Acid-catalysed Cyclisation of *o*-Sulphonamido Ketene Dithioacetal *S*-Oxides: A Novel Synthesis of the Indole Ring System

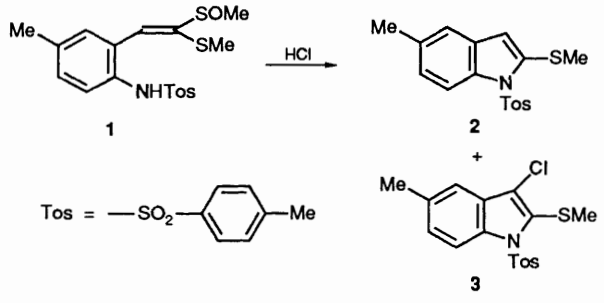
Alan T. Hewson,*[a] Kevin Hughes,[a] Stewart K. Richardson,[a] David A. Sharpe[a] and Alan H. Wadsworth[b]

[a] *Department of Chemistry, Sheffield City Polytechnic, Pond Street, Sheffield, S1 1WB, UK*

[b] *Glaxo Group Research, Ware, Herts, UK*

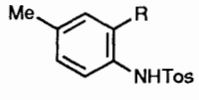
Treatment of *o*-sulphonamido aryl ketene dithioacetal *S*-oxides with hydrochloric acid in the presence of hydrogen sulphide gives 2-methylthioindoles.

We have previously described in preliminary form a novel approach to indoles involving acid-catalysed cyclisation of ketene dithioacetal *S*-oxides **1** (Scheme 1), to give in approximately equal amounts the products **2** and **3**. We now present full details of this work, together with a modification which allows **1** to be converted into compound **2** alone.



Scheme 1

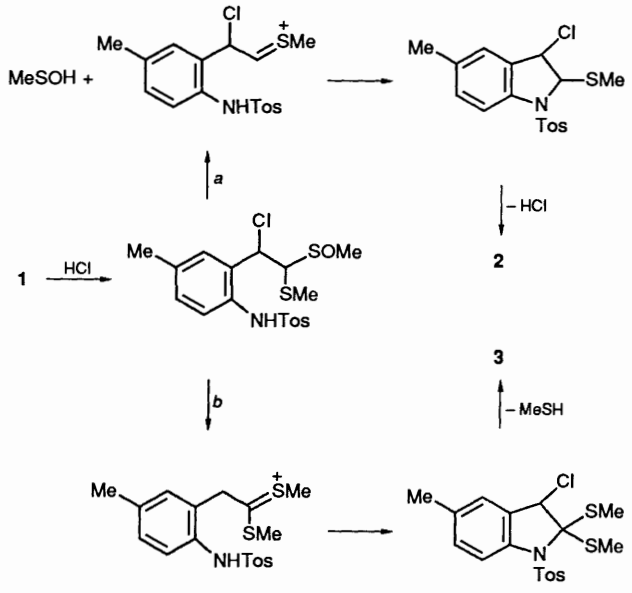
Our original discovery arose serendipitously since we were trying to develop methodology for converting the aldehyde **4** into the corresponding phenylacetic acid **5**. One of the methods reported for carrying out such transformations involves acid hydrolysis of ketene dithioacetal *S*-oxides.[2] Consequently, we converted the aldehyde **4** into compound **1** and treated the latter with conc. hydrochloric acid in dichloromethane. Two products were obtained after chromatography and it was clear that neither was the desired acid **5**. The spectral and analytical data



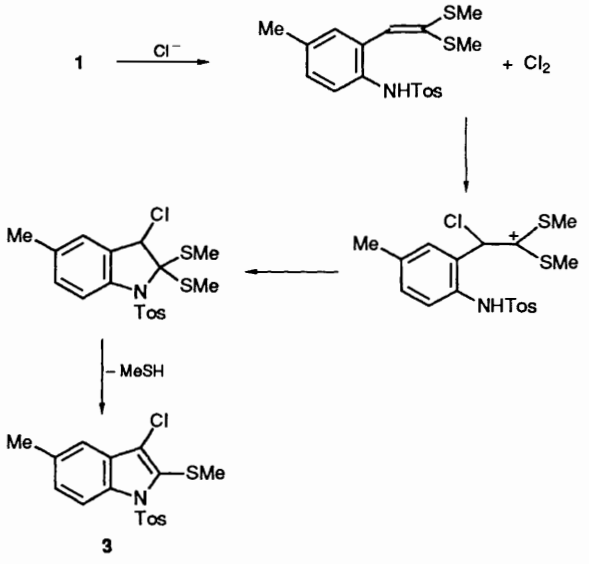
4; R = CHO
5; R = CH_2CO_2H

suggested that the products were the indoles **2** and **3**, and the inter-relationship between the two compounds was proved by treating compound **2** with sulphuryl chloride: the product from this was identical with the 3-chloroindole **3**. Our original mechanistic explanation[1] for the production of compounds **2** and **3** involved addition of HCl to the double bond in **1** followed by either (*a*) loss of methanesulphenic acid, intramolecular cyclisation and aromatisation leading to compound **2**, or (*b*) Pummerer rearrangement, intramolecular cyclisation and aromatisation leading to compound **3** (Scheme 2). However, an alternative mechanism leading to compound **3** could involve oxidation by the sulphoxide in **1** of chloride ion to chlorine[3,4] (Scheme 3).

In order to distinguish between the two possible pathways leading to compound **3**, we investigated the effect of adding, to



Scheme 2



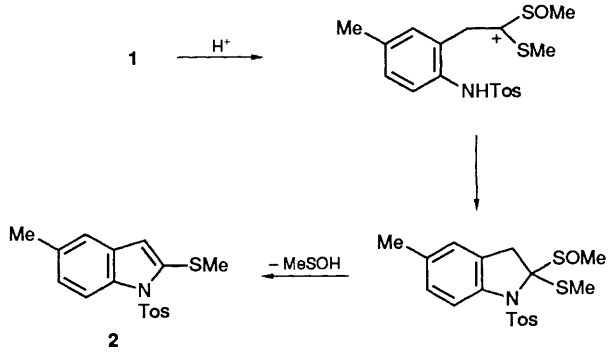
Scheme 3

the reaction mixture, reagents which might interfere with the oxidation–reduction step in Scheme 3. It emerged that if the dichloromethane was saturated with hydrogen sulphide before addition of compound **1** and the HCl, the only product isolated was the 2-methylthioindole **2**. Under these conditions the pathway leading to the 3-chloroindole **3** was blocked. We also

Table 1 Physical data for compounds **6**, **7** and **8**

Compd.	M.p. (°C)	Compd.	Yield for LAH reduction of **4** (%)	M.p. (°C)	Compd.	Yield for PCC oxidation of **5** (%)	M.p. (°C)
6a	113–115	**7a**	89	148–150	**8a**	91	124–127
6b	141–142	**7b**	90	124–125	**8b**	90	84–85
6c	156–158	**7c**	94.5	144–146	**8c**	93	114–115
6d	134–136	**7d**	92	108–110	**8d**	85	138–140
6e	122–123	**7e**	87	122–124	**8e**	88	102–103

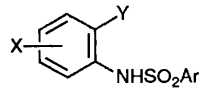
now suggest a simpler mechanism leading to compound **2**, as shown in Scheme 4.



Scheme 4

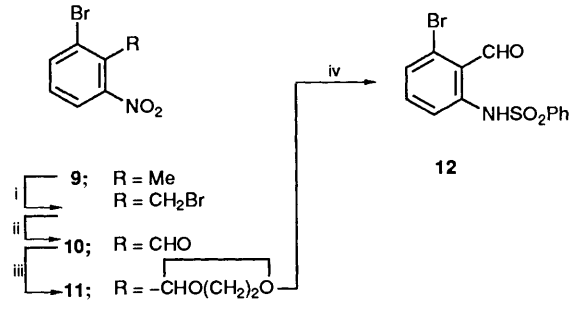
The detailed role of the hydrogen sulphide has not been investigated, but the method now provides a convenient approach to the indole ring system in good yield from the corresponding anthranilaldehyde derivative.

We have now applied the method to a range of indoles. In general, the required aldehydes were prepared from the corresponding anthranilic esters by *N*-sulphonation to provide the esters **6**, lithium aluminium hydride (LAH) reduction to the alcohols **7** and oxidation with pyridinium chlorochromate (PCC) to afford the aldehyde **8** (Table 1). This approach failed



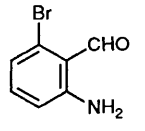
6; Y = CO_2Me
7; Y = CH_2OH
8; Y = CHO

for methyl 2-amino-3,5-dibromobenzoate, where the amine could not be converted into the sulphonamide even under forcing conditions, presumably because of its very hindered environment. The bromobenzaldehyde **12** was prepared from 2-bromo-6-nitrotoluene **9** by the route shown in Scheme 5.

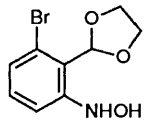


Scheme 5 *Reagents and conditions*: i, NBS (*N*-bromosuccinimide), CCl_4, $(PhCO_2)_2$, *hν*; ii, pyridine then *p*-Ph(NO)(NMe_2), NaOH then H_2SO_4; iii, $HOCH_2CH_2OH$, H^+; iv, $NiCl_2$, $NaBH_4$ then $PhSO_2Cl$, pyridine, then H_3O^+

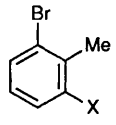
Thus 2-bromo-6-nitrotoluene **9** was oxidised by the Kröhnke method[5] to give the nitro aldehyde **10**. Attempts to reduce compound **10** to the amino aldehyde **13** with ferrous sulphate–ammonia and with sodium dithionite–potassium carbonate gave the desired product, but only in yields of 30 and 15% respectively. It was found to be more efficient to protect the aldehyde in compound **10** before reduction of the acetal **11** with sodium borohydride–nickel(II) chloride,[6] sulphonamide formation and deprotection to give compound **12**. Other methods of reduction of compound **11** were unsuccessful. Catalytic hydrogenation caused loss of both the bromine and the acetal group, anhydrous stannous chloride in ethanol simply caused acetal hydrolysis to give the aldehyde **10** while the sodium dithionite–potassium carbonate product appeared to be the hydroxylamine **14**.



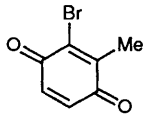
13



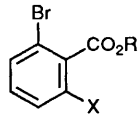
14



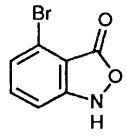
15; X = NH_2
16; X = $NHSO_2Ph$



17



18; R = H, X = NO_2
19; R = Me, X = NO_2
20; R = Me, X = NH_2
22; R = Me, X = NHOH



21

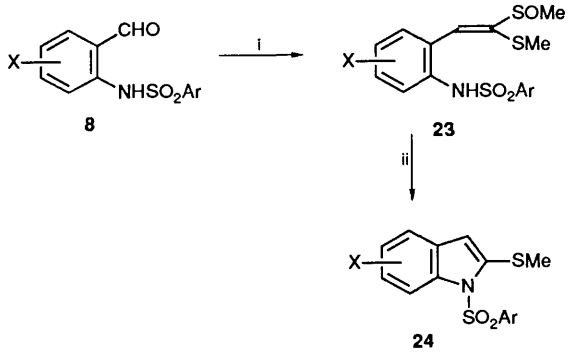
Other approaches for the preparation of the aldehyde **13** from the nitrotoluene **9** were also investigated. Thus reduction of compound **9** with tin–hydrochloric acid gave the amine **15** which was converted into the sulphonamide **16**. A number of toluenes are reported to be oxidised to the corresponding aldehydes with ceric ammonium nitrate,[7] the closest analogy to our case being *o*-acetamidotoluene, whose oxidation was reported to occur in over 90% yield. However, application of these conditions to the sulphonamide **16** unexpectedly gave the *p*-benzoquinone **17**, and we have shown that this reaction has some generality.[8]

Oxidation of the nitrotoluene **9** with basic potassium permanganate gave the acid **18**, but in only *ca.* 30% yield. The derived ester **19**, on reduction with tin–hydrochloric acid did not give the desired amine **20** but gave instead the cyclic system **21**. This arises from the hydroxylamine **22** which undergoes intramolecular cyclisation. A related reaction has been reported.[9]

The various aldehydes **8** were converted into the ketene-dithioacetal *S*-oxides **23** by condensation with methyl methylthiomethyl sulphoxide under basic conditions[2] (Table 2). The

Table 2 Physical data for ketene dithioacetal *S*-oxides **23**

Compd. (molecular formula)	Aldehyde precursor	Yield (%)	M.p. (°C)	% Found (% Required) C	H	N	ν/cm^{-1}	δ_H($CDCl_3$)
23a ($C_{17}H_{19}NO_3S_3$)	**8a**	88	165–168	53.5 (53.52)	5.0 (5.02)	3.35 (3.67)	3100, 2900, 2820, 1600, 1490, 1340, 1040	2.19 (3 H, s), 2.33 (3 H, s), 2.82 (3 H, s), 7.26 (4 H, m), 7.63 (5 H, m)
23b ($C_{17}H_{19}NO_3S_3$)	**8b**	71	111–112	53.3 (53.52)	5.1 (5.02)	3.4 (3.67)	3100, 2830, 1500, 1450, 1410, 1350, 1260	2.05 (3 H, s), 2.35 (3 H, s), 2.8 (3 H, s), 7.0–8.0 (9 H, m)
23c ($C_{18}H_{21}NO_3S_3$)	**8c**	77	160–162	54.25 (54.65)	5.4 (5.35)	3.45 (3.54)	3120, 2920, 2840, 1595, 1330, 1155, 1035	2.03 (3 H, s), 2.32 (6 H, s), 2.72 (3 H, s), 6.80–7.53 (9 H, m)
23d ($C_{17}H_{18}ClNO_3S_3$)	**8d**	68	170–171	49.45 (49.1)	4.30 (4.33)	3.45 (3.37)	3100, 2850, 1600, 1490, 1400, 1350, 1160, 1060	2.01 (3 H, s), 2.37 (3 H, s), 2.78 (3 H, s), 7.0–7.8 (9 H, m)
23e ($C_{16}H_{18}BrNO_3S_3$)	**8e**	55	115–116	42.9 (43.05)	3.5 (3.61)	2.95 (3.14)	3100, 2850, 1480, 1340, 1165, 1150, 1050	2.05 (3 H, s), 2.8 (3 H, s), 7.3–8.0 (9 H, m)
23f ($C_{16}H_{16}BrNO_3S_3$)	**12**	60	181.5–183.5	43.6 (43.05)	3.6 (3.61)	3.15 (3.14)	3100, 2870, 1580, 1470, 1350, 1250	2.11 (3 H, s), 2.86 (3 H, s), 7.20 (1 H, m), 7.50 (7 H, m), 7.78 (1 H, m)



Scheme 6 *Reagents and conditions:* i, $MeSOCH_2SMe$, Triton B; ii, HCl, H_2S, CH_2Cl_2

products, on treatment with HCl–H_2S–CH_2Cl_2 gave the corresponding 2-methylthioindoles **24** (Table 3) (Scheme 6).

Experimental

IR spectra were obtained on Pye-Unicam SP3-100 or Perkin-Elmer 737 spectrophotometers. Samples were prepared as KBR discs or liquid films unless otherwise stated. ^1H NMR spectra were obtained on JEOL C60, Bruker WP80 or WM250 instruments in $CDCl_3$ solution. *J* Values are given in Hz. Mass spectra were obtained on a VG Micromass 30F spectrometer. Microanalyses were performed by the City University, London. Light petroleum refers to that fraction boiling in the range 40–60 °C. Ether refers to diethyl ether.

General Procedure for the Sulphonamido Esters **6**.—The appropriate substituted methyl anthranilate (70 mmol) in dry pyridine (50 cm^3) was added over 20 min to a solution of the arenesulphonyl chloride (70 mmol) in pyridine (50 cm^3) at 0 °C. The mixture was stirred for 3 h at 0 °C and was then acidified with HCl (2 mol dm^{-3}). The precipitate was filtered off, washed with HCl (2 mol dm^{-3}) and water, and dried *in vacuo* to give the product **6**. A small sample was recrystallised from ethanol.

General Procedure for the Sulphonamido Alcohols **7**.—The sulphonamido ester **6** (30 mmol) in dry THF (tetrahydrofuran) (20 cm^3) was added dropwise to $LiAlH_4$ (60 mmol) in dry THF (20 cm^3). When the addition was complete, the mixture was refluxed for 1 h before careful addition of HCl (2 mol dm^{-3}). The layers were separated and the aqueous layer was extracted with ether (3 × 50 cm^3). The combined organic layers were washed with water (100 cm^3), saturated aqueous sodium hydrogen carbonate (100 cm^3) and water (100 cm^3) and dried ($MgSO_4$). The solvent was evaporated to give the product **7** which was pure enough for use in the next step. A small sample was recrystallised from ethanol.

General Procedure for the Sulphonamido Aldehydes **8**.—To a stirred suspension of PCC (15 mmol) in dichloromethane (50 cm^3) was added a solution of the alcohol **7** (10 mmol) in dichloromethane (100 cm^3). The mixture was stirred for 3 h. The liquid was decanted from the solid which was washed several times with ether. The combined solvent was passed through a short pad of Merck 7734 grade silica and evaporated to give the product **8**. A small sample was recrystallised from ethanol.

General Procedure for the Ketene Dithioacetal S-*Oxides* **23**.—Under nitrogen, a mixture of the aldehyde **8** (26 mmol), methyl methylsulphinylmethyl sulphide (39 mmol), THF (200 cm^3) and Triton B (40% solution in methanol; 30 cm^3, 66 mmol) were refluxed for 3 d, allowed to cool and poured into ethyl acetate (300 cm^3). This mixture was washed with saturated aqueous ammonium chloride and the aqueous layer extracted with more ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified either by recrystallisation from ethyl acetate or by column chromatography on silica gel (ethyl acetate–light petroleum mixtures) to give the product **23**.

General Procedure for Indoles **24**.—Hydrogen sulphide was bubbled through dichloromethane (30 cm^3) for 30 min. To this was added the ketene dithioacetal *S*-oxide **23** (13 mmol) and hydrochloric acid (10 mol dm^{-3}; 1.5 cm^3). The mixture was stirred for 1 h, during which time the solid gradually dissolved, and then basified with saturated aqueous sodium hydrogen carbonate. The layers were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give the product, usually as a solid, which was recrystallised from ethanol.

3-*Chloro*-5-*methyl*-2-*methylthio*-1-(p-*tolylsulphonyl*)*indole*

Table 3 Physical data for indoles **24**

Compd. (molecular formula)	Precursor	Yield (%)	M.p. (°C)	% Found (% Required) C	H	N	ν/cm^{-1}	δ_H($CDCl_3$)
24, X = H, Ar = *p*-Tol ($C_{16}H_{15}NO_2S_2$)	**23a**	77	117–119	60.6 (60.5)	4.8 (4.76)	4.3 (4.41)	3080, 2920, 1600, 1490, 1375, 1180, 1090	2.43 (3 H, s), 2.57 (3 H, s), 6.53 (1 H, m), 7.49 (4 H, m), 8.16 (4 H, m)
24, X = 5-Me Ar = Ph ($C_{16}H_{15}NO_2S_2$)	**23b**	80	Oil	60.5 (60.5)	4.95 (4.76)	4.4 (4.41)	3100, 2910, 1600, 1460, 1380, 1220, 1180, 1090	2.3 (3 H, s), 2.45 (3 H, s), 6.23 (1 H, s), 6.9–8.4 (8 H, m)
24, X = 5-Me Ar = *p*-Tol ($C_{17}H_{17}NO_2S_2$)	**23c**	71	Oil	61.45 (61.6)	5.25 (5.17)	4.1 (4.23)	3030, 2915, 1590, 1365, 1175	2.3 (3 H, s), 2.37 (3 H, s), 2.48 (3 H, s), 6.26 (1 H, s), 6.91–7.27 (3 H, m), 7.8 (2 H, d, *J* 8), 8.03 (2 H, d, *J* 8)
24, X = 6-Cl Ar = *p*-Tol ($C_{16}H_{14}ClNO_2S_2$)	**23d**	62	141–142	54.5 (54.62)	3.8 (3.98)	4.15 (3.98)	3050, 2900, 1470, 1390, 1180, 1090	2.36 (3 H, s), 2.46 (3 H, s), 6.26 (1 H, s), 7.0–8.3 (7 H, m)
24, X = 5-Br Ar = Ph ($C_{15}H_{12}BrNO_2S_2$)	**23e**	78	85–86	47.05 (47.13)	3.0 (3.16)	3.75 (3.66)	3050, 1470, 1230, 1170, 1120, 1090	2.6 (3 H, s), 6.26 (1 H, s), 7.1–8.2(8 H, m)
24, X = 4-Br Ar = Ph ($C_{15}H_{12}BrNO_2S_2$)	**23f**	75	132–133	47.4 (47.13)	3.05 (3.16)	3.6 (3.66)	3100, 1500, 1410, 1370, 1170	2.5 (3 H, s), 6.43 (1 H, s), 7.4 (5 H, m), 7.9 (3 H, m)

[a] *J* values are given in Hz.

3.—To a solution of 5-methyl-2-methylthio-1-(*p*-tolylsulphonyl)indole **2** (92 mg, 0.28 mmol) in dichloromethane (1 cm^3) was added sulphuryl chloride (2 drops). The mixture was stirred for 30 min and poured into ethyl acetate–water. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography on silica gel [ethyl acetate–light petroleum (1:25)] to give the *product* **3** (91 mg, 90%), m.p. 118 °C (Found: C, 55.8; H, 4.35; N, 3.85. $C_{17}H_{16}ClNO_2S_2$ requires C, 55.80; H, 4.41; N, 3.83%); ν_{max}/cm^{-1} 3020, 2920, 1590, 1365, 1170 and 1145; δ_H 2.34 (3 H, s), 2.40 (3 H, s), 2.45 (3 H, s), 6.90–7.25 (4 H, m), 7.55 (2 H, d, *J* 8) and 8.05 (1 H, d, *J* 8).

2-Bromo-6-nitrobenzaldehyde **10**.—*α,2-Dibromo-6-nitrotoluene*. 2-Bromo-6-nitrotoluene (25 g, 116 mmol) and *N*-bromosuccinimide (NBS) (26.88 g, 151 mmol) were dissolved in carbon tetrachloride (400 cm^3) and benzoyl peroxide (20 mg) was added. The solution was heated at reflux under a nitrogen atmosphere, and irradiated with a 150 W lamp for 8 d. The mixture was cooled to room temperature, and the succinimide was filtered off through Hyflo. The filtrate was dried ($MgSO_4$) and evaporated to leave an orange solid. This was recrystallised from hexane, to give pure *product* as a beige crystalline solid (34.32 g, 100%), m.p. 61.5–63 °C (Found: C, 28.55; H, 1.6; N, 4.7. $C_7H_5Br_2NO_2$ requires C, 28.51; H, 1.71; N, 4.75%); ν_{max}(Nujol)/cm^{-1} 1525, 1465, 1350, 810 and 750; δ_H 4.89 (2 H, s), 7.35 (1 H, t) and 7.89 (2 H, d).

1-(2-Bromo-6-nitrobenzyl)pyridinium bromide. α-2-Dibromo-6-nitrotoluene (34.30 g, 116 mmol) was dissolved in ethanol (300 cm^3) and pyridine (10 cm^3, 130 mmol) was added. The solution was heated on a steam-bath for 1 h and the solvent was then removed under reduced pressure. The solid residue was recrystallised from absolute ethanol to leave the pure product as pale orange crystals (37.21 g, 86%), m.p. 202–205 °C; ν_{max}(Nujol)/cm^{-1} 1625, 1535, 1430, 1345, 1165 and 740; δ_H([$^2H_6$]-DMSO) 6.22 (2 H, s), 7.85 (1 H, t), 8.28 (4 H, m), 8.75 (1 H, t) and 9.00 (2 H, d).

2-Bromo-6-nitrobenzylidene(p-*dimethylaminophenyl*)*amine N-Oxide*.The above pyridinium salt (37.21 g, 100 mmol) and *p*-nitroso-*N*,*N*-dimethylaniline (18.02 g, 120 mmol) were added to ethanol (300 cm^3) and cooled to 0 °C. Sodium hydroxide (10 g) dissolved in water (90 cm^3) was added dropwise the temperature being kept < 5 °C. The mixture was stirred for 1.5 h and then poured into ice–water with stirring to give a dark yellow–orange precipitate, which was filtered off and washed with water. The product was not purified further; ν_{max}/cm^{-1} 1600, 1540, 1460, 1360, 1180, 790 and 740; δ_H 3.04 (6 H, s), 6.69 (1 H, d), 7.41 (1 H, t), 7.70 (2 H, d), 7.88 (1 H, d), 7.97 (1 H, d) and 8.18 (1 H, s).

2-Bromo-6-nitrobenzaldehyde **10**. The above nitrone (36 g), was stirred for 10 min with sulphuric acid (3 mol dm^{-3}; 500 cm^3). Crushed ice was then added, and the resulting yellow precipitate was filtered off and recrystallised from ethanol to leave pure a yellow crystalline product (19.85 g, 74.5%), m.p. 78–80 °C (lit.,[10] 82 °C); ν_{max}/cm^{-1} 1710, 1530, 1340, 1180, 810, 740 and 725; δ_H 7.55 (1 H, t), 7.95 (1 H, d), 8.01 (1 H, d) and 10.25 (1 H, s).

2-Amino-6-bromobenzaldehyde **13**.—*Method* (*a*). Water (100 cm^3), ferrous sulphate heptahydrate (58 g, 210 mmol), conc. hydrochloric acid (0.3 cm^3) and 2-bromo-6-nitrobenzaldehyde **10** (500 g, 22 mmol) were heated to 90 °C and conc. ammonia solution (14 cm^3) was added, followed by portions (3 × 6 cm^3) of conc. ammonia at 2 min intervals. Immediately after the last portion was added, the mixture was steam distilled. A yellow precipitate formed in the condensate, which was filtered off and dried, to give *product* **13** as a yellow powder (133 g, 30%), m.p. 81–83 °C (Found: C, 42.3; H, 3.0; Br, 39.65; N, 6.95. C_7H_6BrNO requires C, 42.08; H, 3.02; Br, 39.95; N, 7.00%); ν_{max}/cm^{-1} 3440, 3330, 1660, 1610, 1455, 1220, 790 and 780; δ_H 6.48 (2 H, br s), 6.58 (1 H, d), 6.90 (1 H, d), 7.10 (1 H, t) and 10.40 (1 H, s).

Method (*b*). 2-Bromo-6-nitrobenzaldehyde **10** (1.00 g, 4.35 mmol) was suspended in water (20 cm^3), and sodium dithionite (5.91 g, 39 mmol), and sodium carbonate (2.77 g, 18 mmol) were added. The mixture was stirred for 30 min and the product was then extracted with ethyl acetate (3 × 20 cm^3). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel [ethyl acetate–hexane (1:3)] to give the product as yellow solid (0.13 g, 15%), m.p. 80–82 °C; spectral data as above.

2-(2-Bromo-6-nitrophenyl)dioxolane **11**.—2-Bromo-6-nitrobenzaldehyde **10** (25.0 g, 100 mmol) was dissolved in dry

benzene (350 cm^3). To this solution was added ethane-1,2-diol (803 g, 12 mmol) and toluene *p*-sulphonic acid (0.5 g). The solution was refluxed for 24 h (Dean–Stark apparatus), after which time saturated aqueous sodium hydrogen carbonate was added, and the two layers were separated. The organic layer was washed with brine and then dried ($MgSO_4$). Subsequent evaporation gave a pale brown solid residue which was recrystallised from ethanol to give a white crystalline solid (26.77 g, 98%), m.p. 71.5–72.5 °C (Found: C, 39.45; H, 2.95; Br, 29.45; N, 5.1. $C_9H_8BrNO_4$ requires C, 39.44; H, 2.94; Br, 29.15; N, 5.11%); ν_{max}/cm^{-1} 1535, 1480, 1370, 1230, 1200, 980, 745 and 710; δ_H 4.09 (4 H, m), 6.20 (1 H, s), 7.35 (2 H, m) and 7.75 (1 H, dd).

2-Benzenesulphonamido-6-bromobenzaldehyde **12**.—*2-(2-Amino-6-bromophenyl)dioxolane*. The nitro acetal **11** (25.0 g, 100 mmol) and nickel chloride hexahydrate (47.54 g, 200 mmol) were dissolved in methanol (600 cm^3) and the solution was cooled to 0 °C. To this was added slowly sodium borohydride (15.13 g, 400 mmol), the temperature being kept at 0 °C. The black suspension was stirred for 30 min at this temperature, and then allowed to warm to room temperature, at which point it was stirred for a further 5 h. The black nickel boride was filtered off through Hyflo, and the filtrate evaporated down to small bulk. The residue was taken up in ethyl acetate and the solution was washed with brine, dried ($MgSO_4$) and evaporated to leave an orange oil. This was purified by column chromatography on silica gel [ethyl acetate–hexane (1:4)] to give the pure *product* as a yellow solid (12.3 g, 56%), m.p. 74–76 °C (Found: C, 44.9; H, 4.1; N, 5.75. $C_9H_{10}BrNO_2$ requires C, 44.29; H, 4.13; N, 5.74%); ν_{max}/cm^{-1} 3440, 1610, 1595, 1470, 1070, 955 and 780; δ_H 4.15 (4 H, m), 4.60 (2 H, br s), 6.22 (1 H, s), 6.58 (1 H, dd) and 6.93 (2 H, m).

2-Benzenesulphonamido-6-bromobenzaldehyde **12**. The above amino acetal (141 mg, 0.64 mmol) in dry pyridine (2 cm^3) was added to a solution of benzenesulphonyl chloride (0.19 cm^3, 0.77 mmol) in dry pyridine (2 cm^3). The solution was stirred at 0 °C for 3 h. Hydrochloric acid (5 mol dm^{-3}; 4 cm^3) was added and the mixture was stirred for a further 30 min. The solution was then extracted with ethyl acetate (3 cm^3), which was then washed with dilute hydrochloric acid and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel [ethyl acetate–hexane (1:4)] to give the pure *product* **12** as a white crystalline solid (115 mg, 53%), m.p. 103–104 °C (Found: C, 46.4; H, 3.15; Br, 23.2; N, 3.8; S, 9.75. $C_{13}H_{10}BrNO_3S$ requires C, 45.90; H, 2.96; N, 4.12; Br, 23.49; S, 9.42%); ν_{max}/cm^{-1} 3100, 1660, 1440, 1380, 1165 and 930; δ_H 7.26 (1 H, s), 7.30 (1 H, d), 7.50 (2 H, m), 7.68 (1 H, m), 7.9 (2 H, m), 10.25 (1 H, s) and 11.40 (1 H, br s).

2-Bromo-6-nitrobenzoic Acid **18**.—2-Bromo-6-nitrotoluene (2.00 g, 9.26 mmol) and sodium carbonate (4.53 g, 42 mmol) were dissolved in hot water (140 cm^3). To this solution was added potassium permanganate (5.85 g, 37 mmol). The solution was refluxed overnight, and after cooling it was filtered through Hyflo, to remove the manganese dioxide. The filtrate was acidified with dilute hydrochloric acid, and extracted with ethyl acetate (3 × 50 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to leave the *product* **18** as a pale brown solid (0.92 g, 40%), m.p. 172–173 °C (Found: C, 33.75; H, 1.5; Br, 31.85; N, 5.3. $C_7H_4BrNO_4$ requires C, 34.17; H, 1.64; Br, 32.48; N, 5.69%); ν_{max}/cm^{-1} 3200–2800, 1710, 1530, 1150 and 750; δ_H 6.55 (1 H, t), 7.00 (1 H, d) and 7.19 (1 H, d).

Methyl 2-Bromo-6-nitrobenzoate **19**.—2-Bromo-6-nitrobenzoic acid **18** (8.00 g, 33 mmol), was dissolved in dry *N,N*-dimethylformamide (50 cm^3). To this was added sodium hydrogen carbonate (11.09 g, 132 mmol) and methyl iodide (85 cm^3, 132 mmol). The mixture was heated at 60 °C, under nitrogen, for 24 h. The solution was cooled and poured into dilute hydrochloric acid and the precipitate was filtered off and washed with water. The resulting white solid was dried in air, to give the *product* **19** (6.49 g, 76%), m.p. 83–85 °C (Found: C, 36.85; H, 2.2; Br, 30.5; N, 5.24. $C_8H_6BrNO_4$ requires C, 36.95; H, 2.33; Br, 30.73; N, 5.39%); ν_{max}/cm^{-1} 1735, 1540, 1465, 1360, 1285, 750 and 725; δ_H 4.03 (3, H, s), 7.49 (1 H, t), 7.93 (1 H, d) and 8.19 (1 H, d).

4-Bromo-2,1-benzisoxazol-3(1 H)-one **21**.—Methyl 2-bromo-6-nitrobenzoate **19** (6.00 g, 23 mmol) was dissolved in ethanol (50 cm^3) and powdered tin (5.46 g, 46 mmol) and conc. hydrochloric acid (5 cm^3) were added. The mixture was stirred for 24 h. The tin was filtered off through Hyflo, and the pad washed with water. The filtrate was basified with sodium hydrogen carbonate and the resulting precipitate was filtered off. The filtrate was extracted with ethyl acetate (3 × 50 cm^3) and the combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel [ethyl acetate–hexane (1:3)]. The pure *product* **21** was obtained as an off white solid (1.6 g, 33%), m.p. 143.5 °C (Found: C, 39.6; H, 1.8; Br, 37.2; N, 6.4. $C_7H_4BrNO_2$ requires C, 39.28; H, 1.88; Br, 37.34; N, 6.54%); ν_{max}/cm^{-1} 3240–3040, 1730, 1610, 1470, 1330, 1165 and 1080; $\delta_H([^2H_6]\text{-DMSO})$ 7.29 (1 H, d), 7.38 (1 H, d) and 7.55 (1 H, t).

Acknowledgements

We thank SERC (S. K. R.), NAB (D. A. S.) and Glaxo Group Research for financial support.

References

1 A. T. Hewson, L. A. March, I. W. Nowell and S. K. Richardson, *J. Chem. Soc., Chem. Comm.*, 1985, 619.
2 K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, 1972, 1383.
3 U. Nagai and P. G. Sammes, *J. Chem. Soc. C*, 1967, 2230.
4 H. Nieuwenhuyse and R. Louw, *Tetrahedron Lett.*, 1971, 4141.
5 F. Kröhnke, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 380.
6 A. Nose and T. Kudo, *Chem. Pharm. Bull.*, 1981, **29**, 1159.
7 L. Syper, *Tetrahedron Lett.*, 1966, 4495.
8 A. T. Hewson, D. A. Sharpe and A. H. Wadsworth, *Synth. Commun.*, 1989, 2095.
9 E. Bamberger and F. L. Pyman, *Chem. Ber.*, 1909, **42**, 2297.
10 K. Clarke, *J. Chem. Soc.*, 1957, 3807.

Paper 0/05182I
Received 19*th November* 1990
Accepted 8*th February* 1991