Synthesis of Certain 5-Substituted Thieno[2,3-*b*]thiophene-2-sulfonamides and Thieno[2,3-*b*]thiophene-2-sulfonamide 6,6-Dioxides

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A series of the title compounds were prepared for evaluation as inhibitors of carbonic anhydrase II. Oxidation of 5-substituted thieno[2,3-*b*]thiophene-2-sulfonamides provided the first examples of thiophene[2,3-*b*]thiophene-2-sulfonamide 6,6-dioxides. These cyclic vinyl sulfones readily underwent addition to give predominately that 4,5-*cis* addition product.

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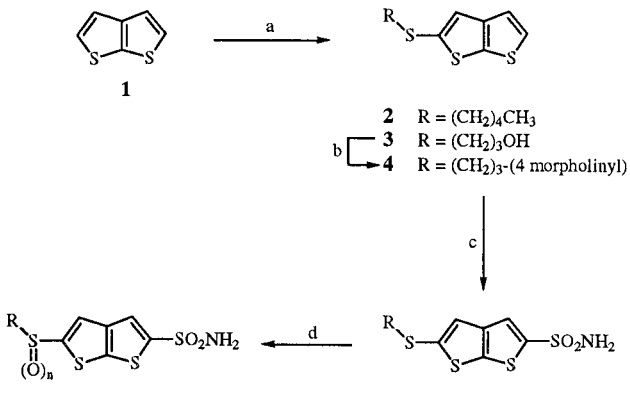
A variety of thieno[2,3-*b*]thiophene-2-sulfonamides and 4,5-dihydrothieno[2,3-*b*]thiophene-2-sulfonamides have been synthesized [1-4] and a number of these have been shown to be potent inhibitors of human carbonic anhydrase II [1]. As an extension of these earlier reports, it was of interest to us to incorporate functionality into the molecule which would increase the acidity of the primary sulfonamide group. It has been established that for the arylsulfonamide inhibitors of carbonic anhydrase II, the anion form of the primary sulfonamide binds to the zinc atom present in the enzyme active site [5]; therefore, an increased ionization of the sulfonamide group at physiologic *p*H would be anticipated to favor an increase in enzyme affinity, resulting in an increased inhibition of the enzyme. Hence, the incorporation of the strongly electron withdrawing sulfone group as a substituent at position five of the thieno[2,3-*b*]thiophene-2-sulfonamide ring was of interest along with the incorporation of a sulfone group at position six of this ring system.

Incorporation of a sulfone group at ring position five was readily accomplished by oxidation of the corresponding sulfide as indicated in Scheme 1. Reaction of thieno[2,3-*b*]-thiophene (**1**) with *n*-butyllithium [7] followed by treatment with elemental sulfur and subsequently bromopentane gave the sulfide **2**. Regioselective sulfamoylation of **2** was achieved by sequential reaction with *n*-butyllithium, sulfur dioxide, and hydroxylamine-*O*-sulfonic acid [8] to give **5**. Selective oxidation of sulfide **5** with potassium peroxymonosulfate compound provided the desired sulfone **8**. By following this same sequence, but using instead 3-hydroxypropanethiol, compound **3** was prepared and transformed to the sulfone **9**. Tosylation of the hydroxyl group of **3** followed by reaction with morpholine gave **4** which was sulfamoylated as above to provide **7**. Selective mono-oxidation of **7** with a slight excess of potassium peroxymonosulfate compound provided the sulfoxide **10** which was isolated as the hydrochloride salt. Oxidation of **7** in the presence of an excess this oxidant gave the desired sulfone **11** which was isolated as the free base.

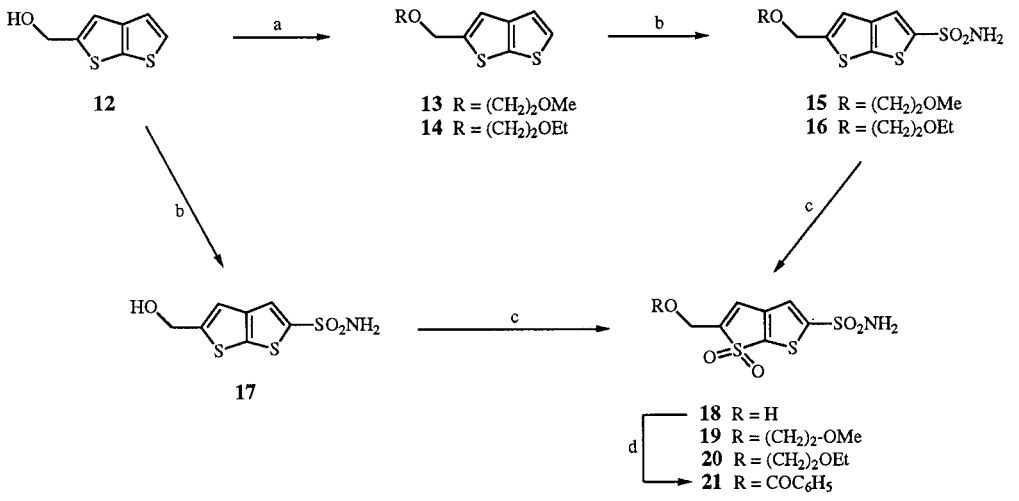
Scheme 1



Reagents: a) *n*-BuLi, sulfur, alkylbromide; b) *p*-toluenesulfonyl chloride, morpholine; c) *n*-BuLi, sulfur dioxide, hydroxylamino-*O*-sulfonic acid; d) potassium peroxymonosulfate compound.

Alkylation of thieno[2,3-*b*]thiophene-2-methanol (**12**) [1] with the desired alkylbromide in the presence of sodium hydride in *N*,*N*-dimethylformamide provided the ethers **13** and **14** which were sulfamoylated as above to give the sulfonamides **15** and **16**, respectively (Scheme 2). Reaction of these sulfonamides with an excess of potassium peroxymonosulfate compound resulted in selective oxidation of the sulfur atom in the more electron rich thiophene ring of the thieno[2,3-*b*]thiophene ring system in each case to give **19** and **20**, respectively. Similarly, oxidation of **17** gave **18**. The regiochemistry of the oxidation products was initially assigned based on the proton nmr

Scheme 2



Reagents: a) Alkylhalide, sodium hydride, dimethylformamine; b) *n*-BuLi, sulfur dioxide, hydroxylamine-*O*-sulfonic acid; c) potassium peroxymonosulfate compound; d) benzoyl chloride.

spectra for these compounds. The protons at positions three and four appear as sharp singlets in the nmr spectra for the 2,5-substituted thieno[2,3-*b*]thiophenes **15**, **16**, and **17**. However, following oxidation of **15** to give **19**, for example, there was not only the anticipated change in the chemical shift of these signals, but also, the more upfield signal now appeared as a one proton triplet. Such multiplicity could only occur through coupling of the proton at ring position four to the methylene group attached to position five, for which the signal now appeared as a doublet rather than a singlet. The observed 1.3-1.5 Hz coupling constant for these signals is consistent with allylic coupling, suggesting that the sulfur atom at ring position six was oxidized, providing the thiophene *b*-face fused cyclic vinyl sulfones. If oxidation had occurred solely at the sulfur atom at ring position one, the above coupling pattern would not have been observed. The structure of the oxidation product was subsequently established unequivocally by determining the X-ray crystal structure of the benzoate derivative **21**, confirming the selective oxidation of the sulfur atom at position six of the thieno[2,3-*b*]thiophene-2-sulfonamides (Figure 1). It is of interest to note the presence of an unusual example of a C-H···O bifurcated hydrogen bond in crystalline **21** (Figure 2). The hydrogen atoms attached to C3 and C4 both form a hydrogen bond with the same oxygen atom of the S6 sulfone of an adjacent molecule.

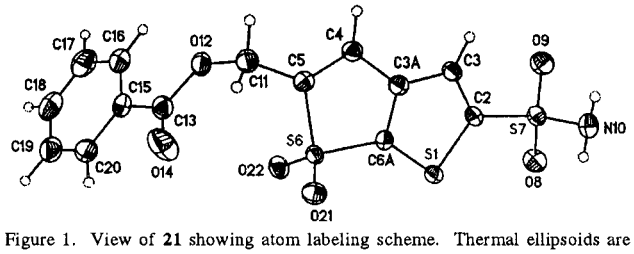


Figure 1. View of **21** showing atom labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogens are drawn to an arbitrary scale.

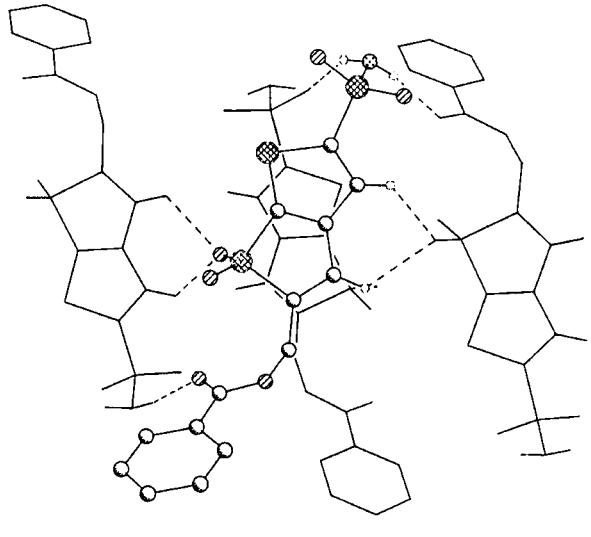
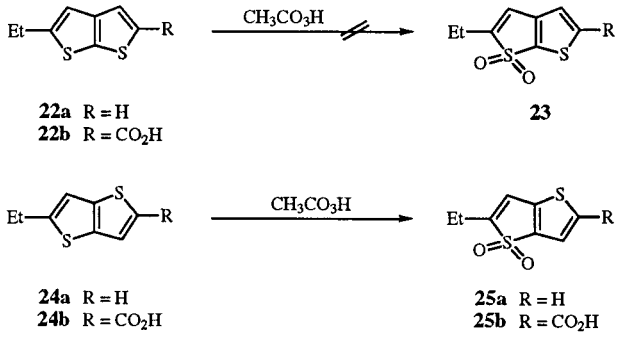


Figure 2. View showing a portion of the extended hydrogen bonding network for **21**. The hydrogen bonding interactions are shown as dashed lines.

The synthesis of compounds **18-20** represents the first successful oxidation of one of the ring sulfur atoms of the thieno[2,3-*b*]thiophene ring system to provide a thieno-[2,3-*b*]thiophene dioxide. A previous attempt to obtain thieno[2,3-*b*]thiophene dioxides **23** by oxidation of **22a-b** with peracetic acid was unsuccessful; however, it was demonstrated that the regioisomeric thieno[3,2-*b*]thiophenes **24a-b** were readily oxidized under these conditions to provide **25a-b** [9,10]. Subsequently, *m*-chloroperbenzoic acid was also used successfully to oxidize the thieno[3,2-*b*]thiophene ring in the preparation of 2,5-dimethylthieno[3,2-*b*]thiophene 1,1-dioxide [11].

Scheme 3



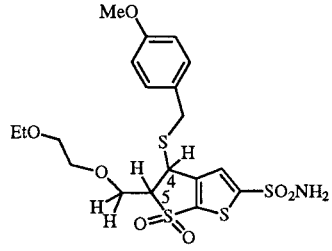
22a R = H
22b R = CO_2H

23

24a R = H
24b R = CO_2H

25a R = H
25b R = CO_2H

The activated double bond of the cyclic vinyl sulfone moiety readily underwent nucleophilic addition which was exemplified by reaction of **20** with 4-methoxy-α-toluenethiol in the presence of base to provide a mixture of the *cis* and *trans* addition products. The structural assignments for these compounds, **26** and **27**, respectively, were based on a comparison of their nOe difference nmr spectra. No significant nOe was observed for either compound when the experiments were performed at ambient temperature, but upon warming to 60° a significant nOe (6%) was observed. Irradiation of the H5 proton of **27** resulted in an internal enhancement ratio of 1:1 for the H4 proton and the 5α methylene protons, respectively. However, similar irradiation of **26** showed an internal enhancement ratio of 6:1 for these same resonances; that is, a six fold higher enhancement of the H4 proton signal compared to that of the 5α methylene protons. Therefore, the smaller internuclear distance between H5 and H4 in **26** substantiate that this compound is the *cis* isomer. The addition product **26** predominated under the conditions of the reaction with an isomer ratio of 2.4:1, based on the isolated compounds. The ratio of the *cis* and *trans* isomers appears to be under kinetic control with protonation occurring from the least hindered side to afford the *cis* isomer as the major product. In contrast to the present observation, it was previously noted [12] that the addition of *p*-toluenethiol to the vinyl sulfone 1-(*p*-toluylsulfonyl)cyclopentene under mildly basic conditions provided exclusively *trans* addition to the cyclopentene ring while addition to 1-(*p*-toluylsulfonyl)cyclohexene under similar conditions gave exclusively the *cis* addition product.



26 4,5-*cis*
27 4,5-*trans*

Table 1
Crystallographic Data for **21**

Formula	$C_{14}H_{11}NO_6S_3$
fw	385.42
a, Å	15.374(1)
b, Å	12.054(1)
c, Å	8.5200(6)
β, (°)	95.388(6)
V, Å^3	1571.9(2)
Z	4
F(000)	792
Crystal System	Monoclinic
Space Group	$P2_1/c$
T, °C	-90
2θ range (°)	4-55
Scan speed (°/min) (1.2° ω scan)	4-8
ρ_{calc}, g/cc	1.63
Reflections measured	4393
Unique reflections	3507
R_{int} (F^2)	0.027
μ, cm^{-1}	3.25
Crystal size, mm	0.14 x 0.75 x 0.79
$R_W(F^2)$ [a]	0.0909
R(F) [b]	0.0391
Goodness of fit, S[c]	1.077
Parameters	261
Max | Δ/σ |	<0.1
Min, max peaks (e$^-$/Å^3)	-0.38, 0.38

[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: $w = 1/\{\sigma^2(|F_o|^2) + (a*P)^2 + b*P\}$; $P = [1/3*(\text{Maximum of } (0 \text{ or } |Fo|^2) + 2/3*|F_c|^2]$. The parameters a and b were suggested during refinement and are 0.0361 and 0.8657, respectively; [b] The conventional R index based on F where the 2752 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

Bond Lengths (Å) and Angles (°) for the Hydrogen Atoms of **21**

1	2	3	1-2	1-2-3
H3	C3	C3A	0.91(2)	127.(2)
H3	C3	C2		123.(2)
H4	C4	C5	0.96(3)	123.(2)
H4	C4	C3A		123.(2)
H10A	N10	H10B	0.87(3)	116.(3)
H10A	N10	S7		112.(2)
H10B	N10	S7	0.85(3)	108.(2)
H11A	C11	H11B	0.94(3)	113.(2)
H11A	C11	O12		105.7(15)
H11A	C11	C5		110.(2)
H11B	C11	O12	0.96(3)	108.3(15)
H11B	C11	C5		109.0(15)
H16	C16	C17	0.95(3)	121.(2)
H16	C16	C15		119.(2)
H17	C17	C18	0.92(3)	124.(2)
H17	C17	C16		115.(2)
H18	C18	C19	0.99(3)	120.(2)
H18	C18	C17		120.(2)
H19	C19	C20	1.01(3)	119.(2)
H19	C19	C18		121.(2)
H20	C20	C15	0.95(3)	118.(2)
H20	C20	C19		122.(2)

Table 3

Torsion Angles (°) for the Non-hydrogen Atoms of **21**

1	2	3	4	1-2-3-4
C2	S1	C6A	C3A	0.7(2)
C2	S1	C6A	S6	176.5(2)
C6A	S1	C2	C3	0.4(2)
C6A	S1	C2	S7	178.26(15)
C3	C2	S7	O8	-165.3(2)
C3	C2	S7	O9	-34.9(2)
C3	C2	S7	N10	80.5(2)
S7	C2	C3	C3A	-179.1(2)
S1	C2	C3	C3A	-1.4(3)
S1	C2	S7	O8	17.1(2)
S1	C2	S7	O9	147.46(13)
S1	C2	S7	N10	-97.1(2)
C2	C3	C3A	C4	-174.7(2)
C2	C3	C3A	C6A	1.9(3)
C4	C3A	C6A	S1	175.7(2)
C4	C3A	C6A	S6	-1.2(3)
C6A	C3A	C4	C5	-1.1(3)
C3	C3A	C4	C5	175.4(2)
C3	C3A	C6A	S1	-1.6(2)
C3	C3A	C6A	S6	-178.5(2)
C3A	C4	C5	S6	2.8(3)
C3A	C4	C5	C11	176.3(2)
S6	C5	C11	O12	-68.4(2)
C11	C5	S6	C6A	-176.9(2)
C11	C5	S6	O21	-63.3(2)
C11	C5	S6	O22	68.5(2)
C4	C5	S6	C6A	-3.0(2)
C4	C5	S6	O21	110.7(2)

Table 3 (continued)

1	2	3	4	1-2-3-4
C4	C5	S6	O22	-117.5(2)
C4	C5	C11	O12	118.8(3)
O21	S6	C6A	S1	75.3(2)
O21	S6	C6A	C3A	-108.8(2)
O22	S6	C6A	S1	-59.0(2)
O22	S6	C6A	C3A	116.9(2)
C5	S6	C6A	S1	-173.6(2)
C5	S6	C6A	C3A	2.3(2)
C5	C11	O12	C13	105.4(2)
C11	O12	C13	O14	-0.2(3)
C11	O12	C13	C15	-179.1(2)
O14	C13	C15	C16	171.6(3)
O14	C13	C15	C20	-7.9(4)
O12	C13	C15	C16	-9.6(4)
O12	C13	C15	C20	170.9(2)
C16	C15	C20	C19	0.3(5)
C20	C15	C16	C17	-0.4(4)
C13	C15	C16	C17	-179.9(2)
C13	C15	C20	C19	179.8(2)
C15	C16	C17	C18	0.5(5)
C16	C17	C18	C19	-0.5(5)
C17	C18	C19	C20	0.3(5)
C18	C19	C20	C15	-0.2(4)

Table 4

Fractional Coordinates and Equivalent Isotropic Thermal Parameters (Å^2) for the Non-hydrogen Atoms of **21**

Atom	x	y	z	U
S1	0.36089(4)	0.17199(5)	0.01037(7)	0.0234(2)
C2	0.33583(14)	0.3120(2)	0.0091(3)	0.0209(6)
C3	0.3977(2)	0.3779(2)	-0.0464(3)	0.0229(7)
C3A	0.4693(2)	0.3143(2)	-0.0864(3)	0.0226(6)
C4	0.5549(2)	0.3417(2)	-0.1393(3)	0.0231(7)
C5	0.6063(2)	0.2546(2)	-0.1537(3)	0.0220(6)
S6	0.55010(4)	0.12922(4)	-0.11155(7)	0.0202(2)
C6A	0.45715(14)	0.2033(2)	-0.0641(3)	0.0212(6)
S7	0.23628(4)	0.36010(5)	0.06892(7)	0.0231(2)
O8	0.20210(12)	0.2710(2)	0.1553(2)	0.0336(6)
O9	0.25278(12)	0.4658(2)	0.1394(2)	0.0343(6)
N10	0.17007(14)	0.3780(2)	-0.0869(3)	0.0300(7)
C11	0.6944(2)	0.2526(2)	-0.2126(3)	0.0270(7)
O12	0.75901(11)	0.21259(14)	-0.0902(2)	0.0274(5)
C13	0.7889(2)	0.1092(2)	-0.1052(3)	0.0276(7)
O14	0.7641(2)	0.0502(2)	-0.2142(2)	0.0499(7)
C15	0.8534(2)	0.0765(2)	0.0275(3)	0.0270(7)
C16	0.8879(2)	0.1524(2)	0.1394(3)	0.0349(8)
C17	0.9481(2)	0.1162(3)	0.2605(4)	0.0445(10)
C18	0.9739(2)	0.0071(3)	0.2692(4)	0.0431(10)
C19	0 9397(2)	-0.0683(3)	0.1578(4)	0.0395(9)
C20	0.8794(2)	0.0338(2)	0.0364(3)	0.0325(8)
O21	0.53276(11)	0.06741(14)	-0.2547(2)	0.0292(5)
O22	0.59216(11)	0.07239(14)	0.0231(2)	0.0283(5)

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.

The novel thieno[2,3-*b*]thiophene-2-sulfonamides reported here were shown to have a high affinity for human carbonic anhydrase II, and in general those compounds with the more acidic sulfonamide group showed the higher affinity (Table 5). However, compounds bearing a 5-substituent which incorporated a polar terminal group (**9-11**, **18**) had a lower affinity (K_i > 1 n*M*) for the enzyme than those compounds where this substituent had a lipophilic terminus (K_i < 1 n*M*). Sulfone **11** (p*K* 8.68) had a higher affinity for the enzyme than sulfoxide **10** (p*K* 9.07). Similarly, sulfones **19** and **20**, with sulfonamide p*K* values of 8.28 and 7.99, respectively, had an approximately two fold higher affinity for human carbonic anhydrase II than the corresponding non-oxidized compounds **15** and **16**; the sulfonamide p*K*a value for **16** was determined to be 8.73. However, this increased enzyme affinity does not appear to provide any increase in enzyme inhibition in view of the comparable inhibition constants for the oxidized and unoxidized compounds.

Table 5

Dissociation Constants and *in vitro* Enzyme Data

No.	p*K*a	K_i (n*M*) [a]	IC_{50} (n*M*) [b]
8	8.64 [c]	0.25 ±0.06	1.06
9	8.75 [c]	1.07 ±0.07	1.43
10	6.56, 9.07 [c]	1.77 ±0.09	4.70
11	6.39, 8.68 [c]	1.16 ±0.16	2.84
15	[d]	0.44 ±0.05	1.50
16	8.73 [c]	0.35 ±0.12	1.30
18	8.41 [e]	1.23 ±0.24	1.87
19	8.28 [e]	0.19 ±0.01	1.88
20	7.99 [c]	0.15 ±0.03	1.76

[a] Reference [13]; [b] Reference [16]; [c] CH_3CN and H_2O mixture; [d] Unable to obtain satisfactory inflection point; [e] H_2O.

EXPERIMENTAL

Melting points were determined in open capillaries using a Thomas-Hoover Uni-Melt Apparatus and are uncorrected. Organic extracts were dried with magnesium sulfate. Chromatography refers to column chromatography conducted on 230-400 mesh silica gel from E. Merck. Silica gel tlc plates were obtained from EM Separation Technology. Potassium peroxymonosulfate compound (Oxone®) was purchased from Aldrich Chemical Co. The ^1H nmr and ^{13}C nmr spectra were determined at 200 MHz with a Varian Model VXR-200 spectrometer or at 600 MHz with a Bruker DRX-600. 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. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia. Evaporations were performed under reduced pressure on a rotary evaporator at 40° unless otherwise indicated.

2-(Pentylthio)thieno[2,3-*b*]thiophene, **2**.

To a solution of thieno[2,3-*b*]thiophene [6] (**1**) (0.88 g, 6.3 mmoles) in anhydrous tetrahydrofuran (30 ml) under nitrogen at -60° was added *n*-butyllithium (1.76 *M* in hexanes, 3.93 ml, 6.91 mmoles) over 5 minutes. The mixture was warmed to -30° and stirred for 30 minutes followed by cooling to -60° and adding sulfur (0.221 g, 6.91 mmoles). This mixture was stirred at -30° for 30 minutes and bromopentane (1.04 g, 6.91 mmoles) was added. After warming to ambient temperature, the mixture was evaporated to a residue which was mixed with 5% aqueous sodium bicarbonate (50 ml) and extracted with ether (2 x 50 ml). The combined extracts were dried and evaporated to a residue which was purified by chromatography (hexane) to give a viscous oil (1.36 g, 89%); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.34 (d, J = 5.3 Hz, 1H, H5), 7.25 (s, 1H, H3), 7.16 (d, J = 5.0 Hz, 1H, H4), 2.81 (t, J = 7.1 Hz, 2H, -SCH_2-), 1.64 (m, 2H, CH_2), 1.35 (m, 4H, CH_2CH_2), 0.88 (t, 3H, CH_3); ms: (CI) m/z 243 (M+1).

Anal. Calcd. for $C_{11}H_{14}S_3$: C, 54.54; H, 5.83; S, 39.68. Found: C, 54.25; H, 5.81; S, 39.93.

2-[(3-Hydroxypropyl)thio]thieno[2,3-*b*]thiophene, **3**.

A solution of **1** (2.90 g, 20.7 mmoles) in anhydrous tetrahydrofuran (40 ml) was treated as described above for the preparation of **2** to give a crude product which was purified by chromatography (30% ethyl acetate in hexane) to give a colorless syrup (3.61 g, 76%); ^1H nmr (deuteriochloroform): δ 7.36 (d, J = 5.4 Hz, 1H, H5), 7.26 (s, 1H, H3), 7.16 (d, J = 5.1 Hz, 1H, H4), 3.77 (t, J = 6.2 Hz, 2H, CH_2OH), 2.93 (t, J = 7.0 Hz, 2H, SCH_2), 1.89 (d, J = 7.0 Hz, 2H, CH_2); ms: (CI) m/z 231 (M+1).

Anal. Calcd. for $C_9H_{10}OS_3$: C, 46.93; H, 4.38; S, 41.75. Found: C, 46.64; H, 4.24; S, 41.96.

2-[[3-(4-Morpholinyl)propyl]thio]thieno[2,3-*b*]thiophene, **4**.

To a solution of **3** (2.30 g, 10.0 mmoles) and triethylamine (3.03 g, 30 mmoles) in anhydrous tetrahydrofuran (100 ml) at 0° was added *p*-toluenesulfonyl chloride (2.86 g, 15 mmoles). The mixture was warmed to ambient temperature and after stirring for 3 hours morpholine (5 ml) was added and stirring continued for 18 hours. The resulting mixture was mixed with 5% aqueous sodium bicarbonate (150 ml) and extracted with ethyl acetate (2 x 100 ml). The combined extracts were dried and evaporated to a residue which was purified by chromatography (30% to 50% ethyl acetate in hexane) to give a viscous oil (1.18 g, 39%); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.63 (d, J = 5.3 Hz, 1H, H5), 7.44 (s, 1H, H3), 7.25 (d, J = 5.2 Hz, 1H, H4), 3.50 (t, J = 4.5 Hz, 4H, CH_2OCH_2), 2.85 (t, 2H, CH_2S), 2.33 (t, 2H, CH_2N), 2.25 (t, 4H, CH_2NCH_2), 1.71 (m, 2H, CH_2); ms: (EI) m/z 300 (M+H).

Anal. Calcd. for $C_{13}H_{17}NOS_3$: C, 52.14; H, 5.72; N, 4.68. Found: C, 51.95; H, 5.67; N, 4.64.

5-(Pentylthio)thieno[2,3-*b*]thiophene-2-sulfonamide, **5**.

To a solution of **2** (1.01 g, 4.17 mmoles) in anhydrous tetrahydrofuran (30 ml) under nitrogen at -60° was added *n*-butyl-

lithium (1.76 *M* in hexanes, 2.61 ml, 4.59 mmoles). The mixture was stirred at -30° for 30 minutes and at -60° for 30 minutes followed by passing sulfur dioxide over the surface of the reaction mixture for about 5 minutes. The reaction mixture was warmed to ambient temperature and evaporated to a residue which was mixed with ice-water (50 ml). Sodium acetate (1.70 g, 12.5 mmoles) and hydroxylamine-*O*-sulfonic acid (0.755 g, 6.67 mmoles) were added and the mixture was stirred for 18 hours and extracted with ethyl acetate (2 x 60 ml). The combined extracts were dried and evaporated to a residue which was purified by chromatography (25% to 50% ethyl acetate in hexane) to give a white solid (0.56 g, 42%), mp 106-108°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.73 (s, 2H, SO_2NH_2), 7.68 (s, 1H, H3), 7.48 (s, 1H, H4), 2.85 (t, J = 7.0 Hz, 2H, SCH_2), 1.55 (m, 2H, CH_2), 1.30 (m, 4H, CH_2CH_2), 0.83 (t, J = 6.8 Hz, 3H, CH_3); ms: (CI) 322 (M+1).

Anal. Calcd. for $C_{11}H_{15}NO_2S_4$: C, 41.12; H, 4.71; N, 4.36. Found: C, 41.17; H, 4.63; N, 4.34.

5-[(3-Hydroxypropyl)thio]thieno[2,3-*b*]thiophene-2-sulfonamide, **6**.

A solution of **3** (1.80 g, 7.83 mmoles) in anhydrous tetrahydrofuran (40 ml) was treated in a manner similar to that described above for the preparation of **5** to give an off-white solid (1.86 g, 77%), mp 126-128°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.74 (bs, 2H, SO_2NH_2), 7.69 (s, 1H, H3), 7.50 (s, 1H, H4), 4.52 (t, 1H, OH), 3.47 (q, J = 5.8 Hz, 2H, CH_2OH), 2.91 (t, J = 6.9 Hz, 2H, SCH_2), 1.70 (q, 2H, $CH_2CH_2CH_2OH$); ms: (CI) 310 (M+1).

Anal. Calcd. for $C_9H_{11}NO_3S_4$: C, 34.96; H, 3.59; N, 4.53. Found: C, 35.00; H, 3.60; N, 4.47.

5-[[3-(4-Morpholinyl)propyl]thio]thieno[2,3-*b*]thiophene-2-sulfonamide, **7**.

A solution of **4** (1.16 g, 3.83 mmoles) in anhydrous tetrahydrofuran (30 ml) was treated in a manner similar to that described above for the preparation of **5** to give, after chromatography (ethyl acetate), a white solid (0.65 g, 44%), mp 109-111°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.76 (bs, 2H, SO_2NH_2), 7.69 (s, 1H, H3), 7.51 (s, 1H, H4), 3.52 (t, J = 4.7 Hz, 4H, $O(CH_2CH_2)_2N$), 2.91 (t, 2H, SCH_2), 2.35 (t, 2H, CH_2), 2.30 (t, 4H, $O(CH_2CH_2)_2N$), 1.72 (m, 2H, $O(CH_2CH_2)_2N)CH_2$); ms: (EI) m/z 379 (M+1).

Anal. Calcd. for $C_{13}H_{18},N_2O_3S_4$: C, 41.25; H, 4.79; N, 7.40. Found: C, 41.39; H, 4.79; N, 7.29.

5-(Pentylsulfonyl)thieno[2,3-*b*]thiophene-2-sulfonamide, **8**.

To a mixture of **5** (0.39 g, 1.2 mmoles) in methanol (50 ml) was added a solution of potassium peroxymonosulfate compound (1.16 g, 1.88 mmoles) in water (30 ml); this mixture was stirred for 18 hours, the methanol was evaporated, and the aqueous was neutralized with a saturated solution of sodium bicarbonate (100 ml) followed by extraction with ethyl acetate (2 x 80 ml). The combined extracts were dried and evaporated to a solid which was recrystallized (ethyl acetate/hexane) to give a white solid (0.362 g, 84%), mp 183-185°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.07 (s, 1H, H4), 7.85 (br s, 2H, SO_2NH_2), 7.85 (s, 1H, H3), 3.42 (t, J = 7.7 Hz, 2H, SO_2CH_2), 1.59 (m, 2H, CH_2), 1.30 (m, 4H, CH_2CH_2), 0.80 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 149.6, 146.9, 143.3, 143.1, 128.2, 123.8, 56.5, 29.6, 22.7, 21.8, 13.9; ir (potassium bromide): γ 3360, 3277, 2957, 2935, 2859, 1339, 1152, 1127, 1006, 646 cm^{-1}; ms: (CI) m/z 354 (M+1).

Anal. Calcd. for $C_{11}H_{15}NO_4S_3$: C, 37.37; H, 4.28; N, 3.96. Found: C, 37.48; H, 4.25; N, 3.97.

5-[(3-Hydroxypropyl)sulfonyl]thieno[2,3-*b*]thiophene-2-sulfonamide, **9**.

A solution of **6** (1.45 g, 4.69 mmoles) in methanol (60 ml) was treated as described for the preparation of **8** to give 1.36 g (85%) of a yellow solid, mp 184-185°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.07 (s, 1H, H4), 7.85 (bs, 2H, SO_2NH_2), 7.85 (s, 1H, H3), 3.43 (m, 4H, SO_2CH_2 and CH_2OH), 1.76 (m, 2H, CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 149.6, 146.7, 142.9, 142.7, 128.0, 123.3, 58.5, 53.8, 26.4; ir (potassium bromide): γ 3448, 3344, 3079, 1487, 1361, 1343, 1298, 1145, 1131, 1008, 645 cm^{-1}; ms: (CI) m/z 342 (M+1).

Anal. Calcd. for $C_9H_{11}NO_5S_4$: C, 31.66; H, 3.25; N, 4.10. Found: C, 31.76; H, 3.31; N, 4.06.

5-[[3-(4-Morpholinyl)propyl]sulfinyl]thieno[2,3-*b*]thiophene-2-sulfonamide Hydrochloride, **10**.

To a solution of **7** (0.35 g, 9.3 mmoles) in 2 *N* hydrochloric acid (20 ml)/methanol (60 ml) was added a solution of potassium peroxymonosulfate compound (0.70 g, 1.14 mmoles) in water (20 ml). After 3 hours the methanol was evaporated and the solution was neutralized by the addition of a saturated solution of sodium bicarbonate (60 ml) followed by extraction with ethyl acetate (2 x 100 ml). The combined extracts were dried and evaporated to a residue which was purified by chromatography (6% to 10% methanol in dichloromethane) to give a solid (0.14 g, 35%) which was dissolved in ethanol and treated with a solution of hydrogen chloride in ethanol; evaporation to dryness under high vacuum afforded the salt as the monohydrate, mp 128-132°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.88 (s, 1H, H4), 7.82 (br s, 2H, SO_2NH_2), 7.79 (s, 1H, H3), 3.99-3.70 (m, 4H, $O(CH_2CH_2)_2N$), 3.38 (m, 4H, $O(CH_2CH_2)_2N$), 3.18 (m, 2H, $SOCH_2$), 3.02 (m, 2H, $O(CH_2CH_2)_2NCH_2$), 2.08 (m, 2H, CH_2); ir (potassium bromide): γ 3421, 2674, 2363, 1333, 1153, 999, 625 cm^{-1}; ms: (EI) m/z 395 (M+1).

Anal. Calcd. for $C_{13}H_{18}N_2O_5S_4 \cdot HCl \cdot H_2O$: C, 34.77; H, 4.71; N, 6.24. Found: C, 34.80; H, 4.80; N, 6.06.

5-[[3-(4-Morpholinyl)propyl]sulfonyl]thieno[2,3-*b*]thiophene-2-sulfonamide, **11**.

A solution of **7** (0.23 g, 6.1 mmoles) in 2 *N* hydrochloric acid (20 ml)/methanol (50 ml) was treated as described for the preparation of **8** to give, after chromatography (6% to 10% methanol in dichloromethane), an off-white solid, mp 168-170°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.10 (s, 1H, H4), 7.86 (s, 3H, H3 and SO_2NH_2), 3.50 (m, 6H, $O(CH_2CH_2)_2N$ and SO_2CH_2), 2.32 (t, 2H, $O(CH_2CH_2)_2NCH_2$), 2.24 (m, 4H, $O(CH_2CH_2)_2N$), 1.77 (m, 2H, CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 149.6, 146.7, 142.9, 142.7, 128.0, 123.3, 66.1, 55.5, 54.3, 52.9, 20.0; ir (potassium bromide): γ 3271, 3108, 3073, 2955, 1344, 1313, 1139, 1004, 873, 647 cm^{-1} ms: (EI) m/z 411 (M+1).

Anal. Calcd. for $C_{13}H_{18}N_2O_5S_4$: C, 38.03; H, 4.42; N, 6.82. Found: C, 37.96; H, 4.42; N, 6.75.

2-[(2-Methoxyethoxy)methyl]thieno[2,3-*b*]thiophene, **13**.

To a solution of thieno[3,2-*e*]thiophene-2-methanol [1] (**12**) (1.5 g, 9.0 mmoles) in anhydrous *N*,*N*-dimethylformamide (50 ml)

at 0° was added sodium hydride (60% dispersion in oil, 0.468 g, 11.7 mmoles). After 10 minutes, bromoethyl methyl ether (1.63 g, 11.7 mmoles) was added and the resulting mixture was stirred at ambient temperature for 45 minutes poured into ice water (100 ml) and extracted with ether (3 x 80 ml). The combined extracts were dried and evaporated to a residue which was purified by chromatography (10% to 20% ethyl acetate in hexane) to give an oil (1.38 g, 68%); ^{1}H nmr (deuteriochloroform): δ 7.31 (d, J = 5.3 Hz, 1H, H5), 7.16 (d, J = 5.3 Hz, 1H, H4), 7.15 (s, 1H, H3), 4.76 (s, 2H, $CH_3O(CH_2)_2OCH_2$), 3.63 (m, 4H, $CH_3O(CH_2)_2O$), 3.31 (s, 3H, OCH_3); ms: (CI) m/z 229 (M+1), 153.

Anal. Calcd. for $C_{10}H_{12}O_2S_2$: C, 52.63; H, 5.30; S, 28.08. Found: C, 52.53; H, 5.31; S, 28.21.

5-[(2-Methoxyethoxy)methyl]thieno[2,3-*b*]thiophene-2-sulfonamide, **15**.

A solution of **13** (1.39 g, 6.07 mmoles) in tetrahydrofuran (30 ml) was treated as described above for the preparation of **5** to give a crude product which was recrystallized (dichloromethane/hexane/ethyl acetate) to give 1.15 g (62%) of an off-white solid, mp 107-110°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.70 (s, 3H, SO_2NH_2 and H3), 7.32 (s, 1H, H4), 4.70 (s, 2H, $CH_3O(CH_2)_2OCH_2$), 3.56 (t, J = 6.1 Hz, 2H, CH_2), 3.46 (t, J = 6.1 Hz, 2H, CH_2), 3.24 (s, 3H, OCH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 147.1, 146.1, 143.6, 140.4, 122.6, 119.7, 71.1, 68.7, 67.3, 58.1; ms: (CI) m/z 232 (M+1 - $CH_3OC_2H_4O$); ir (potassium bromide): γ 3334, 3250, 2883 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_4S_3 \cdot 0.25H_2O$: C, 38.50; H, 4.36; N, 4.49. Found: C, 38.59; H, 4.20; N, 4.44.

5-[(2-Ethoxyethoxy)methyl]thieno[2,3-*b*]thiophene-2-sulfonamide, **16**.

This compound was prepared from **12** (1.74 g, 10.2 mmoles) by following the procedure described for the preparation of **15**, but using bromoethyl ethyl ether in the alkylation step. Recrystallization of the crude product (1.77 g, 82%, dichloromethane/-hexane/ethyl acetate) gave the pure compound, mp 81-82°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.71 (s, 3H, SO_2NH_2 and H3), 7.33 (s, 1H, H4), 4.71 (s, 2H, $C_2H_5O(CH_2)_2OCH_2$), 3.53 (m, 4H, $C_2H_5O(CH_2)_2OCH_2$), 3.43 (q, J = 7.1 Hz, 2H, CH_2CH_3), 1.09 (t, J = 7.21 Hz, 3H, CH_2CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 147.1, 146.1, 143.7, 140.4, 122.6, 119.7, 69.1, 68.9, 67.3, 65.6, 15.1; ms: (CI) m/z 232 (M+1 - $C_2H_5OC_2H_4O$).

Anal. Calcd. for $C_{11}H_{15}NO_4S_3$: C, 41.10; H, 4.70; N, 4.36. Found: C, 41.16; H, 4.71; N, 4.32.

5-(2-Hydroxymethyl)thieno[2,3-*b*]thiophene-2-sulfonamide **17**.

A solution of **12** (1.83 g, 10.8 mmoles) in anhydrous tetrahydrofuran (80 ml) was treated as described above for the preparation of **5** to give a crude product which was triturated with ethyl acetate/hexane (1:1, 10 ml); the filtrate was dried and evaporated to give the intermediate sulfonamide **17** (1.05 g, 39%), mp 208-209°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.69 (br s, 2H, SO_2NH_2), 7.68 (s, 1H, H3), 7.21 (s, 1H, H4), 5.64 (t, J = 5.8 Hz, 1H, OH), 4.66 (d, J = 5.8 Hz, 2H, CH_2); ms: (CI) m/z 250 (M+1).

Anal. Calcd. for $C_7H_7NO_3S_3$: C, 33.72; H, 2.83; N, 5.62. Found: C, 33.76; H, 2.84; N, 5.56.

5-(2-Hydroxymethyl)thieno[2,3-*b*]thiophene-2-sulfonamide 6,6-Dioxide, **18**.

A solution of sulfonamide **17** (0.63 g, 2.53 mmoles) in methanol (25 ml) was treated as described for the preparation of **8** to give an off-white solid (0.321 g, 81%) which was recrystallized from methanol to give **18**, mp 208-210°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.06 (s, 2H, SO_2NH_2), 7.63 (s, 1H, H3), 7.26 (t, J = 1.9 Hz, 1H, H4), 5.69 (t, 1H, OH), 4.40 (m, 2H, $HOCH_2$); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 155.3, 150.2, 141.4, 136.3, 124.0, 121.0, 54.6; ir (potassium bromide): γ 3499, 3381, 1316, 1140 cm^{-1}; ms: (CI) m/z 282 (M+1).

Anal. Calcd. for $C_7H_7NO_5S_3$: C, 29.88; H, 2.51; N, 4.98. Found: C, 30.20; H, 2.57; N, 4.85.

5-[(2-Methoxyethoxy)methyl]thieno[2,3-*b*]thiophene-2-sulfonamide 6,6-Dioxide, **19**.

To a solution of **15** (0.52 g, 1.7 mmoles) in methanol (45 ml) was added a solution of potassium peroxymonosulfate compound (2.08 g, 3.39 mmoles) in water (90 ml). After stirring for 18 hours an additional quantity of the oxidant (1.50 g) was added and the mixture was heated at 40° for 2 hours. The methanol was evaporated and the aqueous was extracted with ethyl acetate (2 x 100 ml). The combined extracts were dried and evaporated to give a residue which was purified by chromatography (50 to 70% ethyl acetate in hexane) to give a solid (0.354 g, 62%) which was recrystallized (ethyl acetate/hexane), mp 103-105°: ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.07 (s, 2H, SO_2NH_2), 7.63 (s, 1H, H3), 7.40 (t, J = 1.5 Hz, 1H, H4), 4.47 (d, J = 1.5 Hz, 2H, $CH_3O(CH_2)_2OCH_2$), 3.62 (t, J = 3.5 Hz, 2H, CH_2), 3.47 (t, J = 3.5 Hz, 2H, CH_2), 3.25 (s, 3H, OCH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 155.5, 146.0, 141.0, 136.5, 124.0, 123.9, 71.0, 69.2, 63.0, 58.1; ms: (CI) m/z 340 (M+1), 264.

Anal. Calcd. for $C_{10}H_{13}NO_6S_3$: C, 35.39; H, 3.86; N, 4.13. Found: C, 35.65; H, 3.83; N, 4.03.

5-[(2-Ethoxyethoxy)methyl]thieno[2,3-*b*]thiophene-5-sulfonamide 6,6-Dioxide, **20**.

This compound was prepared from **16** (0.79 g, 2.5 mmoles) in a manner similar to that described for the preparation of **19**. Recrystallization of the crude product (0.53 g, 60%, water) gave the pure compound, mp 96-98°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.07 (s, 2H, SO_2NH_2), 7.63 (s, 1H, H3), 7.41 (s, 1H, H4), 4.48 (d, J = 1.4 Hz, 2H, $C_2H_5O(CH_2)_2OCH_2$), 3.61 (m, 2H, CH_2), 3.53 (m, 2H, CH_2), 3.43 (q, J = 7.0 Hz, 2H, CH_2CH_3), 1.01 (t, J = 7.0 Hz, 3H, CH_2CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 155.5, 146.0, 141.0; 136.5, 124.0, 123.9, 69.4, 69.0, 65.6, 63.0, 15.1; ms: (CI) m/z 354 (M+1), 264.

Anal. Calcd. for $C_{11}H_{15}NO_6S_3$: C, 37.38; H, 4.28; N, 3.96. Found: C, 37.49; H, 4.29; N, 3.98.

5-(Benzoyloxymethyl)thieno[2,3-*b*]thiophene-5-sulfonamide 6,6-Dioxide, **21**.

To a solution of **18** (30 mg, 0.11 mmole) and triethylamine (21.7 mg, 0.214 mmoles) in anhydrous tetrahydrofuran (5 ml) at 0° was added benzoyl chloride (16.5 mg, 0.117 mmole). After 30 minutes the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into 5% aqueous sodium bicarbonate (30 ml) and extracted with ethyl acetate (2 x 30 ml). The combined extracts were dried and evaporated to a residue which was purified by chromatography (hexane/ethyl acetate, 1:1) to give a solid (16 mg, 39%), recrystallization (methanol/dichloromethane) gave colorless crystals, mp 212-214°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.11 (br s, 2H, SO_2NH_2), 8.01 (dd, J = 7.2 and 1.2 Hz, 2H, phenyl-H2 and H6), 7.69 (t, J = 7.2 Hz, phenyl-H4), 7.68 (s, 1H,

H3), 7.63 (t, J = 1.3 Hz, H4), 7.56 (t, J = 7.2 Hz, 2H, phenyl-H3 and H5), 5.35 (d, J = 1.3 Hz, 2H, CH_2O).

Anal. Calcd. for $C_{14}H_{11}NO_6S_3$: C, 43.63; H, 2.88; N, 3.63. Found: C, 43.57; H, 2.87; N, 3.67.

Reaction of **20** with 4-Methoxy-α-toluenethiol to Give the 4,5-*cis* **26** and 4,5-*trans* **27** Addition Products.

To a solution of **20** (100 mg, 0.280 mmole) in ethanol (20 ml) was added 4-methoxy-α-toluenethiol (297 mg, 1.79 mmoles) and triethylamine (0.1 ml). After stirring for 4 hours at room temperature, the mixture was evaporated to a residue and the two newly formed compounds [tlc, R_f = 0.30 and 0.44; ethyl acetate/hexane, 1:1] were separated by chromatography (30% to 50% ethyl acetate in hexane); **26** (86 mg, yield 59%), viscous syrup (R_f = 0.30); ^1H nmr (600 MHz, 23°, dimethyl sulfoxide-d_6): δ 8.08 (s, 2H, SO_2NH_2), 7.36 (s, 1H, H3), 7.26 (d, J = 8.6 Hz, 2H, phenyl H2, H6), 6.90 (d, J = 8.6 Hz, 2H, phenyl H3, H5), 4.75 (d, J = 7.4 Hz, H4), 4.60 (m, J = 8.3, 7.4, 5.1 Hz, H5), 4.08 (dd, J = 10.7, 8.3 Hz, 1H, 5-C*Ha*HbO-), 3.95 (dd, J = 10.7, 5.1 Hz, 1H, 5-CHa*Hb*O-), 3.91 (d, J = 12.8 Hz, 1H, -SC*Ha*Hb-phenyl), 3.75 (d, J = 12.8 Hz, 1H, -SCHa*Hb*-phenyl), 3.74 (s, 3H, OCH_3), 3.63 (m, 2H, -O*C*H_2CH$_2$O-), 3.51 (t, J = 4.7 Hz, 2H, -OCH$_2$C*H*$_2$O-), 3.44 (q, J = 7.0 Hz, 2H, O*C*H_2CH$_3$), 1.09 (t, J = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); hrms: (fab), (M+Na$^+$); Calcd. for $C_{19}H_{25}NO_7S_4Na$: 530.0412. Found: 530.0409.

Compound **27** was obtained in 25% yield (36 mg) as a gum (R_f = 0.44); ^1H nmr (600 MHz, 23°, dimethyl sulfoxide-d_6): δ 8.07 (s, 2H, SO_2NH_2), 7.39 (s, 1H, H3), 7.26 (d, J = 8.7 Hz, 2H, phenyl H2, H6), 6.88 (d, J = 8.7 Hz, 2H, phenyl H3, H5), 4.47 (d, J = 6.4 Hz, 1H, H4), 4.23 (m, J = 8.5, 6.4, 4.4 Hz, 1H, H5), 3.95 (d, J = 12.7 Hz, 1H, -SC*Ha*Hb-phenyl), 3.93 (dd, J = 11.3, 8.5 Hz, 1H, 5-C*Ha*HbO-), 3.83 (d, J = 12.7 Hz, 1H, -SCHa*Hb*-phenyl), 3.78 (dd, J = 11.4, 4.4 Hz, 1H, 5-CHa*Hb*O-), 3.74 (s, 3H, OCH_3), 3.58 (m, 2H, -O*C*H_2CH$_2$O-), 3.47 (m, 2H, -OCH$_2$C*H*$_2$O-), 3.42 (q, J = 7.0 Hz, O*C*H_2CH$_3$), 1.09 (t, J = 7.0 Hz, 3H, OCH$_2$C*H*$_3$).

X-ray Crystallography.

Crystals of **21** grew as colorless plates from a mixture of methanol and dichloromethane. The data crystal was cut into a triangular prism of approximate dimensions; 0.14 x 0.75 x 0.80 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 (2,2,0; -4,0,6; 0,3,3; 2,1,3) were remeasured every 97 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 0.987 to 1.00. The data were corrected for Lp effects but not for absorption. Data reduction, decay and Lp corrections, structure solution and refinement were performed using the SHELXTL/PC software package [18]. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 with anisotropic thermal parameters for the non-H atoms. The hydrogen atom positions were observed in a F map and refined with isotropic displacement parameters. The function, $w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[((F_o))^2 + (0.0361*P)^2 + (0.8657P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992) [19]. Other computer programs used in this work are listed elsewhere [20].

p*K*a Determination.

Ionization constants were determined by potentiometric titration (Kyoto AT-310 Potentiometric Titrator) in water or a mixture of water and an organic solvent such as methanol, acetone, or acetonitrile. If a solvent mixture was used, the nominal p*K*a values were plotted against the percentage of organic solvent to provide by extrapolation the p*K*a of the compound in water.

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REFERENCES AND NOTES

[1] J. D. Prugh, G. D. Hartman, P. J. Mallorga, B. M. McKeever, S. R. Michelson, M. A. Murcko, H. Schwam, R. L. Smith, J. M. Sondey, J. P. Springer and M. F. Sugrue, *J. Med. Chem.*, **34**, 1805 (1991).

[2] T. M. Williams, R. J. Hudcosky, C. A. Hunt and K. L. Shepard, *J. Heterocyclic Chem.*, **28**, 13 (1991).

[3] J. J. Baldwin, T. M. Williams, R. J. Hudcosky and K. L. Shepard, European Patent Application 480,692 (1992).

[4] J. J. Baldwin, H. G. Selnik, G. S. Ponticello and E. M. Radzilowski, European Patent Application 480,745 (1992).

[5] J. Vidgren, A. Lilyas and N. P. C. Walker, *Int. J. Biol. Macromol.*, **12**, 342 (1990).

[6] S. Gronowitz and B. Persson, *Acta Chem. Scand.*, **21**, 812 (1967).

[7] A. Bugge, *Acta Chem. Scand.*, **22**, 63 (1968).

[8] S. L. Grahm and T. H. Seholz, *Synthesis,* 1031 (1986).

[9] V. P. Litvinov and Y. L. Goldfarb, *Izv. Akad. Nauk. USSR, Ser. Khim.,* 2183 (1963).

[10] V. P. Litvinov and Y. L. Goldfarb, in *Advances Heterocyclic Chemistry,* A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, Vol **19**, (1976) p 123.

[11] F. de Jong and M. Janssen, *J. Chem. Soc., Perkin Trans. II,* 572 (1972).

[12] W. E. Truce and A. J. Levy, *J. Org. Chem.*, **28**, 679 (1963).

[13] Inhibitor-enzyme binding constants were determined using a fluorometric assay similar to that previously described, see references 14 and 15.

[14] R. F. Chen and J. C. Kernohan, *J. Biol. Chem.*, **242**, 5813 (1967).

[15] G. S. Ponticello, M. B. Freedman, C. N. Habecker, P. A. Lyle, H. Schwam, S. L. Barga, M. E. Christy, W. C. Tandall and J. J. Baldwin, *J. Med. Chem.*, **30**, 591 (1987).

[16] Inhibition of human carbonic anhydrase II was determined using a *p*H-stat assay similar to that previously described, see references 15 and 17.

[17] K. C. Leibman, D. Alford and R. A. Boudet, *J. Pharm. Exp. Ther.*, **131**, 271 (1961).

[18] G. M. Sheldrick, SHELXTL/PC (Version 5.03) (1994), Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.

[19] A. J. C. Wilson, ed, International Tables for X-ray Crystallography, Vol **C**, Tables 4.2.6.8 and 6.1.1.4, Kluwer Academic Press, Boston, 1992.

[20] S. M. Gadol and R. E. Davis, *Organometallics*, **1**, 1607 (1982).