Synthesis of Indolin-2-ones (Oxindoles) Related to Mitomycin A

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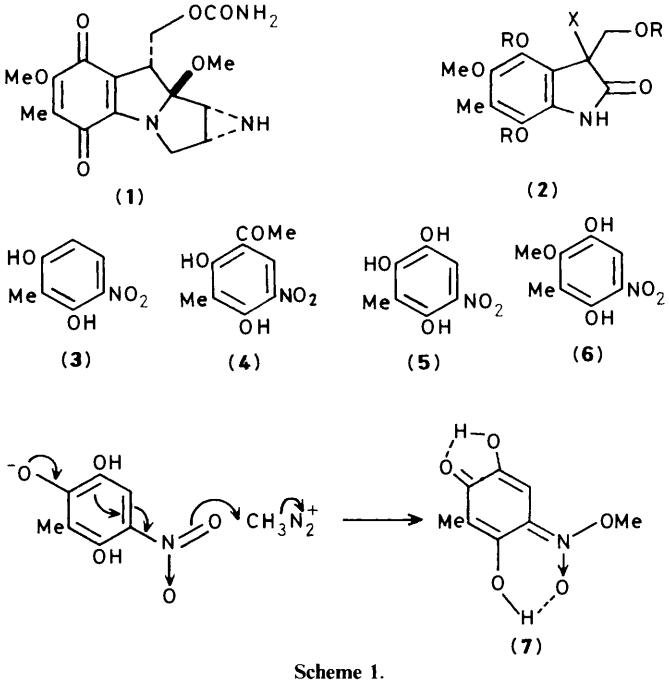
Oxindoles (indolin-2-ones) containing the functionality of the first two rings of the mitomycin A structure have been synthesized. Attempts to employ the oxindole grouping to construct the third ring were unsuccessful because of the resistance of the oxindole group or its derivatives towards nucleophilic attack. An unusual methylation of 3-methyl-5-nitrobenzene-1,2,4-triol to give the (*E*)-3,6-dihydroxy-2-methyl-1,4-benzoquinone 4-methoxyimine *N*-oxide is noted. A novel indole formation is described.

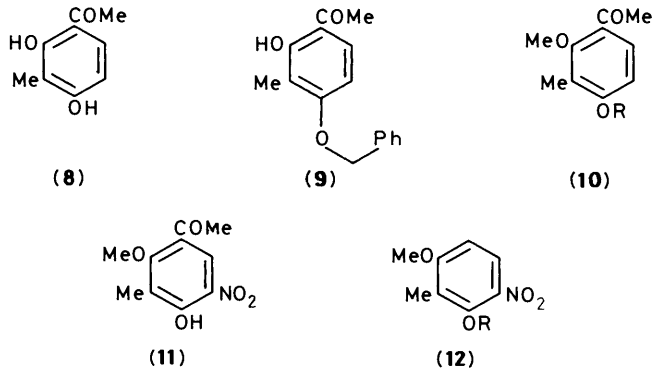
The mitomycins, exemplified by mitomycin A (**1**), are a structurally related group of mould metabolites which have attracted considerable attention because of their antibiotic action and antitumour activity. Synthetic approaches to these systems have been intensively studied, culminating in the brilliant synthesis of mitomycin A and other members of the group by Kishi and his co-workers.[1] To examine an alternative, possibly shorter, approach we planned to synthesize precursor oxindoles (indolin-2-ones) of type (**2**). It was hoped that the required third ring could be constructed by interaction between the carbonyl group of (**2**), or a derivative thereof, and a suitable acetylenic nucleophile. The envisaged ready elimination of the resulting tertiary oxygen function in the product to give an indole was to be prevented by a removable blocking group X in the starting indole.

Oxindoles of type (**2**) where the blocking group X is SMe were synthesized by the following route. Nitrosation of 2-methylresorcinol and subsequent oxidation with dilute nitric acid gave the mononitro compound (**3**); an attempted direct nitration was unsuccessful. Friedel-Crafts acetylation yielded the substituted acetophenone (**4**) which was oxidised to the nitro triol (**5**) by alkaline hydrogen peroxide. The action of diazomethane on (**5**) was expected to involve the most acidic phenolic centre to give the required 2-methoxy-3-methyl-5-nitrobenzene-1,4-diol (**6**). This was indeed obtained, but as a by-product there was formed a deep scarlet compound[2] shown by *X*-ray crystallography[3] to possess the structure (**7**). The formation of (**7**) may be readily rationalised by the pathway shown (Scheme 1). Because of the intervention of this unwanted, though interesting, product a more efficient process for the preparation of (**6**) was worked out. Acetylation of 2-methylresorcinol with boron trifluoride–acetic anhydride gave the dihydroxyacetophenone (**8**), which was selectively benzylated at the non-hydrogen bonded hydroxy group to give (**9**). Methylation of (**9**) and hydrogenolytic debenzylation then produced (**10**; R = H) which was nitrated to give the nitrophenolic ketone (**11**). Baeyer-Villiger oxidation of (**11**) gave the same hydroquinone (**6**) as that obtained by the first route; this procedure also provided unambiguous indication of the position of the methoxy group in (**6**). Attempts were also made to obtain the intermediate ketone (**11**) by acetylation of the nitrophenol (**12**; R = H), readily obtainable by selective methylation of the nitroresorcinol (**3**). However, (**12**) proved very resistant to electrophilic attack under a variety of conditions.

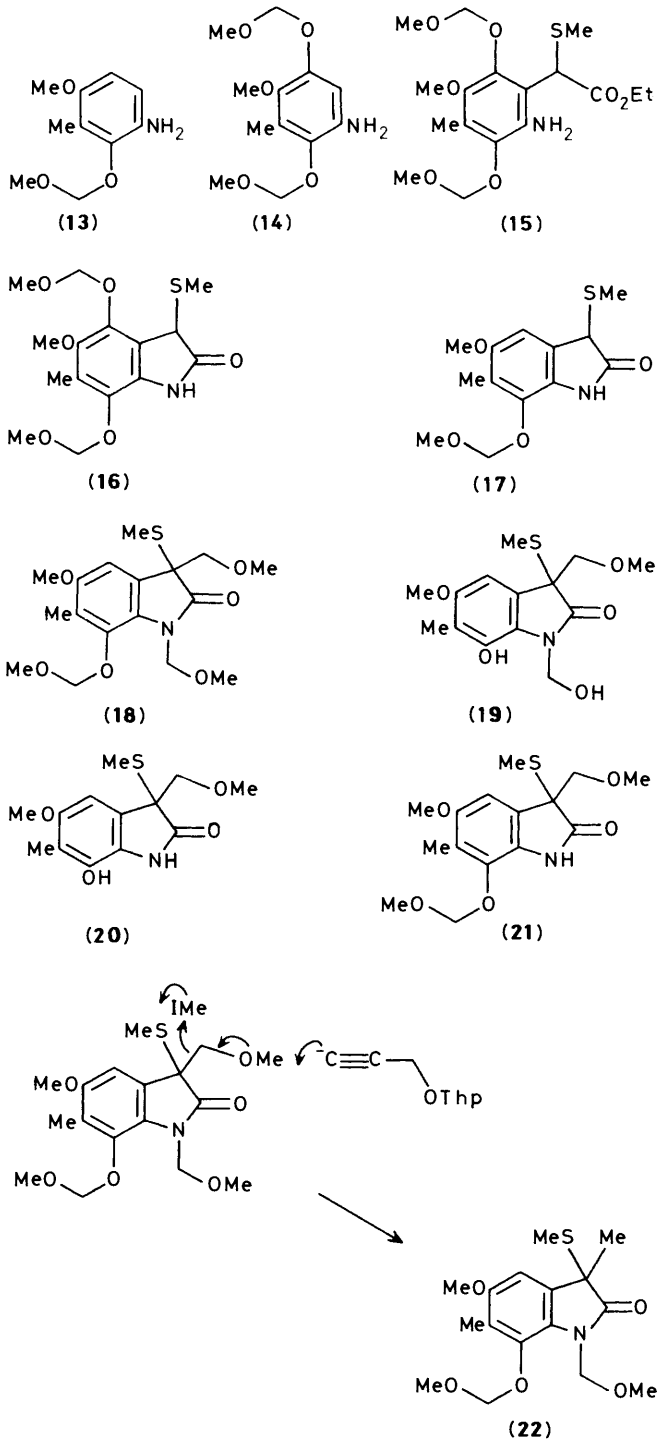
The hydroquinone (**6**) was converted into its bismethoxymethyl ether, which was catalytically hydrogenated to give the corresponding amine (**14**). Treatment of this amine by the Gassman procedure[4] with the chlorosulphonium chloride derived from ethyl methylthioacetate and chlorine and then with triethylamine at −78 °C produced the required amino ester (**15**), which was cyclised in fair yield to the oxindole (**16**) by boiling xylene. The related more readily available amine



Scheme 1.



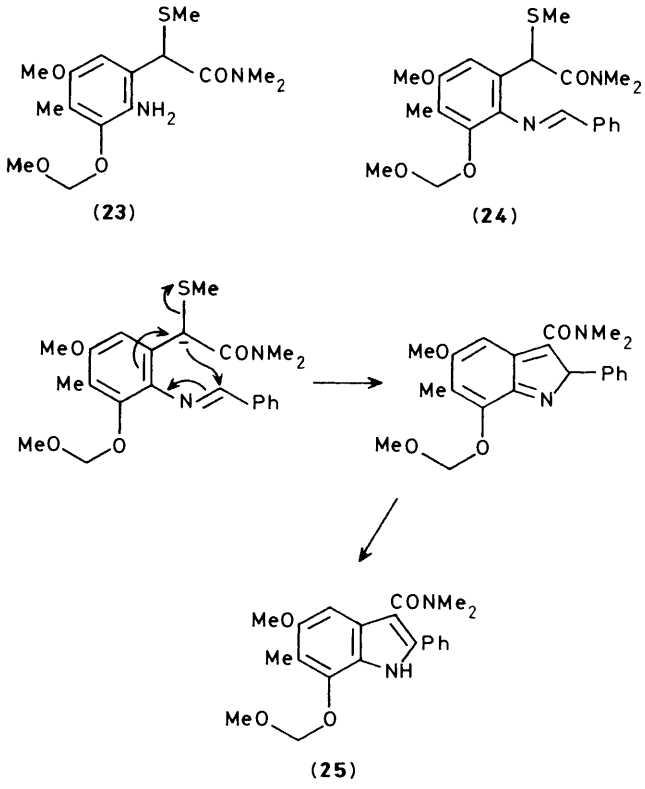
(**13**) similarly gave the corresponding oxindole (**17**) in high yield, and this more accessible oxindole was used as a model for further elaboration. Attempted methoxymethylation at C-3 with chloromethyl methyl ether and a variety of bases gave very unpromising results. However, use of the unusual base lithio-(tetrahydropyranyloxy)propyne (LTPP) was very effective, and methoxymethylation gave the *C*,*N*-dialkylated oxindole (**18**) in high yield. Attempts to monoalkylate (**17**) selectively at C-3 were unsuccessful; use of one equivalent of the base produced



Scheme 2.

only a mixture of dialkylated product (**18**) and starting material. However, the monoalkylated compound (**21**) could be prepared from (**18**) by the following procedure. Hydrolysis of (**18**) with aqueous acid gave the isolable *N*-hydroxymethyl compound (**19**), which by treatment with LTPP gave the phenol (**20**). Alkylation of this product with chloromethyl methyl ether and di-isopropylethylamine gave the required compound (**21**).

The subsequent synthetic plan involved interaction of the carbonyl group of the oxindole (**18**) or (**21**) with LTPP-(now functioning as a nucleophile) followed by *O*-methylation of the

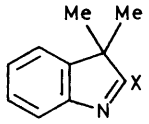


Scheme 3.

resulting alkoxide. Procedures of catalytic partial hydrogenation, aziridine formation at the resulting *Z*-double bond, and subsequent cyclisation would provide a plausible route to the third ring of the mitomycin structure. However, the oxindole (**18**) proved to be very resistant towards attack by LTPP or the corresponding Grignard derivative, and use of forcing conditions gave intractable mixtures. Treatment of (**18**) with LTPP in *N*,*N*-dimethylformamide at 75 °C followed by quenching with methyl iodide did give a modest yield of isolable material. However, this proved to be the C-3 methylated product (**22**) presumably formed by base-induced elimination of formaldehyde (Scheme 2).

In view of this inertness of the carbonyl group of the oxindole (**18**) it was decided to obtain the tertiary amide of its open-chain precursor to see whether the acyclic carbonyl function would be more amenable to nucleophilic attack to provide a synthetically useful ketone. Accordingly the Gassman procedure was carried out using the amine (**13**) and the chlorosulphonium chloride derived from *N*,*N*-dimethyl(methylthio)acetamide. The conversion proceeded in fair yield to give the required amino amide (**23**), treatment of which with benzaldehyde furnished the imine (**24**). Attempted methoxymethylation of this product with chloromethyl methyl ether and base surprisingly gave the α-phenylindole (**25**) exclusively. The formation of (**25**) may be rationalised as a cyclisation involving extrusion of methanethiolate (Scheme 3).

The imino chloride or imino ether derived from the oxindole (**21**) could be envisaged as alternative candidates for nucleophilic attack by LTPP. However, this was not attempted in view of the discouraging results obtained with the corresponding derivatives of the simple model 3,3-dimethyloxindole. The corresponding imino chloride (**26**; X = Cl) reacted readily with water to reform the starting oxindole, and with lithium phenylmethanethiolate to give the sulphide (**26**; X = SCH_2Ph). However, it was completely resistant to LTPP,



(26)

the corresponding copper(I) and silver salts, and the trimethylsilyl derivative in the presence of aluminium chloride. The corresponding imino ether (**26**; X = OMe) was likewise inert to carbon nucleophiles.

Experimental

^{1}H N.m.r. spectra were run with Varian HA100 and CFT-20 instruments (tetramethylsilane as internal standard). I.r. spectra were recorded with a Perkin-Elmer 257 grating instrument, and u.v. spectra with a Unicam SP 1800 spectrometer. Mass spectra were recorded with a Kratos MS30 instrument. Analytical t.l.c. was carried out on Merck Kieselgel 60 F_{254} pre-coated plates, and preparative thick layer chromatography on 20 × 20 cm plates coated to a thickness of 1.3 mm with Kieselgel PF_{254}. M.p.s were measured with a Kofler hot-stage apparatus.

2-Methyl-4-nitrosoresorcinol.—A solution of sulphuric acid (5 ml) in water (200 ml) was added dropwise over 30 min to a vigorously stirred mixture of 2-methylresorcinol (16.1 g, 130 mmol), sodium nitrite (21.3 g, 340 mmol), ice (750 g), and water (250 ml). The mixture was stirred for a further 30 min and the yellow precipitate filtered off, washed with a little cold water, and dried *in vacuo*. The product (19.5 g, 98%) crystallised from aqueous ethanol as a yellow *monohydrate*, m.p. 161—163 °C (decomp.) (Found: C, 49.1; H, 5.2; N, 8.25. $C_7H_7NO_3 \cdot H_2O$ requires C, 49.1; H, 5.3; N, 8.2%); $\nu_{max.}$ (Nujol) 3 100—3 500, 1 620, 1 100, 1 080, and 865 cm^{-1}; δ[$(CD_3)_2SO$] 1.78 (3 H, s, ArMe), 6.24 (1 H, d, *J* 10 Hz, ArH), and 7.39 (1 H, d, *J* 10 Hz, ArH); *m/z* 153 (M^+, 100%), 136 (24), 109 (25), 108 (15), and 107 (25).

2-Methyl-4-nitroresorcinol (**3**).—2-Methyl-4-nitrosoresorcinol (15 g, 98 mmol) was stirred in water (15 ml) and concentrated nitric acid (40 ml) added dropwise over 1 h at room temperature. The mixture was stirred for a further 1 h, diluted with saturated brine (150 ml), and extracted with ether (3 × 150 ml). Washing (brine), drying ($MgSO_4$), and evaporation gave a residue that was dissolved in ether (30 ml) and chromatographed on Florisil (250 g; 80—100 mesh). Elution with ether, evaporation, and crystallisation from benzene gave the *nitro compound* (10.65 g, 64%) as yellow needles, m.p. 128—129 °C (Found: C, 50.1; H, 4.15; N, 8.15. $C_7H_7NO_4$ requires C, 49.7; H, 4.15; N, 8.25%); $\nu_{max.}$ (Nujol) 3 400, 1 620, and 1 600 cm^{-1}; δ[$(CD_3)_2CO$] 2.16 (3 H, s, ArMe), 6.55 (1 H, d, *J* 10 Hz, ArH), and 7.82 (1 H, d, *J* 10 Hz, ArH); *m/z* 169 (M^+, 100%), 151 (16), 139 (11), and 123 (20).

2′,4′-Dihydroxy-3′-methyl-5′-nitroacetophenone (**4**).—2-Methyl-4-nitroresorcinol (15 g) was added in portions to a stirred solution of aluminium chloride (26.6 g) in nitrobenzene (200 ml) cooled to 5 °C. Acetic anhydride (12.5 ml) was then added dropwise and the resulting red mixture heated at 80 °C for 7 h. The cooled mixture was poured into ice–water (*ca.* 500 g) and extracted with chloroform (3 × 100 ml). The product was removed from this extract by washing with aqueous sodium hydroxide (5%; 5 × 100 ml). The aqueous extract was acidified with concentrated hydrochloric acid and the precipitated product taken up in chloroform. Treatment with charcoal, drying ($MgSO_4$), and evaporation followed by crystallisation from toluene gave the *ketone* (**4**) as cream plates (13.7 g, 73%), m.p. 178—179 °C (Found: C, 51.0; H, 4.4; N, 6.5. $C_9H_9NO_5$ requires C, 51.05; H, 4.3; N, 6.25%); $\nu_{max.}$($CHCl_3$) 3 300—2 600, 1 645, 1 620, and 1 460 cm^{-1}; δ($CDCl_3$) 2.15 (3 H, s, ArMe), 2.7 (3 H, s, COMe), 8.58 (1 H, s, ArH), 11.29 (1 H, s, ArOH), and 13.1 (1 H, s, ArOH); *m/z* 211 (M^+, 50%), 196 (100), 150 (27).

2-Methoxy-3-methyl-5-nitro-1,4-hydroquinone (**6**) *and* (E)-*3,6-Dihydroxy-2-methyl-1,4-benzoquinone 4-Methoxyimine N-Oxide* (**7**).—Hydrogen peroxide solution (6%; 176 ml) was added dropwise over 45 min to a stirred solution of 2′,4′-dihydroxy-3′-methyl-5′-nitroacetophenone (17.5 g) in aqueous sodium hydroxide (0.5M; 503 ml) at 0 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for a further 2 h. Cooling in ice and acidification with concentrated hydrochloric acid precipitated the nitrohydroquinone as an orange solid. After extraction with ether (3 × 250 ml), washing with brine, and drying ($MgSO_4$), the ethereal solution was evaporated under reduced pressure (to 250 ml) and cooled to 0 °C. Ethereal diazomethane was then added dropwise until t.l.c. indicated disappearance of starting material (6 h). The precipitated *N*-oxide (**7**) was filtered off and the filtrate evaporated to dryness; the residue was chromatographed on a silica column (500 g; Merck Kieselgel 60). Elution with ether–light petroleum (1:9) gave a small forerun (400 mg) of the dimethoxy derivative. The main monomethoxy product was eluted with ether–light petroleum (3:7) to yield, after evaporation, the *nitrohydroquinone* (**6**) which crystallised from benzene in yellow needles (7.1 g, 43%), m.p. 137—139 °C (Found: C, 48.15; H, 4.6; N, 7.1. $C_8H_9NO_5$ requires C, 48.1; H, 4.55; N, 7.0%); $\nu_{max.}$($CHCl_3$) 3 540, 1 480, 1 106, 1 046, 995, and 872 cm^{-1}; $\lambda_{max.}$(EtOH) 221 (ε 10 600), 314 (6 100), and 407 nm (3 700); δ($CDCl_3$) 2.27 (3 H, s, ArMe), 3.91 (3 H, s, ArOMe), 5.4 (1 H, s, ArOH), 7.58 (1 H, s, ArH), and 10.8 (1 H, s, ArOH); *m/z* 199 (M^+, 100%).

The precipitate of (**7**) was washed with ether and crystallised from acetonitrile to give scarlet needles (1.3 g, 8%), m.p. 146 °C (decomp.) (Found: C, 48.35; H, 4.65; N, 6.9. $C_8H_9NO_5$ requires C, 48.1; N, 4.55; N, 7.0%); $\nu_{max.}$(Nujol) 3 280, 1 590, 1 158, 900, and 830 cm^{-1}; $\lambda_{max.}$(EtOH) 217 (ε 10 700), 281 (5 000), and 346 nm (8 700); δ(CF_3CO_2D) 2.29 (3 H, s, =CMe), 4.43 (3 H, s, NOMe), and 7.45 (1 H, s, =CH); *m/z* 199 (M^+, 27%), 183 (6), 180 (13), 169 (60), 168 (67), 167 (100), 153 (47), and 138 (17).

2′,4′-Dihydroxy-3′-methylacetophenone (**8**).—To a stirred mixture of boron trifluoride–ether complex (100 ml) and 2-methylresorcinol (49.7 g) at 0 °C acetic anhydride (46 g) was added dropwise, and the mixture was then heated at 70—80 °C for 6 h. The cooled mixture was then poured into ice–water and the precipitated oil stirred until solidification was complete. Decantation and crystallisation from water gave the *ketone* (**8**) as needles (52 g, 78%), m.p. 157—158 °C (Found: C, 64.85; H, 6.35. $C_9H_{10}O_3$ requires C, 65.06; H, 6.05%); $\nu_{max.}$(Nujol) 3 200, 1 630, and 1 595 cm^{-1}; δ[$(CD_3)_2CO$] 2.06 (3 H, s, ArMe), 2.52 (3 H, s, ArCOMe), 6.46 (1 H, d, *J* 9 Hz, ArH), 7.58 (1 H, d, *J* 9 Hz, ArH), 9.1 (1 H, s, OH), and 13.04 (1 H, s, OH); *m/z* 166 (M^+, 40%) and 151 (100).

4′-Benzyloxy-2′-hydroxy-3′-methylacetophenone (**9**).—A mixture of the ketone (**8**) (50 g), benzyl chloride (40 g), potassium iodide (5 g), and anhydrous potassium carbonate (43.6 g) in acetone (500 ml) was stirred and heated under reflux for 18 h, cooled, filtered, and evaporated. The residue crystallised from methanol to give the benzylated *acetophenone* (**9**) as needles (62.5 g, 81%), m.p. 87—88 °C (Found: C, 75.0; H, 6.4. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%); $\nu_{max.}$($CHCl_3$) 1 630, 1 105, 775, 735, and 705 cm^{-1}; δ($CDCl_3$) 2.18 (3 H, s, ArMe), 2.54 (3 H, s, ArCOMe), 5.16 (2 H, s, CH_2Ph), 6.47 (1 H, d, *J* 9 Hz, ArH), 7.38

(5 H, s, CH_2Ph), 7.54 (1 H, d, *J* 9 Hz, ArH), and 12.76 (1 H, br s, OH); *m/z* 256 (M^+, 45%) and 91 (100).

4'-Benzyloxy-2'-methoxy-3'-methylacetophenone (**10**; R = $PhCH_2$).—A mixture of the ketone (**9**) (62 g), dimethyl sulphate (35.6 g), and anhydrous potassium carbonate (167 g) in acetone (500 ml) was stirred and heated under reflux for 30 h. The cooled mixture was filtered and evaporated, and the product chromatographed on a silica column (500 g; Merck Kieselgel 60) using ethyl acetate–light petroleum as eluant. Removal of solvent left the *acetophenone* (**10**: R = $PhCH_2$) as an oil, b.p. 152—158 °C at 0.5 mmHg (53.5 g, 82%) (Found: C, 75.7; H, 6.7. $C_{17}H_{18}O_3$ requires C, 75.55; H, 6.5%); $\nu_{max.}$($CHCl_3$) 1 670, 1 590, 1 275, and 1 110 cm^{-1}; δ($CDCl_3$) 2.2 (3 H, s, ArMe), 2.57 (3 H, s, ArCOMe), 3.72 (3 H, s, ArOMe), 5.07 (2 H, s, CH_2Ph), 6.67 (1 H, d, *J* 9 Hz, ArH), 7.34 (5 H, s, CH_2Ph), and 7.53 (1 H, d, *J* 9 Hz, ArH); *m/z* 270 (M^+, 35%) and 91 (100).

4'-Hydroxy-2'-methoxy-3'-methylacetophenone (**10**; R = H).—A solution of the acetophenone (**10**; R = $PhCH_2$) (53 g) in ethanol (500 ml) was hydrogenated at room temperature and pressure in the presence of palladium–carbon (10%; 1.5 g) until reaction was complete. Filtration and evaporation gave the *phenol* (**10**; R = H), which crystallised from aqueous ethanol in needles (33.5 g, 92%), m.p. 130—132 °C (Found: C, 66.8; H, 6.7. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.65%); $\nu_{max.}$ (Nujol) 3 580, 3 290, 1 675, and 1 275 cm^{-1}; δ[$CDCl_3$—$(CD_3)_2SO$] 2.16 (3 H, s, ArMe), 2.57 (3 H, s, ArCOMe), 3.74 (3 H, s, ArOMe), 6.66 (1 H, d, *J* 9 Hz, ArH), and 7.44 (1 H, d, *J* 9 Hz, ArH); *m/z* 180 (M^+, 50%), 166 (40), 165 (100), and 151 (52).

4'-Hydroxy-2'-methoxy-3'-methyl-5'-nitroacetophenone (**11**).—To a solution of the phenol (**10**; R = H) (32 g) in acetic acid (100 ml) was added 5 ml of a solution of concentrated nitric acid (12 ml) in acetic acid (25 ml). The solution was warmed to 40 °C and, after an initial period of 15 min, the remaining nitric–acetic mixture was added dropwise with stirring. After a further 1 h at room temperature, water (25 ml) was added, and the solution was reduced in volume (50 ml) under reduced pressure, poured into water, and extracted with ether (3 × 300 ml). Washing with brine, drying ($MgSO_4$), treatment with charcoal, filtration, and evaporation gave the *nitrophenol* (**11**), which crystallised from aqueous ethanol as yellow needles (26 g, 64%), m.p. 69 °C (Found: C, 53.1; H, 5.0; N, 6.1. $C_{10}H_{11}NO_5$ requires C, 53.3; H, 4.9; N, 6.2%); $\nu_{max.}$($CHCl_3$) 3 200, 1 685, 1 615, 1 530, 1 360, 1 280, and 1 155 cm^{-1}; δ($CDCl_3$) 2.28 (3 H, s, ArMe), 2.63 (3 H, s, ArCOMe), 3.87 (3 H, s, ArOMe), 8.4 (1 H, s, ArH), and 11.31 (1 H, s, OH); *m/z* 225 (M^+, 27%), 210 (100), 164 (25), and 151 (30).

Treatment of this product in dichloromethane with *m*-chloroperbenzoic acid and sulphuric acid (catalyst) gave 2-methoxy-3-methyl-5-nitro-1,4-hydroquinone (**6**) (77%) identical with the compound obtained as already described.

3-Methoxy-2-methyl-6-nitrophenol (**12**; R = H).—A mixture of 2-methyl-4-nitroresorcinol (20 g), anhydrous potassium carbonate (17.2 g), dimethyl sulphate (15.7 g), and acetone 150 ml) was stirred for 18 h. The acetone was removed under reduced pressure and the residue triturated with water (100 ml), acidified with hydrochloric acid (2M), and extracted with ether (3 × 150 ml). Washing with brine, drying ($MgSO_4$), and evaporation gave the *nitrophenol* (**12**; R = H), which crystallised from light petroleum in yellow prisms (17.1 g, 79%), m.p. 68—69 °C (Found: C, 52.3; H, 4.75; N, 7.4. $C_8H_9NO_4$ requires C, 52.45; H, 4.95, N, 7.65%); $\nu_{max.}$($CHCl_3$) 3 200, 1 625, 1 540, 1 485, and 1 115 cm^{-1}; δ($CDCl_3$) 2.12 (3 H, s, ArMe), 3.91 (3 H, s, ArOMe), 6.47 (1 H, d, *J* 9 Hz, ArH), 7.95 (1 H, d, *J* 9 Hz, ArH), and 11.03 (1 H, s, OH); *m/z* 183 (M^+, 100%).

6-Methoxy-2-methoxymethoxy-3-nitrotoluene (**12**; R = CH_2OMe).—To a solution of the nitrophenol (**12**; R = H) (20 g) and *N*,*N*-di-isopropylethylamine (21.2 g) in dichloromethane (100 ml) cooled to 0 °C was added dropwise a solution of chloromethyl methyl ether (13.2 g). The mixture was allowed to warm to room temperature and stirred for 30 min. Washing with water (150 ml), ice-cold hydrochloric acid (0.1M; 2 × 100 ml), and water (100 ml), drying ($MgSO_4$), and evaporation gave the *nitro ether* (**12**; R = CH_2OMe), which crystallised in needles (23.5 g, 95%), m.p. 42—43 °C (Found: C, 53.0; H, 5.7; N, 6.25. $C_{10}H_{13}NO_5$ requires C, 52.85; H, 5.75; N, 6.15%); $\nu_{max.}$ 1 595, 1 522, 1 350, 1 285, 1 122, 1 080, and 980 cm^{-1}; δ($CDCl_3$) 2.2 (3 H, s, ArMe), 3.56 (3 H, s, OCH_2OMe), 3.9 (3 H, s, ArOMe), 5.04 (2 H, s, OCH_2O), 6.64 (1 H, d, *J* 9 Hz, ArH), and 7.78 (1 H, d, *J* 9 Hz, ArH); *m/z* 227 (M^+, 100%), 197 (25), 181 (21), 166 (25), and 165 (35).

6-Methoxy-2,5-bis(methoxymethoxy)-3-nitrotoluene.—This was prepared analogously from the nitrohydroquinone (**6**) (7.0 g), *N*,*N*-di-isopropylethylamine (13.64 g), and chloromethyl methyl ether (5.95 g) in dichloromethane (100 ml). The crude product was purified by chromatography on silica (300 g; Merck Kieselgel 60) using ether–light petroleum (1:1) as eluant to give the *nitro ether* as a yellow oil (7.5 g, 74%) (Found: C, 50.45; H, 6.15; N, 5.05. $C_{12}H_{17}NO_7$ requires C, 50.15; H, 5.95; N, 4.9%); $\nu_{max.}$ ($CHCl_3$) 1 530, 1 485, 1 350, and 1 160 cm^{-1}; δ($CDCl_3$) 2.28 (3 H, s, ArMe), 3.52 and 3.57 (6 H, 2 × s, OCH_2OMe), 3.91 (3 H, s, ArOMe), 5.02 and 5.22 (4 H, 2 × s, OCH_2O), and 7.55 (1 H, s, ArH); *m/z* 287 (M^+, 43%) and 187 (100).

3-Amino-6-methoxy-2-methoxymethoxytoluene (**13**).—A solution of the nitro ether (**12**; R = CH_2OMe) (3 g) in methyl acetate (100 ml) was hydrogenated at room temperature and pressure over a prereduced palladium oxide–carbon catalyst (0.5 g; 10%). Removal of catalyst and solvent left the *amine* (**13**) as an oil (2.5 g, 96%), which rapidly darkened and was best used immediately (Found: C, 60.9; H, 7.8; N, 6.9. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.65; N, 7.1%); $\nu_{max.}$($CHCl_3$) 3 440, 3 360, 1 500, and 1 263 cm^{-1}; δ($CDCl_3$) 2.14 (3 H, s, ArMe), 3.58 (3 H, s, OCH_2OMe), 3.73 (3 H, s, ArOMe), 4.97 (2 H, s, OCH_2O), and 6.41—6.6 (2 H, ABq, *J* 9 Hz, ArH); *m/z* 197 (M^+, 100%), 165 (96), 152 (57), 150 (50), and 124 (41).

3-Amino-6-methoxy-2,5-bis(methoxymethoxy)toluene (**14**).—In analogous fashion the corresponding nitro ether (7.0 g) in methyl acetate (100 ml) was hydrogenated over a prereduced palladium oxide–carbon catalyst (0.5 g; 10%) to give the *amine* (**14**) as an oil (6.1 g, 97%) (Found: C, 56.3; H, 7.6; N, 5.6. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.45; N, 5.45%); $\nu_{max.}$($CHCl_3$) 3 450, 3 360, 1 611, 1 489, and 1 151 cm^{-1}; δ($CDCl_3$) 2.18 (3 H, s, ArMe), 3.5 and 3.58 (6 H, 2 × s, OCH_2OMe), 3.72 (3 H, s, ArOMe), 4.92 and 5.12 (4 H, 2 × s, OCH_2O), and 6.44 (1 H, s, ArH); *m/z* (M^+, 71%), 225 (14), 212 (48), and 180 (100).

5-Methoxy-4,7-bis(methoxymethoxy)-6-methyl-3-methylthioindolin-2-one (**16**).—Ethyl (methylthio)acetate (1.56 g) was added to a solution of chlorine (0.83 g) in dichloromethane (27 ml) cooled to −78 °C under nitrogen. After 5 min the stirred solution was treated dropwise with a solution of the amine (**14**) (6 g) in dichloromethane, the temperature being kept below −60 °C. The deep orange solution was stirred for 1 h at −78 °C; triethylamine (1.78 g) was then added and the stirring continued for 30 min. The mixture was allowed to attain room temperature and dry ether was added to precipitate triethylamine hydrochloride. Filtration and evaporation followed by chromatography on silica (500 g; Merck Kieselgel 60) using ether–light petroleum (1:1) as eluant furnished the methylthio

ester (**15**) (2.3 g) and unchanged amine (2 g). The unstable (**15**) (2.3 g) dissolved in xylene was heated under reflux for 40 min under nitrogen. Removal of solvent under reduced pressure and trituration with ether–light petroleum gave a solid which was crystallised from cyclohexane to give the *indolinone* (**16**) as plates, m.p. 104—105 °C (1.5 g, 74%) (Found: C, 52.6; H, 6.15; N, 3.65. $C_{15}H_{21}NO_6S$ requires C, 52.45; H, 6.15; N, 4.1%); $\nu_{max.}$($CHCl_3$) 3 315, 1 716, 1 158, and 1 063 cm^{-1}; δ($CDCl_3$) 2.14 (3 H, s, SMe), 2.2 (3 H, s, ArMe), 3.62 and 3.63 (6 H, 2 × s, CH_2OMe), 3.78 (3 H, s, ArOMe), 4.35 (1 H, s, C*H*SMe), 5.0 and 5.18 (4 H, 2 × s, OCH_2O), and 8.68 (1 H, br s, NH); *m/z* 343 (M^+, 28%), 252 (18), 251 (100), 219 (28), and 206 (14).

5-*Methoxy*-7-*methoxymethoxy*-6-*methyl*-3-*methylthio*-*indolin*-2-*one* (**17**).—In exactly the same manner, interaction of ethyl (methylthio)acetate (5.5 g) and chlorine (2.9 g) in dichloromethane (100 ml) with the amine (**13**) (16.1 g) gave the corresponding methylthio ester (7.8 g) and unchanged amine (4.7 g). Heating the unstable methylthio ester (4.75 g) in xylene gave the *indolinone* (**17**), which crystallised from toluene in needles (3.65 g, 90%), m.p. 150—151 °C (Found: C, 54.95; H, 6.15; N, 4.8. $C_{13}H_{17}NO_4S$ requires C, 55.1; H, 6.05; N, 4.95%); $\nu_{max.}$($CHCl_3$) 3 320, 1 715, 1 600, 1 473, 1 128, and 1 060 cm^{-1}; δ($CDCl_3$) 2.03 (3 H, s, SMe), 2.12 (3 H, s, ArMe), 3.61 (3 H, s, OCH_2OMe), 3.8 (3 H, s, ArOMe), 4.22 (1 H, s, C*H*SMe), 5.01 (2 H, s, OCH_2), 6.7 (1 H, s, ArH), and 8.54 (1 H, br s, NH); *m/z* 283 (M^+, 100%), 236 (52), 204 (22), and 191 (72).

5-*Methoxy*-7-*methoxymethoxy*-1,3-*bis*(*methoxymethyl*)-6-*methyl*-3-*methylthioindolin*-2-*one* (**18**).—A solution of butyl-lithium (1.6M in hexane; 3.64 ml) was added to tetrahydropyranyloxypropyne (0.82 g) in tetrahydrofuran (10 ml) cooled to −78 °C under nitrogen. To the mixture was added a solution of the indolinone (**17**) (0.75 g) in tetrahydrofuran (15 ml), and the stirred mixture was allowed to warm to −20 °C. Chloromethyl methyl ether (0.47 g) was then added and stirring continued at room temperature for 1 h. Evaporation, chromatography on silica, and crystallisation from aqueous ethanol gave the indolinone (**18**) (0.85 g, 85%), m.p. 65—68 °C (Found: C, 55.25; H, 7.0; N, 3.6%; M^+, 371.1392. $C_{17}H_{25}NO_6S$ requires C, 55.0; H, 6.8; N, 3.75%; *M*, 371.1403); $\nu_{max.}$ ($CHCl_3$) 1 710, 1 473, and 1 141 cm^{-1}; δ($CDCl_3$) 2.08 (3 H, s, SMe), 2.22 (3 H, s, ArMe), 3.32 (3 H, s, CCH_2OMe), 3.39 (3 H, s, OCH_2OMe), 3.59 (3 H, s, NCH_2OMe), 3.86 (3 H, s, ArOMe), 3.9 (2 H, s, CCH_2O), 5.06 (2 H, s, OCH_2O), 5.41 (2 H, s, NCH_2O), and 6.74 (1 H, s, ArH).

7-*Hydroxy*-1-*hydroxymethyl*-5-*methoxy*-3-*methoxymethyl*-6-*methyl*-3-*methylthioindolin*-2-*one* (**19**).—The indoline (**18**) (0.5 g) was dissolved in tetrahydrofuran (25 ml), hydrochloric acid (1M; 5 ml) was added, and the solution was heated under reflux under nitrogen for 6 h. Evaporation under reduced pressure, addition of ether (100 ml), washing with brine, drying ($MgSO_4$), and removal of solvent gave a product which was purified by preparative t.l.c. using ether as eluant. The *indolinone* (**19**) was obtained as a viscous oil (345 mg, 84%) (Found: M^+, 313.0986. $C_{14}H_{19}NO_5S$ requires *M*, 313.0984); $\nu_{max.}$($CHCl_3$) 3 300, 1 700, 1 700, 1 605, 1 472, and 1 120 cm^{-1}; δ($CDCl_3$) 1.96 (3 H, s, SMe), 2.13 (3 H, s, ArMe), 3.2 (3 H, s, CCH_2OMe), 3.8 (3 H, s, ArOMe), 3.82 (2 H, s, CCH_2O), 5.2—5.6 (2 H, ABq, *J* 6 Hz, CH_2OH), and 6.49 (1 H, s, ArH).

7-*Hydroxy*-5-*methoxy*-3-*methoxymethyl*-6-*methyl*-3-*methyl*-*thioindolin*-2-*one* (**20**).—A solution of butyl-lithium (1.6M in hexane; 0.81 ml) was added to tetrahydropyranyloxypropyne (187 mg) in tetrahydrofuran (2.5 ml) cooled to −78 °C under nitrogen. To the mixture was added a solution of the indolinone (**19**) (100 mg) in tetrahydrofuran, and the mixture was stirred at room temperature for 10 min. Hydrochloric acid (2M; 2 ml) and brine (25 ml) were added, and the mixture was extracted with ether (2 × 50 ml). The extract was washed with brine, treated with charcoal, and dried ($MgSO_4$). Evaporation left a residue which was purified by preparative t.l.c. using ether as eluant. Extraction of the major band gave the *indolinone* (**20**), obtained as a crystalline powder (45 mg, 48%), m.p. 184—187 °C (from aqueous ethanol) (Found: C, 54.9; H, 6.2; N, 4.75. $C_{13}H_{17}NO_4S$ requires C, 55.1; H, 6.05; N, 4.95%); $\nu_{max.}$($CHCl_3$) 3 300, 1 695, 1 610, 1 476, 1 340, and 1 135 cm^{-1}; δ($CDCl_3$) 1.96 (3 H, s, SMe), 2.16 (3 H, s, ArMe), 3.29 (3 H, s, CH_2OMe), 3.82 (3 H, s, ArOMe), 3.9 (2 H, s, CH_2O), and 6.5 (1 H, s, ArH); *m/z* 283 (M^+ 75%), 238 (110), 205 (64), and 136 (60).

The corresponding 7-methoxymethoxy derivative (**21**) was obtained by treating at 0 °C a solution of (**20**) (10 mg) and di-isopropylethylamine (7 mg) in dichloromethane (0.5 ml) with chloromethyl methyl ether (4.5 mg). The solution was allowed to warm to room temperature and stirred for a further 10 min. Removal of solvent under reduced pressure and purification by preparative t.l.c. gave the *indolinone* (**21**) as a cream coloured solid (10.5 mg), m.p. 115—119 °C (decomp.) (Found: M^+, 327.1136. $C_{15}H_{21}NO_5S$ requires *M*, 327.1141); $\nu_{max.}$($CHCl_3$) 3 300, 1 715, 1 130, and 1 070 cm^{-1}; δ($CDCl_3$) 1.96 (3 H, s, SMe), 2.16 (3 H, s, ArMe), 3.29 (3 H, s, CH_2OMe), 3.82 (3 H, s, ArOMe), 3.9 (2 H, s, OCH_2O), and 6.5 (1 H, s, ArH).

5-*Methoxy*-7-*methoxymethoxy*-1-*methoxymethyl*-3,6-*dimethyl*-3-*methylthioindolin*-2-*one* (**22**).—A solution of the indolinone (**18**) (50 mg) in dry dimethylformamide (1 ml) was added to a solution of the lithium acetylide prepared by treating 3-tetrahydropyranyloxypropyne (19 mg) in dimethylformamide (2 ml) at −78 °C under nitrogen with butyl-lithium (1.6M in hexane; 0.09 ml). The mixture was heated at 75 °C for 30 min and then quenched by addition of methyl iodide (1 ml). Solvent and the excess of iodide were removed under reduced pressure and the residue was purified by preparative t.l.c. using ether–light petroleum (65:35) as eluant, to yield a pale yellow oil (10 mg) identified as the *indolinone* (**22**) (Found: M^+, 341.1306. $C_{16}H_{23}NO_5S$ requires *M*, 341.1297); $\nu_{max.}$($CHCl_3$) 1 715, 1 475, and 1 120 cm^{-1}; δ($CDCl_3$) 1.72 (3 H, s, CMe), 2.02 (3 H, s, SMe), 2.26 (3 H, s, ArMe), 3.43 (3 H, s, OCH_2OMe), 3.62 (3 H, s, NCH_2OMe), 3.88 (3 H, s, ArOMe), 5.07 (2 H, s, OCH_2O), 5.41 (2 H, s, NCH_2O), and 6.74 (1 H, s, ArH).

N,N-*Dimethyl*(*methylthio*)*acetamide*.—A solution of *S*-methylthioglycolic acid (2.8 g) in thionyl chloride (7 ml) was stirred at room temperature for 3 h and the excess of thionyl chloride was then removed under reduced pressure. The resulting acid chloride was dissolved in ether and cooled to 0 °C, and an excess of anhydrous dimethylamine was added with vigorous stirring. Filtration (removal of the amine hydrochloride), removal of solvent, and column chromatography (75 g; Merck Kieselgel 60; ethyl acetate as eluant) gave the *amide* as an oil (3 g 85%) (Found: C, 44.6; H, 8.55; N, 10.6. $C_5H_{11}NOS$ requires C, 45.1; H, 8.55; N, 10.55%); $\nu_{max.}$ ($CHCl_3$) 1 640, 1 400, and 1 120 cm^{-1}; δ($CDCl_3$) 2.2 (3 H, s, SMe), 3.0 and 3.08 (6 H, 2 × br s, NMe_2), and 3.29 (2 H, s, CH_2).

α-(2-*Amino*-5-*methoxy*-3-*methoxymethoxy*-4-*methylphenyl*)-α-*methylthio*-N,N-*dimethylacetamide* (**23**).—A solution of *N,N*-dimethyl(methylthio)acetamide (1.45 g) in dichloromethane (7.5 ml) was added dropwise to a solution of chlorine in dichloromethane (25 ml of 1.1 × 10^{-2}M Cl_2) cooled to −78 °C under nitrogen; during the addition a thick white suspension developed. The mixture was stirred at −78 °C for 15 min and then a solution of the aniline (**13**) (4.3 g) in dichloromethane (10 ml) was added dropwise, with the temperature maintained below −60 °C. The resulting suspension was stirred at −78 °C

for 90 min and then triethylamine (1.6 g) was added dropwise. The purple solution was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred for a further 1 h. Dry ether (50 ml) was added, the precipitated triethylamine hydrochloride was filtered off, and the solvent was removed. Chromatography of the residue (250 mg; Merck Kieselgel 60; ethyl acetate as eluant) gave starting material (2 g) and the *aniline* (**23**) (2.82 g), which crystallised from ether–light petroleum as colourless crystals, m.p. 81—83 °C (Found: C, 54.95; H, 7.25; N, 8.3. $C_{15}H_{24}N_2O_4S$ requires C, 54.85; H, 7.35; N, 8.55); $\nu_{max.}$($CHCl_3$) 3 420, 3 370, 1 641, 1 400, 1 060, and 915 cm^{-1}; δ($CDCl_3$) 2.02 (3 H, s, SMe), 2.12 (3 H, s, ArMe), 2.85 and 2.97 (6 H, 2 × s, NMe_2), 3.57 (3 H, s, OCH_2OMe), 3.71 (3 H, s, ArOMe), 4.22 (1 H, s, CHS), 4.97 (2 H, s, OCH_2O), and 6.48 (1 H, s, ArH); *m/z* 329 (M^+, 20%), 328 (100), 283 (24), 281 (60), and 256 (35).

α-(5-*Methoxy*-3-*methoxymethoxy*-4-*methyl*-2-*phenylmethyleneaminophenyl*)-α-*methylthio*-N,N-*dimethylacetamide* (**24**).—To a solution of the aniline (**23**) (500 mg) in benzaldehyde (5 ml) was added activated molecular sieve (4 Å; 100 mg), and the mixture was set aside overnight. The excess of benzaldehyde was removed under high vacuum at 30 °C and the residue chromatographed (50 g; Merck Kieselgel 60; ether as eluant) to give the *imine* (**24**) (430 mg, 68%) as a yellow oil which rapidly crystallised. Recrystallisation from aqueous ethanol gave yellow plates, m.p. 101—102 °C (Found: C, 62.9; H, 6.95; N, 6.65. $C_{22}H_{28}N_2O_4S$ requires C, 63.45; H, 6.8; N, 6.75%); $\nu_{max.}$ 1 630, 1 575, and 1 128 cm^{-1}; δ($CDCl_3$) 1.96 (3 H, s, SMe), 2.19 (3 H, s, ArMe), 2.89 and 3.0 (6 H, 2 × s, NMe_2), 3.35 (3 H, s, OCH_2OMe), 3.84 (3 H, s, ArOMe), 4.75 (2 H, s, OCH_2O), 5.34 (1 H, s, CHS), 7.04 (1 H, s, ArH), 7.4—8.0 (5 H, m, ArH), and 8.52 (1 H, s, CH=N); *m/z* 416 M^+, 47%), 371 (38), 370 (100), 369 (75), 344 (22), 337 (58), 325 (32), and 324 (90).

5-*Methoxy*-7-*methoxymethoxy*-6-*methyl*-2-*phenylindol*-3-*yl*-(N,N-*dimethylcarboxamide*) (**25**).—A solution of lithium diisopropylamide [from the amine (16 mg)] in tetrahydrofuran (1 ml) was added to a solution of the *imine* (**24**) (60 mg) in tetrahydrofuran (1 ml) cooled to −78 °C under nitrogen; a blood-red colouration developed. After 10 min stirring the mixture was allowed to reach room temperature and stirring was continued for a further 15 min. The solvent was removed under reduced pressure and the residue purified by preparative t.l.c. (ether as eluant). Extraction of the major band (MeOH—CH_2Cl_2) gave the *indole* (**25**) (24 mg), which crystallised from chloroform–light petroleum as a powder, m.p. 195—197 °C (Found: C, 67.0; H, 6.7; N, 7.4. $C_{21}H_{24}N_2O_4 \cdot 0.5H_2O$ requires C, 66.8; H, 6.6; N, 7.4%); $\nu_{max.}$($CHCl_3$) 3 340, 1 610, 1 065, and 913 cm^{-1}; δ($CDCl_3$) 2.26 (3 H, s, ArMe), 2.74 and 3.15 (6 H, 2 × br s, NMe_2), 3.75 (3 H, s, OCH_2OMe), 3.89 (3 H, s, ArOMe), 5.24 (2 H, s, OCH_2O), 6.86 (1 H, s, ArH), 7.3—7.8 (5 H, m, ArH), and 9.75 (1 H, s, NH); *m/z* 368 (M^+, 71%), 337 (16), 324 (27), 292 (50), 276 (92), 274 (94), and 221 (100). Attempted trapping of the initially formed anion with chloromethyl methyl ether gave only the indole.

2-*Benzylthio*-3,3-*dimethyl*-3H-*indole* (**26**; X = SCH_2Ph).—To a solution of 3,3-dimethylindolin-2-one[5] (161 mg) in dichloromethane (5 ml) were added pyridine (240 mg) and a solution of phosgene (500 mg) in toluene (4.1 ml). After 3 h stirring at room temperature the solvents were removed under reduced pressure at room temperature and the residue was triturated with dry ether. Removal of the pyridine hydrochloride by filtration and evaporation of the ether left the imidoyl chloride (**26**; X = Cl) as an extremely moisture-sensitive yellow oil (140 mg); $\nu_{max.}$($CHCl_3$) 1 552, 1 470, 1 456, 1 040, and 1 015 cm^{-1}; δ($CDCl_3$) 1.41 (6 H, s, CMe_2) and 7.0—7.65 (4 H, m, ArH). Without further purification the chloride was dissolved in tetrahydrofuran (5 ml) and treated with a solution of lithium phenylmethanethiolate in tetrahydrofuran (from phenylmethanethiol (124 mg) and butyl-lithium (1.5M in hexane; 0.067 ml)]. Stirring for 15 min at room temperature, removal of solvent, and purification by preparative t.l.c. (5% ethyl acetate–benzene) gave the *imino sulphide* (**26**; X = SCH_2Ph) (118 mg) as a crystalline mass, m.p. 58—60 °C (Found: M^+, 267.1083. $C_{17}H_{17}NS$ requires *M*, 267.1082); $\nu_{max.}$($CHCl_3$) 1 502, 1 467, 1 451, and 1 038 cm^{-1}; δ($CDCl_3$) 2.3 (6 H, s, CMe_2), 4.5 (2 H, s, SCH_2), and 7.0—7.6 (9 H, m, ArH).

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