Synthesis of a Novel Tetracyclic Acridine. A Sulphoxide-based Route to the 1,2,3,4-Tetrahydrobenzo[*b*][1,8]phenanthroline Ring System

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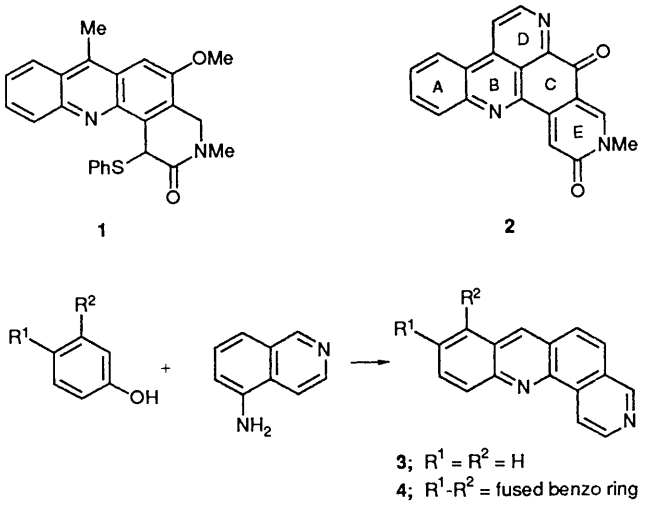
The ambit of the classical acridine synthesis, *via* acid-mediated cyclisation of 2-oxodiphenylamines, has been extended to include a sulphoxide-containing precursor. This adaption produced the tetracyclic system of **1** in a single step from **25**.

The potential of acridine derivatives as bioactive compounds continues to focus attention on their synthesis and medicinal applications.[1] The carcinogenic, anticarcinogenic, antibacterial and antimalarial properties of acridines are well established.[2]

As a consequence, the synthetic chemistry of many families of acridine derivatives has been thoroughly investigated. We report in this paper the preparation of, to our knowledge, the first example of the tetrahydrobenzo[*b*][1,8]phenanthroline family of heterocyclo[*c*]acridine derivatives **1**.

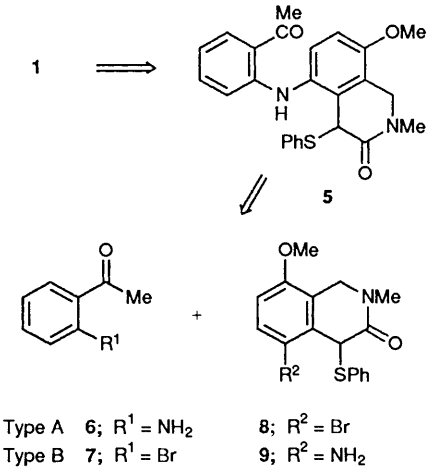
Results and Discussion

Our original interest in this system derived from its potential as a precursor of a pyridoacridine subunit of the natural product amphimedine **2**.[3] Examples of the basic tetracyclic framework of **1** could be found but were restricted to compounds in which both heteroatoms were constituents of aromatic systems, *e.g.* **3**[4] and **4**,[5] *i.e.* benzo- and naphtho-derivatives of the phenanthroline. These compounds had been constructed by application of classical acridine-forming methodologies to precursors in which the 3,4-substituted pyridine ring was ready-made (Scheme 1). Our work focused on the extension of one such methodology, *viz* cyclisation of a suitably functionalised diphenylamine, to the acridine **1**.



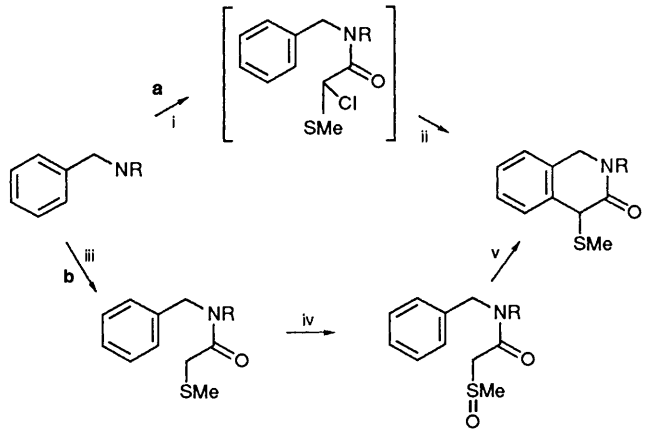
Scheme 1

At the outset we had envisaged that **1** could be constructed *via* acid-catalysed cyclisation of diphenylamine **5** which, in turn, could be formed by Ullmann-type coupling of *o*-aminoacetophenone **6** with the tetrahydroisoquinoline **8**[6] (Scheme 2).



Scheme 2

We proposed to apply Tamura's[7] approach to the preparation of **8**. This method involves the option of an intramolecular Friedel-Crafts cyclisation of a chloro sulphide or a Pummerer-type cyclisation of a sulphoxide, both intermediates deriving from a common benzylamine precursor, as in Scheme 3.[8]



Scheme 3 [R = H or Me] *Reagents:* i, $MeSCH(Cl)COCl$, $N(Et)_3$, CH_2Cl_2, 0 °C; ii, $SnCl_4$; iii, $MeSCH_2COCl$, $N(Et)_3$, CH_2Cl_2, 0 °C; iv, MCPBA, 0 °C; v, *p*-TsOH, CCl_4, reflux

We chose to examine the chloro sulphide option foremost. The necessary benzylamine, **11**, was prepared from commercially available 5-bromo-*o*-anisaldehyde by condensation with

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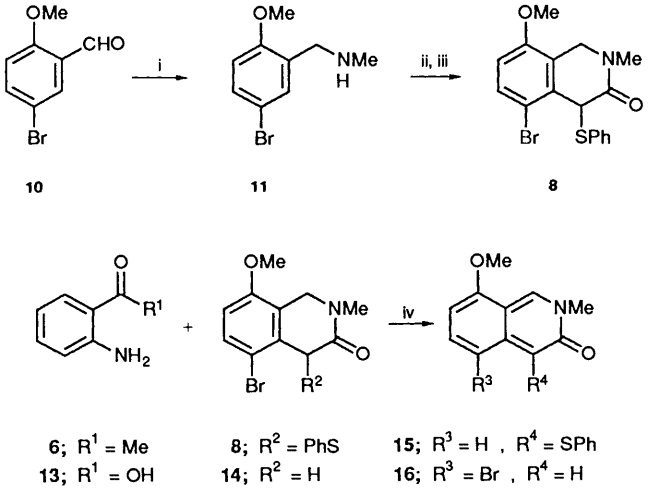
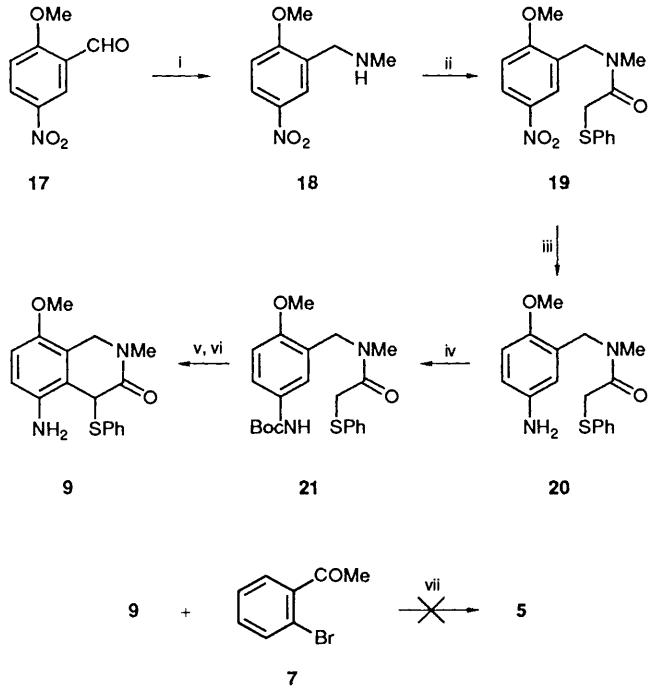


Scheme 4 *Reagents:* i, $MeNH_2$, $NaCNBH_3$, H^+, MeOH; ii, $PhSCH(Cl)COCl$ *i.e.* **12**, $N(Et)_3$, CH_2Cl_2, 0 °C; iii, $SnCl_4$; iv, Na_2CO_3, Cu (catalytic), KI (catalytic), $C_6H_5NO_2$, reflux



Scheme 5 *Reagents:* i, $MeNH_2$, $NaCNBH_3$, H^+, MeOH; ii, $PhSCH_2COCl$, $N(Et)_3$, CH_2Cl_2, 0 °C; iii, 10% Pd(C), 80 psi H_2, EtOAc; iv, $[(CH_3)_3CCO_2]_2O$, $CHCl_3$, reflux; v, NCS, CCl_4; vi, $SnCl_4$, CH_2Cl_2; vii, Na_2CO_3, Cu (catalytic), KI (catalytic), $C_5H_{12}OH$, reflux

methylamine, followed by reduction with sodium cyanoborohydride (65%),[9] and the acyl chloride, **12**, was available from thiophenoxyacetic acid by successive treatment with thionyl chloride and *N*-chlorosuccinimide (79%).[7] The reaction of **11** with **12** proceeded smoothly to afford the expected isoquinolone **8** (69%) (Scheme 4).

When **6** was treated with **8** under the standard Ullmann coupling conditions previously applied to related systems,[6] *i.e.* refluxing nitrobenzene containing sodium carbonate and a catalytic amount of copper powder, none of the target diphenylamine **5** was obtained. The isoquinolone compounds **15** and **16** were the only identified products.[10] These compounds could be formed by simply heating **8** in nitrobenzene in the presence of sodium carbonate and a catalytic amount of copper. The desulphurised derivative **14** (56% by treatment of **8** with zinc in refluxing acetic acid[11]) afforded only **16** under the same conditions. Using anthranilic acid, **13**, in place of **6** was no more productive, **8** being recovered intact.*

Turning our attention to the alternative combination from Scheme 2 of **7** and **9**, we examined the synthesis of aniline **9**. In the case of the related 2-carboxydiphenylamines, the type B reaction is generally superior to type A.[1]

Reductive amination of aldehyde **17**,† under the conditions used for preparation of **11**, afforded benzylamine **18** (72%). The presence of the nitro substituent in **18**, with its attendant deactivation of the aromatic nucleus, contraindicated the application of the strategy applied to **11**; furthermore, the known generation of the oxindole product on application of the method to an aniline substrate precluded the use of the aniline derivative of **18**.

A solution was forthcoming when we found that **19**, the amide derivative of **18**, underwent facile catalytic hydrogenation to aniline **20**,[12] which, when BOC-protected, could be cyclised to **9** (50%), *via* the chloro sulphide as for the latter part of route (**a**) in Scheme 3. No subsequent deprotection step was necessary since the aniline was formed directly, presumably, by the agency of the equivalent of hydrochloric acid liberated in the cyclisation reaction. Unfortunately, **9** when treated with 2-bromoacetophenone under the conditions applied to **8** above (solvent excepted), produced a complex mixture and none of the expected diphenylamine was isolated (Scheme 5).

In examining the possible contribution of the nitrobenzene solvent as an inhibitory factor, the reaction of **6** and **8** was repeated using alternative solvents, *viz* pentan-1-ol and DMF. Both had previously been used in coupling reactions of this type.[1] In neither case could any diphenylamine product be recovered, though employing pentan-1-ol the chief product was **16**. The recurrence of the isoquinolone product **16** over a temperature range of nearly 75 °C (b.p. pentan-1-ol 136 °C and b.p. nitrobenzene 210 °C) suggested that the bicyclic character of the reactants, **8** and **9**, could be implicated as the impediment, and that an alternative strategy of condensation of **6** with a suitably functionalised monocyclic relative of **8** would succeed.

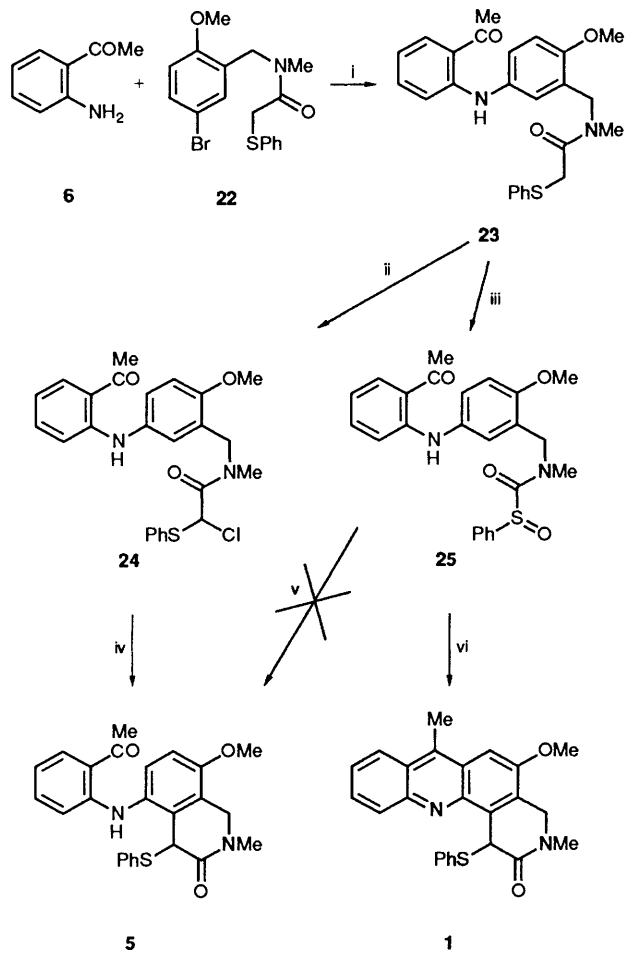
The successful reaction of **6** with the amide derivative **22** to afford diphenylamine **23** (59%) demonstrated the accuracy of this suggestion (Scheme 6). With the appropriate diphenylamine in hand it, initially, seemed desirable that the tetracyclic system be constructed by the sequential assembly of the isoquinolone and acridine systems in that order, thus avoiding the potential ambiguity in regioselectivity posed by direct exposure of **23** to acridine-forming conditions.

Accordingly, we investigated the applicability of the Scheme 3 options to **23**. In the expectation that the unprotected amine functionality would complicate the chlorination[13] and/or oxidation reactions we attempted, unsuccessfully, the *N*-protection of **23**. In the event, protection was unnecessary as both chlorination (NCS) and oxidation (MCPBA) proceeded smoothly on **23** to afford **24** and **25** respectively.

When **24** and **25** were treated under the cyclisation conditions applied to their respective parallels in Scheme 3, none of the expected product was recovered. In both cases it was necessary to modify the reaction conditions to produce acridine **1**. In the case of the chloro sulphide, a gradual rather than rapid introduction of the catalyst was sufficient to permit recovery of the anilino isoquinoline **5** (68%). After purification **5** was cyclised, under the strongly acidic conditions generally

* The eventual cyclisation product would, of course, have been an acridanone rather than an acridine, in this case.

† Prepared from 5-nitrosalicylic acid or 2-methoxy-5-nitrobenzyl bromide.



Scheme 6 *Reagents:* i, Na_2CO_3, Cu (catalytic), $C_6H_5NO_2$, reflux; ii, NCS, CCl_4; iii, MCPBA, CH_2Cl_2; iv, $SnCl_4$, $N(Et)_3$, CH_2Cl_2; v, *p*-TSOH, CCl_4; vi, c.H_2SO_4, AcOH, 130 °C

employed to effect cyclisation of 2-oxodiphenylamines to acridines,[6] to afford **1** (79%). When the sulphoxide **25** was subjected to these strongly acidic cyclisation conditions potential regiochemical complications notwithstanding the target acridine was formed directly (37%) without isolation of an intermediate. The identity of the product as **1** was corroborated by an NOE experiment. No attempt was made to optimise the reaction conditions or to determine the order of priority or efficiency of the cyclisation reactions. Despite the modest yield, the concomitant formation of acridine and isoquinolone systems marks the transformation as economic overall. An investigation of the possibilities for selective oxidation of the acridinylmethyl substituent and the phenylthio functionality proved unproductive in the short term, though desulphurisation was shown to be viable.

In summary, the novel tetracyclic acridine system **1** has been synthesised in three steps from simple benzenoid precursors.

Experimental

^{1}H NMR spectra were recorded at 60 and 250 MHz using Varian EM360 and Bruker WM250 instruments respectively with tetramethylsilane as the internal reference. ^{13}C NMR spectra were recorded at 62.9 MHz on the latter instrument using the broad band decoupling mode, all *J* values are given in Hz. IR spectra were obtained using Perkin-Elmer 257, or 298 instruments. Mass spectra were recorded on a VG Micromass 7070B spectrometer at 70 eV employing a direct insertion probe. M.p.s were recorded on a Reichert microscope hot stage, or on a Thomas-Hoover capillary melting point apparatus. Unless specifically indicated otherwise, column chromatography was conducted on silica H, type 60 or silica gel (0.063–0.2 mm) (Merck). Standard purification and drying procedures were used for the relevant solvents. Light petroleum refers to the fraction of b.p. 40–60 °C unless specifically designated otherwise.

*5-Bromo-2-methoxy-*N*-methylbenzylamine* **11**.—5-Bromo-*o*-anisaldehyde **10** (10.7 g, 0.05 mol) was dissolved in a stirred mixture of 33% methylamine in industrial methylated spirits (36.3 cm^3, 33% w/w) and hydrochloric acid (5 mol dm^{-3}; 20 cm^3) in methanol (89 cm^3). Sodium cyanoborohydride (1.89 g, 0.03 mol) was added to the stirred solution in one portion at room temperature and the mixture was stirred for 48 h at ambient temperature.

Concentrated hydrochloric acid was added to the resulting mixture to adjust it to pH 1. After 15 min the solvent was removed under reduced pressure and the residue dissolved in water (100 cm^3) and extracted with diethyl ether (3 × 70 cm^3). The separated aqueous layer was adjusted to pH 14 stagewise by the addition of solid potassium hydroxide, and saturated with sodium chloride. The resulting milky mixture was extracted with ether (3 × 70 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a brown oil which was chromatographed to give the *title compound* **11** (7.5 g, 65%) as a light-orange oil, b.p. 120 °C/0.03 mmHg (Found: C, 46.9; H, 5.5; Br, 34.7; N, 6.0; $C_9H_{12}BrNO$ requires C, 47.0; H, 5.2; Br, 34.8; N, 6.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3330 (NH), 2920, 2840, 2800, 1592, 1460 and 1093; δ_H(250 MHz; $CDCl_3$) 2.38 (3 H, s), 3.67 (2 H, s), 3.80 (3 H, s), 6.72 (1 H, d, *J* 8) and 7.26–7.37 (2 H, m), NH not observed; *m/z* 230/228 (M^+, 38%), 216/214 (21), 200/198 (31), 171/169 (19), 150 (66) and 44 (100).

2-Chloro-2-(phenylthio)acetyl Chloride **12**.—A mixture of thiophenoxyacetic acid (4.18 g, 0.025 mol) and thionyl chloride (5.44 cm^3, 0.075 mol) was stirred at 20 °C under nitrogen for 1.5 d. The excess of thionyl chloride was removed under reduced pressure and the residual orange oil distilled at reduced pressure to afford the acyl chloride (4.22 g, 91%), b.p. 80 °C/0.3 mmHg, as a lemon-coloured oil.

N-Chlorosuccinimide (3.32 g, 0.025 mol) was added in portions (*Caution:* exothermic reaction!) to a stirred solution of the above acyl chloride (4.12 g, 0.022 mol) in thionyl chloride (3 cm^3) at ambient temperature. The mixture was stirred for 40 min and the copious precipitate of succinimide was filtered off and rinsed with thionyl chloride (2 cm^3). The excess of thionyl chloride was removed under reduced pressure and the residue was filtered through glass wool and distilled under reduced pressure to afford the *title compound* **12** (4.22 g, 86%) as a lemon-coloured oil, b.p. 115 °C/0.45 mmHg (Found: C, 43.3; H, 2.8; S, 14.5. $C_8H_6Cl_2OS$ requires C, 43.5; H, 2.7; S, 14.5%); ν_{max}(thin film)/cm^{-1} 3060, 2960, 1790, 1470, 1449, 978, 733, 704 and 690; δ_H(60 MHz; CCl_4) 5.60 (1 H, s) and 7.20–7.80 (5 H, m).

5-Bromo-1,4-dihydro-8-methoxy-2-methyl-4-phenylthio-3(2H)-isoquinolone **8**.—A solution of the chloro sulphide **12** (0.053 g, 0.24 mmol) in dichloromethane (0.5 cm^3) was added dropwise to a stirred solution of benzylamine **11** (0.055 g, 0.24 mmol) and triethylamine (0.024 g, 0.24 mmol) in dry dichloromethane (0.25 cm^3) at 0 °C. After the mixture had been stirred at 20 °C for 20 min, a solution of anhydrous stannic chloric (0.075 g, 0.29 mmol) in dichloromethane (0.4 cm^3) was added to it, in one portion, causing a vivid red colour to develop instantly. The solution was stirred at ambient temperature for 1 h and then diluted with dichloromethane (4 cm^3) and poured

into ice–water (20 cm^3). The separated organic phase was washed with water (2 × 15 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed to afford the *title compound* **8** (0.062 g, 69%) as a lemon–green crystalline solid, m.p. 152–154 °C (from dichloromethane–light petroleum) (Found: C, 53.8; H, 4.2; N, 3.8; S, 8.8. $C_{17}H_{16}BrNO_2S$ requires C, 54.0; H, 4.2; N, 3.7; S, 8.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1647, 1587, 1457, 1294, 1087 and 907; δ_H(250 MHz; $CDCl_3$) 2.85 (3 H, s), 3.10 (1 H, d, *J* 17.7), 3.68 (3 H, s), 3.96 (1 H, d, *J* 17.7), 4.80 (1 H, s), 6.55 (1 H, d, *J* 8.9), 7.07–7.30 (5 H, m) and 7.42 (1 H, d, *J* 8.9); irradiation of the doublet at δ 3.10 generated a singlet at δ 3.96; δ_C(62.9 MHz; $CDCl_3$) 34.38, 47.54, 50.75, 55.68, 110.30, 113.88, 123.48, 128.39, 129.11, 131.46, 132.37, 133.43, 135.77, 154.04 and 166.63; *m/z* 379/377 (M^+, 6%), 269/267 (100), 242/240 (27) and 226/224 (9).

5-Bromo-1,4-dihydro-8-methoxy-2-methyl-3(2H)-isoquinolone **14**.—A mixture of the isoquinolone **8** (0.250 g, 0.66 mmol), acid-washed zinc powder (0.63 g, 9.6 mmol) and acetic acid (8 cm^3) was heated under reflux for 6 h. The mixture was filtered off through filter aid under suction and the collected solids were rinsed thoroughly with dichloromethane. The filtrate was concentrated under reduced pressure to a viscous orange oil which solidified with time at ambient temperature.

This solid was purified by chromatography to afford the *title compound* **14** (0.099 g, 56%) as a yellow crystalline solid, m.p. 196.5–198 °C (Found: C, 48.6; H, 4.4; N, 5.1. $C_{11}H_{12}BrNO_2$ requires C, 48.9; H, 4.5; N, 5.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1638, 1590, 1460 and 1290; δ_H(250 MHz; $CDCl_3$) 3.12 (3 H, s), 3.62 (2 H, brs), 3.84 (3 H, s), 4.46 (2 H, t, *J* 2.1), 6.65 (1 H, d, *J* 8.7) and 7.45 (1 H, d, *J* 8.7); *m/z* 271/269 (M^+, 57%), 214/212 (44) and 190 (100).

8-Methoxy-2-methyl-4-phenylthio-3(2H)-isoquinolone **15** *and 5-Bromo-8-methoxy-2-methyl-3(2H)-isoquinolone* **16**.—(*a*) A mixture of **8** (0.100 g, 0.27 mmol), *o*-aminoacetophenone (0.036 g, 0.81 mmol), sodium carbonate (0.056 g, 0.54 mmol), finely divided copper powder (0.010 g), potassium iodide (0.002 g), and nitrobenzene (3 cm^3) was heated under reflux for 3 h. The resulting mixture was dissolved in dichloromethane (40 cm^3) and water (20 cm^3). The separated organic layer was washed with water (3 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residual nitrobenzene was removed at high vacuum (0.2 mbar/80–100 °C) leaving a viscous black oil. Analysis of this oil by TLC showed that it consisted of a multiplicity of components, of which, the dominant two were highly coloured (neutral alumina–dichloromethane), yellow and yellow–orange respectively.

These compounds were subsequently identified, by their isolation from the reactions described in (*b*) and (*c*) below, as the *title compounds* **15** and **16**.

(*b*) A mixture of **8** (0.150 g, 0.4 mmol) finely divided copper powder (0.004 g), sodium carbonate (0.072 g, 0.7 mmol) and nitrobenzene (0.75 cm^3) was heated under reflux for 3 h. The cooled mixture was dissolved in dichloromethane (10 cm^3) and water (10 cm^3). The separated organic phase was washed with water (2 × 10 cm^3) and brine (1 × 11 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to a black oil. This oil was chromatographed on neutral alumina to afford a mixture of **15** and **16** (65 mg, 2:1 ratio with **15** dominant) from which **15** could be fractionally crystallised (dichloromethane–light petroleum (0.025 g, 21%) as a bright-yellow solid, m.p. 215–217 °C (Found: M^+, 297.0833. $C_{17}H_{15}NO_2S$ requires *M*, 297.0824); $\nu_{max}(CHCl_3)/cm^{-1}$ 1660 and 1590; δ_H(250 MHz; $CDCl_3$) 3.80 (3 H, s), 3.97 (3 H, s), 6.20 (1 H, d, *J* 8), 7.03–7.23 (6 H, m), 7.64 (1 H, d, *J* 8) and 8.55 (1 H, s); *m/z* 297 (M^+, 100%), 282 (8), 269 (15) and 254 (38).

(*c*) The conditions described for (*a*) above were repeated exactly, with the exception that pentan-1-ol was substituted for nitrobenzene.

The crude product was purified by chromatography on silica to afford **16** (0.040 g, 56%) as a yellow–orange solid, m.p. 227–230 °C (from acetone–light petroleum) (Found: C, 49.2; H, 3.8; N, 5.1. $C_{11}H_{10}BrNO_2$ requires C, 49.3; H, 3.7; N, 5.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1660 and 1600; δ_H(250 MHz; $CDCl_3$) 3.84 (3 H, s), 3.91 (3 H, s), 6.05 (1 H, d, *J* 8.1), 7.02 (1 H, s), 7.46 (1 H, d, *J* 8.1) and 8.51 (1 H, s); *m/z* 269/267 (M^+, 43%) and 51 (100).

This isoquinolone was also obtained (26%) when the conditions described in (*a*) above were applied to **14**.

N-(2-Methoxy-5-nitrobenzyl)-N-methyl(phenylthio)acetamide **19**.—The procedure described for **11** above was applied to 5-nitro-*o*-anisaldehyde **17** (0.763 g, 4 mmol) to afford benzylamine **18** (0.562 g, 72%).

To a cooled and stirred solution of the benzylamine **18** (0.265 g, 1.35 mmol) and triethylamine (0.19 cm^3, 1.35 mmol) in dry dichloromethane (4 cm^3) at 0 °C was added dropwise a solution of the acyl chloride precursor of **12** (0.253 g, 1.35 mmol) in dichloromethane (4 cm^3). After 13 h at ambient temperature the separated organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography to afford the *title compound* **19** (0.409 g, 88%) as a colourless oil which crystallised with time, m.p. 100–101 °C (Found: C, 58.7; H, 5.2; N, 8.0, $C_{17}H_{18}N_2O_4S$ requires C, 59.0; H, 5.2; N, 8.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1643, 1590, 1340 and 1085; δ_H(250 MHz; $CDCl_3$) 2.93/3.08 (3 H, 2s, NMe), 3.81/3.83 (2 H, 2s), 3.90/3.93 (3 H, 2s, OMe), 4.54/4.59 (2 H, 2s), 6.90/6.95 (1 H, 2d, *J* 9), 7.15–7.52 (5 H, m), 7.81/7.97 (1 H, 2d, *J* 2.8) and 8.22/8.15 (1 H, 2dd, J_1 9, J_2 2.8); *m/z* 346 (M^+, 1.1%), 316 (1) and 237 (2).

N-(3-Amino-6-methoxybenzyl)-N-methyl(phenylthio)acetamide **20**.—A mixture of compound **19** (0.409 g, 1.2 mmol), 10% palladium on charcoal (0.175 g) and ethyl acetate (17 cm^3) was stirred under an 80 psi* pressure of hydrogen for 18 h. The catalyst was filtered off and rinsed with dichloromethane (3 × 15 cm^3). Removal of the solvents under reduced pressure afforded the *title compound* **20** (0.365 g, 98%) as a colourless oil which needed no further purification (Found: C, 64.9; H, 6.6; N, 9.0; S, 10.2. $C_{17}H_{20}N_2O_2S$ requires C, 64.6; H, 6.3; N, 8.9; S, 10.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440 (NH), 3380 (NH), 1638, 1462, 1438, 1400, 1082 and 1022; δ_H(250 MHz; $CDCl_3$) 2.80 (2 H, br s, NH), 2.94/3.01 (3 H, 2s), 3.74 (3 H, s), 3.82/3.84 (2 H, 2s), 4.46/4.56 (2 H, 2s), 6.38–6.74 (3 H, m) and 7.15–7.50 (5 H, m); *m/z* 316 (M^+, 82%), 207 (25) and 94 (100).

N-(3-tert-Butoxycarbonylamino-6-methoxybenzyl)-N-methyl(phenylthio)acetamide **21**.—Di-*tert*-butyl dicarbonate (0.70 cm^3, 3 mmol) was added to a solution of **20** (0.365 g, 1.2 mmol) in dry chloroform (12 cm^3). After 4 h at reflux the cooled solution was diluted with dichloromethane (40 cm^3), washed with water (2 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography to afford the *title compound* **21** (0.445 g, 93%) as a white solid, m.p. 131–133 °C (Found: C, 63.7; H, 6.9; N, 6.7; S, 7.7. $C_{22}H_{28}N_2O_4S$ requires C, 63.5; H, 6.7; N, 6.7; S, 7.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440 (NH), 1720, 1640, 1365, 1156 and 908; δ_H(250 MHz; $CDCl_3$) 1.50 (9 H, s), 2.91/3.02 (3 H, 2s), 3.76/3.78 (3 H, 2s), 3.83/3.87 (2 H, 2s), 4.48/4.57 (2 H, 2s), 6.14/6.34 (1 H, 2 br s), 6.72–6.91 (2 H, m) and 7.16–7.55 (6 H, m); *m/z* 342 ($M^+ - C_4H_{10}O$, 29%), 233 (100) and 162 (71).

* 1 psi = *ca.* 6.895 × 10^3 Pa.

5-*Amino*-1,4-*dihydro*-8-*methoxy*-2-*methyl*-4-*phenylthio*-3(2H)-*isoquinolone* **9**.—*N*-Chlorosuccinimide (0.027 g, 0.2 mmol) was added, in one portion, to a solution of **21** (0.080 g, 0.19 mmol) in carbon tetrachloride (4 cm^3) and the mixture was stirred at ambient temperature for 1.5 h. The precipitated succinimide was filtered off and rinsed thoroughly with carbon tetrachloride and the filtrate was concentrated under reduced pressure to a white foam. This foam was dissolved in dichloromethane (3 cm^3) and to the solution was added a solution of stannic chloride (0.05 g, 0.19 mmol) in dichloromethane (55 mm^3), rapidly, in one portion. An indigo-coloured precipitate formed immediately and the mixture was stirred for a further hour. The contents of the reactor were poured into ice–water (50 cm^3). The separated aqueous layer was extracted with dichloromethane (4 × 10 cm^3) and then neutralised with ammonia and extracted with further dichloromethane (2 × 10 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography to afford the *title compound* **9** (0.030 g, 50%) as a viscous brown oil which could be crystallised from acetone–light petroleum as a brown solid, m.p. 69–71 °C (Found: M^+, 314.1077. $C_7H_{18}N_2O_2S$ requires *M*, 314.1089); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (br), 1646 and 1484; δ_H(250 MHz; $CDCl_3$) 2.80 (2 H, br s, NH), 2.96 (3 H, s), 3.08 (1 H, d, *J* 17), 3.67 (3 H, s), 4.04 (1 H, d, *J* 17), 4.64 (1 H, s), 6.60 (1 H, d, *J* 8.5), 6.68 (1 H, d, *J* 8.5) and 7.10–7.37 (5 H, m); *m/z* 314 (M^+, 28%) and 205 (100). The compound could not be obtained microanalytically pure and tended to darken rapidly with time or in solution, *e.g.* in $CDCl_3$.

N-(3-*Bromo*-6-*methoxybenzyl*)-N-*methyl*(*phenylthio*)*acetamide* **22**.—A solution of α-(phenylthio)acetyl chloride (1.76 g, 9.41 mmol) in dry dichloromethane (20 cm^3) was added dropwise to a stirred solution of benzylamine **11** (2.165 g, 9.41 mmol) and triethylamine (1.29 cm^3, 9.41 mmol) in dry dichloromethane (80 cm^3) at 0 °C. After being stirred for 1 h at ambient temperature the mixture was washed with water (2 × 100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography to afford the *title compound* **22** (3.31 g, 93%) as a colourless oil which crystallised with time, m.p. 77–79 °C (Found: C, 53.6; H, 4.7; Br, 20.8; N, 3.6; S, 8.7. $C_{17}H_{18}BrNO_2S$ requires C, 53.7; H, 4.7; Br, 21.0; N, 3.7; S, 8.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1640, 1350, 1120, 1085 and 1022; δ_H(250 MHz; $CDCl_3$) 2.9/3.0 (3 H, 2s), 3.76/3.77 (3 H, 2s), 3.78/3.80 (2 H, 2s), 4.47/4.55 (2 H, 2s), 6.70/6.73 (1 H, 2d, *J* 7.5) and 7.11–7.49 (7 H, m); *m/z* 381/379 (M^+, 26%), 272/270 (100) and 201/199 (62).

N-[3-(2-*Acetylanilino*)-6-*methoxybenzyl*]-N-*methyl*(*phenylthio*)*acetamide* **23**.—A mixture of compound **22** (3.31 g, 8.7 mmol), *o*-aminoacetophenone (3.54 g, 8.71 mmol), sodium carbonate (1.84 g, 17.4 mmol), finely-divided copper powder (0.05g, 0.8 mmol) and nitrobenzene (50 cm^3) was heated under reflux for 4 h. An analysis of the mixture (silica, 20% diethyl ether in dichloromethane) indicated a dominant mobile constituent with a distinctive yellow colour. The cooled mixture was filtered and the collected solids were rinsed thoroughly with dichloromethane. The filtrate was concentrated under reduced pressure, (0.8 mbar) at 100 °C to remove the nitrobenzene residue. The black oily residue was purified by chromatography to afford the *title compound* **23** (2.23 g, 59%) as a very viscous red oil which was converted into yellow blocky crystals with time, m.p. 108–110 °C (Found: C, 68.9; H, 6.0; N, 6.3; S, 7.5. $C_{25}H_{26}N_2O_3S$ requires C, 69.1; H, 6.0; N, 6.5; S, 7.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3260 (w), 1640, 1604, 1571, 1497, 1452, 1357, 1322, 1163, 1113 and 954; δ_H(250 MHz; $CDCl_3$) 2.64/2.66 (3 H, 2s), 2.93/3.04 (3 H, 2s), 3.79/3.87 (2 H, 2s), 3.81/3.83 (3 H, 2s), 4.52/4.62 (2 H, 2s), 6.67 (1 H, q, *J* 7.5), 6.80–7.47 (10 H, m), 7.80 (1 H, t, *J* 7.5) and 10.36 (1 H, br s); *m/z* 434 (M^+, 100%), 326 (20), 283 (38), 268 (41) and 110 (39).

5-(2-*Acetylanilino*)-1,4-*dihydro*-8-*methoxy*-2-*methyl*-4-*phenylthio*-3(2H)-*isoquinolone* **5**.—To a stirred solution of compound **23** (4.9 g, 11.3 mmol) in dry carbon tetrachloride (150 cm^3) at 0 °C under argon was added *N*-chlorosuccinimide (1.7 g, 12.7 mmol) in one portion. After being stirred at room temperature overnight the slurry was filtered, and the solids washed well with chilled carbon tetrachloride. The solvents were then removed from the combined organic solutions under reduced pressure and the residue was redissolved in dry dichloromethane (50 cm^3) and cooled in an ice-bath under argon. To this solution was added dropwise a solution of stannic chloride (1 mol dm^{-3} in dichloromethane; 11.3 cm^3) in dichloromethane (30 cm^3). After 2 h, brine (200 cm^3) was added with vigorous stirring. After 10 min the aqueous layer was decanted off. This process was repeated twice and the organic solution remaining was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on silica (eluting with ether) gave the *title compound* **5** (3.3 g, 68%) as an unstable yellow solid, m.p. 172–174 °C (Found: M^+, 432.1507. $C_{25}H_{24}N_2O_3S$ requires M, 432.1508); $\nu_{max}(CHCl_3)/cm^{-1}$ 3250(br), 2960, 2931, 1730, 1667, 1647, 1572 and 1270; δ_H(500 MHz; $CDCl_3$) 10.42 (1 H, br s), 7.79 (1 H, dd, 8.0, *J* 1.5), 7.35–7.15 (8 H, m), 6.79 (1 H, d, *J* 8.5), 6.73 (1 H, dd, *J* 8.5, 1.0), 6.69 (1 H, td, *J* 7.0, 1.0), 4.72 (1 H, s), 4.10 (1 H, d, *J* 17.0), 3.81 (3 H, s), 3.20 (1 H, d, *J* 17.0), 2.95 (3 H, s) and 2.65 (3 H, s); *m/z* (220 °C) 432 (M^+, 13%), 323 (59), 305 (58) and 110 (100).

N-[3-(2-*Acetylanilino*)-6-*methoxybenzyl*]-N-*methyl*(*phenylsulphinyl*)*acetamide* **25**.—*m*-Chloroperoxybenzoic acid (80–85%; 0.750 g, 3.47 mmol) was added in portions over 20 min to a solution of compound **23** (1.503 g, 3.46 mmol) in dry dichloromethane (40 cm^3) at 0 °C. The mixture was stirred at ambient temperature for a further 40 min and then washed with saturated aqueous sodium hydrogen carbonate (3 × 40 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography to afford the *title compound* **25** (1.349 g, 87%) as a bright yellow foam (Found: C, 66.7; H, 5.8; N, 6.1; $C_{25}H_{26}N_2O_4S$ requires C, 66.7; H, 5.8; N, 6.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3270w, 1637, 1570, 1360, 1163, 1082, 1020, 953 and 907; δ_H(250 MHz; $CDCl_3$) 2.66 (3 H, s), 2.87/2.89 (3 H, 2s), 3.78/3.82 (3 H, 2s), 3.82–4.70 (4 H, m), 6.62–7.86 (12 H, m) and 10.34 (1 H, br s); *m/z* 450 (M^+, 27%), 434 (100), 340 (16), 326 (21), 283 (65), 268 (65) and 110 (65).

5-*Methoxy*-3,7-*dimethyl*-1-*phenylthio*-3,4-*dihydrobenzo*[b]-[1,8]*phenanthrolin*-2(1H)-*one* **1**.—(*a*) *From* **25**. Concentrated sulphuric acid (7 cm^3) was added, in one portion, to a solution of compound **25** (1.349 g, 3 mmol) in glacial acetic acid (50 cm^3). The mixture was immediately immersed in an oil bath preheated to 130 °C. The solution became dark red after 0.5 min at reflux. Heating at reflux was continued for a further 10 min. This reaction was repeated on a further portion of **25** (0.15 g, 0.33 mmol), again employing sulphuric acid (1 cm^3) and glacial acetic acid (4 cm^3). After cooling to room temperature the respective solutions were combined and added cautiously dropwise to a mixture of ammonia (*d* 0.88; 90 cm^3) and ice (100 g). The resulting mixture, containing a light green precipitate, was extracted with dichloromethane (4 × 60 cm^3) and diethyl ether (1 × 50 cm^3). These extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue (a dark green foam) was purified by chromatography to afford the *title compound* **1** (0.454 g, 37%) as a light brown foam which could be crystallised from dichloromethane–light

petroleum (b.p. 60–80 °C) as shiny grey-green crystals, m.p. 237–241 °C (Found: C, 72.5; H, 5.3; N, 6.7; S, 7.9. $C_{25}H_{22}N_2O_2S$ requires C, 72.5; H, 5.3; N, 6.8; S, 7.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1647, 1571, 1466, 1462, 1420, 1352, 1329, 1270, 1128, 1093, 988 and 918; δ_H(250 MHz; $CDCl_3$) 3.67, [6 H, 2s, (3.673, NMe) and (3.665, COMe)], 3.20 (1 H, dd, J_1, 18.1, J_2 1.9), 3.93 (3 H, s), 4.09 (1 H, dd, J_1 18.1, J_2 0.9), 6.11 (1 H, s), 7.11 (1 H, s), 7.13–7.39 (5 H, m), 7.52 (1 H, t, J 7.8), 7.68 (1 H, t, J 7.8) and 8.14 (1 H, t, J 8.1); δ_C(62.9 MHz; $CDCl_3$) 167.52, 152.52, 146.64, 141.45, 138.96, 136.25, 132.76, 132.35, 131.25, 128.91, 128.49, 128.21, 127.36, 125.93, 125.82, 125.49, 123.76, 98.76, 55.50, 48.56, 46.09, 34.45 and 13.68; m/z 414 (M^+, 10%), 304 (100), 276 (20), 233 (38) and 110 (92); pre-irradiation of the singlet at δ 3.93 (OMe) resulted in enhancement of the singlet at δ 7.11 [–C*H*=C(OMe)].

(*b*) *from* **5**. To a stirred solution of **5** (3.0 g, 6.9 mmol) in glacial acetic acid (100 cm^3) was added concentrated sulphuric acid (10 cm^3) diluted in acetic acid (10 cm^3). This solution was stirred under vigorous reflux for 30 min and then allowed to cool. After neutralisation of the solution with concentrated aqueous ammonia the product was extracted with dichloromethane (3 × 100 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed on silica (eluting with chloroform–methanol) to give the *title compound* **1** which was crystallised from dichloromethane–light petroleum as a grey–green solid (2.27 g, 79%) with data as described previously.

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