7-Substituted Benzo[*b*]thiophenes and 1,2-Benzisothiazoles. Part 1. Hydroxy- or Methoxy-derivatives

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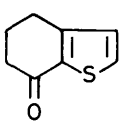
Readily available 2-hydroxy-3-methoxybenzaldehyde (orthovanillin) is converted, *via* thermal rearrangement (Newman–Kwart) of the *O*-aryl-*NN*-dimethylthiocarbamate, into 2-mercapto-3-methoxybenzaldehyde (3). This thiol undergoes base-catalysed condensation with compounds of the type $ClCH_2X$ (*e.g.* X = CO_2H, Ac, or CN), to give the appropriate 2-(X-substituted)-7-methoxybenzo[*b*]thiophene. Successive demethylation and decarboxylation of 7-methoxybenzo[*b*]thiophene-2-carboxylic acid provides a convenient route to 7-hydroxybenzo[*b*]thiophene. 7-Methoxybenzo[*b*]thiophene undergoes bromination and nitration at the 4-position; the structure of the 4-bromo compound is confirmed by an unambiguous synthesis. 2-Mercapto-3-methoxybenzaldehyde (3) reacts with chloramine to provide a simple synthesis of 7-methoxy-1,2-benzisothiazole. 2-Mercapto-3-methoxybenzonitrile, obtained as above from the corresponding 2-hydroxy compound, gives 2-acetyl-3-amino-7-methoxybenzo[*b*]-thiophene when treated with chloropropanone, and 3-amino-7-methoxy-1,2-benzisothiazole when treated with chloramine.

The preparations of 4-, 5-, and 6-hydroxybenzo[*b*]thiophene are well documented,[1,2] and these phenols and their simple derivatives have been used extensively for the preparation of sulphur isosteres of biologically active hydroxyindoles.[3,4] Derivatives of 7-hydroxybenzo[*b*]thiophene have received far less attention, mainly because of their inaccessibility.

Sunthankar and Tilak prepared 7-methoxybenzo[*b*]thiophene (18%) by cyclodehydration of (2-methoxyphenylthio)-ethanal dimethyl acetal and demethylated it with pyridine hydrochloride.[5] The resulting phenol was said to darken and decompose on being kept. 7-Hydroxybenzo[*b*]thiophene has also been obtained in low yield (19%) by oxygenation of the Grignard reagent derived from 7-chlorobenzo[*b*]thiophene; its 3-methyl derivative may be obtained (63%) by treating the 7-chloro compound with aqueous sodium hydroxide under forcing conditions.[6] Other routes to 7-hydroxy- or 7-methoxybenzo[*b*]thiophenes are more specialised,[1,2] and the products often possess functionality elsewhere in the ring.[7]

5,6-Dihydrobenzo[*b*]thiophen-7(4*H*)-one (1) should be capable of being dehydrogenated to 7-hydroxybenzo[*b*]-thiophene. Unfortunately, it is obtained by a lengthy route



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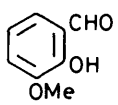

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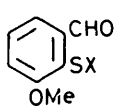


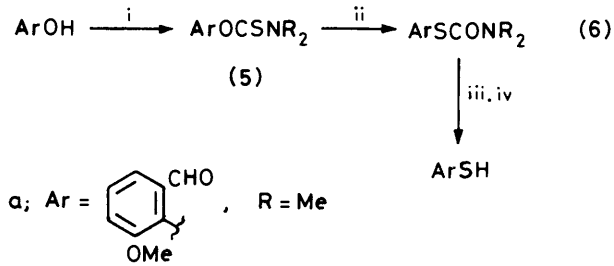
(3) X = H

(4) X = CH_2CO_2H

from a 3-substituted thiophene derivative,[8] and is not therefore readily accessible.

Results and Discussion

Benzo[b]*thiophene Derivatives.*—We aimed to prepare a 7-(oxygen-substituted)benzo[*b*]thiophene starting from a 1,2,3-trisubstituted benzene derivative containing respectively a carbonyl, sulphur, and oxygen function. Such compounds are unknown. However, commercially available 2-hydroxy-3-methoxybenzaldehyde (orthovanillin) (2) is cheap, and needs only to be converted into the corresponding mercapto compound (3) which would be a versatile intermediate. Analogous

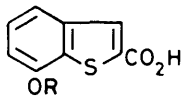


Scheme 1. *Reagents and conditions:* i, R_2NCSCl–KOH; ii, heat (Newman–Kwart rearrangement); iii, OH^-; iv, H^+

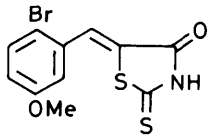
transformations have previously been achieved in variable yield by the route shown in Scheme 1,[9,10] in which the key step is the Newman–Kwart thermal rearrangement of an *O*-arylthiocarbamate (5) into the isomeric *S*-aryl compound (6). When applied previously to *O*-(2,6-disubstituted aryl)thiocarbamates (5), the rearrangement step had proceeded in only low yield.[9,11] Furthermore, there were, to our knowledge, no previous examples of the rearrangement (5) ⟶ (6) for which the aryl group (Ar) contained a formyl substituent.

Reaction of orthovanillin (2) with *NN*-dimethylthiocarbamoyl chloride in tetrahydrofuran (THF) at <10 °C in the presence of potassium hydroxide readily gave the *O*-arylthiocarbamate (5a) (85%). Heating this, either alone or in sulpholane (tetrahydrothiophene 1,1-dioxide), gave intractable products. However, the rearrangement proceeded smoothly (90%) in diphenyl ether under carefully controlled conditions (15 min at 240 °C). Heating in 1,2-bis(methoxyethoxy)ethane (triethylene glycol dimethyl ether) was less effective, but the product (6a) (60%) could be recovered easily by dilution with water.

The *S*-arylthiocarbamate (6a) was readily hydrolysed to the required thiol (3) (90%), provided that the base was sufficiently dilute to prevent the Cannizzaro reaction from occurring and that the minimum reaction time (t.l.c.) was used. The thiol (3) was unstable, so it was used directly as the sodium salt. On condensation with sodium chloroacetate, this gave the aldehydo acid (4) (90%), which was quantitatively cyclised on being heated in basic solution to give (after acidification) 7-methoxybenzo[*b*]thiophene-2-carboxylic acid (7). By increasing the amount of base and extending the reaction period, the carboxylic acid (7) was obtained directly from the thiol (3). In



(7) R = Me
(8) R = H



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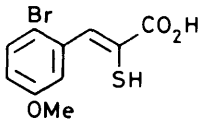

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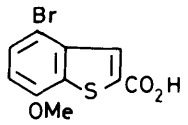

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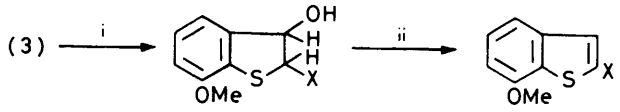
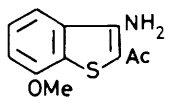


(12) X = CN
(13) X = CO_2Me
(14) X = CN
(15) X = Ac

Scheme 2. *Reagents and conditions:* i, $ClCH_2X$–base; ii, alkaline solution, room temperature



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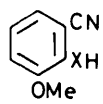
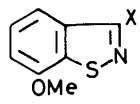


(17) X = O
(18) X = S



(19) X = H
(20) X = NH_2

fact, it could be obtained directly from the *O*-arylthiocarbamate (5a) in a one-flask reaction, but generally it was more convenient to isolate the thiol after the rearrangement stage. We had hoped that the aldehydo acid (4) might undergo decarboxylative cyclisation in a single synthetic step on being heated with Ac_2O–NaOAc; similar reactions have been used widely in benzo[*b*]thiophene and benzo[*b*] furan chemistry.[1] However, under these conditions, only the 2-carboxylic acid (7) could be obtained (90%).

7-Methoxybenzo[*b*]thiophene-2-carboxylic acid (7) was decarboxylated (70%) (Cu–quinoline) to oily 7-methoxybenzo[*b*]thiophene, which was demethylated to 7-hydroxybenzo[*b*]thiophene (55%) by use of boron tribromide in dichloromethane. It was preferable to demethylate the methoxy carboxylic acid (7) with hydrobromic acid in acetic acid to yield the crystalline hydroxy acid (8) (90%), which was then decarboxylated to 7-hydroxybenzo[*b*]thiophene (85%). In contrast to a previous report,[5] this was a stable compound, which underwent some decomposition only on exposure to sunlight.

We have previously shown that the Fries rearrangement of 7-acetoxybenzo[*b*]thiophene in benzene in the presence of $AlCl_3$ is complicated by reduction of the 2,3-double bond and by incorporation of the solvent into the 3-position.[12] We now confirm that the Claisen rearrangement of 7-allyloxybenzo[*b*]thiophene in boiling *NN*-dimethylaniline gives the expected 6-allyl-7-hydroxybenzo[*b*]thiophene (74%) (compare the similar results for 7-allyloxy-3-methylbenzo[*b*]thiophene [13]).

We next studied the bromination and nitration of 7-methoxybenzo[*b*]thiophene in order to compare the results with those obtained for the 4-methoxy isomer, for which substitution takes place at the 7-position,[14,15] and for the 7-methoxy-3-methyl compound, which is substituted at the 4- and 6-position.[13] The structures of the products were not immediately evident, since it was not easy (*cf.* ref. 1) to distinguish between 4,7- and 6,7-disubstituted benzo[*b*]thiophenes by their ^1H n.m.r. spectra, especially as there was no evidence of long-range coupling [1] between 2-H and 6-H. 4-Bromo-7-methoxybenzo[*b*]thiophene was therefore synthesized unambiguously. 2-Bromo-5-methoxybenzaldehyde condensed with 2-thioxothiazolidin-4-one (rhodanine) to give the arylidene compound (9) (70%), which then underwent alkaline hydrolysis to the mercaptoacrylic acid (10) (85%). This was cyclised by iodine in boiling THF, but not by chlorine in tetrachloromethane,[16] to give 4-bromo-7-methoxybenzo[*b*]-thiophene-2-carboxylic acid (11) (50%); this on decarboxylation gave 4-bromo-7-methoxybenzo[*b*]thiophene (68%), identical with the product from the bromination of 7-methoxybenzo[*b*]thiophene. In view of the relative difficulty of the cyclisation step, the method was not pursued as a practicable route to other 7-methoxy derivatives. In order to confirm that the nitration reaction had occurred at the 4-position, the nitro compound was reduced (Sn–HCl), then the resulting amine was converted into the corresponding bromo compound (Sandmeyer). The last was identical with the 4-bromo-7-methoxybenzo[*b*]thiophene already described.

We next showed that the thiol (3) could be converted into a range of benzo[*b*]thiophene derivatives (13)—(15) (Scheme 2), the 2-substituent of which should be capable of elaboration to give compounds of potential biological importance. Surprisingly, the ester (13) was obtained in low yield (11%), but the 2-cyano (14) and 2-acetyl compounds (15) were obtained in high yields. Unexpectedly, the thiol (3) reacted with chloroacetonitrile under mild basic conditions at 0 °C to give the 2,3-dihydro-3-hydroxy compound (12) (77%). Such hydroxy compounds are postulated as intermediates in many aldol-like cyclisations leading to benzo[*b*]thiophene derivatives, but this is the first time to our knowledge that one has been isolated. By carrying out the reaction at 20 °C, or by keeping an alkaline solution of the hydroxy intermediate (12) at room temperature, the required 2-cyano compound (14) was obtained in 80% yield.

The sequence shown in Scheme 2 was next extended to include the preparation of the 2-acetyl-3-amino compound (16). Compounds which contain adjacent amino and acetyl functions are versatile intermediates for the synthesis of fused heterocyclic compounds; in the benzo[*b*]thiophene field, such compounds are normally not readily available because of the inaccessibility of the benzenoid precursor (an *o*-mercaptobenzonitrile).[2] In this case, however, orthovanillin was converted by standard procedures into the corresponding hydroxy nitrile (17), which then smoothly underwent the sequence of reactions already described (*cf.* Scheme 1) to give the mercapto nitrile (18) in high overall yield. Reaction of the sodio derivative of the thiol (18) with chloropropanone then gave the amino ketone (16) (87%) directly. Clearly, the thiol (18) might also be used to prepare other 2-substituted 3-amino-7-methoxybenzo[*b*]thiophenes (*cf.* Scheme 2).

1,2-*Benzisothiazoles*.—Relatively few 7-substituted 1,2-benzisothiazoles have been reported,[17] and these have often been obtained by electrophilic substitution of a preformed 1,2-benzisothiazole. 2-Mercapto-3-methoxybenzaldehyde (3) seemed an obvious, readily available precursor for 7-methoxy-1,2-benzisothiazole. *o*-Mercaptobenzaldehydes are normally converted into 1,2-benzisothiazoles either by treatment of the oxime with polyphosphoric acid,[18] or by similar treatment of the oxime of the *S*-(t-butyl) derivative.[19] Their reaction with chloramine, followed by cyclisation of the resulting sulphenamide (*cf.* ref. 20), would obviate the need to prepare the oxime. Nevertheless, this potentially useful route to 1,2-benzisothiazoles has apparently not been exploited. However, we found that the oxidation of an alkaline ammoniacal solution of the thiol (3) with sodium hypochlorite proceeded smoothly to produce 7-methoxy-1,2-benzisothiazole (19) in 70% yield. Similar treatment of the *o*-mercaptobenzonitrile (18) readily gave 3-amino-7-methoxy-1,2-benzisothiazole (20) (73%). This reaction could be of general application, since 3-amino-1,2-benzisothiazoles are commonly obtained indirectly and with difficulty by treatment of the corresponding 3-chloro compound with ammonia.[21]

Experimental

^{1}H N.m.r. spectra were obtained at 60 MHz with a JNM-PMX-60 spectrometer for 5—10% solutions in $CDCl_3$ (unless otherwise stated) with tetramethylsilane as internal standard. Molecular weights were obtained with an A.E.I. MS902 mass spectrometer; values for bromine-containing compounds relate to the ^{79}Br isotope. Purity of compounds was established by t.l.c. (on Merck silica gel 60 F_{254}) and by h.p.l.c. (high-pressure liquid chromatography) (Varian 8 500 pump coupled to a Perkin-Elmer u.v. detector; Partisil C8 reversed-phase column). Unless stated otherwise, light petroleum had b.p. 60—80 °C. Ether refers to diethyl ether.

NN-*Dimethylthiocarbamoyl Chloride*.—This was prepared by the method used for the diethyl analogue.[22]

O-(2-*Formyl*-6-*methoxyphenyl*)-NN-*dimethylthiocarbamate* (5a).—A solution of *NN*-dimethylthiocarbamoyl chloride (46 g, 0.37 mol) in dry THF (100 ml) was added during 20—30 min to a stirred, cooled (0 °C) solution of 2-hydroxy-3-methoxybenzaldehyde (57 g, 0.37 mol) and potassium hydroxide (21 g) in water (250 ml) at such a rate that the temperature did not exceed 12 °C. The mixture was then stirred for 10 min at room temperature, aqueous 10% potassium hydroxide (125 ml) was added, and organic material was extracted into benzene. Evaporation of the washed (saturated aqueous sodium chloride, water) and dried solution gave yellow *plates* (75 g, 85%), m.p. 113.5—114.5 °C (from methanol) (Found: C, 55.15; H, 5.5; N, 5.6%; M^+, 239. $C_{11}H_{13}NO_3S$ requires C, 55.2; H, 5.5; N, 5.85%; *M*, 239); $\nu_{max.}$ 1 700 (C=O) and 1 540 cm^{-1} (C=S); δ 3.43 and 3.46 (each s, together NMe_2), 3.95 (s, OMe), and 10.30 (s, CHO).

S-(2-*Formyl*-6-*methoxyphenyl*)-NN-*dimethylthiocarbamate* (6a).—(a) *In diphenyl ether*. A solution of *O*-(2-formyl-6-methoxyphenyl)-*NN*-dimethylthiocarbamate (5a) (3 g) in diphenyl ether (55 ml) was kept under nitrogen at 240—250 °C until reaction was complete (t.l.c.) (10—15 min). Light petroleum (360 ml) was added to the cooled solution, then the mixture was kept overnight at 0 °C. The resulting brown solid was filtered off and crystallised from light petroleum (b.p. 40—60 °C) to give pale yellow *needles* (2.7 g, 90%), m.p. 83—83.5 °C (Found: C, 55.4; H, 5.45; N, 5.85%; M^+, 239); $\nu_{max.}$ 1 670 and 1 690 cm^{-1} (C=O); δ 3.15 (6 H, s, NMe_2), 3.95 (s, OMe), and 10.60 (s, CHO).

(b) *In* 1,2-*bis*(*methoxyethoxy*)*ethane*. The above reaction was carried out for 20 min at 220—225 °C in triethylene glycol dimethyl ether (40 ml). Water was then added and the mixture was kept overnight at 0 °C, then worked up to give a brown solid (60%), identical with that obtained in (a).

2-*Mercapto*-3-*methoxybenzaldehyde* (3).—A solution of the *S*-arylthiocarbamate (6a) (5 g, 0.02 mol) in methanol (20 ml) was stirred under reflux under nitrogen for 1 h with aqueous 10% sodium hydroxide (10 ml, 0.025 mol). The cooled mixture was washed with chloroform, then acidified. Extraction with ether gave yellow crystals (3.02 g, 90%), m.p. 41—42 °C, which were almost pure (t.l.c. and h.p.l.c.), but which were not easily recrystallised (Found: M^+, 168. $C_8H_8O_2S$ requires *M*, 168); $\nu_{max.}$ 1 685 (C=O) and 2 560 cm^{-1} (SH); δ 4.00 (s, OMe), 5.80 (s, SH), and 10.25 (s, CHO).

(2-*Formyl*-6-*methoxyphenylthio*)*acetic Acid* (4).—The alkaline solution of 2-mercapto-3-methoxybenzaldehyde (3) (2.2 g) from the reaction just described was treated, without prior acidification, with a solution of sodium chloroacetate [from chloroacetic acid (1.3 g) and sodium carbonate] in water (4 ml). The mixture was then heated under reflux for 4 h, cooled, and acidified. The resulting white solid formed *needles* (2.65 g, 90%), m.p. 104—105 °C (from water) (Found: C, 52.95; H, 4.45%; M^+, 226. $C_{10}H_{10}O_4S$ requires C, 53.1; H, 4.45%; *M*, 226); $\nu_{max.}$ 1 685 (CHO) and 1 715 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 3.70 (s, SCH_2), 4.00 (s, OMe), and 10.85 (s, CHO).

7-*Methoxybenzo*[b]*thiophene*-2-*carboxylic Acid* (7).—(*a*) When the reaction just described was carried out under reflux for 8 h, the resulting solid was the acid (7), which crystallised from methanol–water (3 : 1) as white *needles* (90%), m.p. 241—242 °C (Found: C, 57.75; H, 3.9%; M^+, 208. $C_{10}H_8O_3S$ requires C, 57.7; H, 3.85%; *M*, 208); $\nu_{max.}$ 1 680 cm^{-1} (C=O), δ 4.05 (s, OMe) and 8.25 (s, 3-H).

(*b*) (2-Formyl-6-methoxyphenylthio)acetic acid (4) (10 g) was kept at 100 °C for 1 h with an excess of aqueous 10% sodium hydroxide. Acidification gave the acid (7) (9.2 g, 100%), identical with that just described.

(*c*) Following the thermal rearrangement reaction, the solution of the *S*-arylthiocarbamate (6a) in diphenyl ether was vigorously stirred at 100 °C for 6 h with aqueous 10% sodium hydroxide. The aqueous layer was separated and treated with sodium chloroacetate as before, to give the acid (7) (30% overall), m.p. and mixed m.p. 240—242 °C.

7-*Methoxybenzo*[b]*thiophene*.—A mixture of 7-methoxybenzo[*b*]thiophene-2-carboxylic acid (7) (3 g), dry redistilled quinoline (25 ml), and copper bronze (1.2 g) was stirred vigorously at 210—220 °C for 2 h under nitrogen, then cooled to 100 °C, filtered (Hyflo), and poured into aqueous 50% hydrochloric acid (350 ml). Neutral material was extracted into ether in the usual way to give, after work-up, an oil (1.65 g, 70%), b.p. 85—90 °C at 0.2 mmHg (lit.,[5] 140—145 °C at 15 mmHg); δ 3.95 (s, OMe), 6.65 (dd, *J* 8 and 2 Hz, 6-H), and 7.25 (br s, other protons).

7-*Hydroxybenzo*[b]*thiophene*-2-*carboxylic Acid* (8).—The corresponding 7-methoxy compound (7) (5 g) was heated under reflux for 5 h with a mixture of hydrobromic acid (48% w/w; 75 ml) and glacial acetic acid (75 ml), then the solution was cooled and poured into ice–water. The resulting dark red solid formed grey *needles* (4.2 g, 90%), m.p. 275.5—

276 °C [from methanol–water (1 : 1) (charcoal)] (Found: C, 55.8; H, 3.3%; M^+, 194. $C_9H_6O_3S$ requires C, 55.65, H, 3.1%; *M*, 194); $\nu_{max.}$ 1 675 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 8.2 (s, 3-H) and 10.65 (s, OH).

7-*Hydroxybenzo*[b]*thiophene*.—(*a*) A solution of boron tribromide (1.2 g) in dry dichloromethane was added to a solution of 7-methoxybenzo[*b*]thiophene (3 g) in dichloromethane (15 ml) at −78 °C. The stirred, wine-red solution was kept at room temperature overnight, then cooled in ice, and treated with water (10 ml). Isolated in the usual way, the phenol crystallised from hexane as white needles (1.51 g, 55%), m.p. 68.5—69.5 °C (lit.,[5] 67—68 °C); $\nu_{max.}$ (film) 3 400 br, (CCl_4) 3 600 cm^{-1} (OH); δ 7.3 (2 H, s, 2- and 3-H), 6.65 (dd, *J* 8 and 2 Hz, 6-H), and 7.3—7.35 (m, 4- and 5-H).

(*b*) 7-Hydroxybenzo[*b*]thiophene-2-carboxylic acid (8) (10 g) was decarboxylated by the method used for the corresponding 7-methoxy compound (7), except that the temperature was 190—200 °C and the reaction time 1.5 h. The phenol was extracted from the ethereal solution with sodium hydroxide, then the alkaline solution was treated with charcoal prior to acidification and extraction with ether. The product (6.6 g, 85%) was identical with that from (a).

7-*Allyloxybenzo*[b]*thiophene*.—A mixture of 7-hydroxybenzo[*b*]thiophene (2 g), allyl bromide (3 ml), anhydrous potassium carbonate (6 g), and butanone (80 ml) was stirred under reflux for 3 h, then cooled, filtered, and evaporated, to give a pale yellow *oil* (2.2 g, 87%), b.p. 105—108 °C at 0.5 mmHg (Found: C, 69.75; H, 5.15%; M^+, 190. $C_{11}H_{10}OS$ requires C, 69.45: H, 5.3%; *M*, 190); δ 4.65 (d, OCH_2).

6-*Allyl*-7-*hydroxybenzo*[b]*thiophene*.—The foregoing allyl ether (1 g) was heated under reflux for 6 h with freshly distilled *NN*-dimethylaniline (20 ml), then the cooled solution was poured into ice-cold dilute hydrochloric acid (100 ml). Extraction with ether and isolation of phenolic material in the usual way gave a pale yellow *oil* (0.74 g, 74%), b.p. 92—94 °C at 0.4 mmHg (Found: C, 69.45; H, 5.3%; M^+, 190); $\nu_{max.}$ (CCl_4) 3 520 cm^{-1} (OH); δ 3.5 (m, CH_2) and 5.15 (br s, OH).

4-*Bromo*-7-*methoxybenzo*[b]*thiophene*.—A solution of bromine (0.98 g, 1 mol equiv.) in dry tetrachloromethane (10 ml) was added dropwise during 3 h to a stirred solution of 7-methoxybenzo[*b*]thiophene (1 g) in tetrachloromethane (30 ml) at 0 °C. After a further 1.5 h at 0 °C, the product was isolated in the usual way, to give off-white *plates* (1.36 g, 92%), m.p. 58—59 °C (from ethanol) (Found: C, 44.7; H, 2.95%; M^+, 242. C_9H_7BrOS requires C, 44.45; H, 2.9%; M^+, 242); δ 3.95 (s, OMe), 6.55 (d, $J_{5,6}$ 8.0 Hz, 6-H), 7.25 (d, 5-H), 6.7 (d, $J_{2,3}$ 6.0 Hz, 2-H), and 7.5 (d, 3-H).

7-*Methoxy*-4-*nitrobenzo*[b]*thiophene*.—A solution of concentrated nitric acid (1.7 ml) in glacial acetic acid (10 ml) was added dropwise during 3.5 h to a stirred solution of 7-methoxybenzo[*b*]thiophene (1 g) in acetic acid (20 ml) at 0 °C. The mixture was stirred for a further 1 h at 0 °C, then poured into water. The precipitate formed brown *needles* (1.03 g, 81%), m.p. 112—113 °C (from ethanol) (Found: C, 51.85; H, 3.4; N, 6.7%; M^+, 209. $C_9H_7NO_3S$ requires C, 51.65; H, 3.35; N, 6.7%; *M*, 209); δ 4.05 (s, OMe), 6.7 (d, $J_{5,6}$ 8.0 Hz, 6-H), 8.25 (d, 5-H), 7.55 (d, $J_{2,3}$ 5.8 Hz, 2-H), and 8.05 (d, 3-H).

Reduction (Sn–HCl) of the 4-nitro compound in the usual way, and subjection of the resulting crude amine to the Sandmeyer procedure (CuBr–HBr),[23] gave the 4-bromo compound, m.p. and mixed m.p. 57—58 °C.

5-(2-*Bromo*-5-*methoxybenzylidene*)*rhodanine* (9).—A mixture of rhodanine (66.5 g, 0.5 mol), glacial acetic acid (12 ml), sodium acetate (4 g), and benzene (500 ml) was boiled under reflux for 5 min, then 2-bromo-5-methoxybenzaldehyde [24] (107 g, 0.5 mol) was added in one portion, and the stirred mixture was boiled for 3 h. During the reaction, water was removed *via* a Dean–Stark separator. The benzene was then distilled off and the crude product was washed well with water. It formed yellow *needles* (115 g, 70%) m.p. 213—215 °C (from ethanol) (Found: C, 39.85; H, 2.45; N, 4.1%; M^+, 329. $C_{11}H_8BrNO_2S_2$ requires C, 40.0; H, 2.45; N, 4.25%; M^+, 329); $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 3.95 (s, OMe).

β-(2-*Bromo*-5-*methoxyphenyl*)-α-*mercaptoacrylic Acid* (10).—The arylidenerhodanine (9) (102.6 g) was kept at 100 °C for 0.75 h with a solution of sodium hydroxide (65 g) in water (700 ml). The resulting rose-coloured solution was cooled to 0 °C and acidified by the slow, dropwise addition of ice-cold dilute hydrochloric acid. The precipitated solid formed yellow *needles* (76.6 g, 85%), m.p. 148—149 °C (from toluene) (Found: C, 41.55; H, 3.1%; M^+, 288. $C_{10}H_9BrO_3S$ requires C, 41.55; H, 3.15%; M^+, 288); $\nu_{max.}$ 2 540 (SH) and 1 675 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 3.85 (s, OMe).

4-*Bromo*-7-*methoxybenzo*[b]*thiophene*-2-*carboxylic Acid* (11).—A stirred solution of the mercaptoacrylic acid (10) (5 g, 0.017 mol) and iodine (7.66 g, 0.03 mol) in dry THF (50 ml) was heated under reflux for 48 h in a stream of nitrogen. Most of the solvent was removed under reduced pressure, then the mixture was poured into a solution of sodium hydrogen sulphite (50 g) in water (100 ml). Acidic material was isolated in the usual way [extraction with ether, $NaHCO_3$ (charcoal)], to give white *needles* (2.46 g, 50%), m.p. 308—311 °C (from ethanol) (Found: C, 41.95; H, 2.5%; M^+, 286. $C_{10}H_7BrO_3S$ requires C, 41.8; H, 2.45%; M^+, 286); $\nu_{max.}$ 1 675 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 4.10 (s, OMe), 4.75 (s, OH), 7.10 (d, $J_{5,6}$ 8.0 Hz, 6-H), 7.75 (d, 5-H), and 8.20 (s, 3-H).

When the carboxylic acid (11) was decarboxylated as before (2.5 h at 220 °C), the product (68%) was identical with that obtained by the bromination of 7-methoxybenzo[*b*]thiophene.

Methyl 7-*Methoxybenzo*[b]*thiophene*-2-*carboxylate* (13).—Methyl chloroacetate (1.4 g, 0.013 mol) was added dropwise during 5 min to a stirred aqueous solution of 2-mercapto-3-methoxysodiobenzaldehyde (2.2 g, 0.013 mol) under nitrogen. The mixture was kept for 4 h, then cooled in ice–water. The solid which separated formed *needles* (0.33 g, 11%), m.p. 88—89 °C (from ethanol) (Found: C, 59.65; H, 4.55%; M^+, 222. $C_{11}H_{10}O_3S$ requires C, 59.45; H, 4.55%; *M*, 222); $\nu_{max.}$ 1 730 cm^{-1} (C=O); δ 3.65 and 3.95 (each s, OMe).

7-*Methoxybenzo*[b]*thiophene*-2-*carbonitrile* (14).—The reaction just described was carried out at −10 to 0 °C for 0.5 h with chloroacetonitrile (1 mol equiv.). The resulting brown solid crystallised from acetone–water (1 : 4) to give 2,3-*dihydro*-3-*hydroxy*-7-*methoxybenzo*[b]*thiophene*-2-*carbonitrile* (12) as pale yellow needles (2.07 g, 77%), m.p. 46—46.5 °C (Found: C, 58.2; H, 4.45; N, 6.7%; M^+, 207. $C_{10}H_9NO_2S$ requires C, 57.95; H, 4.35; N, 6.75%; *M*, 207); $\nu_{max.}$ 2 220 (C≡N) and 3 300br cm^{-1} (OH); δ [$(CD_3)_2SO$] 3.80 (s, OMe), 5.10 (d, $J_{2,3}$ 6.5 Hz, 2-H), and 5.60 (t, $J_{3,OH}$ 6.5 Hz, 3-H).

When the experiment was repeated at room temperature, or when an aqueous alcoholic solution of the dihydro compound (12) was kept at room temperature for 0.5 h, 7-*methoxybenzo*[b]*thiophene*-2-*carbonitrile* (14) (80%) was obtained as white needles, m.p. 96—96.5 °C (from ethanol) (Found: C, 63.55; H, 3.7; N, 7.4%; M^+, 189. $C_{10}H_7NOS$ requires C,

63.45; H, 3.7; N, 7.4%; *M*, 189); $\nu_{max.}$ 2 210 cm^{-1} (C≡N); δ [$(CD_3)_2SO$] 3.95 (s, OMe) and 8.35 (s, 3-H).

2-*Acetyl*-7-*methoxybenzo*[b]*thiophene* (15).—Prepared in the usual way (0 °C) for 1 h from chloropropanone and alkaline 2-mercapto-3-methoxybenzaldehyde, this formed cream *needles* (95%), m.p. 65—66 °C (from methanol) (Found: C, 63.95; H, 4.85%; M^+, 206. $C_{11}H_{10}O_2S$ requires C, 64.05; H, 4.9%; *M*, 206); $\nu_{max.}$ (CS_2) 1 680 cm^{-1} (C=O); δ 2.65 (s, Ac), 4.0 (s, OMe), and 7.95 (s, 3-H).

The *oxime* had m.p. 165—166 °C (needles from benzene) (Found: C, 59.75; H, 4.95; N, 6.35%; M^+, 221. $C_{11}H_{11}NO_2S$ requires C, 59.7; H, 5.0; N, 6.35%; *M*, 221); δ [$(CD_3)_2SO$] 12.2 (s, OH). It was recovered unchanged after attempted Beckmann rearrangement with ethereal phosphorus pentachloride.

2-*Hydroxy*-3-*methoxybenzonitrile* (17).—*Method A.* A mixture of orthovanillin (16.2 g, 0.1 mol), hydroxylamine hydrochloride (10.4 g), sodium formate (14 g), and formic acid (150 ml) was heated under reflux for 6 h, then diluted with water. Extraction with ether and evaporation of the washed ($NaHCO_3$) and dried extracts gave pale brown *plates* (12.2 g, 82%), m.p. 47—48 °C (from ethanol–water) (Found: C, 64.35; H, 4.7; N, 9.35%; M^+, 149. $C_8H_7NO_2$ requires C, 64.4; H, 4.75; N, 9.4%; M^+, 149); $\nu_{max.}$ 2 220 cm^{-1} (C≡N); δ 3.80 (s, OMe) and 6.20 (br s, OH).

Method B. Thionyl chloride (11 ml) was added dropwise to a stirred suspension of 2-hydroxy-3-methoxybenzaldehyde oxime (3.4 g) in dry ether (20 ml), so that gentle refluxing was maintained. When the reaction had subsided, the solvents were removed under reduced pressure, leaving the nitrile (17) (1.5 g, 51%), identical with that obtained by Method A.

O-(2-*Cyano*-6-*methoxyphenyl*)-NN-*dimethylthiocarbamate.*—2-Hydroxy-3-methoxybenzonitrile (17) was treated with *NN*-dimethylthiocarbamoyl chloride by the method already described, to give pale yellow *needles* (92%), m.p. 139—140 °C (from methanol) (Found: C, 55.85; H, 5.15; N, 11.85%; M^+, 236. $C_{11}H_{12}N_2O_2S$ requires C, 55.9; H, 5.1; N, 11.85%; *M*, 236); $\nu_{max.}$ 1 540 cm^{-1} (C=S); δ 3.45 and 3.55 (each s, together NMe_2), and 3.90 (s, OMe).

S-(2-*Cyano*-6-*methoxyphenyl*)-NN-*dimethylthiocarbamate.*—The foregoing product (3 g) was rearranged as before in diphenyl ether (0.5 h at 240—250 °C) to give *needles* (2.85 g, 95%), m.p. 111—112 °C [from light petroleum (b.p. 40—60 °C)] (Found: C, 55.95; H, 5.15; N, 11.85%; M^+, 236); $\nu_{max.}$ 1 680 cm^{-1} (C=O); δ 3.10 (s, NMe_2) and 3.95 (s, OMe).

2-*Mercapto*-3-*methoxybenzonitrile* (18).—The *S*-arylthiocarbamate (2 g) was hydrolysed as before to give a pale yellow solid (1.19 g, 90%), m.p. 40—41 °C (Found: M^+, 165. C_8H_7NOS requires *M*, 165); $\nu_{max.}$ 2 565 cm^{-1} (SH); δ 4.10 (s, OMe) and 5.75 (s, SH).

2-*Acetyl*-3-*amino*-7-*methoxybenzo*[b]*thiophene* (16).—Prepared from the thiol (18) and chloropropanone, this formed *needles* (87%), m.p. 190—190.5 °C (from ethanol) (Found: C, 59.55; H, 5.05; N, 6.25%; M^+, 221. $C_{11}H_{11}NO_2S$ requires C, 59.7; H, 5.0; N, 6.35%; *M*, 221) $\nu_{max.}$ 1 615 (C=O) and 3 335 cm^{-1} (NH_2); δ [$(CD_3)_2SO$] 2.10 (s, Ac), 3.75 (s, OMe), and 5.25 (br, NH_2).

7-*Methoxy*-1,2-*benzisothiazole* (19).—Aqueous 5% sodium hypochlorite (15 ml) was added dropwise during 20 min to a stirred mixture of 2-mercapto-3-methoxysodiobenzaldehyde (3; X = Na) (2.2 g, 0.013 mol) and aqueous ammonia (*d* 0.88; 20 ml) under nitrogen at −5 to 0 °C. The mixture was stirred for 1 h at this temperature, then the product was extracted into ether. Work-up gave a yellow *oil* (1.5 g, 70%), b.p. 135—138 °C at 7 mmHg (Found: C, 58.2; H, 4.25; N, 8.4%; M^+, 165. C_8H_7NOS requires C, 58.15; H, 4.25; N, 8.5%; *M*, 165); $\nu_{max.}$ (CCl_4) 2 820 cm^{-1} (OMe); δ 3.95 (s, OMe), 6.75 (dd, $J_{5,6}$ 8.0 and $J_{4,6}$ 2.0 Hz, 6-H), 7.25 (t, $J_{4,5}$ 8.0 Hz, 5-H), 7.55 (dd, 4-H), and 8.75 (s, 3-H).

Repetition of this reaction on 2-mercapto-3-methoxybenzonitrile (18) (reaction time 3 h) gave 3-*amino*-7-*methoxy*-1,2-*benzisothiazole* (20) as white needles (73%), m.p. 157—158 °C (from ethanol) (Found: C, 53.1; H, 4.55; N, 15.4%; M^+, 180. $C_8H_8N_2OS$ requires C, 53.3; H, 4.45; N, 15.55%; *M*, 180); $\nu_{max.}$ 3 430 cm^{-1} (NH_2); δ 5.5 (br, NH_2), 6.90 (dd, $J_{5,6}$ 8.0 and $J_{4,6}$ 2.0 Hz, 6-H), 7.35 (t, $J_{4,5}$ 8.0 Hz, 5-H), and 7.50 (dd, 4-H).

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