Synthesis of Thieno-[2,3-*b*]-, -[3,2-*b*]- and -[3,4-*b*]-thiophenes and Thieno-[3',2':4,5]-, -[2',3':4,5]- and -[3',4':4,5]-thieno[3,2-*d*]pyrimidin-7(6*H*)-ones Starting from Thiophene[1]

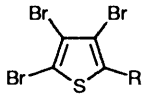
David W. Hawkins,[a] Brian Iddon,*[,b] Darren S. Longthorne[b] and Peter J. Rosyk[b]
[a] *Rhône-Poulenc Agriculture Ltd., Fyfield Road, Ongar, Essex CM5 0HW, UK*
[b] *The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, UK*

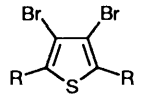
3-Bromo-, 3,5-dibromo- and 3,4,5-tribromo-2-thienyllithium have been prepared by bromine ⟶ lithium exchange and converted into a number of thiophene derivatives, including the corresponding 2-carbaldehydes. The aldehydes have been converted into the corresponding thiophene-2-carbonitriles. Metallation of 2,5-dibromo- or 2,4,5-tribromo-thiophene with LDA occurred at a vacant 3-position but the resulting 3-lithiated thiophenes rearranged (mechanism discussed) to 3,5-dibromo- and 3,4,5-tribromo-2-thienyllithium, which were quenched with various electrophiles. Attempts to dilithiate 2,5-dibromothiophene with LDA were unsuccessful. 3,4-Dibromo-2,5-dilithiothiophene was prepared from 2,3,4,5-tetrabromothiophene but it failed to yield the 2,5-dicarbaldehyde with *N,N*-dimethylformamide. The title thienothiophenes were prepared by reaction of a 3-bromothiophene-2-carbaldehyde, a 2-bromothiophene-3-carbaldehyde (prepared by bromination of a thiophene-3-carbaldehyde) or a 4-bromothiophene-3-carbaldehyde, or a corresponding nitrile, with ethyl 2-sulfanylacetate or 2-sulfanylacetamide. Thienothiophenes carrying an *o*-aminocarboxamide substitution pattern gave the title thienothieno[3,2-*d*]pyrimidinones with triethyl orthoformate.

In continuation of our studies[2] on the synthesis of polysubstituted homo- and hetero-aromatic compounds *via* metallation or bromine ⟶ lithium exchange strategies, involving the poly- or per-bromo derivatives of the parent heterocycles, we now report an extension of this work to the synthesis of all the title compounds starting with commercially available thiophene. Hitherto most thienothiophenes have been available only by inconvenient or multistage syntheses,[3-6] *e.g.* 5-ethylthieno[2,3-*b*]thiophene can be prepared from 2-ethylthiophene in five steps[7] (however, see later).

Elemental bromination of thiophene gives 2-bromothiophene, a mixture of 2,5-(major product), 2,3- and 2,4-dibromo-, and 2,3,5-tribromo-thiophene, or a readily separable mixture of 2,3,5-tribromo- and 2,3,4,5-tetrabromo-thiophene, depending on the reaction conditions.[8] These polybromothiophenes, which are interconvertible, have been employed widely in the synthesis of thiophene derivatives, usually through the intermediacy of an organo-magnesium or -lithium reagent.[8] For example, with 1 or 2 mol equiv. of butyllithium the tetrabromo derivative yields 3,4,5-tribromo-2-thienyllithium **1**[9,10] or 3,4-dibromo-2,5-dilithiothiophene **10**, respectively.[9] With an excess of this reagent it apparently gives 2,3,4,5-tetralithiothiophene.[11]

Butyllithium in hexane was added to a solution of 2,3,4,5-tetrabromothiophene in tetrahydrofuran (THF) at −70 °C (all temperatures recorded here were measured internally) then, usually after 15 min, an electrophilic quenching reagent was added, to give the corresponding 2-substituted 3,4,5-tribromothiophene **2**–**7** (Table 1). 2,3,4-Tribromothiophene **2**[9,10] and the 2-carboxylic acid **4**[12] have been prepared similarly previously. Compound **5** was characterised as the ether **8**. When reactions were quenched with dimethyl or diphenyl disulfide, it was extremely difficult to isolate the corresponding monomethyl- (or -phenyl-) sulfanyl derivative, *e.g* **6**; the major product isolated in each case was 3,4-dibromo-2,5-bis(methyl- or -phenyl-sulfanyl)thiophene **11** (63%)[13,14] or **12** (58%), respectively. A moderate yield (44%) (Table 1) of the methylsulfanyl derivative **6** could be isolated only if the reaction





1 R = Li
2 R = H
3 R = CHO
4 R = CO_2H
5 R = $C(OH)Ph_2$
6 R = SMe
7 R = $SiMe_3$
8 R = $C(OEt)Ph_2$
9 R = CN

10 R = Li
11 R = SMe
12 R = SPh
13 R = CHO
14 R = CO_2H

Table 1 2-Substituted 3,4,5-tribromothiophenes

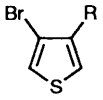
Compd.	Reagent	Yields (%)[a]
2	H_2O	70 (> 90)
3	DMF	90 (60)
4	CO_2	70 (95–100)
5	Ph_2CO	85 (80)
6	Me_2S_2[b]	44 (47)
7	Me_3SiCl	66 (66)

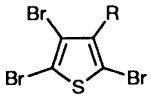
[a] The yields in parentheses are those obtained starting with 2,3,5-tribromothiophene. [b] Water in THF was added 2 min after addition of Me_2S_2 (at −70 °C)

mixture was treated with wet THF 2 min after addition of the dimethyl disulfide. We obtained a similar result[2] when 2,4-dichloro- or 2,4-dibromo-thiazol-5-yllithium was quenched

with dimethyl disulfide. A possible explanation of the present result is that the initially generated 3,4,5-tribromo-2-methyl- (or -phenyl-) sulfanylthiophene reacts further with the liberated methane- (or benzene-)thiolate anion (MeS^- or PhS^-) prior to work-up. Alternatively, the initially generated product may react further with unquenched 3,4,5-tribromo-2-thienyllithium, to give 3,4-dibromo-5-methyl- (or phenyl-)sulfanyl-2-thienyllithium which is quenched with the dimethyl or diphenyl disulfide present, to yield 3,4-dibromo-2,5-bis(methyl- or -phenyl-sulfanyl)thiophene, **11** or **12**, respectively. Chromatographic separation of the methylsulfanyl **6** and bis(methylsulfanyl) derivative **11** was extremely tedious, requiring large amounts of silica (typically 80 g for each gram of mixture). It was not possible to obtain a pure sample of 3,4,5-tribromo-2-phenylsulfanylthiophene by chromatography on silica owing to its contamination with starting material and the bis(phenylsulfanyl) compound **12** on its elution.

3,4-Dibromothiophene, prepared by debromination of 2,3,4,5-tetrabromothiophene,[9,11,15] was converted into 4-bromo-3-thienyllithium **15**[9] which was quenched at −78 °C with *N*,*N*-



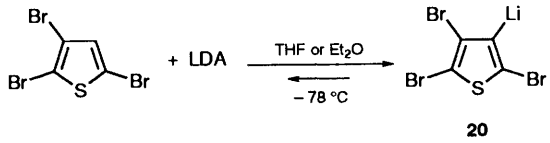


15	R = Li	**20**	R = Li
16	R = CHO	**21**	R = CHO
17	R = CO_2H	**22**	R = CO_2H
18	R = $C(OH)Ph_2$	**23**	R = CN
19	R = CN		

dimethylformamide (DMF), carbon dioxide, or benzophenone, to give compounds **16** (75%),[16] **17** (70%)[9] and **18** (80%), respectively. The aldehyde **16** was brominated with elemental bromine in dichloromethane in the presence of aluminium chloride, *cf.*[17] to give 2,4,5-tribromothiophene-3-carbaldehyde **21** (60%).[18] 2,4,5-Tribromothiophene-3-carboxylic acid **22** (76%) was prepared similarly from 4-bromothiophene-3-carboxylic acid **17**.*cf.*[9]

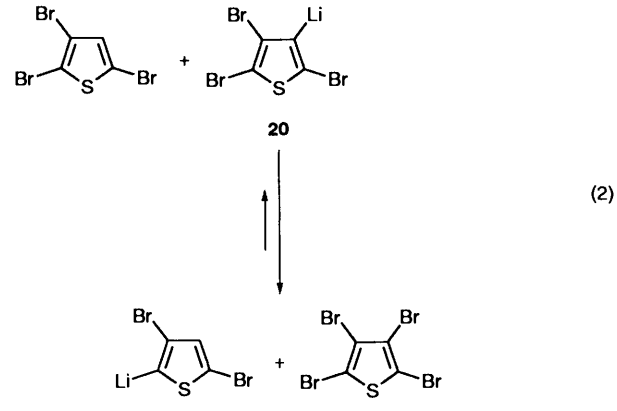
An attempt to prepare 2,4,5-tribromothiophene-3-carbaldehyde **21** *via* deprotonation of 2,3,5-tribromothiophene with lithium diisopropylamide (LDA) in diethyl ether or THF followed, after 15 min, by quenching the resulting mixture at −78 to −85 °C with DMF gave 3,4,5-tribromothiophene-2-carbaldehyde **3** (60%) (see Table 1) instead. None of the isomeric 3-carbaldehyde **21** could be detected in this product. Similar reaction mixtures, quenched 15 min after addition of the LDA with carbon dioxide, benzophenone, dimethyl disulfide (wet THF added 2 min after addition of Me_2S_2; see before) or trimethylsilyl chloride, gave compounds **4**–**7**, respectively (see Table 1). Quenching with dimethyl or diphenyl disulfide gave compound **11** (59%) or **12** (53%) if the reaction mixtures were stirred for longer than 2 min prior to addition of wet THF and work-up. Mass spectroscopic analysis of the crude 3,4,5-tribromo-2-trimethylsilylthiophene **7**, prepared in this way, indicated the presence of a small amount (2%) of 3,4-dibromo-2,5-bis(trimethylsilyl)thiophene, suggesting the generation of a trace of 3,4-dibromo-2,5-dilithiothiophene **10**. In an attempt to trap 2,4,5-tribromo-3-thienyllithium **20** before it rearranged we generated it as described before and added it immediately to a slurry of solid carbon dioxide in anhydrous diethyl ether. This gave the 2-carboxylic acid **4** containing a trace (*ca.* 2%) of 3,4-dibromothiophene-2,5-dicarboxylic acid **14**. A similar mixture quenched 2 min after addition of LDA with water (at −78 °C) gave, after work-up, a mixture shown by HPLC analysis to contain *ca.* 2% of 3,4-dibromothiophene in the 2,3,4-tribromothiophene obtained as the major product (> 90%).

To explain rearrangement of 2,4,5-tribromo-3-thienyllithium **20** [generated as shown in eqn. (1)] to its 2-isomer **1** we propose



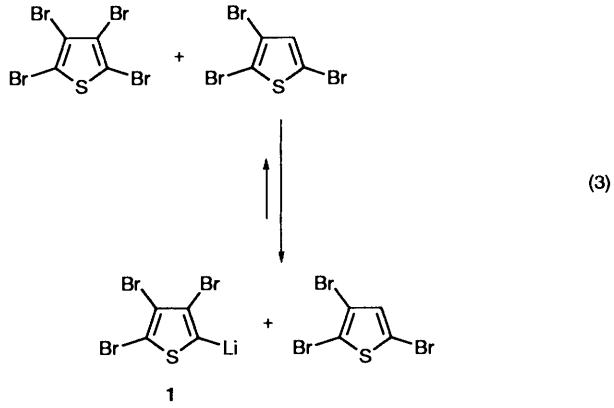
(1)

20



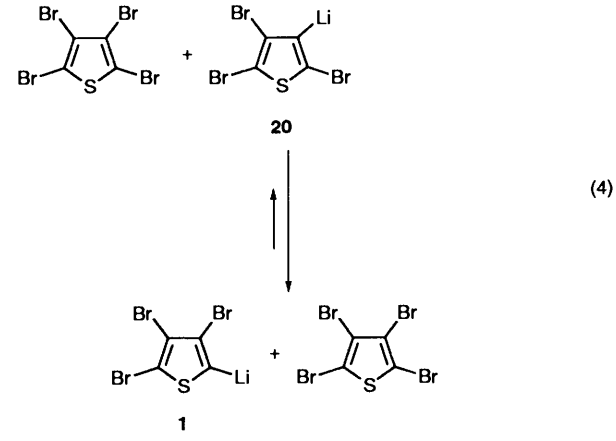
(2)

the series of transmetallation reactions [eqns. (2)–(4)]. A key step is the generation of 2,3,4,5-tetrabromothiophene [eqn. (2)]



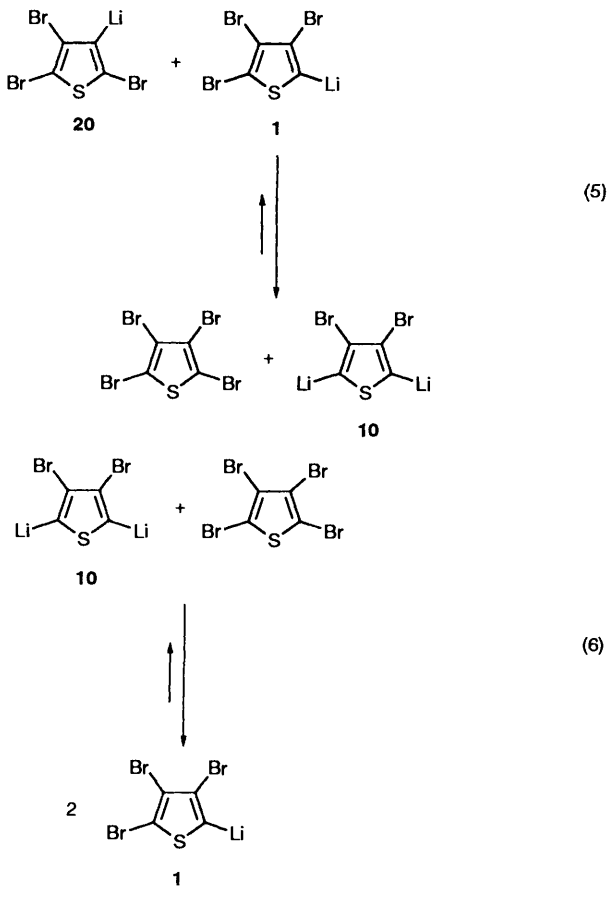
(3)

1



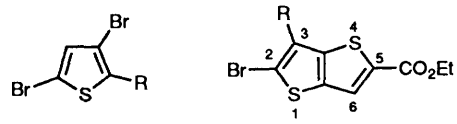
(4)

1



via a reaction between the initially generated lithium compound **20** and starting material. The generation of the tetrabromo compound 'drives' the rearrangement process, as shown in eqns. (3) and (4). α-Lithiated thiophenes are well-known to be more stable than their β-isomers. Several bromo-substituted 3-thienyllithium compounds have been synthesised previously[9,19-29] and a number of groups have reported their rearrangement.[9,19,20,22-24,26-29] The most extensive study of these rearrangements has been carried out recently by Fröhlich's group.[27-29] Whereas previously they were believed to be 'catalysed' by the base (*i.e.* examples of 'base-catalysed halogen dance reactions'[31]), a key fact that has emerged from Fröhlich's work is that they are 'catalysed' by a bromo- (or polybromo)-thiophene generated early in the process, a finding in keeping with the mechanism proposed in eqns. (1)–(4). Eqn. (5) accounts for the formation of 3,4-dibromo-2,5-dilithiothiophene **10**, whilst eqn. (6) explains why its concentration is kept low.*

Not surprisingly, when 2,5-dibromothiophene was treated with 1 equiv. of LDA in diethyl ether or THF, the initially generated 2,5-dibromo-3-thienyllithium rearranged to 3,5-dibromo-2-thienyllithium **24**,[24-26,29] presumably by a mechanism similar to the one discussed above. Addition of DMF, carbon dioxide, or benzophenone to the resulting mixture gave compound **25** (80%), **26** (90%), or **27** (86%), respectively. We obtained the same compounds in similar yields when 2,3,5-tribromothiophene in THF was treated with butyllithium at −70 °C and the resulting mixture quenched with the appropriate electrophile.[32] When 2 mol equiv. of LDA were added to



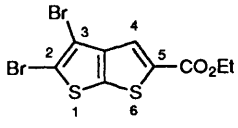
24 R = Li
25 R = CHO
26 R = CO_2H
27 R = $C(OH)Ph_2$

28 R = Br
29 R = H

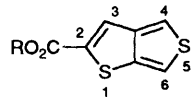
2,5-dibromothiophene in diethyl ether or THF at −78 °C and the mixture quenched with carbon dioxide only 3,5-dibromothiophene-2-carboxylic acid **26** (72%) was isolated.

Previously we have synthesised thieno[2,3-*d*]imidazoles[33] and thieno[2,3-*d*]thiazoles[34] by reaction of 4-bromoimidazole-5-carbaldehydes or 4-chlorothiazole-5-carbaldehydes with ethyl 2-sulfanylacetate or 2-sulfanylacetamide in the presence of a base. The title thienothiophenes have been prepared similarly from the bromothiophenecarbaldehydes whose preparations were described in the preceding paragraphs.

Thus, when 3,4,5-tribromothiophene-2-carbaldehyde **3** was treated with ethyl 2-sulfanylacetate either in DMF at ambient temperature in the presence of potassium carbonate or in refluxing anhydrous ethanol in the presence of sodium ethoxide, ethyl 2,3-dibromothieno[3,2-*b*]thiophene-5-carboxylate **28** was obtained in 61 and 72% yield, respectively. If the ethanol is not anhydrous hydrolysis of the ester **28** occurs *in situ*, to yield the corresponding carboxylic acid. Thienothiophene **28** (66%) was also prepared by treatment of 3,4,5-tribromothiophene-2-carbaldehyde **3** with ethyl 2-sulfanylacetate in liquid ammonia, a reaction which probably proceeds *via* a $S_{RN}1$ displacement of bromine.[35] Reaction of 3,5-dibromothiophene-2-carbaldehyde **25** with ethyl 2-sulfanylacetate (DMF/K_2CO_3) surprisingly gave thienothiophene **29** in only 8% yield. Similarly, 2,4,5-tribromothiophene-3-carbaldehyde **21** ($HSCH_2CO_2Et/DMF/K_2CO_3$) gave the isomeric thienothiophene system **30** (58%).



30



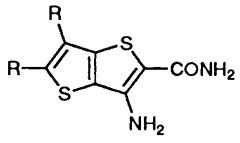
31 R = Me
32 R = Et

4-Bromothiophene-3-carbaldehyde **16**[16] failed to react under these conditions. Previously[36] this aldehyde has been converted into methyl thieno[3,2-*b*]thiophene-2-carboxylate **31** through protection of its aldehyde group, exchange of the bromine atom for lithium with butyllithium, addition of elemental sulfur to the resulting 3-thienyllithium derivative followed by addition of methyl chloroacetate, deprotection of the resulting aldehyde and cyclisation of the product with sodium methoxide in methanol. A shorter route to this thienothiophene system was obviously desirable. Based on reports that β-halogenothiophenes react with oxygen and sulfur nucleophiles in the presence of copper compounds[37-42] we treated 4-bromothiophene-3-carbaldehyde **16** with ethyl 2-sulfanylacetate in ethanol in the presence of potassium iodide and copper(I) oxide, which gave a low yield (21%) of ethyl thieno[3,4-*b*]thiophene-2-carboxylate **32**. With 2-sulfanylacetamide, the bromoaldehyde **16** similarly gave thieno[3,4-*b*]-thiophene-2-carboxamide (*cf.* **31** or **32**; CO_2R = $CONH_2$) also in low yield (22%).

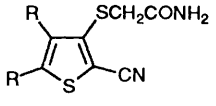
* Dr. Johannes Frölich, of The Technical University in Vienna is conducting a detailed investigation of these reactions, which we carried out originally in the mid-1980s. Preliminary results have shown that the products obtained are extremely dependent on reaction conditions and the ratio of LDA to substrate.

Since completion of our work Brandsma and Verkruijsse[43] have synthesised the parent heterocycle, thieno[3,2-*b*]thiophene, in > 50% yield starting with 3,4-dibromothiophene by a sequence of Pd^{II}–Cu^{I}-catalysed cross-coupling with trimethylsilylacetylene, bromine ⟶ lithium exchange, thiolation of the resulting 3-thienyllithium derivative with elemental sulfur and ring-closure in aqueous medium. In 1983, the same group[5,44] reported a convenient synthesis of thieno[2,3-*b*]thiophene which involves a double ring-closure of 1-trimethylsilylpenta-1,3-diyne with carbon disulfide under basic conditions.

Each of the bromothiophenecarbaldehydes **3**, **16** and **21** was converted *via* dehydration of its oxime into the corresponding thiophene-2(or 3)-carbonitrile **9** (77%), **19** (66%) and **23** (57%), respectively. 3-Bromothiophene-2-carbonitrile (73%) was prepared similarly by a literature procedure.[45] Surprisingly, when 3,4,5-tribromothiophene-2-carbonitrile **9** was treated with 2-sulfanylacetamide in DMF at ambient temperature in the presence of potassium carbonate, it failed to yield any isolable thienothiophene **33**; only a small amount (< 20%) of the



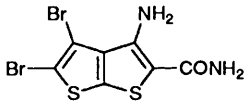
33 R = Br
34 R = H



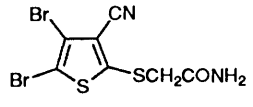
35 R = Br
36 R = H

intermediate **35** could be isolated together with an unidentified compound which mass spectroscopy showed to have a molecular weight of 282 (based on ^{79}Br) and to contain two Br atoms. Using sodium ethoxide in refluxing ethanol a similar result was obtained. In this case the molecular weight of the unidentified product was 389 (based on ^{79}Br); mass spectroscopy showed the presence of three bromine atoms, and its IR spectrum exhibited a nitrile stretching frequency. Copper catalysis of these reactions failed also. By contrast, when 3-bromothiophene-2-carbonitrile was treated with 2-sulfanylacetamide (DMF/K_2CO_3; ambient temperature) it gave compound **36**, which was heated in refluxing DMF in the presence of potassium carbonate, to yield 3-aminothieno[3,2-*b*]thiophene-2-carboxamide **34** in 64% yield.

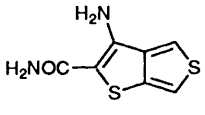
2,4,5-Tribromothiophene-3-carbonitrile **23** was converted similarly into 3-amino-4,5-dibromothieno[2,3-*b*]thiophene-2-carboxamide **37** (84%) *via* intermediate **38** whilst 3-amino-



37



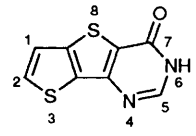
38



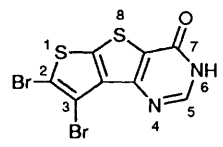
39

thieno[3,4-*b*]thiophene-2-carboxamide **39** (55%) was obtained when 4-bromothiophene-3-carbonitrile **19** was treated with 2-sulfanylacetamide in DMF at 100 °C in the presence of potassium carbonate. Thieno[3,4-*b*]thiophenes **32** and **39** are light sensitive and fluoresce strongly in UV light.

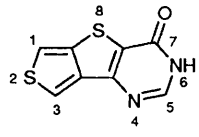
3-Aminothieno[3,2-*b*]thiophene-2-carboxamide**34**, 3-amino-4,5-dibromothieno[2,3-*b*]thiophene-2-carboxamide **37** and 3-aminothieno[3,4-*b*]thiophene-2-carboxamide **39** gave thi-



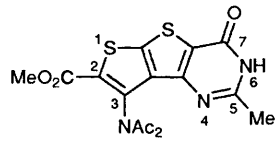
40



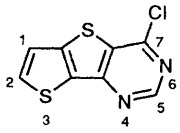
41



42



43



44

eno[2′,3′:4,5]- **40** (46%), thieno[3′,2′:4,5]- **41** (59%) and thieno[3′,4′:4,5]-thieno[3,2-*d*]pyrimidin-7(6*H*)-one **42** (40%), respectively, when treated with triethyl orthoformate in refluxing acetic anhydride. Recently, we reported[46] the synthesis of the novel thiazolo[4′,5′:4,5]thieno[3,2-*d*]pyrimidine ring system by a similar procedure. Ring systems **40** and **42** appear to be novel whilst we can find only one reference in the literature to a derivative of ring system **41**, namely compound **43**.[47] With phosphorus oxychloride thieno[2′,3′:4,5]-thieno[3,2-*d*]pyrimidin-7(6*H*)-one **40** was converted into the 7-chloro derivative **44** (85%).

With a view to the annelation of three thiophene rings we decided to investigate the synthesis of 3,4-dibromothiophene-2,5-dicarbaldehyde **13**. Lawesson[9] prepared 3,4-dibromo-2,5-dilithiothiophene **10** from 2,3,4,5-tetrabromothiophene and hydrolysed it to 3,4-dibromothiophene. We were able to repeat this procedure but all attempts to quench the dilithiated thiophene **10** with an excess of DMF (THF; −70 °C) gave only 3,4-dibromothiophene-2-carbaldehyde. We converted the dilithiated thiophene **10** (prepared in diethyl ether at 0 °C) into 3,4-dibromothiophene-2,5-dicarboxylic acid **14** (58%)[48] by quenching it with carbon dioxide, but it gave only a low yield (18%) of 3,4-dibromothiophene-2-carbaldehyde when prepared under these conditions and quenched with an excess of DMF. Next, we attempted to introduce the two aldehyde groups stepwise starting with 2,3,4,5-tetrabromothiophene and using a 'one-pot' procedure similar to that reported by Michael and Gronowitz[49] but this again resulted in the formation of 3,4-dibromothiophene-2-carbaldehyde (18%). Noteworthy is the report[32] that 3-bromo-2,5-dilithiothiophene gives only a low yield of 3-bromothiophene-2,5-dicarbaldehyde when quenched with DMF; the major product is 3,5-dibromothiophene-2-carbaldehyde.

Elemental bromination of thiophene-2,5-dicarbaldehyde, prepared in 74% yield by successive treatment of 2,5-dibromothiophene with 2 mol equiv. of butyllithium and DMF, in the presence of aluminium chloride[*cf.* 17] and preparation of the 2,5-bis(Grignard) compound from 2,3,4,5-tetrabromothiophene and magnesium in the presence of 1,2-dibromoethane[9] and its treatment with an excess of DMF also failed to yield the desired dialdehyde **13**.

Experimental

IR spectra were recorded with a Pye-Unicam SP3-100 or Perkin-Elmer 1710 FT IR spectrometer (liquids as films and

solids as Nujol mulls between sodium chloride plates); ^{1}H NMR spectra were recorded with a Varian Associates EM360 (60 MHz) or Bruker AC300 FT (300.13 MHz) instrument with tetramethylsilane as internal standard, J values in Hz; low-resolution mass spectra were recorded using a Kratos MS30 or Finnegan 4500 machine and high-resolution mass spectra were obtained with a Kratos Concept 1S mass spectrometer, all operating at 70 eV (EI unless stated otherwise). Reported molecular weights are given for the isotope ^{79}Br. The isotopic abundance ratios were as expected for the compounds containing bromine.

Camlab Polygram silica G/UV_{254} or Alumina N/UV_{254} plates were used for TLC, flash chromatography was carried out on silica gel (Sorbil C_{60} from Rhône-Poulenc), standard column chromatography was performed using gradient elution techniques on Merck Kieselgel type 60H silica, and HPLC separations were achieved using a Waters Associates Pump M6000A in conjunction with a Waters Associates detector (RI) R401 with RSIL silica as the stationary phase and pentane as the mobile phase.

All reactions involving organolithium reagents were carried out under dry, oxygen-free nitrogen or argon and reagents and solvents were dried by standard procedures. Reagents were transferred with syringes through a rubber septum cap fitted to the reaction vessel.

Light petroleum refers to the fraction of b.p. 60–80 °C unless stated otherwise. Ether refers to diethyl ether. In all cases organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure on a rotary evaporator.

Small-scale distillations were carried out with a Kugelrohr microdistillation apparatus and the b.p. temperatures recorded are those of the oven at the time of distillation. M.p.s were recorded with a Gallenkamp m.p. apparatus and are uncorrected.

Microanalytical (for C, H and N) results were supplied by Butterworth Laboratories Ltd. of Teddington.

Preparation of Known Compounds.—A mixture of 2,3,4,5-tetrabromothiophene (73%), m.p. 118–119 °C (from ethanol with charcoal) (lit., m.p. 117–118 °C[50] and 114 °C[11]) and 2,3,5-tribromothiophene (7%), b.p. 125 °C at 10 mmHg, m.p. 28–29 °C (lit., m.p. 28–29 °C[9] and b.p. 125 °C at 10 mmHg[11]) was prepared and separated as described by Janda *et al.*[11]

Elemental bromination of thiophene (ratio 6:1) in trichloromethane[9] (addition time 3 h at ambient temperature; stirred for a further 24 h, then heated at reflux for 2 h; reaction mixture heated at reflux for 4 h with potassium hydroxide in aqueous ethanol before work-up; products were separated by fractional distillation) gave a mixture of 2,5-dibromothiophene (11%), b.p. 38–40 °C at 1.0 mmHg (lit.,[9] b.p. 79–81 °C at 9.0 mmHg) and 2,3,5-tribromothiophene (53%), identical with the sample prepared as described before.

3,4-Dibromothiophene was prepared by the methods of Janda *et al.*[11] (70% yield; lit.,[11] 75%), Lawesson[9] (60%; lit.,[9] 74%) and Gronowitz[15] (72%; lit.,[15] 68%).

Thiophene-2,5-dicarbaldehyde **13** (74%) was prepared from 2,5-dibromothiophene using a procedure similar to that reported by Robba *et al.*,[51] m.p. 113 °C [eluted from a silica column with light petroleum–ethyl acetate (10:1)] (lit.,[51] m.p. 114 °C).

The following compounds were prepared also by literature methods: 3-bromothiophene-2-carbaldehyde (60%), liquid (lit.,[16] 70% yield, m.p. 24–25 °C, b.p. 113–115 °C at 10 mmHg); 3-bromothiophene-2-carbaldehyde oxime (78%), m.p. 157–159 °C (from ethanol) (lit.[45] 89% and m.p. 159 °C); 3-bromothiophene-2-carbonitrile (73%), m.p. 50–52 °C (from hexane–ethyl acetate) (lit.,[45] 70% and m.p. 50 °C); and 4-bromothiophene-3-carbaldehyde **16** (49%), liquid (lit.,[16] 47% as a liquid). Thiophene and 2,3-dibromothiophene were supplied by Synthetic Chemicals Ltd.

2-Substituted 3,4,5-Tribromothiophenes **2–7**.—*General method.* 1.5 mol dm^{-3} Butyllithium in hexane (9.2 cm^3, 13.8 mmol) was added dropwise to a stirred solution of 2,3,4,5-tetrabromothiophene (5.0 g, 12.5 mmol) in THF (60 cm^3) initially at −78 °C (all temperatures recorded internally) whilst the temperature was maintained at < −70 °C. The mixture was stirred for a further 15 min at −70 °C, after which the appropriate quenching reagent was added and the reaction worked up according to one of the following procedures:

(1) *Carbon dioxide as the quenching reagent.* Carbon dioxide gas was generated by sublimation of solid carbon dioxide and dried by successive passage through Dreschel bottles containing concentrated sulfuric acid, solid sodium hydrogen carbonate, and glass wool; it was then bubbled through the reaction mixture until, after removal of the cooling bath, the temperature of the latter reached 0 °C. Distilled water (30 cm^3) was added to the reaction mixture and the aqueous layer was separated and extracted with ethyl acetate (2 × 25 cm^3). The aqueous phase was acidified with aqueous hydrochloric acid and the precipitated solid was extracted with ethyl acetate (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent distilled off to give the crude product **4** which was recrystallised from ethanol (with charcoal).

(2) *Water, DMF, benzophenone, or trimethylsilyl chloride as the quenching reagent.* After addition of the reagent (1.1 mol equiv.) at −70 °C the mixture was allowed to warm to 0 °C, whereupon 2 mol dm^{-3} hydrochloric acid (30 cm^3) was added to it. The aqueous phase was extracted with dichloromethane (3 × 30 cm^3) and the combined organic phase and extracts were dried ($MgSO_4$) and the solvent distilled off to give the crude product. This was purified by chromatography on silica eluting with light petroleum–ethyl acetate (10:1) to give the product (in the case of the trimethylsilyl derivative light petroleum alone was used). Solids were recrystallised from ethanol whilst liquids were resubjected to chromatography until pure by TLC (usually once more).

(3) *Dimethyl or diphenyl disulfide as the quenching reagent.* After addition of the reagent (1.1 mol equiv.) at −70 °C to the reaction mixture it was allowed to warm to 0 °C, whereupon 2 mol dm^{-3} sodium hydroxide (30 cm^3) was added to it. The aqueous layer was separated and extracted with dichloromethane (3 × 30 cm^3) and the combined organic layer and extracts were dried ($MgSO_4$) and the solvent distilled off to give the crude product which was purified by chromatography on silica eluting with light petroleum.

The following compounds were prepared according to the general method (yields in Table 1): 2,3,4-tribromothiophene **2**, m.p. 43–44 °C (lit.,[50] m.p. 43–46 °C); δ_H(60 MHz; $CDCl_3$) 7.20 (1 H, s, 5-H); 3,4,5-tribromothiophene-2-carbaldehyde **3**, m.p. 140–141 °C (from ethyl acetate) (lit.,[52] m.p. 141–142 °C), ν_{max}/cm^{-1} 1660 (CO); δ_H(60 MHz; $CDCl_3$) 9.95 (1 H, s, CHO); 3,4,5-tribromothiophene-2-carboxylic acid **4**, m.p. 258 °C (lit.,[12] 73% and m.p. 258–261 °C), ν_{max}/cm^{-1} 1660–1690 (CO); *diphenyl(3,4,5-tribromo-2-thienyl)methanol* **5**, m.p. 134–136 °C, ν_{max}/cm^{-1} 3555 (OH); δ_H(60 MHz; $CDCl_3$) 3.90 (1 H, s, exchangeable, OH) and 7.35 (10 H, m, ArH) [characterised by conversion into the ether **8** (see later)]; *3,4,5-tribromo-2-methylsulfanylthiophene* **6**, liquid; δ_H(60 MHz; $CDCl_3$) 2.45 (3 H, s, Me) (Found: C, 16.3; H, 0.9%; M^+, 364. $C_5H_3Br_3S_2$ requires C, 16.4; H, 0.8%; M, 364), 3,4,5-*tribromo-2-trimethylsilylthiophene* **7**, liquid; δ_H(60 MHz; $CDCl_3$) 0.5 (9 H, s, Me) (Found: M^+, 389.7740. $C_7H_9Br_3SSi$ requires M, 389.7744).

3,4,5-*Tribromo*-2-(*ethoxydiphenylmethyl*)*thiophene* **8**.—A stirred mixture of diphenyl(3,4,5-tribromo-2-thienyl)methanol **5** (2.0 g, 4.0 mmol) and ethyl acetate (45 cm^3) containing traces of ethanol and acetic acid was heated under reflux for 30 min. The solvents were distilled off and the residue was purified by chromatography on silica eluting with light petroleum–ethyl acetate (10:1) to give *product* **8** (1.7 g, 80%), m.p. 145 °C (from ethanol); δ_H(60 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7.0, Me), 3.18 (2 H, q, *J* 7.0, CH_2) and 7.15–7.60 (10 H, m, ArH) (Found: C, 43.3; H, 3.0%; M^+, 528. $C_{19}H_{15}Br_3OS$ requires C, 43.0; H, 2.85; *M*, 528).

3,4-*Dibromo*-2,5-*bis*(*methylsulfanyl*)*thiophene* **11** (63%), m.p. 66 °C (from ethanol) (lit., m.p. 67.5 °C[53] and 65–66 °C[13,14]) δ_H(60 MHz; $CDCl_3$) 2.45 (6 H, s, 2 × Me)] was prepared in a manner analogous to that described above for the synthesis of compound **6** (1.1 mol equiv. Me_2S_2 used) with the exception that wet THF was added to the reaction mixture 30 min after addition of the dimethyl disulfide (see Table 1).

3,4-*Dibromo*-2,5-*bis*(*phenylsulfanyl*)*thiophene* **12** (58%) was prepared similarly and had m.p. 70–72 °C (from ethanol), ν_{max}/cm^{-1} 1570 (C=C); δ_H(60 MHz; $CDCl_3$) 7.20–7.55 (10 H, m, ArH) (Found: C, 41.9; H, 2.2%; M^+, 456. $C_{16}H_{10}Br_2S_3$ requires C, 41.9; H, 2.2%; *M*, 456).

3-*Substituted* 4-*Bromothiophenes* **16–18**.—*General procedure.* 1.5 mol dm^{-3} Butyllithium in hexane (12 cm^3, 18.0 mmol) was added dropwise to a stirred solution of 3,4-dibromothiophene (4.0 g, 16.3 mmol) in ether (60 cm^3) at −80 °C whilst the temperature was maintained at < −70 °C. After 10 min the quenching reagent, DMF (1.5 cm^3, 20.0 mmol), carbon dioxide gas (an excess) or benzophenone (3.64 g, 20.0 mmol) was added to the mixture which was then worked up using either procedure (1), (2) or (3), as described above.

The following compounds were prepared in this way: 4-bromothiophene-3-carbaldehyde **16** (75%), liquid (lit.,[16] yield 47%); 4-bromothiophene-3-carboxylic acid **17** (70%), m.p. 154 °C (from aqueous ethanol) (lit.,[9] m.p. 157–159 °C and yield 73%); and (4-*bromo*-3-*thienyl*)*diphenylmethanol* **18** (80%), m.p. 85–86 °C (from ethanol), ν_{max}/cm^{-1} 3530 (OH); δ_H(60 MHz; $CDCl_3$) 3.83 (1 H, s, exchangeable, OH), 6.45 (2 H, d, 2-H and 5-H) and 7.10–7.50 (10 H, m, ArH) (Found: C, 59.5; H, 3.85%; M^+, 343.9871. $C_{17}H_{13}BrOS$ requires C, 59.2; H, 3.8%; *M*, 343.9871).

2,4,5-*Tribromothiophene*-3-*carbaldehyde* **21**.—Aluminium chloride (3.49 g, 0.25 mol equiv.) was added to a stirred solution of 4-bromothiophene-3-carbaldehyde **16** (2.0 g, 1.047 mol) in dichloromethane (40 cm^3) and the resulting mixture was heated under reflux for 1 h and then cooled. Bromine (4.2 g, 26.19 mmol) in dichloromethane (10 cm^3) was added to the mixture which was then heated under reflux for a further 4 h, cooled and poured into saturated aqueous sodium hydrogen carbonate (40 cm^3). The organic layer was separated and dried ($MgSO_4$), and the solvent distilled off to give the product **21** (2.2 g, 60%), m.p. 100 °C (from ethanol with charcoal) (lit.,[17,18] m.p. 100–101 °C); ν_{max}/cm^{-1} 1675 (CO); δ_H(60 MHz; $CDCl_3$) 9.95 (1 H, s, CHO).

2,4,5-Tribromothiophene-3-carboxylic acid **22** (76%), m.p. 203–204 °C (from aqueous ethanol) (lit.,[9] m.p. 202–204 °C) was prepared by elemental bromination of 4-bromothiophene-3-carboxylic acid **17** in acetic acid using a procedure analogous to that used by Lawesson[9] to brominate 2,3-dibromothiophene-4-carboxylic acid.

Reaction of 2,3,5-*Tribromothiophene with LDA.*—*General procedure.* 1.5 mol dm^{-3} Butyllithium in hexane (11.4 cm^3, 17.6 mmol) was added to a stirred solution of diisopropylamine (2.7 cm^3, 19.4 mmol) in either THF or ether (100 cm^3) at −70 °C after which the mixture was cooled to −80 °C. A solution of 2,3,5-tribromothiophene (5.0 g, 15.6 mmol) in THF or ether (20 cm^3) was then added dropwise to it whilst the temperature was maintained at < −78 °C. After 15 min the quenching reagent was added to the mixture which was then worked up using either procedure (1), (2) or (3), as described above. The products, **2–7**, **11** and **12** were identical in all respects with those prepared as described before (yields are given in Table 1; see also Discussion for further details).

2-*Substituted* 3,5-*Dibromothiophenes* **25–27**.—*General procedures.* (a) 1.5 mol dm^{-3} Butyllithium in hexane (9.1 cm^3, 13.64 mmol) was added to a stirred solution of diisopropylamine (1.9 cm^3, 19.0 mmol) in either THF or ether (60 cm^3) at −70 °C after which the mixture was cooled to −80 °C and 2,5-dibromothiophene (3.0 g, 1.4 cm^3, 12.40 mmol) was added dropwise to it whilst the temperature was maintained at < −78 °C. After 15 min DMF (1 cm^3, 13.64 mmol), carbon dioxide gas (an excess) or benzophenone (2.48 g, 13.64 mmol) was added to the mixture which was then worked up by procedure (1), (2) or (3), as described above.

(b) 1.5 mol dm^{-3} Butyllithium in hexane (6.9 cm^3, 10.3 mmol) was added dropwise to a stirred solution of 2,3,5-tribromothiophene (3.0 g, 9.3 mmol) in THF or ether (60 cm^3) at −80 °C after which the mixture was allowed to warm to −70 °C. After 10 min, the reaction mixture was treated as described in the preceding experiment.

The following compounds were prepared by these procedures: 3,5-dibromothiophene-2-carbaldehyde **25** [80% by procedure (a) and 75% by procedure (b)], m.p. 48 °C (from ethanol) [lit., 85% by procedure (a),[24] m.p. 48 °C by procedure (b)[32]]: 3,5-dibromothiophene-2-carboxylic acid **26** [90% by procedure (a) and 60% by procedure (b)], m.p. 210 °C (from aqueous ethanol) [lit.,[54] 36% and m.p. 210–212 °C by procedure (a)]: and (3,5-*dibromo*-2-*thienyl*)*diphenylmethanol* **27** [86% by procedure (a) and 82% by procedure (b)], m.p. 91–92 °C (from ethanol), ν_{max}/cm^{-1} 3500; δ_H(60 MHz; $CDCl_3$) 3.75 (1 H, s, exchangeable, OH), 6.95 (1 H, s, 4-H) and 7.30 (10 H, m, ArH) (Found: C, 47.9; H, 2.9%; M^+, 422. $C_{17}H_{12}Br_2OS$ requires C, 48.1; 2.85%; *M*, 422).

Ethyl 2,3-*Dibromothieno*[3,2-b]*thiophene*-5-*carboxylate* **28**.—(a) *With potassium carbonate in DMF.* 3,4,5-Tribromothiophene-2-carbaldehyde **3** (2.0 g, 5.7 mmol) was added to a stirred suspension of potassium carbonate (5.0 g, excess) in DMF (10 cm^3) containing ethyl 2-sulfanylacetate (0.7 cm^3, 6.4 mmol) at ambient temperature and the resulting mixture was stirred overnight and then poured into water. The precipitate was filtered off, dried and subjected to chromatography on silica eluting with light petroleum–ethyl acetate (10:1) to give the *product* **28** (1.29 g, 61%), m.p. 137–140 °C (from ethanol), ν_{max}/cm^{-1} 1705 (CO); δ_H(60 MHz; $CDCl_3$) 1.35 (3 H, t, Me), 4.40 (2 H, q, CH_2) and 7.80 (1 H, m, 6-H) (Found: C, 29.1; H, 1.6%; M^+, 368. $C_9H_6Br_2O_2S_2$ requires C, 29.2; H, 1.6%; *M*, 368.

(b) *With sodium ethoxide in ethanol.* Sodium (1.5 g), ethyl 2-sulfanylacetate (1.73 cm^3, 16.0 mmol) and 3,4,5-tribromothiophene-2-carbaldehyde **3** (5.0 g, 14.0 mmol) were added successively to stirred anhydrous ethanol (50 cm^3) at ambient temperature and the resulting mixture was heated under reflux for 4 h. The solvent was removed by distillation and water (30 cm^3) was added to the residue; this mixture was then extracted with dichloromethane (3 × 30 cm^3) and the extract worked up to give the crude product **28**. This was subjected to chromatography as described above in (a). The pure product **28** (72% yield) was identical in all respects with the sample prepared as described in (a).

(c) *With liquid ammonia.* Ethyl 2-sulfanylacetate (0.17 cm^3, 1.58 mmol) was added with stirring to liquid ammonia (80 cm^3) at −33 °C followed by 3,4,5-tribromothiophene-2-carbaldehyde **3** (0.5 g, 1.43 mmol). The resulting mixture was stirred for a

further 2 h after which the ammonia was evaporated to leave the crude product **28** which was purified as described in (a). The pure product **28** (66% yield) was identical in all respects with the sample prepared as described in (a).

The following compounds were prepared similarly [with potassium carbonate in DMF; procedure (a)]: *ethyl* 2,3-*dibromothieno*[2,3-b]*thiophene-5-carboxylate* **30** (58%), m.p. 124 °C (from ethanol), ν_{max}/cm^{-1} 1730 (CO); δ_H(60 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.0, Me), 4.30 (2 H, q, *J* 7.0, CH_2) and 7.75 (1 H, m, 4-H) (Found: C, 29.4; H, 1.7%; M^+, 368): and *ethyl* 2-*bromothieno*[3,2-b]*thiophene-5-carboxylate* **29** (8%), m.p. 73–74 °C (from ethanol), ν_{max}/cm^{-1} 1700 (CO); δ_H(60 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.0, Me), 4.24 (2 H, q, *J* 7.0, CH_2), 7.10 (1 H, s, 3-H) and 7.70 (1 H, s, 6-H) (Found: C, 37.5; H, 2.5%; M^+, 289.9082. $C_9H_7BrO_2S_2$ requires C, 37.1; H, 2.4%; *M*, 289.9071).

Ethyl Thieno[3,4-b]*thiophene-2-carboxylate* **32**.—Sodium (0.36 g, 15.7 mmol) was added portionwise to anhydrous ethanol (50 cm^3) followed by ethyl 2-sulfanylacetate (1.72 cm^3, 1.89 g, 15.7 mmol). The resulting solution was stirred at ambient temperature for 30 min after which a solution of 4-bromothiophene-3-carbaldehyde **16** (1.0 g, 5.24 mmol) in ethanol (10 cm^3) was added to it followed by copper(I) oxide (0.25 g, 1.75 mmol) and potassium iodide (*ca.* 5 mg). The resulting mixture was heated under reflux under argon for 5 h after which it was filtered whilst hot through Celite and the residue was washed with hot ethanol (40 cm^3). Evaporation of the combined filtrate and washings under reduced pressure gave a residue which was purified by flash chromatography on silica eluting with ethyl acetate–hexane (10 : 90) to give the *product* **32** (0.23 g, 21%), m.p. 87–88 °C, ν_{max}/cm^{-1} 1705 (CO); δ_H(300 MHz; $CDCl_3$) 1.37 (3 H, t, *J* 7.2, Me), 4.36 (2 H, q, *J* 7.2, CH_2), 7.27 (1 H, d, *J* 2.5, 4-H or 6-H), 7.57 (1 H, d, *J* 2.5, 6-H or 4-H) and 7.69 (1 H, s, 3-H) (Found: C, 50.6; H, 3.5%; $M^+ + 18$, 230.0316. $C_9H_8O_2S_2$ requires C, 50.9; H, 3.8%; $M + 18$, 230.0309) (MS by CI).

Using 2-sulfanylacetamide in place of the ethyl 2-sulfanylacetate *thieno*[3,4-b]*thiophene-2-carboxamide* (**31** or **32**; $CO_2R = CONH_2$) (22%) was prepared similarly, m.p. 191–193 °C (with decomp.) (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1644 (CO) and 3167–3396 (several bands) (NH_2); δ_H(300 MHz; [$^2H_6$]DMSO) 6.84 (1 H, br s, NH), 7.50 (1 H, br s, NH), 7.58 (1 H, d, *J* 2.65, 4-H or 6-H), 7.68 (1 H, s, 3-H) and 7.79 (1 H, d, *J* 2.65, 6-H or 4-H) (Found: C, 45.3; H, 2.8; N, 7.5%; $M^+ + 1$, 183.9887. $C_7H_5NOS_2$ requires C, 45.9; H, 2.75; N, 7.6%; $M + 1$, 183.9891) (MS by CI).

3,4,5-*Tribromothiophene-2-carbaldehyde Oxime*.—A solution of 3,4,5-tribromothiophene-2-carbaldehyde **3** (1.0 g, 2.87 mmol) in ethanol (80 cm^3) was added to a solution of hydroxylamine hydrochloride (0.40 g, 5.76 mmol) and sodium hydrogen carbonate (0.48 g, 5.71 mmol) in water (5 cm^3) and the resulting mixture was stirred at ambient temperature for 2 h. The ethanol was distilled off under reduced pressure and water (40 cm^3) was added to the residue. Extraction of the resulting mixture with ethyl acetate and work-up of the extract gave the *oxime* (0.95 g, 91%), m.p. 190 °C (with decomp.) (from ethanol); δ_H(300 MHz; [$^2H_6$]Me_2CO) 7.86 (1 H, s, CH) and 12.00 (1 H, br s, OH) (Found: C, 16.85; H, 0.7; N, 4.2%; $M^+ + 1$, 361.7488. $C_5H_2Br_3NOS$ requires C, 16.5; H, 0.55; N, 3.85%; $M + 1$, 361.7488).

The following compounds were prepared similarly: 2,4,5-*tribromothiophene-3-carbaldehyde oxime* (54%) from the aldehyde **21**, m.p. 186 °C (from ethyl acetate–hexane), ν_{max}/cm^{-1} 3245 *br* (OH); δ_H(300 MHz; [$^2H_6$]DMSO–$CDCl_3$) 7.53 (1 H, s, CH) and 11.08 (1 H, s, OH) (Found: C, 16.7; H, 0.35; N, 3.8%; $M^+ + 1$, 361.7513. $C_5H_2Br_3NOS$ requires C, 16.5; H, 0.55; N, 3.85%; $M + 1$, 361.7488); and 4-bromothiophene-3-carbaldehyde oxime (98%) from the aldehyde **16**, m.p. 112–114 °C (from ethanol) (lit.,[45] 76% and m.p. 104 °C).

3,4,5-*Tribromothiophene-2-carbonitrile* **9**.—A mixture of 3,4,5-tribromothiophene-2-carbaldehyde oxime (1.81 g, 4.97 mmol) in acetic anhydride (10 cm^3) was heated at 120 °C for 1 h and then allowed to cool. The mixture was cooled further for 1 h in an ice-bath when the *product* **9** (1.32 g, 77%) crystallised out, m.p. 119–121 °C (from ethyl acetate–hexane), ν_{max}/cm^{-1} 2202 (CN) (Found: C, 17.75; N, 4.3%; $M^+ + 1$, 343.7385. C_5Br_3NS requires C, 17.4; N, 4.05%; $M + 1$, 343.7381).

The following compounds were prepared similarly: 2,4,5-*tribromothiophene-3-carbonitrile* **23** (57%), m.p. 124 °C (from ethyl acetate–hexane), ν_{max}/cm^{-1} 2229 (CN) (Found: C, 17.7; N, 3.9%; $M^+ + 18$, 360.7652. C_5Br_3NS requires C, 17.4; N, 4.05%; $M + 18$, 360.7647) (MS by CI); and 4-bromothiophene-3-carbonitrile **19** (66%) [acetic anhydride was distilled off under reduced pressure and the residue was purified by flash chromatography on silica eluting with ethyl acetate–hexane (15:85) to give the product], m.p. 56–57 °C (lit.,[45] 62% and m.p. 56 °C).

(4,5-*Dibromo-2-cyano-3-thienylsulfanyl*)*acetamide* **35**.—3,4,5-Tribromothiophene-2-carbonitrile (**9**) (1.0 g, 2.89 mmol) was added to a stirred suspension of 2-sulfanylacetamide (0.29 g, 19.0 mmol) and potassium carbonate (2.5 g, excess) in DMF (5 cm^3) at ambient temperature and the resulting mixture was stirred overnight. It was then poured into water (250 cm^3) and the resulting precipitate was filtered off, dried and purified by flash chromatography on silica. Ethyl acetate–hexane (10:90) eluted an unidentified compound (0.29 g, 35%), ν_{max}/cm^{-1} 2220 (CN) and $M^+ + 1$, 282 (with an isotopic distribution pattern corresponding to two Br atoms). Ethyl acetate–hexane (70:30) gave compound **35** (0.20 g, 19%), m.p. 210 °C (from acetonitrile), ν_{max}/cm^{-1} 3289–3440 (NH_2), 2213 (CN) and 1678 (CO); δ_H(300 MHz; [$^2H_6$]DMSO–$CDCl_3$) 3.73 (2 H, s, CH_2), 7.22 (1 H, s, NH) and 7.63 (1 H, s, NH) (Found: $M^+ + 1$, 355. $C_7H_4Br_2N_2OS_2$ requires $M + 1$, 355).

3,4,5-Tribromothiophene-2-carbonitrile **9** (1.0 g, 2.89 mmol) in ethanol (15 cm^3) was added at ambient temperature to a solution of sodium ethoxide in anhydrous ethanol (5 cm^3) [prepared by addition of sodium (0.073 g, 3.17 mmol) to the ethanol] and the resulting mixture was heated under reflux for 2.5 h. The solvent was then distilled off under reduced pressure and water (30 cm^3) added to the residue. The product was purified by flash chromatography on silica eluting with ethyl acetate–hexane (10:90) to give an unidentified compound (0.34 g, 30%), m.p. 118 °C, ν_{max}/cm^{-1} 2220 (CN) (Found: 22.5; H. 0.4; N, 5.0%; $M^+ + 1$, 389, with an isotopic distribution pattern corresponding to three Br atoms).

3-*Aminothieno*[3,2-b]*thiophene-2-carboxamide* **34**.—2-Sulfanylacetamide (1.81 g, 20.0 mmol) was added to a stirred suspension of potassium carbonate (6.31 g, excess) in DMF (20 cm^3) followed by 3-bromothiophene-2-carbonitrile (3.40 g, 18.0 mmol) and the mixture was stirred overnight at ambient temperature and then poured into water (100 cm^3). The precipitate was filtered off and examined by TLC and IR and ^1H NMR spectroscopy which revealed it to be a mixture of the required product **34** and (2-cyano-3-thienyl)sulfanylacetamide **36**. This amide product was added to a suspension of potassium carbonate (6.97 g, excess) in DMF (40 cm^3) and the resulting mixture was heated under reflux for 1 h; it was then cooled and poured into water (200 cm^3). Extraction with ethyl acetate gave the crude product which was purified by flash chromatography on silica eluting with ethyl acetate–hexane (80:20) to give compound **34** (2.30 g, 64%), m.p. 156–158 °C (from ethanol), ν_{max}/cm^{-1} 1662 (CO) and 3188–3421 (several bands) (NH_2

and $CONH_2$); δ_H(300 MHz; [$^2H_6$]DMSO) 7.00 (4 H, br s, NH_2 and $CONH_2$), 7.34 (1 H, d, *J* 4.8, 5-H or 6-H) and 7.80 (1 H, d, *J* 4.8, 6-H or 5-H) (Found: C, 42.3; H, 3.1; N, 14.1%; $M^+ + 1$, 199.0006. $C_7H_6N_2OS_2$ requires C, 42.4; H, 3.05; N, 14.2%; *M* + 1, 199.0000).

3-*Amino*-4,5-*dibromothieno*[2,3-b]*thiophene*-2-*carboxamide* **37**. This compound (84%) was prepared similarly in a two-stage process (in the second step the mixture was heated at 100 °C for 2 h) and had m.p. 235–236 °C (from acetonitrile–dimethyl sulfoxide), ν_{max}/cm^{-1} 1637 (CO) and 3171–3433 (several bands) (NH_2 and $CONH_2$); δ_H(300 MHz; [$^2H_6$]DMSO–$CDCl_3$) 6.91 (2 H, s, NH_2) and 6.51 (2 H, s, NH_2) (Found: C, 23.9; H, 1.3; N, 7.65%; $M^+ + 18$, 371.8488. $C_7H_4BrN_2O_2S_2$ requires C, 23.6; H, 1.1; N, 7.9%; *M* + 18, 371.8477).

3-*Aminothieno*[3,4-b]*thiophene*-2-*carboxamide* **39**.—4-Bromothiophene-3-carbonitrile **19** (0.5 g, 2.66 mmol) was added to a stirred suspension of 2-sulfanylacetamide (0.27 g, 2.93 mmol) and potassium carbonate (2.0 g, excess) in DMF (5.0 cm^3) and the mixture was heated overnight at 100 °C. It was then poured into cold water (100 cm^3) and the aqueous solution was neutralised by addition of 2 mol dm^{-3} hydrochloric acid. The mixture was extracted with ethyl acetate and the extract worked up to provide the product which was purified by flash chromatography on silica eluting with ethyl acetate–hexane (80:20). This gave the *title compound* **39** (0.29 g, 55%), m.p. 148–150 °C (with decomp.) (from acetonitrile), ν_{max}/cm^{-1} 1638 (CO) and 3095–3435 (several bands; NH_2 and $CONH_2$); δ_H(300 MHz; [$^2H_6$]DMSO–$CDCl_3$) 7.85 (1 H, d, *J* 2.4, 4-H or 6-H), 7.13 (1 H, d, *J* 2.4, 6-H or 4-H) and 6.33 (4 H, br s, NH_2 and $CONH_2$) (Found: C, 42.6; H, 2.7; N, 13.9%; $M^+ + 1$, 198.9995. $C_7H_6N_2OS_2$ requires C, 42.4; H, 3.1; N, 14.2%; *M* + 1, 199.0000).

2,3-*Dibromothieno*[3′,2′:4,5]*thieno*[3,2-d]*pyrimidin*-7(6H)-*one* **41**.—A mixture of 3-amino-4,5-dibromothieno[2,3-*b*]thiophene-2-carboxamide **37** (160 mg, 4.49 × 10^{-4} mol), acetic anhydride (3 cm^3) and triethyl orthoformate (2.67 g, 3 cm^3; excess) was heated under reflux for 1.5 h and then cooled and poured into water (50 cm^3). The mixture was extracted with ethyl acetate (5 × 60 cm^3) and the combined extracts were worked up to provide a product which was subjected to flash chromatography on silica eluting with ethyl acetate. This afforded the *title compound* **41** (94 mg, 59%), m.p. > 350 °C (from acetonitrile–dimethyl sulfoxide); ν_{max}/cm^{-1} 1661 (CO); δ_H(300 MHz; [$^2H_6$]DMSO) 8.30 (1 H, s, 5-H) and 12.75 (1 H, br s, NH) (Found: C, 26.8; H, 0.7; N, 7.3%; $M^+ + 1$, 364.8054. $C_8H_2Br_2N_2OS_2$ requires C, 26.4; H, 0.55; N, 7.7%; *M* + 1, 364.8055).

The following compounds were prepared similarly (reaction time and elution solvent shown in parentheses): *thieno*[2′,3′:4,5]*thieno*[3,2-d]*pyrimidin*-7(6H)-*one* **40** (46%) [1.75 h; the mixture was poured into water and the resulting precipitate was filtered off and purified by flash chromatography on silica eluting with ethyl acetate–hexane (85:15)], m.p. 288–290 °C (with decomp.) (from ethanol), ν_{max}/cm^{-1} 1658 (CO); δ_H(300 MHz; [$^2H_6$]DMSO–$CDCl_3$) 7.51 (1 H, d, *J* 5.3, 1-H or 2-H), 7.92 (1 H, d, *J* 5.3, 2-H or 1-H), 8.16 (1 H, s, 5-H) and 10.79 (1 H br s, NH) (Found: C, 45.9; H, 2.0; N, 13.0%; $M^+ + 1$, 209.9835. $C_8H_4N_2OS_2$ requires, C, 46.1; H, 1.9; N, 13.45%; *M* + 1, 208.9843); and *thieno*[3′,4′:4,5]*thieno*[3,2-d]*pyrimidin*-7(6H)-*one* **42** (40%) [4 h; the mixture was poured into water and the precipitate was filtered off and purified by flash chromatography on silica eluting with ethyl acetate–hexane (85:15)], m.p. > 310 °C (from acetonitrile–dimethyl sulfoxide), ν_{max}/cm^{-1} 1677 (CO); δ_H(300 MHz; [$^2H_6$]DMSO) 7.87 (1 H, d, *J* 2.65, 1-H or 3-H), 8.26 (1 H, s, 5-H), 8.31 (1 H, d, *J* 2.65, 3-H or 1-H) and 12.81 (1 H, br s, NH) (Found: 45.8; H, 1.85; N, 13.0%; $M^+ + 18$, 226.0107. $C_8H_4N_2OS_2$ requires C, 46.1; H, 1.9; N, 13.45%; *M* + 1, 226.0109).

7-*Chlorothieno*[2′,3′:4,5]*thieno*[3,2-d]*pyrimidine* **44**.—A mixture of thieno[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-7(6*H*)-one (**40**) (0.25 g, 1.20 mmol) and phosphorus oxychloride (10 cm^3; excess) was heated under reflux for 2 h and then cooled and poured into ice-water (60 cm^3). The mixture was stirred at ambient temperature for 1 h, after which it was extracted with ethyl acetate (4 × 60 cm^3) and the combined extracts were worked up to afford a product which was flash chromatographed on silica eluting with ethyl acetate–hexane (20:80) to give the *title compound* **44** (0.232 g, 85%), m.p. 182–183 °C (from ethyl acetate–hexane); δ_H(300 MHz; $CDCl_3$) 7.44 (1 H, d, *J* 5.2, 1-H or 2-H), 7.88 (1 H, d, *J* 5.2, 2-H or 1-H) and 8.98 (1 H, s, 5-H) (Found: C, 41.7; H, 1.2; N, 12.0%; M^+, 226.9509. $C_8H_3ClN_2S_2$ requires C, 42.5; H, 1.3; N, 12.4%; *M*, 226.9505).

3,4-*Dibromothiophene*-2,5-*dicarboxylic Acid* **14**.—1.5 mol dm^{-3} Butyllithium in hexane (18.3 cm^3, 2.2 mol equiv.) was added dropwise to a stirred solution of 2,3,4,5-tetrabromothiophene (5.0 g, 12.5 mmol) in ether (60 cm^3) at −20 °C whilst the temperature was maintined at < 0 °C. The resulting mixture was stirred for 45 min after which carbon dioxide was bubbled through it. Work-up as described before gave the product **14** (2.41 g, 58%), m.p. 315 °C (with decomp.) (from ethanol) (lit.,[48] m.p. 317–318 °C).

Acknowledgements

We thank the SERC (CASE Award to D. S. L.) and Rhône-Poulenc Agriculture Ltd., Ongar, Essex for financial support, John H. Young and Synthetic Chemicals Ltd., Four Ashes, Nr. Wolverhampton for supplies of thiophene and its derivatives, Mrs. Ruth Howard for recording low-resolution mass spectra, Mrs. Valerie Boote (University of Manchester) for recording the high-resolution mass spectral data, Dr. M. A. Stuckey for recording ^1H NMR spectra at 300 MHz, and Dr. Johannes Fröhlich, Technical University, Vienna, for fruitful discussions.

References

1 Preliminary communcation: B. Iddon and P. J. Rosyk, paper presented at The 11th International Congress of Heterocyclic Chemistry, Heidelberg, 1987, abstract no. SC57, p. 192.
2 S. Athmani, A. Bruce and B. Iddon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 215 and previous Parts in this series.
3 V. P. Litvinov and Ya. L. Gol'dfarb, *Adv. Heterocycl. Chem.*, 1976, **19**, 123.
4 M. P. Cava and M. V. Lakshmikantham, in 'Comprehensive Heterocyclic Chemistry', eds. C. W. Bird and G. W. H. Cheeseman, Series eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 4, p. 1037.
5 T. Otsubo, Y. Kono, N. Hozo, H. Miyamoto, Y. Aso, F. Ogura, T. Tanaka and M. Sawada, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2033, and references cited therein.
6 K. S. Choi, K. Sawada, H. Dong, M. Hoshino and J. Nakayama, *Heterocycles*, 1994, **38**, 143, and references cited therein.
7 Ya. L. Gol'dfarb and V. P. Litvinov, *Bull. Akad. Sci. U.S.S.R.* (*Engl. Transl.*), 1963, 310.
8 M. G. Reinecke and P. Pedaja, in 'Thiophene and Its Derivatives, Part 2', ed. S. Gronowitz, Wiley Interscience, New York, 1986, ch. III, p. 159 (in particular p. 194).
9 S.-O. Lawesson, *Arkiv. Kemi*, 1957, **11**, 325 and 373 (simpler procedures for the syntheses of 2,3,5-tribromothiophene and 2,5-dibromothiophene have been reported since the completion of this part of our work, L. Brandsma and H. D. Verkruijsse, *Syn. Commun.*, 1988, **18**, 1763 and M. A. Keegstra and L. Brandsma, *Synthesis*, 1988, 890, respectively).
10 B. Decroix, J. Morel, C. Paulmier and P. Pastour, *Bull. Soc. Chim. Fr.*, 1972, 1848.

11 M. Janda, J. Štrogl, I. Stibor, M. Němec and P. Vopatrná, *Synthesis*, 1972, 545.
12 S.-O. Lawesson, *Arkiv. Kemi*, 1957, **11**, 345.
13 K. Kobayashi, *Chem. Lett.*, 1985, 1423.
14 S. Gronowitz, M. Temciuc and A.-B. Hörnfeldt, *J. Heterocycl. Chem.*, 1993, **30**, 1111.
15 S. Gronowitz, *Acta Chem. Scand.*, 1959, **13**, 1045.
16 S. Gronowitz, P. Moses, A.-B. Hörnfeldt and R. Håkansson, *Arkiv. Kemi*, 1961, **17**, 165.
17 S. Gronowitz and I. Ander, *Tetrahedron*, 1976, **32**, 1403.
18 J. D. Coyle, E. J. Haws, O. Oduntan and J. T. Rogers, *Heterocycles*, 1984, **22**, 1175.
19 P. Moses and S. Gronowitz, *Arkiv. Kemi*, 1962, **18**, 119.
20 S. Gronowitz and B. Holm, *Acta Chem. Scand.*, 1969, **23**, 2207.
21 G. M. Davies and P. S. Davies, *Tetrahedron Lett.*, 1972, 3507.
22 S. Gronowitz, B. Cederlund and A.-B. Hörnfeldt, *Chem. Scriptica*, 1974, **5**, 217.
23 M. G. Reinecke, J. G. Newsom and K. A. Almqvist, *Synthesis*, 1980, 327.
24 S. Kano, Y. Yuasa, T. Yokomatsu and S. Shibuya, *Heterocycles*, 1983, **20**, 2035.
25 C. van Pham, R. S. Macomber, H. B. Mark and H. Zimmer, *J. Org. Chem.*, 1984, **49**, 5250.
26 Ref. 8, p. 372.
27 F. Sauter, H. Fröhlich and W. Kalt, *Synthesis*, 1989, 771.
28 H. Fröhlich and W. Kalt, *J. Org. Chem.*, 1990, **55**, 2993 (see ref. 9 in this article for further references).
29 H. Fröhlich, *Prog. Heterocycl. Chem.*, 1994, **6**, in the press (see also ref. 30).
30 E. C. Taylor and D. E. Vogel, *J. Org. Chem.*, 1985, **50**, 1002 and references cited therein.
31 J. F. Bunnett, *Acc. Chem. Res.*, 1972, **5**, 139.
32 C. Paulmier, J. Morel, P. Pastour and D. Semard, *Bull. Soc. Chim. Fr.*, 1969, 2511.
33 B. Iddon, N. Khan and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1457.
34 S. Athmani, M. F. Farhat and B. Iddon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 973.
35 R. Beugelmans, M. Bois-Choussy and B. Boudet, *Tetrahedron*, 1983, **39**, 4153.
36 V. P. Litvinov and G. Fraenkel, *Bull. Akad. Sci. U.S.S.R. (Engl. Transl.)*, 1968, 1729.
37 J. Sicé, *J. Amer. Chem. Soc.*, 1953, **75**, 3697.
38 S. Gronowitz, *Arkiv. Kemi.*, 1958, **12**, 239.
39 Ya. L. Gol'dfarb, M. A. Kalik and V. K. Zav'yalova, *Chem. Heterocycl. Compds. (Engl. Transl.)*, 1981, **17**, 126.
40 Ref. 8, p. 305.
41 M. A. Keegstra, T. H. A. Peters and L. Brandsma, *Syn. Commun.*, 1990, **20**, 213.
42 R. Rossi, A. Carpita, M. Ciofalo and V. Lippolis, *Tetrahedron*, 1991, **47**, 8443.
43 L. Brandsma and H. D. Verkruijsse, *Syn. Commun.*, 1990, **20**, 2275.
44 R. L. P. de Jong and L. Brandsma, *J. Chem. Soc., Chem. Commun.*, 1983, 1056.
45 P. Fournari, R. Guilard and M. Person, *Bull. Chim. Soc. Fr.*, 1967, 4115.
46 S. Athmani and B. Iddon, *Tetrahedron*, 1992, **48**, 7689.
47 D. Briel, *Pharmazie*, 1990, **45**, 895.
48 W. Steinkopf and W. Köhler, *Justus Liebigs Ann. Chem.*, 1937, **532**, 250.
49 U. Michael and S. Gronowitz, *Acta Chem. Scand.*, 1968, **22**, 1353.
50 W. Steinkopf, H. Jacob and H. Penz, *Justus Liebigs Ann. Chem.*, 1934, **512**, 136.
51 M. Robba, R. C. Moreau and B. Roques, *Compt. Rend.*, 1964, **259**, 3568.
52 W. Steinkopf, *Justus Liebigs Ann. Chem.*, 1934, **513**, 281.
53 Ya. L. Gol'dfarb, M. A. Kalik and M. L. Kirmalova, *Bull. Acad. Sci. U.S.S.R. (Engl. Transl.)*, 1969, 1638.
54 S.-O. Lawesson, *Acta Chem. Scand.*, 1956, **10**, 1020.

Paper 4/03052D
Received 23*rd May* 1994
Accepted 13*th June* 1994