Articles

Synthesis and Antifungal Activity of 1,3,2-Benzodithiazole S-Oxides

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The preparation of 1,3,2-benzodithiazole S-oxide analogs exhibiting *in vitro* antifungal activity against several strains of *Candida* is described. For the preparation of derivatives bearing aromatic substituents, a novel electrophilic aromatic thiolation reaction was utilized which produced substituted aromatic 1,2-dithiol intermediates. The reactions of nucleophiles with the parent heterocyclic system have led to an efficient transamidation process which allows for the direct production of these analogs. The S-oxide bond exhibits poor stereochemical stability and has been found to epimerize under ambient conditions. The structure–activity data report that a side chain of greater than 10 carbons effects a loss in activity as does the placement of polar groups in this chain.

The incidence of fungal infections has recently increased due to a number of factors such as intensive use of chemotherapy for bacterial infections and cancer,[1] wider use of catheterization, and an increase in the number of patients who are immune-suppressed due to organ transplantation and AIDS.[2] Amphotericin B is the most widely used systemic antifungal agent, despite its poor bioavailability and its considerable mammalian toxicity.[3] Fluconazole is one of the newest members of the azole class of antifungal compounds, which, although quite effective, all suffer from the disadvantage of being fungistatic and not fungicidal.[4] In view of the scarcity of agents currently available to the physician, there is an evident need for accelerated development of new, more effective, and less toxic antifungal drugs, especially for treating systemic fungal infections.

It has been shown that compounds containing the isothiazolone ring exhibit antifungal activity, though no *in vivo* activity has been reported.[5] We have found that the substitution of the carbonyl group in this system with a sulfoxyl group as in 1,3,2-benzodithiazole S-oxide **1** results in a novel series of antifungal analogs. We report herein[6] the preparation and the antifungal activity of this new heterocyclic system along with a study of its reactivity with amine nucleophiles and the stereochemical integrity of the S-oxide function.

Chemistry

The report[7] of Chen and Donatelli first described the preparation of the 1,3,2-dithiazole system **3** through halogenation of an aromatic 1,2-dithiol and reaction with a primary amine. Some of these symmetrical compounds show low but measurable *in vitro* activity against *Candida albicans* and other common fungal pathogens; however, when this ring is treated with 1 equiv of an oxidizing agent such as *m*-chloroperoxybenzoic acid (mCPBA), the S-oxide derivatives are formed and exhibit increased *in vitro* antifungal activity. Further oxidation of these compounds produces a pair of 1,3-bis-S,S′-oxides and, finally, the 1,3-bis-S,S′-dioxides. All the analogs of higher oxidation state than **1** exhibit no antifungal activity.

Although we initially prepared several derivatives in the manner shown in Scheme 1, we sought a more convenient method for analog preparation in order to avoid repeated production and use of the capricious benzene-1,2-bis-sulfenyl chloride **2**. The N–S bond is known to be labile, relative to attack by nucleophiles, and in this regard, sulfenamides have often been utilized as sulfenylating agents.[8] In this case however, **3** was inert when treated with primary amine nucleophiles. In contrast, treatment of **1** with primary amines led to an equilibrium mixture of starting and product 1,3,2-benzodithiazole S-oxide. This equilibrium could be biased by adding an excess of the desired amine addend or, better, by removal of unreacted amine through distillation. Toward this end, we prepared the N-propyl analog **4** as our key S-oxide, and by refluxing in toluene with 3–5 equiv of the desired higher boiling amine, near quantitative yields of new S-oxides were produced. Other analogs from lower boiling amines such as allyl, ethyl, or methyl were produced either directly through reaction with **2** or by using great excesses of the adding amine. Compounds prepared by either the direct or transamidation methods are shown in Table 1. Reaction with other nucleophiles such as thiols also occurs readily to give ring-opened disulfides presumedly from addition of the thiol to the unoxidized ring sulfur.

Since this new heterocyclic ring system contains an asymmetric sulfoxyl center, we sought to establish whether the enantiomers could be isolated and, if so, whether they had similar biological activity. Toward this end, the (S)-1-methoxy-3-phenyl-2-aminopropane adduct **5** was prepared via the transamidation reaction. Separation of the diastereomers by HPLC was attempted, and though near base-line separation could be achieved in the time course of collection and reinjection of fractions of any ratio of these diastereomers, the resultant HPLC trace reflected a 1:1 mix of the two components.[9] Several other chiral amine adducts were processed in a similar manner using solvent systems of varied pH, but all exhibited this same ease of epimerization. Therefore, we believe that the

† Drug Safety Evaluation.

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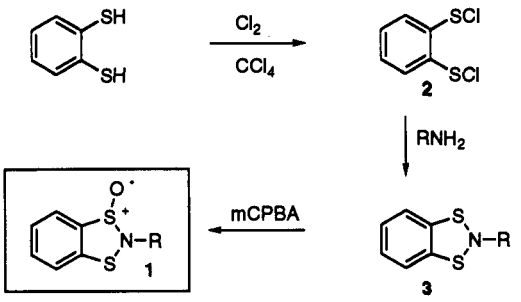
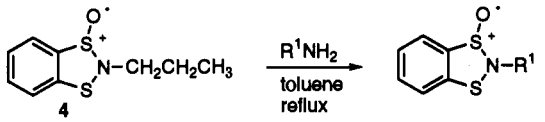
Scheme 1



Scheme 2



S-oxide function in these 1,3,2-benzodithiazole rings is not stereochemically stable. This result is in clear contrast to the documented stereochemical integrity of the sulfinamide function in many acyclic examples. Further work involved with elucidating the effect of this ring system on the sulfoxyl center is in progress.

In order to study what effect ring A has on the activity, we prepared analogs bearing various ring substituents which in turn required substituted aromatic 1,2-dithiols as starting materials. Only the 4-methyl- and unsubstituted 1,2-dithiol analogs were commercially available,[10] and except for the tetrafluoro-dithiol compound which was prepared through low-yield metalation–thiolation of tetrafluorobenzene,[11] few others had been reported in the literature.

Through some earlier work,[12] we discovered a new reaction of aromatic dithioic esters **8** which involved an oxidative electrophilic thiolation to produce the dithioles such as **9**. We noted that cleavage of the bis(carboethoxymethylene) moiety from these compounds could afford the desired dithiol intermediates **10**, and toward this end, we reacted the diesters **9** with ethylenediamine in refluxing ethanol. Although the requisite cleavage took place, only low yields of the resultant dithiols could be isolated, most probably due to the formation of disulfides. By taking advantage of the known stability of the zinc salts of these dithiols and the insolubility of such salts, we found that the addition of zinc acetate to this reaction mixture served to trap the excised dithiol portion of **9** by causing a precipitation of the dithiolate salts directly from the reaction mixture. In this way, a three-step synthesis of aromatic 1,2-dithiols from the corresponding thiol was discovered. After filtering and drying, the zinc dithiolate can be stored indefinitely and, prior to use, can be treated with either acid or base to produce the dithiol or dithiolate, respectively.[13] Aromatic halo or ether substituents were among those compatible to these conditions. Treating these dithiols as previously described through chlorination, amination, and oxidation with mCPBA led to analogs bearing substituents on ring A, and these products are listed in Table 2. In cases where these substituents allow for multiple ring thiolation sites, mixtures of regioisomers are normally seen.

Biological Activity

Although the mode of action of these compounds is, as yet, unknown, they do not exhibit any perturbation of the cell wall or other nonselective mechanisms such as inhibition of DNA or protein synthesis. The MIC's (measured in μg/mL) of these derivatives are shown in Table 3. At the concentrations listed in Table 3, these compounds are fungistatic; however, studies are ongoing as to their character at higher concentrations.

In general, all alkyl, alkenyl, and alkynyl side chains showed good activity until the length became greater than 10 carbons, in which case a dropoff of activity was noted with increasing length. Smaller chains were generally more active. Aromatic rings were not only compatible but showed improved activity when attached to an existing side-chain carbon, such as benzyl and phenylethyl, etc; however, all *N*-phenyl analogs exhibited poor activity. This result does not correlate with the expected abilities of the sulfoxanilide and alkylsulfoxamine to serve as leaving groups following nucleophilic cleavage of the ring system.

Steric arguments also do not totally correlate with the data since the *tert*-butyl analog **27** exhibits good *in vitro* activity. Polar functionalities in the side chain were not well tolerated, as amino, carboxyl, and hydroxyl greatly decreased the activity of their respective analogs. Ring A substituents such as alkyl groups did not greatly affect the activity, being quite similar to the parent unsubstituted compounds.

We prepared analog **55**[14] in order to study the inherent antifungal activity of the S(O)–N–S heteroatomic array. This structure differed from one of our most active compounds, **40**, due to its acyclic form; however, the MIC's for **55** were found to be >100 μg/mL. Furthermore, the 1,3-benzodithiole corresponding to **40** which was prepared by first condensing nonanal with 1,2-benzenedithiol and oxidizing with 1 molar equiv of mCPBA exhibited no antifungal activity. These results suggest that the electronic character of this particular heteroatomic ring is important for activity.

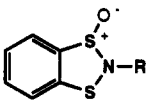
Metabolism of 1,3,2-Benzodithiazole *S*-Oxides

Several of these compounds exhibited good *in vivo* activity against a systemic *Candidiasis* infection through ip administration in mice;[15] however, problems with the reproducibility of these results led us to suspect that metabolic deactivation of these compounds was occuring. To investigate this possibility, an *in vivo* rat metabolism study with radiolabeled **40** was initiated.

Excretion of **40**-^{14}C from the rat following a single 5 mg/kg iv dose was rapid and mainly via the kidneys, with over 88% of the total radioactive dose present in the 0–24-h urine. Plasma concentrations of total radioactivity at 30 min following administration averaged 4.6 μg equiv/mL. No detectable amounts of **40** were found in either the urine or the 30-min plasma samples by HPLC analysis, indicating both rapid and complete metabolic transformation. Two radioactive components, which eluted from the HPLC column much earlier than the parent compound, were present in both the urine and plasma samples. The major metabolite, representing 87% of the urinary radioactivity and 69% of the plasma radioactivity, was characterized as hippuric acid by both cochromatography and LC/MS. The other minor metabolite was characterized by cochromatography as benzoic acid and accounted for 6% of the urinary radioactivity and 19% of the plasma radioactivity.

On the basis of these findings, the initial metabolic conversion appears to be the release of radiolabeled benzylamine from the heterocyclic ring system. The metabolism of benzylamine to benzoic acid is well known,

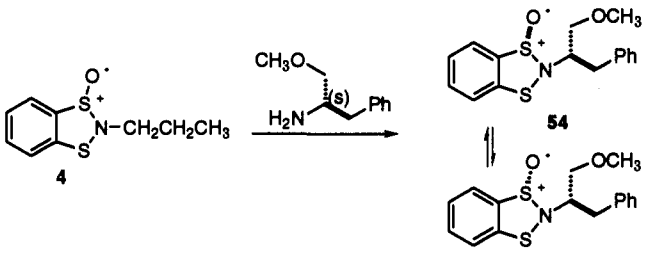
Table 1. 1,3,2-Benzodithiazoles and *S*-Oxides



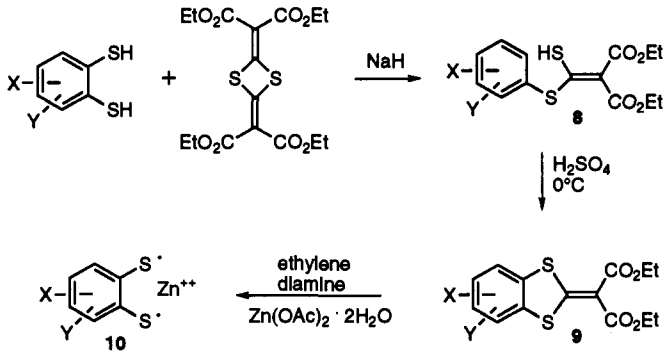
cpd	R	method[a]	yield (%) C	yield (%) O	cpd	R	method[a]	yield (%) C	yield (%) O	yield (%) T
11	CH_3	A	23	69	34	2-piperidinylethyl	A	65	36	
12	$CH_2CH_2CH_3$ (unoxidized)	A	69		35	3-(dimethylamino)propyl	A	50	45	
13	$CH_2CH_2CH_3$	A		71	36	C_6H_5	A	58	95	
14	$CH_2(CH_2)_3CH_3$	A	64	60	37	$3,4\text{-}F_2C_6H_3$	A	21	65	
15	$CH_2(CH_2)_5CH_3$	A	98	72	38	$3,4\text{-}(OCH_2O)C_6H_3$	A	33	42	
16	$CH_2(CH_2)_6CH_3$	A	98	71	39	$CH_2C_6H_5$ (unoxidized)	A	63		
17	$CH_2(CH_2)_7CH_3$	A	55	38	40	$CH_2C_6H_5$	A		65	
18	$CH_2(CH_2)_8CH_3$	A	72	72	41	$CH_2CH_2C_6H_5$	A	70	74	
19	$CH_2(CH_2)_{14}CH_3$	A	66	63	42	CH_2CH_2-(4-pyridyl)	A	57	47	
20	oleoyl	A	52	80	43	$CH_2(CH_2)_2C_6H_5$)	B			54
21	$CH_2CH{=}CH_2$	A	75	70	44	CH_2-(2-thienyl)	B			87
22	$CH_2CH{\equiv}CH_2$	A	92	75	45	CH_2-cyclohexyl	A	92	75	
23	cyclopropyl (unoxidized)	A	71		46	$CH_2\text{-}2,4\text{-}Cl_2C_6H_3$	A	55	51	
24	cyclopropyl	A		58	47	$CH_2\text{-}4\text{-}(Me_2N)C_6H_4$	B			32
25	cyclooctyl	A	60	74	48	$CH_2\text{-}3,4\text{-}F_2C_6H_3$	B			69
26	1-adamantyl	A	67	54	49	$CH_2\text{-}2,6\text{-}F_2C_6H_3$	B			84
27	*tert*-butyl	A	77	67	50	$CH_2\text{-}3,4,5\text{-}(OMe)_3C_6H_2$	B			93
28	3-pentyl	A	35	85	51	CH_2-(2-naphthyl)	B			90
29	3,3-dimethylbutyl	A	78	67	52	$CH(CH_3)C_6H_5$ (*S*)	B			71
30	1,1,3,3-tetramethylbutyl	A	59	85	53	$CH(C_6H_5)_2$	B			60
31	4,4-diethoxybutyl	A	69	74	54	$CH(CH_2OMe)CH_2C_6H_5$ (*S*)	B			67
32	2-hydroxyethyl	A	32	88	55	[PhS(O)N($CH_2C_6H_5$)SPh]	A	*b*	47	
33	2-(triethylsiloxy)ethyl	A	67	70						

[a] Method A = cyclitive amination (C); mCPBA oxidation (O). Method B = transamidation (T). [b] Reference 14.

Scheme 3



Scheme 4



as is the conjugation of benzoic acid with glycine to form hippuric acid, both of which were identified in the urine and the plasma from rats given **40**-^{14}C. The metabolic fate of the sulfur-containing residue from **40** is not yet known. If the intact heterocyclic ring is responsible for the antifungal activity of these compounds, these metabolism results may explain the irreproducibility of the *in vivo* activity data.

Experimental Section

^{1}H NMR spectra were recorded on a General Electric QE300 spectrometer using Me_4Si as an internal standard. Elemental analyses were performed by Oneida Research Services, Whitesboro, NY. The high-resolution MS were obtained on a Kratos MS50 instrument at Abbott Laboratories. E. Merck silica gel (230–400 mesh) obtained from VWR Scientific was used for column chromatography. Melting points were measured with a Fisher-Johns apparatus and are uncorrected. Methylene chloride was distilled from calcium hydride, and THF was distilled from sodium. All other solvents were HPLC grade and were not purified prior to use. Unless otherwise noted, all reactions were carried out under an inert (N_2) atmosphere.

1,2-Benzenedisulfenyl Chloride. Chlorine gas (9.6 mL, 3 equiv) was bubbled through a cooled (0 °C) solution of 1,2-benzenedithiol (10 g, 70 mmol) in 200 mL of carbon tetrachloride (CCl_4) over a period of an hour. The reaction mixture was stirred for an additional hour at 0 °C and then concentrated *in vacuo* to give 13.4 g (90% yield) of the title compound as an orange solid.

General Synthesis of *N*-Substituted 1,3,2-Benzodithiazoles.[7] A solution of 1,2-benzenedisulfenyl chloride (0.9 g, 4.26 mmol) in 10 mL of diethyl ether was added dropwise over a period of 20 min to a mixture of the appropriate amine (4.30 mmol), triethylamine (1.2 mL, 8.6 mmol), and 100 mL of diethyl ether at −20 °C. The reaction mixture was kept at −20 °C for 1 h and at room temperature for 16 h. After filtration to remove the triethylamine hydrochloride, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane to give the title compound.

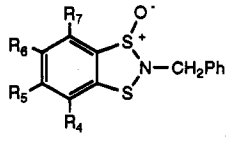
***N*-Propyl-1,3,2-benzodithiazole (12):** ^{1}H NMR ($CDCl_3$) δ 7.36 (dd, 2H, ArH), 7.17 (dd, 2H, ArH), 2.86 (t, 2H, N-CH_2-), 1.6 (sextet, 2H, -CH_2-), 0.88 (t, 3H, -CH_3); MS (DCI/NH_3) *m/z* 198 (M + 1). Anal. ($C_9H_{11}NS_2$) C, H; N: calcd, 32.45; found, 31.94.

***N*-Cyclopropyl-1,3,2-benzodithiazole (23):** ^{1}H NMR ($CDCl_3$) δ 7.36 (dd, 2H, ArH), 7.17 (dd, 2H, ArH), 2.87 (ddd, 1H, N-CH), 0.57–0.76 (m, 4H, -CH_2-); MS (DCI/NH_3) *m/z* 196 (M + 1). Anal. ($C_9H_9NS_2$) C, H, N.

***N*-Benzyl-1,3,2-benzodithiazole (39):** ^{1}H NMR ($CDCl_3$) δ 7.18–7.4 (m, 9H, ArH), 4.01 (s, 2H, -CH_2); MS (DCI/NH_3) *m/z* 246 (M + 1), 263 (M + 18). Anal. ($C_{13}H_{11}NS_2$) C, H, N.

General Synthesis of *N*-Substituted 1,3,2-Benzodithiazole *S*-Oxides. Method A. Oxidation of *N*-Substituted 1,3,2-Benzodithiazoles. To a solution of the appropriate *N*-substituted 1,3,2-benzodithiazole (2 mmol) in 30 mL of chloroform at −20 °C was added portionwise 56% *m*-chloroperoxybenzoic acid (mCPBA) (0.64 g, 2 mmol). The reaction mixture was allowed

Table 2. Ring-A-Substituted 1,3,2-Benzodithiazole *S*-Oxides



cpd	R_4	R_5	R_6	R_7	yield[a] Cl	C	O
61	CH_3	H	H	CH_3	84	85	68
62	H	OMe	H	H	85	76	55[b]
63	H	F	H	H	85	76	60[c]
64a	CH_3	H	H	H	87	47	32[d]
64b	H	H	H	CH_3			22[d]
65	F	F	F	F	95	14	52
66	F	morpholino	F	F		77[e]	

[a] Cl: chlorination of 1,2-dithiol. C: cyclitive amination. O: oxidation. [b] Mixture from oxidation 5-OMe:6-OMe, 9:1. [c] Mixture from oxidation 5-F:6-F, 3:1. [d] Mixture from oxidation **64a**:**64b**, 3:2. [e] Prepared by heating **65** with morpholine.

Table 3. Antifungal Activity[a] of 1,3,2-Benzodithiazole *S*-Oxides versus *Candida albicans*[b] (μg/mL)

cpd	*C. albicans* CCH 442	*C. albicans* 10231	*C. albicans* 579A	*C. albicans* 38247	cpd	*C. albicans* CCH 442	*C. albicans* 10231	*C. albicans* 579A	*C. albicans* 38247
amphotericin B	0.78	1.56	1.56	25	**37**	25	25	100	25
11	1.56	1.56	1.56		**38**	25	12.5	25	25
12	12.5	3.12	3.12	25	**39**	12.5	6.25	6.25	25
13	0.78	0.78	0.78	3.12	**40**	0.78	0.78	0.78	6.25
14	0.78	0.78	0.78	3.12	**41**	1.56	0.78	0.39	1.56
15	0.78	0.39	0.2	0.78	**42**	100	100	100	100
16	0.2	0.2	0.2	0.39	**43**	3.12	1.56	3.12	12.5
17	1.56	1.56	0.78	1.56	**44**	0.78	1.56	0.78	1.56
18	6.25	1.56	6.25	6.25	**45**	1.56	1.56	1.56	3.12
19	>100	>100	>100	>100	**46**	6.25	3.12	1.56	12.5
20	>100	100	100	>100	**47**	6.25	1.56	3.12	3.12
21	0.78	0.39	0.39	6.25	**48**	1.56	1.56	1.56	3.12
22	0.78	0.39	0.78		**49**	1.56	0.78	0.78	1.56
23	50	25	25	50	**50**	12.5	12.5	12.5	3.12
24	1.56	1.56	0.78	3.12	**51**	6.25	3.12	3.12	12.5
25	3.12	3.12	3.12	6.25	**52**	1.56	1.56	1.56	3.12
26	25	6.25	12.5	50	**53**	12.5	25	6.25	25
27	1.56	1.56	1.56	6.25	**54**	3.12	3.12	3.12	3.12
28	100	100	100	50	**55**	>100	>100	>100	50
29	1.56	1.56	3.12	25	**61**	3.12	1.56	3.12	25
30	1.56	6.25	3.12	1.56	**62**	0.78	0.78	0.78	3.12
31	1.56	6.25	3.12	1.56	**63**	0.78	0.78	0.78	1.56
32	12.5	12.5	12.5	1.56	**64a**	25	12.5	12.5	25
33	50	25	25	3.12	**64b**	1.56	0.78	0.78	1.56
34	25	25	25	12.5	**65**	12.5	6.25	6.25	12.5
35	50	50	50	12.5	**66**	50	50	25	12.5
36	25	25	12.5	25					

[a] MIC's were determined by microtiter broth dilution testing in YNBG. See Experimental Section. [b] CCH 442, 579A, and 10231 (ATCC) are clinical isolates; 38247 is a nonclinical, ampho-resistant strain.

to warm to 0 °C over a 2-h period, and then, the reaction was quenched at 10 °C with 20 mL of 1 M aqueous sodium bicarbonate solution. The organic layer was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with chloroform ($CHCl_3$) to give the title compound.

Method B. Transamidation of *N*-Propyl-1,3,2-benzodithiazole *S*-Oxide. A solution of *N*-propyl-1,3,2-benzodithiazole *S*-oxide (**13**) (206 mg, 0.96 mmol) and the appropriate amine (2.9 mmol) in 20 mL of toluene was heated at reflux for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with ether/hexane to give the title compound.

***N*-Methyl-1,3,2-benzodithiazole *S*-Oxide (11):** ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.28 (s, 3H, CH_3); MS (DCl/NH_3) *m/z* 186 (M + 1), 203 (M + 18). Anal. ($C_7H_7NOS_2$) C, H, N.

***N*-Propyl-1,3,2-benzodithiazole *S*-Oxide (13):** ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.49 (t, 2H, N-CH_2-), 1.85 (sextet, 2H, -CH_2-), 1.03 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 214 (M + 1), 231 (M + 18). Anal. ($C_9H_{11}NOS_2$) C, H, N.

***N*-Pentyl-1,3,2-benzodithiazole *S*-Oxide (14):** ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.5 (t, 2H, N-CH_2-), 1.81 (quintet, 2H, -CH_2-), 1.35–1.41 (m, 4H, -CH_2-), 0.91 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 242 (M + 1), 259 (M + 18). Anal. ($C_{11}H_{15}NOS_2$) C, H, N.

***N*-Heptyl-1,3,2-benzodithiazole *S*-Oxide (15):** ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.5 (t, 2H, N-CH_2-), 1.81 (quintet, 2H, -CH_2-), 1.25–1.42 (m, 8H, -CH_2-), 0.88 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 270 (M + 1), 287 (M + 18). Anal. ($C_{13}H_{19}NOS_2$) C, H, N.

***N*-Octyl-1,3,2-benzodithiazole *S*-Oxide (16):** ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.5 (t, 2H, N-CH_2-), 1.81 (quintet, 2H, -CH_2-), 1.2–1.4 (m, 10H, -CH_2-), 0.88 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 284 (M + 1), 301 (M + 18). Anal. ($C_{14}H_{21}NOS_2$) C, H, N: calcd, 22.59; found, 23.2.

***N*-Nonyl-1,3,2-benzodithiazole *S*-Oxide (17):** ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.5 (t, 2H, N-CH_2-), 1.82 (quintet, 2H, -CH_2-), 1.2–1.4 (m, 10H, -CH_2-), 0.88 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 298 (M + 1), 315 (M + 18). Anal. ($C_{15}H_{23}NOS_2$) C, H, N.

***N*-Decyl-1,3,2-benzodithiazole *S*-Oxide (18):** ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH),

3.5 (t, 2H, N-CH_2-), 1.81 (quintet, 2H, -CH_2-), 1.25–1.54 (m, 14H, -CH_2-), 0.88 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 312 (M + 1), 329 (M + 18). Anal. ($C_{16}H_{25}NOS_2$) C, H, N.

***N*-Hexadecyl-1,3,2-benzodithiazole *S*-Oxide (19)**: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.5 (t, 2H, N-CH_2-), 1.81 (quintet, 2H, -CH_2-), 1.25–1.44 (m, 26H, -CH_2-), 0.88 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 396 (M + 1), 413 (M + 18). Anal. ($C_{22}H_{37}NOS_2$) C, H, N.

***N*-Oleoyl-1,3,2-benzodithiazole *S*-Oxide (20)**: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 5.34 (m, 2H, -CH=CH-), 3.5 (t, 2H, N-CH_2-), 2.01 (m, 4H, -CH_2C=C-), 1.81 (quintet, 2H, -CH_2-), 1.25–1.44 (m, 22H, -CH_2-), 0.88 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 422 (M + 1), 439 (M + 18). Anal. ($C_{24}H_{39}NOS_2$) C, H; N: calcd, 3.32; found, 3.8.

***N*-Propenyl-1,3,2-benzodithiazole *S*-Oxide (21)**: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.33 (m, 1H, ArH), 6.0 (m, 1H, -CH=C), 5.33–5.47 (m, 2H, -C=CH_2), 4.12 (m, 2H, N-CH_2-); MS (DCl/NH_3) *m/z* 212 (M + 1), 229 (M + 18). Anal. ($C_9H_9NOS_2$) C, H, N.

***N*-Propargyl-1,3,2-benzodithiazole *S*-Oxide (22)**: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, ArH), 7.51 (m, 2H, ArH), 7.35 (m, 1H, ArH), 4.34 (dd, 1H, -CH_2-), 4.2 (dd, 1H, -CH_2-), 2.38 (t, 1H, -CH). Anal. ($C_9H_7NOS_2$) C, H, N.

***N*-Cyclopropyl-1,3,2-benzodithiazole *S*-Oxide (24)**: ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, ArH), 7.47 (m, 2H, ArH), 7.32 (m, 1H, ArH), 2.94 (ddd, 1H, N-CH-), 0.9–1.1 (m, 4H, -CH_2-); MS (DCl/NH_3) *m/z* 212 (M + 1). Anal. ($C_9H_9NOS_2$) C, H, N.

***N*-Cyclooctyl-1,3,2-benzodithiazole *S*-Oxide (25)**: ^{1}H NMR ($CDCl_3$) δ 7.8 (d, 1H, ArH), 7.47 (m, 2H, ArH), 7.28 (m, 1H, ArH), 4.01 (ddd, 1H, N-CH-), 1.46–2.16 (m, 14H, -CH_2-); MS (DCl/NH_3) *m/z* 282 (M + 1). Anal. ($C_{14}H_{19}NOS_2$) C, H, N.

***N*-(1-Adamantyl)-1,3,2-benzodithiazole *S*-Oxide (26)**: ^{1}H NMR ($CDCl_3$) δ 7.8 (d, 1H, ArH), 7.47 (m, 2H, ArH), 7.28 (m, 1H, ArH), 2.18 (m, 9H, CH and CH_2), 1.71 (m, 6H, N-CCH_2-); MS (DCl/NH_3) *m/z* 306 (M + 1). Anal. ($C_{16}H_{19}NOS_2$) C, H, N.

***N*-*tert*-Butyl-1,3,2-benzodithiazole *S*-Oxide (27)**: ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 1H, ArH), 7.47 (m, 2H, ArH), 7.31 (m, 1H, ArH), 1.56 (s, 9H, CH_3); MS (DCl/NH_3) *m/z* 228 (M + 1). Anal. ($C_{10}H_{13}NOS_2$) C, H, N.

***N*-(3-Pentyl)-1,3,2-benzodithiazole *S*-Oxide (28)**: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.48 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.68 (m, 1H, N-CH-), 1.62–1.7 (m, 4H, -CH_2-), 1.05 (t, 3H, -CH_3); MS (DCl/NH_3) *m/z* 242 (M + 1), 259 (M + 18). Anal. ($C_{11}H_{15}NOS_2$) C, H, N.

***N*-(3,3-Dimethylbutyl)-1,3,2-benzodithiazole *S*-Oxide (29)**: ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, ArH), 7.48 (m, 2H, ArH), 7.33 (m, 1H, ArH), 3.52 (m, 2H, N-CH_2-), 1.76 (ddd, 2H, -CH_2-), 0.96 (t, 9H, -CH_3); MS (DCl/NH_3) *m/z* 256 (M + 1), 273 (M + 18). Anal. ($C_{12}H_{17}NOS_2$) C, H, N.

***N*-(1,1,3,3-Tetramethylbutyl)-1,3,2-benzodithiazole *S*-Oxide (30)**: ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, ArH), 7.48 (m, 2H, ArH), 7.31 (m, 1H, ArH), 1.71 (dd, 2H, -CH_2-), 1.73 (s, 3H, -CH_3), 1.61 (s, 3H, -CH_3), 0.98 (t, 9H, -CH_3); MS (DCl/NH_3) *m/z* 284 (M + 1), 301 (M + 18). Anal. ($C_{14}H_{21}NOS_2$) C, H, N.

***N*-(4,4-Diethoxybutyl)-1,3,2-benzodithiazole *S*-Oxide (31)**: ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, ArH), 7.48 (m, 2H, ArH), 7.33 (m, 1H, ArH), 4.52 (t, 1H, -CH-OEt), 3.53 (t, 2H, NCH_2-), 3.43–3.7 (m, 4H, -OCH_2-), 1.7–1.94 (m, 4H, -CH_2-), 1.2 (dt, 6H, -CH_3). Anal. ($C_{14}H_{21}NOS_2$) C, H, N.

***N*-(2-Hydroxyethyl)-1,3,2-benzodithiazole *S*-Oxide (32)**: ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H, ArH), 7.52 (m, 2H, ArH), 7.37 (m, 1H, ArH), 3.7–3.92 (m, 4H, -CH_2-), 2.7 (br s, 1H, OH); MS (DCl/NH_3) *m/z* 216 (M + 1), 233 (M + 18). Anal. ($C_8H_9NO_2S_2$) C, H, N.

***N*-[2-[(Triethylsilyl)oxy]ethyl]-1,3,2-benzodithiazole *S*-Oxide (33)**: ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 1H, ArH), 7.48 (m, 2H, ArH), 7.32 (m, 1H, ArH), 3.62–3.94 (m, 4H, -CH_2-), 0.92 (t, 9H, -CH_3), 0.55 (q, 6H, $SiCH_2$-); MS (DCl/NH_3) *m/z* 330 (M + 1). Anal. ($C_{14}H_{23}NO_2S_2Si$) C, H, N.

***N*-(2-Piperidinoethyl)-1,3,2-benzodithiazole *S*-Oxide (34)**: ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, ArH), 7.48 (m, 2H, ArH), 7.30 (m, 1H, ArH), 3.5–3.8 (m, 2H, $SNCH_2$-), 2.35–2.7 (m, 2H, -CH_2N), 2.1–2.45 (m, 4H, NCH_2-), 1.35–1.55 (m, 6H, -CH_2); MS (DCl/NH_3) *m/z* 283 (M + 1). Anal. ($C_{13}H_{18}N_2OS_2$) C, H, N.

***N*-[(Dimethylamino)propyl]-1,3,2-benzodithiazole *S*-Oxide (35)**: ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, ArH), 7.48 (d, 2H, ArH), 7.33 (m, 1H, ArH), 3.38 (m, 2H, NCH_2-), 2.42 (t, 2H, -CH_2N), 2.26 (s, 6H, NCH_3), 1.98 (quintet, 2H, -CH_2-); MS (DCl/NH_3) *m/z* 257 (M + 1). Anal. ($C_{11}H_{16}N_2OS_2$) C, H, N.

***N*-Phenyl-1,3,2-benzodithiazole *S*-Oxide (36)**: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H, ArH), 7.2–7.6 (m, 8H, ArH); MS (DCl/NH_3) *m/z* 248 (M + 1), 265 (M + 18). Anal. ($C_{12}H_9NOS_2$) C, H, N.

***N*-(3,4-Difluorophenyl)-1,3,2-benzodithiazole *S*-Oxide (37)**: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H, ArH), 7.1–7.6 (m, 6H, ArH); MS (DCl/NH_3) *m/z* 284 (M + 1). Anal. ($C_{12}H_7F_2NOS_2$) C, H, N.

***N*-[3,4-(Methylenedioxy)phenyl]-1,3,2-benzodithiazole *S*-Oxide (38)**: ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H, ArH), 6.77–7.55 (m, 6H, ArH); MS (DCl/NH_3) *m/z* 292 (M + 1), 309 (M + 18). Anal. ($C_{13}H_9NO_3S_2$) C, H, N.

***N*-Benzyl-1,3,2-benzodithiazole *S*-Oxide (40)**: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, ArH), 7.3–7.5 (m, 8H, ArH), 4.65 (dd, 2H, N-CH_2-); MS (DCl/NH_3) *m/z* 262 (M + 1), 279 (M + 18). Anal. ($C_{13}H_{11}NOS_2$) C, H, N.

***N*-(Phenethyl)-1,3,2-benzodithiazole *S*-Oxide (41)**: ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, ArH), 7.48 (d, 2H, ArH), 7.2–7.35 (m, 6H, ArH), 3.68–3.84 (m, 2H, NCH_2-), 3.1 (t, 2H, -CH_2-); MS (DCl/NH_3) *m/z* 276 (M + 1), 293 (M + 18). Anal. ($C_{14}H_{13}NOS_2$) C, H, N.

***N*-(4-Pyridinoethyl)-1,3,2-benzodithiazole *S*-Oxide (42)**: ^{1}H NMR ($CDCl_3$) δ 8.52 (d, 2H, ArH), 7.80 (d, 1H, ArH), 7.14–7.38 (d, 5H, ArH), 3.78 (m, 2H, NCH_2-), 3.1 (t, 2H, -CH_2-); MS (DCl/NH_3) *m/z* 277 (M + 1). Anal. ($C_{13}H_{12}N_2OS_2$) C, H, N.

***N*-(3-Phenylpropyl)-1,3,2-benzodithiazole *S*-Oxide (43)**: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, ArH), 7.50 (d, 2H, ArH), 7.2–7.35 (m, 6H, ArH), 3.51 (t, 2H, NCH_2-), 2.76 (t, 2H, -CH_2Ar), 2.13 (m, 2H, -CH_2-); MS (DCl/NH_3) *m/z* 290 (M + 1), 307 (M + 18). Anal. ($C_{15}H_{15}NOS_2$) C, H, N.

***N*-(2-Thienylmethyl)-1,3,2-benzodithiazole *S*-Oxide (44)**: ^{1}H NMR ($CDCl_3$) δ 7.83 (dt, 1H, ArH), 7.0–7.5 (m, 6H, ArH), 4.82 (dd, 2H, N-CH_2-); MS (DCl/NH_3) *m/z* 268 (M + 1), 285 (M + 18). Anal. ($C_{11}H_9NOS_3$) C, H, N.

***N*-(Cyclohexylmethyl)-1,3,2-benzodithiazole *S*-Oxide (45)**: ^{1}H NMR ($CDCl_3$) δ 7.83 (dt, 1H, ArH), 7.3–7.5 (m, 3H, ArH), 3.33 (d, 2H, N-CH_2-), 0.8–2.0 (m, 11H, cyclohexyl); MS (DCl/NH_3) *m/z* 268 (M + 1), 285 (M + 18). Anal. ($C_{13}H_{17}NOS_2$) C, H, N.

***N*-[(2,4-Dichlorophenyl)methyl]-1,3,2-benzodithiazole *S*-Oxide (46)**: ^{1}H NMR ($CDCl_3$) δ 7.85 (dt, 1H, ArH), 7.25–7.52 (m, 6H, ArH), 4.71 (d, 2H, N-CH_2-); MS (DCl/NH_3) *m/z* 330 (M + 1), 347 (M + 18). Anal. ($C_{13}H_9Cl_2NOS_2$) C, H, N.

***N*-[[4-(Dimethylamino)phenyl]methyl]-1,3,2-benzodithiazole *S*-Oxide (47)**: ^{1}H NMR ($CDCl_3$) δ 7.82 (dt, 1H, ArH), 7.25–7.48 (m, 5H, ArH), 6.72 (d, 2H, ArH), 4.55 (dd, 2H, N-CH_2-), 2.99 (s, 6H, NCH_3); MS (DCl/NH_3) *m/z* 305 (M + 1), 322 (M + 18). Anal. ($C_{15}H_{16}N_2OS_2$) C, H, N.

***N*-[(3,4-Difluorophenyl)methyl]-1,3,2-benzodithiazole *S*-Oxide (48)**: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, ArH), 7.15–7.55 (m, 6H, ArH), 4.6 (dd, 2H, N-CH_2-); MS (DCl/NH_3) *m/z* 298 (M + 1), 315 (M + 18). Anal. ($C_{13}H_9F_2NOS_2$) C, H, N.

***N*-[(2,6-Difluorophenyl)methyl]-1,3,2-benzodithiazole *S*-Oxide (49)**: ^{1}H NMR ($CDCl_3$) δ 7.85 (dt, 1H, ArH), 7.25–7.55 (m, 4H, ArH), 6.93 (t, 2H, ArH), 4.72 (dd, 2H, N-CH_2-); MS (DCl/NH_3) *m/z* 298 (M + 1), 315 (M + 18). Anal. ($C_{12}H_9F_2NOS_2$) C, H, N.

***N*-[(3,4,5-Trimethoxyphenyl)methyl]-1,3,2-benzodithiazole *S*-Oxide (50)**: ^{1}H NMR ($CDCl_3$) δ 7.85 (dt, 1H, ArH), 7.3–7.55 (m, 3H, ArH), 6.65 (s, 2H, ArH), 4.57 (dd, 2H, N-CH_2-), 3.78 (s, 3H, OCH_3), 3.77 (s, 6H, OCH_3); MS (DCl/NH_3) *m/z* 352 (M + 1), 369 (M + 18). Anal. ($C_{16}H_{17}NO_4S_2$) C, H, N.

***N*-Naphthyl-1,3,2-benzodithiazole *S*-Oxide (51)**: ^{1}H NMR ($CDCl_3$) δ 7.15–8.15 (m, 11H, ArH), 5.08 (dd, 2H, N-CH_2-); MS (DCl/NH_3) *m/z* 312 (M + 1), 329 (M + 18). Anal. ($C_{17}H_{13}NOS_2$) C, H, N.

***N*-(1-(*S*)-Phenylethyl)-1,3,2-benzodithiazole *S*-Oxide (52)**: 1:1 mix of diastereomers; ^{1}H NMR ($CDCl_3$) δ 7.2–7.9 (m, 18H, ArH), 4.98 (q, 1H, N-CH-, isomer a), 4.82 (q, 1H, N-CH-, isomer b), 1.85 (2 overlapping d, 6H, CH_3); MS (DCl/NH_3) *m/z* 276 (M + 1), 293 (M + 18). Anal. ($C_{14}H_{13}NOS_2$) C, H, N.

***N*-(Diphenylmethyl)-1,3,2-benzodithiazole *S*-Oxide (53)**: ^{1}H NMR ($CDCl_3$) δ 7.75 (dt, 1H, ArH), 7.3–7.6 (m, 13H, ArH),

5.75 (s, 1H, N-CH); MS (DCl/NH_3) m/z 338 (M + 1), 355 (M + 18). Anal. ($C_{19}H_{15}NOS_2$) C, H, N.

N-(2-(S)-1-Methoxy-3-phenylpropyl)-1,3,2-benzodithiazole S-Oxide (54): 1:1 mix of diastereomers; ^{1}H NMR ($CDCl_3$) δ 7.8 (d, 1H, ArH, isomer a), 7.6 (d, 1H, ArH, isomer b), 7.0–7.5 (m, 14H, ArH), 4.23 (m, 2H, N-CH-), 3.6 (m, 2H), 3.35 (s, 3H, OCH_3, isomer a), 2.85–3.3 (m, 6H), 2.8 (s, 3H, OCH_3, isomer a); MS (DCl/NH_3) m/z 320 (M + 1), 327 (M + 18). Anal. ($C_{16}H_{17}NO_2S_2$) C, H, N.

N,N-Bis(phenylthio)benzylamine Mono-S-oxide (55): starting material bisbenzenesulfenimide obtained as per Mukaiyama;[14] ^{1}H NMR ($CDCl_3$) δ 7.7 (m, 2H, ArH), 7.5 (m, 4H, ArH), 7.3 (m, 7H, ArH), 7.08 (m, 2H, ArH), 4.31 (d, 2H, $-CH_2-$); MS (DCl/NH_3) m/z 340 (M + 1), 358 (M + 18). Anal. ($C_{19}H_{17}NOS_2$) H, N; C: calcd, 67.22; found 66.7.

General Procedure for the Substituted 1,2-Benzenedithiols. The corresponding substituted 1,3-benzodithiole (5.9 mmol), $Zn(OAc)_2 \cdot 2H_2O$ (6 equiv), and ethylenediamine (10 equiv) were heated in 50 mL of *i*-PrOH at reflux for 1 week. The precipitated white solid was filtered, washed with MeOH, suspended in hot $CHCl_3$, and filtered. These salts could not be characterized via combustion analysis or high-resolution mass spectral analysis. This solid was dissolved and stirred in 40 mL of 4 M H_2SO_4 at room temperature for 20 min. The solution was extracted with CH_2Cl_2, and the organic layer was washed with water and dried ($MgSO_4$) to yield an oil which was used in the next step without further purification. These dithiols were not stable enough for characterization via combustion analysis; therefore, high-resolution mass spectral analysis was used.

3,6-Dimethyl-1,2-benzenedithiol (56). In a similar manner, **56** was prepared from 6 g of the corresponding benzodithiole to give 3.8 g (92%) of the zinc adduct which on hydrolysis gave 2.36 g (85%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 2H, ArH), 3.89 (s, 2H, SH), 2.47 (s, 6H, CH_3); HRMS (EI) ($C_8H_{10}S_2$) calcd 170.0224, found 170.0232.

4-Methoxy-1,2-benzenedithiol (57). In a similar manner, **57** was prepared from 1.7 g of the corresponding benzodithiole to give 0.5 g (42%) of the zinc adduct which on hydrolysis gave 0.25 g (69%) of the title comopund as an oil: ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 1H, ArH), 6.92 (d, 1H, ArH), 6.63 (dd, 1H, ArH), 4.03 (s, 1H, SH), 3.78 (s, 3H, OCH_3), 3.39 (s, 1H, SH); HRMS (EI) ($C_7H_8OS_2$) calcd 172.0017, found 172.0018.

4-Fluoro-1,2-benzenedithiol (58). In a similar manner, **58** was prepared from 3.5 g of the corresponding benzodithiole to give 2.04 g (85%) of the zinc adduct which on hydrolysis gave 0.9 g (62%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 7.48 (dd, 1H, ArH), 7.1 (dd, 1H, ArH), 6.79 (dt, 1H, ArH), 4.0 (s, 1H, SH), 3.5 (s, 1H, SH); HRMS (EI) ($C_6H_5S_2F$) calcd 159.9817, found 159.9817.

3-Methyl-1,2-benzenedithiol (59). In a similar manner, **59** was prepared from 5 g of the corresponding benzodithiole to give 3.3 g (98%) of the zinc adduct which on hydrolysis gave 2.2 g (95%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, ArH), 6.92–7.04 (m, 2H, ArH), 3.91 (s, 1H, SH), 3.7 (s, 1H, SH), 2.49 (s, 3H, CH_3); HRMS (EI) ($C_7H_8S_2$) calcd 156.0067, found 156.0066.

4,7-Dimethyl-N-benzyl-1,3,2-benzodithiazole S-Oxide (61). The dithiol **56** was treated with Cl_2, reacted with benzylamine as for compound **39**, and oxidized with mCPBA as above to give **61**: ^{1}H NMR ($CDCl_3$) δ 7.35–7.48 (m, 5H, ArH), 7.13 (d, 1H, ArH), 7.01 (d, 1H, ArH), 4.66 (dd, 2H, N-CH_2-), 2.64 (s, 3H, CH_3), 2.23 (s, 3H, CH_3); MS (DCl/NH_3) m/z 290 (M + 1), 307 (M + 18). Anal. ($C_{15}H_{15}NOS_2$) C, H, N.

5-Methoxy-N-benzyl-1,3,2-benzodithiazole S-Oxide (62). The dithiol **57** was treated with Cl_2, reacted with benzylamine as for compound **39**, and oxidized with mCPBA as above to give a 9:1 mixture of **61** and the 6-methoxy isomer in 55% yield. The isomers were separated by column chromatography on silica gel using 1% methanol in chloroform as the eluant: ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H, ArH), 7.32–7.46 (m, 5H, ArH), 6.81–6.88 (m, 2H, ArH), 4.58 (dd, 2H, N-CH_2-), 3.83 (s, 3H, OCH_3); MS (DCl/NH_3) m/z 292 (M + 1), 309 (M + 18). Anal. ($C_{14}H_{13}NO_2S_2$) C, H, N.

5- and 6-Fluoro-N-benzyl-1,3,2-benzodithiazole S-Oxide (63a,b). The dithiol **58** was treated with Cl_2, reacted with benzylamine as for compound **39**, and oxidized with mCPBA as above to give a 3:1 mixture of **63a** and the 6-fluoro isomer **63b** in 60% yield. The isomers could not be separated after column chromatography on silica gel using chloroform as the eluant. **63a**: ^{1}H NMR ($CDCl_3$) δ 7.81 (dd, 1H, ArH), 7.32–7.46 (m, 5H, ArH), 7.11 (dd, 1H, ArH), 7.02 (dt, 1H, ArH), 4.62 (dd, 2H, N-CH_2-). **63b**: ^{1}H NMR ($CDCl_3$) δ 7.54 (dd, 1H, ArH), 7.32–7.46 (m, 6H, ArH), 7.22 (dt, 1H, ArH), 4.64 (dd, 2H, N-CH_2-). **63**: 3:1, **a:b**; MS (DCl/NH_3) m/z 280 (M + 1), 297 (M + 18). Anal. ($C_{13}H_{10}FNOS_2$) C, N, H.

4- and 7-Methyl-N-benzyl-1,3,2-benzodithiazole S-Oxide (64a,b). The dithiol **59** was treated with Cl_2, reacted with benzylamine as for compound **39**, and oxidized with mCPBA as above to give a 3:2 mixture of **64a** and the 7-methyl isomer **64b** in 54% yield. The mixture was purified by column chromatography on silica gel using chloroform as the eluant, and 15 mg each of the isomer was separated by C-18 reverse-phase semipreparative HPLC (gradient from 40% to 70% water/acetonitrile in 50 min at a rate of 6.5 mL/min and at a detection wavelength of 281 nm). **64a**: ^{1}H NMR ($CDCl_3$) δ 7.68 (t, 1H, ArH), 7.36–7.48 (m, 5H, ArH), 7.24–7.31 (m, 2H, ArH), 4.67 (dd, 2H, N-CH_2-), 2.29 (s, 3H, CH_3); MS (DCl/NH_3) m/z 276 (M + 1), 293 (M + 18). Anal. ($C_{14}H_{13}NOS_2$) C, H, N. **7-Methyl-N-benzyl-1,3,2-benzodithiazole S-oxide (64b)**: ^{1}H NMR ($CDCl_3$) δ 7.36–7.48 (m, 5H, ArH), 7.33 (d, 1H, ArH), 7.22 (d, 1H, ArH), 7.07 (d, 1H, ArH), 4.62 (dd, 2H, N-CH_2-), 2.69 (s, 3H, CH_3); MS (DCl/NH_3) m/z 276 (M + 1), 293 (M + 18). Anal. ($C_{14}H_{13}NOS_2$) C, H, N.

4,5,6,7-Tetrafluoro-N-benzyl-1,3,2-benzodithiazole S-Oxide (65). The dithiol 3,4,5,6-tetrafluoro-1,2-benzenedithiol (**60**)[11] was treated with Cl_2, reacted with benzylamine as for compound **39**, and oxidized with mCPBA as above to give **65** in 52% yield after chromatography on silica gel using chloroform as the eluant: ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 5H, ArH), 4.61 (dd, 2H, N-CH_2-); MS (DCl/NH_3) m/z 334 (M + 1), 351 (M + 18). Anal. ($C_{13}H_7F_4NOS_2$) C, H, N.

5-Morpholino-4,6,7-trifluoro-N-benzyl-1,3,2-benzodithiazole S-Oxide (66). A mixture of **65** (78 mg, 0.23 mmol), morpholine (24 mg, 0.27 mmol), and 3 mL of pyridine was heated at 60 °C for 18 h. The solvent was evaporated, and the residual oil was purified by column chromatography on silica gel eluting with chloroform to give **66** in 77% yield: ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 5H, ArH), 4.55 (dd, 2H, N-CH_2-), 3.8 (t, 4H, morpholine), 3.3 (m, 4H, morpholine); MS (DCl/NH_3) m/z 401 (M + 1), 418 (M + 18). Anal. ($C_{17}H_{15}F_3N_2O_2S_2$) C, H, N.

Antifungal Activity. Minimum inhibitory concentrations (MIC) were determined by microtiter broth dilution testing in yeast nitrogen base (Difco) containing 0.05% glucose.[16] Frozen spore suspensions of filementous fungi or growth from an overnight plate culture (yeast) were prepared in YNBG, and wells were inoculated to a final concentration of 5×10^4 cfu/mL. Plates were incubated at 35 °C for 24–48 h and the MIC's defined as the lowest concentration of drug completely inhibiting visible growth.

Metabolism Study. Compound **40**, radiolabeled with ^{14}C in the benzylic position,[17] was used to study the metabolism of the 1,3,2-benzodithiozole *S*-oxides in rats. For dosing, **40-^{14}C** was mixed with unlabeled **40** and prepared as a 5 mg/mL solution in a mixture of ethanol, propyleneglycol, and saline (20:35:45, v/v/v). A 5 mg/kg dose of **40-^{14}C** was administered to two male and three female rats by intravenous injection, with each rat receiving ~15 μCi of ^{14}C. Thirty minutes following administration, one male and two female rats were anesthetized with CO_2 and exsanguinated by cardiac puncture. Plasma was obtained from the heparinized whole blood by centrifugation at 4 °C for 15 min. Urine and feces excreted by the remaining two rats were collected daily for 3 days following drug administration.

Duplicate aliquots of plasma and urine samples were radioassayed by liquid scintillation counting in Insta-Gel (Packard) liquid scintillation fluid. Fecal samples were homogenized in water, and duplicate aliquots of the homogenate were placed in Combusto-Cones (Packard) containing cellulose powder (Whatman) and burned in a Packard Tri-Carb Model 307 sample oxidizer. Resulting $^{14}CO_2$ was trapped in Carbo-Sorb and radioassayed in Permafluor V (Packard) liquid scintillation fluid. All liquid scintillation samples were counted in a Packard Tri-Carb Model 2500 liquid scintillation spectrometer and corrected for quenching with an automatic external standardization technique.

Metabolic profiles of plasma and urine samples were obtained by HPLC analysis using a 4- × 125-mm, 5-μm LiChrospher 100 RP-18 column. Components of interest were eluted using a 35-min, stepwise linear gradient from 100% 0.05 M ammonium acetate to 100% acetonitrile at a flow rate of 1 mL/min. Eluate from the column was monitored by UV detection at 260 nm and radioactive flow detection in series.

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References

(1) Bodey, G. P. Candidiasis in cancer patients. *Am. J. Med.* **1984**, *77*, 13–19.
(2) Chandler, F. Pathology of the mycoses in patients with acquired immunodeficiency sydrome (AIDS). In *Current Topics in Medical Mycology*; McGinnis, M. R., Ed.; Springer-Verlag: New York, 1985; pp 1–23. Polak, A.; Hartman, P. G. Antifungal Chemotherapy—Are we winning? *Prog. Drug Res.* **1991**, *37*, 181–269. Maggon, K. K.; Slee, A. M.; Demos, C. H. Development of Antifungal Agents by the Pharmaceutical Industry. *Drugs Today* **1991**, *27*, 317–330.
(3) Barriere, S. L. Pharmacology and Pharmacokinetics of Traditional Systemic Antifungal Agents. *Pharmacotherapy* **1990**, *10* (Suppl.), 134S–140S. Warnock, D. W. Amphotericin B: an introduction. *J. Antimicrob. Chemother.* **1991**, *28* (Suppl. B), 27–38. Hammond, S. M. Biological activity of polyene macrolide antibiotics. *Prog. Med. Chem.* **1977**, *14*, 105–179. Haber, R. W.; Joseph, M. Neurological manifestations after amphotericin B therapy. *Br. Med. J.* **1962**, *1*, 230–231.
(4) Sud, I. J.; Feingold, D. S. Heterogeneity of Action Mechanisms Among Antimycotic Imidazoles. *Antimicrob. Agents Chemother.* **1981**, *20*, 71–74. Hughes, C. E.; Bennett, R. L.; Tuna, I. C.; Beggs, W. H. Activities of Fluconazole (UK 49,858) and Ketoconazole against Ketoconazole-Susceptible and -Resistant *Candida albicans*. *Antimicrob. Agents Chemother.* **1988**, *32*, 209–212.
(5) Vicini, P.; Mazza, P. Biological Studies on 1,2-Benzoisothiazole Derivatives. *Farmaco* **1989**, *44*, 511–517. Poni, R.; Vitali, T.; Amoretti, L.; Mossini, F. Preparazione Ed Attivita Antifungma Di bis(2-Carbossiamidofenil)disolfuri E Di 1,2-Benzoisotiazolin-3-oni. (Preparation and Antifungal Activity of Bis(2-carboxamidophenyl)disulfides and 1,2-Benzoisothiazolin-3-ones.) *Farmaco* **1967**, *22*, 935–946.
(6) Preliminary presentation of this work: Abstract MEDI 0061, ACS Meeting, San Francisco, April 1992.
(7) Chen, C. H.; Donatelli, B. A. Synthesis of 5-Methyl-1,3,2-Benzodithiazoles. *J. Heterocycl. Chem.* **1979**, *16*, 183–185.
(8) Davis, F. A. Chemistry of the Sulfur-Nitrogen Bond in Sulfenamides. *Int. J. Sulfur Chem.* **1973**, *8*, 71–81.
(9) TLC analysis of an unequal mix of the components following an attempted separation by preparative TLC showed that after 15 min in ether/hexane solvents the ratio changed to 1:1.
(10) Available from Aldrich Co., Milwaukee, WI.
(11) Bock, H.; Rittmeyer, P. Zur Darstellung von Benzodithiet-Derivaten Durch Thermolyse 1,2-Dithio-Substituierter Benzole. (Gas Phase Reactions. 67. Preparation of Benzodithiete Derivatives by Thermolysis of 1,2-Dithio-substituted Benzenes.) *Phosphorus Sulfur Relat. Elem.* **1988**, *35*, 291–307.
(12) Yeung, C. M.; Klein, L. L. Cyclization of Aromatic Dithioic Esters: Synthesis of 1,3-Benzodithioles. *Tetrahedron Lett.* **1990**, *31*, 2121–2124.
(13) Clark, R. E. D. o-Dithiols in Analysis. *Analyst* **1958**, *83*, 396–402.
(14) Mukaiyama, T.; Taguchi, T. A Convenient Method for the Preparation of Primary Alkylamines by the Use of Bisbenzenesulfenimide. *Tetrahedron Lett.* **1970**, *39*, 3411–3414.
(15) Unpublished data from Dr. Jeffrey Alder, D-47T, Abbott Laboratories.
(16) Shadomy, S.; Pfaller, M. A. Laboratory studies with antifungal agents: susceptibility tests and quantitation in body fluids. In *Manual of Clinical Microbiology*, 5th ed.; Balows, A., et al., Eds.; American Society for Microbiology: Washington, DC, 1991; pp 1173–1183.
(17) The radiolabeled **40** was prepared via the transamidation route by reacting Ph-*CH_2-NH_2 with the propyl analog **13**. Our thanks to J. Uchic and S. Thomas in the radiolabeling lab.