A Convenient Synthesis of the Novel 5*H*-Thieno[2,3-*e*]-4,1,2-oxathiazepine Ring System *via* an Alkoxycarbenium Ion Intermediate

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3-(Methoxymethoxymethyl)-2-thiophenesulfonamides and 3-hydroxymethyl-*N*-methoxymethyl-2-thiophenesulfonamides have been shown to undergo cyclization when treated under anhydrous acidic conditions to provide the novel 2,3-dihydro-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine ring system. Incorporation of a primary sulfonamide group into position seven of the molecule provided compounds which inhibit human carbonic anhydrase II.

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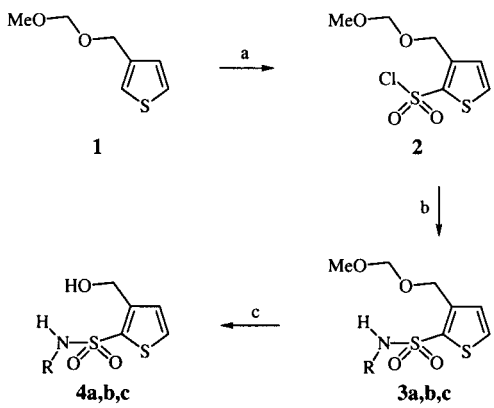
The methoxymethyl ether group has found wide utility for the protection of hydroxyl groups and has been employed during the pursuit of innumerable synthetic targets. The broad utility of this protective group is clearly demonstrated by the large number of methods which have been developed for its incorporation into a molecule, and likewise, by the broad spectrum of cleavage conditions which have been developed for its removal [1,2]. Additionally, methoxymethyl protected alcohols have been shown to undergo rapid acetal-acetal interchange, providing a facile preparation of symmetrical formaldehyde acetals [3]. In this report we describe our recent observation that the methoxymethyl ether moiety can also serve as an intermediate for the preparation of a cyclic *N,O*-acetal, providing a new heterocyclic ring system by a novel cyclization method.

Scheme 1



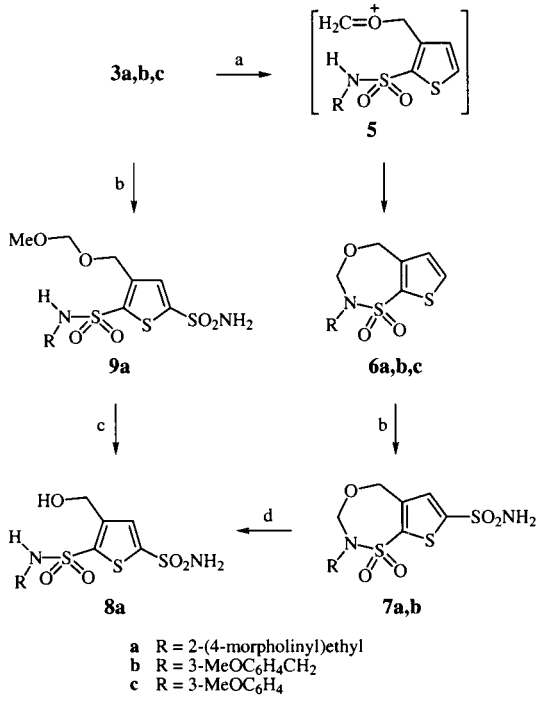
a R = 2-(4-morpholinyl)ethyl
b R = 3-MeOC$_6$H$_4$CH$_2$
c R = 3-MeOC$_6$H$_4$

Reagents: (a) *n*-BuLi, sulfur dioxide, *N*-chlorosuccinimide; (b) RNH_2; (c) Ethanol/HCl, 70°C.

In conjunction with a program directed toward the synthesis of novel carbonic anhydrase inhibitors, it was of interest to develop a general method for the preparation of *N*-substituted 3-hydroxymethyl-2-thiophenesulfonamides which were desired as synthetic intermediates. A procedure which was found to be quite useful for obtaining these intermediates is shown in Scheme 1. Protection of 3-thiophenemethanol as the methoxymethyl ether (**1**) followed by regioselective metallation with *n*-butyllithium and subsequent reaction of the 2-lithio-thiophene intermediate with sulfur dioxide gave the 2-sulfinate which was treated with *N*-chlorosuccinimide to provide the methoxymethyl protected thiophenesulfonyl chloride (**2**) [4]. Reaction of **2** with the desired amines provided the 2-thiophenesulfonamides **3**, and finally, removal of the methoxymethyl protective group with acidic ethanol provided a variety of *N*-substituted 3-hydroxymethyl-2-thiophenesulfonamides (**4**).

In support of our desire to broaden the range of amines which could be incorporated into **4** when prepared by the method of Scheme 1, it was of interest to investigate the removal of the methoxymethyl group from **3** under milder acidic conditions. During the evaluation of a variety of reaction conditions it was observed that when deprotection of the methoxymethyl ether was achieved a second compound was consistently formed in addition to the desired alcohol. For example, treatment of a solution of **3b** in methanol containing a few drops of concentrated hydrochloric acid at ambient temperature gave a 9:1 mixture of **4b** and the secondary compound, while treatment of an ethanol solution of **3b** with anhydrous hydrochloric acid at 70° gave an 8:1 mixture of these compounds. Furthermore, heating a tetrahydrofuran solution of **3b** containing camphorsulfonic acid (60°), or a tetrahydrofuran solution of **3a** containing a few drops of concentrated hydrochloric acid gave an equimolar mixture of the desired alcohol and the secondary compound (Scheme 2).

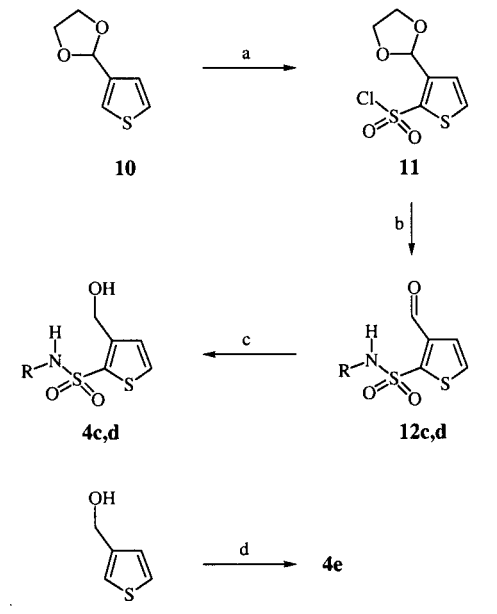
Scheme 2



a R = 2-(4-morpholinyl)ethyl
b R = 3-$MeOC_6H_4CH_2$
c R = 3-$MeOC_6H_4$

Reagents: (a) HCl or *p*-toluenesulfonic acid, tetrahydrofuran; (b) *n*-BuLi, sulfur dioxide, H_2NOSO_3H; (c) Ethanol/HCl, 70°C; (d) *p*H 1 at 75°C.

Scheme 3



c R = 3-$MeOC_6H_4$
d R = $MeO(CH_2)_2$
e R = H

Reagents: (a) *n*-BuLi, sulfur dioxide, *N*-chlorosuccinimide; (b) RNH_2, HCl; (c) Ethanol/$NaBH_4$; (d) *N*-BuLi, sulfur dioxide, H_2NOSO_3H

A previous report [3] regarding the formation of cyclic formaldehyde acetals upon hydrolysis of dimethoxymethyl protected diols under anhydrous conditions, suggested a similar intramolecular reaction might be occurring during the hydrolysis of compounds **3**. The analytical data (nmr, ms) obtained for the second compound formed during the hydrolysis of **3a** were consistent with the formation of a cyclic *N,O*-acetal, specifically the novel fused bicyclic compound 2,3-dihydro-2-[2-(4-morpholinyl)ethyl]-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine 1,1-dioxide (**6a**). Furthermore, it was subsequently observed that treatment of **3b** with acid under anhydrous conditions (tetrahydrofuran and *p*-toluenesulfonic acid) resulted in the exclusive formation of a cyclized product, **6b**, in very good yield. Alternate procedures which were also useful for the preparation of sulfonamides **4**, but starting from 3-thiophenecarboxaldehyde or 3-thiophenemethanol, are outlined in Scheme 3.

There are few reports on the synthesis of any of the numerous isomeric oxathiazepines or fused ring systems containing these structures described in the literature [5], and no prior report of the 2,3-dihydro-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine heterocycle was identified. Furthermore, the synthesis of only one 1,4,3-oxathiazepine has been reported, a single organometallic derivative, synthesized by the cycloaddition of dicarbonyl(*pentahaptocyclopentadienyl*)(allenyl)iron with *N*-carboxymethylsulfonylamine to give **A** (Figure 1) [6]. Similarly, only a single thiophene fused oxathiazepine has been reported; the thiophene fused 3,1,4-oxathiazepine **B** was prepared by the spontaneous cyclization of the corresponding *ortho*-thiocyanato thienylcarbaldoxime [7]. Thermolysis of 2-phenoxybenzenesulfonyl azide provided the tricyclic 1,4,5-oxathiazepine **C** by an intramolecular cyclization of the intermediate sulfonylnitrene [8]. Antiviral eudistomins C, E, L and K with the tetracyclic skeleton **D**, which contains the 1,3,7-oxathiazepine ring, represent the most extensively explored oxathiazepine-containing ring system [9].

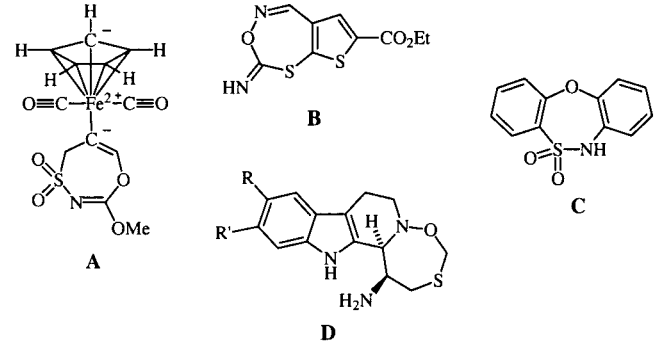


Figure 1. Structures of oxathiazepine containing compounds.

Formation of an *N,O*-acetal from **3a** to give the oxathiazepine ring can be envisioned to occur by intramolecular capture by the weakly nucleophilic sulfonamide nitrogen

atom of the relatively stable methoxycarbenium ion **5** (Scheme 2); the latter formed under acidic conditions by elimination of the protonated methoxide from the methoxymethyl moiety, a formaldehyde acetal. The proximity of the nitrogen atom and the developing alkoxycarbenium ion favors formation of the stable cyclic *N,O*-acetal, particularly under anhydrous conditions. There is ample precedent for the formation of stable 5- and 6-membered cyclic *N,O*-acetals from 1,2- and 1,3-amino alcohols, respectively, by using normal acetal (ketal) formation conditions [10], particularly when the amine has been rendered electron deficient by appropriate substitution. To our knowledge, the utility of the methoxymethyl ether group for the preparation of a fused N-C-O heterocycle (cyclic *N,O*-acetal) has not been previously noted. However, recent studies on the gas phase reactions of glycine [11] and cysteine [12] with methoxymethyl cation have identified oxazolidinone cations and thiazolidine carboxylic acid cations, respectively, among the products of these gas phase reactions.

It was of interest to evaluate the feasibility of preparing **6** directly from **4** by reaction with dimethoxymethane in the presence of *p*-toluenesulfonic acid (Scheme 4). After 72 hours at ambient temperature, **4d** provided a mixture of the methoxymethyl ether **3d** (25%) and the desired oxathiazepine **6d** (46%), with no indication of any methoxymethylation on nitrogen. Similar treatment of **4c** and **4e** provided the oxathiazepines **6c** (49%) and **6e** (62%), respectively. It is of interest to note that upon treatment of **4c** with chloromethyl methyl ether in the presence of *N,N*-diisopropylamine the product of *N*-alkylation (**13**) was the only isolable product, with no indication of ether formation. Subsequent treatment of **13** under anhydrous acidic conditions provided **6c** in good yield. Hence, either a methoxymethyl ether (*e.g.* **3**) or a methoxymethyl amide **13** can serve as a suitable substrate for cyclization via either an alkoxycarbenium ion **5** or an iminium ion intermediate, respectively, to provide the thieno[2,3-*e*]-4,1,2-oxathiazepines **6**. Alkylation of **6e** with 3-methoxybenzyl chloride in dimethyl sulfoxide in the presence of potassium carbonate gave **6b** in very good yield; this is in contrast to unsuccessful attempts to alkylate **4e** in a similar manner. Sulfamoylation of **6a** or **6b** by a sequence employing *n*-butyllithium, sulfur dioxide, and hydroxylamine-*O*-sulfonic acid provided the corresponding sulfonamides **7a** and **7b**, though in only low isolated yield, 19% and 20% respectively (Scheme 2). However, it should be noted that the efficiency of conversion for **7b** was significantly higher, since unreacted **6b** (62%) was recovered.

Confirmation of the structure of the cyclized product was further provided by determination of the X-ray crystal structure of **6e** (Figure 2). Selected pertinent crystallographic data for **6e** are provided in Tables 1-3. The dihydrooxathiazepine ring of **6e** was shown to assume a chair-like conformation in the solid state.

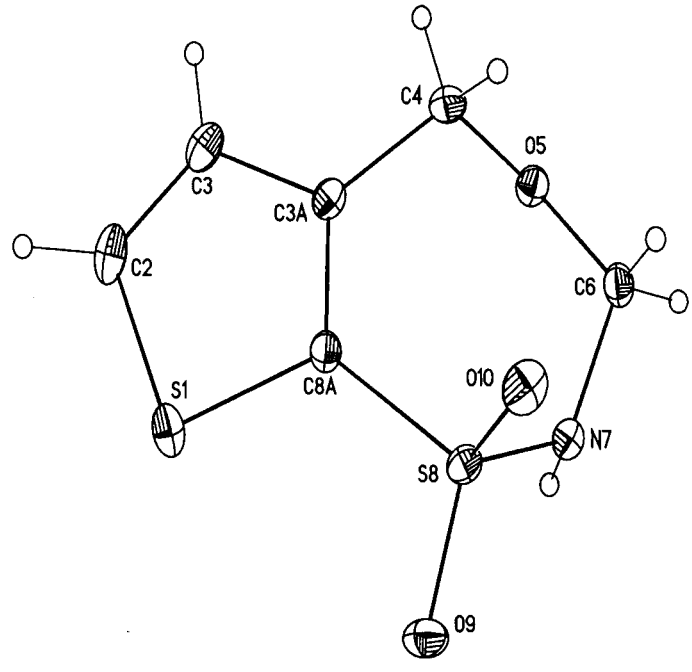
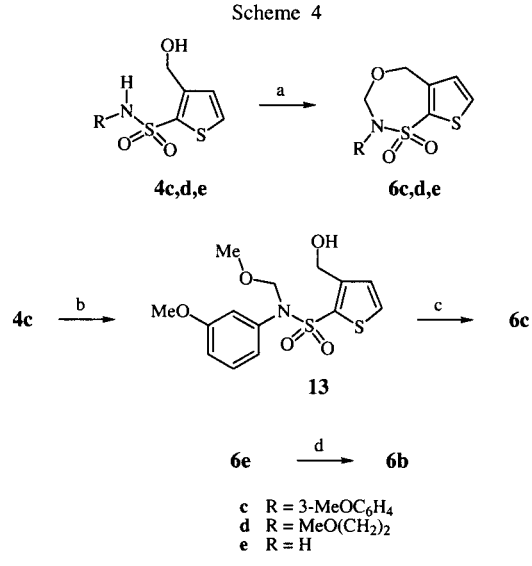


Figure 2. A view of **6e** showing the atom labeling scheme. Thermal ellipsoids are plotted at the 30% probability level. Hydrogen atoms are drawn to an arbitrary scale.

The increased stability of the oxathiazepine ring to cleavage under acidic conditions is illustrated by the conversion of **6d** to **4d**; this hydrolysis required an extended reaction time compared to that necessary for the hydrolysis of the methoxymethyl ether of **3a**. The stability of **7a** under acidic conditions was further evaluated by monitoring the disappearance of **7a** from a buffered aqueous solution main-

Scheme 4



Reagents: (a) $MeOCH_2OMe$, *p*-toluenesufonic acid, LiBr, tetrahydrofuran; (b) $ClCH_2OCH_3$, $(iPr)_2NEt$, dichloromethane; (c) *p*-toluensulfonic acid, tetrahydrofuran, (d) (3-MeO- $C_6H_4)CH_2Cl$, dimethyl sulfoxide, potassium carbonate

Table 1

Crystallographic Data for **6e**

Formula	$C_6H_7NO_3S_2$
fw	205.25
a, Å	8.0872(6)
b, Å	6.9980(5)
c, Å	14.572(1)
β, °	98.886(7)
V, Å^3	814.79(9)
Z	4
F(000)	424
Crystal System	Monoclinic
Space Group	$P2_1/c$
T, °C	-90
ρ_{calc}, g/cc	1.67
Reflections measured	5383
Unique reflections	2375
R_{int} (F^2)	0.020
μ, mm^{-1}	0.616
$R_w(F^2)$ [a]	0.0766
R(F) [b]	0.0282
Goodness of fit, S [c]	1.070
Parameters	138
Max $\|\Delta/\sigma\|$	<0.1
Min, max peaks (e$^-$/Å^3)	-0.26, 0.48

[a] $R_w = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ and where the weight, w, is defined as follows: $w = 1/\{\sigma^2(|F_o|^2) + (a*P)^2 + b*P\}$; $P = [1/3*(\text{Maximum of } (0 \text{ or } |F_o|^2) + 2/3*|F_c|^2]$. The parameters a and b were suggested during refinement and are 0.0414 and 0.2616, respectively. [b] The conventional R index based on F where the 2099 observed reflections have $F_o > 4(\sigma(F_o))$. [c] $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

Table 2

Fractional Coordinates and Equivalent Isotropic Thermal Parameters (Å^2) for the Non-hydrogen Atoms of **6e**

Atom	x	y	z	U
S1	0.80913(5)	0.32265(6)	0.47159(2)	0.02728(11)
C2	0.7573(2)	0.5432(3)	0.42568(10)	0.0318(4)
C3	0.7063(2)	0.6641(2)	0.48861(10)	0.0273(4)
C3A	0.7059(2)	0.5787(2)	0.57683(9)	0.0197(3)
C4	0.6530(2)	0.6781(2)	0.65899(10)	0.0222(3)
O5	0.77841(12)	0.67189(14)	0.74015(7)	0.0222(3)
C6	0.7728(2)	0.5042(2)	0.79436(9)	0.0224(3)
N7	0.85285(14)	0.3377(2)	0.76007(8)	0.0197(3)
S8	0.76113(4)	0.23071(4)	0.66747(2)	0.01828(9)
C8A	0.7581(2)	0.3921(2)	0.57645(8)	0.0189(3)
O9	0.86328(13)	0.0724(2)	0.64887(7)	0.0276(3)
O10	0.59205(12)	0.1960(2)	0.68100(8)	0.0268(3)

For anisotropic atoms, the U value is U_{eq}, calculated as $U_{eq} = 1/3\ \Sigma_i \Sigma_j U_{ij}\ a_i^* a_j^* A_{ij}$ where A_{ij} is the dot product of the i^{th} and j^{th} direct space unit cell vectors.

Table 3

Bond Lengths and Angles for the Non-hydrogen Atoms of **6e** [a]

1	2	3	1-2 (Å)	1-2-3 (deg)
C2	S1	C8A	1.708(2)	90.84(7)
C8A	S1		1.7135(12)	
C3	C2	S1	1.358(2)	112.34(12)
C3A	C3	C2	1.418(2)	113.16(14)
C4	C3A	C8A	1.503(2)	124.68(12)
C4	C3A	C3		124.61(12)
C8A	C3A	C3	1.373(2)	110.70(12)
O5	C4	C3A	1.435(2)	112.98(11)
C6	O5	C4	1.419(2)	113.85(10)
N7	C6	O5	1.459(2)	114.57(11)
S8	N7	C6	1.6193(11)	118.97(8)
C8A	S8	O9	1.7392(13)	107.36(6)
C8A	S8	O10		108.29(6)
C8A	S8	N7		106.62(6)
O9	S8	O10	1.4326(11)	119.05(6)
O9	S8	N7		108.17(6)
O10	S8	N7	1.4321(11)	106.74(6)
S1	C8A	C3A		112.95(9)
S1	C8A	S8		121.26(8)
C3A	C8A	S8		125.65(10)

[a] See Figure 2 for atom numbering.

tained at 75°. As shown in Table 4, compound **7a** is very stable at *p*H 3 and above; however, hplc analysis showed significant degradation at *p*H 1 with concomitant formation of a single major product (>90%), identified as **8a** by co-injection of an authentic sample prepared from **3a** (Scheme 2).

Sulfonamides **7a**, **7b** and **8a** were evaluated in an *in vitro* enzyme assay for their ability to inhibit human carbonic anhydrase isozyme II [13]. Thiophenesulfonamide **8a** was determined to be a modest inhibitor of this enzyme (IC_{50} = 82.6 n*M*, concentration required to inhibit fifty percent of enzyme activity). However, oxathiazepines **7a** and **7b** displayed a higher level of inhibition of human carbonic anhydrase II with IC_{50} values of 12.9 n*M* and 1.11 n*M*, respectively. The oxathiazepine ring appears to allow a more favorable association with the hydrophobic active site of the enzyme, perhaps by masking unfavorable interactions between the enzyme and the polar hydroxyl and secondary sulfonamide groups present in **8a**.

Table 4

Stability of **7a** at 75°C

*p*H [a]	Time, days	Degradation, %
7.4	14	0.38
5.0	7	1.08
3.0	0.71	0.00
1.0 [b]	0.71	9.95
	3	44.9

[a] 0.1 *N* Sodium phosphate buffer; [b] 0.1 *N* HCl.

EXPERIMENTAL

Melting points were determined in open capillaries using a Thomas-Hoover Uni-Melt Apparatus and are uncorrected. The ^{1}H-nmr spectra were determined at 200 MHz and the ^{13}C-nmr spectra were determined at 50.3 MHz with a Varian Model VXR-200 spectrometer. Spectra were recorded in deuteriochloroform or dimethyl sulfoxide-d_6, and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as internal standard. Isobutane

chemical ionization mass spectra were obtained with a Finniagan TSQ 46 triple-quadrupole mass spectrometer operated with an ion source temperature of 150° and an indicated reagent gas pressure of 0.3 torr. Samples were introduced via a platinum-wire tipped direct exposure probe. Electrospray mass spectra were obtained on a Finnigan CCQ mass spectrometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia. Column chromatography was conducted on 230-400 mesh silica gel from E. Merck. Evaporations were performed under reduced pressure on a rotary evaporator at 40° unless otherwise indicated.

3-(Methoxymethoxymethyl)-2-thiophenesulfonyl Chloride (**2**).

To a suspension of sodium hydride (9.0 g) in tetrahydrofuran (250 ml) was added a solution of 3-thiophenemethanol (25.5 g, 0.22 mole) in tetrahydrofuran (100 ml) and the mixture was heated at reflux temperature for 30 minutes, then cooled to room temperature. A solution of chloromethyl methyl ether (16.9 ml, 0.22 mole) in tetrahydrofuran (50 ml) was added and this mixture was heated at reflux temperature for 1 hour. After cooling to room temperature, the mixture was filtered and the filtrate, which consisted of **1**, was further cooled to -40° in a dry ice/2-propanol bath. A solution of *n*-butyllithium in hexanes (90.0 ml of a 2.5 *M* solution) was added and the mixture was stirred at 0° for one hour followed by cooling to -20°. An excess of sulfur dioxide gas was introduced into the flask (15 minutes), and the reaction mixture was stirred for 16 hours at room temperature. The solvent and excess sulfur dioxide were removed under reduced pressure and the residue was suspended in tetrahydrofuran (200 ml). *N*-Chlorosuccinimide (29.8 g, 0.23 mole) was added and the mixture was stirred at room temperature for 18 hours, diluted with ether (200 ml), and filtered. After washing the solids with ether, the combined filtrates were evaporated to give a residue which was flushed through a short bed of silica (25% ethyl acetate in hexane) to give **2** as an oil (17.7 g, 31%) which was used in subsequent reactions without further purification: ir (film): γ 2949, 1379, 1178, 1151, 1108, 1048 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.75 (d, J = 5.1 Hz, 1H, H5), 7.34 (d, J = 5.1 Hz, 1H, H4), 4.94 (s, 2H, CH_3OCH_2O), 4.76 (s, 2H, thienyl-CH_2O), 3.41 (s, 3H, OCH_3); ms: (CI) m/z 257 (M+1).

3-(Methoxymethoxymethyl)-*N*-[2-(4-morpholinyl)ethyl]-2-thiophenesulfonamide (**3a**).

A solution of **2** (5.0 g, 19.5 mmoles) in tetrahydrofuran (15 ml) was added to a solution of 4-(2-aminoethyl)morpholine (7.7 ml, 58.4 mmoles) in tetrahydrofuran (5 ml) at 0°. After 5 minutes the solvent was removed and water (10 ml) and ethyl acetate (10 ml) were added. The ethyl acetate layer was separated, washed with brine, dried (potassium carbonate), and concentrated to a residue which was purified by column chromatography (40% hexane in ethyl acetate) to provide **3a** as an oil (4.23 g, 62%); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.84 (d, J = 5.1 Hz, 1H, H5), 7.21 (d, J = 5.1 Hz, 1H, H4), 4.78 (s, 2H, CH_3OCH_2O), 4.70 (s, 2H, OCH_2), 3.50 (m, 4H, $O(CH_2CH_2)_2N$), 3.32 (s, 3H, OCH_3), 2.96 (br t, J = 7.0 Hz, 2H, SO_2NHCH_2), 2.24 (6H, $O(CH_2CH_2)_2NCH_2$); ms: (CI) m/z 351 (M+1).

Anal. Calcd. for $C_{13}H_{22}N_2O_5S_2 \cdot 0.3\ (CH_3)_2NCHO$: C, 45.29; H, 6.79; N, 8.60. Found: C, 44.83; H, 6.52; N, 8.65.

3-(Methoxymethoxymethyl)-*N*-[(3-methoxyphenyl)methyl]-2-thiophenesulfonamide (**3b**).

A solution of **2** (2.5 g, 9.7 mmoles) in tetrahydrofuran (15 ml) was added to a solution of 3-methoxybenzylamine (5.1 ml, 39.5 mmoles) in tetrahydrofuran (5 ml) and treated as described above. Column chromatography was conducted using 30% ethyl acetate in hexane to give an amber oil (2.3 g, 66%); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.86 (m, 1H, H5), 7.17 (m, 2H, H4 and NH), 6.79 (m, 4H, phenyl-H), 4.71 (s, 2H, CH_3OCH_2O), 4.66 (s, 2H, thienyl-CH_2O), 3.75 (s, 2H, $NHCH_2$), 3.69 (s, 3H, phenyl-OCH_3), 3.29 (s, 3H, OCH_3); ms: (CI) m/z 358 (M+1).

Anal. Calcd. for $C_{15}H_{19}NO_5S_2$: C, 50.40; H, 5.36; N, 3.92. Found: C, 50.42; H, 5.41; N, 3.88.

3-(Methoxymethoxymethyl)-*N*-(3-methoxyphenyl)-2-thiophenesulfonamide (**3c**).

A solution of **2** (0.9 g, 3.5 mmoles) in tetrahydrofuran (15 ml) was added to a solution of *m*-anisidine (2.5 ml, 20.7 mmoles) in tetrahydrofuran (10 ml) and treated as described above. Purification by column chromatography (20% to 30% ethyl acetate in hexane) gave an oil (0.7 g, 57%): ^1H nmr (deuteriochloroform): δ 7.41 (d, J = 5.0 Hz, 1H, H5), 7.38 (br s, 1H, NH), 7.17 (s, 1H, phenyl-H), 7.14 (d, J = 5.0 Hz, 1H, H4), 6.77 (m, 1H, phenyl-H), 6.68 (m, 1H, phenyl-H), 6.65 (m, 1H, phenyl-H), 4.83 (s, 2H, CH_3OCH_2O), 4.68 (s, 2H, thienyl-CH_2O), 3.75 (s, 3H, phenyl-OCH_3), 3.46 (s, 3H, OCH_3); ms: (ES) m/z 342 (M+1).

Anal. Calcd. for $C_{14}H_{17}NO_5S_2 \cdot 0.2\ H_2O$: C, 48.46; H, 5.05; N, 4.04. Found: C, 48.13; H, 4.92; N, 3.92.

3-(Hydroxymethyl)-*N*-[2-(4-morpholinyl)ethyl]-2-thiophenesulfonamide (**4a**).

Ethanolic hydrochloric acid (2.0 ml of a 1.5 *M* solution) was added to a solution of **3a** (0.18 g, 0.51 mmole) in ethanol (2.0 ml) and this mixture was heated at 70° for 1 hour. The mixture was evaporated to a residue which was dissolved in a saturated aqueous solution of sodium bicarbonate (50 ml) and this solution was extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with brine (2 x 50 ml), dried (magnesium sulfate), and evaporated to give an oil which crystallized from ethyl acetate to give **4a** (0.10 g, 64%), mp 115-116°; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.80 (d, J = 5.0 Hz, 1H, H5), 7.24 (d, J = 5.0 Hz, 1H, H4), 6.90 (t, J = 5.8 Hz, 1H, OH), 5.43 (br s, 2H, CH_2OH), 3.52 (m, 4H, $O(CH_2CH_2)_2N$), 3.01 (m, 2H, SO_2NHCH_2), 2.40 (m, 4H, $O(CH_2CH_2)_2N$), 2.30 (m, 2H, NCH_2); ms: (CI) m/z 307 (M+1), 251.

Anal. Calcd. for $C_{11}H_{18}N_2O_4S_2$: C, 43.12; H, 5.92; N, 9.14. Found: C, 43.01; H, 5.96; N, 9.05.

3-Hydroxymethyl-*N*-[(3-methoxyphenyl)methyl]-2-thiophenesulfonamide (**4b**).

An ethanol solution of **3b** (0.30 g, 0.84 mmole) was treated as described above to give **4b** (0.21 g, 80%) as an oil: ^1H nmr (deuteriochloroform): δ 7.41 (d, J = 5.2 Hz, 1H, H5), 7.16 (d, J = 8.4 Hz, 1H, phenyl-H), 7.09 (d, J = 8.4 Hz, 1H, phenyl-H), 7.04 (d, J = 5.2 Hz, 1H, H4), 6.72 (m, 3H, phenyl-H), 4.80 (s, 2H, CH_2OH), 3.74 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 160.3, 145.0, 137.3, 135.0, 130.6, 129.9, 129.8, 114.7, 111.9, 108.3, 58.8, 55.4; ms: (EI) m/z 298 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_4S_2$: C, 49.82; H, 4.82; N, 4.47. Found: C, 49.67; H, 4.84; N, 4.46.

3-Hydroxymethyl-*N*-(3-methoxyphenyl)-2-thiophenesulfonamide (**4c**).

Method A.

An ethanol solution of **3c** (0.27 g, 0.79 mmole) was treated as described above to give **4c** as an oil (0.13 g, 51%): ^1H nmr (deuteriochloroform): δ 7.41 (d, J = 5.2 Hz, 1H, H5), 7.14 (dd, J = 7.6 and 8.4

Hz, 1H, aromatic), 7.06 (d, J=5.2 Hz, 1H, H4), 6.66-6.76 (m, 3H, phenyl H4, H5, H6), 4.80 (s, 2H, CH_2OH), 3.74 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 160.3, 145.0, 137.3, 134.9, 130.6, 129.9, 129.8, 114.7, 113.9, 108.3, 58.5, 55.4; ms: (ES) m/z 298 (M-H).

Anal. Calcd. for $C_{12}H_{13}NO_4S_2$: C, 48.15; H, 4.38; N, 4.68. Found: C, 48.07; H, 4.43; N, 4.62.

Method B.

To a solution of **12c** (0.6 g, 2.0 mmoles) in ethanol (10 ml) at room temperature was added sodium borohydride (0.08 g, 2.1 mmoles). After 5 hours, ethanol was evaporated and brine (50 ml) was added to the residue. This mixture was extracted with ethyl acetate (3 x 50 ml) and the combined extracts were washed with brine (25 ml), dried (magnesium sulfate), and evaporated to a residue which was purified by column chromatography (60% ethyl acetate in hexane) to give **4c** (0.49 g, 82%) as an oil: ^1H nmr, ms and tlc were identical to that of **4c** prepared from **3c**.

3-Hydroxymethyl-*N*-[2-methoxyethyl]-2-thiophenesulfonamide (**4d**).

To a suspension of **12d** (1.78 g, 7.1 mmoles) in ethanol (10 ml) at room temperature was added sodium borohydride (0.29 g, 7.1 mmoles). After 30 minutes ethanol was evaporated and brine (100 ml) was added to the residue; this mixture was extracted with ethyl acetate (3 x 100 ml). The combined extracts were washed with brine (25 ml), dried (magnesium sulfate), and evaporated to a residue which was purified by column chromatography (30% ethyl acetate in hexane) to give an oil (1.55 g, 87%); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.86 (br s, 1H, SO_2NH), 7.80 (d, J = 4.8 Hz, 1H, H5), 7.25 (d, J = 4.8 Hz, 1H, H4), 5.20 (s, 2H), 5.38 (br s, 1H, OH), 4.68 (s, 2H, CH_2OH), 3.31 (t, 2H, J = 4.4 Hz, CH_2OCH_3), 3.34 (s, 3H, OCH_3), 2.96 (t, 2H, J = 4.4 Hz, NCH_2); ms: (CI) m/z 251 (M+1), 234.

Anal. Calcd. for $C_8H_{13}NO_4S_2$: C, 38.23; H, 5.21: N, 5.57. Found: C, 38.07; H, 5.26; N, 5.51.

From **6d**.

To a solution of **6d** (0.12 g, 0.45 mmole) in ethanol (2.0 ml) at ambient temperature was added a solution of hydrochloric acid in ethanol (2.0 ml, 1.5 *N*) and this mixture was heated at 70° for 24 hours. Solvent was evaporated and the residue extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with brine (100 ml), dried (magnesium sulfate), and evaporated to give a product (oil, 0.90 g, 84%) which was identical to **4d** by tlc, ^1H nmr, and ms.

3-Hydroxymethyl-2-thiophenesulfonamide (**4e**).

To a solution of 3-thiophenemethanol (3.62 g, 32 mmoles) in tetrahydrofuran (40 ml) at –78° was added a 2.0 *M* solution of *n*-butyllithium in hexane (35.0 ml, 70.4 mmoles). After stirring at this temperature for 45 minutes, sulfur dioxide gas was passed over the surface of the reaction mixture for 15 minutes. Additional tetrahydrofuran (20 ml) was added and the reaction mixture was allowed to warm to room temperature. After 3 hours the reaction mixture was evaporated to a residue which was dissolved in water (100 ml) and cooled to 0°; sodium acetate (13.9 g, 102.0 mmoles) and hydroxylamine-*O*-sulfonic acid (6.87 g, 61.0 mmoles) were added. The reaction proceeded as described for **7a**; purification by chromatography (gradient 5% to 10% methanol in dichloromethane) gave a colorless solid (2.6 g, 42%), mp 118-120°; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.70 (d, J = 4.0 Hz, 1H, H5), 7.57 (br s, 2H, SO_2NH_2), 7.18 (d, J = 4.0 Hz, 1H, H4), 5.38 (br s, 1H, OH), 4.72 (s, 2H, CH_2OH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 145.6, 137.8, 128.8, 128.6, 57.32; ms: (CI) m/z 194 (M+1).

Anal. Calcd. for $C_5H_7NO_3S_2$: C, 31.08; H, 3.65; N, 7.25. Found: C, 31.05; H, 3.69; N, 7.18.

2,3-Dihydro-2-[2-(4-morpholinyl)ethyl]-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine 1,1-Dioxide (**6a**).

A mixture of **3a** (12.7 g, 36.2 mmoles), tetrahydrofuran (50 ml) and concentrated hydrochloric acid (5 drops) was heated at reflux temperature for 4 hours, cooled and then diluted with water (15 ml). The mixture was neutralized (*p*H 7.0) with 2 *N* sodium hydroxide and extracted with ethyl acetate (3 x 15 ml). The extracts were combined, washed with a saturated solution of sodium chloride and concentrated to a residue which consisted predominately of two compounds; these were separated and purified by column chromatography (50% hexane/ethyl acetate). The anticipated product **4a** was obtained as an oil (2.5 g, 23%).

The second compound to be eluted was **6a** which remained an oil (2.7 g, 24%); ir (film): γ 2956, 1345, 1158, 1116, 1073, 749, 675 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.58 (d, J = 4.9 Hz, 1H, H7), 6.96 (d, J = 4.9 Hz, 1H, H6), 5.30 (s, 2H, H5), 4.98 (s, 2H, H3), 3.65 (t, J = 4.6 Hz, 4H, $O(CH_2CH_2)_2N$), 3.24 (t, J = 6.8 Hz, 2H, $O(CH_2CH_2)_2NCH_2CH_2$), 2.60 (t, J = 6.8 Hz, 2H, $O(CH_2CH_2)_2NCH_2$), 2.45 (t, J = 4.6 Hz, 4H, $O(CH_2CH_2)_2N$),); ^{13}C nmr (deuteriochloroform): δ 140.3, 139.1, 129.2 (2), 82.8, 68.9, 66.8 (2), 57.4, 53.5 (2), 42.8; ms: (CI) m/z 319 (M+1). A portion of the syrup was converted to the hydrochloride salt for determination of combustion analysis.

Anal. Calcd. for $C_{12}H_{18}N_2O_4S_2$•HCl: C, 40.62; H, 5.40; N, 7.89 Found: C, 40.58; H, 5.44; N, 7.83.

2,3-Dihydro-2-[(3-methoxyphenyl)methyl]-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine 1,1-Dioxide (**6b**).

To a solution of **3b** (0.90 g, 2.52 mmoles) in tetrahydrofuran (10 ml) was added *p*-toluenesulfonic acid (0.67 g, 3.50 mmoles); this mixture was heated at reflux temperature for 20 hours. The solvent was evaporated and the residue was purified by column chromatography (gradient, 20% to 50% ethyl acetate in hexane) to give **6b** (0.71 g, 87%), mp 120-122°; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.89 (d, 1H, H7), 7.25 (m, 2H, H6 and phenyl-H2), 6.88 (m, 3H, phenyl-H4, H5, H6), 5.06 (m, 4H, H3 and H5), 4.18 (s, 2H, NCH_2-phenyl), 3.74 (s, 3H, OCH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 160.0, 143.5, 138.0, 137.9, 131.9, 130.9, 130.5, 121.3, 114.7, 114.1, 81.9, 69.1, 55.9, 49.9; ms: (CI) m/z 326 (M+1).

Anal. Calcd. for $C_{14}H_{15}NO_4S_2$: C, 51.68; H, 4.65; N, 4.30. Found: C, 51.72; H, 4.67; N, 4.28.

Synthesis from **6e**.

To a solution of **6e** (0.12 g, 0.58 mmole) in dimethyl sulfoxide (3 ml) at ambient temperature was added potassium carbonate (0.24 g, 1.74 mmoles) followed by 3-methoxybenzyl chloride (0.11 ml, 0.69 mmole). This mixture was stirred for 20 hours, diluted with brine (50 ml), and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with brine (2 x 50 ml), dried (magnesium sulfate), and evaporated to a residue which was purified by column chromatography (50% ethyl acetate in hexane) to give **6b** (0.16 g, 85%) identical to that prepared from **3b**.

2,3-Dihydro-2-(3-methoxyphenyl)-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine 1,1-Dioxide (**6c**).

Method A.

Prepared by reaction of **3c** (0.11 g, 0.32 mmole) in the manner described above for **6b**. Purification by column chromatography (20% ethyl acetate in hexane) gave **6c** (0.07 g, 70%, crystallization

from methanol-ether), mp 103-105°; ^{1}H nmr (deuteriochloroform): δ 7.42 (d, J = 5.0 Hz, 1H, H7), 7.13-7.26 (m, 1H, phenyl H2), 7.05 (d, J = 5.0 Hz, 1H, H6), 6.82-6.93 (m, 3H, phenyl H4, H5, H6), 5.49 (s, 2H, H5), 5.18 (s, 2H, H3), 3.75 (s, 3H, OCH_3); ms: (CI) m/z 312 (M+1).

Anal. Calcd. for $C_{13}H_{13}NO_4S_2$: C, 50.15; H, 4.21; N, 4.50. Found: C, 50.27; H, 4.34; N, 4.37.

Method B.

To a solution of **4c** (0.055 g, 1.85 mmoles) in dimethoxymethane (5 ml) at ambient temperature was added *p*-toluenesulfonic acid (4 mg, 0.02 mmole) followed by lithium bromide (3.5 mg, 0.04 mmole); this suspension was warmed to 38° and stirred for 40 hours. Evaporation of the solvent gave a residue which was suspended in ethyl acetate (100 ml) and this mixture was washed with a saturated aqueous solution of sodium bicarbonate (10 ml), brine (10 ml), dried (magnesium sulfate), and evaporated to a residue which was purified by column chromatography (gradient, 20% ethyl acetate in hexane) to provide **6c** (28 mg, 49%) which was identical to that prepared from **3c**.

Method C.

Reaction of **13** (0.070 g, 0.204 mmole) using the conditions described above for the preparation of **6b** provided **6c** (0.045 g, 72%) which was identical to that prepared from **3c**.

2,3-Dihydro-2-(2-methoxyethyl)-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine 1,1-Dioxide (**6d**) and 3-(Methoxymethoxymethyl)-*N*-(2-methoxyethyl)-2-thiophenesulfonamide (**3d**).

A solution of **4d** (1.02 g, 4.10 mmoles) in dimethoxymethane (10 ml) at ambient temperature containing *p*-toluenesulfonic acid (0.08 g, 0.41 mmole) and lithium bromide (0.70 g, 0.80 mmole) was stirred for 72 hours. After treatment as described for the preparation of **6c** (Method B) above, two products, **6d** (0.50 g, 46%) and **3d** (0.30 g, 25%) were obtained.

Compound **6d**.

This compound had mp 168°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.85 (d, J = 5.0 Hz, 1H, H7), 7.22 (d, J = 5.0 Hz, 1H, H6), 5.19 (s, 2H, H5), 4.98 (s, 2H, H3), 3.50 (t, J = 6.0 Hz, 2H, CH_2OCH_3), 3.22 (s, 3H, OCH_3), 3.17 (t, J = 6.0 Hz, 2H, NCH_2CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 143.0, 140.0, 132.6, 131.8, 84.3, 72.0, 69.9, 59.8, 47.2; ms: (CI) m/z 264 (M+1).

Anal. Calcd. for $C_9H_{13}NO_4S_2$: C, 41.06 H, 4.98; N, 5.32. Found: C, 41.24; H, 5.05; N, 5.28.

Compound **3d**.

This compound was an oil which readily decomposed upon heating under vacuum; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.01 (t, J = 5.8 Hz, 1H, SO_2NH), 7.85 (d, J = 5.0 Hz, 1H, H5), 7.22 (d, J = 5.0 Hz, 1H, H4), 4.75 (s, 2H, CH_3OCH_2O), 4.69 (s, 2H, thienyl-CH_2O), 3.32 (m, 2H, $CH_2CH_2OCH_3$), 3.26 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 3.0 (dd, J = 5.6 Hz, 2H, $NHCH_2$); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 144.6, 138.1, 133.1, 131.8, 98.4, 72.9, 65.1, 60.4, 57.5, 44.6; ms: (CI) m/z 296 (M+1), 264 (-OCH_3).

Anal. Calcd. for $C_{10}H_{17}NO_5S_2$•0.4$(CH_3)_2NCHO$•0.2 H_2O: C, 40.76; H, 6.23; N, 5.94. Found: C, 41.11; H, 6.61; N, 5.47; (N difference 0.47).

2,3-Dihydro-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine 1,1-Dioxide (**6e**).

To a solution of **4e** (0.61 g, 3.16 mmoles) in dimethoxymethane (6 ml) and tetrahydrofuran (4 ml) at ambient temperature was added *p*-toluenesulfonic acid (0.06 g, 0.31 mmole) and the suspension stirred for 72 hours. Evaporation of the solvent gave a residue which was dissolved in ethyl acetate (100 ml); this solution was washed with saturated aqueous sodium bicarbonate (50 ml) and brine (100 ml), dried (magnesium sulfate), and evaporated to give a residue which was purified by column chromatography (gradient, 30% ethyl acetate in hexane to 50% ethyl acetate in hexane) to give **6e** as a colorless solid (0.40 g, 62%). Recrystallization from a mixture of dichloromethane and ethyl acetate (1:1) gave large colorless plates, mp 130-131°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.02 (t, J = 6.8 Hz, 1H, SO_2NH), 7.76 (d, J = 5.0 Hz, 1H, H7), 7.02 (d, J = 5.0 Hz, 1H, H6), 4.93 (s, 2H, H5), 4.88 (d, J = 6.8 Hz, 2H, H3); ms: (CI) m/z 206 (M+1).

Anal. Calcd. for $C_6H_7NO_3S_2$: C, 35.11; H, 3.44; N, 6.82. Found: C, 35.15; H, 3.47; N, 6.76

2,3-Dihydro-2-[2-(4-morpholinyl)ethyl]-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine-7-sulfonamide 1,1-Dioxide Hydrochloride (**7a**).

A solution of **6a** (1.63 g, 5.11 mmoles) in tetrahydrofuran (20 ml) was cooled to -40° and *n*-butyllithium (2.5 ml of a 2.06 *M* solution in hexanes) was added. This solution was warmed to 0° and stirred for 2 hours followed by cooling to -50° and introducing an excess of sulfur dioxide gas (15 minutes) into the flask. The mixture was stirred for 16 hours at room temperature and then evaporated to a residue which was dissolved in water (15 ml) and cooled to 0°; sodium acetate (0.84 g, 10.2 mmoles) was added followed by hydroxylamine-*O*-sulfonic acid (0.89 g, 7.67 mmoles) and the mixture was stirred at room temperature for 16 hours. After saturating the reaction mixture with sodium chloride it was extracted with ethyl acetate (3 x 100 ml). The combined extracts were dried (magnesium sulfate) and evaporated to give a residue which was purified by column chromatography (gradient: 50% ethyl acetate in hexane to ethyl acetate) to provide the free base which was converted to the hydrochloride salt **7a** (0.32 g, 19%): mp 180-183°; ir (potassium bromide): γ 3384, 2970, 1352, 1157 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.19 (br s, 1H, N^+H), 8.10 (s, 2H, SO_2NH_2), 7.70 (s, 1H, H6), 5.28 (s, 2H, H5), 5.05 (s, 2H, H3), 3.00-4.00 (m, 12H, $O(CH_2CH_2)_2$-NCH_2CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 148.7, 141.4, 140.2, 131.4, 81.9, 68.0, 63.0 (2), 53.4, 51.2 (2), 40.5; ms: (CI): m/z 398 (M+1).

Anal. Calcd. for $C_{12}H_{19}N_3O_6S_3$•HCl •0.6 C_2H_5OH: C, 34.34; H, 5.15; N, 9.10. Found: C, 34.29; H, 4.82; N, 8.94.

2,3-Dihydro-2-[(3-methoxyphenyl)methyl]-5*H*-thieno[2,3-*e*]-4,1,2-oxathiazepine-7-sulfonamide 1,1-Dioxide (**7b**).

A solution of **6b** (0.71 g, 2.18 mmoles) in tetrahydrofuran (10 ml) was treated as described above to give a residue which was purified by column chromatography (gradient, 60% to 80% ethyl acetate in hexane), providing **7b** as a viscous syrup (0.18 g, 20%) and unreacted starting material (0.44 g); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.06 (br s, 2H, SO_2NH_2), 7.63 (s, 1H, H6), 7.28 (m, 1H, phenyl-H2), 6.90 (m, 3H, phenyl-H4,H5,H6), 5.75 (s, 2H, H5), 5.06 (s, 2H, H3), 4.25 (s, 2H, NCH_2-phenyl), 3.74 (s, 3H, OCH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 159.3, 148.4, 141.1(2), 136.7, 131.4, 129.7, 120.3, 113.8, 113.3, 81.0, 68.1, 54.9, 43.2; ms: (CI) m/z 405 (M+1).

Anal. Calcd. for $C_{14}H_{16}N_2O_6S_3$: C, 41.57; H, 3.99; N, 6.93. Found: C, 41.82; H, 3.97; N, 6.75.

4-(Hydroxymethyl)-N^5-[2-(4-morpholinyl)ethyl]-2,5-thiophenedisulfonamide Hydrochloride (**8a**).

To a solution of **3a** (7.0 g, 20.0 mmoles) in tetrahydrofuran at -70° was added a 2.5 *M* solution of *n*-butyllithium in hexane (17.6 ml, 44.0 mmoles); this mixture was stirred for 50 minutes. A stream of sulfur dioxide gas was passed over the surface of the solution for 20 minutes followed by stirring at room temperature for 2 hours. The reaction mixture was evaporated to a residue which was dissolved in water (50 ml) and sodium acetate trihydrate (8.2 g, 60.0 mmoles) was added followed by cooling the mixture (0°) and adding hydroxylamine-*O*-sulfonic acid (4.5 g, 40.0 mmoles). The reaction proceeded as described for **7a**; purification by chromatography (gradient: 20% to 50% methanol in dichloromethane) gave **9a** as an oil (4.6 g, 66%). A solution of **9a** (1.25 g) in ethanol (6 ml) was treated with a solution of 1.5 *N* hydrochloric acid in ethanol (2 ml) at 70° for 30 minutes followed by evaporation to give an amorphous solid which was crystallized from a water/methanol mixture to give **8a** (0.65 g, 68%) as colorless crystals, mp 202-204°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.10 (br s, 1H, N$^+$H), 8.70 (br t, 1H, SO_2NH), 7.99 (s, 2H, SO_2NH_2), 7.65 (s, 1H, H3), 5.70 (br s, 1H, OH), 4.68 (s, 2H, CH_2OH), 4.00-3.10 (m, 12H, $O(CH_2CH_2)_2NCH_2CH_2$); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 148.3, 147.3, 135.8, 130.9, 63.1, 56.9, 55.2, 51.2, 36.8; ms: (CI) m/z 356 (M$^+$- CHO).

Anal. Calcd. for $C_{11}H_{19}N_3O_6S_3$•HCl: C, 31.31; H, 4.77; N, 9.96. Found: C, 31.34; H, 4.64; N, 9.82.

3-(1,3-Dioxolan-2-yl)thiophene-2-sulfonyl Chloride (**11**).

To a solution of **10** [14] (20.0 g, 143 mmoles) in tetrahydrofuran (200 ml) at -78° was added a 2.5 *M* solution of *n*-butyllithium in hexane (85.7 ml, 214 mmoles). After stirring at this temperature for 1 hour, sulfur dioxide gas was passed over the surface of the reaction mixture for 15 minutes, and the solution warmed to room temperature and maintained at this temperature for 2 hours. The reaction mixture was evaporated to a residue which was dissolved in dichloromethane (200 ml), cooled to 0°, and *N*-chlorosuccinimide (30.0 g, 220 mmoles) was added in portions. This mixture was stirred for 3 hours and then warmed to room temperature and stirred for an additional 2 hours. The solid which formed was removed by filtration and the filtrate was evaporated to give **11** as a brown syrup which was used in the next reaction without further purification (17 g, 47%): ir (film): γ 2949, 1378, 1181, 1151 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.72 (d, J = 5.4 Hz, 1H, H5), 7.33 (d, J = 5.4 Hz, 1H, H4), 6.40 (s, 1H, OCHO), 4.21 (m, 4H, OCH_2CH_2O).

3-Formyl-*N*-(3-methoxyphenyl)-2-thiophenesulfonamide (**12c**).

m-Anisidine (4.0 ml, 36.0 mmoles) was added to a solution of **11** in tetrahydrofuran (40 ml) which had been cooled to 0°. The mixture was allowed to warm to room temperature and stirred for 18 hours followed by evaporation to a residue which was dissolved in tetrahydrofuran (20 ml) and treated with 4 *N* hydrochloric acid (10 ml) at room temperature for 16 hours. Water was added and the mixture extracted with ethyl acetate (3 x 60 ml). The combined extracts were washed with brine (25 ml), dried (magnesium sulfate) and evaporated to a residue which was purified by column chromatography (50% ethyl acetate in hexane) to give **12c** (0.6 g, 31%): ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.71 (s, 1H, SO_2NH), 10.05 (s, 1H, CHO), 7.92 (d, J = 6.0 Hz, 1H, H5), 7.46 (d, J = 6.0 Hz, 1H, H4), 7.21 (dd, J = 8.0 and 10.0 Hz, 1H, phenyl H5), 6.78-6.66 (m, 3H, phenyl H4, H6, H2), 3.68 (s, 3H, OCH_3); ms: (ES) m/z 296 (M-H).

Anal. Calcd. for $C_{12}H_{11}NO_4S_2$: C, 48.47; H, 3.73; N, 4.71. Found: C, 48.25; H, 3.79; N, 4.64.

3-Formyl-*N*-(2-methoxyethyl)-2-thiophenesulfonamide (**12d**).

2-Methoxyethylamine (30 ml, 300 mmoles) was added to a solution of **11** in tetrahydrofuran (200 ml) which had been cooled to 0°. This mixture was allowed to warm to room temperature and stirred 16 hours. The mixture was evaporated to a residue which was dissolved in tetrahydrofuran (200 ml) and treated with 4 *N* hydrochloric acid (50 ml) at room temperature for 16 hours. Water (100 ml) was added and the mixture was extracted with ethyl acetate (3 x 300 ml). The combined extracts were washed with brine (25 ml) dried (magnesium sulfate), and evaporated to a residue which was purified by column chromatography (30% to 50% ethyl acetate in hexane) to give **12d** as an oil (17.0 g, 48%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.32 (s, 1H, CHO), 8.43 (t, J = 5.0 Hz, 1H, SO_2NH), 7.92 (d, J = 5.3 Hz, 1H, H5), 7.53 (d, J = 5.3 Hz, 1H, H4), 3.32 (m, 2H, CH_2OCH_3), 3.31 (s, 3H, OCH_3), 3.06 (m, 2H, $NHCH_2$); ms: (CI) m/z 250 (M+1), 232.

Anal. Calcd. for $C_8H_{11}NO_4S_2$: C, 38.54; H, 4.45; N, 5.62. Found: C, 38.60; H, 4.49; N, 5.65.

3-Hydroxymethyl-*N*-methoxymethyl-*N*-(3-methoxyphenyl)-2-thiophenesulfonamide (**13**).

To a solution of **4c** (0.48 g, 1.61 mmoles) in dichloromethane (5.0 ml) at room temperature was add *N,N*-diisopropylethylamine (0.36 ml, 2.09 mmoles) followed by chloromethyl methyl ether (0.16 ml, 2.09 mmoles). After 18 hours, the reaction mixture was diluted with brine (50 ml) and extracted with ethyl acetate (3 x 40 ml). The combined extracts were washed with brine (10 ml), dried (magnesium sulfate) and evaporated to give a residue which was purified by column chromatography (20% ethyl acetate in hexane to 30% ethyl acetate in hexane) to give an oil (0.22 g, 40%): ^{1}H nmr (deuteriochloroform): δ 7.51 (d, J = 6.0 Hz, 1H, H5), 7.26-7.28 (m, 1H, phenyl H2), 7.10 (d, J = 6.0 Hz, 1H, H4), 6.92 (m, 1H, phenyl H), 6.78 (m, 1H, phenyl H), 6.77 (s, 1H, phenyl H), 5.05 (s, 2H, CH_3OCH_2O), 4.42 (d, J = 6.0 Hz, 2H, CH_2OH), 3.75 (s, 3H, phenyl-OCH_3), 3.43 (s, 3H, OCH_3), 2.51 (t, J = 6.0 Hz, 1H, CH_2OH), ms: (ES) 313 (M-OCH_3).

Anal. Calcd. for $C_{14}H_{17}NO_5S_2$: C, 48.97; H, 4.99; N, 4.08. Found: C, 48.91; H, 5.04; N, 4.14.

X-ray Structure Determination.

Crystals of **6e** grew as very large colorless plates by slow evaporation from a mixture (1:1) of dichloromethane and ethyl acetate. The data crystal was a was cut from a much larger crystal and had approximate dimensions; 0.34 x 0.42 x 0.49 mm. The data were collected at -90° on a Siemens P4 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using a graphite monochromator with MoKα radiation (λ = 0.71073Å). Details of crystal data, data collection and structure refinement are listed in Table 1. Four reflections (-2,-3,-1; -4,-2,1; 1,-1,-8; 3,3,0) were remeasured every 96 reflections to monitor instrument and crystal stability. A smoothed curve of the intensities of these check reflections was used to scale the data. The scaling factor ranged from 0.9826-1.012. The data were corrected for Lp effects but not for absorption. Data reduction, decay correction, structure solution and refinement were performed using the SHELXTL/PC software package [15]. The structure was solved by direct methods and refined by full-

matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms. The hydrogen atom positions were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2-|F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0414*P)^2 + (0.2616P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + 8.4(4)x10^{-5}* F_c^2 \lambda^3/\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography [16]. Other computer programs used in this work are listed elsewhere [17]. Figures were generated using SHELXTL/PC [15].

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