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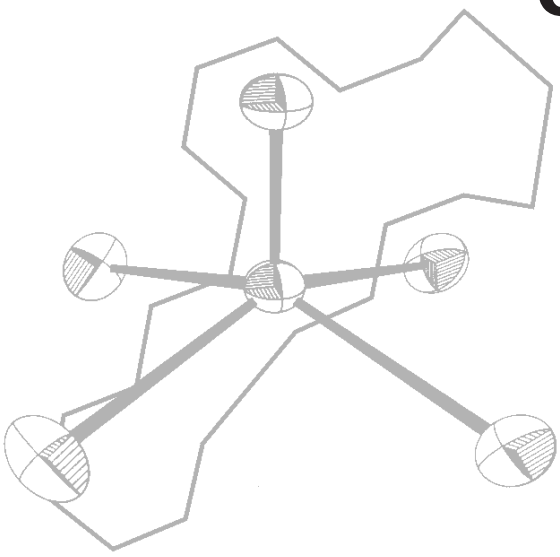

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Antifungal Thiosulfonates: Potency with Some Selectivity

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A series of thiosulfonates have been prepared and tested against *Aspergillus niger* and *Aspergillus flavus*. In general, the thiosulfonates are moderate antifungal agents—more potent than corresponding inactive disulfides and less potent than corresponding very active fungitoxic disulfides. A pair of thiosulfonates show high selectivity, each killing only one kind of fungus.

Keywords. Antifungal; fungitoxins; thiosulfonate synthesis; structure–activity.

Introduction

In recent papers,[1–3] we have described design principles, and exploited them, to construct potent sulfur-rich antifungal compounds. The lead structure from which the work began is the naturally occurring disulfide dysoxysulfone (1).[4]

$CH_3SO_2CH_2SCH_2SSCH_2SO_2CH_3$
(1)

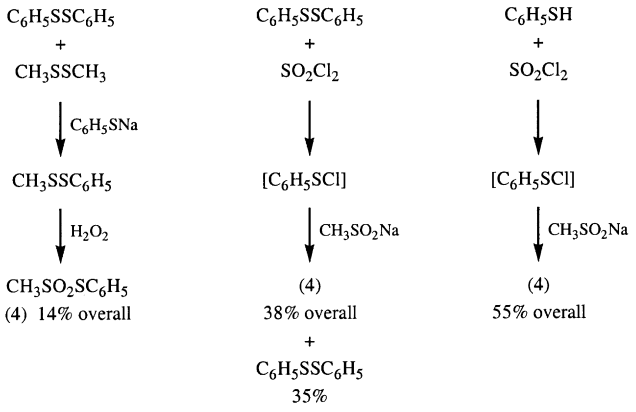
Although some disulfides were inactive against test fungi (*Aspergillus niger* and *Aspergillus flavus*), all of our previously described fungitoxins[1–3] are disulfides (see compounds (2) and (3) in Table 1 for representative structures). In virtually every case,[1–3] a given previously described antifungal disulfide showed comparable toxicities for each test fungus. Inactive non-disulfides included in our screens feature sulfone, sulfide, mercaptan and sulfonate ester functionalities. Therefore, this study is focused on structures which retain the critical SS bond but which have been modified by appending two oxygen atoms to one of the sulfur atoms (i.e. RSO_2SR').

This report addresses the following issues. (i) What are reliable approaches for routine synthesis of thiosulfonates? (ii) Are thiosulfonates more potent antifungals than disulfides? (iii) Does structural modification of the SS linkage lead to some selectivity in the killing of fungus?

Results and Discussion

(a) Synthetic Approaches to Thiosulfonates

Established approaches to the preparation of thiosulfonates have been reviewed by Field.[5] Three of the approaches he describes have been applied to the preparation of phenyl methanethiosulfonate (4) in order to determine which would be generally preferred. Scheme 1 presents results for (i) preparation and peroxide oxidation of methyl phenyl disulfide, (ii) diphenyl disulfide chlorination, followed by nucleophilic substitution with sulfinate anions, and (iii) benzenethiol chlorination followed by reaction with sulfinate anions.



Scheme 1. Three approaches to phenyl methanethiosulfonate (4) preparation, with overall yields, from commercially available starting materials.

Clearly, the best approach would utilize a mercaptan and a sulfinic acid salt when they are readily available.

Although only a few sulfinic acid salts are presently available commercially, there is well established preparative methodology for aromatic sulfinic acid salts.[6] We have devised a related approach for the preparation of alkyl sulfinic acid salts which is applied in Scheme 2 to the preparation of methyl ethanethiosulfonate (5).

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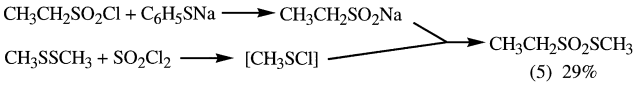
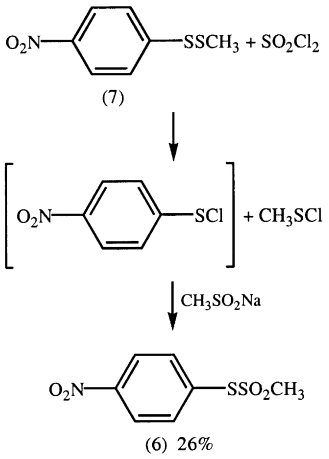


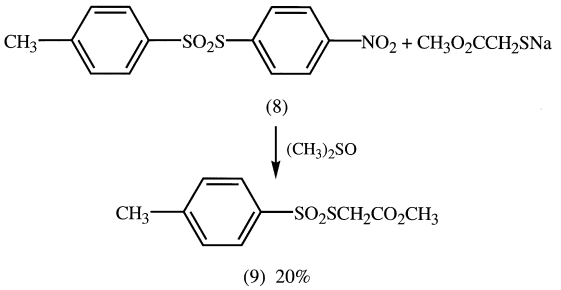
Scheme 2. Preparation of methyl ethanethiosulfonate (5) with a sodium alkanesulfinate salt which is not commercially available.

The preparation of *p*-nitrophenyl methanethiosulfonate (6) and related thiosulfonates presented a problem. *p*-Nitrophenyl disulfide has very low solubility in common organic solvents which frustrated attempts to react it with sulfuryl chloride. Furthermore, *p*-nitrophenyl mercaptan is not commercially available. Methyl *p*-nitrophenyl disulfide (7)[3] is a suitable precursor for thiosulfonate (6) preparation (see Scheme 3).



Scheme 3

Because each thiosulfonate offers a soft acid site (sulfenyl sulfur), they are well established sulfenylating agents for mercaptide anions which are soft bases.[5] Unexpectedly, *p*-nitrophenyl thiosulfonate serves as a transsulfenylating agent in a novel approach to thiosulfonate synthesis (see Scheme 4).



Scheme 4

Since the Scheme 4 reaction appears to involve soft base attack at a hard acid site, this approach is unlikely to be generally useful for the preparation of thiosulfonates, unless the leaving group's nucleofugality is further enhanced. With effective access to thiosulfonates in hand, work progressed to the biological testing phase.

(b) Thiosulfonates as Antifungal Agents

In exploring the development of new, potent antifungal disulfides,[1–3] we have adopted the view that fungitoxicity is likely to be associated with biochemical sulfenylations accomplished by these disulfides. Hence, it seemed that thiosulfonates, which can effectively sulfenylate mercaptide anions, might also be effective fungitoxins.

Dimethyl disulfide (10) shows no antifungal behaviour, while the two closely related thiosulfonates (5) and (11) have measurable toxicity (see Table 1). Methyl methanethiosulfonate (11) is the first compound we have examined which is effective against only one of the test fungi. Note that the enhanced toxicity of (5) is not unexpected since, up to a chain length of nine carbons, longer unbranched alkyl groups are known to enhance pharmacological effects.[7]

Table 1. Sulfur compounds as antifungal agents

Each compound was introduced onto a small paper disk which was placed in a culture medium. The diameter of the clear zone (the area where fungus—*Aspergillus niger* or *Aspergillus flavus*—did not grow) around each disk indicated antifungal activity

Sulfur compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3SO_2CH_2SSCH_3$ (2)[2]	25	2.7	3.8
$CH_3SS(C_6H_4)$-*o*-NO_2 (3)[3]	10	2.8	1.9
CH_3SSCH_3 (10)[3]	100	0	0
$CH_3SO_2SCH_3$ (11)[8]	100	3.3	0
$CH_3CH_2SO_2SCH_3$ (5)[9]	50	2.0	1.3
$C_6H_5SSCH_3$ (12)[3]	100	0	0
$CH_3SO_2SC_6H_5$ (4)[A]	25	0	3.7
p-$CH_3(C_6H_4)SO_2SCH_3$ (13)	25	1.4	3.6
$C_6H_5SSC_6H_5$ (14)[3]	100	0	0
$C_6H_5SO_2SC_6H_5$ (15)	25	3.9	3.8
p-$CH_3(C_6H_4)SO_2SC_6H_5$ (16)	25	4.3	3.3
$CH_3SS(C_6H_4)$-*o*-CO_2CH_3 (17)[3]	25	2.8	4.3
$CH_3SO_2S(C_6H_4)$-*o*-CO_2CH_3 (18)	100	0	0
$CH_3SS(C_6H_4)$-*p*-NO_2 (7)[3]	10	3.8	4.0
$CH_3SO_2S(C_6H_4)$-*p*-NO_2 (6)	25	1.9	1.2
p-$CH_3(C_6H_4)SO_2S(C_6H_4)$-*p*-$NO_2$ (8)	25	3.0	2.0
$CH_3SSCH_2CO_2CH_3$ (20)[1]	100	0	0
p-$CH_3(C_6H_4)SO_2SCH_2CO_2CH_3$ (9)	50	2.9	1.7

[A] Compound (4) had no measurable fungitoxicity against *A. niger* at 100 μg/disk.

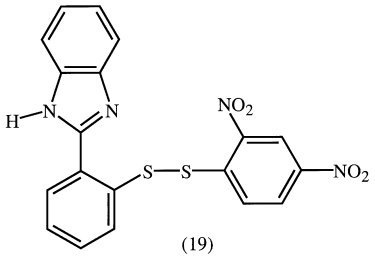
For the series of compounds (4), (12) and (13), the disulfide was inactive and the thiosulfonates antifungal. Interestingly, the thiosulfonate (4) killed only *A. flavus* in contrast to (11) which selectively inhibited the growth of *A. niger*.

Compounds (14)–(16) also demonstrate the superior antifungal potency of thiosulfonates relative to simple disulfides (see Table 1) but, for this set, no selectivity for either of the fungi was observed.

Compound (17) (Table 1) is the first potent second-generation antifungal disulfide to be considered here. Perhaps surprisingly, the closely related thiosulfonate (18) is not antifungal at all. Similar results (diminished fungitoxicity for the thiosulfonates relative to the disulfide) were obtained for the set of compounds (6)–(8). It now appears that thiosulfonates tend to have moderate fungitoxicity—enhanced relative to inactive disulfides and diminished relative to more potent antifungal disulfides. The results in Table 1 open

up the possibility that there might be a pharmacological equivalent to the well known reactivity selectivity principle in organic chemistry.[10] The pharmacological equivalent might assert that structural modifications which decrease the potency of a particular agent may be associated with enhanced selectivity in toxicity within a set of closely related organisms.

Our interest in antifungal disulfides was encouraged by the recent observations[11–13] that fungal infections frequently prove to be lethal for immunocompromised patients. A disulfide (19) related to our potent aryl disulfide fungitoxins (e.g. (7) and (17) in Table 1) has been patented for use in inhibiting the production of Interleukin-1β and Tumour Necrosis Factor α.[14] Finally, the α-ester disulfide (20) (see Table 1) had no antifungal activity.[1] Nonetheless, when tested, it showed promise as a lead compound in fighting leukaemia.[15] The related thiosulfonate (9) shows clearly enhanced antifungal activity but has not yet been assessed as an antileukaemic agent.



(19)

At this point, potent fungitoxic disulfides show little selectivity, whereas the selectivity of antifungal thiosulfonates is not associated with high potency. We hope that insight gained in developing more potent antifungal disulfides may be applicable to the design of more potent, selective fungitoxic thiosulfonates.

Experimental

Infrared spectra were recorded on a Perkin–Elmer 710B grating spectrophotometer for chloroform solutions unless otherwise specified. ^{1}H n.m.r. spectra (60 MHz) were obtained on a Varian EM360L instrument. ^{1}H n.m.r. (270 MHz) and ^{13}C n.m.r. spectra were obtained on a JEOL JNM-GSX 270 Fourier-transform n.m.r. system. Unless otherwise specified, all n.m.r. spectra were obtained for (D)chloroform solutions with tetramethylsilane as internal standard. Mass spectra were obtained on a Hewlett–Packard 5988A g.l.c./m.s. system. Melting points were determined on a Gallenkamp MFB-595 capillary melting point apparatus and are uncorrected.

Biological Testing

Details have been provided earlier.[1]

Previously Prepared Compounds (Table 1)

Compound (2) was prepared as described earlier.[2] The preparations of compounds (3), (12), (17) and (7) were outlined previously.[3] The synthesis of compound (20) has been reported.[1] Syntheses for compounds (4), (13), (15) and (16) have been described in refs 16, 17, 18 and 19 respectively.

Three Approaches to Synthesis of S-*Phenyl Methanethiosulfonate (4)*

(A) *Disulfide oxidation*. Methyl phenyl disulfide[3] (1.0 g, 6.4 mmol) and hydrogen peroxide (30%, 1.5 g) were dissolved in glacial acetic acid (25 ml) and the reaction mixture refluxed *behind a safety shield* for 0.5 h. Chloroform (100 ml) was added and the resultant mixture extracted with 2.5% sodium hydroxide solution (three 50-ml aliquots). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The crude product was chromatographed on silica gel (100 g) employing 1 : 1 chloroform/light petroleum (100-ml fractions) for elution. Fractions 11 and 12 were combined and concentrated affording clean phenyl methanethiosulfonate (4)[16] (0.20 g, 1.1 mmol, 17%). Recrystallized (4) (methanol) had m.p. 88.9–90.4°C. I.r. 1335, 1145 cm^{-1}. ^{1}H n.m.r. (270 MHz) δ 3.19, s, 3H; 7.54, m, 3H; 7.72, d, 2H. ^{13}C n.m.r. δ 47.39, 127.93, 129.92, 131.67, 136.24. *m/z* 188 (35%, $M^{+\bullet}$), 125 (57), 109 (100).

(B) *Benzenesulfenyl chloride from disulfide, then reaction with methanesulfinate anion*. Diphenyl disulfide (1.0 g, 4.6 mmol) was dissolved in dry methylene chloride (5 ml) and a solution of sulfuryl chloride (0.6 g, 4.6 mmol) in dry methylene chloride (5 ml) added dropwise. Upon completion of the addition, the reaction mixture was refluxed for 0.5 h. A solution of sodium methanesulfinate (0.94 g, 9.2 mmol) in acetone (40 ml) and water (10 ml) was added to the reaction mixture which was then immersed in a constant-temperature bath at 50°C for 1 h. The workup described for part (A) furnished diphenyl disulfide (0.35 g, 35%, from column fractions 2 and 3) and the thiosulfonate (4)[16] (0.66 g, 3.5 mmol, 38%, from fractions 7–17).

(C) *Benzenesulfenyl chloride from mercaptan, then reaction with methanesulfinate anion*. Benzenethiol (1.0g, 9.0 mmol) was reacted with sulfuryl chloride (1.3 g, 9.7 mmol) and sodium methanesulfinate (0.96 g, 9.4 mmol) as described for diphenyl disulfide in part (B). Extractive workup and column chromatography, as described in part (B), furnished diphenyl disulfide (0.11 g, from fraction 3) and the thiosulfonate (4)[16] (0.95 g, 5.0 mmol, 55%, from fractions 7–11).

Preparation of S-*Methyl Ethanethiosulfonate (5)*

(A) Sodium benzenethiolate (2.1 g, 15.6 mmol) was dissolved in acetone (50 ml) and ethanesulfonyl chloride (1.0 g, 7.8 mmol) added. The reaction mixture was refluxed for 1 h. Chloroform (200 ml) was added and the resultant mixture washed with water (100 ml). The aqueous layer was concentrated and dried in vacuum for 8 h, producing a mixture (1.12 g) of sodium ethanesulfinate and sodium chloride. The product had ^{1}H n.m.r. (270 MHz, D_2O + $(CH_3)_3Si(CH_2)_3SO_3Na$) δ 1.08, t, 3H; 2.33, q, 2H. ^{13}C n.m.r. δ 7.90, 56.44.

(B) Dimethyl disulfide (0.45 g, 4.8 mmol) was dissolved in dry methylene chloride (5 ml) and a solution of sulfuryl chloride (0.65 g, 4.8 mmol) in dry methylene chloride (5 ml) added dropwise. Upon completion of the addition, the reaction mixture was refluxed for 0.5 h. A solution of the mixture of sodium ethanesulfinate and sodium chloride (1.12 g) in water (10 ml) and acetone (40 ml) was added. The reaction mixture was immersed in a constant-temperature bath at 50°C for 1 h. Chloroform (200 ml) was added and the resultant mixture extracted with water (100 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The crude product was chromatographed on silica gel (100 g) employing 1 : 1 chloroform/light petroleum (30–60°, 100-ml fractions) for elution. Fractions 7–9 were concentrated and combined affording oily methyl ethanethiosulfonate[9] (5) (0.32 g, 2.3 mmol, 29%). I.r. 1325, 1140 cm^{-1}. ^{1}H n.m.r. (270 MHz) δ 1.48, t, 3H; 2.66, s, 3H; 3.34, q, 2H. ^{13}C n.m.r. δ 8.37, 18.21, 55.61. *m/z* 140 (75%, $M^{+\bullet}$), 61 (47), 48 (100).

Preparation of S-p-*Nitrophenyl Methanethiosulfonate (6)*

Methyl *p*-nitrophenyl disulfide[3] (7) (1.0 g, 5.0 mmol) was dissolved in dry methylene chloride (5 ml) and a solution of sulfuryl chloride (0.67 g, 5.0 mmol) in dry methylene chloride (5 ml) added dropwise. The reaction mixture was refluxed for 0.5 h. A solution of sodium methanesulfinate (0.5 g, 5.0 mmol) in acetone (40 ml) and water (10 ml) was added and the reaction mixture immersed in a constant-temperature bath at 50°C for 1 h. Chloroform (200 ml) was added and the resultant mixture washed with water (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude was recrystallized from methanol (8 ml) and the first crop chromatographed on silica gel (50 g) employing chloroform (50-ml fractions) for elution. Fraction 4 was concentrated affording clean *p*-nitrophenyl methanethiosulfonate (6)

(0.31 g, 1.3 mmol, 26%). Crystalline nitro thiosulfonate (6) consisted of opaque, pale yellow *sheets* and had m.p. 98–99°C (Found: C, 36.1; H, 3.0. $C_7H_7NO_4S_2$ requires C, 36.0; H, 3.0%). I.r. 1530, 1440, 1145 cm^{-1}. ^1H n.m.r. (270 MHz) δ 3.27, s, 3H; 7.92, d, 2H; 8.33, d, 2H. ^{13}C n.m.r. δ 48.56, 124.63, 135.40, 136.73, 149.56. *m/z* 233 (79%, $M^{+\bullet}$), 170 (100).

Preparation of S-p-*Nitrophenyl* p-*Toluenethiosulfonate (8)*

Methyl *p*-nitrophenyl disulfide (7)[3] (2.5 g, 12.4 mmol) was converted into *p*-nitrophenyl *p*-toluenethiosulfonate (8) by using the procedure (replace sodium methanesulfinate with sodium *p*-toluenesulfinate) outlined above for the preparation of (6). Crude product was not recrystallized but was chromatographed on silica gel (150 g) employing 1 : 1 chloroform/light petroleum (30–60°, 100-ml fractions) for elution. Fractions 3–10 were combined and concentrated and the product was recrystallized (methanol). Recrystallized (8) was sublimed (110°C/2 Torr/12 h) affording *p*-nitrophenyl *p*-toluenethiosulfonate (8) (1.4 g, 4.6 mmol, 37%). Crystalline thiosulfonate (8) consisted of pale yellow *clumps* and had m.p. 135–137°C (Found: C, 49.6; H, 3.4. $C_{13}H_{11}NO_4S_2$ requires C, 50.5; H, 3.6%). I.r. 1525, 1345, 1145 cm^{-1}. ^1H n.m.r. (270 MHz) δ 2.44, s, 3H; 7.25, d, *J* 8.1 Hz, 2H; 7.50, d, *J* 8.1 Hz, 2H; 7.60, d, 2H; 8.18, d, *J* 8.1 Hz, 2H. ^{13}C n.m.r. δ 21.73, 124.15, 127.57, 129.76, 135.77, 137.10, 140.17, 145.60, 149.38.

*Preparation of Methyl 2-(*p-*Tolylsulfonylthio)acetate (9)*

A solution of *p*-nitrophenyl *p*-toluenethiosulfonate (8) (1.0 g, 3.2 mmol) in dimethyl sulfoxide (5 ml) was added to a solution of the sodium salt of methyl thioglycolate (0.4 g, 3.2 mmol) in dimethyl sulfoxide (5 ml) and the reaction mixture stirred at ambient temperature for 2.5 h. Hydrochloric acid (2.5%, 200 ml) was added and the resultant mixture extracted with diethyl ether (three 100-ml aliquots). The organic layers were combined and concentrated and the extractive procedure was repeated. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated. Crude product was chromatographed on silica gel (100 g) employing chloroform (100-ml fractions) for elution. Fractions 6 and 7 were combined and concentrated, yielding oily *thiosulfonate* (9). I.r. 1745, 1320, 1150 cm^{-1}. ^1H n.m.r. (270 MHz) δ 2.47, s, 3H; 3.72, s, 3H; 4.11, s, 2H; 7.38, d, 2H; 7.82, d, 2H. ^{13}C n.m.r. δ 21.73, 53.08, 60.93, 128.54, 129.90, 135.71, 145.52, 162.99. *m/z* 228 ($M^{+\bullet}$ – S, 24%) (Found: 228.0456. $C_{10}H_{12}O_4S$ requires 228.0454), 155 (37), 105 (23), 91 (100).

Preparation of Methyl o-*(Methylsulfonylthio)benzoate (18)*

Methyl *o*-mercaptobenzoate[3] (2.0 g, 11.9 mmol) was dissolved in dry methylene chloride (5 ml) and a solution of sulfuryl chloride (1.6 g, 11.9 mmol) in dry methylene chloride (5 ml) added dropwise. The reaction mixture was refluxed for 0.5 h. A solution of sodium methanesulfinate (1.2 g, 11.9 mmol) in acetone (40 ml) and water (10 ml) was added to the reaction mixture which was immersed in a constant-temperature bath at 50°C for 1 h. Chloroform (200 ml) was added and the resultant mixture washed with water (100 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. Crude product was chromatographed on silica gel (100 g) employing 1 : 1 chloroform/light petroleum (100-ml fractions) for elution. Fractions 8–18 were combined and concentrated affording thiosulfonate (18) (2.0 g, 8.1 mmol, 68%). After recrystallization from methanol, *o*-(methoxycarbonyl)phenyl methanethiosulfonate (18) consisted of very fine colourless *crystals* and had m.p. 37.9–38.4°C (Found: C, 44.4; H, 4.1. $C_9H_{10}O_4S_2$ requires C, 43.9; H, 4.1%). I.r. 1730, 1335, 1140 cm^{-1}. ^1H n.m.r. (270 MHz) δ 3.24, s, 3H; 3.95, s, 3H; 7.61, m, 2H; 7.91, m, 2H. ^{13}C n.m.r. δ 48.73, 52.79, 127.54, 130.60, 131.25, 132.35, 135.73, 138.34, 168.83. *m/z* 167 (100%, $M^{+\bullet} - CH_3SO_2$).

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