Condensed Isothiazoles.† Part 5.[1] Thieno[2,3-*d*]isothiazoles and Thieno[3,2-*d*]isothiazoles

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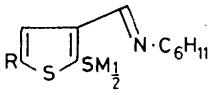
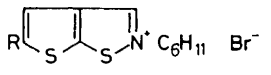
2,3-Disubstituted thiophens containing a sulphur function (SH, SMe, or SCN) and a carbonyl group (CHO or Ac) have been prepared and converted into thieno[2,3-*d* or 3,2-*d*]isothiazoles. Methods used to prepare 1,2-benzisothiazoles are often inapplicable in the thiophen series. For example, an (*E*)-methyl (2-methylthio-3-thienyl) *O*-*p*-nitrobenzoylketoxime (6) in hot diethylene glycol or acetic acid gave the corresponding 3-acetamido-2-methylthiothiophen (15); in concentrated sulphuric acid at −5 °C, it gave the Beckmann rearranged product (15) and a thieno[3,2-*d*]thiazole (19). Similarly, (*E*)-methyl (3-methylthio-2-thienyl) *O*-*p*-nitrobenzoylketoxime (42) gave 2-methylthieno[2,3-*d*]thiazole with concentrated sulphuric acid, but with acetic acid it gave the thieno[2,3-*d*]isothiazole (43) and 2-acetamido-3-methylthiothiophen. Heating the (*E*)-2-mercaptothiophen-3-carbaldoxime (27) in an inert solvent gave the corresponding thieno[3,2-*d*]isothiazole (14); the (*E*)-3-mercaptothiophen-2-carbaldoxime (47) cyclised in hot AcOH–Ac_2O, to give the thieno[2,3-*d*]isothiazole (44). Thieno[3,2-*d*]isothiazoles were also prepared by treating a methyl (2-mercapto-3-thienyl) ketone (21) with chloramine and by heating a 2-iminothieno[3,2-*d*]-3,1,4-oxathiazepine (29) in an inert solvent. The products obtained by selective *S*-alkylation of 3,5-bis(sodiomercapto)isothiazole-4-carbonitrile with ethyl bromoacetate and iodomethane were cyclised, to give 4-aminothieno[3,2-*d* or 2,3-*c*]isothiazole derivatives (34) and (36).

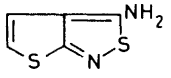
SURPRISINGLY little is known about thienoisothiazoles. Russian workers [2-4] have cyclised the metal complexes (1) with either bromine or *N*-bromosuccinimide, to give the 2-cyclohexylthieno[3,2-*d*]isothiazolium salts (2).



(1) M = Zn or Ni, R = H or Et



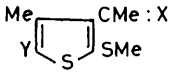
(2) R = H or Et



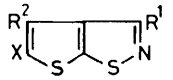
(3)

Isomeric thieno[2,3-*d*]isothiazolium salts were formed similarly from appropriate precursors. A series of 3-aminothieno[2,3-*c*]isothiazoles [*cf.* (3)] has been prepared [5] by treatment of a substituted 2-aminothiophen-3-carbonitrile with hydrogen sulphide, and cyclisation of the resulting thioamide with hydrogen peroxide in pyridine.

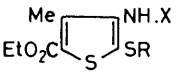
Thieno[3,2-d]*isothiazoles.*—(a) *From 2,3-disubstituted thiophens.* Many of the appropriately 2,3-disubstituted thiophens which we needed as precursors had not been described previously, and often their synthesis presented a considerable challenge. First, we treated pentane-2,4-dione with carbon disulphide in the presence of potassium hydroxide,[6] to give the dianion, $Ac_2C{:}CS_2^{2-}$, which on successive treatment with ethyl bromoacetate, iodomethane (each 1 mol. equiv.), and alkali, afforded ethyl 4-acetyl-3-methyl-5-methylthiothiophen-2-carboxylate (4) in 52% overall yield. Crawford and Woo [7] had previously prepared 3-methyl-1,2-benzisothiazole (60%) by heating *O*-*p*-nitrobenzoyl (*E*)-*o*-methylthioacetophenone oxime in tetrachloroethane. We expected the oxime ester (6) to cyclise by a similar method, to give the thieno[3,2-*d*]isothiazole (11). The major oxime (5) formed from the ketone (4) underwent Beckmann rearrangement (PCl_5–Et_2O), to give ethyl 4-acetamido-3-methyl-5-methylthiothiophen-2-carboxylate (15) (93%). Deacetylation of the last compound with BF_3–MeOH gave the corresponding amino-compound (16) (88%). Whilst it is accepted that the product of a Beckmann



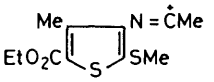
(4) X = O, Y = CO_2Et
(5) X = NOH, Y = CO_2Et
(6) X = N·O·CO·C_6H_4·NO_2-*p*, Y = CO_2Et
(7) X = O, Y = H
(8) X = N·O·CO·C_6H_4·NO_2-*p*, Y = H
(9) X = N·OAc, Y = CO_2Et
(10) X = N·O·CO·C_6H_4·OMe-*p*, Y = CO_2Et

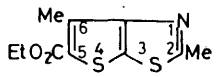


(11) X = CO_2Et, R^1 = R^2 = Me
(12) X = H, R^1 = R^2 = Me
(13) R^1 = R^2 = X = H
(14) R^1 = R^2 = H, X = CO_2Et



(15) X = Ac, R = Me
(16) X = H, R = Me
(17) X = H, R = H





(18) (19)

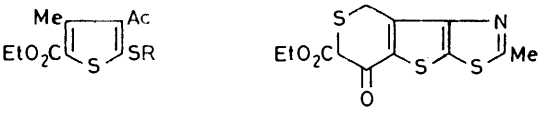
rearrangement does not unambiguously establish the configuration of the starting oxime, in view of the possibility of isomerisation during the course of the reaction,[8] it has been shown that the conditions which we

† Previous Parts were entitled '1,2-Benzisothiazoles'.

used are the least likely to promote such an isomerisation. We were confident, therefore, that the oxime (5) had the sterically favoured (from models) *E*-configuration, and noted further that the OH signal in its ^1H *n.m.r.* spectrum in $(CD_3)_2SO$ was at lower field (δ 11.37) than that of the minor oxime (δ 10.72) present in the mixture obtained by oximation of ketone (4).* This parallels the behaviour of other (*E*)- and (*Z*)-arylketoximes.[9] Heating the oxime ester (6) in tetrachloroethane, dimethyl sulphoxide, or diethylene glycol [10] gave multicomponent tars which contained none of the required product (11). Instead, the Beckmann product (15) predominated, and was most readily isolated from the reaction in diethylene glycol at 150 °C (34%) or in boiling acetic acid (81%). In an attempt to increase the nucleophilicity of the methylthio-group and thereby promote cyclisation to the isothiazole, we removed the ethoxycarbonyl group from the keto-ester (4) (see Experimental section). However, attempted cyclisation of the *O*-*p*-nitrobenzoate (8) gave results similar to those just described for oxime ester (6). Since the ease of Beckmann rearrangement of oxime esters is proportional to the strength of the esterifying acid,[11] we next attempted to cyclise the *O*-acetyl (9) and *O*-*p*-methoxybenzoyl (10) derivatives of oxime (5). By decreasing the rate of Beckmann rearrangement, we should increase the chances of cyclisation. Again, however, no cyclised product could be detected. Finally, we treated the oxime ester (6) with concentrated sulphuric acid. We hoped that protonation of the carbonyl group of the aroyl ester would weaken the N–O bond by aiding the loss of *p*-nitrobenzoic acid, and thus make the nitrogen atom more susceptible to nucleophilic attack by the sulphur atom. Further, by working at −5 °C, we hoped to suppress the Beckmann rearrangement. After 10 min we isolated the Beckmann product (15) (32%) and a cyclised product (40%), spectral data † for which were consistent with those expected for the required thienoisothiazole (11). However, as the reaction mixture had become intensely yellow, we suspected (*cf.* ref. 7) that the nitrilium ion (18) may have been formed by rearrangement; this could cyclise to the thieno[3,2-*d*]thiazole (19) or undergo hydrolysis to the amide (15). Unambiguous synthesis of structure (19) confirmed that cyclisation had indeed been accompanied by rearrangement. It is interesting that the proportions of the Beckmann product (15) and the thienothiazole (19) were not altered markedly by increasing either the temperature of the reaction (to 20 °C) or the time (to 2 h). The amide (15) was not the precursor of the cyclised product (19), since the former was unaffected by concentrated sulphuric acid at room temperature. Under similar conditions, the oxime (5) was recovered unchanged.

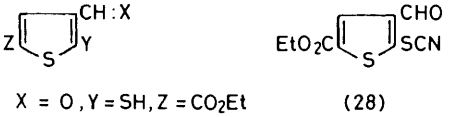
To synthesise the thienothiazole (19), we started from the 2-benzylthiothiophen (20), which was prepared by a method analogous to that used for the methylthio-compound (4). Beckmann rearrangement of the corresponding oxime, followed by debenzylation of the resulting acetamido-compound with $AlCl_3$ in benzene, gave ethyl 4-acetamido-5-mercapto-3-methylthiophen-2-carboxylate, treatment of which with $AcOH–H_2SO_4$ gave the authentic thienothiazole (19).

In connection with other work, we required fused thiazoles containing a 2-side-chain. We hoped, therefore, that the 2,6-dimethyl compound (19) might be selectively brominated by *N*-bromosuccinimide in the 2-position. However, the 6-bromomethyl compound (87%) was formed in this reaction, since the bromine atom could be displaced by $EtO_2C{\cdot}CH_2{\cdot}\bar{S}$, and the product then cyclised by the Dieckmann method, to give the thiopyrano-compound (23) (80% oxo, 20% enol in chloroform solution) (80%).



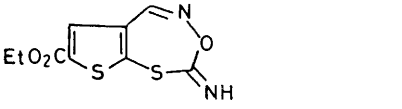
(20) R = CH_2Ph
(21) R = H
(22) R = NH_2

(23)



(24) X = O, Y = SH, Z = CO_2Et
(25) X = NOH, Y = SH, Z = H
(26) X = O, Y = Cl, Z = CO_2Et
(27) X = NOH, Y = SH, Z = CO_2Et

(28)



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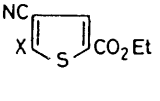


(30) X = Cl
(31) X = SH

Our failure to obtain thieno[3,2-*d*]isothiazoles from the ketone (4) led us to investigate alternative routes from ethyl 4-acetyl-5-mercapto-3-methylthiophen-2-carboxylate (21); this was easily obtained (47%) by an appropriate modification of the method used to prepare the methylthio-compound (4). Unfortunately, when treated with ethereal chloramine or with cyanogen bromide, it readily formed the disulphide, and attempts to convert the disulphide into the sulphenyl chloride, and thence [12] into the isothiazole gave intractable products. An attempt to form the sulphenamide (22) by treating the disulphide with ammoniacal silver nitrate [13] was also unsuccessful. However, we found that the thiol (21) reacted smoothly with aqueous chloramine at 0 °C to give the sulphenamide (22), which cyclised spontaneously to the required thienoisothiazole (11) (81%). Successive

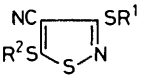
* This method was used to establish the *E*-configuration of all oximes used in this work.

† A spectroscopic study of thienothiazoles and thienoisothiazoles will be reported later.

hydrolysis and decarboxylation then afforded 3,4-dimethylthieno[3,2-*d*]isothiazole (12) (90%).

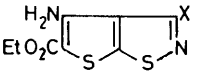
It seemed probable that the preparation of the parent thieno[3,2-*d*]isothiazole (13) might be less difficult, for by using an appropriate aldoxime we would avoid the difficulties associated with the Beckmann rearrangement. We therefore started with 2-chlorothiophen-3-carbaldehyde,[14] from which we hoped to prepare 2-mercaptothiophen-3-carbaldoxime (25). However, although the chlorine atom was replaced by SH, the resulting mercapto-aldehyde readily polymerised (*cf.* similar compounds in the thiophen series [15]). Further, 2-chlorothiophen-3-carbaldoxime resisted all attempts to convert it directly into the corresponding mercapto-oxime (25). We therefore decided to increase the lability of the chlorine atom by introducing an electron-withdrawing 2-ethoxycarbonyl group. 2-Chloro-3-methylthiophen reacted with Bu^nLi–CO_2, to give 5-chloro-4-methylthiophen-2-carboxylic acid (89%), the ethyl ester of which was photobrominated in an attempt to obtain the 4-bromomethyl compound, from which the required aldehyde (26) would be obtained by the Sommelet reaction. The reaction was difficult to stop at the monobromination stage (*cf.* ref. 14), but with bromine (2 mol equiv.) the corresponding dibromomethyl compound was obtained in 94% yield. This was unaffected by sodium carbonate–pyridine,[14] but it was readily hydrolysed by concentrated sulphuric acid to the required aldehyde (26) (90%). Fortunately, the chlorine atom in the corresponding oxime was labile, and treatment of the oxime with sodium hydrogensulphide in acetone–dimethyl sulphoxide gave the mercapto-oxime (27) (79%). The oxime (27) gave intractable products when treated with reagents which are normally used to cyclise *o*-mercapto-oximes (*e.g.* polyphosphoric acid [16] and acetic anhydride [17]), but heating it alone in an inert solvent gave the required thieno[3,2-*d*]isothiazole (14), cleanly and in high yield (*e.g.* 74% from dimethyl sulphoxide at 170 °C). The parent thieno[3,2-*d*]isothiazole (13) was then obtained by successive hydrolysis (90%) and decarboxylation (85%) of the ester (14). In an alternative preparation of the ester (14), the chloro-aldehyde (26) reacted with ethanolic sodium sulphide to give the unstable sodio-derivative of ethyl 4-formyl-5-mercaptothiophen-2-carboxylate (24), which was treated immediately with cyanogen bromide, to give ethyl 4-formyl-5-thiocyanatothiophen-2-carboxylate (28) (52% overall). The thiocyanato-compound (28) could not be obtained by direct treatment of the chloro-aldehyde (26) with SCN^-. The oxime of the aldehyde (28) cyclised spontaneously to the thieno[3,2-*d*]oxathiazepine (29), from which cyanic acid was extruded at 200 °C in diethylene glycol,[1] to give the thieno[3,2-*d*]isothiazole (14) (66%). We had hoped to extend the scope of this synthesis by using a range of appropriate 2-thiocyanato-compounds, prepared from the corresponding readily available [18] 2-aminothiophens. Unfortunately the diazotisation reaction did not proceed cleanly, and the required thiocyanato-compounds were obtained in very low yield. Next we tried to prepare 3-chloro- and 3-oxothieno[3,2-*d*]isothiazoles from the readily available ethyl 5-chloro-4-formylthiophen-2-carboxylate (26). Accordingly, we converted it into the nitrile (30) and thence into the unstable thiol (31). The latter formed a stable disulphide, which we intended to convert into ethyl 3-chlorothieno[3,2-*d*]isothiazole-5-carboxylate by treatment with either chlorine or sulphuryl chloride.[12] However, only the chloro-nitrile (30) could be isolated from this reaction. The cyano-thiol (31) just mentioned was converted into the corresponding carbamoyldisulphide but, this too, failed to undergo cyclisation to a 3-oxothieno[3,2-*d*]isothiazole.[19]

(b) *From 4,5-disubstituted isothiazoles.* We next obtained thienoisothiazoles from precursors containing a pre-formed isothiazole ring. It is known [20] that 3,5-bis(sodiomercapto)isothiazole-4-carbonitrile [21] undergoes stepwise alkylation, giving first the 3-alkylthio-derivative. We therefore treated it successively with iodomethane and ethyl bromoacetate to give the isothiazole (32) (77%), which underwent base-catalysed cyclisation to the thieno-[3,2-*d*]isothiazole (34) (88%). Reversing the order of



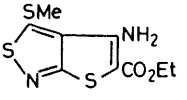
(32) R^1 = Me, R^2 = $CH_2 \cdot CO_2Et$

(33) R^1 = $CH_2 \cdot CO_2Et$, R^2 = Me



(34) X = SMe

(35) X = Cl



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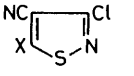
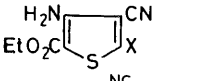
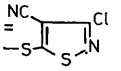


(37) X = Cl

(38) X = $S \cdot CH_2 \cdot CO_2Et$

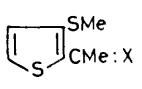


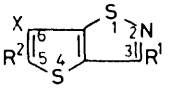
(39) X = 

(40) X = S^-

alkylation gave ester (33) (81%), cyclisation of which gave the thieno[2,3-*c*]isothiazole (36) (94%). We also tried to prepare the 3-chlorothieno[3,2-*d*]isothiazole (35) by taking advantage of the fact that the 5-chloro-atom in 3,5-dichloroisothiazole-4-carbonitrile [22] (37) is more easily substituted than the 3-chloro-atom. Successive treatment of the dichloro-compound (37) with sodium sulphide and ethyl bromoacetate gave the 3-chloro-derivative (38), but attempts to cyclise it, even under mild conditions, gave a complex mixture of products, presumably because of the tendency of 3-chloroisothiazoles to undergo ring-fission.[23] Surprisingly, attempts to prepare the ester (38) directly by treatment of the dichloro-compound (37) with ethyl mercaptoacetate and base gave the sulphide (39) (54%); this was identified spectroscopically (see Experimental section). We believe that the required ester (38) cyclised to the 3-chloroisothiazole (35), which then underwent ring fission in the presence of $\bar{S} \cdot CH_2 \cdot CO_2Et$ (*cf.* ref. 23). The resulting anion (40) would then displace the reactive 5-chloro-substituent from another molecule of the dichloro-compound (37), to give the observed product.

Thieno[2,3-d]*isothiazoles*.—Some thieno[2,3-*d*]isothiazole derivatives were prepared by methods analogous to those already described. 3-Methylthiothiophen [24] was acetylated in the presence of tin(IV) chloride, to give the 2-acetyl derivative (41) (78%). The oxime *O*-*p*-nitrobenzoate (42) gave intractable products under Crawford and Woo's [7] conditions, but refluxing acetic acid con-



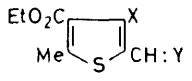


(41) X = O

(42) X = N·O·CO·C_6H_4·NO_2-*p*

(43) R^1 = Me, R^2 = X = H

(44) R^1 = H, R^2 = Me, X = CO_2Et



(45) X = Cl, Y = O

(46) X = SH, Y = O

(47) X = SH, Y = NOH

verted it into a mixture of the required 3-methylthieno-[2,3-*d*]isothiazole (43) (67%) and the Beckmann product, 2-acetamido-3-methylthiothiophen (23%). This result was unexpected in view of our earlier observation that the analogous 2-methylthio-derivative (6) underwent only Beckmann rearrangement under these conditions. Our observations on the oxime esters (6) and (42), especially when compared with those [7] for *o*-methylthioacetophenone oxime *O*-*p*-nitrobenzoate, confirm that the anchimeric effect of a sulphur atom is sensitive to small changes in the proximity and stereochemistry of the neighbouring group.[25] With concentrated sulphuric acid at 0 °C, the oxime ester (42) behaved similarly to its analogue (6) in undergoing rearrangement and cyclisation, to give 2-methylthieno[2,3-*d*]thiazole (37%); it did not, however, give any of the uncyclised Beckmann product. No other organic material was recovered from the reaction, suggesting that sulphonation may have taken place to give water-soluble products. The thieno[2,3-*d*]isothiazole (43) was most easily obtained (68%) by heating 2-acetyl-3-methylthiothiophen oxime with AcOH–Ac_2O.

Lastly, we obtained ethyl 4-chloro-5-formyl-2-methylthiophen-3-carboxylate (45) (54%) by treating ethyl 4-hydroxy-2-methylthiophen-3-carboxylate [26] with a Vilsmeier reagent. The oxime failed to react with sodium hydrogensulphide to give a mercapto-oxime analogous to (25). Fortunately, the chloro-aldehyde (45) itself gave a stable mercapto-aldehyde (46) (82%), from which the mercapto-oxime (47) was obtained in 88% yield. The last gave a complex mixture of products when heated in an inert solvent [contrast mercapto-oxime (25)], but it was cyclised by Ac_2O–AcOH to give the thieno[2,3-*d*]isothiazole (44) (79%).

In conclusion, we stress that, although the reactions described above are all consistently reproducible, optimum yields are obtained only by careful attention to experimental detail.

EXPERIMENTAL

General experimental directions are given in ref. 23.

Ethyl 4-Acetyl-3-methyl-5-methylthiothiophen-2-carboxylate (4).—Pentane-2,4-dione (40 g, 0.4 mol) was added under nitrogen to a cold (0 °C), stirred mixture of aqueous potassium hydroxide (85% w/w; 52.7 g, 0.8 mol) and aqueous 90% dimethylformamide (400 ml), then a solution of carbon disulphide (30.4 g, 0.4 mol) was added dropwise during 0.25 h. The resulting dark red solution was stirred at 0 °C for 1.5 h, then a solution of ethyl bromoacetate (60 g, 0.36 mol) in dimethylformamide (40 ml) was added dropwise during 1 h. The mixture was stirred at 0 °C for 0.5 h, treated with iodomethane (71 g, 0.5 mol), stirred for 1 h more at 0 °C, then treated with one portion of aqueous 25% potassium hydroxide (40 ml). The cold (0 °C) mixture was stirred for 10 min, then poured into ice–water. The precipitate was filtered off and crystallised from methanol, to give *prisms* 48.5 g, 52%), m.p. 75—76 °C (Found: C, 51.3; H, 5.4%; M^+, 258. $C_{11}H_{14}O_3S_2$ requires C, 51.15; H, 5.45%; *M*, 258); $\nu_{max.}$ 1 708 (ester C=O) and 1 638 (ketone C=O) cm^{-1}; δ (CCl_4) 1.36 (t, CH_2*Me*), 2.45, 2.50, 2.61 (s, Me), and 4.24 (q, C*H*$_2$Me).

The (E)-*oxime* (5), prepared in the usual way in ethanol (10 h reflux) formed prisms (86%), m.p. 115—116 °C (from methanol) (Found: C, 48.35; H, 5.6; N, 5.05%; M^+, 273. $C_{11}H_{15}NO_3S_2$ requires C, 48.35; H, 5.55; N, 5.1%; *M*, 273); $\nu_{max.}$ 1 677 cm^{-1} (C=O); δ[$(CD_3)_2SO$] 1.33 (t, CH_2*Me*), 2.10, 2.39, 2.49 (s, Me), 4.28 (q, C*H*$_2$Me), and 11.37 (s, OH).

Ethyl 4-Amino-3-methyl-5-methylthiothiophen-2-carboxylate (16).—Powdered phosphorus pentachloride (3 g) was added portionwise to a stirred solution of oxime (5) (3 g) in dry ether (50 ml) at 0 °C. The mixture was stirred at room temperature for 0.5 h, then treated with an excess of aqueous sodium hydrogencarbonate. Ether extraction gave ethyl 4-acetamido-3-methyl-5-methylthiothiophen-2-carboxylate (15) as *microneedles* (2.8 g, 93%), m.p. 155—156 °C (from ethanol) (Found: C, 48.25; H, 5.55; N, 5.1%; M^+, 273); $\nu_{max.}$ 1 702 (ester C=O) and 1 658 (amide C=O) cm^{-1}; δ 1.38 (t, CH_2*Me*), 2.15, 2.28, 2.46 (s, Me), 4.31 (q, C*H*$_2$Me), and 7.86br (NH).

A solution of the amide (15) (2 g) in methanolic boron trifluoride (10% w/v; 30 ml) was heated under reflux for 24 h, then cooled and poured into water (100 ml). The resulting solution was basified with aqueous 10% sodium hydroxide, then extracted with ether, to give the amine (16) as yellow *rosettes* (1.5 g, 88%), m.p. 77—78 °C (from light petroleum) (Found: C, 46.7; H, 5.75; N, 6.2%; M^+, 231. $C_9H_{13}NO_2S_2$ requires C, 46.75; H, 5.65; N, 6.05%; *M*, 231), $\nu_{max.}$ 1 670 cm^{-1} (C=O); δ 2.30, 2.37 (s, Me), and 3.99br (NH_2).

(E)-*Methyl* (5-*Ethoxycarbonyl*-4-*methyl*-2-*methylthio*-3-*thienyl*) O-p-*Nitrobenzoylketoxime* (6).—A solution of the oxime (5) (16.4 g, 0.06 mol) in dry ether (150 ml) and dimethylformamide (30 ml) was added dropwise during 0.5 h to a suspension of sodium hydride (1.44 g, 0.06 mol) in dry ether (50 ml), then the mixture was stirred under dry nitrogen for 2 h. A solution of *p*-nitrobenzoyl chloride (11.2 g, 0.06 mol) in ether (100 ml) was then added dropwise during 0.25 h, and stirring was continued for 2 h. The product was filtered off, washed successively with ether and water, dried, and crystallised from ethanol, to give pale

yellow *needles* (21.8 g, 86%), m.p. 122—123 °C (Found: C, 51.35; H, 4.35; N, 6.65%; M^+, 422. $C_{18}H_{18}N_2O_6S_2$ requires C, 51.2; H, 4.3; N, 6.65%; *M*, 422); $\nu_{max.}$ 1 753 and 1 690 cm^{-1} (C=O); δ 2.42, 2.49, and 2.56 (s, Me).

Prepared similarly were: (a) the O-p-*methoxybenzoylketoxime* (10) (84%), which formed needles, m.p. 116—117 °C (from ethanol) (Found: C, 55.8; H, 5.0; N, 3.4%; M^+, 407. $C_{19}H_{21}NO_5S_2$ requires C, 56.0; H, 5.2; N, 3.45%; *M*, 407); $\nu_{max.}$ 1 750 and 1 708 cm^{-1} (C=O); δ 2.36, 2.48, 2.52, and 3.83 (s, Me); (b) the O-*acetylketoxime* (9) (76%), which crystallised from methanol as cubes, m.p. 51—52 °C (Found: C, 49.6; H, 5.4; N, 4.35%; M^+, 315. $C_{13}H_{17}NO_4S_2$ requires C, 49.5; H, 5.45; N, 4.45%; *M*, 315); $\nu_{max.}$ 1 772 and 1 707 cm^{-1} (C=O); δ 2.24, 2.27, 2.46, and 2.54 (s, Me).

Attempts to cyclise the oxime esters (6), (9), and (10) by heating them in a solvent gave the results described in the text.

Methyl (4-*Methyl*-2-*methylthio*-3-*thienyl*) *Ketone* (7).—(*a*) Hydrolysis of the ester (4) with aqueous ethanolic sodium hydroxide gave 4-*acetyl*-3-*methyl*-5-*methylthiothiophen*-2-*carboxylic acid* (95%), m.p. 220—221 °C (from ethanol–dimethylformamide) (Found: C, 46.65; H, 4.4%; M^+, 230. $C_9H_{10}O_3S_2$ requires C, 46.95; H, 4.35%; *M*, 230); $\nu_{max.}$ 1 704 (acid C=O) and 1 612 (ketone C=O) cm^{-1}; δ [$(CD_3)_2SO$] 2.52, 2.57, and 2.69 (s, Me).

(*b*) Decarboxylation of the foregoing acid with copper in quinoline (*cf.* method below) at 190—200 °C gave the *ketone* (7) as microneedles (91%), m.p. 51—52 °C (Found: C, 51.4; H, 5.5%; M^+, 186. $C_8H_{10}OS_2$ requires C, 51.6; H, 5.4%; *M*, 186); $\nu_{max.}$ 1 650 cm^{-1} (C=O); δ 2.52, 2.54 (s, Me), 2.37 (d, 4-Me), and 6.78 (q, 5-H, *J* 1.0 Hz).

(E)-*Methyl* (4-*Methyl*-2-*methylthio*-3-*thienyl*) O-p-*Nitrobenzoylketoxime* (8).—In boiling ethanol (2 h), ketone (7) gave the *oxime* (91%) as cubes, m.p. 68—69 °C (from light petroleum) (Found: C, 47.5; H, 5.3; N, 6.9%; M^+, 201. $C_8H_{11}NOS_2$ requires C, 47.75; H, 5.5; N, 6.95%; *M*, 201); δ[$(CD_3)_2SO$] 11.52 (OH). It underwent Beckmann rearrangement as before, to give 3-*acetamido*-4-*methyl*-2-*methylthiothiophen* (83%) as microcrystals, m.p. 99—100 °C (from ethanol) (Found: C, 47.45; H, 5.5; N, 6.85%; M^+, 201); $\nu_{max.}$ 1 658 cm^{-1} (C=O); δ 2.16, 2.33 (s, Me), 2.08 (d, 4-Me), 6.92 (q, 5-H, *J*, 0.75 Hz), and 7.34br (NH).

The oxime was treated as before with *p*-nitrobenzoyl chloride and the product was isolated with ether, to give the oxime ester (8) as yellow *needles* (79%), m.p. 91—92 °C (from ethanol) (Found: C, 51.7; H, 3.9; N, 8.05%; M^+, 350. $C_{15}H_{14}N_2O_4S_2$ requires C, 51.4; H, 4.0; N, 8.0%; *M*, 350); $\nu_{max.}$ 1 748 cm^{-1} (C=O).

Ethyl 4-*Acetyl*-5-*benzylthio*-3-*methylthiophen*-2-*carboxylate* (20).—This was prepared from pentane-2,4-dione by a method similar to that used for the methylthio-compound (4), except that benzyl chloride (1 mol equiv.) was used instead of iodomethane. The resulting mixture was stirred at room temperature for 2 h, then basified as before, and poured into water. Extraction with ether gave *needles* (49%), m.p. 60—61 °C (from methanol) (Found: C, 61.0; H, 5.4%; M^+, 334. $C_{17}H_{18}O_3S_2$ requires C, 61.05; H, 5.4%; *M*, 334); $\nu_{max.}$ 1 708 (ester C=O) and 1 647 (ketone C=O) cm^{-1}; δ 2.45, 2.66 (s, Me), and 4.17 (s, CH_2).

The (*E*)-oxime was obtained as a pale yellow oil (93%) (Found: M^+, 349. $C_{17}H_{19}NO_3S_2$ requires *M*, 349); $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 1.99, 2.38 (s, Me), 4.02 (s, CH_2), and 11.41 (s, OH).

Ethyl 4-*Acetamido*-5-*mercapto*-3-*methylthiophen*-2-*carboxylate*.—The foregoing oxime was treated as before with phosphorus pentachloride in ether, first at −10 °C, then for 1 h at room temperature, to give *ethyl* 4-*acetamido*-5-*benzylthio*-3-*methylthiophen*-2-*carboxylate* as needles (83%), m.p. 114—115 °C (from methanol) (Found: C, 58.3; H, 5.4; N, 4.0%; M^+, 349. $C_{17}H_{19}NO_3S_2$ requires C, 58.4; H, 5.5; N, 4.0%; *M*, 349); $\nu_{max.}$ 1 690 (ester C=O) and 1 660 (amide C=O) cm^{-1}; δ 1.96, 2.25 (s, Me), 3.90 (s, CH_2), and 6.72br (NH).

Finely powdered aluminium chloride (8 g, 0.06 mol) was added portionwise during 0.5 h to a stirred solution of the foregoing benzylthio-compound (14 g, 0.04 mol) in benzene (300 ml) under nitrogen, then the mixture was stirred for 2 h. Ice–water (200 ml) and ether (300 ml) were added successively, and the thiol was extracted from the organic layer with aqueous 5% sodium hydroxide (3 × 100 ml). Acidification of the alkaline extracts gave a precipitate, which crystallised from ethanol, to give the *thiol* as pale yellow needles (8.0 g, 77%), m.p. 127—128 °C (Found: C, 46.55; H, 4.9; N, 5.45%; M^+, 259. $C_{10}H_{13}NO_3S_2$ requires C, 46.3; H, 5.05; N, 5.4%; *M*, 259); $\nu_{max.}$ 2 510 (SH), 1 690 (ester C=O), and 1 655 (amide C=O) cm^{-1}; δ 2.16, 2.27 (s, Me), 3.73br (SH), and 7.73br (NH).

Ethyl 2,6-*Dimethylthieno*[3,2-d]*thiazole*-5-*carboxylate* (19).—(*a*) A stirred solution of ethyl 4-acetamido-5-mercapto-3-methylthiophen-2-carboxylate (2.6 g, 0.01 mol) in glacial acetic acid (25 ml) was treated dropwise with concentrated sulphuric acid (1 ml), then the mixture was heated under reflux for 10 min, cooled, poured onto ice, and basified. Ether extraction gave pale yellow material, which crystallised from ether–light petroleum (b.p. 40—60 °C) as translucent *prisms* (2.1 g, 87%), m.p. 129—130 °C (Found: C, 49.9; H, 4.5; N, 5.8%; M^+, 241. $C_{10}H_{11}NO_2S_2$ requires C, 49.75; H, 4.6; N, 5.8%; *M*, 241); $\nu_{max.}$ 1 704 cm^{-1} (C=O); δ 2.78 and 2.82 (s, Me).

(*b*) The *O*-*p*-nitrobenzoylketoxime (6) (20 g) was added in portions during 10 min to vigorously stirred concentrated sulphuric acid (100 ml) at −5 °C. The resulting yellow solution was stirred at −5 °C for 10 min, then poured onto ice, and basified. Extraction with ethyl acetate * gave a two-component (t.l.c.) mixture, which was triturated with light petroleum. The resulting solid crystallised from ethanol, to give the Beckmann-rearranged product (15) (4.1 g, 32%), m.p. 154—156 °C, identical with that obtained before. The same product was obtained (81%) by heating the oxime ester (6) under reflux with acetic acid for 1 h.

The light petroleum solution was evaporated, to give the thienothiazole (19) (4.6 g, 40%), m.p. 129—130 °C, identical with that obtained in (*a*).

Ethyl 5,6-*Dihydro*-2-*methyl*-5-*oxo*-8H-*thiopyrano*[3′,4′:4,5]*thieno*[3,2-d]*thiazole*-6-*carboxylate* (23).—(*a*) Bromination of the thieno[3,2-*d*]thiazole (9) with *N*-bromosuccinimide in the usual way [28] gave ethyl 6-bromomethyl-2-methylthieno[3,2-*d*]thiazole-5-carboxylate as *microcrystals* (87%), m.p. 140—141 °C (from ethyl acetate) (Found: C, 37.6; H, 3.1; N, 4.2%; M^+, 319/321. $C_{10}H_{10}BrNO_2S_2$ requires C, 37.5; H, 3.15; N, 4.4%; M^+, 319/321); $\nu_{max.}$ 1 702 cm^{-1} (C=O); δ 2.84 (s, Me) and 5.06 (s, CH_2Br).

(*b*) An ice-cooled, stirred mixture of the bromomethyl compound (1.6 g, 0.005 mol), ethyl mercaptoacetate (0.6 g, 0.005 mol), and ethanol (30 ml) was treated dropwise with piperidine (0.43 g, 0.005 mol), then the mixture was stirred at room temperature for 2 h, and poured into water. Ether

*Acidification of the residual basic solution gave *p*-nitrobenzoic acid (7.4 g, 94%). Repetition of the reaction at 20 °C gave the amide (15) (23%) and the cyclised product (19) (37%).

extraction gave an oil which slowly solidified, to give ethyl {(5-ethoxycarbonyl-2-methyl-6-thieno[3,2-*d*]thiazolylmethyl)thio}acetate as *needles* (1.65 g, 92%), m.p. 63—64 °C (from ether–light petroleum) (Found: C, 47.05; H, 4.85; N, 3.9%; M^+, 359. $C_{14}H_{17}NO_4S_3$ requires C, 46.8; H, 4.75; N, 3.9%; *M*, 359); $\nu_{max.}$ 1 730 (aliph. ester) and 1 704 (arom. ester) cm^{-1}; δ 3.46 (s, S·CH_2·CO) and 4.58 (s, S·CH_2Ar).

(*c*) A solution of the diester (1.44 g, 0.004 mol) in dry benzene (20 ml) was added to a cold (0 °C) suspension of sodium ethoxide [from sodium (0.19 g, 0.0082 g atom)] in benzene (30 ml), then the mixture was stirred at room temperature for 0.5 h, and acidified. The product (23), isolated with benzene, formed yellow *needles* (1.0 g, 80%), m.p. 136—138 °C (from methanol–light petroleum) (Found: C, 46.25; H, 3.5; N, 4.6%; M^+, 313. $C_{12}H_{11}NO_3S_3$ requires C, 46.0; H, 3.55; N, 4.45%; *M*, 313); $\nu_{max.}$ 1 726 and 1 640 cm^{-1} (C=O); δ (oxo) 3.96 and 4.41 (dd, 8-CH_2, *J* 17.0 Hz) and 4.19 (s, 6-H); δ (enol) 3.44 (s, 8-CH_2) and 12.41br (OH) (20% enol).

Ethyl 4-Acetyl-5-mercapto-3-methylthiophen-2-carboxylate (21).—This was prepared by the method used for the 5-methylthio-compound (4), with the omission of iodomethane. The reaction mixture was poured into ice–water and acidified with dilute hydrochloric acid. The resulting precipitate was filtered off, washed, and dissolved in aqueous 10% sodium hydrogencarbonate. The solution was filtered and acidified to give the thiol, which crystallised from light petroleum as yellow *needles* (47%), m.p. 61—62 °C (Found: C, 49.45; H, 5.1%; M^+, 244. $C_{10}H_{12}O_3S_2$ requires C, 49.15; H, 4.95%; *M*, 244); $\nu_{max.}$ 2 495 (SH), 1 690 (ester C=O), and 1 656 (ketone C=O) cm^{-1}; δ 2.53, 2.65 (s, Me), and 5.02br (SH). Attempts to form an oxime were unsuccessful.

Reactions of the Thiol (21).—(*a*) *With cyanogen bromide.* The dry sodio-derivative (0.01 mol) (prepared from ethanolic sodium ethoxide) was added portionwise during 10 min to a stirred solution of cyanogen bromide (0.01 mol) in acetone at 0 °C. The mixture was kept at 0 °C for 10 min, then poured into water, to give *bis-(3-acetyl-5-ethoxycarbonyl-4-methyl-2-thienyl) disulphide* (95%) as pale pink fibrous needles, m.p. 177—178 °C (from ethanol–dimethylformamide) (Found: C, 49.25; H, 4.5%; M^+, 486. $C_{20}H_{22}O_6S_4$ requires C, 49.35; H, 4.55%; *M*, 486); no SH or SCN absorption in the i.r. spectrum.

(*b*) *With chloramine.* A solution of the thiol (4.9 g, 0.02 mol) in aqueous 5% sodium hydroxide (25 ml) was added dropwise during 0.25 h to stirred, ice-cooled, aqueous chloramine (5% w/v; 50 ml). Stirring was continued for 10 min at 0 °C, then the product was filtered off, washed, and crystallised from ethanol, to give ethyl 3,4-dimethylthieno[3,2-*d*]isothiazole-5-carboxylate (11) (3.9 g, 81%) as pale yellow *platelets*, m.p. 97—98 °C (Found: C, 49.65; H, 4.6; N, 5.85%; M^+, 241. $C_{10}H_{11}NO_2S_2$ requires C, 49.75; H, 4.6; N, 5.8%; *M*, 241); $\nu_{max.}$ 1 708 cm^{-1} (C=O); δ 2.72 and 2.81 (s, Me).

3,4-Dimethylthieno[3,2-d]*isothiazole* (12).—Heating the ester (21) with aqueous 10% sodium hydroxide for 0.5 h gave the *carboxylic acid* (92%), which crystallised from ethanol–dimethylformamide as pale orange microcrystals, m.p. 230 °C (decomp.) (Found: C, 44.85; H, 3.35; N, 6.65%; M^+, 213. $C_8H_7NO_2S_2$ requires C, 45.05; H, 3.3; N, 6.55%; *M*, 213); $\nu_{max.}$ 1 673 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 2.67 and 2.76 (s, Me).

A mixture of the foregoing carboxylic acid (2.13 g, 0.01 mol), dry, redistilled quinoline (20 ml), and powdered copper bronze (0.5 g) was stirred at 190—200 °C for 0.5 h under nitrogen. It was then cooled and filtered (Hyflo), and the filtrate was poured into ice-cold hydrochloric acid (30% v/v; 50 ml). Extraction with ether gave *prisms* (1.5 g, 88%), m.p. 113—114 °C [from light petroleum (charcoal)] (Found: C, 49.6; H, 4.2; N, 8.3%; M^+, 169. $C_7H_7NS_2$ requires C, 49.65; H, 4.15; N, 8.3%; *M*, 169); δ 2.39 (d, 4-Me), 2.63 (s, 3-Me), and 6.89 (q, 5-H, *J* 1.0 Hz).

5-Chloro-4-methylthiophen-2-carboxylic Acid.—A solution of 2-chloro-3-methylthiophen [27] (99.4 g, 0.75 mol) in dry ether (100 ml) was added dropwise during 1 h to a stirred solution of n-butyl-lithium (0.75 mol) in dry ether (750 ml) at room temperature under nitrogen. The mixture was heated under reflux for 2 h, then cooled to −70 °C, and poured into a slurry of solid carbon dioxide and ether (1.5 l). The carbon dioxide was allowed to evaporate, then water (1.5 l) was added and the mixture was stirred vigorously for 10 min. The aqueous phase was separated, washed with ether, and acidified, to give the *acid* as needles (118 g, 89%), m.p. 199—201 °C (from ethanol–water) (Found: C, 40.7; H, 2.95%; M^+, 176/178. $C_6H_5ClO_2S$ requires C, 40.8; H, 2.85%; M^+, 176/178); $\nu_{max.}$ 1 675 cm^{-1} (C=O); δ 2.17 (s, Me), 7.54 (s, 3-H), and 12.80br (OH).

The *ethyl ester* (94%), obtained in the usual way from the crude acid chloride (from acid + $SOCl_2$), had b.p. 86—88 °C at 0.2 mmHg (Found: C, 46.8; H, 4.4%; M^+, 204/206. $C_8H_9ClO_2S$ requires C, 46.95; H, 4.45%; M^+, 204/206); $\nu_{max.}$ 1 712 cm^{-1} (C=O).

Ethyl 5-Chloro-4-(dibromomethyl)thiophen-2-carboxylate.—A solution of bromine (160 g, 1 mol) in dry tetrachloromethane (250 ml) was added dropwise during 5 h to a stirred, irradiated (500 W), boiling solution of the foregoing ester (100 g, 0.49 mol) in tetrachloromethane (1 l). Solvent (600 ml) was removed, and the remaining solution was washed ($NaHCO_3$, H_2O), dried, and evaporated, to give the product as an *oil* (166 g, 94%), b.p. 146—148 °C at 0.3 mmHg [Found: C, 26.7; H, 2.1%; M^+, 360 (for ^{35}Cl and ^{79}Br). $C_8H_7Br_2ClO_2S$ requires C, 26.5; H, 1.95%; M^+, 360]; $\nu_{max.}$ 1 715 cm^{-1} (C=O); δ 6.64 (s, $CHBr_2$) and 8.01 (s, 3-H).

Ethyl 5-Chloro-4-formylthiophen-2-carboxylate (26).—The foregoing dibromomethyl compound (140 g) was added dropwise during 1 h to stirred concentrated sulphuric acid (500 ml). Dry nitrogen was passed through the resulting solution to remove bromine then, after 3 h, the mixture was poured onto crushed ice (2 kg). Ether extraction gave the aldehyde (26) as an *oil* (76 g, 90%), b.p. 122—126 °C at 3.0 mmHg (Found: C, 44.15; H, 3.1%; M^+, 218/220. $C_8H_7ClO_3S$ requires C, 43.95; H, 3.2%; M^+, 218/220); $\nu_{max.}$ 1 715 and 1 690 cm^{-1} (C=O); δ 7.86 (s, 3-H) and 9.94 (s, CHO).

The (E)-*oxime*, prepared in ethanol (2 h at 0 °C), formed cubes (92%), m.p. 159—160 °C (Found: C, 41.2; H, 3.4; N, 6.0%; M^+, 233/235. $C_8H_8ClNO_3S$ requires C, 41.1; H, 3.45; N, 6.0%; M^+, 233/235; $\nu_{max.}$ 1 695 cm^{-1} (C=O), δ[$(CD_3)_2SO$] 7.83 (s, 3-H), 8.13 (s, CH), and 11.86 (s, OH).

(E)-*5-Ethoxycarbonyl-2-mercaptothiophen-3-carbaldoxime* (27).—A mixture of the foregoing oxime (23.3 g, 0.1 mol), anhydrous sodium hydrogensulphide (16.8 g, 0.3 mol), dry dimethyl sulphoxide (50 ml), and dry acetone (200 ml) was heated under reflux for 2 h, then poured into ice–water, and acidified with dilute hydrochloric acid. The resulting precipitate gave dark yellow *cubes* (18.2 g, 79%), m.p. 108—109 °C (from ethyl acetate) (Found: C, 41.7; H, 3.95;

N, 6.1%; M^+, 231. $C_8H_9NO_3S_2$ requires C, 41.55; H, 3.9; N, 6.05%; M, 231); $\nu_{max.}$ 2 515 (SH) and 1 685 (C=O) cm^{-1}; δ [$(CD_3)_2SO$] 11.56 (OH).

Ethyl 4-Formyl-5-thiocyanatothiophen-2-carboxylate (28).—A solution of the chloro-aldehyde (26) (15.3 g, 0.07 mol) in ethanol (30 ml) was added dropwise during 0.5 h to a stirred solution of hydrated sodium sulphide (16.8 g, 0.07 mol) in ethanol (200 ml), then the mixture was stirred for 1 h, filtered, and evaporated. The residue was triturated with ether, and dried, to give the sodiomercapto-derivative as a yellow powder. The oxime of aldehyde (26) was unaffected under these conditions.

The salt was added portionwise during 0.25 h to a stirred solution of cyanogen bromide (7.4 g, 0.07 mol) in acetone (100 ml) at 0—5 °C, then the mixture was stirred at room temperature for 2 h and poured into water. Extraction with ether gave pale yellow *needles* (8.8 g, 52%), m.p. 104—105 °C [from ethanol (charcoal)] (Found: C, 44.8; H, 2.85; N, 6.0%; M^+, 241. $C_9H_7NO_3S_2$ requires C, 44.8; H, 2.9; N, 5.8%; M, 241); $\nu_{max.}$ 2 165 (SCN), 1 708 (ester C=O), and 1 667 (aldehyde C=O) cm^{-1}; δ 8.12 (s, 3-H) and 9.96 (s, CHO).

Ethyl 2-Iminothieno[3,2-*d*]-3,1,4-*oxathiazepine-7-carboxylate* (29).—A mixture of the aldehyde (28) (4.8 g), hydroxylamine hydrochloride (21 g), sodium acetate (2.5 g), and ethanol (100 ml) was stirred at 0 °C for 1 h, then poured into water. The product, isolated with ether, formed dark yellow *plates* (3.4 g, 68%), m.p. 172—173 °C (decomp.) [from ethanol (charcoal)] (Found: C, 42.4; H, 3.2; N, 10.85%; M^+, 256. $C_9H_8N_2O_3S_2$ requires C, 42.2; H, 3.15; N, 10.95%; M, 256); $\nu_{max.}$ 3 200br (NH) and 1 704 (C=O) cm^{-1} (no SCN absorption); δ 7.95, 8.37 (s, 5-H and 6-H), and 12.28 (s, NH).

Ethyl Thieno[3,2-d]*isothiazole-5-carboxylate* (14).—(*a*) *From the oxime* (27). The oxime (10 g) was added in portions during 5 min to stirred, hot (170 °C) dimethyl sulphoxide, then the mixture was poured onto crushed ice (500 g). Extraction with ether gave pale yellow *platelets* (6.8 g, 74%), m.p. 97—98 °C [from methanol (charcoal)] (Found: C, 45.1; H, 3.25; N, 6.65%; M^+, 213. $C_8H_7NO_2S_2$ requires C, 45.05; H, 3.3; N, 6.55%; M, 213); $\nu_{max.}$ 1 718 cm^{-1} (C=O); δ 7.99 (s, 4-H) and 8.68 (s, 3-H).

(*b*) *From the oxathiazepine* (29). A solution of the oxathiazepine (2 g) in diethylene glycol (30 ml) was kept at 200 °C for 0.5 h, then poured into ice–water (150 ml). Extraction with ether gave a brown solid, a benzene solution of which was passed through silica gel. Elution with ether–light petroleum (1 : 5) gave a product (66%), identical with that just described.

Thieno[3,2-d]*isothiazole* (13).—(*a*) Hydrolysis of the ester (14) (5 g) with sulphuric acid (40% v/v; 30 ml) at 100 °C for 1 h gave the *carboxylic acid* (3.9 g, 90%), which crystallised from ethanol–dimethylformamide as microcrystals, m.p. 234—236 °C (decomp.) (Found: C, 39.05; H, 1.55; N, 7.6%; M^+, 185. $C_6H_3NO_2S_2$ requires C, 38.9; H, 1.65; N, 7.55%; M, 185); $\nu_{max.}$ 1 700 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 8.10 (s, 4-H) and 8.90 (s, 3-H). Alkaline hydrolysis gave a much lower yield of product.

(*b*) Decarboxylation of the carboxylic acid with copper bronze gave the product (13), which was purified by short-path distillation at 85 °C (bath) and 0.8 mmHg to give an *oil* (85%) (Found: C, 42.7; H, 2.1; N, 9.85%; M^+, 141. $C_5H_3NS_2$ requires C, 42.5; H, 2.15; N, 9.9%; M, 141); δ 7.27 (d, 4-H), 7.41 (d, 5-H, J 5.0 Hz), and 8.59 (s, 3-H). The *picrate* had m.p. 113—114 °C (from ethanol) (Found: C, 35.5; H, 1.6; N, 15.05. $C_{11}H_6N_4O_7S_2$ requires C, 35.7; H, 1.6; N, 15.15%).

Ethyl 5-Chloro-4-cyanothiophen-2-carboxylate (30).—A solution of 2-chloro-5-ethoxycarbonylthiophen-3-carbaldoxime (35 g) in acetic anhydride (300 ml) was heated under reflux for 4 h, then cooled and poured into water (1.5 l). The mixture was stirred for 0.5 h, then kept at 0 °C until the resulting oil had crystallised. It formed *needles* (30 g, 93%), m.p. 70—71 °C (from methanol) (Found: C, 44.7; H, 2.8; N, 6.4%; M^+, 215/217. $C_8H_6ClNO_2S$ requires C, 44.55; H, 2.8; N, 6.5%; M^+, 215/217); $\nu_{max.}$ 2 230 (C≡N) and 1 718 (C=O) cm^{-1}; δ 7.77 (s, 3-H).

Ethyl 4-Carbamoyl-5-chlorothiophen-2-carboxylate.—A mixture of the nitrile (30) (6.5 g), hydrogen peroxide (30% w/v; 12 ml), aqueous 30% sodium hydroxide (2 ml), and ethanol (50 ml) was heated under reflux for 2 h, then cooled, and poured into water. The product was collected and crystallised from ethanol–dimethylformamide, to give *flakes* (5.9 g, 84%), m.p. 213—214 °C (Found: C, 41.3; H, 3.6; N, 5.95%; M^+, 233/235. $C_8H_8ClNO_3S$ requires C, 41.1; H, 3.45; N, 6.0%; M^+, 233/235); $\nu_{max.}$ 1 710 (ester C=O) and 1 663 (amide C=O) cm^{-1}.

Bis-(3-cyano-5-ethoxycarbonyl-2-thienyl) Disulphide.—The chloro-nitrile (30) was treated with sodium hydrogensulphide at room temperature for 2 h [*cf.* preparation of the thiol (27)]. The crude thiol (31) was purified by dissolution in aqueous 3% sodium hydroxide and reprecipitation with acid. The resulting pale yellow material decomposed rapidly, and was used without further purification. It had m.p. 105—107 °C (decomp.) (Found: M^+, 213. $C_8H_7NO_2S_2$ requires M, 213); $\nu_{max.}$ 2 525 (SH), 2 220 (C≡N), and 1 712 (C=O)cm^{-1}.

When the thiol (31) was treated with iodine (1 mol equiv.) in ethanol, the disulphide separated from the cooled (0 °C) solution as pale yellow *microcrystals* (77%), m.p. 73—74 °C (from methanol) (Found: C, 45.2; H, 2.9; N, 6.45%; M^+, 424. $C_{16}H_{12}N_2O_4S_4$ requires C, 45.25; H, 2.85; N, 6.6%; M, 424); $\nu_{max.}$ 2 230 (C≡N) and 1 720 (C=O) cm^{-1}.

Bis-(3-carbamoyl-5-ethoxycarbonyl-2-thienyl) Disulphide.—Prepared like the thiol (31), the unstable ethyl 4-carbamoyl-5-mercaptothiophen-2-carboxylate (93%) had m.p. 217—218 °C (decomp.) (Found: M^+, 231. $C_8H_9NO_3S_2$ requires M, 231); $\nu_{max.}$ 2 500—2 250 cm^{-1} (SH).

A solution of iodine (2 g) in aqueous 20% potassium iodide (15 ml) was added dropwise during 10 min to a stirred solution of the crude thiol (3.7 g) in aqueous 2% sodium hydroxide (40 ml). The disulphide was filtered off and recrystallised from ethanol–dimethylformamide to give *microcrystals* (3.3 g, 89%), m.p. 238 °C (decomp.) (Found: C, 41.45; H, 3.5; N, 6.25%; M^+, 460. $C_{16}H_{16}N_2O_6S_4$ requires C, 41.7; H, 3.5; N, 6.1%; M, 460).

Attempts to cyclise the disulphides just described gave the results indicated in the text.

Ethyl [(*4-Cyano-3-methylthio-5-isothiazolyl*)*thio*]*acetate* (32).—Iodomethane (25.5 g, 0.18 mol) was added dropwise during 0.5 h to a stirred solution of 3,5-bis(sodiomercapto)-isothiazole-4-carbonitrile [21] (40 g, 0.183 mol) in methanol (500 ml), then the mixture was stirred for 1 h, and ethyl bromoacetate (32 g, 0.19 mol) was added. After 12 h, the mixture was poured into ice–water (2 l), to give the product, which formed *needles* (38.5 g, 77%), m.p. 66—67 °C [from methanol (× 2)] (Found: C, 39.4; H, 3.6; N, 10.1%; M^+, 274. $C_9H_{10}N_2O_2S_3$ requires C, 39.4; H, 3.65; N, 10.2%; M, 274); $\nu_{max.}$ 2 220 (C≡N) and 1 727 (C=O) cm^{-1}; δ 2.69 (s, SMe) and 3.88 (s, CH_2).

Similarly prepared, except that the order of addition of the halogeno-compounds was reversed, ethyl [(4-cyano-5-methylthioisothiazol-3-yl)thio]acetate (33) (81%) formed *needles*, m.p. 76—77 °C (from methanol) (Found: C, 39.6; H, 3.7; N, 10.0%; M^+, 274); $\nu_{max.}$ 2 217 (C≡N) and 1 737 (C=O) cm^{-1}; δ 2.73 (s, SMe) and 4.06 (s, CH_2).

Ethyl 4-*Amino*-3-*methylthiothieno*[3,2-d]*isothiazole*-5-*carboxylate* (34).—A solution of sodium ethoxide [from sodium (0.05 g)] in ethanol (10 ml) was added to a solution of ester (32) (20 g) in ethanol (200 ml), then the mixture was stirred for 1 h, and cooled in ice. The product was collected and recrystallised from ethanol–dimethylformamide to give yellow *needles* (17.6 g, 88%), m.p. 170—171 °C (Found: C, 39.5; H, 3.55; N, 10.15%; M^+, 274); $\nu_{max.}$ 3 407, 3 315 (NH_2), and 1 668 (C=O) cm^{-1}; δ [$(CD_3)_2SO$] 2.70 (s, Me) and 6.42br (NH_2).

Obtained similarly from ester (33), ethyl 4-amino-3-methylthiothieno[2,3-*c*]isothiazole-5-carboxylate (36) formed bright yellow *needles* (94%), m.p. 160—161 °C (from ethanol–dimethylformamide) (Found: C, 39.25; H, 3.55; N, 10.2%; M^+, 274); $\nu_{max.}$ 3 430, 3 325 (NH_2), and 1 657 (C=O) cm^{-1}; δ [$(CD_3)_2SO$] 2.82 (s, SMe) and 6.73br (NH_2).

Reactions of 3,5-*Dichloroisothiazole*-4-*carbonitrile* (37).—(*a*) *With* Na_2S–$BrCH_2{\cdot}CO_2Et$. A solution of the nitrile [22] (37) (7.16 g) in methanol (40 ml) was added dropwise during 0.5 h to a stirred solution of sodium sulphide (9.6 g) in methanol (100 ml) and water (10 ml) under nitrogen at 30—40 °C. The mixture was kept at this temperature for 1 h, then ethyl bromoacetate (7 g) was added, and stirring was continued at room temperature for 3 h. Addition of water and extraction with ether gave ethyl [(3-chloro-4-cyanoisothiazol-5-yl)thio]acetate (38) as *needles* (7.6 g, 72%), m.p. 41—43 °C (from ether–light petroleum) (Found: C, 36.5; H, 2.7; N, 10.8%; M^+, 262/264. $C_8H_7ClN_2O_2S_2$ requires C, 36.55; H, 2.7; N, 10.65%; M^+, 262/264); $\nu_{max.}$ 2 227 (C≡N) and 1 735 (C=O) cm^{-1}; δ 3.92 (s, CH_2).

(*b*) *With* $\bar{S}{\cdot}CH_2{\cdot}CO_2Et$. A solution of the nitrile (37) (1.8 g) in ethanol (20 ml) was added dropwise during 0.25 h to a stirred, cooled (0 °C) solution of ethyl sodiomercaptoacetate [from ethyl mercaptoacetate (1.2 g) and sodium (0.23 g)] in ethanol (20 ml). The mixture was stirred at 0 °C for 2 h, then poured into water to precipitate ethyl 3-amino-5-[(3-chloro-4-cyanoisothiazol-5-yl)thio]-4-cyanothiophen-2-carboxylate (39). It gave dark yellow *needles* (1 g, 54%), m.p. 172—173 °C (from ethanol) [Found: C, 38.55; H, 1.95; N, 14.9%; M^+ (for ^{35}Cl), 369.929. $C_{12}H_7ClN_4O_2S_3$ requires C, 38.85; H, 1.9; N, 15.1%; M^+, 369.942]; $\nu_{max.}$ 3 430, 3 320, 1 627 (NH_2), 2 225 (C≡N), and 1 690 (C=O) cm^{-1}; δ [$(CD_3)_2SO$] 1.30 (t, CH_2Me), 4.30 (q, CH_2Me), and 7.07br (NH_2).

2-*Acetyl*-3-*methylthiothiophen* (41).—A solution of 3-methylthiothiophen [24] (19.5 g, 0.15 mol) and acetyl chloride (11.8 g, 0.15 mol) in dry dichloromethane (30 ml) was added dropwise during 1 h to a stirred solution of tin(IV) chloride (42 g, 0.16 mol) in dichloromethane (150 ml) at 0 °C, then the mixture was stirred at 0 °C for 0.5 h and treated with ice-cold aqueous 10% hydrochloric acid (300 ml). Neutral material, isolated with chloroform, gave straw-coloured *needles* (20.1 g, 78%), m.p. 66—67 °C [from ether–light petroleum (charcoal)] (Found: C, 48.8; H, 4.5%; M^+, 172. $C_7H_8OS_2$ requires C, 48.8; H, 4.7%; *M*, 172); $\nu_{max.}$ 1 648 cm^{-1} (C=O); δ 2.48, 2.50 (s, Me), 7.01 (d, 4-H), and 7.54 (d, 5-H, *J* 5.0 Hz).

(E)-*Methyl* (3-*Methylthio*-2-*thienyl*) O-p-*Nitrobenzoylketoxime* (42).—Ketone (41) formed an *oxime* (88%), m.p. 96—97 °C (from ethyl acetate–light petroleum) (Found: C, 44.75; H, 4.9; N, 7.45%; M^+, 187. $C_7H_9NOS_2$ requires C, 44.9; H, 4.85; N, 7.5%; *M*, 187); δ[$(CD_3)_2SO$] 2.20, 2.44 (s, Me), 7.13 (d, 4-H), 7.60 (d, 5-H, *J* 6.0 Hz), and 11.25 (s, OH). The oxime underwent Beckmann rearrangement with PCl_5–Et_2O, to give 2-*acetamido*-3-*methylthiothiophen* as pale yellow flakes (84%), m.p. 60—61 °C (from ether–light petroleum) (Found: C, 45.2; H, 4.75; N, 7.7%; M^+, 187); $\nu_{max.}$ 1 660 cm^{-1} (C=O); δ 2.23 (s, 2 × Me) and 8.55br (NH).

The oxime reacted as before with *p*-nitrobenzoyl chloride, to give the oxime ester (42), as bright yellow *needles* (87%), m.p. 160—162 °C (decomp.) (from dimethylformamide–ethanol) (Found: C, 50.3; H, 3.65; N, 8.5%; M^+, 336. $C_{14}H_{12}N_2O_4S_2$ requires C, 50.0; H, 3.6; N, 8.35%; *M*, 336); $\nu_{max.}$ 1 745 cm^{-1} (C=O); δ 2.44 and 2.55 (s, Me).

3-*Methylthieno*[2,3-d]*isothiazole* (43).—(*a*) A solution of the oxime ester (42) (10 g) in glacial acetic acid (100 ml) was heated under reflux for 0.25 h, then poured into ice–water. Isolation of neutral material with ether gave a pale brown oil, which was shown by i.r. spectroscopy to contain the cyclised product (43) [74%; from absorbance at 1 087 cm^{-1} ($CHCl_3$)] and 2-acetamido-3-methylthiothiophen [25%; from absorbance at 1 683 cm^{-1} ($CHCl_3$)]. Distillation gave the *thienoisothiazole* (43) as an *oil* (3.1 g, 67%), b.p. 90—92 °C at 1.0 mmHg (Found: C, 46.2; H, 3.4; N, 9.1%; M^+, 155. $C_6H_5NS_2$ requires C, 46.4; H, 3.25; N, 9.0%; *M*, 155); δ 2.57 (s, Me), 7.21 (d, 6-H), and 7.66 (d, 5-H, *J* 5.0 Hz). The *picrate* formed yellow needles, m.p. 128—130 °C (from ethanol) (Found: C, 37.4; H, 2.15; N, 14.8. $C_{12}H_8N_4O_7S_2$ requires C, 37.5; H, 2.1; N, 14.6%).

The residue from the distillation was dissolved in benzene and eluted from silica gel with ether–light petroleum (1 : 3) to give 2-acetamido-3-methylthiothiophen (1.3 g, 23%), identical with an authentic sample.

(*b*) A mixture of 2-acetyl-3-methylthiothiophen oxime (0.5 g), acetic anhydride (2.0 ml), and glacial acetic acid (10 ml) was heated under reflux for 1 h, then cooled and poured into water. The resulting neutral material (0.5 g) had a composition similar to that described in (*a*), and yielded 3-methylthieno[2,3-*d*]isothiazole (0.28 g, 67%).

2-*Methylthieno*[2,3-d]*thiazole*.—The oxime ester (42) (10 g) was added portionwise during 10 min to vigorously stirred, cold (0 °C) concentrated sulphuric acid (50 ml). The resulting yellow solution was kept at room temperature for 3 h, then poured onto ice, and basified. Ether extraction gave the product as an oil (1.7 g, 37%), b.p. 96—98 °C at 5 mmHg (lit.,[29] 102—104 °C at 7 mmHg); δ 2.77 (s, 2-Me), 7.11 (d, 6-H), and 7.27 (d, 5-H, *J* 5.0 Hz); picrate, m.p. 131—132 °C (from ethanol) (lit.,[29] 131—132 °C). It was identical with an authentic [29] sample.

Ethyl 4-*Chloro*-5-*formyl*-2-*methylthiophen*-3-*carboxylate* (45).—A solution of ethyl 4-hydroxy-2-methylthiophen-3-carboxylate [26] (55.8 g, 0.3 mol) in warm dimethylformamide (100 ml) was added rapidly to a solution of the Vilsmeier reagent obtained from phosphoryl chloride (85 g, 0.55 mol) and ice-cold dimethylformamide (66 g, 0.9 mol). The mixture was stirred at 100 °C for 10 min, cooled rapidly, poured into ice-cold aqueous 10% sodium acetate (1 l), then stirred for 0.5 h. Ether extraction gave the aldehyde as pale yellow *needles* (37 g, 53%), m.p. 62—63 °C [from methanol (charcoal)] (Found: C, 46.5; H, 3.9%; M^+, 232/234. $C_9H_9ClO_3S$ requires C, 46.45; H, 3.9%; M^+, 232/234); $\nu_{max.}$ 1 665 cm^{-1} (C=O); δ 10.15 (CHO).

Ethyl 5-*Formyl*-4-*mercapto*-2-*methylthiothiophen*-3-*carb*-

oxylate (46).—A mixture of the chloro-aldehyde (45) (11.6 g), anhydrous sodium hydrogensulphide (5.6 g), and dry acetone (100 ml) was stirred for 2 h, then poured into ice–water, and acidified with dilute hydrochloric acid. The resulting precipitate gave pale yellow *microcrystals* (9.4 g, 82%), m.p. 74—75 °C (from ether–light petroleum) (Found: C, 46.9; H, 4.2%; M^+, 230. $C_9H_{10}O_3S_2$ requires C, 46.95; H, 4.35%; *M*, 230); $\nu_{max.}$ 2 495 (SH), 1 700 (ester C=O), and 1 638 (aldehyde C=O) cm^{-1}; δ 2.72 (s, 2-Me), 7.08br (SH), and 9.81 (s, CHO).

The *oxime* (47), formed after 1 h at room temperature, gave pale yellow needles (88%), m.p. 145—146 °C (from ethanol–light petroleum) (Found: C, 43.7; H, 4.5; N, 5.9%; M^+, 245. $C_9H_{11}NO_3S_2$ requires C, 44.05; H, 4.5; N, 5.7%; *M*, 245); δ [$(CD_3)_2SO$] 2.58 (s, 2-Me), 5.90br (SH), 8.36 (s, :CH), and 11.39br (NOH).

Ethyl 5-Methylthieno[2,3-d]*isothiazole-6-carboxylate* (44).—Acetic anhydride (1 ml) was added dropwise during 2—3 min to a solution of the oxime (47) (2 g) in boiling glacial acetic acid (25 ml), then heating was continued for 5 min, and the mixture was poured into ice–water. Neutral material, isolated with ether, crystallised from methanol (charcoal) as pale yellow *needles* (1.46 g, 79%), m.p. 70—71 °C (Found: C, 47.85; H, 3.9; N, 6.05%; M^+, 227. $C_9H_9NO_2S_2$ requires C, 47.55; H, 4.0; N, 6.15%; *M*, 227); $\nu_{max.}$ 1 708 cm^{-1} (C=O); δ 2.84 (s, 5-Me) and 8.50 (s, 3-H).

We thank the S.R.C. for a studentship (to W. R. F.) and G. Collier (i.r.), Dr. D. F. Ewing (n.m.r.), and A. D. Roberts (m.s.) for physical data. We are grateful to Mrs. M. Vickers for help with some of the experimental work.

[9/1103 *Received*, 11*th July*, 1979]

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