7-Substituted Benzo[*b*]thiophenes and 1,2-Benzisothiazoles. Part 2.[1] Chloro and Nitro Derivatives

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The 7-chloro and 7-nitro derivatives of benzo[*b*]thiophene and 1,2-benzisothiazole have been prepared from readily available precursors, which for each substituent are common to both ring systems. 7-Chlorobenzo[*b*]thiophene has been obtained from 3-chloro-2-mercaptobenzoic acid *via* 7-chlorobenzo[*b*]thiophen-3(2*H*)-one, or from 2,3-dichlorobenzaldehyde, either *via* β-(2,3-dichlorophenyl)-α-mercaptoacrylic acid (16) or, preferably, *via* 7-chlorobenzo[*b*]thiophene-2-carboxylic acid. Hexamethylphosphoric triamide is a particularly useful solvent in which to effect the selective nucleophilic replacement of the 2-chloro substituent in 2,3-dichlorobenzaldehyde. 7-Chloro-1,2-benzisothiazole is available by treatment of 3-chloro-2-mercaptobenzaldehyde with chloramine (57%), or by heating 2,3-dichlorobenzaldehyde with sulphur and aqueous ammonia (46%).

7-Nitrobenzo[*b*]thiophene has been obtained by treatment of 2-bromo-3-nitrobenzaldehyde with mercaptoacetic acid under alkaline conditions, followed by decarboxylation of the resulting 2-carboxylic acid. Cyclisation of 2-(n- or t-butylthio)-3-nitrobenzaldoxime with polyphosphoric acid gives 7-nitro-1,2-benzisothiazole in high yield. 3-Nitro-2-t-butylthiobenzaldehyde behaves unexpectedly with chloramine, to give what is believed to be 7-nitro-2-t-butyl-1,2-benzisothiazolium chloride (24) (73%).

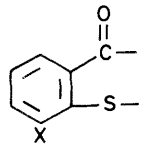
Problems associated with the preparation of 7-substituted benzo[*b*]thiophenes and 1,2-benzisothiazoles in general have already been outlined.[1] We required the 7-chloro and 7-nitro derivatives of each system in connection with a study of biologically active compounds, and we here describe efficient procedures for their synthesis.

7-Chlorobenzo[*b*]thiophene has been obtained (40%) by cyclisation of (2-chlorophenylthio)acetaldehyde dimethyl acetal with polyphosphoric acid (PPA),[2] but the starting 2-chlorobenzenethiol is not readily accessible. Substituted 7-chlorobenzo[*b*]thiophenes have been made by thio-Claisen rearrangement of the sulphide, $2\text{-}ClC_6H_4SCH_2C(=CH_2)Cl$,[3] by base-catalysed displacement of the nitro group from methyl 3-chloro-2-nitrobenzoate with methyl mercaptoacetate and Dieckmann cyclisation of the resulting diester,[4] and by treatment of 3′-chlorocinnamic acid with thionyl chloride in pyridine.[5] However, the last three methods generally provide unwanted substituents, which are difficult to remove.

7-Nitrobenzo[*b*]thiophene cannot be prepared from 2-nitrobenzenethiol by a method similar to that described for the chloro compound,[2] because of deactivation of the electrophilic cyclisation step by the nitro group. It has been obtained in poor yield by decomposition of the rather inaccessible benzo[*b*]thiophene-7-diazonium hexanitritocobaltate(III) salt with aqueous sodium nitrite in the presence of copper(I) oxide and copper(II) sulphate.[6] A pure sample has been made by decarboxylation of 7-nitrobenzo[*b*]thiophene-3-carboxylic acid,[7] but as the latter is one of several products from a nitration reaction, this is not a satisfactory preparative procedure.

7-Nitro- and 7-chloro-1,2-benzisothiazoles are even less readily accessible than their benzo[*b*]thiophene counterparts. The former has been obtained (24%), in admixture with the 5-nitro isomer, from the nitration of the rather inaccessible parent 1,2-benzisothiazole.[8,9] Conventional reduction afforded 7-amino-1,2-benzisothiazole, the diazonium salt of which was said to undergo the Sandmeyer reaction, to give the 7-chloro compound.[8] However, later workers have shown that the major product from the Sandmeyer reaction is 1,2,3-benzothiadiazole-7-carbaldehyde.[9]

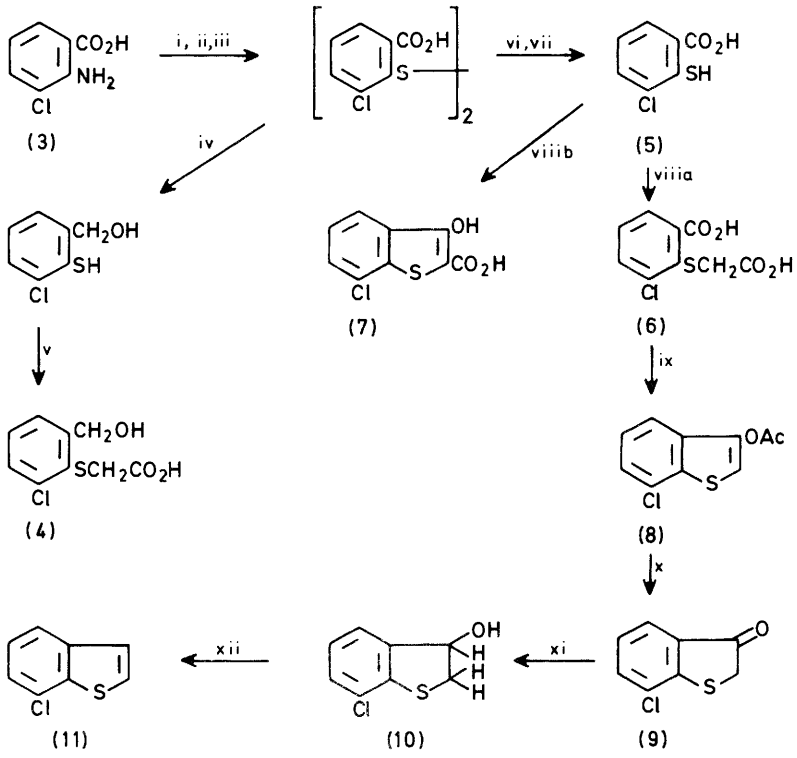
7-Chloro Derivatives.—We aimed to prepare a 1,2,3-trisubstituted benzenoid derivative (1) containing a chlorine



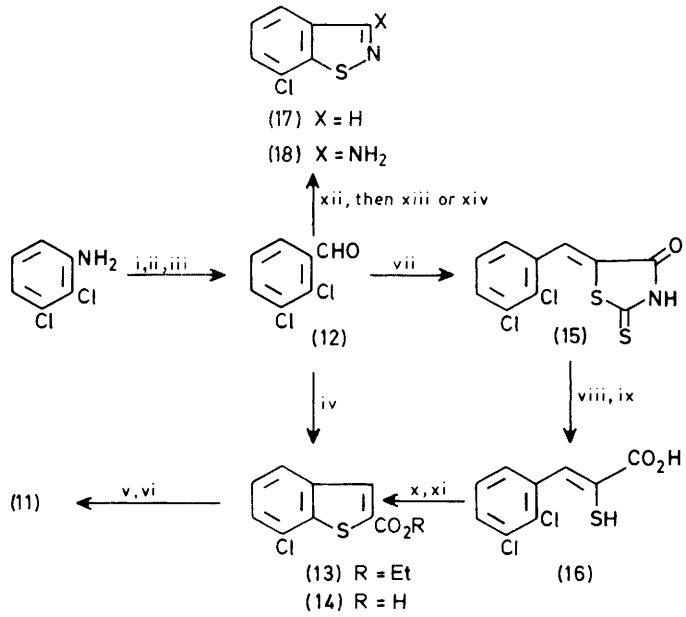
(1) X = Cl
(2) X = NO_2

atom, a sulphur-containing function, and a carbonyl group in that order, which would serve as a common precursor of both the benzo[*b*]thiophene and 1,2-benzisothiazole derivatives. Such compounds are rare. However, the commercially available 2-chloro-6-methylaniline could be readily converted into 2-amino-3-chlorobenzoic acid (3),[10] which then underwent the reactions shown in Scheme 1. We had hoped to oxidise the benzylic alcohol (4) to the corresponding aldehyde, in the expectation that the latter would readily cyclise to 7-chlorobenzo[*b*]thiophene-2-carboxylic acid. However, attempted oxidation with activated manganese dioxide gave a mixture of products, containing only a little aldehydic material. Instead, we treated the thiol (5) with chloroacetic acid in aqueous sodium carbonate in the hope that the initially formed diacid (6) might undergo decarboxylative cyclisation (*cf.* ref. 11) to the thioindoxyl (9). Instead, the 3-hydroxy-2-carboxylic acid (7) (68%) was obtained. However, heating the diacid (6) with Ac_2O–NaOAc gave 3-acetoxy-7-chlorobenzo[*b*]thiophene (8) (82%), which underwent alkaline hydrolysis to the thioindoxyl (9) (68%). Metal–acid reduction [12] of the last was unsuccessful; instead, we reduced it ($NaBH_4$) to the crystalline 2,3-dihydro-3-hydroxy compound (10) (90%), which underwent acid-catalysed dehydration to 7-chlorobenzo[*b*]thiophene (11) (88%).

In view of the length of the above sequence, we next sought a precursor (1) which contained a formyl, rather than a carboxy group, so as to avoid cyclisation to an undesired thioindoxyl derivative. 2,3-Dichlorobenzaldehyde has been obtained in low overall yield from 2-methyl-6-nitroaniline.[13] We found that it was more conveniently obtained (55%) by treatment of the diazonium salt of the cheap 2,3-dichloroaniline with formaldoxime, followed by acidic hydrolysis of the initially formed product (Beech's method [14]) (Scheme 2).

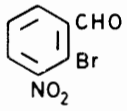


Scheme 1. *Reagents and conditions:* i, diazotisation; ii, Na_2S_2; iii, H^+; iv, $LiAlH_4$; v, $ClCH_2CO_2H$–Na_2CO_3; vi, $Na_2S_2O_4$–Na_2CO_3; vii, H^+; viii, $ClCH_2CO_2H$–Na_2CO_3 (a) 1 h, (b) 4 h; ix, Ac_2O–NaOAc; x, NaOH; xi, $NaBH_4$; xii, H^+



Scheme 2. *Reagents and conditions:* i, diazotisation; ii, HCH=NOH–NaOAc; iii, H^+; iv, $NaSCH_2CO_2Et$–HMPT; v, hydrolysis; vi, Cu–quinoline; vii, rhodanine–NaOAc; viii, OH^-; ix, H^+; x, OH^-–HMPT; xi, H^+; xii, NaSH; xiii, chloramine; xiv, S, aqueous NH_3 at 160 °C

Initial attempts to replace selectively the 2-chloro atom in the 2,3-dichloroaldehyde (12) by a sulphur nucleophile were unsuccessful: the aldehyde was recovered after treatment in the usual solvents with sodium hydrogen sulphide, sodium disulphide, and even the copper salt of ethyl mercaptoacetate. However, use of ethyl sodiomercaptoacetate in hexamethylphosphoric triamide (HMPT) effectively displaced the 2-chloro atom and the product cyclised spontaneously, to give ethyl 7-chlorobenzo[*b*]thiophene-2-carboxylate (13) (85%). This was converted by standard procedures into 7-chlorobenzo[*b*]thiophene (11), thus providing convenient access to the latter compound. In order to investigate whether this method might provide a general ' one-flask ' route to benzo[*b*]thiophene-2-carboxylic esters, which are normally obtained



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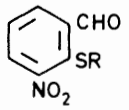
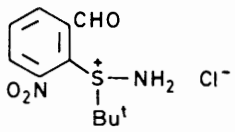


(20) R = Bu^t
(21) R = Bu^n



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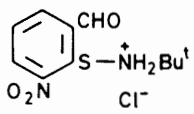

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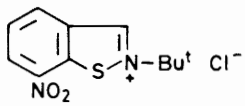

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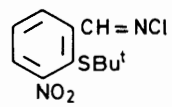

(25)

by more lengthy procedures, we treated 2-chlorobenzaldehyde with ethyl sodiomercaptoacetate in the manner just described, and obtained ethyl benzo[*b*]thiophene-2-carboxylate in 83% yield.

In another approach to 7-chlorobenzo[*b*]thiophene-2-carboxylic acid, the aldehyde (12) was converted in the usual way [1] into the mercaptoacrylic acid (16). This cyclised (30%) when treated with sodium hydroxide in HMPT at 80 °C. This method has fewer practical advantages over those already described, but it is of interest as the first example, to our knowledge, of the preparation of a benzo[*b*]thiophene derivative by intramolecular displacement of a chlorine atom by a mercapto group.

Treating 2,3-dichlorobenzaldehyde (12) with sodium hydrogen sulphide in HMPT at 60—80 °C gave sodio-3-chloro-2-mercaptobenzaldehyde. As had been hoped, this reacted with chloramine to provide 7-chloro-1,2-benzisothiazole (17) (57% overall) (Scheme 2). Clearly this is a much simpler approach to this compound than that used previously.[8,9] In order to extend the scope of this reaction, we successively treated 2,3-dichlorobenzonitrile with sodium hydrogen sulphide and chloramine, to give 3-amino-7-chloro-1,2-benzisothiazole (18) (62%).

It has been shown [15] that 2,6-dichlorobenzaldehyde affords 4-chloro-1,2-benzisothiazole when heated with sulphur and ammonia at 160 °C. Under similar conditions, 2,3-dichlorobenzaldehyde gave 7-chloro-1,2-benzisothiazole (46%). The rather low yield is not unexpected in view of the fact that nucleophilic substitution reactions can be unselective under such harsh conditions.

7-Nitro Derivatives.—The necessary precursor of type (2) was obtained from 2-bromo-3-nitrobenzoic acid, for which 3-nitrophthalic acid is a readily available starting material.[16,17] 2-Bromo-3-nitrobenzoic acid was first converted into the corresponding aldehyde (19), either by reduction of the acid chloride with lithium tri-t-butoxyaluminium hydride (20%) or, preferably, by reduction with diborane (98% yield) and oxidation of the resulting alcohol with activated manganese dioxide (90%). The reactive bromine atom in the bromonitroaldehyde (19) was easily replaced by the SCH_2CO_2H group and the product cyclised under the alkaline reaction conditions to give 7-nitrobenzo[*b*]thiophene-2-carboxylic acid (78%), from which 7-nitrobenzo[*b*]thiophene (82%) was obtained by decarboxylation.

It has been shown that benzo[*b*]thiophenes containing an electron-withdrawing 4-, 5-, or 6-substituent generally undergo electrophilic substitution in the 3-position.[11,18] We have now established by ^1H n.m.r. spectroscopy (see Experimental section) that the 3-bromo derivative (80%) is obtained when 7-nitrobenzo[*b*]thiophene is brominated in acetic acid.

For the preparation of 7-nitro-1,2-benzisothiazole, we made use of the observation of Meth-Cohn and his group [19] that the oxime of 2-(t-butylthio)benzaldehyde will cyclise to 1,2-benzisothiazole when treated with PPA. 2-Bromo-3-nitrobenzaldehyde (19) readily gave the 2-t-butylthio compound (20) on treatment with 2-methylpropane-2-thiol; cyclisation of its oxime with PPA gave 7-nitro-1,2-benzisothiazole (79%). We next investigated whether Meth-Cohn's procedure [19] might also succeed with the n-butylthio compound (21) which, presumably for steric reasons, was obtained even more readily than its isomer (20) from the bromo compound (19). The n-butylthio group in the oxime of aldehyde (21) was cleaved almost as readily as that in its t-butyl isomer (20), to give 7-nitro-1,2-benzisothiazole (72%). Very small concentrations of butanethiol and 2-methylpropane-2-thiol in the atmosphere give rise to a smell similar to that of town gas. After the Gas Board had spent many hours on the campus looking for gas leaks, and after a suspected gas leak had caused the evacuation of a school half a mile away, we were encouraged to discontinue our experiments using these thiols.

2-Bromo-3-nitrobenzoic acid also provided a useful starting material for the preparation of 3-amino-7-nitro-1,2-benzisothiazole: it was converted (see Experimental section) into the corresponding nitrile, which reacted with sodium hydrogen sulphide in acetone to give sodio-2-mercapto-3-nitrobenzonitrile. The last reacted as before with chloramine, and gave 3-amino-7-nitro-1,2-benzisothiazole (78%).

We wondered whether 3-nitro-2-t-butylthiobenzaldehyde (20) would react with chloramine to give the salt (22), which might then cyclise to 7-nitro-1,2-benzisothiazole with loss of t-butyl chloride, and thus provide a new route to 1,2-benzisothiazole derivatives. However, the product (73%) was a stable 1,2-benzisothiazolium salt which seemingly contained an *N*-t-butyl group, because the 3-H signal in the ^1H n.m.r. spectrum appeared at much lower field than is usual for a 1,2-benzisothiazole derivative. The isomeric *S*-alkyl 1,2-benzisothiazolium salt would not have shown such a low-field signal, and would also be expected to be unstable (*cf.* ref. 20). At first we believed that the salt had arisen by alkylation of the initially formed 7-nitro-1,2-benzisothiazole with the t-butyl chloride generated in the reaction. However, treatment of authentic 7-nitro-1,2-benzisothiazole with t-butyl chloride under the conditions of the reaction failed to produce the salt (24). It seems likely, therefore, that the Bu^t group in the intermediate (22) migrates to the nitrogen atom, which is better able to accommodate the positive charge. The resulting intermediate (23) would lose a proton under the basic conditions of the reaction, then cyclise to the salt (24).

The alternative *N*-chloroaldimine structure (25) would also satisfy the analytical and ^1H n.m.r. data for the compound from the chloramine reaction. This would be unstable and would be expected to lose HCl readily, to give the corresponding carbonitrile. However, the base peak in the mass spectrum of the unknown compound was formed by loss of Bu^tCl from the molecular ion; this behaviour is consistent with that expected for structure (24).

Experimental

General experimental directions are given in Part 1.[1] Ether refers to diethyl ether. Mass spectral data for chlorine- and bromine-containing compounds relate to the ^{35}Cl and ^{79}Br isotopes, respectively.

Bis(2-carboxy-6-chlorophenyl) Disulphide.—2-Amino-3-chlorobenzoic acid[10] (10 g) was diazotised in hydrochloric acid in the usual way, then the resulting solution was added during 15—20 min to a stirred mixture of sodium disulphide [from sodium sulphide (15 g), water (17 ml), and sulphur (2 g)], sodium hydroxide (2.3 g), and water (6 ml) at 0—5 °C. The mixture was stirred at room temperature for 2 h, then acidified with concentrated hydrochloric acid, to give the product, which formed white *needles* (8.6 g, 79%), m.p. 298—299 °C (decomp.) (from ethanol) (Found: C, 44.65; H, 2.05%; M^+, 374. $C_{14}H_8Cl_2O_4S_2$ requires C, 44.8; H, 2.15%; M^+, 374); $\nu_{max.}$ 1 680 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 7.30—8.03 (m, ArH).

3-Chloro-2-mercaptobenzyl Alcohol.—The foregoing disulphide (19.5 g) was reduced with lithium aluminium hydride (3 g) in boiling ether (300 ml) during 9 h. The usual work-up gave *needles* (6.6 g, 73%), m.p. 68—69 °C (from ethanol) (Found: C, 48.25; H, 4.0%; M^+, 174. C_7H_7ClOS requires C, 48.15; H, 4.05%; M^+, 174); $\nu_{max.}$ (film) 2 535 (SH) and 3 200—3 500 cm^{-1} (br, OH); δ 2.16 (s, SH), 4.26 (s, OH), and 4.56 (s, CH_2).

(6-Chloro-2-hydroxymethylphenylthio)acetic Acid (4).—A mixture of chloroacetic acid (0.27 g) and 3-chloro-2-mercaptobenzyl alcohol (0.5 g) was heated under reflux for 1 h with an excess of aqueous 15% sodium carbonate, then cooled and acidified. The resulting precipitate formed white *plates* (0.6 g, 90%), m.p. 119—120 °C (from water) (Found: C, 46.85; H, 4.0%; M^+, 232. $C_9H_9ClO_3S$ requires C, 46.45; H, 3.9%; M^+, 232); $\nu_{max.}$ 3 280 (OH) and 1 700 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 3.56 (4 H, s, 2 × CH_2) and 4.83 (s, OH).

3-Chloro-2-mercaptobenzoic Acid (5).—A mixture of the corresponding disulphide (9.7 g), disodium dithionite (6.3 g), sodium carbonate (7.6 g), and water (70 ml) was heated under reflux for 0.5 h, then cooled and filtered. Acidification of the filtrate at −5 to 0 °C, followed by ether extraction, gave a yellow *solid* (8.75 g, 90%), m.p. 172—173 °C (Found: M^+, 188. $C_7H_5ClO_2S$ requires M^+, 188); $\nu_{max.}$ 1 690 (C=O) and 2 535 cm^{-1} (SH). It could not be crystallised, but was sufficiently pure for use in subsequent reactions.

(2-Carboxy-6-chlorophenylthio)acetic Acid (6).—This was obtained (70%) by treatment of the thiol (5) with sodium chloroacetate for 1 h in the manner already described. It crystallised from water as off-white *needles*, m.p. 178—179 °C (Found: C, 43.8; H, 2.85%; M^+, 246. $C_9H_7ClO_4S$ requires C, 43.8; H, 2.85%; M^+, 246); $\nu_{max.}$ 1 700 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 3.60 (s, CH_2).

When the reaction time was increased to 4 h, the product was *7-chloro-3-hydroxybenzo*[b]*thiophene-2-carboxylic acid* (7) (68%), which formed needles, m.p. 193—193.5 °C (from water) (Found: C, 47.5; H, 2.25%; M^+, 228. $C_9H_5ClO_3S$ requires C, 47.25; H, 2.2%; M^+, 228); $\nu_{max.}$ 3 400 (OH) and 1 690 cm^{-1} (C=O).

3-Acetoxy-7-chlorobenzo[b]*thiophene* (8).—A mixture of (2-carboxy-6-chlorophenylthio)acetic acid (6) (6 g), anhydrous sodium acetate (3 g), and acetic anhydride (8 ml) was heated under reflux for 1 h, then cooled. Red neutral material, obtained by ether extraction, was distilled, to give a colourless *oil* (4.52 g, 82%), b.p. 132—133 °C at 5 mmHg (Found: C, 53.15; H, 3.0%; M^+, 226. $C_{10}H_7ClO_2S$ requires C, 53.0; H, 3.1%; M^+, 226); $\nu_{max.}$ (film) 1 770 cm^{-1} (C=O); δ 2.33 (s, OAc).

7-Chlorobenzo[b]*thiophen-3(2H)-one* (9).—A mixture of the acetoxy compound (8) (4.2 g) and aqueous 10% sodium hydroxide (50 ml) was heated under reflux for 1 h, then cooled and acidified with glacial acetic acid. Steam distillation gave white needles (2.33 g, 68%), m.p. 107—107.5 °C (lit.,[21] 103—106 °C); $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ 3.83 (s, CH_2).

7-Chloro-2,3-dihydro-3-hydroxybenzo[b]*thiophene* (10).—A mixture of the foregoing thioindoxyl (2.9 g), sodium borohydride (1.2 g), and ethanol was heated under reflux for 1 h, then poured into water. Acidification with acetic acid and extraction with ether gave *plates* of (10) (2.64 g, 90%), m.p. 68—69 °C (from water) (Found: C, 51.5; H, 3.85%; M^+, 186. C_8H_7ClOS requires C, 51.5; H, 3.8%; M^+, 186); $\nu_{max.}$ 3 200 cm^{-1} (OH) (no C=O) absorption; δ 2.1 (br, OH), 3.23 (dd, $J_{2,2'}$ 14 and $J_{2,3}$ 5 Hz, 2-H), 3.56 (dd, $J_{2',3}$ 7.5 Hz, 2'-H), and 5.43 (dd, 3-H).

7-Chlorobenzo[b]*thiophene* (11).—A mixture of the dihydro compound (10) (1.3 g), aqueous 70% ethanol (20 ml), and concentrated hydrochloric acid (2 ml) was heated under reflux for 3 h, then diluted with water and basified with aqueous 5% sodium hydroxide. Extraction with ether gave a pale yellow residue which yielded a colourless oil (1.03 g, 88%), b.p. 90—94 °C at 0.7 mmHg (lit.,[2] 115 °C at 10 mmHg); δ 7.70 (dd, *J* 8 and 2 Hz, 4-H) and 7.32 (br s, other H).

2,3-Dichlorobenzaldehyde (12).—2,3-Dichloroaniline (44 g) was diazotised with sodium nitrite (17.5 g) and hydrochloric acid (*d* 1.18; 57 ml) in water (75 ml) and ice (100 g). The resulting solution was neutralised with hydrated sodium acetate (22 g) in water (35 ml), then introduced below the surface of a stirred mixture of aqueous 10% formaldoxime (250 ml), hydrated copper(II) sulphate (6.25 g), anhydrous sodium sulphite (1 g), sodium acetate (16.5 g), and water (180 ml). Stirring was continued for 2 h, then the mixture was acidified with hydrochloric acid and heated under reflux for 2 h. Distillation in steam gave pale yellow needles (26 g, 55%), m.p. 66—67 °C [from ethanol–water (1 : 1)] (lit.,[13] 65—67 °C); $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ 10.40 (s, CHO).

Ethyl Benzo[b]*thiophene-2-carboxylate.*—A mixture of ethyl mercaptoacetate (1.4 g), sodium (0.3 g), and ethanol (5 ml) was stirred for 0.5 h, then treated with dry ether (20 ml). The precipitated sodio derivative (1.37 g) was filtered off, dried, and stirred under nitrogen at 80 °C for 8 h with 2-chlorobenzaldehyde (1 g) and sodium carbonate (0.75 g) in HMPT (20 ml). The mixture was then added to saturated aqueous sodium chloride (250 ml). Extraction with ether gave needles (1.22 g, 83%), m.p. 36—36.5 °C (lit.,[22] 36—37 °C) (from ethanol); $\nu_{max.}$ (film) 1 710 cm^{-1} (C=O); identical with authentic material.

Ethyl 7-Chlorobenzo[b]*thiophene-2-carboxylate* (13).—This was prepared similarly from 2,3-dichlorobenzaldehyde (reaction time 24 h), and crystallised from ethanol as *plates* (85%), m.p. 52—53 °C (Found: C, 55.15; H, 3.8%; M^+, 240. $C_{11}H_9ClO_2S$ requires C, 54.9; H, 3.75%; M^+, 240); $\nu_{max.}$ 1 720 cm^{-1} (C=O).

Hydrolysis with aqueous ethanolic sodium hydroxide gave the *acid* (14) as microcrystals (90%), m.p. 151—152 °C (Found: C, 50.95; H, 2.55%; M^+, 212. $C_9H_5ClO_2S$ requires C, 50.8; H, 2.35%; M^+, 212); $\nu_{max.}$ 1 675 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 8.06 (s, 3-H).

Decarboxylation in the usual way (*cf.* ref. 1) gave 7-chlorobenzo[*b*]thiophene (70%), identical with that obtained before.

5-(2,3-*Dichlorobenzylidene*)*rhodanine* (15).—This was prepared by reaction of 2,3-dichlorobenzaldehyde for 6 h with rhodanine in acetic acid in the presence of sodium acetate (*cf.* ref. 1). It formed yellow *needles* (70%), m.p. 202—203 °C (from benzene) (Found: C, 41.25; H, 1.8; N, 4.75%; M^+, 289. $C_{10}H_5Cl_2NOS_2$ requires C, 41.4; H, 1.75; N, 4.8%; M^+, 289); $\nu_{max.}$ 1 700 cm^{-1} (C=O).

β-(2,3-*Dichlorophenyl*)-α-*mercaptoacrylic Acid* (16).—Alkaline hydrolysis (*cf.* ref. 1) of the arylidenerhodanine (15) gave cream *needles* (85%), m.p. 179—180 °C (from toluene) (Found: C, 43.55; H, 2.55%; M^+, 248. $C_9H_6Cl_2O_2S$ requires C, 43.4; H, 2.4%; M^+, 248); $\nu_{max.}$ 2 535 (SH) and 1 680 cm^{-1} (C=O).

The mercapto acid (16) (2 g) was stirred under nitrogen with sodium hydroxide (0.4 g) for 5.5 h at 80 °C in HMPT (30 ml) and the reaction was worked up as already described. The resulting 7-chlorobenzo[*b*]thiophene-2-carboxylic acid (14) (30%) was identical with that obtained before.

7-*Chloro*-1,2-*benzisothiazole* (17).—*Method A.* A mixture of 2,3-dichlorobenzaldehyde (3.5 g), sulphur (0.65 g), aqueous ammonia (*d* 0.88; 10 ml), and 2-methoxyethanol (70 ml) was stirred in an autoclave at 160 °C for 6 h, then cooled. The solvent was partially removed and water (50 ml) was added to the residue. Extraction with dichloromethane and filtration of a trichloromethane solution of the crude product through silica gel afforded material which was purified by short-path distillation [65—70 °C (bath) at 0.2 mmHg], to give needles of (17) (1.56 g, 46%), m.p. 49—50 °C (lit.,[8] 49—50 °C); δ 7.33 (t, $J_{4,5} = J_{5,6} = 8.0$ Hz, 5-H), 7.43 (dd, $J_{4,6}$ 2.0 Hz, 6-H), 7.94 (dd, 4-H), and 8.83 (s, 3-H).

Method B. A mixture of 2,3-dichlorobenzaldehyde (3.5 g), sodium hydrogen sulphide (0.7 g), and HMPT (20 ml) was kept under nitrogen at 120 °C for 24 h, then poured into water. The thiol was extracted into ether, then obtained as an aqueous solution of its sodium salt by shaking the ethereal extracts with aqueous 3% sodium hydroxide (20 ml). The alkaline solution was then treated successively with aqueous ammonia (*d* 0.88; 20 ml) and aqueous 5% sodium hypochlorite (18 ml; added dropwise at −5 to 0 °C). After 1 h, neutral material was obtained by ether extraction, to give a product (1.93 g, 57%), identical with that from method A.

2,3-*Dichlorobenzonitrile*.—Concentrated sulphuric acid (30 ml) was added slowly to a stirred mixture of 2,3-dichloroaniline (32.5 g), water (80 ml), and glacial acetic acid (100 ml), then the mixture was heated to effect dissolution, and cooled to 0 °C. A solution of sodium nitrite (15.4 g) in water (30 ml) was added below the surface of the amine salt solution during 15 min and stirring was continued for a further 3 h; the diazonium salt solution was then added below the surface of a stirred solution, pre-prepared by mixing hydrated copper(II) sulphate (60 g), water (300 ml), ice (100 g), and potassium cyanide (65 g) with sodium hydrogen carbonate (134 g) and water (150 ml) at 0—5 °C. When the reaction was complete (t.l.c.), neutral material was extracted into benzene. After purification by distillation in steam, it formed pale yellow *needles* (17.5 g, 51%), m.p. 56—57 °C (from benzene–light petroleum) (Found: C, 49.15; H, 1.85; N, 8.15%; M^+, 171. $C_7H_3Cl_2N$ requires C, 48.9; H, 1.75; N, 8.15%; M^+, 171); $\nu_{max.}$ 2 215 cm^{-1} (C≡N).

3-*Amino*-7-*chloro*-1,2-*benzisothiazole* (18).—Reaction of the foregoing nitrile with chloramine for 1.5 h, using the procedure already described, gave *needles* (62%), m.p. 169—170 °C (from ethanol) (Found: C, 45.65; H, 2.95; N, 15.25%; M^+, 184. $C_7H_5ClN_2S$ requires C, 45.5; H, 2.7; N, 15.15%; M^+, 184); $\nu_{max.}$ 3 320 cm^{-1} (NH_2); δ 6.10 (br s, NH_2), 7.37 (t, $J_{4,5} = J_{5,6} = 8.0$ Hz, 5-H), 7.53 (dd, $J_{4,6}$ 2.0 Hz, 6-H), and 7.91 (dd, 4-H).

2-*Bromo*-3-*nitrobenzaldehyde* (19).—*Method A.* (*a*) 2-Bromo-3-nitrobenzoyl chloride (70%), prepared from the carboxylic acid and thionyl chloride, had m.p. 66—67 °C (lit.,[23] 66—66.5 °C) (from light petroleum).

(*b*) A solution of lithium tri-t-butoxyaluminium hydride (7 g) in dry diglyme (25 ml) was added during 1 h to a stirred solution of the acid chloride (6.5 g) in dry diglyme at −78 °C. The mixture was then stirred at −78 °C for 0.5 h, allowed to attain room temperature, and poured into a stirred slurry of concentrated hydrochloric acid (20 ml) and ice (20 g). After saturation of the mixture with sodium chloride, neutral material was extracted into ether in the usual way, to give pale yellow *needles* (1.13 g, 20%), m.p. 108—109 °C (Found: C, 36.55; H, 1.8; N, 5.95%; M^+, 229. $C_7H_4BrNO_3$ requires C, 36.55; H, 1.75; N, 6.1%; M^+, 229); $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ 10.16 (s, CHO).

Method B. (*a*) Diborane [from sodium borohydride (2.6 g) and boron trifluoride–diethyl ether (9.65 g) in dry diglyme (100 ml)] was passed in a stream of nitrogen into a solution of 2-bromo-3-nitrobenzoic acid (4.2 g) in dry tetrahydrofuran (100 ml) at 0 °C. The mixture was kept at room temperature for 24 h, then aqueous 50% tetrahydrofuran (100 ml) and an excess of potassium carbonate were added successively. Ether extraction gave 2-bromo-3-nitrobenzyl alcohol as *needles* (3.88 g, 98%), m.p. 76—77 °C (from benzene) (Found: C, 36.25; H, 2.55; N, 5.8%; M^+, 231. $C_7H_6BrNO_3$ requires C, 36.25; H, 2.6; N, 6.05%; M^+, 231); $\nu_{max.}$ 3 100—3 460 cm^{-1} (br, OH); δ 2.43 (br, OH) and 4.86 (s, CH_2).

(*b*) A mixture of 2-bromo-3-nitrobenzyl alcohol (3 g), activated manganese dioxide (5 g), and dry trichloromethane (60 ml) was stirred at room temperature for 3 h; additional manganese dioxide (2 × 3 g) was added at 2 × 3 h intervals, by which time the reaction was complete (t.l.c.). Filtration (Hyflo) and evaporation gave the aldehyde (2.7 g, 90%), identical with that obtained by method A.

7-*Nitrobenzo*[b]*thiophene-2-carboxylic Acid.*—2-Bromo-3-nitrobenzaldehyde reacted with mercaptoacetic acid in aqueous sodium carbonate under the conditions used for compound (4), to give yellow *needles* (78%), m.p. 288—289 °C [from acetic acid–water (1 : 3)] (Found: C, 48.45; H, 2.25; N, 6.25%; M^+, 223. $C_9H_5NO_4S$ requires C, 48.4; H, 2.25; N, 6.3%; *M*, 223); $\nu_{max.}$ 1 680 cm^{-1} (C=O).

7-*Nitrobenzo*[b]*thiophene*.—The 2-carboxylic acid just described was decarboxylated with copper in quinoline (*cf.* ref. 1), to give yellow needles (82%), m.p. 116—117 °C (lit.,[7] 116—117 °C) (from light petroleum); $\nu_{max.}$ 1 330 and 1 515 cm^{-1} (NO_2).

3-*Bromo*-7-*nitrobenzo*[b]*thiophene*.—A mixture of 7-nitrobenzo[*b*]thiophene (0.5 g), bromine (0.45 g), anhydrous sodium acetate (2.3 g), and glacial acetic acid (20 ml) was heated under reflux for 4 h, then cooled and poured into water. The precipitate gave *needles* (0.58 g, 80%), m.p. 163—164 °C (from ethanol) (Found: C, 37.35; H, 1.65; N, 5.45%; M^+, 257. $C_8H_4BrNO_2S$ requires C, 37.2; H, 1.55; N, 5.4%; M^+, 257); δ 7.50 (t, $J_{4,5} = J_{5,6} = 8.1$ Hz, 5-H), 7.52 [d (under high resolution), $J_{2,6}$ 0.5 Hz, 2-H], 8.03 (dd, $J_{4,6}$ 1.5 Hz, 6-H), and 8.30 (dd, 4-H).

3-*Nitro*-2-*t*-*butylthiobenzaldehyde* (20).—A solution of 2-bromo-3-nitrobenzaldehyde (19) (20 g) in ethanol (600 ml) was added dropwise under nitrogen at 0 °C during 1 h to a stirred mixture of 2-methylpropane-2-thiol (9 g), potassium carbonate (12 g), and ethanol (100 ml). Stirring was continued overnight at room temperature, then the mixture was poured into water. The precipitate formed yellow *needles* (19.3 g, 93%), m.p. 63—63.5 °C [from light petroleum (b.p. 40—60 °C)] (Found: C, 55.45; H, 5.5; N, 6.05%; M^+, 239. $C_{11}H_{13}NO_3S$ requires C, 55.2; H, 5.5; N, 5.85%; *M*, 239); $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ 1.30 (s, Bu^t) and 10.56 (s, CHO).

The *oxime* crystallised from benzene–light petroleum as yellow cubes, m.p. 118—119 °C (Found: C, 51.9; H, 5.55; N, 10.85%; M^+, 254. $C_{11}H_{14}N_2O_3S$ requires C, 51.95; H, 5.55; N, 11.0%; *M*, 254); δ 1.30 (s, Bu^t) and 8.96 (s, OH).

2-*n*-*Butylthio*-3-*nitrobenzaldehyde* (21).—Prepared by the method just described for the t-butyl isomer, this was isolated by extraction with ether, to give a pale yellow *oil* (90%), b.p. 120—122 °C at 0.4 mmHg (Found: C, 55.35; H, 5.5; N, 6.0%; M^+, 239); $\nu_{max.}$ (film) 1 690 cm^{-1} (C=O); δ 0.96 (t, Me) and 10.60 (s, CHO).

The *oxime* could not be crystallised. Analytically pure material had b.p. 132—134 °C at 0.4 mmHg (Found: C, 51.8; H, 5.5; N, 11.05%; M^+, 254); δ 0.96 (t, Me) and 8.83 (s, OH).

7-*Nitro*-1,2-*benzisothiazole*.—A mixture of 3-nitro-2-t-butylthiobenzaldoxime (1 g) and polyphosphoric acid (40 g) was stirred at 100 °C for 0.5 h, diluted with ice (50 g) and water (100 ml), and neutralised with aqueous 5% sodium hydroxide. Ether extraction gave yellow needles (0.56 g, 79%), m.p. 162—163 °C (lit.,[8] 161—162 °C); δ 8.72 (s, 3-H).

The same product (72%) was obtained by analogous treatment of the oxime of the n-butyl isomer (21).

2-*Bromo*-3-*nitrobenzonitrile*.—A stirred mixture of phosphorus pentachloride (7.85 g), 2-bromo-3-nitrobenzoic acid (3 g), and toluene-*p*-sulphonamide (3.3 g) was warmed gently until a vigorous reaction had set in. When this had subsided and the mixture had liquefied, the temperature was raised slowly, then maintained at 205 °C until no more distillate passed over. Cooling the mixture gave a solid, which was dissolved in warm pyridine (7 ml). Water (33 ml) was added cautiously to the stirred solution, then the resulting suspension was cooled, to give a precipitate which formed off-white *needles* (2.25 g, 81%), m.p. 136—137 °C (from ethanol) (Found: C, 37.25; H, 1.4; N, 12.55%; M^+, 226. $C_7H_3BrN_2O_2$ requires C, 37.05; H, 1.35; N, 12.35%; M^+, 226); $\nu_{max.}$ 2 220 cm^{-1} (C≡N).

3-*Amino*-7-*nitro*-1,2-*benzisothiazole*.—A mixture of 2-bromo-3-nitrobenzonitrile (1 g), sodium hydrogen sulphide (0.4 g), and acetone (25 ml) was stirred under nitrogen for 6 h, then the acetone was distilled off. A solution of the residual sodio derivative in water (25 ml) was then treated with chloramine as described before, to give pale yellow *needles* (0.67 g, 78%), m.p. 247—248 °C (from acetone–water) (Found: C, 43.15; H, 2.65; N, 21.55%; M^+, 195. $C_7H_5N_3O_2S$ requires C, 43.05; H, 2.6; H, 21.5%; *M*, 195); $\nu_{max.}$ 3 420 cm^{-1} (NH_2); δ 5.20 (br s, NH_2), 7.30 (t, $J_{4,5} = J_{5,6} = 8.2$ Hz, 5-H), 8.15 (dd, $J_{4,6}$ 2.0 Hz, 4-H), and 8.22 (dd, 6-H).

7-*Nitro*-2-*t*-*butyl*-1,2-*benzisothiazolium Chloride* (24).—Treatment of 3-nitro-2-t-butylthiobenzaldehyde (20) with chloramine in the usual way gave yellow *needles* of (24) (73%), m.p. 215—216 °C (decomp.) (from ethanol) (Found: C, 48.55; H, 4.9; N, 10.25. $C_{11}H_{13}ClN_2O_2S$ requires C, 48.45; H, 4.8; N, 10.25%); δ 1.30 (9 H, s, Bu^t), 9.40 (1 H, s, 3-H), and 7.6—8.6 (3 H, m, ArH); *m*/*z* 180 (M^+ – Bu^tCl).

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