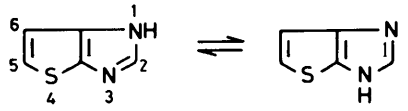
Azoles. Part 7.[1,2] A Convenient Synthesis of Thieno[2,3-*d*]imidazoles

Brian Iddon,* Nazir Khan, and Bee Lan Lim
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT

A number of 1-mono- and 1,2-di-protected 4-bromoimidazole-5-carbaldehydes, (**7**), (**8**), (**11**), and (**13**)—(**15**), reacted with ethyl thioglycollate in ethanol in the presence of sodium ethoxide to give the corresponding title compound, (**16**), (**17**), or (**19**)—(**22**), respectively (65—70% yield). Shorter reaction times allowed intermediates to be isolated, *e.g.* (**13**) gave (**20**) (69%) and (**23**) (12%). Several attempts to obtain the parent system, 1*H*- or 3*H*-thieno[2,3-*d*]imidazole, failed. Attempts to prepare the title compounds from imidazoles by several classical syntheses used for annelated thiophene systems (due to Tilak, Campaigne, and Krollpfeiffer) failed as did attempts to prepare imidazolethiols through chlorosulphonation or thiocyanation of imidazoles or *via* their reaction with 2,4-dinitrobenzenesulphenyl chloride. Several unsuccessful approaches to the title compounds from thiophenes are also described.

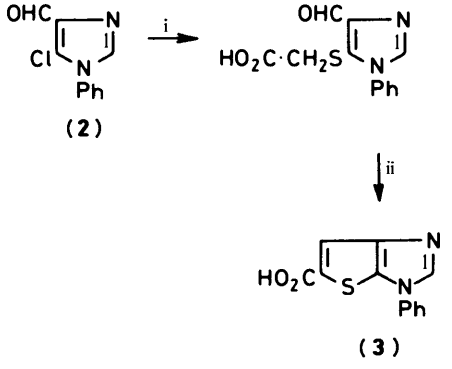
In connection with our previous work on thienopyrazoles[3] we became interested in thienoimidazoles. The parent system, 1*H*- or 3*H*-thieno[2,3-*d*]imidazole (**1**),† is unknown and existing routes to the few known derivatives (mainly substituted at N-3),



(**1**)

which start from either imidazole[4,5] or thiophene[6–9] precursors, are unsatisfactory in that the starting materials are either not very accessible, unstable, or both. Our initial attempts, described herein, to prepare thieno[2,3-*d*]imidazoles from 2,3-diaminothiophenes failed, presumably due to the notorious instability of this type of compound. This approach has failed also in the hands of others,[10,11] although, more recently, Binder's group[7–9] have had some success.

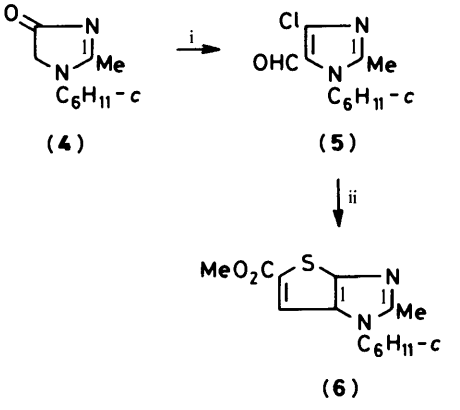
We were attracted to a synthesis (see Scheme 1)[4] of 3-



Scheme 1. *Reagents:* i, $HSCH_2CO_2H$–KOH; ii, NaOMe–MeOH

phenyl-3*H*-thieno[2,3-*d*]imidazole-5-carboxylic acid (**3**) from thioglycollic acid (2-mercaptoacetic acid) and 5-chloro-1-phenylimidazole-4-carbaldehyde (**2**). This suffers from two disadvantages: (i) a description of the synthesis of the chloroaldehyde (**2**), prepared from anilinoacetamide, $PhNHCH_2CONH_2$, under Vilsmeier conditions ($POCl_3$–DMF), is not readily available in the literature;[12] and (ii) although the product (**3**) can be decarboxylated,[4] the N-3 phenyl group is almost impossible to remove. Recently, the chloroaldehyde (**5**) (Scheme 2) has been synthesized by Becher *et al.*[5] from imidazolone (**4**) *via* a Vilsmeier reaction, and converted into thienoimidazole (**6**). Unfortunately, imidazolones are not well-known compounds[13] and, consequently, this route to thienoimidazoles cannot be considered general at present.

Benzothienoimidazoles are similarly difficult to synthesise.[10,14,15] Thieno[3,4-*d*]imidazoles have attracted interest,[16,17] particularly as intermediates for biotin.[17]

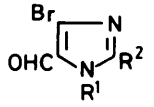


Scheme 2. *Reagents:* i, $POCl_3$–DMF; ii, $HSCH_2CO_2Me$–Na_2CO_3

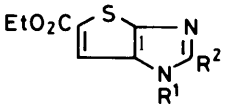
Previously, we[2] have described a general synthesis of the bromoaldehydes (**7**)—(**9**) and (**11**)—(**15**), which involves successive treatment of the corresponding 4,5-dibromoimidazole with 1 mol equiv. each of butyl-lithium, *N*,*N*-dimethylformamide (DMF), and acid. We now report that the 1*H*-thieno[2,3-*d*]imidazoles (**16**), (**17**), and (**19**)—(**22**) can be prepared in 65—70% yield by heating the corresponding bromoaldehyde with ethyl thioglycollate (ethyl 2-mercaptoacetate) in refluxing ethanol for 4 h in the presence of sodium ethoxide. Shorter reaction times allow the intermediates involved in these reactions to be isolated. Thus, when the bromoaldehyde (**13**) was treated with ethyl thioglycollate under these conditions but for only 3 h, a mixture of the corresponding 1*H*-thieno[2,3-*d*]imidazole (**20**) (69% yield) and the intermediate sulphide (**23**) (12% yield) was obtained. The intermediate sulphide (**23**) cyclised rapidly to give 1*H*-thieno[2,3-*d*]imidazole (**20**) (100% yield) in ethanol in the presence of sodium ethoxide. Ethyl 3-

† We used an incorrect nomenclature in our preliminary communication.

trityl-3*H*-thieno[2,3-*d*]imidazole-5-carboxylate (**24**) (60% yield) was obtained likewise from 5-chloro-1-tritylimidazole-4-carbaldehyde.[2] We failed to isolate the expected 1*H*-thieno[2,3-*d*]imidazole (**18**) from the reaction of the bromoaldehyde (**9**) with ethyl thioglycollate under these conditions; the product appeared to be unstable. Nevertheless, our synthesis of 1*H*-thieno[2,3-*d*]imidazoles represents the most general synthesis reported to date.



(**7**) $R^1 = CH_2Ph$, $R^2 = H$
(**8**) $R^1 = CH_2C_6H_4OMe$-4, $R^2 = H$
(**9**) $R^1 = CH_2C_6H_3(OMe)_2$-3,4, $R^2 = H$
(**10**) $R^1 = CH_2OMe$, $R^2 = H$
(**11**) $R^1 = CH_2OMe$, $R^2 = SCH_2Ph$
(**12**) $R^1 = CH_2OMe$, $R^2 = SPh$
(**13**) $R^1 = CH_2OEt$, $R^2 = SMe$
(**14**) $R^1 = CH_2Ph$, $R^2 = SCH_2Ph$
(**15**) $R^1 = CH_2Ph$, $R^2 = SPh$



(**16**) $R^1 = CH_2Ph$, $R^2 = H$
(**17**) $R^1 = CH_2C_6H_4OMe$-4, $R^2 = H$
(**18**) $R^1 = CH_2C_6H_4(OMe)_2$-3,4, $R^2 = H$
(**19**) $R^1 = CH_2OMe$, $R^2 = SCH_2Ph$
(**20**) $R^1 = CH_2OEt$, $R^2 = SMe$
(**21**) $R^1 = CH_2Ph$, $R^2 = SCH_2Ph$
(**22**) $R^1 = CH_2Ph$, $R^2 = SPh$

The oxime (**25**) of the bromoaldehyde (**7**) was treated in boiling toluene with phosphorus pentaoxide in an attempt to prepare the nitrile (**26**) but, in addition to the nitrile (28% yield), this reaction also gave the amide (**27**) (49.5%). Treatment of the oxime (**25**) with boiling phosphorus oxychloride, however, gave an 83% yield of the nitrile (**26**), which was treated with ethyl thioglycollate under the conditions described before, to give a mainly intractable product from which a compound believed to be the 1*H*-thieno[2,3-*d*]imidazole (**28**) was isolated in only 5% yield.

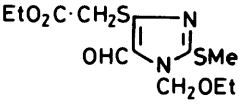
Alkaline hydrolysis of the 1*H*-thieno[2,3-*d*]imidazole (**17**) gave the corresponding carboxylic acid (87% yield).

The bromoaldehyde (**13**) was converted into its ethylene acetal (**29**) (71% yield) which was treated successively with butyl-lithium and di(methoxycarbonylmethyl) disulphide, $(MeO_2CCH_2)_2S_2$, in the hope that this would yield the sulphide (**30**). This reaction gave, however, only the debrominated product (**31**) (72% yield).

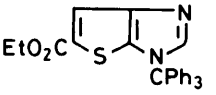
Attempts to remove the benzyl group from ethyl 1-benzyl-1*H*-thieno[2,3-*d*]imidazole-5-carboxylate (**16**) with either sodium in liquid ammonia or trimethylsilyl iodide failed. Catalytic hydrogenolysis failed too in this case (**16**) and also in the case of ethyl 1-(4-methoxybenzyl)-1*H*-thieno[2,3-*d*]imidazole-5-carboxylate (**17**), possibly due to catalyst poisoning by the ring S-atom. Attempts to N-1 deprotect thienoimidazoles (**17**) and (**24**) with acids, using conditions previously successful with imidazoles,[1] failed; the former compound was returned unchanged whilst the latter gave a quantitative yield of triphenylmethanol but none of the required ethyl 1*H*- or 3*H*-thieno[2,3-*d*]imidazole-5-carboxylate. Like thienopyrroles[18] and thieno-1,2,3-triazoles[19] it appears that some thieno[2,3-*d*]imidazoles, especially those lacking N-1 protecting groups, are unstable.

Beck *et al.*[20] have synthesised condensed thiophene ring systems *via* nucleophilic displacements of *ortho*-activated nitro groups with methyl thioglycollate; thus *o*-nitrobenzonitrile yields methyl 3-aminobenzo[*b*]thiophene-2-carboxylate. Starting material was recovered when 1-benzyl-4-nitroimidazole-5-carbonitrile (**32**)[21] was subjected to these reaction conditions.

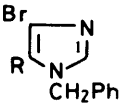
An attempt to prepare the dihydrothienoimidazole (**33**) *via* cyclisation of the acid (**36**) failed because 1-methoxymethyl-4-nitroimidazole (**34**) would not react with methyl thioglycollate in hexamethylphosphoramide (hexamethylphosphoric triamide) (HMPA) in the presence of lithium hydroxide (*cf.* ref. 22) to yield the ester (**35**).



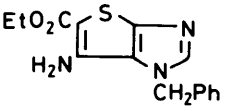
(**23**)



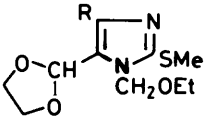
(**24**)



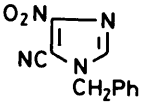
(**7**) R = CHO
(**25**) R = CH=NOH
(**26**) R = CN
(**27**) R = $CONH_2$



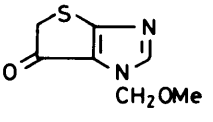
(**28**)



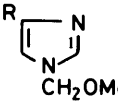
(**29**) R = Br
(**30**) R = SCH_2CO_2Me
(**31**) R = H



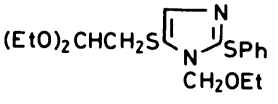
(**32**)



(**33**)



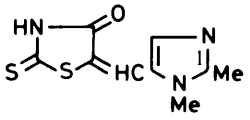
(**34**) R = NO_2
(**35**) R = SCH_2CO_2Me
(**36**) R = SCH_2CO_2H



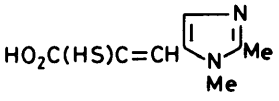
(**37**)

Attempts to cyclise the acetal (**37**)[23] under acidic conditions (analogous to Tilak's synthesis of benzo[*b*]thiophenes[24,25]) also failed. Condensation of 1,2-dimethylimidazole-5-carbaldehyde[26] with rhodanine and hydrolysis of the product (**38**) (93% yield) with aqueous sodium hydroxide gave the α-mercaptoacrylic acid derivative (**39**) (91%). Attempts to cyclise this acid (**39**) with chlorine in either benzene or dioxane

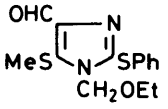
heated under reflux (analogous to Campaigne's synthesis of benzo[*b*]thiophenes[24,27]) failed, giving only starting material (100% return), presumably because of the insolubility of the acid (which probably exists as an internal salt) in these solvents. Attempts to bring about reaction of the aldehyde (**40**)[23] with chloroacetic acid or ethyl chloroacetate, under various conditions, to give sulphonium salts of use in a Krollpfeiffer synthesis [*e.g.* (**41**) ⟶ (**42**)[24]], gave only intractable tars.



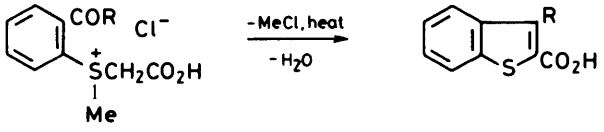
(**38**)



(**39**)



(**40**)

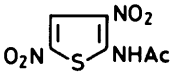


(**41**) (**42**)

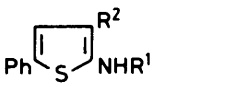
We have also studied various methods of introducing sulphur substituents into imidazole rings particularly with a view to providing intermediates, such as thiols, of use in the construction of a thiophene ring. Attempts to reduce imidazole-4(5)-sulphonyl chloride[28,29] and 4(5)-bromoimidazole-5(4)-sulphonyl chloride[28,30] to the corresponding thiols failed and an attempt to bring about reaction of 1,2-dimethylimidazole with 2,4-dinitrobenzenesulphenyl chloride[31] in 1,2-dichloroethane in the presence of tin(IV) chloride gave only bis(2,4-dinitrophenyl) disulphide (29% yield) and what appears from the experimental data to be the hexachlorostannate salt of 1,2-dimethylimidazole (50%). Thiocyanatoimidazoles are unknown.[28] Various attempts to thiocyanate 1,2-dimethylimidazole and 2-amino-1-methylimidazole[32–34] using conditions employed successfully to thiocyanate other heterocycles[35–37] all failed as did attempts to bring about reaction of 1,2-dimethyl-5-trimethylstannylimidazole[26] with lead(II) thiocyanate and chlorine in acetic acid at ambient temperature (*cf.* ref. 38) and 1,2-dimethyl-5-trimethylsilylimidazole[26] with bromine in anhydrous carbon tetrachloride either at 0 °C or ambient temperature.

We also attempted to prepare thienoimidazoles from some thiophene derivatives which were available to us. Numerous attempts to reduce 2-acetamido-3,5-dinitrothiophene (**43**), hopefully selectively in the 3-position, all failed (*cf.* refs. 6, 7, and 11) as did an attempt to reduce 2-amino-3,5-dinitrothiophene with hydrogen and 10% palladium–charcoal in ethyl formate in the presence of a few drops of concentrated hydrochloric acid (cyclisation of the initial product was expected under these conditions).

2-Amino-5-phenylthiophene-3-carboxamide (**44**) was also available to us and we planned to protect its amino group and subject the protected derivatives to Hofmann rearrangement conditions. Acetylation of the amide (**44**) with acetic anhydride in the presence of a small amount of concentrated sulphuric acid gave the *N,N'*-diacetyl compound (**47**) (100% yield) but, with a mixture of acetic anhydride and acetic acid (ratio 9:1), the



(**43**)



(**44**) $R^1 = H, R^2 = CONH_2$
(**45**) $R^1 = COMe, R^2 = CONH_2$
(**46**) $R^1 = COPh, R^2 = CONH_2$
(**47**) $R^1 = COMe, R^2 = CONHAc$
(**48**) $R^1 = COPh, R^2 = CN$

monoacetyl compound (**45**) (100%) was obtained. Under standard Hofmann conditions the monoacetyl compound (**45**) failed to react, presumably owing to its insolubility. A completely homogeneous mixture was obtained only at 70 °C at which temperature hypobromite is unstable.[39] Because this amide (**45**) is also poorly soluble in dioxane[39,40] we prepared 2-benzamido-5-phenylthiophene-3-carboxamide (**46**) (86.5%) by treating the amine (**44**) with benzoyl chloride in benzene in the presence of pyridine, and subjected it to a Hofmann reaction in dioxane at 0—70 °C. This gave only intractable material, whilst the use of sodium hypochlorite at 0—55 °C gave only starting material. The conversion of thiophene-3-carboxamide into 3-aminothiophene[41] appears to be the only successful Hofmann reaction of a thiophene-carboxamide reported to date. Binder's group[7,8] have synthesised protected 2-acetamido-3-aminothiophenes by Curtius rearrangements of thiophene-3-carboxylic acid azides in t-butyl alcohol.

Experimental

The instruments used to record i.r., m.s., and ^1H and ^{13}C n.m.r. spectra, and the general experimental conditions used were the same as those described previously.[26,42]

The following compounds were prepared by literature procedures: 4(5)-nitroimidazole (61.5%), m.p. 306—307 °C (lit.,[43] 309—310 °C); 1-benzyl-4-nitroimidazole-5-carbonitrile (**32**) (56% yield), m.p. 130.5—131.5 °C (lit.,[21] 56% and m.p. 130.5—131.5 °C); imidazole-4(5)-sulphonyl chloride (3% yield), m.p. 175—177 °C (lit.,[29] 67% and m.p. 177—179 °C); 4(5)-bromoimidazole-5(4)-sulphonyl chloride (30%), m.p. 188—189 °C (lit.,[30] 51% and m.p. 186—188 °C); and 2-amino-1-methylimidazole (30%), b.p. 70—72 °C at 0.1 mmHg (lit.,[32] b.p. 136—137 °C at 5.0 mmHg and m.p. 81.5—82.5 °C). 2,4,5-Tribromo-1-ethoxymethylimidazole,[44] 4-bromo-5-chloro-1-tritylimidazole,[2] 4-bromoimidazole-5-carbaldehydes (**7**)—(**9**) and (**11**)—(**15**),[2] 1-ethoxymethyl-5-methylthio-2-phenylthioimidazole-4-carbaldehyde (**40**),[23] 2-(1-ethoxymethyl-2-phenylthioimidazol-5-ylthio)acetaldehyde diethylacetal (**37**),[23] 1,2-dimethyl-5-trimethylsilyl(and trimethylstannyl)imidazole,[26] and 1,2-dimethylimidazole-5-carbaldehyde[26] were prepared as described by us previously. 1,2-Dimethylimidazole and chloromethyl methyl ether (**CAUTION**: carcinogenic) were available commercially.

For the sake of brevity details (other than those given in the Discussion) of unsuccessful reactions have been omitted; these are available in refs. 11, 45 and 46.

1-*Methoxymethyl*-4-*nitroimidazole* (**34**).—Triethylamine (6.12 ml, 4.44 g, 44.0 mmol) and chloromethyl methyl ether (**CAUTION**: carcinogenic) (3.54 g, 44.0 mmol) were added successively dropwise to a stirred suspension of 4(5)-nitroimidazole (5.0 g, 44.0 mmol) in anhydrous benzene (50 ml) at 0 °C, and the mixture was stirred at ambient temperature for 3 h. Further triethylamine (3 ml, 2.22 g, 22.0 mmol) was added, stirring was continued for a further 15 min, then more chloromethyl methyl ether (1.77 g, 22.0 mmol) was added dropwise. After a further 1 h the mixture was heated under

reflux for 1 h. The solvents and excess of reagents were removed by distillation under reduced pressure and water (50 ml) was added to the residue. Extraction with chloroform gave a colourless oil (4.8 g, 69.5%), which solidified, m.p. 64—64.5 °C (from ethanol–light petroleum) (lit.,[47] m.p. 66.5—67 °C and 46% yield); δ(CDCl$_3$) 3.46 (3 H, s, Me), 5.43 (2 H, s, CH$_2$), 7.61 (1 H, s, 5-H), and 7.93 (1 H, s, 2-H) (Found: C, 38.0; H, 4.4; N, 26.9%; M^+, 157. $C_5H_7N_3O_3$ requires C, 38.2; H, 4.5; N, 26.7%; *M*, 157). *Structural* assignments to alkylated derivatives of 4(5)-nitroimidazoles have been discussed in Part 4.[42]

4,5-*Dibromo*-1-*ethoxymethyl*-2-*methylthioimidazole*.—This was an oil, and was prepared in 68% yield by a procedure analogous to that described previously[44] for the synthesis of 4,5-dibromo-1-ethoxymethyl-2-phenylthioimidazole. It had δ(CDCl$_3$) 1.19 (3 H, t, Me), 2.60 (3 H, s, SMe), 3.53 (2 H, q, OCH$_2$), and 5.30 (2 H, s, NCH$_2$) (Found: C, 25.5; H, 3.0; N, 8.5%; M^+, 328. $C_7H_{10}Br_2N_2OS$ requires C, 25.5; H, 3.05; N, 8.5%; *M*, 328) (product eluted from an alumina column with ethyl acetate–light petroleum). A better method* for the synthesis of this type of compound has been described in Part 4.[42]

4-*Bromo*-1-*ethoxymethyl*-2-*methylthioimidazole*-5-*carbaldehyde* (**13**).—1.0M-Butyl-lithium in hexane (4.5 ml, 4.50 mmol) was added to a stirred solution of 4,5-dibromo-1-ethoxymethyl-2-methylthioimidazole (1.4 g, 4.24 mmol) in ether (120 ml) at such a rate that the temperature did not rise above −74 °C. The resulting mixture was kept at −74 °C for a further 4 h, DMF (0.9 g, 12.7 mmol) was added, and the mixture was allowed to warm slowly to ambient temperature. Aqueous ammonium chloride (20%, 20 ml) was added after which the aqueous layer was extracted with ether (3 × 20 ml). The organic layer and ethereal extracts were combined, concentrated, washed with water, dried (MgSO$_4$), and distilled to give a viscous orange oil, which solidified. This was chromatographed on an alumina column. Ethyl acetate–light petroleum eluted the *title compound* (**13**) (0.62 g, 53%), m.p. 79—80 °C (from light petroleum); $\nu_{max.}$ 1 660 cm^{-1} (CO); δ_H(CDCl$_3$) 1.18 (3 H, t, Me), 2.70 (3 H, s, SMe), 3.57 (2 H, q, OCH$_2$), 5.69 (2 H, s, NCH$_2$), and 9.63 (1 H, s, CHO); δ_C(CDCl$_3$) 177.55 (d, CHO), 154.35 (s, C-2), 131.06 (s, C-5), 127.77 (s, C-4), 73.58 (t, NCH$_2$), 64.53 (t, OCH$_2$), and 14.44 p.p.m. (m, SMe and Me) (Found: C, 34.45; H, 4.1; N, 10.1%; M^+, 278. $C_8H_{11}BrN_2O_2S$ requires C, 34.4; H, 4.0; N, 10.0%; *M*, 278); and 1-*ethoxymethyl*-2,4-*bis*(*methylthio*)*imidazole*-5-*carbaldehyde* (0.16 g, 15%),† m.p. 45—46 °C (from light petroleum); $\nu_{max.}$ 1 680 cm^{-1} (CO); δ_H(CDCl$_3$) 1.21 (3 H, t, Me), 2.46 (3 H, s, 4-SMe), 2.71 (3 H, s, 2-SMe), 3.60 (2 H, q, OCH$_2$), 5.44 (2 H, s, NCH$_2$), and 10.02 (1 H, s, CHO); δ_C(CDCl$_3$) 183.43 (d, CHO), 149.26 (s, C-2), 142.55 (s, C-5), 135.47 (s, C-4), 72.49 (t, NCH$_2$) 64.31 (t, OCH$_2$), 20.25 (q, 2-SMe), and 14.42 p.p.m. (m, 4-SMe and Me) (Found: C, 43.7; H, 5.8; N, 11.4%; M^+, 246. $C_9H_{14}N_2O_2S_2$ require C, 43.9; H, 5.7; N, 11.4%; *M*, 246): *oxime* (92%), m.p. 107—108 °C (from carbon tetrachloride–light petroleum); $\nu_{max.}$ 960 (N–O) and 3 100 cm^{-1} (OH); δ(CDCl$_3$) 1.20 (3 H, t, Me), 2.32 (3 H, s, 4-SMe), 2.75 (3 H, s, 2-SMe), 3.55 (2 H, q, OCH$_2$), 5.40 (2 H, s, NCH$_2$), 7.30 (1 H, s, CH), and 8.30 (1 H, s, exchangeable, OH) (Found: C, 41.35; H, 5.8; N, 16.0%; M^+, 261. $C_9H_{15}N_3O_2S_2$ requires C, 41.4; H, 5.8; N, 16.1%; *M*, 261).

Ethyl 1-*Ethoxymethyl*-2-*methylthio*-1H-*thieno*[2,3-d]*imidazole*-5-*carboxylate* (**20**).—(a) Ethyl thioglycollate (0.43 g, 3.58 mmol) was added to a stirred solution of sodium ethoxide (0.24 g, 3.58 mmol) in ethanol (15 ml) and the mixture was stirred for 1 h at ambient temperature. Then 4-bromo-1-ethoxymethyl-2-methylthioimidazole-5-carbaldehyde (**13**) (0.5 g, 1.79 mmol) in ethanol (50 ml) was added and the resulting mixture was heated under reflux for 3 h. The solvent was distilled off, water (10 ml) was added to the residue, and extraction of the product with chloroform gave a bright yellow oil (0.47 g) which was chromatographed on alumina. Ethyl acetate–light petroleum eluted: (i) a trace of unreacted starting material; (ii) the 1H-*thieno*[2,3-d]*imidazole* (**20**) (0.365 g, 69%), m.p. 70 °C (from light petroleum); $\nu_{max.}$ 1 695 cm^{-1} (CO); δ_H(CDCl$_3$) 1.20 (3 H, t, Me of CH$_2$OEt), 1.39 (3 H, t, Me of CO$_2$Et), 2.75 (3 H, s, SMe), 3.53 (2 H, q, OC*H*$_2$CH$_3$), 4.37 (2 H, q, CO$_2$C*H*$_2$CH$_3$), 5.51 (2 H, s, NCH$_2$), and 7.65 (1 H, s, ArH); δ_C(CDCl$_3$) 217.03 (s, CO), 163.22 (s, C-2), 153.32 (s, C-3a), 136.73 (s, C-6a), 128.67 (s, C-5), 114.37 (d, C-6), 74.81 (t, NCH$_2$), 64.82 (t, CO$_2$*C*H$_2$CH$_3$), 60.93 (t, CH$_2$O*C*H$_2$CH$_3$), 15.37 (q, SMe), 14.52 (q, CO$_2$CH$_2$*C*H$_3$), and 14.17 p.p.m. (q, CH$_2$OCH$_2$*C*H$_3$) (Found: C, 48.0; H, 5.4; N, 9.4%; M^+, 300. $C_{12}H_{16}N_2O_3S_2$ requires C, 48.0; H, 5.4; N, 9.3%; *M*, 300); and (iii) *ethyl* 2-(1-*ethoxymethyl*-5-*formyl*-2-*methylthioimidazol*-4-*ylthio*)*acetate* (**23**) (0.07 g, 12%), an oil; $\nu_{max.}$ 1 650 (CHO) and 1 740 cm^{-1} (CO); δ(CDCl$_3$) 1.19 (3 H, t, CH$_2$OCH$_3$C*H*$_3$), 1.30 (3 H, t, CO$_2$CH$_2$C*H*$_3$), 2.70 (3 H, s, SMe), 3.60 (2 H, q, CH$_2$OC*H*$_2$CH$_3$), 3.92 (2 H, s, SCH$_2$), 4.22 (2 H, q, CO$_2$C*H*$_2$CH$_3$), 5.65 (2 H, s, NCH$_2$), and 9.80 (Found: M^+, 318.0707. $C_{12}H_{18}N_2O_4S_2$ requires *M*, 318.0707).

(b) A solution of compound (**23**) (0.1 g, 0.31 mmol) in ethanol (2.5 ml) was added to a stirred solution of sodium ethoxide (0.3 g, 0.44 mmol) in ethanol (10 ml) and the mixture was heated under reflux for 5 min. The solvent was distilled off, water (5 ml) was added to the residue followed by 4M-hydrochloric acid to neutrality; the product was then extracted with chloroform (3 × 10 ml) to give the thienoimidazole (**20**) as a bright yellow oil (0.09 g, 100%), which solidified, m.p. 70 °C (from light petroleum), identical in other respects (t.l.c. and i.r. and ^{1}H n.m.r. spectra) with the sample prepared as described in (a).

Ethyl 2-*Benzylthio*-1-*methoxymethyl*-1H-*thieno*[2,3-d]*imidazole*-5-*carboxylate* (**19**).—Ethyl thioglycollate (1.055 g, 8.79 mmol) in ethanol (10 ml) was added dropwise during 1 h to a stirred solution of sodium ethoxide (0.60 g, 8.79 mmol) in ethanol (50 ml) at ambient temperature. Then 2-benzylthio-4-bromo-1-methoxymethylimidazole-5-carbaldehyde (**11**) (3.0 g, 8.79 mmol) in ethanol (10 ml) was added and the mixture was heated under reflux for 4 h. The solvent was distilled off under reduced pressure and water (50 ml) was added to the residue. Extraction with chloroform (4 × 25 ml) gave a pale-yellow oil which was chromatographed on alumina. Ethyl acetate–light petroleum eluted the *product* (**19**) (02.07 g, 65%), m.p. 83—84 °C (from light petroleum); $\nu_{max.}$ 1 690 (CO); δ(CDCl$_3$) 1.40 (2 H, t, Me), 3.20 (3 H, s, OMe), 4.40 (3 H, q, CH$_2$), 4.50 (2 H, s, SCH$_2$), 5.25 (2 H, s, NCH$_2$), 7.25 (5 H, m, ArH), and 7.65 (1 H, s, 6-H) (Found: C, 55.1; H, 5.1; N, 7.8%; M^+, 362. $C_{17}H_{18}N_2O_3S_2$ requires C, 56.3; H, 5.0; N, 7.7%; *M*, 362).

The following compounds were prepared similarly: *ethyl* 1-*benzyl*-1H-*thieno*[2,3-d]*imidazole*-5-*carboxylate* (**16**) (70%) (product eluted from alumina with ethanol–light petroleum), m.p. 98—100 °C (from ethanol); $\nu_{max.}$ 1 690 cm^{-1} (CO); δ(CDCl$_3$) 1.33 (3 H, t, Me), 4.35 (2 H, q, CH$_2$), 5.26 (2 H, s, NCH$_2$), 7.82 (1 H, s, ArH), and 7.10—7.50 (6 H, m, ArH) (Found: C, 63.2; H, 4.8; N, 9.9%; M^+, 286. $C_{15}H_{14}N_2O_2S$ requires C, 62.9; H, 4.9; N, 9.8%; *M*, 286): *ethyl* 1-(4-*methoxybenzyl*)-1H-*thieno*[2,3-d]*imidazole*-5-*carboxylate* (**17**) (68%) (product eluted from alumina with ethyl acetate–ethanol), m.p. 84—85 °C (from ethanol); $\nu_{max.}$ 1 690 cm^{-1} (CO); δ(CDCl$_3$) 1.36 (3 H, t, Me), 3.83 (3 H, s, OMe), 4.36 (2 H, q,

* These two experiments were carried out[45] prior to more recent improvements[46] reported in Part 4.[42]

† In this experiment we believe that the starting material was contaminated with a small amount of dimethyl disulphide, which would account for formation of the by-product.

CH_2), 5.20 (2 H, s, NCH_2), 6.88 (2 H, d, ArH), 7.24 (4 H, d, ArH), 7.50 (1 H, s, 2-H), and 7.88 (1 H, s, 6-H) (Found: C, 60.6; H, 5.3; N, 8.3%; M^+, 316. $C_{16}H_{16}N_2O_3S$ requires C, 60.7; H, 5.1; N, 8.85%; *M*, 316): *ethyl* 1-*benzyl*-2-*benzylthio*-1H-*thieno*[2,3-d]-*imidazole*-5-*carboxylate* (**21**) (68%) (ethyl acetate–light petroleum eluted product from alumina), m.p. 136—138 °C (from ethyl acetate); $\nu_{max.}$ 1 690 cm^{-1} (CO); δ($CDCl_3$) 1.33 (3 H, t, Me), 4.33 (2 H, q, CH_2), 4.48 (2 H, s, SCH_2), 5.10 (2 H, s, NCH_2), and 7.00—7.40 (11 H, m, ArH) (Found: C, 64.7; H, 5.1; N, 6.7%; M^+, 408. $C_{22}H_{20}N_2O_2S_2$ requires C, 64.7; H, 4.9; N, 6.85%; *M*, 408): and *ethyl* 1-*benzyl*-2-*phenylthio*-1H-*thieno*[2,3-d]*imidazole*-5-*carboxylate* (**22**) (69.5%) (ethyl acetate–light petroleum eluted product from alumina), m.p. 73—75 °C (from ethanol); $\nu_{max.}$ 1 690 cm^{-1} (CO); δ($CDCl_3$) 1.30 (3 H, t, Me), 4.30 (2 H, q, CH_2), 5.35 (2 H, s, NCH_2), and 6.90—7.40 (11 H, m, ArH) (Found: C, 63.9; H, 4.6; N, 6.8%; M^+, 394. $C_{21}H_{18}N_2O_2S_2$ requires C, 63.9; H, 4.6; N, 7.1%; *M*, 394).

Reactions of 1-*Benzyl*-4-*bromoimidazole*-5-*carbaldehyde* (**7**) *Oxime* (**25**).—(a) *With phosphorus pentaoxide.* A mixture of the oxime (**25**) (4.0 g, 14.28 mmol), phosphorus pentaoxide (2.0 g, 14.28 mmol), and toluene (50 ml) was heated under reflux for 6 h after which solvent was distilled off under reduced pressure and the residue added to ice–water. Extraction with chloroform gave a colourless oil which solidified. The i.r. spectrum of the resulting solid suggested that it was a mixture of a nitrile and an amide. Recrystallisation of the mixture from ethyl acetate gave 1-*benzyl*-4-*bromoimidazole*-5-*carboxamide* (**27**) (1.98 g, 49.5%), m.p. 147—149 °C; $\nu_{max.}$ 1 660 (CO) and 3 290 and 3 400 cm^{-1} (NH_2); δ($CDCl_3$) 2.25 (2 H, s, NH_2), 5.76 (2 H, s, NCH_2), 7.51 (5 H, m, ArH), and 7.70 (1 H, s, 2-H) (Found: C, 46.45; H, 3.6; N, 14.6%; M^+, 279.0008. $C_{11}H_{10}BrN_3O$ requires C, 47.2; H, 3.6; N, 15.0%; *M*, 278.9998). Several recrystallisations of the residue (left after removal of the ethyl acetate) from ethyl acetate–light petroleum gave 1-*benzyl*-4-*bromoimidazole*-5-*carbonitrile* (**26**) (1.05 g, 28%), m.p. 75—77 °C; $\nu_{max.}$ 2 230 cm^{-1} (CN); δ($CDCl_3$) 5.16 (2 H, s, NCH_2), 7.40 (5 H, m, ArH), and 7.15—7.50 (1 H, s, 2-H) (Found: C, 50.2; H, 3.1; N, 15.9%; M^+, 261. $C_{11}H_8BrN_3$ requires C, 50.4; H, 3.1; N, 16.0%; *M*, 261).

(b) *With phosphorus oxychloride.* A mixture of the oxime (**25**) (5.0 g, 17.86 mmol) and phosphorus oxychloride (20 ml, excess) was heated under reflux for 30 min and then cooled and poured into ice–water. The precipitate was filtered off and recrystallised from ethyl acetate–light petroleum, to give 1-benzyl-4-bromoimidazole-5-carbonitrile (**26**) (3.9 g, 83%), m.p. 75—77 °C, identical in all other respects with the sample prepared as described in (a).

Ethyl 6-*Amino*-1-*benzyl*-1H-*thieno*[2,3-d]*imidazole*-5-*carboxylate* (**28**).—Ethyl thioglycollate (1.37 g, 11.45 mmol) in ethanol (5.0 ml) was added dropwise to a stirred solution of sodium ethoxide (0.78 g, 11.45 mmol) in ethanol (50 ml) and the mixture was stirred at ambient temperature for 1 h. Then 1-benzyl-4-bromoimidazole-5-carbonitrile (**26**) (3.0 g, 11.45 mmol) in ethanol (15 ml) was added and the mixture was heated under reflux for 4 h. The solvent was distilled off under reduced pressure, water (50 ml) was added to the residue, and extraction with chloroform gave a black oil which was chromatographed on silica. Ethyl acetate–light petroleum eluted a compound with the properties expected for product (**28**) (0.18 g, 5%), m.p. 203—204 °C; $\nu_{max.}$ 1 695 (CO) and 3 255 and 3 400 cm^{-1} (NH_2); δ($CDCl_3$) 1.30 (3 H, t, Me), 3.55 (2 H, s, NH_2), 4.22 (2 H, q, CH_2), 5.40 (2 H, s, NCH_2), 6.90—7.40 (5 H, m, ArH), and 7.75 (1 H, s, 2-H, followed by an intractable tar.

1-(4-*Methoxybenzyl*)-1H-*thieno*[2,3-d]*imidazole*-5-*carboxylic Acid.*—A mixture of ethyl 1-(4-methoxybenzyl)-1*H*-thieno[2,3-*d*]imidazole-5-carboxylate (**17**) (0.8 g, 2.53 mmol) and 10% aqueous sodium hydroxide (25 ml) was heated under reflux for 30 min and then cooled and made acid by addition of 10% hydrochloric acid. The precipitate was filtered off and recrystallised from ethanol to give the *acid* (0.635 g, 87%), m.p. 215—216 °C; $\nu_{max.}$ 1 680 cm^{-1} (CO); δ[$(CD_3)_2SO$] 3.78 (3 H, s, OMe), 5.22 (2 H, s, NCH_2), 6.87 (2 H, d, ArH), 7.22 (2 H, d, ArH), 7.39 (1 H, s, 2-H), and 7.52 (1 H, s, 6-H) (Found: C, 58.1; H, 4.3; N, 9.8%; M^+, 288. $C_{14}H_{12}N_2O_3S$ requires C, 58.3; H, 4.2; N, 9.7%; *M*, 288).

4-*Bromo*-1-*ethoxymethyl*-2-*methylthioimidazole*-5-*carbaldehyde Ethylene Acetal* (**29**).—A stirred mixture of the bromoaldehyde (**13**) (0.5 g, 1.79 mmol), ethylene glycol (0.22 g, 3.58 mmol) and a small amount of toluene-4-sulphonic acid in anhydrous benzene (50 ml) was heated under reflux for 2 h with azeotropic removal of water. The cooled mixture was washed successively with 20% aqueous sodium carbonate and water, then dried ($MgSO_4$), and distilled to give a yellow oil (0.51 g) which was chromatographed on alumina. Ethyl acetate–light petroleum eluted starting material (50 mg, 10%) and the *acetal* (**29**) (0.37 g, 71% based on starting material consumed), as an oil; δ($CDCl_3$) 1.15 (3 H, t, Me), 2.65 (3 H, s, SMe), 3.55 (2 H, q, OCH_2), 4.05 (4 H, m, $-OCH_2CH_2O-$), 5.30 (2 H, s, NCH_2), and 5.95 (1 H, s, CH) (Found: M^+, 321.9983. $C_{10}H_{15}BrN_2O_3S$ requires *M*, 321.9985).

1-*Ethoxymethyl*-2-*methylthioimidazole*-5-*carbaldehyde Ethylene Acetal* (**31**).—1.12M-Butyl-lithium in hexane (1.1 ml, 1.24 mmol) was added dropwise to a stirred solution of 4-bromo-1-ethoxymethyl-2-methylthioimidazole-5-carbaldehyde ethylene acetal (**29**) (0.37 g, 1.15 mmol) in ether (30 ml) at −70 °C. After 1 h, this solution was added dropwise by syringe to a solution of di(methoxycarbonylmethyl) disulphide [$(MeO_2CCH_2)_2S_2$] (0.36 g, 1.71 mmol) in ether (10 ml) at −40 °C. The resulting mixture was allowed to warm gradually to ambient temperature after which 50% aqueous ammonium chloride (10 ml) was added, and work-up in the usual way gave a yellow oil which was chromatographed on a silica gel column under medium pressure. Ethyl acetate–light petroleum eluted unchanged disulphide (0.25 g) and the *product* (**31**) (0.2 g, 72%) as an oil; δ_H($CDCl_3$) 1.15 (3 H, t, Me), 2.58 (3 H, s, SMe), 3.48 (2 H, q, OCH_2), 4.01 (4 H, m, $-OCH_2CH_2O-$), 5.35 (2 H, s, NCH_2), 6.01 (1 H, s, CH), and 7.11 (1 H, s, 4-H); δ_C($CDCl_3$) 146.37 (s, C-2), 129.93 (s, C-5), 129.13 (d, C-4), 97.30 (d, CH), 73.53 (t, NCH_2), 64.71 (m, OCH_2CH_2O), 63.95 (t, OCH_2), 15.71 (q, SMe), and 14.95 p.p.m. (q, Me) (Found: M^+, 244.0880. $C_{10}H_{16}N_2O_3S$ requires *M*, 244.0881).

Attempted Synthesis of Ethyl 1H- *or* 3H-*Thieno*[2,3-d]*imidazole*-5-*carboxylate from* 4-*Bromo*-5-*chloro*-1-*tritylimidazole.*[2]—(a) 5-Chloro-1-tritylimidazole-4-carbaldehyde (46%) was prepared as a pale-yellow oil from 4-bromo-5-chloro-1-tritylimidazole in a manner similar to that described previously[2] for the synthesis of 4-bromo-1-methoxymethyl-2-phenylthioimidazole-5-carbaldehyde. It had $\nu_{max.}$ 1 720 cm^{-1} (CO); δ($CDCl_3$) 6.90—7.60 (16 H, m, ArH) and 9.28 (1 H, s, CHO) (Found: M^+. 372. $C_{23}H_{17}ClN_2O$ requires *M*, 372).

(b) Reaction of the aldehyde prepared as described in (a) with ethyl thioglycollate in a manner similar to that described before in this paper for the synthesis of thienoimidazole (**19**) gave ethyl 3-trityl-3*H*-thieno[2,3-*d*]imidazole-5-carboxylate (**24**) (60%) (ethyl acetate–light petroleum eluted the product from alumina) as a viscous pale-yellow oil; $\nu_{max.}$ 1 720 cm^{-1} (CO); δ($CDCl_3$) 1.39 (3 H, t, Me), 3.37 (2 H, q, CH_2), and 7.65 (17 H, m, ArH).

(c) A solution of thienoimidazole (**24**) (1.20 g, 2.74 mmol) in methanol (25 ml) containing 5% acetic acid (6 ml) was heated under reflux for 4 h. The solvent was distilled off under reduced pressure and water (25 ml) was added to the residue. The

precipitate (0.51 g, 71%) was filtered off and identified as triphenylmethanol. Sodium carbonate was added to the aqueous layer until evolution of carbon dioxide ceased. Extraction with various organic solvents yielded no organic material.

5-(1,2-*Dimethylimidazol*-5-*ylmethylene*)-2-*thioxo*-4-*thiazolidone* (**38**).—1,2-Dimethylimidazole-5-carbaldehyde (1.0 g, 8.0 mmol) was added to a stirred mixture of rhodanine (1.16 g, 8.7 mmol), benzene (60 ml), sodium acetate (4.0 g), and acetic acid (15 ml) heated under reflux with azeotropic removal of water for 2 h. The remaining benzene (20 ml) was distilled off and the mixture heated under reflux for a further 2 h. Water (20 ml) was added to the cooled mixture and the precipitate was filtered off and washed with water. Concentration of the filtrate and addition of water (20 ml) to the residue gave a second crop of the *product* (**38**) (total yield 1.77 g, 93%), m.p. 245 °C (from acetic acid); $\nu_{max.}$ 1 010 (CS), 1 720 (CO), and 3 300—3 500 cm^{-1} (NH); $\delta(CF_3CO_2D)$ 2.83 (3 H, s, 2-Me), 4.00 (3 H, s, NMe), 7.60 (1 H, s, CH), and 7.68 (1 H, s, 4-H) (Found: C, 45.2; H, 3.85; N, 17.7%; M^+, 239. $C_9H_9N_3OS_2$ requires C, 45.2; H, 3.8; N, 17.6%; *M*, 239).

3-(1,2-*Dimethylimidazol*-5-*yl*)-2-*mercaptoacrylic Acid* (**39**).—A stirred solution of the rhodanine derivative (**38**) (0.67 g, 2.8 mmol) in 15% aqueous sodium hydroxide (50 ml) was heated at 75 °C for 30 min after which it was cooled and made acidic by addition of 4M-hydrochloric acid. The precipitate was filtered off, washed with water, and dried in a vacuum desiccator to give the *product* (**39**) (0.5 g, 91%), m.p. 175 °C; $\nu_{max.}$ 1 660 (CO), 2 050 (SH), and 2 700—3 200 cm^{-1} (OH); $\delta(CF_3CO_2D)$ 2.80 (3 H, s, 2-Me), 3.90 (3 H, s, NMe), 7.75 (1 H, s, CH), and 7.90 (1 H, s, 4-H) (Found: M^+, 198. $C_8H_{10}N_2O_2S$ requires *M*, 198). This compound could be recrystallised only with great difficulty (*e.g.* from light petroleum–methanol) and was used without further purification in the cyclisation step (see Discussion).

Reaction of 1,2-*Dimethylimidazole with* 2,4-*Dinitrobenzenesulphenyl Chloride*.—A stirred mixture of 1,2-dimethylimidazole (0.77 g, 8.0 mmol) and 2,4-dinitrobenzenesulphenyl chloride [48] (1.88 g, 8.0 mmol) in 1,2-dichloroethane (40 ml) was heated almost to reflux temperature when anhydrous tin(IV) chloride (2.6 g, 10.0 mmol) was added dropwise. The mixture was heated under reflux for 2 h and then cooled; ethanol (25 ml) was then added followed by 2M-hydrochloric acid (40 ml). The precipitate (0.9 g, 29%) of bis(2,4-dinitrophenyl) disulphide [identical, by t.l.c. and i.r. and ^1H n.m.r. spectroscopy, with an authentic sample prepared in 41% yield using a procedure identical to that used [49] to prepare bis(*o*-nitrophenyl) disulphide; **CAUTION**: explodes when heated [50]!] was filtered off and distillation of the solvent from the filtrate gave a viscous brown oil which, on trituration with ether, gave a compound which we believe to be 1,2-dimethylimidazolium tin(IV) hexachloride (2.1 g, 50%), m.p. 280—287 °C (crude), m.p. 277—283 °C (after sublimation); $\nu_{max.}$ 3 300 cm^{-1} (NH); $\delta_H[(CD_3)_2SO]$ 2.58 (3 H, s, 2-Me), 3.50 (NH, br s, and H_2O from solvent overlapping), 3.74 (3 H, s, NMe), 7.48 (1 H, d, 5-H), and 7.57 (1 H, d, 4-H); $\delta_C[(CD_3)_2SO]$ 144.21 (s, C-2), 122.84 (d, C-4), 117.23 (d, C-5), 34.09 (q, NMe), and 10.31 p.p.m. (q, 2-Me) (Found: C, 23.7; H, 3.6; N, 10.6. $C_{10}H_{18}Cl_6N_4Sn$ requires C, 22.85; H, 3.45; N, 10.7%) (it was difficult to obtain an analytically pure sample by sublimation).

N,N′-*Diacetyl*-2-*amino*-5-*phenylthiophene*-3-*carboxamide* (**47**).—A stirred mixture of 2-amino-5-phenylthiophene-3-carboxamide (1.0 g, 4.6 mmol) and acetic anhydride (20 ml) containing 2 drops of concentrated sulphuric acid heated at 60 °C for 30 min gave the *product* (**47**) (1.39 g, 100%) as a precipitate which was filtered off from the cooled mixture; it had m.p. 270 °C (from aqueous DMF); $\nu_{max.}$ 1 650 and 1 690 (CO) and 3 200—3 300 cm^{-1} (NH); $\delta[(CD_3)_2SO]$ 2.27 (3 H, s, $NHCOCH_3$), 2.40 (3 H, s, $CONHCOCH_3$), 7.30—7.70 (5 H, m, ArH), 8.17 (1 H, d, 4-H), 10.61 (1 H, s, exchangeable, NH), and 11.42 (1 H, s, exchangeable, NH) (Found: C, 59.6; H, 4.7; N, 9.3%; M^+, 302. $C_{15}H_{14}N_2O_3S$ requires C, 59.6; H, 4.7; N, 9.3%; *M*, 302).

2-Acetamido-3,5-dinitrothiophene (**43**) (92%), m.p. 177—179 °C (crude) (lit.,[51] m.p. 180 °C), was prepared similarly and used without further purification.

2-*Acetamido*-5-*phenylthiophene*-3-*carboxamide* (**45**).—A stirred mixture of 2-amino-5-phenylthiophene-3-carboxamide (**44**) (1.0 g, 4.6 mmol), acetic anhydride (18 ml), and acetic acid (2 ml) was heated on a steam-bath for 1 h and then cooled; the precipitate was then filtered off and washed with ice-cold water to give the *product* (**45**) (1.2 g, 100%), m.p. 232 °C (from chloroform–carbon tetrachloride); $\nu_{max.}$ 1 650 (CO) and 3 050—3 200, 3 325, and 3 425 cm^{-1} (NH and NH_2); $\delta[CDCl_3$–$(CD_3)_2SO]$ 2.21 (3 H, s, Me), 7.20—7.65 (7 H, m, ArH and NH_2), 7.76 (1 H, s, 4-H), and 12.13 (1 H, s, exchangeable, NH) (Found: C, 60.0; H, 4.7; N, 10.8%; M^+, 260. $C_{13}H_{12}N_2O_2S$ requires C, 60.0; H, 4.65; N, 10.8%; *M*, 260).

Reaction of 2-*Amino*-5-*phenylthiophene*-3-*carboxamide* (**44**) *with Benzoyl Chloride*.—Benzoyl chloride (1.0 ml) was added to a stirred solution of 2-amino-5-phenylthiophene-3-carboxamide (**44**) (1.0 g, 4.6 mmol) in anhydrous benzene (20 ml) and pyridine (8 ml) and the mixture was heated under reflux for 30 min and then poured into water (200 ml). The organic layer was separated and the aqueous layer was extracted with benzene. Hexane was added to the combined dried organic layer and extracts, to give 2-*benzamido*-5-*phenylthiophene*-3-*carboxamide* (**46**) (1.28 g, 86.5%) as a pale yellow precipitate, m.p. 258—259 °C (filtered off, washed with hexane, and recrystallised from acetone–carbon tetrachloride); $\nu_{max.}$ 1 640 and 1 660 (CO), and 3 180, 3 350, and 3 450 cm^{-1} (NH_2 and NH); $\delta[CDCl_3$–$(CD_3)_2SO]$ 2.53 (2 H, s, exchangeable, NH_2), 7.30—8.10 (11 H, m, 2 × Ph and 4-H), and 13.15 (1 H, s, exchangeable, NH) (Found: C, 67.1; H, 4.3; N, 8.6%; M^+, 322. $C_{18}H_{14}N_2O_2S$ requires C, 67.1; H, 4.4; N, 8.7%; *M*, 322). The mother-liquor was concentrated to give an orange syrup which was dissolved in the minimum amount of benzene and then hexane was added; the resulting precipitate was identified as 2-*benzamido*-5-*phenylthiophene*-3-*carbonitrile* (**48**) (0.1 g, 7%), m.p. 188—189 °C (from carbon tetrachloride); $\nu_{max.}$ 1 680 (CO), 2 240 (CN), and 3 450 cm^{-1} (NH); $\delta[(CD_3)_2SO]$ 7.35—8.20 (11 H, m, 2 × Ph and 4-H) and 10.78 (1 H, br s, exchangeable, NH) (Found: 71.0; H, 4.0; N, 9.2%; M^+, 304. $C_{18}H_{12}N_2OS$ requires C, 71.0; H, 4.0; N, 9.2%; *M*, 304).

Acknowledgements

We thank I.C.I. Organics Division, Blackley, Manchester for gifts of 2-amino-3,5-dinitrothiophene and 2-amino-5-phenylthiophene-3-carboxamide and the Government of Brunei and the S.E.R.C. for research studentships (to B. L. L. and N. K., respectively).

References

1 Part 6, B. Iddon and N. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1987, preceding paper.
2 For preliminary communications see ref. 2 in Part 5, B. Iddon and N. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1445.
3 V. M. Colburn, B. Iddon, H. Suschitzky, and P. T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1337; *J. Chem. Soc., Chem. Commun.*, 1978, 453; V. M. Colburn, B. Iddon, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2436.

4 R. V. Khozeeva, I. Ya. Kvitko, E. L. Baranov, and A. V. El'tsov, *J. Org. Chem. U.S.S.R.* (*Engl. Transl.*), 1977, **13**, 215.
5 J. Becher, P. H. Olesen, and K. Brøndum, personal communication from Odense University, Denmark.
6 D. R. Hoff and L. H. Peterson, S. Afr. Pat. 68 00,904/1969 (*Chem. Abstr.*, 1970, **72**, 100702).
7 D. Binder, F. Hillebrand, and C. R. Noe, *J. Chem. Res.*, 1979, (*S*), 96; (*M*), 1151.
8 D. Binder, C. R. Noe, and F. Hillebrand, *Arch. Pharm.* (*Weinheim, Ger.*), 1979, **312**, 845.
9 D. Binder, C. R. Noe, H. Kollmann, and B. Rosenwirth, *Arch. Pharm.* (*Weinheim, Ger.*), 1985, **318**, 40.
10 P. N. Preston and S. K. Good, *J. Chem. Soc., Perkin Trans. 1*, 1976, 80.
11 V. M. Colburn, Ph.D. Thesis, University of Salford (1977).
12 R. V. Khozeeva, I. Ya Kvitko, A. V. El'tsov, and E. L. Baranov, U.S.S.R. P. 525,676/1976 (*Chem. Abstr.*, 1977, **86**, 89818).
13 B. B. Lim and R. S. Hosmane, *J. Org. Chem.*, 1985, **50**, 5111 and references cited therein; T. Winkler, W. Lutz, and H. Kristinsson, *Justus Liebigs Ann. Chem.*, 1985, 433.
14 M. S. El Shanta, R. M. Scrowston, and M. V. Twigg, *J. Chem. Soc. C*, 1967, 2364.
15 P. I. Abramenko, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1970, 1373.
16 H. Berner and H. Reinshagen, *Monatsh. Chem.*, 1976, **107**, 299; see also D. H. Klaubert and S. C. Bell, U.S. P. US 4,447,611/1984 (*Chem. Abstr.*, 1984, **101**, 151845).
17 Ph. Rossy, F. G. M. Vogel, W. Hoffmann, J. Praust, and A. Nurrenbach, *Tetrahedron Lett.*, 1981, **22**, 3493; R. Mozingo, S. A. Harris, D. E. Wolf, C. E. Hoffhine, N. R. Easton, and K. Folkers, *J. Am. Chem. Soc.*, 1945, **67**, 2092; Ph. Rossy and F. G. M. Vogel, Ger. Offen. DE 3,018,134/1981 and DE 3,018,109/1981 (*Chem. Abstr.*, 1982, **96**, 68721 and 68722).
18 F. Garcia and C. Galvez, *Synthesis*, 1985, 143; see also C.-K. Sha and C. P. Tsou, *J. Chem. Soc., Chem. Commun.*, 1986, 310.
19 B. Iddon and M. Nicholas, unpublished results.
20 J. R. Beck, *Tetrahedron*, 1978, **34**, 2057; *J. Org. Chem.*, 1972, **37**, 3224.
21 N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, 1965, **2**, 291.
22 P. Goldman and J. D. Wuest, *J. Am. Chem. Soc.*, 1981, **103**, 6224; P. Goldman, S. M. Ramos, and J. D. Wuest, *J. Org. Chem.*, 1984, **49**, 932; see also V. S. Mokrushin, N. A. Belyaev, M. Yu, Kolobov, and A. N. Fedotov, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1983, **19**, 650.
23 Part 2, B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1983, 279; *J. Chem. Soc., Chem. Commun.*, 1981, 1095.
24 B. Iddon and R. M. Scrowston, *Adv. Heterocycl. Chem.*, 1970, **11**, 177; B. Iddon, in 'New Trends in Heterocyclic Chemistry,' (R. B. Mitra, N. R. Ayyangar, V. N. Gogte, R. M. Acheson, and N. Cromwell, eds.), Elsevier, Amsterdam, 1979, ch. 12, 250; B. Iddon, *Methodicum Chimicum*, (F. Korte, ed.), Band 4 (J. Falbe, ed.), Section 6.4.2, 1980, 282.
25 M. J. Bevis, E. J. Forbes, N. N. Naik, and B. C. Uff, *Tetrahedron*, 1971, **27**, 1253.
26 Part 1, B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1983, 271.
27 T. R. Bosin and E. Campaigne, *Int. J. Sulfur Chem.* (*A*), 1972, **2**, 261.
28 K. Schofield, M. R. Grimmett, and B. R. T. Keene, in 'Heteroaromatic Nitrogen Compounds, The Azoles,' Cambridge University Press, Cambridge, 1976, ch. 4, p. 133; M. R. Grimmett, *Adv. Heterocycl. Chem.*, 1980, **27**, 241 and 1970, **12**, 103.
29 R. L. Ellis, U.S.P. 3,932,444/1976 (*Chem. Abstr.*, 1976, **84**, 136515).
30 L. L. Bennett and H. T. Baker, *J. Am. Chem. Soc.*, 1957, **79**, 2188.
31 R. D. Schuetz and W. L. Fredericks, *J. Org. Chem.*, 1962, **27**, 1301.
32 B. A. Tertov, V. V. Burykin, and A. V. Koblik, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1972, **8**, 1403.
33 A. Lawson, *J. Chem. Soc.*, 1956, 307.
34 B. T. Storey, W. W. Sullivan, and C. L. Moyer, *J. Org. Chem.*, 1964, **29**, 3118.
35 *e.g.* A. Maggiolo, *J. Am. Chem. Soc.*, 1951, **73**, 5815; C. E. Hall and A. Taurins, *Can. J. Chem.*, 1966, **44**, 2465 and 2473; A Taurins and R. K.-C. Hsia, *ibid.*, 1971, **49**, 4054; A. Maggiolo and G. H. Hitchings, *J. Am. Chem. Soc.*, 1951, **73**, 4226; J. A. Baker and P. V. Chatfield, *J. Chem. Soc. C*, 1969, 603; V. Bellavita, *Ann. Chim. Appl.*, 1948, **38**, 449 (*Chem. Abstr.*, 1950, **44**, 154); E. Söderback, *Acta Chem. Scand.*, 1954, **8**, 1851; R. K. Olsen and H. R. Snyder, *J. Org. Chem.*, 1965, **30**, 184.
36 S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv. Kemi*, 1962, **18**, 151.
37 D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, 1957, **22**, 1500; *J. Am. Chem. Soc.*, 1957, **79**, 3610.
38 M. L. Bullpitt and W. Kitching, *J. Organomet. Chem.*, 1972, **34**, 321.
39 E. Magnien and R. Baltzly, *J. Org. Chem.*, 1958, **23**, 2029.
40 R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, 1940, **62**, 161.
41 E. Campaigne and P. A. Monroe, *J. Am. Chem. Soc.*, 1954, **76**, 2447.
42 Part 4, B. Iddon and N. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1437.
43 S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, V. V. Sevast'yanova, and L. V. Epishina, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1970, **6**, 457.
44 Part 3: B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1983, 735.
45 B. L. Lim, Ph.D. Thesis, University of Salford (1981).
46 N. Khan, Ph.D. Thesis, University of Salford (1985).
47 J. S. G. Cox, C. Fitzmaurice, A. R. Katritzky, and G. J. T. Tiddy, *J. Chem. Soc. B*, 1967, 1251; C. Fitzmaurice, B.P. 1,026,631/1966 (*Chem. Abstr.*, 1966, **64**, 9630).
48 N. Kharasch, H. L. Wehrmeister, and H. Tigerman, *J. Am. Chem. Soc.*, 1947, **69**, 1612.
49 M. T. Bogert and A. Stull, *Org. Synth.*, Coll. Vol. I, 1941, 2nd edn., 220.
50 H. W. Talen, *Recl. Trav. Chim. Pays-Bas*, 1928, **47**, 782.
51 H. M. Priestley and C. D. Hurd, *J. Am. Chem. Soc.*, 1947, **69**, 1173.

Received 13*th June* 1986; *Paper* 6/1193