Optimisation of substitution at the 2- and 5- positions of 3,4-dialkoxythiophenes *via* the Mannich reaction: the influences of steric crowding, electrophile reactivity and temperature

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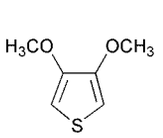
A number of 3,4-dialkoxythiophene compounds have been synthesised and their reactivities assessed *via* the Mannich reaction with secondary amines. These reactions surprisingly gave the bis-Mannich bases substituted at the 2- and 5-positions as well as the expected mono-Mannich bases substituted at the 2-position. Conditions were optimised to give symmetrical bis-2,5-Mannich bases in one step and asymmetrical bis-2,5-Mannich bases in two steps. Several bis(thien-2-ylmethyl)amines derived from 3,4-dialkoxythiophenes are reported, their synthesis being performed under both normal and high dilution conditions. Some syntheses also afforded the (thien-2-ylmethyl)amine oligomers. Further substitution of the bis(thien-2-ylmethyl)amines at the 5-position *via* the Mannich reaction also proved successful. The factors affecting the yields and substitution patterns are discussed, together with molecular modelling of the spatial requirements.

Introduction

The first genuine Mannich reaction of a thiophene ring was reported by Barker *et al.*[1] who reacted electron rich alkoxythiophenes with secondary amines and formaldehyde to afford a number of Mannich bases substituted at the 2-position. The work presented here extends the use of this reaction to link the alkoxythiophene units and investigate substitution at the 5-position using various alkoxythiophenes. The reactivities of the alkoxythiophenes were assessed *via* the yields of the Mannich bases produced in each case under identical conditions.



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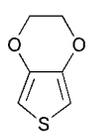

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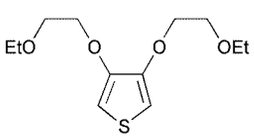

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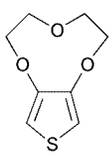

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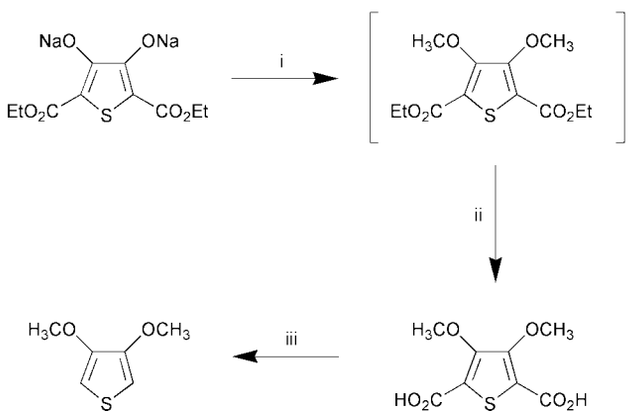
Results and discussion

Synthesis of the 3,4-dialkoxythiophenes

3,4-Dimethoxythiophene **1** was prepared from disodium 2,5-bis(ethoxycarbonyl)thiophene-3,4-diolate essentially by the literature method,[2] Scheme 1.

In order to obtain a reference sample of diethyl 3,4-dimethoxythiophene-2,5-dicarboxylate, in one instance the intermediate diethyl ester was isolated. Further preparations of 3,4-dimethoxythiophene-2,5-dicarboxylic acid were carried out without isolation of the diester. Decarboxylation of the dicarboxylic acid was attempted using the procedure of Overberger and Lal,[3] but with limited success. Their route relied upon the thermal decarboxylation of the diacid derivative in the presence of copper metal under reduced pressure, giving 3,4-dimethoxythiophene as a distillate. Attempts to reproduce this work only gave low yields (*ca.* 5–10%), and replacing the copper metal with copper(I) oxide gave only a moderate improvement (21%).



Scheme 1 (i) Me_2SO_4, Δ, 0.5 h; (ii) 6 M NaOH (aq), Δ, 1 h, then H_3O^+ (yield, 74%); (iii) Cu_2O, quinoline, Δ, 0.5 h, N_2 (yield, 74%).

The synthesis of **2** was achieved by the alkylation procedure used by Dallacker and Mues[4] which employed DMF and potassium carbonate as the solvent and base, and by substituting 1,2-dibromoethane for bromochloromethane. This gave the diester in 78% yield. Subsequent saponification and decarboxylation gave 2,3-dihydrothieno[3,4-*b*][1,4]dioxin in sufficient quantities to allow purification by distillation.

Compounds **3** and **4** were synthesised similarly employing 1-tosyl-2-ethoxyethane and bis(2-tosylethyl) ether as the alkylating agents respectively.

Application of the Mannich reaction to 3,4-dimethoxythiophene, 1

Barker *et al.* observed an apparent lack of reactivity of 3,4-dimethoxythiophene in their study of the Mannich reaction

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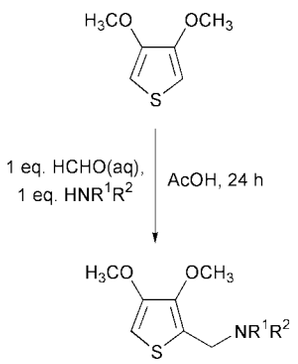
of electron rich thiophene systems.[1] However only the reaction of 3,4-dimethoxythiophene with formaldehyde and dimethylamine in glacial acetic acid was reported, the bulk of their paper dealing with the Mannich reactions of 2- and 3-methoxythiophene. The aim of the present study was to broaden our understanding of the reactive nature of dialkoxythiophenes. An extension of the work of Barker *et al.*, employing one equivalent of aqueous formaldehyde and one equivalent of dimethylamine, piperidine or morpholine, was undertaken. In order to standardise the reaction conditions so that comparisons could be made, all reactions were carried out at room temperature for a period of 24 hours, Scheme 2.



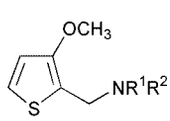
5a-c

a, $R^1 = R^2 = Me$, 5%
b, $R^1,R^2 = (CH_2)_5$, 5%
c, $R^1,R^2 = (CH_2)_2O(CH_2)_2$, 53%

Scheme 2

The Mannich bases **5a** and **5b** were isolated in very low yields as oils, although that derived from morpholine (**5c**) was formed in much higher yield (53%). Purification of these amines was achieved by extracting the basic components into an aqueous solution of hydrochloric acid, followed by basification. The residue obtained from this was purified further by column chromatography since none of the Mannich bases derived from 3,4-dimethoxythiophene withstood distillation. The NMR spectra of material obtained by distillation showed the presence of approximately 50% of **1**, indicating that some of the crude material had undergone a thermal retro-Mannich reaction. Methiodides of the above Mannich bases were formed very readily by their treatment, in diethyl ether, with methyl iodide; the salts were used in conjunction with the free amine to obtain microanalytical data, particularly for those Mannich bases isolated as oils.

For a direct comparison of the reactivity of 3,4-dimethoxythiophene with that of 3-methoxythiophene, the latter was reacted under the conditions shown in Scheme 2. This gave the Mannich bases **6a**, **6b** and **6c** in yields of 62, 75 and 87% respectively.



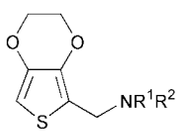
6a-c

a, $R^1 = R^2 = Me$
b, $R^1,R^2 = (CH_2)_5$
c, $R^1,R^2 = (CH_2)_2O(CH_2)_2$

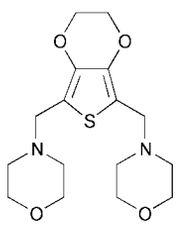
Given the yields of **5a**–**c** and **6a**–**c**, 3,4-dimethoxythiophene must exhibit lower reactivity than 3-methoxythiophene. Clearly electronic influences cannot explain this phenomenon. We attribute this effect to the spatial requirements of the adjacent methoxy groups. Molecular modelling calculations† show that the two groups are forced away from each other and towards the 2- and 5-positions of the thiophene ring, thus inhibiting any attack by the iminium electrophile. There is no bulky substituent on the 4-position of 3-methoxythiophene so that the 2-position is more open to attack by the incoming electrophile.

Application of the Mannich reaction to other 3,4-dialkoxythiophene systems

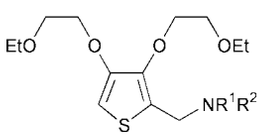
The performances of compounds **2**, **3** and **4** (**4** limited to dimethylamine) in the Mannich reaction were assessed using the standard reaction conditions developed earlier. The yields of the Mannich bases derived from 2,3-dihydrothieno[3,4-*b*]-[1,4]dioxin, **2**, were generally higher than those derived from **1**; dimethylamine and piperidine gave 72 and 82% yields of the expected tertiary amines **7a** and **7b** respectively. These greatly improved yields over the dimethoxy counterpart reinforce the proposal that steric effects hinder the substitution of 3,4-dimethoxythiophene, **1**, as clearly there can be no crowding of the 2- and 5-positions for **2**.



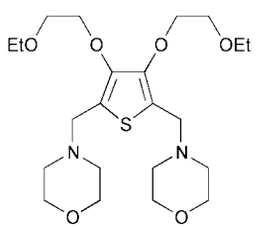
7a-c



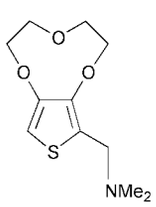
11c



8a-c



12c



9a

a, $R^1 = R^2 = Me$
b, $R^1,R^2 = (CH_2)_5$
c, $R^1,R^2 = (CH_2)_2O(CH_2)_2$

The Mannich base **7a** was tolerant of distillation, the distillate showing no trace of **2**. Interestingly the reaction employing morpholine gave a mixture of two products, the expected mono-Mannich base **7c** (52%), and the bis-Mannich base **11c** (13%). This particular reaction was exceedingly exothermic, requiring prolonged cooling to attain a steady ambient temperature. The fact that some **7c** underwent further substitution also indicates that the remaining 5-position must be relatively unhindered.

Compound **3** gave low yields of the Mannich base **8a** (12%), the yields of **8b** were moderate (42%), and the results obtained

with morpholine again indicated the presence of both the mono- and bis-Mannich bases **8c** (22%) and **12c** (24%). The latter two compounds showed similar chromatographic properties to those of their 2,3-dihydrothieno[3,4-*b*][1,4]dioxin counterparts. Compound **4** gave the Mannich base **9a** (89%) when reacted with dimethylamine. From these results it may be seen that generally where dimethylamine and piperidine are used, **3** is intermediate in reactivity between **1** (the least reactive) and **2** (the most reactive). †

The yields of those Mannich bases derived from morpholine were generally higher than those yields obtained with the other secondary amines. From these data, conclusions about the reactivity of the iminium electrophiles may be drawn. Under the conditions employed here, the *N*,*N*-dimethyl-*N*-methyleneammonium ion is similar in reactivity to the 1-methylenepiperidinium ion. The most reactive species is the 4-methylenemorpholinium ion. Some corroboration of the reactivity of the 4-methylenemorpholinium ion is afforded by Jasor *et al.*[5] They observed that in the reaction of unsymmetrical ketones with ammonium salts, the salt 4-methylenemorpholinium trifluoroacetate exhibited enhanced reaction rates.

Substitution at the 5-position

Given that the 3,4-dimethoxythiophene, **1**, was somewhat unreactive under the conditions hitherto employed, we embarked upon a study to investigate the conditions for optimum reaction.

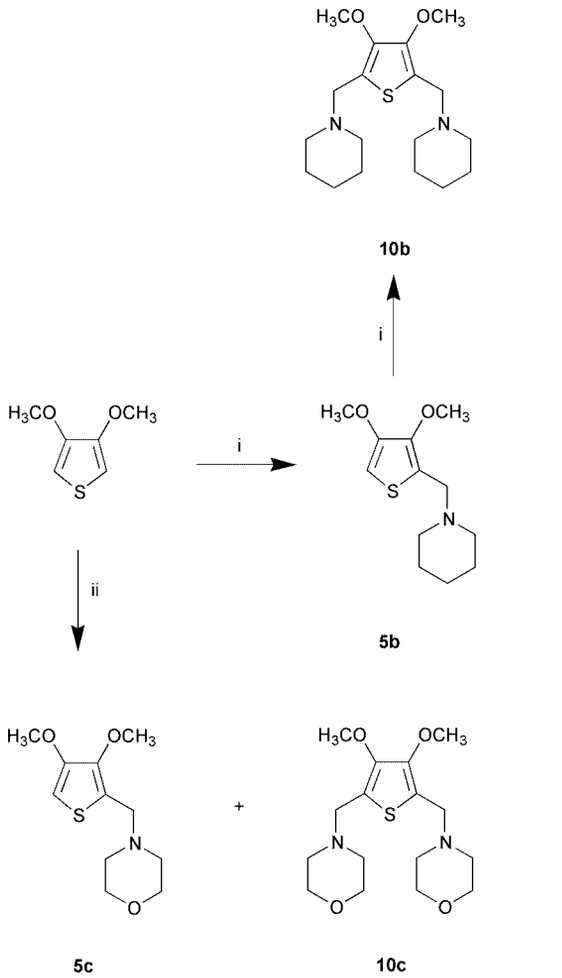
By reaction of the compound with the reagents used thus far, but employing elevated temperatures, *e.g.* 100 °C, some reasonable yields of Mannich bases were obtained. For example in this manner 3,4-dimethoxythiophene gave a 53% yield of the Mannich base **5b**, which in turn was further reacted under identical conditions to give the bis-Mannich base, **10b** (27%) (Scheme 3). Because of the innate high reactivity of the 4-methylenemorpholinium electrophile it was felt unnecessary to use high reaction temperatures in a synthesis of the mono-Mannich base, **5c**. At higher temperatures an excellent yield (78%) of the bis-Mannich base, **10c**, was obtained, some mono-substituted product also being isolated.

The dialkoxythiophene, **3**, was also found to give a number of Mannich bases in improved yields when the reactions were carried out at 100 °C (Scheme 4).

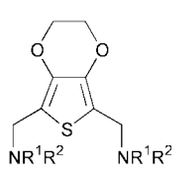
The yields of the compounds **8a**, **8c**, **12b** and **12c** agree with the predictions made about the reactivities of the thiophene moieties and the iminium electrophiles.

Thus far 3,4-ethylenedioxythiophene, **2**, had proved to be the most susceptible to the Mannich reaction relative to **1** and **3**. This was illustrated further when only the bis-Mannich bases were formed on reaction at elevated temperature. The bis-Mannich bases **11b** (86%) and **11c** (91%) were synthesised directly by the treatment of 2,3-dihydrothieno[3,4-*b*][1,4]dioxin with 2.2 equivalents of both formaldehyde and secondary amine at 100 °C, giving excellent yields of the desired products.

A successful synthesis of the bis-Mannich base **11a** could not be achieved, whether starting from the thiophene moiety **2** or from the mono-Mannich base, **7a**. This was not surprising as the iminium electrophile formed from dimethylamine had consistently proven to be the least reactive.

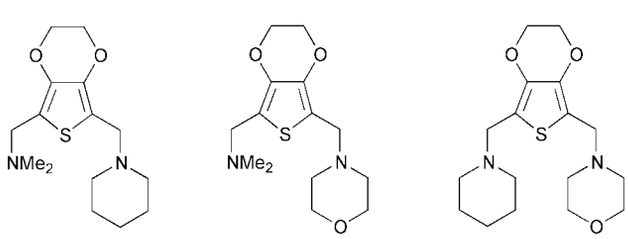


Scheme 3 (i) 1 eq. 37% HCHO(aq), 1 eq. piperidine, AcOH, 100 °C, 4 h (yields **5b**, 53%, **10b**, 27%); (ii) 2.2 eq. 37% HCHO(aq), 2.2 eq. morpholine, AcOH, 100 °C, 4 h (yields, **5c**, 21%, **10c**, 78%).



11b,c

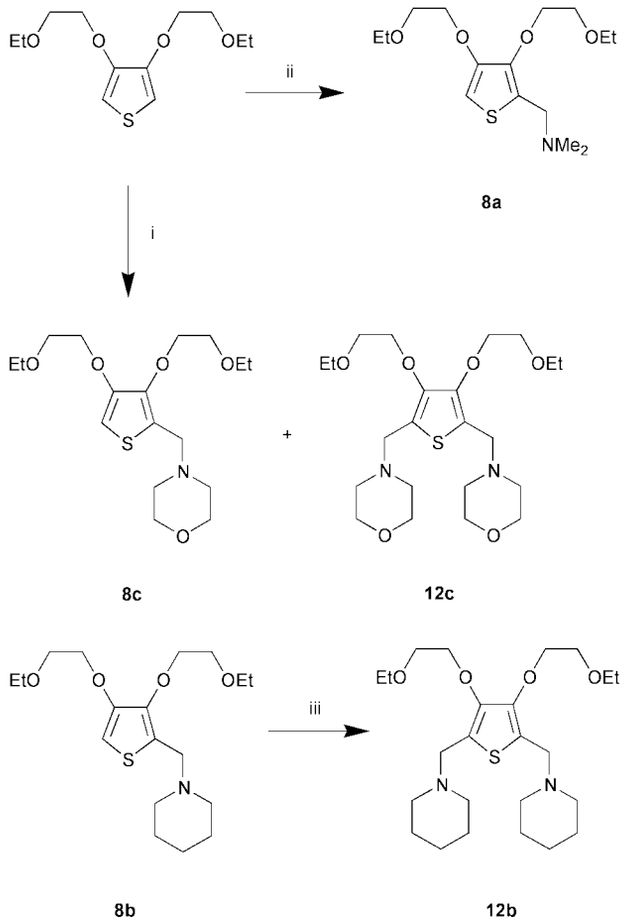
b, $R^1,R^2 = (CH_2)_5$
c, $R^1,R^2 = (CH_2)_2O(CH_2)_2$



13 **14** **15**

Syntheses of "mixed" bis-Mannich bases **13**, **14** and **15** were also attempted. The general strategy used here was to substitute the vacant 5-position of a mono-Mannich base with the more reactive iminium moiety. Thus, **7a** was reacted at elevated temperatures with formaldehyde and either piperidine or morpholine in acetic acid to give the bis-Mannich bases **13** and **14** in yields of 54 and 74%, respectively. However, both were unstable and although satisfactory NMR spectra were

† The lowest energy conformer of 3,4-dimethoxythiophene, **1**, was obtained *via* systematic modification of the two methyl–thiophene torsions (defined by atoms C2-C3-O1-C6 and C5-C4-O2-C7) from 0–180 degrees in 20 degree increments (one being fixed at 0, then −20 degrees *etc.*) and subsequent single point energy calculation. The energy calculation was carried out *via* MOPAC[10] using the PM3 semi-empirical method. The coordinates of the lowest energy conformer (C2-C3-O1-C6 and C5-C4-O2-C7 = 0 degrees) were then used as the starting point for a full geometry optimisation *via* GAUSSIAN98W[11] at the HF/6-31+G(d) level of theory. Harmonic frequencies were computed in order to characterise the stationary point. No imaginary frequencies were present.



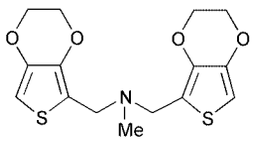
Scheme 4 (i) 2.2 eq. HCHO(aq), 2.2 eq. morpholine, AcOH, 100 °C, 4 h (yields, **8c**, 52%, **12c**, 16%); (ii) 1 eq. HCHO(aq), 1 eq. Me_2NH(aq), AcOH, 100 °C, 4 h (yield, **8a**, 37%); (iii) 1 eq. HCHO(aq), 1 eq. piperidine, AcOH, 100 °C, 4 h (yield, **12b**, 35%).

obtained, no microanalytically pure samples of **13** and **14** or their methiodide salts could be isolated. Compound **15** was synthesised by the reaction of **7b** with formaldehyde and morpholine to give a 91% yield of the desired bis-Mannich base.

Linking the thiophene moieties: synthesis of bis(thien-2-ylmethyl) Mannich bases

Having studied the aminomethylation of a variety of 3,4-dioxythiophenes and optimised substitution conditions for both the 2- and 5-positions the work was extended to link the thiophene moieties through primary amines or secondary diamines. Thus, the reaction of methylamine and two equivalents of 2,3-dihydrothieno[3,4-*b*][1,4]dioxin was initially performed under non-high dilution conditions, which, with two equivalents of formaldehyde gave the desired Mannich base, **16** (37%), accompanied by the oligomeric compound, **17** (21%). The latter was easily identifiable from the carbon-13 NMR spectrum, which showed six signals in the aromatic region, two signals arising from a symmetrically substituted 2,3-dihydrothieno[3,4-*b*][1,4]dioxin moiety, and four signals ascribed to a 2,3-dihydrothieno[3,4-*b*][1,4]dioxin ring substituted in the 2-position. However, the compound decomposed too rapidly for satisfactory microanalyses and mass spectra to be obtained.

Unfortunately, under these reaction conditions, polymerisation was extensive with the secondary diamines *N*,*N*′-dimethylethylenediamine and piperazine. *N*,*N*′-Dimethylethylenediamine gave a polymeric oil which was highly unstable, darkening rapidly in the air. Piperazine afforded high yields (>80%) of an amorphous white solid possessing high thermal stability, not decomposing until *ca.* 300 °C. In view of these disappointing results, a series of high dilution Mannich reactions were performed in which separate glacial acetic acid



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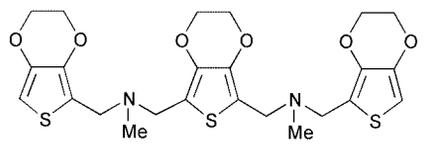

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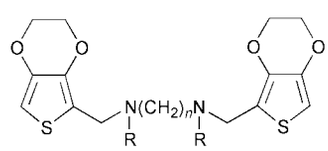
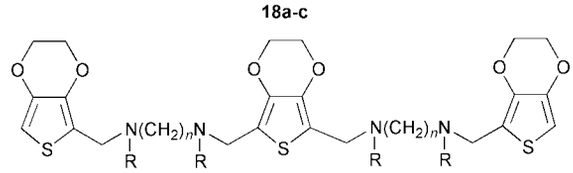
solutions of 3,4-ethylenedioxythiophene and the diamine, together with two equivalents of aqueous formaldehyde, were fed at a rate of 2.2 mmol h^{-1} into a further small volume of glacial acetic acid. The same two secondary diamines were employed in this study, and a third, *N*,*N*′-dimethylpropane-1,3-diamine, was also used. Under these conditions polymerisation was still the dominating reaction, although this tendency was at its lowest with *N*,*N*′-dimethylethylenediamine, which gave the highest yield (45%) of the desired bis(thien-2-ylmethyl) derivative, **18a**. The homologous *N*,*N*′-dimethylpropane-1,3-diamine showed the greatest tendency to polymerise, with the result that only a 12% yield of compound **18b** was obtained. 1,4-Bis(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl)piperazine, **18c**, was given in a yield intermediate between the previous two (22%). The nature of compounds **18a**–**c** was clear from their NMR and mass spectra. In all cases, the bis(thien-2-ylmethyl) derivatives were accompanied by small quantities of the oligomer **19a** (7%), (**19b**) 6% or **19c** (9%).



18a-c

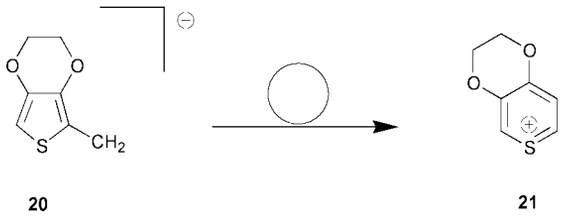


19a-c

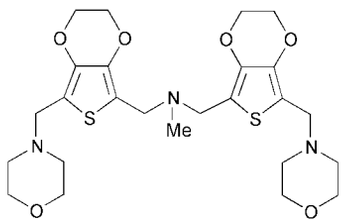
a, R = Me, *n* = 2
b, R = Me, *n* = 3
c, R,R = CH_2CH_2 , *n* = 2

Neither of the oligomers **19a** or **19b** were sufficiently stable when isolated to obtain microanalytical data or mass spectra. The mass spectrum of **18c** is worthy of further discussion. In common with all the thien-2-ylmethyl Mannich bases, compound **18c** gave an intense signal with an *m*/*e* value of 155 (89%). This was attributed to a 5-methylene-2,3-dihydrothieno-[3,4-*b*][1,4]dioxin fragment, **20**, which by comparison with the cycloheptatriene cation (the tropylium ion), obtained when toluene is subjected to mass spectroscopic analysis, may be assumed to undergo a rearrangement to a thiopyrylium ion, **21**. Apart from the molecular ion the only other signal of any note was that with an *m*/*e* value of 249 (100%) corresponding to the loss of fragment **20** from the molecule **18c**.

The reactive thiophene macrocycle, **4**, was also used in the synthesis of a bis(thien-2-ylmethyl) compound, by the reaction



20 21



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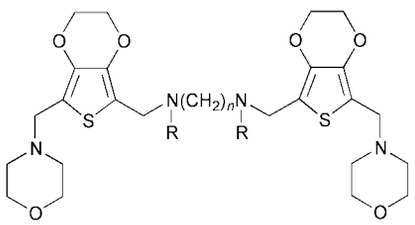
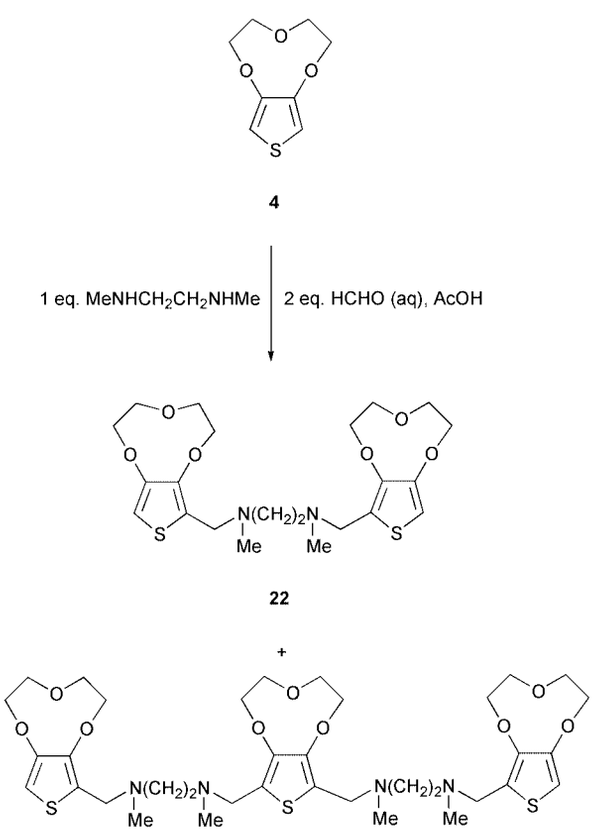


25a-c

a, R = Me, *n* = 2
b, R = Me, *n* = 3
c, R,R = CH_2CH_2 , *n* = 2

with *N*,*N*′-dimethylethylenediamine and two equivalents of formaldehyde under the high dilution conditions described. This gave compound **22** (46%), accompanied by the tetraamine, **23** (5%), Scheme 5. Compound **23**, like the related compounds



4

1 eq. $MeNHCH_2CH_2NHMe$ | 2 eq. HCHO (aq), AcOH

22

+

23

Scheme 5

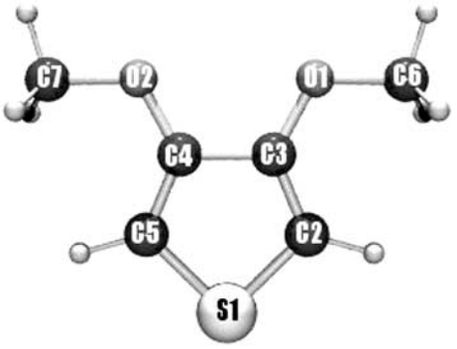


Fig. 1 Bond lengths: S(1)–C(2) 1.733 Å, S(1)–C(5) 1.733 Å, O(1)–C(3) 1.337 Å, O(1)–C(6) 1.400 Å, C(2)–C(3) 1.346 Å, O(2)–C(4) 1.337 Å, O(2)–C(7) 1.400 Å, C(3)–C(4) 1.449 Å, C(4)–C(5) 1.346 Å. Bond angles: C(2)–S(1)–C(5) 91.30°, C(3)–O(1)–C(6) 117.74°, S(1)–C(2)–C(3) 111.86°, C(4)–O(2)–C(7) 117.74°, O(1)–C(3)–C(2) 129.09°, O(1)–C(3)–C(4) 118.42°, C(2)–C(3)–C(4) 112.49°, O(2)–C(4)–C(3) 118.42°, O(2)–C(4)–C(5) 129.09°, C(3)–C(4)–C(5) 112.49°, S(1)–C(5)–C(4) 111.86°.

19a,**b**, was not sufficiently stable to permit mass spectroscopic or microanalysis, but NMR spectroscopy supported the structural assignment given.

Substitution at the 5-position of the thien-2-ylmethyl Mannich bases

In a study of the behaviour towards a further Mannich reaction of the 2-thienylmethyl Mannich bases, **16** and **18a**–**c**, the bases were treated with morpholine and two equivalents of formaldehyde. In this way, a series of morpholine derivatives, **24** (97%), **25a** (97%), **25b** (92%) and **25c** (83%) were prepared in excellent yields.

Conclusions

The reactivities of 3,4-dialkoxythiophenes towards electrophilic substitution *via* the Mannich reaction were found to be dependent on the nature of the oxygen substituents, the electrophile employed and the temperature of the reaction. The nature of the groups attached to the oxygens at the 3- and 4-positions influences the reactivity of the thiophene moiety *via* the steric crowding imposed at the 2- and 5-positions. Hence 3,4-dimethoxythiophene, **1**, is less likely to undergo the Mannich reaction under the standard conditions used than is 2,3-dihydrothieno[3,4-*b*][1,4]dioxin, **2**. This is easily visualised from the molecular modelling† where for compound **1** the lowest energy conformer (Fig. 1) has both the 2- and 5-positions crowded by the methoxy groups, whereas for compound **2** clearly the 2- and 5-positions must be unhindered and open to attack by the electrophile.

The nature of the electrophile employed influences the yields of the Mannich bases. For the amines used in this work the order of reactivity of the iminium electrophiles proved to be morpholine > piperidine > dimethylamine. The greater reactivity of the morpholine ion was also demonstrated by the fact that in the mono-substitution reactions, often some bis-Mannich base substituted at both the 2- and 5-positions was obtained.

To optimise reaction at the 5-position elevated temperature was employed. Substitution at both the 2- and 5-positions in one reaction was achieved, giving symmetrical Mannich bases in high yields. Asymmetrical Mannich bases were prepared *via* isolation of the mono-Mannich base, which was then subjected to the Mannich reaction at elevated temperature with the appropriate amine.

In order to link the thiophene moieties the best results were achieved under high dilution conditions. Even under these conditions some oligomeric compounds containing three thiophene moieties (one thiophene moiety undergoing substitution

at the 2- and 5-positions) were isolated in low yields although these were generally unstable. Substitution at the 5-position of the bis(thien-2-ylmethyl) Mannich bases was achieved at elevated temperature using the more reactive morpholine electrophile.

In conclusion, a series of 2- and 2,5-substituted 3,4-dialkoxythiophenes were prepared and the optimum conditions for mono- and disubstitution investigated. The important factors affecting reaction conditions were found to be the crowding imposed upon the 2- and 5-positions by the 3- and 4-substituents, the nature of the electrophile and the temperature of reaction. This investigation is part of our ongoing work on novel thiophene based ligands and macrocycles.[6–8]

Experimental

General

All reagents and solvents were used as supplied unless otherwise stated. In general, organic solutions of products were dried ($MgSO_4$), filtered, and the solvent was removed by rotary evaporation. Solvents for chromatographic analysis were distilled prior to use. Unless otherwise stated, light petroleum refers to the fraction bp 40–60 °C.

Chromatographic analysis

For thin layer chromatography (TLC), 250 pm silica gel 60A MK 6F plates were used. Alumina plates were aluminium oxide $150F_{254}$, neutral (type T), layer thickness 0.2 mm. For column chromatography, silica gel 0.06–0.2 mm, pore diameter *ca.* 4 nm was employed. Alumina was neutral Brockmann Grade 1 for chromatographic analysis. For centrifugal chromatography, a Chromatotron Model 7924 T was used. The adsorbents used to coat the rotors were silica gel $60PF_{254}$, containing gypsum and aluminium oxide, $60PF_{254}$, Type E. The coatings with alumina were glue bound to the rotors, added at a rate of 1–5 cm^3 per 60 g of adsorbent, to the initial slurry.

Instrumentation

Where a syringe pump was used, the type was a model A pump fitted with motors colour coded yellow, manufactured by Razel Scientific Instruments Inc., Stamford, Connecticut, USA. These motors gave flow rates of 0.661, 1.179 and 2.412 $cm^3\ h^{-1}$ with 10, 20, and 50 cm^3 syringes, respectively. Melting points were taken on a Gallenkamp apparatus model 3A 5120, and are reported uncorrected.

Infrared spectra were obtained using a Perkin–Elmer 1600 series FTIR Spectrophotometer. Nuclear magnetic resonance spectroscopy (NMR) was performed with a JEOL EX 270 MHz machine; solvents used were deuterated chloroform or deuterated dimethyl sulfoxide. The solvent is specified in the experimental section in parenthesis before the NMR data. Mass spectra were obtained using a Finnigan Mat LCQ(TM) mass spectrometer. Microanalyses were carried out by the University of Nottingham analytical services department.

3,4-Dialkoxythiophenes

These were prepared (with appropriate adaptation) *via* the reactions outlined in Scheme 1, employing methods previously reported in the literature.[2–4,9] Details of treatment after the final (decarboxylation) reaction are given.

3,4-Dimethoxythiophene, 1. Prepared from disodium 2,5-bis-(ethoxycarbonyl)thiophen-3,4-diolate by the literature method.[2] The crude material was distilled to give the title compound (74%), bp 115–118 °C/20 mmHg (Literature[3] 110 °C/17 mmHg).

2,3-Dihydrothieno[3,4-*b*][1,4]dioxin, 2. Prepared by the literature method,[4] employing DMF and potassium carbonate as solvent and base, and by substituting 1,2-bromoethane for bromochloromethane. Distillation afforded the title compound (71%), bp 110–112 °C/20 mmHg. The spectroscopic data were in accordance with the literature values[9] (Found: C, 50.98; H, 4.34. $C_6H_6O_2S$ requires C, 50.69; H, 4.25%); *m/e* 142 (M^+).

3,4-Bis(2-ethoxyethoxy)thiophene, 3. Prepared by the literature method,[4] employing DMF and potassium carbonate as solvent and base, and by substituting 1-tosyl-2-ethoxyethane for bromochloromethane. Distillation gave the title *aromatic ether* (70%), bp 162–164 °C/2 mmHg; ν_{max}(film) 3110, 2980, 2930, 2870 and 1565 cm^{-1}; $\delta_H(CDCl_3)$ 1.22 (6H, t, *J* 6.93, OCH_2CH_3), 3.58 (4H, q, *J* 6.93, OCH_2CH_3), 3.76–3.80 (4H, m, $EtOCH_2$), 4.11–4.17 (4H, m, $ArOCH_2$), 6.23 (2H, s, ArH); $\delta_C(CDCl_3)$ 15.1 and 15.2 (CH_3), 66.8, 68.7 and 69.9 (OCH_2), 97.7–98.5 (C2/C5), 147.2 (C3/C4) (Found: C, 55.53; H, 7.97. $C_{12}H_{20}O_4S$ requires C, 55.36; H, 7.74%).

2,3,5,6-Tetrahydrothieno[3,4-*b*][1,4,7]trioxonin, 4. Prepared by the literature method,[4] employing DMF and potassium carbonate as solvent and base, and by substituting bis(2-tosylethyl) ether for bromochloromethane. Purification by column chromatography (silica; light petroleum–EtOAc, 3 : 1) gave the title *aromatic ether* as a colourless oil (74%); ν_{max}(film) 3100, 2940, 2860 and 1550 cm^{-1}; $\delta_H(CDCl_3)$ 3.87–3.90 (4H, m, CH_2OCH_2), 4.27–4.30 (4H, m, $ArOCH_2$), 6.56 (2H, s, ArH); $\delta_C(CDCl_3)$ 72.4 and 74.2 (OCH_2), 107.8 (C2/C5), 150.0 (C3/C4) (Found: C, 51.50; H, 5.58. $C_8H_{10}O_3S$ requires C, 51.60; H, 5.41%).

Application of the Mannich reaction to 3,4-dialkyloxythiophene systems: synthesis of mono-Mannich bases from secondary amines.[1] General method

The amine (40% aqueous solution, for dimethylamine) (1.1 eq.) and aqueous formaldehyde (37%, 1.1 eq.) were added to glacial acetic acid (0.3 $cm^3\ mmol^{-1}$) with ice cooling. The thiophene moiety (1.0 eq.) was added and the reaction was stirred for 24 hours. Basification with aqueous sodium hydroxide (4 M) and extraction with diethyl ether (3 × 30 cm^3) gave the free organic components. The ethereal solution was extracted with aqueous hydrochloric acid (2 M, 3 × 50 cm^3). The aqueous acidic layer was basified with sodium hydroxide solution (4 M) and extracted with dichloromethane (3 × 30 cm^3). The organic phase was treated in the usual way, to give the crude Mannich base. Purification was by centrifugal chromatography (alumina; light petroleum–EtOAc, 6 : 1), unless stated otherwise.

***N*-[(3,4-Dimethoxythien-2-yl)methyl]-*N*,*N*-dimethylamine, 5a.** Purification by column chromatography (alumina; light petroleum–EtOAc, 2 : 1) gave the title compound (5%) as an oil, mp (methiodide) 152–154 °C; $\delta_H(CDCl_3)$ 2.27 (6H, s, $N(CH_3)_2$), 3.53 (2H, s, $ArCH_2N$), 3.81 (6H, s, $ArOCH_3$), 6.10 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 45.1 (NCH_2), 54.5 ($ArCH_2N$), 57.1 (OCH_3 on C4), 60.8 (OCH_3 on C3), 94.4 (C5), 123.9 (C2), 144.7 (C3), 150.3 (C4) (Found: C, 53.63; H, 7.75; N, 6.75. $C_9H_{15}NO_2S$ requires C, 53.70; H, 7.51; N, 6.96%); *m/e* 201 (M^+).

1-[(3,4-Dimethoxythien-2-yl)methyl]piperidine, 5b. 5% (reaction at 100 °C gives 53%), oil, mp (methiodide) 148–150 °C; $\delta_H(CDCl_3)$ 1.43 (2H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.57 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.41–2.44 (4H, m, NCH_2), 3.59 (2H, s, $ArCH_2N$), 3.81 (6H, s, $ArOCH_3$), 6.08 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 24.3 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 54.0 ($ArCH_2N$), 54.1 (NCH_2), 57.0 (OCH_3 on C4), 60.8 (OCH_3 on C3), 94.1 (C5), 124.0 (C2), 144.6 (C3), 150.3 (C4) (Found: C, 60.18; H, 8.22; N, 5.81. $C_{12}H_{19}NO_2S$ requires C, 59.82; H, 7.94; N, 5.80%); *m/e* 241 (M^+).

4-[(3,4-Dimethoxythien-2-yl)methyl]morpholine, 5c. 53%, oil, mp (methiodide) 143–145 °C; $\delta_H(CDCl_3)$ 2.48–2.51 (4H, m,

NCH_2), 3.60 (2H, s, $ArCH_2N$), 3.68–3.72 (4H, m, CH_2OCH_2), 3.81 (3H, s, $ArOCH_3$), 3.82 (3H, s, $ArOCH_3$), 6.10 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 53.2 (NCH_2), 53.7 ($ArCH_2N$), 57.1 (OCH_3 on C4), 60.8 (OCH_3 on C3), 67.0 (morpholino OCH_2), 94.5 (C5), 122.8 (C2), 144.9 (C3), 150.3 (C4) (Found: C, 54.29; H, 7.20; N, 5.74. $C_{11}H_{17}NO_3S$ requires C, 54.30; H, 7.04; N, 5.76%); *m/e* 243 (M^+).

Compounds 6a–c. The analytical data for these compounds agreed with the literature values.[1]

***N*-[(2,3-Dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)methyl]-*N*,*N*-dimethylamine, 7a.** 72%, oil, bp 115 °C/18 mmHg; $\delta_H(CDCl_3)$ 2.27 (6H, s, $N(CH_3)_2$), 3.48 (2H, s, $ArCH_2N$), 4.18 (4H, s, $ArOCH_2$), 6.24 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 44.9 (NCH_3), 53.8 ($ArCH_2N$), 64.6 ($ArOCH_2$), 97.6 (C5), 114.1 (C2), 139.2 (C3), 141.2 (C4) (Found: C, 53.96; H, 6.77; N, 6.88. $C_9H_{13}NO_2S$ requires C, 54.25; H, 6.58; N, 7.03%); *m/e* 199 (M^+).

1-[(2,3-Dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)methyl]piperidine, 7b. 82%, oil, mp (methiodide) 161–163 °C; $\delta_H(CDCl_3)$ 1.47 (2H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.57 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.42–2.45 (4H, m, NCH_2), 3.56 (2H, s, $ArCH_2N$), 4.17 (4H, s, $ArOCH_2$), 6.22 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 24.2 ($CH_2CH_2CH_2$), 25.9 ($CH_2CH_2CH_2$), 53.3 ($ArCH_2N$), 53.8 (NCH_2), 64.6 ($ArOCH_2$), 97.5 (C5), 114.2 (C2), 139.2 (C3), 141.2 (C4) (Found: C, 60.11; H, 7.55; N, 5.67. $C_{12}H_{17}NO_2S$ requires C, 60.22; H, 7.16; N, 5.85%); *m/e* 239 (M^+).

4-[(2,3-Dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)methyl]morpholine, 7c. 52% (and **11c**, 13%), oil, mp (methiodide) 116–118 °C; $\delta_H(CDCl_3)$ 2.45–2.49 (4H, m, NCH_2), 3.55 (2H, s, $ArCH_2N$), 3.66–3.69 (4H, m, CH_2OCH_2), 4.14 (4H, s, $ArOCH_2$), 6.23 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 52.9 ($ArCH_2N$), 53.0 (NCH_2), 64.4 ($ArOCH_2$), 64.5 ($ArOCH_2$), 66.8 (morpholino OCH_2), 97.8 (C5), 113.2 (C2), 139.4 (C3), 141.1 (C4) (Found: C, 54.66; H, 6.54; N, 5.67. $C_{11}H_{15}NO_3S$ requires C, 54.75; H, 6.27; N, 5.80%); *m/e* 241 (M^+).

***N*-{[3,4-Bis(2-ethoxyethoxy)thien-2-yl]methyl}-*N*,*N*-dimethylamine, 8a.** Purification by column chromatography (alumina; light petroleum–EtOAc, 10 : 1) gave the title compound (12%) as an oil; $\delta_H(CDCl_3)$ 1.22 (3H, t, *J* 6.93, OCH_2CH_3), 1.24 (3H, t, *J* 5.61, OCH_2CH_3), 2.27 (6H, s, NCH_3), 3.57 (2H, s, $ArCH_2N$), 3.57 (2H, q, *J* 6.93, OCH_2CH_3), 3.58 (2H, q, *J* 5.61, OCH_2CH_3), 3.65–3.69 (2H, m, CH_2OEt), 3.76–3.79 (2H, m, CH_2OEt), 4.08–4.11 (2H, m, $ArOCH_2$), 4.14–4.18 (2H, m, $ArOCH_2$), 6.12 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 15.2 and 15.3 (OCH_2CH_3), 45.1 (NCH_3), 54.4 ($ArCH_2N$), 66.5, 66.8, 68.8, 69.4, 69.5 and 72.0 (OCH_2), 95.4 (C5), 124.4 (C2), 143.5 (C3), 149.1 (C4) (Found: C, 56.71; H, 8.92; N, 4.59. $C_{15}H_{27}NO_4S$ requires C, 56.75; H, 8.57; N, 4.41%); *m/e* 273 (M − $N(Me)_2$).

1-{[3,4-Bis(2-ethoxyethoxy)thien-2-yl]methyl}piperidine, 8b. Purification by column chromatography (alumina; light petroleum–EtOAc, 10 : 1) gave the title compound (42%) as an oil; $\delta_H(CDCl_3)$ 1.22 (3H, t, *J* 6.93, OCH_2CH_3), 1.24 (3H, t, *J* 6.93, OCH_2CH_3), 1.42 (2H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.56 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.41 (4H, m, NCH_2), 3.56 (2H, q, *J* 6.93, OCH_2CH_3), 3.58 (2H, q, *J* 6.93, OCH_2CH_3), 3.62 (2H, s, $ArCH_2N$), 3.64–3.69 (2H, m, CH_2OEt), 3.76–3.79 (2H, m, CH_2OEt), 4.07–4.11 (2H, m, $ArOCH_2$), 4.14–4.17 (2H, m, $ArOCH_2$), 6.09 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 15.2 and 15.3 (OCH_2CH_3), 24.3 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 54.1 (NCH_2), 53.9 ($ArCH_2N$), 66.5, 66.8, 68.9, 69.4, 69.5 and 72.0 (OCH_2), 95.2 (C5), 124.3 (C2), 143.5 (C3), 149.2 (C4) (Found: C, 60.46; H, 9.17; N, 3.90. $C_{18}H_{31}NO_4S$ requires C, 60.47; H, 8.74; N, 3.92%); *m/e* 155 (M − $N(CH_2)_5$ − 2(CH_2OEt)).

4-{[3,4-Bis(2-ethoxyethoxy)thien-2-yl]methyl}morpholine, 8c. 46% (and **12c**, 24%), oil; $\delta_H(CDCl_3)$ 1.22 (3H, t, *J* 6.93, OCH_2CH_3), 1.24 (3H, t, *J* 6.93, OCH_2CH_3), 2.48–2.52 (4H, m, NCH_2), 3.57 (2H, q, *J* 6.93, OCH_2CH_3), 3.58 (2H, q, *J* 6.93, OCH_2CH_3), 3.64 (2H, s, $ArCH_2N$), 3.65–3.79 (4H, m, CH_2OEt and 4H, m, morpholino OCH_2), 4.07–4.11 (2H, m, $ArOCH_2$), 4.15–4.19 (2H, m, $ArOCH_2$), 6.12 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 15.2 and 15.3 (OCH_2CH_3), 53.2 (NCH_2), 53.5 ($ArCH_2N$), 66.5, 66.8, 68.8, 69.4, 69.5 and 72.0 (OCH_2), 67.0 (morpholino OCH_2) 95.6 (C5), 123.2 (C2), 143.9 (C3), 149.2 (C4) (Found: C, 56.59; H, 8.22; N, 3.82. $C_{17}H_{29}NO_5S$ requires C, 56.8; H, 8.13; N, 3.90%); *m/e* 314 (M − OEt).

***N*,*N*-Dimethyl[(2,3,5,6-tetrahydrothieno[3,4-*b*][1,4,7]trioxonin-8-yl)methyl]amine, 9a.** Purification by column chromatography (alumina; light petroleum–EtOAc, 4 : 1) gave the title compound (89%) as an oil, mp (methiodide) 178–180 °C; $\delta_H(CDCl_3)$ 2.27 (6H, s, NCH_3), 3.51 (2H, s, $ArCH_2N$), 3.87–3.92 (4H, m, CH_2OCH_2), 4.24–4.29 (4H, m, $ArOCH_2$), 6.49 (1H, s, Ar-H); $\delta_C(CDCl_3)$ 45.2 (NCH_3), 54.7 ($ArCH_2N$), 71.9, 72.3, 73.6, 74.3 (OCH_2) (Found: C, 54.18; H, 7.25; N, 5.52. $C_{11}H_{17}NO_3S$ requires C, 54.30; H, 7.04; N, 5.76%); highest fragment *m/e* 182.

Substitution at the 5-position: synthesis of the bis-Mannich bases. General method

The bis-Mannich bases were obtained as by-products from the mono-substitution reactions or were prepared by the reaction of either: the mono-Mannich base (1.0 eq.) with the amine (1.1 eq.) and aqueous formaldehyde (37%, 1.1 eq.) in glacial acetic acid (1 cm^3 $mmol^{-1}$); or the 3,4-dialkoxythiophene (1.0 eq.) with the amine (2.2 eq.) and aqueous formaldehyde (37%, 2.2 eq.) in glacial acetic acid (1 cm^3 $mmol^{-1}$). Heat was applied for 4 hours by means of an oil bath (100 °C). The cooled reaction mixture was basified with aqueous sodium hydroxide (4 M) and extracted with diethyl ether (3 × 30 cm^3). The ethereal portions were treated in the usual fashion. The bis-Mannich bases were purified by centrifugal chromatography (alumina; light petroleum–EtOAc, 6 : 1) unless stated otherwise.

2,5-Bis(piperidin-1-ylmethyl)-3,4-dimethoxythiophene, 10b. Purification by centrifugal chromatography (alumina; light petroleum–EtOAc, 30 : 1) gave the title compound (27%) as an oil; $\delta_H(CDCl_3)$ 1.41 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.57 (8H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.41–2.45 (8H, m, CH_2NCH_2), 3.55 (4H, s, $ArCH_2N$), 3.81 (6H, s $ArOCH_3$); $\delta_C(CDCl_3)$ 24.3 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 54.1 (NCH_2), 54.1 ($ArCH_2N$), 60.7 ($ArOCH_3$), 121.4 (C2/C5), 146.8 (C3/C4) (Found: C, 63.89; H, 9.17; N, 8.19. $C_{18}H_{30}N_2O_2S$ requires C, 63.87; H, 8.93; N, 8.28%); *m/e* 241 (M − $CH_2N(CH_2)_5$).

2,5-Bis(morpholin-4-ylmethyl)-3,4-dimethoxythiophene, 10c. 78%, mp 85.5–87.5 °C; $\delta_H(CDCl_3)$ 2.48–2.51 (8H, m, CH_2NCH_2), 3.57 (4H, s, $ArCH_2N$), 3.69–3.72 (8H, m, CH_2OCH_2), 3.82 (6H, s $ArOCH_3$); $\delta_C(CDCl_3)$ 53.2 (NCH_2), 53.7 ($ArCH_2N$), 60.8 ($ArOCH_3$), 67.0 (CH_2OCH_2), 120.8 (C2/C5), 147.2 (C3/C4) (Found: C, 56.29; H, 7.93; N, 8.35. $C_{16}H_{26}N_2O_4S$ requires C, 56.12; H, 7.65; N, 8.18%); *m/e* 240 (M − $CH_2N(CH_2CH_2)_2O$ − 2H).

2,5-Bis(piperidin-1-ylmethyl)-2,3-dihydrothieno[3,4-*b*][1,4]-dioxin, 11b. 86%, mp 98–100 °C; $\delta_H(CDCl_3)$ 1.39 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.58 (8H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.43–2.46 (8H, m, CH_2NCH_2), 3.56 (4H, s, $ArCH_2N$), 4.16 (4H, s $ArOCH_2$); $\delta_C(CDCl_3)$ 24.2 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 53.2 (NCH_2), 53.9 ($ArCH_2N$), 64.6 ($ArOCH_2$), 111.8 (C2/C5), 138.6 (C3/C4) (Found: C, 64.26; H, 8.61; N, 8.30. $C_{18}H_{28}N_2O_2S$ requires C, 64.25; H, 8.39; N, 8.33%); *m/e* 336 (M^+).

2,5-Bis(morpholin-4-ylmethyl)-2,3-dihydrothieno[3,4-*b*][1,4]-dioxin, 11c. 91%, mp 83–85 °C; $\delta_H(CDCl_3)$ 2.49–2.52 (8H, m, CH_2NCH_2), 3.56 (4H, s, $ArCH_2N$), 3.69–3.73 (8H, m, CH_2OCH_2), 4.17 (4H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 52.9 ($ArCH_2N$), 53.0 (NCH_2), 64.7 ($ArOCH_2$), 66.9 (CH_2OCH_2), 111.4 (C2/C5), 138.9 (C3/C4) (Found: C, 56.43; H, 7.18; N, 8.42. $C_{16}H_{24}N_2O_4S$ requires C, 56.45; H, 7.11; N, 8.23%); *m/e* 254 (M − $N(CH_2CH_2)_2O$).

2,5-Bis(piperidin-1-ylmethyl)-3,4-bis(2-ethoxyethoxy)thiophene, 12b. 35%, oil; $\delta_H(CDCl_3)$ 1.23 (6H, t, *J* 6.93, OCH_2CH_3), 1.39 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.57 (8H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.43–2.46 (8H, m, CH_2NCH_2), 3.56 (4H, q, *J* 6.93, OCH_2CH_3), 3.62 (4H, s, $ArCH_2N$), 3.64–3.69 (4H, m, CH_2OEt), 4.11–4.15 (4H, m, $ArOCH_2$); $\delta_C(CDCl_3)$ 15.3 (OCH_2CH_3), 24.3 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 53.5 ($ArCH_2N$), 54.1 (NCH_2), 66.6, 69.4 and 72.4 (OCH_2), 121.8 (C2/C5), 145.7 (C3/C4) (Found: C, 63.51; H, 9.50; N, 6.05. $C_{24}H_{42}N_2O_4S$ requires C, 63.40; H, 9.31; N, 6.16%); *m/e* 454 (M^+).

2,5-Bis(morpholin-4-ylmethyl)-3,4-bis(2-ethoxyethoxy)thiophene, 12c. 24%, oil; $\delta_H(CDCl_3)$ 1.23 (6H, t, *J* 6.93, OCH_2CH_3), 2.49–2.52 (8H, m, CH_2NCH_2), 3.56 (4H, q, *J* 6.93, OCH_2CH_3), 3.61 (4H, s, $ArCH_2N$), 3.64–3.68 (4H, m, CH_2OEt), 3.69–3.73 (8H, m, morpholino OCH_2), 4.12–4.16 (4H, m, $ArOCH_2$); $\delta_C(CDCl_3)$ 15.3 (OCH_2CH_3), 53.2 (NCH_2), 53.6 ($ArCH_2N$), 66.6, 69.4 and 72.4 (OCH_2), 67.0 (morpholino OCH_2), 121.5 (C2/C5), 146.1 (C3/C4) (Found: C, 57.80; H, 8.35; N, 5.99. $C_{22}H_{38}N_2O_6S$ requires C, 57.62; H, 8.35; N, 6.11%); *m/e* 458 (M^+).

***N*,*N*-Dimethyl-*N*-{[7-(piperidin-1-ylmethyl)-2,3-dihydrothieno-[3,4-*b*][1,4]dioxin-5-yl]methyl}amine, 13.** 54%, oil; $\delta_H(CDCl_3)$ 1.39 (2H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.56 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.21 (6H, s, $N(CH_3)_2$), 2.41–2.44 (4H, m, CH_2NCH_2), 3.51 (2H, s, $ArCH_2N$), 3.53 (2H, s, $ArCH_2N$), 4.17 (4H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 24.1 ($CH_2CH_2CH_2$), 25.9 ($CH_2CH_2CH_2$), 45.0 (NCH_3), 53.0 ($ArCH_2N$), 53.2 (NCH_2), 54.2 ($ArCH_2N$), 64.6, 64.7 ($ArOCH_2$), 110.8, 112.5 (C2/C5), 138.5, 138.9 (C3/C4).

***N*,*N*-Dimethyl-*N*-{[7-(morpholin-4-ylmethyl)-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl]methyl}amine, 14.** 74%, oil; $\delta_H(CDCl_3)$ 2.21 (6H, s, $N(CH_3)_2$), 2.50–2.52 (4H, m, CH_2NCH_2), 3.52 (2H, s, $ArCH_2N$), 3.53 (2H, s, $ArCH_2N$), 3.68–3.72 (4H, m, CH_2OCH_2), 4.17 (4H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 44.9 (NCH_3), 53.0 ($ArCH_2N$), 53.8 (NCH_2), 54.6 ($ArCH_2N$), 64.6, 64.7 ($ArOCH_2$), 67.2 (CH_2OCH_2), 110.7, 112.4 (C2/C5), 138.5, 138.9 (C3/C4).

4-{[7-(Piperidin-1-ylmethyl)-2,3-dihydrothieno[3,4-*b*][1,4]-dioxin-5-yl]methyl}morpholine, 15. 91%, mp 64–66 °C; $\delta_H(CDCl_3)$ 1.40 (2H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 1.58 (4H, quintet, *J* 5.61, $CH_2CH_2CH_2$), 2.42–2.45 (4H, m, piperidino CH_2NCH_2), 2.49–2.52 (4H, m, morpholino CH_2NCH_2), 3.55 (2H, s, $ArCH_2N$), 3.56 (2H, s, $ArCH_2N$), 3.69–3.73 (4H, m, CH_2OCH_2), 4.17 (4H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 24.2 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 52.9 ($ArCH_2N$), 53.0 (NCH_2), 53.2 ($ArCH_2N$), 53.9 (NCH_2), 64.6, 64.7 ($ArOCH_2$), 67.0 (CH_2OCH_2), 110.8, 112.3 (C2/C5), 138.6, 138.9 (C3/C4) (Found: C, 60.12; H, 7.91; N, 8.04. $C_{17}H_{26}N_2O_3S$ requires C, 60.33; H, 7.74; N, 8.28%); *m/e* 252 (M − $N(CH_2CH_2)_2O$).

Linking the thiophene moieties: synthesis of bis(thien-2-ylmethyl) Mannich bases. General method

The thiophene moiety (2.0 eq.) was dissolved in glacial acetic acid (1.25 cm^3 $mmol^{-1}$). To an equal volume of glacial acetic acid was added the secondary diamine or primary amine (40% aqueous solution for methylamine) (1.0 eq.) and aqueous formaldehyde (37%, 2.0 eq.) with ice cooling. The solutions were fed separately and simultaneously into glacial acetic acid (0.3 cm^3 $mmol^{-1}$) by means of a syringe pump with stirring. After addition was complete, the solution was stirred for a further 12 hours. The solvent was removed *in vacuo* to give a dark oily residue. The work-up was similar to that applied to the mono-Mannich bases. Purification by column chromatography (alumina; light petroleum–EtOAc, 5 : 1) gave the required Mannich base. Also isolated in these experiments were a series of oligomeric Mannich bases containing three thiophene moieties, **17**, **19a**–**c** and **23**.

***N*,*N*-Bis[(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)methyl]-*N*-methylamine, 16.** 37%, mp 78–80 °C; $\delta_H(CDCl_3)$ 2.29 (3H, s, NCH_3), 3.65 (4H, s, $ArCH_2N$), 4.18 (8H, s, $ArOCH_2$), 6.25 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 41.7 (NCH_3), 51.0 ($ArCH_2N$), 64.7 ($ArOCH_2$), 97.8 (C5), 114.6 (C2), 139.2 (C3), 141.2 (C4) (Found: C, 53.20; H, 5.05; N, 4.06. $C_{15}H_{17}NO_4S_2$ requires C, 53.08; H, 5.05; N, 4.13%); *m/e* 339 (M^+).

5,7-Bis{[2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl-(methyl)amino]methyl}-2,3-dihydrothieno[3,4-*b*][1,4]dioxin, 17. 21%, oil; $\delta_H(CDCl_3)$ 2.28 (6H, s, NCH_3), 3.63, 3.64 (4H, s, $ArCH_2N$), 4.16 (4H, s, $ArOCH_2$), 4.17 (8H, s, $ArOCH_2$), 6.23 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 41.5 (NCH_3), 50.8, 50.9 ($ArCH_2N$), 64.6 ($ArOCH_2$), 97.9 (C5′), 112.1 (C2/C5), 114.2 (C2′), 138.7 (C3/C4), 139.3 (C3′), 141.2 (C4′).

***N*^{1},*N*^{2}-Bis(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine, 18a.** 45%, mp 75.5–77.5 °C, $\delta_H(CDCl_3)$ 2.29 (6H, s, $N(CH_3)$), 2.58 (4H, s, R_2NCH_2), 3.63 (4H, s, $ArCH_2N$), 4.17 (8H, s, $ArOCH_n$), 6.25 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 42.4 (NCH_3), 52.0 (NCH_2), 54.2 ($ArCH_2N$), 64.6 and 64.7 ($ArOCH_2$), 97.7 (C5), 114.0 (C2), 139.3 (C3), 141.2 (C4) (Found: C, 54.62; H, 6.18; N, 6.77; $C_{18}H_{24}N_2O_4S_2$ requires C, 54.52; H, 6.10; N, 7.07%); *m/e* 396 (M^+).

***N*^{1},*N*^{3}-Bis(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl)-*N*^{1},*N*^{3}-dimethylpropane-1,3-diamine, 18b.** 12%, oil, $\delta_H(CDCl_3)$ 1.73 (2H, quintet, *J* 7.59 Hz, $CH_2CH_2CH_2$), 2.26 (6H, s, $N(CH_3)$), 2.39–2.44 (4H, s, R_2NCH_2), 3.58 (4H, s, $ArCH_2N$), 4.16 (8H, s, $ArOCH_n$), 6.22 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 25.2 ($CH_2CH_2CH_2$), 42.2 (NCH_3), 52.0 (NCH_2), 54.2 ($ArCH_2N$), 64.3 and 64.6 ($ArOCH_2$), 97.5 (C5), 114.5 (C2), 139.1 (C3), 141.2 (C4) (Found: C, 55.52; H, 6.58; N, 6.99. $C_{19}H_{20}N_2O_4S_2$ requires C, 55.59; H, 6.38; N, 6.82%); *m/e* 410 (M^+).

1,4-Bis(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl)piperazine, 18c. 22%, mp 158 °C (decomp.), $\delta_H(CDCl_3)$ 2.55 (6H, s, $N(CH_3)$), 2.55 (4H, s, R_2NCH_2), 3.59 (4H, s, $ArCH_2N$), 4.17 (8H, s, $ArOCH_n$), 6.22 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 52.4 (NCH_2), 52.5 ($ArCH_2N$), 64.6 ($ArOCH_2$), 97.7 (C5), 113.6 (C2), 139.3 (C3), 141.2 (C4) (Found: C, 55.52; H, 6.58; N, 6.99. $C_{18}H_{22}N_2O_4S_2$ requires C, 55.59; H, 6.38; N, 6.82%); *m/e* 394 (M^+).

5,7-Bis{[{2-[(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl)-(methyl)amino]ethyl}(methyl)amino]methyl}-2,3-dihydrothieno-[3,4-*b*][1,4]dioxin, 19a. 7%, oil; $\delta_H(CDCl_3)$ 2.30 (6H, s, $N(CH_3)$), 2.31 (6H, s, $N(CH_3)$), 2.62 (8H, m, NCH_2), 3.61 (4H, s, $ArCH_2N$), 3.62 (4H, s, $ArCH_2N$), 4.16 (8H, s, $ArOCH_2$), 4.18 (8H, s, $ArOCH_2$), 6.24 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 42.3, 42.4 (NCH_3), 51.8, 52.0 (NCH_2), 54.1, 54.2 ($ArCH_2N$), 64.6 ($ArOCH_2$), 97.7 (C_5′), 111.7 (C_2/C_5), 114.0 (C_2′), 138.8 (C_3/C_4), 139.3 (C_3′), 141.2 (C_4′).

5,7-Bis{[{3-[(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl)-(methyl)amino]propyl}(methyl)amino]methyl}-2,3-dihydrothieno-[3,4-*b*][1,4]dioxin, 19b. 6%, oil; $\delta_H(CDCl_3)$ 1.70–1.78 (4H, m, $CH_2CH_2CH_2$), 2.27 (12H, s, $N(CH_3)$), 2.41 (8H, m, NCH_2), 3.61

(8H, s, $ArCH_2N$), 4.17 (12H, s, $ArOCH_2$), 6.23 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 24.7 ($CH_2CH_2CH_2$), 41.9, 42.0 (NCH_3), 52.9, 53.0 (NCH_2), 54.4 ($ArCH_2N$), 64.6 ($ArOCH_2$), 97.8 (C_5'), 112.3 (C_2/C_5), 113.7 (C_2'), 138.1 (C_3/C_4), 139.3 (C_3'), 141.2 (C_4').

5,7-Bis{[4-(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-ylmethyl)-piperazin-1-yl]methyl}-2,3-dihydrothieno[3,4-*b*][1,4]dioxin, 19c. 9%, mp 285 °C (decomp.); $\delta_H(CDCl_3)$ 2.55 (16H, s, NCH_2), 3.56 (4H, s, $ArCH_2N$), 3.60 (4H, s, $ArCH_2N$), 4.16 (8H, s, $ArOCH_2$), 4.17 (8H, s, $ArOCH_2$), 6.22 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 52.4 (NCH_2), 52.5 ($ArCH_2N$), 64.6 ($ArOCH_2$), 97.7 (C_5'), 111.5 (C_2/C_5), 113.6 (C_2'), 138.8 (C_3/C_4), 139.3 (C_3'), 141.3 (C_4') (Found: C, 55.71; H, 5.85; N, 8.46. $C_{30}H_{38}N_4O_6S_3$ requires C, 55.71; H, 5.92; N, 8.66%); *m/e* 646 (M^+).

***N*^{1},*N*^{2}-Dimethyl-*N*^{1},*N*^{2}-bis(2,3,5,6-tetrahydrothieno[3,4-*b*]-[1,4,7]trioxonin-8-ylmethyl)ethane-1,2-diamine, 22.** 46%, oil; $\delta_H(CDCl_3)$ 2.28 (6H, s, $N(CH_3)$), 2.57 (4H, s, R_2NCH_2), 3.62 (4H, s, $ArCH_2N$), 3.84–3.89 (8H, m, CH_2OCH_2), 4.21–4.27 (8H, m, $ArOCH_n$), 6.46 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 42.5 (NCH_3), 53.0 (NCH_2), 54.5 ($ArCH_2N$), 71.8, 72.2, 73.5, 74.2 ($ArOCH_2$ and OCH_2), 105.6 (C_5), 112.7 (C_2), 146.6 (C_3), 149.4 (C_4) (Found: C, 54.68; H, 6.81; N, 5.98. $C_{22}H_{32}N_2O_6S_2$ requires C, 56.40; H, 6.66; N, 5.78%); *m/e* 484 (M^+).

8,10-Bis{[{2-[(2,3,5,6-tetrahydrothieno[3,4-*b*][1,4,7]trioxonin-8-ylmethyl)(methyl)amino]ethyl}(methyl)amino]methyl}-2,3,5,6-tetrahydrothieno[3,4-*b*][1,4,7]trioxonin, 23. 5%, oil; $\delta_H(CDCl_3)$ 2.32 (6H, s, $N(CH_3)$), 2.33 (6H, s, $N(CH_3)$), 2.69 (8H, s, NCH_2), 3.71 (4H, s, $ArCH_2N$), 3.72 (4H, s, $ArCH_2N$), 3.87–3.88 (12H, m, CH_2OCH_2), 4.23–4.31 (12H, m, $ArOCH_2$), 6.52 (2H, s, Ar-H); $\delta_C(CDCl_3)$ 41.7 (NCH_3), 52.1, 52.3 (NCH_2), 53.1 ($ArCH_2N$), 71.6, 71.7, 72.4, 72.9, 73.3 (OCH_2), 106.8 (C_5'), 118.9 (C_2/C_5), 119.9 (C_2'), 146.7 (C_3'), 147.0 (C_3/C_4), 149.5 (C_4').

Substitution at the 5-position of the thien-2-ylmethyl Mannich bases: bis-morpholino derivatives of the bis(thien-2-ylmethyl) Mannich bases. General method

To the bis(thien-2-ylmethyl) Mannich base (0.50 g) in glacial acetic acid (3 cm^3), cooled in ice, was added aqueous formaldehyde (37%, 2.2 eq.) and morpholine (2.2 eq.). The mixture was stirred for 12 hours. Basification with aqueous sodium hydroxide (4 M) was followed by extraction with dichloromethane (3 × 10 cm^3). The organic phase was worked up in the usual manner, and the crude product was then purified by column chromatography (alumina; light petroleum–EtOAc, 4 : 1).

***N*-Methyl-*N*,*N*-bis{[7-(morpholin-4-ylmethyl)-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl]methyl}amine, 24.** 97%, mp 90–92 °C; $\delta_H(CDCl_3)$ 2.28 (3H, s, $N(CH_3)$), 2.49–2.53 (8H, m, NCH_2), 3.57 (4H, s, morpholino $ArCH_2N$), 3.61 (4H, s, bridging $ArCH_2N$), 3.70–3.73 (8H, m, morpholino OCH_2), 4.17 (8H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 41.7 (NCH_3), 51.0 (bridging $ArCH_2N$), 52.9 (morpholino $ArCH_2N$), 53.0 (morpholino CH_2N), 64.6 ($ArOCH_2$), 64.7 ($ArOCH_2$), 67.0 (morpholino CH_2O), 111.1 (C_5), 112.8 (C_2), 138.7 (C_3), 138.9 (C_4) (Found: C, 55.91; H, 6.43; N, 7.66. $C_{25}H_{35}N_3O_6S_2$ requires C, 55.85; H, 6.56; N, 7.62%); *m/e* 537 (M^+).

***N*^{1},*N*^{2}-Dimethyl-*N*^{1},*N*^{2}-bis{[7-(morpholin-4-ylmethyl)-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl]methyl}ethane-1,2-diamine, 25a.** 97%, mp 111–113 °C; $\delta_H(CDCl_3)$ 2.27 (6H, s, $N(CH_3)$), 2.48–2.51 (8H, m, NCH_2), 2.56 (4H, s, bridging NCH_2), 3.55 (4H, s, morpholino $ArCH_2N$), 3.60 (4H, s, bridging $ArCH_2N$), 3.68–3.72 (8H, m, morpholino OCH_2), 4.17 (8H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 42.4 (NCH_3), 52.0 (bridging CH_2N), 52.9 (morpholino $ArCH_2N$), 53.0 (morpholino CH_2N), 64.6 ($ArOCH_2$), 64.7 ($ArOCH_2$), 67.0 (morpholino CH_2O), 111.0 (C_5), 112.3 (C_2), 138.7 (C_3), 138.9 (C_4) (Found: C, 56.39; H, 7.23; N, 9.28. $C_{28}H_{42}N_4O_6S_2$ requires C, 56.54; H, 7.12; N, 9.42%); *m/e* 594 (M^+).

***N*^{1},*N*^{3}-Dimethyl-*N*^{1},*N*^{3}-bis{[7-(morpholin-4-ylmethyl)-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl]methyl}propane-1,3-diamine, 25b.** 92%, oil; $\delta_H(CDCl_3)$ 1.73 (2H, quintet, *J* 7.59 Hz, $CH_2CH_2CH_2$), 2.25 (6H, s, $N(CH_3)$), 2.39–2.45 (4H, m, bridging NCH_2), 2.48–2.51 (8H, m, morpholino NCH_2), 3.55 (8H, s, $ArCH_2N$), 3.68–3.72 (8H, m, morpholino OCH_2), 4.16 (8H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 52.4 (bridging CH_2N), 52.4 (bridging $ArCH_2N$), 52.9 (morpholino $ArCH_2N$), 53.1 (morpholino CH_2N), 64.6 ($ArOCH_2$), 67.0 (morpholino CH_2O), 111.2 (C_5), 111.6 (C_2), 138.8 (C_3), 138.9 (C_4) (Found: C, 56.93; H, 7.46; N, 9.60. $C_{29}H_{44}N_4O_6S_2$ requires C, 57.21; H, 7.29; N, 9.20%); *m/e* 608 (M^+).

1,4-Bis{[7-(morpholin-4-ylmethyl)-2,3-dihydrothieno[3,4-*b*]-[1,4]dioxin-5-yl]methyl}piperazine, 25c. 83%, mp 220 °C (decomp.); $\delta_H(CDCl_3)$ 2.48–2.51 (8H, m, morpholino NCH_2), 2.55 (8H, m, bridging NCH_2), 3.54 (4H, s, morpholino $ArCH_2N$), 3.59 (4H, s, bridging $ArCH_2N$), 3.68–3.73 (8H, m, morpholino OCH_2), 4.16 (8H, s, $ArOCH_2$); $\delta_C(CDCl_3)$ 52.4 (bridging CH_2N), 52.4 (bridging $ArCH_2N$), 52.9 (morpholino $ArCH_2N$), 53.1 (morpholino CH_2N), 64.6 ($ArOCH_2$), 67.0 (morpholino CH_2O), 111.2 (C_5), 111.6 (C_2), 138.8 (C_3), 138.9 (C_4) (Found: C, 56.59; H, 6.79; N, 9.65. $C_{28}H_{40}N_4O_6S_2$ requires C, 56.73; H, 6.80; N, 9.45%); *m/e* 592 (M^+).

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