{max}(film)/cm^{-1} 3055, 3000 and 1615; δ_H(250 MHz; $CDCl_3$) 7.96 (1 H, d, *J* 9.1), 7.36 (10 H, m, Ph_2), 6.42 (2 H, m), 5.85 (1 H, s, C*H*Ph_2) and 3.72 (3 H, s, OMe); δ_C(62.9 MHz; $CDCl_3$) 164.87, 154.81, 140.29, 128.83 (CH), 128.41, 128.21 (CH), 128.04 (CH), 127.38, 126.51, 126.35 (CH), 105.35 (CH), 102.25 (CH), 82.81 (*C*HPh_2) and 55.69 (OMe); *m/z* (EI) 184 ($^+OCHPh_2$, 38%), 165 (10), 153 (M^+ − $OCHPh_2$) and 105 (100).

3-Benzhydryloxy-5-methoxy-2-nitrophenylacetonitrile **6**.—A solution of the nitrobenzene **5** (0.095 g, 0.28 mmol) and 4-chlorophenoxyacetonitrile (0.052 g, 0.31 mmol) in DMF (5 cm^3) was added dropwise to a solution of potassium *tert*-butoxide (0.069 g, 0.62 mmol) in DMF (10 cm^3) at −20 to −10 °C. The reaction mixture was stirred at this temperature for 30 min after which it was poured into ice-cold hydrochloric acid (5%). The oily products were extracted with ether and the extract washed with aqueous sodium hydroxide (2%) and water, dried ($MgSO_4$) and concentrated. The crude material was purified by chromatography (50% light petroleum/50% ether elution) yielding the nitrile **6** (0.021 g, 20%) as colourless crystals, m.p. 142–144 °C (Found: M^+, 374.1273. $C_{22}H_{18}N_2O_4$ requires *M*, 374.1266); $\nu_{max}(CHCl_3)/cm^{-1}$ 3026, 2900 and 1598; δ_H(250 MHz; $CDCl_3$) 7.34 (10 H, m, Ph_2), 6.61 (1 H, d, *J* 2.3), 6.47 (1 H, d, *J* 2.3), 6.27 (1 H, s, $CHPh_2$), 3.81 (2 H, s, CH_2CN) and 3.74 (3 H, s, OMe); *m/z* (EI) 375 (MH^+, 4%), 374 (M^+, 6), 357 (29) and 356 (100).

4-Benzyloxy-5-methoxyindole **9**.—Bis(triphenylphosphine)-carbonylrhodium(I) chloride (1.04 g, 1.51 mmol) was suspended in dry degassed mesitylene (65 cm^3) and warmed to 80 °C. After

10 min, 1,3-bis(diphenylphosphino)propane (1.25 g, 4.41 mmol) was added to the mixture to give a yellow precipitate. After a further 10 min, 4-benzyloxy-5-methoxyindole-2-carbaldehyde **8** (5.31 g, 18.9 mmol) was added to the mixture and the flask plunged into a Woods metal bath at 190 °C. The mixture was refluxed for 2 h after which it was concentrated and the residue purified by column chromatography (50% light petroleum/50% ether solution) yielding the *indole* **9** as a colourless solid (3.85 g, 75%), m.p. 83–84 °C (Found: C, 75.9; H, 5.9; N, 5.5. $C_{16}H_{15}NO_2$ requires C, 75.9; H, 6.0; N, 5.5%) (Found: M^+, 253.1100. $C_{16}H_{15}NO_2$ requires *M*, 253.1103); ν_{max}(film)/cm^{-1} 3023, 2960 and 1475; δ_H(250 MHz; $CDCl_3$) 8.09 (1 H, br s, NH), 7.53 (2 H, m), 7.35 (3 H, m), 7.14 (2 H, m), 6.93 (1 H, d, *J* 8.7), 6.55 (1 H, H, *J* 1.0), 5.24 (2 H, s, CH_2Ph) and 3.89 (3 H, s, OMe); δ_C(62.9 MHz; $CDCl_3$) 144.93, 141.06, 138.25, 133.17, 128.31 (CH), 128.24 (CH), 128.16 (CH), 128.08 (CH), 127.77 (CH), 122.98, 111.85 (CH), 106.44 (CH), 99.60 (CH), 75.00 (CH_2Ph) and 58.45 (OMe); *m*/*z* (EI) 253 (M^+, 29%), 162 (100) and 91 (58).

4-Benzyloxy-5-methoxyindole-3-carbaldehyde **3b**.—DMF (1.2 g, 16 mmol) and phosphorus oxychloride (0.56 g, 3.7 mmol) were stirred at −5 °C for 30 min after which a solution of the methoxyindole **9** (0.84 g, 3.3 mmol) in DMF (3 cm^3) was added slowly dropwise to the mixture the temperature being maintained < 10 °C. After the addition was completed the mixture was stirred at 35 °C for 1 h. Ice–water (10 cm^3) followed by aqueous sodium hydroxide (37%; 10 cm^3) were added to the mixture which was then extracted with ether. The extract was dried ($MgSO_4$) and concentrated and the crude residue was purified by chromatography (50% light petroleum/ether) and recrystallized (light petroleum/ether) yielding the aldehyde **3b** (0.64 g, 69%) as off-white crystals (data given above).

4-Benzyloxy-5-methoxy-1-methylindole-3-carbaldehyde **10**.—To a stirred suspension of potassium hydride (0.13 g, 3.3 mol) in DMF (15 cm^3) at 0 °C was added dropwise a solution of the carbaldehyde **3b** (0.62 g, 2.2 mmol) in DMF (10 cm^3). The mixture was stirred at room temperature for 45 min after which iodomethane (0.41 g, 2.9 mmol) was added dropwise to it at 0 °C, the mixture was then allowed to warm to room temperature. The reaction was monitored by TLC and was completed within an hour. Saturated aqueous ammonium chloride was added to the mixture which was then extracted with ether. The ether layer was washed twice with water, dried ($MgSO_4$) and concentrated. The crude product was recrystallized (light petroleum/ether) to give the *N-methylindole* **10** (0.51 g, 78%) as a colourless crystalline solid, m.p. 107–108 °C (Found: M^+, 295.1200. $C_{18}H_{17}NO_3$ requires *M* 295.1208); ν_{max}(film)/cm^{-1} 3054, 1651, 1522 and 1497; δ_H(250 MHz; $CDCl_3$) 10.31 (1 H, s, CHO), 7.77 (1 H, s), 7.47 (2 H, m), 7.33 (3 H, m), 7.05 (2 H, s), 5.22 (2 H, s, CH_2Ph), 3.95 (3 H, s, OMe) and 3.80 (3 H, s, NMe); δ_C(62.9 MHz; $CDCl_3$) 186.40 (CHO), 147.86, 142.56, 137.44, 134.16 (CH), 128.47 (CH), 128.44 (CH), 128.09 (CH), 123.09, 117.10, 111.66 (CH), 105.90 (CH), 74.97 (CH_2Ph), 57.68 (OMe) and 33.84 (NMe): *m*/*z* (EI) 296 (MH^+, 6%), 295 (M^+, 24), 267 (14), 204 (100), 189 (31) and 91 (52).

4-Benzyloxy-5-methoxy-1-methylindole-3-carboxylic Acid **11**.—To a solution of the carbaldehyde **10** (0.40 g, 1.3 mmol) in acetone (33 cm^3) was added a solution of potassium permanganate (0.51 g, 3.2 mmol) in water (10 cm^3) and the mixture was stirred overnight. The crude mixture was decolourized with hydrogen peroxide (10%) and the resulting suspension was filtered, concentrated and acidified. The resulting precipitate was collected and purified by chromatography (ethyl acetate elution) yielding the *acid* **11** (0.12 g, 30%) as a colourless crystalline solid, m.p. 163–165 °C (Found: M^+, 311.1160. $C_{18}H_{17}NO_4$ requires *M*, 311.1157); ν_{max}(film)/cm^{-1} 3120, 3040, 2895 and 1715; δ_H(250 MHz; $CDCl_3$) 7.86 (1 H, s), 7.48 (2 H, m), 7.50 (3 H, m), 7.07 (2 H, d, *J* 3.6), 5.34 (2 H, s, CH_2Ph), 3.99 (3 H, s, OMe) and 3.76 (3 H, s, NMe); δ_C(62.9 MHz; $CDCl_3$) 164.22 (CO_2H), 146.41, 138.62 (CH), 137.36 134.72, 134.04, 129.44 (CH), 128.91 (CH), 128.51 (CH), 119.17, 111.33 (CH), 106.72 (CH), 106.26, 76.51 (CH_2Ph), 57.49 (OMe) and 33.61 (NMe); *m*/*z* (EI) 312 (MH^+, 11%), 311 (M^+, 53) and 267 (100).

4-Benzyloxy-5-methoxy-1-methylindole **12**.—To a stirred suspension of potassium hydride (0.91 g, 22.8 mmol) in DMF (50 cm^3) at 0 °C was added dropwise a solution of the indole **9** (3.83 g, 15.2 mmol) in DMF (20 cm^3). The mixture was stirred at room temperature for 45 min after which iodomethane (2.8 g, 19.7 mmol) was added dropwise to it at 0 °C. The mixture was then allowed to warm to room temperature. After 1 h, saturated aqueous ammonium chloride was added to the mixture which was then extracted with ether. The ether layer was washed twice with water, dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (50% light petroleum/50% ether elution) yielding the *methylindole* **12** as a pale yellow oil (3.7 g, 91%) (Found: C, 76.2; H, 6.4; N, 5.1. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%); ν_{max}(film)/cm^{-1} 2942, 2900 and 1496; δ_H(250 MHz; $CDCl_3$) 7.53 (2 H, m), 7.39 (3 H, m), 6.95 (3 H, m), 6.48 (1 H, m), 5.32 (2 H, s, CH_2Ph), 3.89 (3 H, s, OMe) and 3.71 (3 H, s, NMe); δ_C(62.9 MHz; $CDCl_3$) 144.92, 141.13, 138.38, 134.26, 129.03 (CH), 128.30 (CH), 128.03 (CH), 127.72 (CH), 123.42, 111.77 (CH), 104.43 (CH), 98.08 (CH), 74.96 (CH_2Ph), 58.60 (OMe) and 32.99 (NMe); *m*/*z* (EI) 268 (MH^+, 9%), 267 (M^+, 48) and 176 (100).

4-Benzyloxy-(N-chlorosulfonyl)-5-methoxy-1-methylindole-3-carboxamide **13**.—Chlorosulfonyl isocyanate (2.75 g, 19.4 mmol), distilled under nitrogen immediately prior to use, was added dropwise to a stirred solution of the indole **12** (1.3 g, 4.9 mmol) in dry ether (30 cm^3) at 0 °C. The mixture was stirred at room temperature for 20 min after which the resulting precipitate was filtered off yielding the *N-chlorosulfonylamide* **13** as a yellow solid (1.94 g, 97%), decomposes 125 °C; ν_{max}($CHCl_3$)/cm^{-1} 3032, 2940 and 1687; δ_H(250 MHz; $CDCl_3$) 13.06 (1 H, s, $CONHSO_2Cl$), 8.01 (1 H, s, NCH=C), 7.35 (5 H, m), 6.97 (2 H, m), 5.40 (2 H, s, CH_2Ph), 3.98 (3 H, s, OMe) and 3.77 (3 H, s, NMe); δ_C(62.9 MHz; $CDCl_3$) 159.52 ($CONHSO_2Cl$), 147.32, 139.67 (CH), 137.57, 134.60, 134.25, 129.55 (CH), 129.02 (CH), 128.56 (CH), 118.35, 111.56 (CH), 107.08 (CH), 106.75, 76.76 (CH_2Ph), 57.38 (OMe) and 34.00 (NMe).

4-Benzyloxy-5-methoxy-1-methylindole-3-carboxamide **14**.—A mixture of the carboxamide **13** (1.94 g, 4.73 mmol), tributyltin hydride (2.75 g, 9.45 mmol) and AIBN (12 mg, 0.075 mmol) in benzene (40 cm^3) was refluxed for 45 min. The solvent was evaporated and the crude residue purified by column chromatography (50% light petroleum/50% ether–ethyl acetate–isopropyl alcohol elution) yielding the *amide* **14** (1.28 g, 88%) as an off-white solid, m.p. 170–171 °C (Found: C, 69.4; H, 5.8; N, 8.9. $C_{18}H_{18}N_2O_3$ requires C, 69.6; H, 5.8; N, 9.0%) (Found: M^+, 310.1317. $C_{18}H_{18}N_2O_3$ requires *M*, 310.1317); ν_{max}($CHCl_3$)/cm^{-1} 3475, 3336, 2997 and 1636; δ_H(250 MHz; $CDCl_3$) 8.55 (1 H, br s, NH) 7.89 (1 H, s, NCH=C), 7.51 (2 H, m), 7.37 (3 H, m), 7.06 (2 H, d, *J* 2.4), 5.29 (1 H, br s, NH), 5.16 (2 H, s, CH_2Ph), 3.97 (3 H, s, OMe) and 3.76 (3 H, s, NMe); δ_C(62.9 MHz; $CDCl_3$) 166.20 ($CONH_2$), 147.04, 139.98, 137.47 (CH), 136.84, 134.80, 129.05 (CH), 128.58 (CH), 119.20, 111.10 (CH), 109.76, 106.28 (CH), 76.41 (CH_2Ph), 57.76 (OMe) and 33.53 (NMe); *m*/*z* (EI) 311 (MH^+, 10%), 310 (M^+, 45), 267 (73), 219 (59) and 91 (100).

4-Benzyloxy-5-methoxy-1-methylindole-3-thiocarboxamide **15**.—A solution of the carboxamide **14** (0.57 g, 1.84 mmol) in

benzene (10 cm^3) and Lawesson's reagent (0.44 g, 1.09 mmol) was refluxed for 1 h. The crude mixture was concentrated and the resulting residue was purified by column chromatography (ether elution) yielding the *thioamide* **15** (0.55 g, 94%) as a yellow crystalline solid, m.p. 142–144 °C (Found: C, 66.4; H, 5.6; N, 8.85. $C_{18}H_{18}N_2O_2S$ requires C, 66.24; H, 5.56; N, 8.59%); (Found: M^+, 326.1090. $C_{18}H_{18}N_2O_2S$ requires *M*, 326.1089) $\nu_{max}(CHCl_3)/cm^{-1}$ 3462, 3276, 3190, 2957, 1609, 1576 and 1523; δ_H(250 MHz; $CDCl_3$) 9.91 (1 H, br s, NH), 8.37 (1 H, s), 7.48 (2 H, m), 7.38 (3 H, m), 7.11 (1 H, br s, NH), 7.06 (2 H, d, *J* 2.4), 5.12 (2 H, s, CH_2Ph), 3.97 (3 H, s, OMe) and 3.77 (3 H, s, NMe); δ_C(62.9 MHz; $CDCl_3$) 192.04 ($CSNH_2$), 147.85, 142.70 (CH), 139.09, 135.68, 135.12, 129.05 (CH), 128.82 (CH), 118.03, 115.54, 111.08 (CH), 106.73 (CH), 77.05 (CH_2Ph), 57.54 (OMe) and 33.73 (NMe); *m/z* (EI) 327 (MH^+, 10%), 326 (M^+, 45) and 292 (100).

Ethyl 2-(4-*Hydroxy*-5-*methoxy*-1-*methylindol*-3-*yl*)*thiazole*-4-*carboxylate* **16**.—The thiocarboxamide **15** (0.21 g, 0.64 mmol) and ethyl bromopyruvate (0.24 g, 1.23 mmol) were refluxed for 15 min in ethanol (30 cm^3). The crude mixture was concentrated and the residue purified by column chromatography (ethyl acetate–isopropyl alcohol elution) yielding the *thiazole* **16** slightly impure (NMR). A small sample was repurified for characterization, m.p. 155–157 °C (Found: M^+, 332.0830. $C_{16}H_{16}N_2O_4S$ requires *M*, 322.0830); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3137, 3025, 2936, 1717 and 1558; δ_H(250 MHz; $CDCl_3$) 12.41 (1 H, br s, OH), 7.86 (1 H, s), 7.43 (1 H, s), 7.02 (1 H, d, *J* 8.7), 6.65 (1 H, d, *J* 8.7), 4.43 (2 H, q, *J* 7.11, CH_2CH_3), 3.95 (3 H, s, OMe), 3.71 (3 H, s, NMe) and 1.45 (3 H, t, *J* 7.1, CH_2CH_3); δ_C(62.9 MHz; $CDCl_3$) 165.39 (C=O), 160.74 (C=N), 145.19, 142.05, 141.96, 134.95, 129.49 (CH), 128.19, 123.19 (CH), 113.79 (CH), 111.58 (CH), 109.70, 99.33 (CH), 61.56 (CH_2CH_3), 58.40 (OMe), 33.55 (NMe) and 14.37 (CH_2CH_3); *m/z* (EI) 332 (MH^+, 100%) 317 (45) and 271 (81).

Ethyl 2-(5-*Methoxy*-1-*methyl*-4,7-*dioxoindol*-3-*yl*)*thiazole*-4-*carboxylate* **17**.—A solution of potassium nitrosodisulfate (0.47 g, 1.42 mmol) in water (10 cm^3) was added to a stirred solution of the carboxylate **16** (0.195 g, 0.59 mmol) in acetone (10 cm^3), buffered with sodium dihydrogen phosphate (0.17 mol dm^{-3}; 10 cm^3) and the mixture stirred overnight. It was then concentrated and the resulting residual oil extracted with dichloromethane. The extract was dried ($MgSO_4$) and purified by column chromatography (ethyl acetate–isopropyl alcohol elution) to give the *quinone* **17** (0.132 g) in 65% yield from the thioamide as a pale orange solid, m.p. 254–256 °C (Found: C, 55.35; H, 4.0; N, 8.05. $C_{16}H_{14}N_2O_5S$ requires C, 55.48; H, 4.08; N, 8.09%) (Found: M^+, 346.0623. $C_{16}H_{14}N_2O_5S$ requires *M*, 346.0623); $\nu_{max}(CHCl_3)/cm^{-1}$ 3026, 3013, 2939, 1722, 1674 and 1645; λ_{max}(MeOH)/nm 448 (ε 3195), 374 (3661), 280 (10066), 249 (12789) and 133 (12303); δ_H(250 MHz; $CDCl_3$) 8.17 (1 H, s), 7.85 (1 H, s), 5.76 (1 H, s), 4.43 (2 H, q, *J* 7.1, CH_2CH_3), 4.04 (3 H, s, OMe), 3.88 (3 H, s, NMe) and 1.42 (3 H, t, *J* 7.1, CH_2CH_3); δ_C(62.9 MHz; $CDCl_3$) 178.54 (C=O), 177.06 (C=O), 161.44 (CO_2Et), 160.21 (C=N), 159.76, 146.44, 131.09 (CH), 129.86, 127.83 (CH), 119.27, 117.81 (C=C), 106.67 (CH), 61.31 CH_2CH_3), 56.68 (OMe), 36.79 (NMe) and 14.28 (CH_2CH_3); *m/z* (EI) 346 (M^+, 100%), 274 (66) and 234 (26).

2-(5-*Amino*-1-*methyl*-4,7-*dioxoindol*-3-*yl*)*thiazole*-4-*carboxamide* **1** (BE 10988).—A solution of the carboxylate **17** (0.012 g, 0.035 mmol) in dichloromethane (5 cm^3) was placed in a Young's tube and ammonia was bubbled into the solution at −78 °C. When a final volume of *ca.* 30 cm^3 was obtained, the tube was sealed and the mixture stirred at room temperature for 4 days. Prior to the tube being opened the mixture was cooled to −78 °C and then allowed to warm up slowly over a period of a few hours. The crude mixture was purified by column chromatography (ethyl acetate elution) yielding the desired *amide* **1** (0.0076 g, 72%) as a dark red solid, m.p. > 300 °C (Found: M^+, 302.0474. $C_{13}H_{10}N_4O_3S$ requires *M*, 302.0473); ν_{max}(DMSO)/cm^{-1} 3444, 3390, 1680 and 1610; λ_{max}(MeOH)/nm 505, 384, 279 and 237; δ_H(400 MHz; DMSO) 8.17 (1 H, s, SCH=C), 7.94 (1 H, s, NCH=C), 7.79 and 7.65 (2 H, 2 s, $CONH_2$), 7.20 (2 H, br s, NH_2), 5.38 [1 H, s (H_2N)C=CH] and 3.97 (3 H, s, NMe); δ_C(100.6 MHz; DMSO) 178.66 (CO), 177.74 (CO), 162.47 ($CONH_2$), 158.99 (SC=N), 151.06 (H_2NC), 149.81 [=NC=($CONH_2$)], 131.60 [COC=C(NMe)], 130.07 (NCH), 123.76 (SCH=C), 117.04 (COC=C), 116.40 (C-thiazole), 98.35 (H_2NC=C) and 36.53 (NMe); *m/z* (EI) 303 (MH^+, 20%), 302 (M^+, 100), 284 (12), 275 (15), 258 (29), 229 (20) and 202 (14) [lit.,[5] dark red crystals m.p. > 300 °C (Found: M^+, 302.0511. $C_{13}H_{10}N_4O_3S$ requires *M*, 302.0473); ν_{max}(KBr)/cm^{-1} 3450, 3390, 1662, 1620, 1590, 1540 and 1500; λ_{max}(MeOH)/nm 503.5, 385, 280 and 213; δ_H(DMSO) 8.15 (1 H, s), 7.89 (1 H, s), 7.78 and 7.62 (2 H, 2 br s, $CONH_2$), 7.15 (2 H, br s, NH_2), 5.37 (1 H, s) and 3.94 (3 H, s, NMe); δ_C(DMSO) 178.5, 177.6, 162.4, 158.9, 150.9, 149.7, 131.5, 129.9, 123.6, 116.3, 98.3 and 36.4].

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References

1 Preliminary communication, C. J. Moody and E. Swann, *Tetrahedron Lett.*, 1993, **34**, 1987.
2 R. J. Epstein, *Lancet*, 1988, 521; W. E. Ross, *Biochem. Pharmacol.*, 1985, **34**, 4191.
3 For some recent examples, see: D. C. Radisky, E. S. Radisky, L. R. Barrows, B. R. Copp, R. A. Kramer and C. M. Ireland, *J. Am. Chem. Soc.*, 1993, **115**, 1632.
4 H. Oka, T. Yoshinari, T. Murai, K. Kawamura, F. Satoh, K. Funaishi, A. Okura, H. Suda, M. Okanishi and Y. Shizuri, *J. Antibiotics*, 1991, **44**, 486.
5 H. Suda, K. Matsunaga, S. Yamamura and Y. Shizuri, *Tetrahedron Lett.*, 1991, **32**, 2791.
6 T. Martin and C. J. Moody, *J. Chem. Soc., Perkins Trans. 1*, 1988, 241.
7 G. B. Jones and C. J. Moody, *J. Chem. Soc., Perkins Trans. 1*, 1989, 2455.
8 H. Suda, M. Ohkubo, K. Matsunaga, S. Yamamura, W. Shimomoto, N. Kimura and Y. Shizuri, *Tetrahedron Lett.*, 1993, **34**, 3797.
9 M. Somei, F. Yamada, M. Kunimoto and C. Kaneko, *Heterocycles*, 1984, **22**, 797.
10 A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor and G. McGillivray, *Tetrahedron Lett.*, 1969, 2427.
11 M. Makosza, W. Danikiewicz and K. Wojciechowski, *Liebigs Ann. Chem.* 1988, 203.
12 H. H. Hodgson and H. Clay, *J. Chem. Soc.*, 1929, 2775.
13 D. Dobson, A. Todd and J. Gilmore, *Synth. Commun.*, 1991, **21**, 611.
14 G. B. Jones, PhD Thesis, University of London, 1989.
15 N. O'Sullivan, PhD Thesis, Loughborough University of Technology, 1992.
16 M. D. Meyer and L. I. Kruse, *J. Org. Chem.*, 1984, **49**, 3195.
17 A. Andreoni, D. Bonazzi, M. Rambaldi, A. Guarnieri, F. Andreoni, P. Strocchi and N. Montanaro, *J. Med. Chem.*, 1977, **20**, 1344.
18 K. Nakagawa, H. Onoue and K. Minami, *Chem. Commun.*, 1966, 17.
19 N. W. Gilman, *J. Chem. Soc., Chem. Commun.*, 1971, 733.
20 I. E. Markó and A. Mekhalfia, *Tetrahedron Lett.*, 1990, **31**, 7237.
21 H. Vorbrüggen, *Tetrahedron Lett.*, 1968, 1631.
22 T. Sasaki, S. Eguchi and Y. Hirako, *Tetrahedron*, 1976, **32**, 437.
23 A. L. Mndzhoyan and G. L. Papayan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, 1961, **14**, 603 (*Chem. Abstr.*, 1963, 4497d).

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