AD-A165 839 SYNTHESIS OF AMINO DERIVATIVES OF DITHIO ACIDS AS POTENTIAL RADIATION PROTECTIVE AGENTS(U) MASSACHUSETTS COLL OF PHARMACY BOSTON W O FOYE MAR 85 1/1

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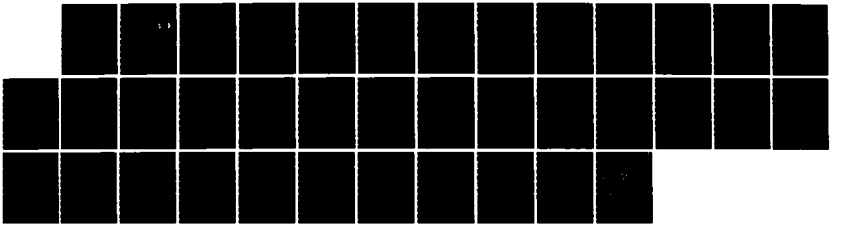

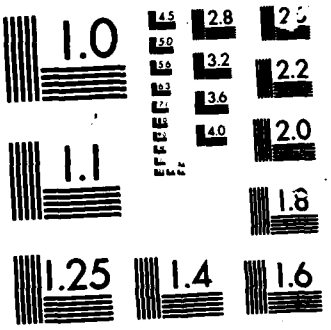

MICROCOPY RESOLUTION TEST CHART

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Synthesis of Amino Derivatives of Dithio Acids as Potential Radiation Protective Agents

Final Report

William O. Foye, Ph.D.

March 1985

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07	03		
07	05		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Good radiation-protective properties (>50% survival of irradiated mice) were found in a series of N-methylquinolinium-2-dithioacetic acid derivatives at exceptionally low dosage levels (2-10 mg/kg). The most effective compounds were the [bis(2-methylthio)-vinyl]- and [2-methylthio amino]-vinyl-N-methylquinolinium iodides, which apparently are not active as H atom transfer agents. Addition of longer chain amino functions, containing hydroxy, alkoxy, or additional amino groups did not improve activity. Similar activities were found in a series of N-methylpyridinium-2-dithioacetic acid derivatives, the most active being the 2-methylthio piperidino compound. Further modification of both the methylthio and amino functions to increase lipophilicity did not improve protective activity. No activity was found with a couple of aminocyclopentenedithio acids, but moderate protective activity was found in a series of 3-amino-2-aryldithiopropenoates. No activity was found in the 4-aryl-dithiole-3-thione precursors, known to raise glutathione levels in cells. Reduction to the 3-amino-2-phenylpropanedithio acid bis(methyl) esters

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19.

gave an inactive compound in the one example tested. Preparation of a copper complex of N-methyl-2-bis(2-methylthio)vinylquinolinium iodide gave a compound having only a little less activity than the uncomplexed compound, indicating that the bis(methylthio) and methylthio amino derivatives of the quinolinium and pyridinium dithioacetic acids may be acting as copper complexes.

Summary

Based on the premise that dithio acids should act more effectively as hydrogen atom transfer agents than the aminoalkanethiols, to repair oxidized lesions of DNA or other cellular substances, the synthesis of amino-containing dithio acids was attempted. Both aromatic and aliphatic amino dithio acids and esters have been prepared. Compounds that were obtained include the following:

1-Methylquinolinium-2-dithioacetic acids

1-Methyl-2-bis(2-methylthio)vinylquinolinium iodides

1-Methyl-2-(2-amino-2-methylthio)vinylquinolinium iodides

1-Methyl-2-bis(2-methylthio)vinylpyridinium iodides

1-Methyl-2-(2-amino-2-methylthio)vinylpyridinium iodides

Copper complexes of 1-methyl-2-bis(2-methylthio)vinylquinolinium iodides and 1-methyl-2-(2-amino-2-methylthio)vinylquinolinium iodides

Aminocyclopentenedithio acids

3-Amino-2-phenyldithiopropenoate esters

3-Amino-2-phenyl-bis(methylthio)-1-propenes

3-Heterocyclicamino-2-phenyldithiopropenoate esters

Good radiation-protective properties (>50% survival of irradiated mice vs. 1000 rads) were found in both the quinolinium and pyridinium dithioacetic acid derivatives. The most effective compound in each series was the 2-methylthio-2-piperidino derivative. These compounds were active at much lower dosage levels (2-10 mg/kg) than either the dithioacid zwitterions or the aminoalkanethiols. Only fair activity (25-50%) was found for the aliphatic amino dithio acids. The copper complex of 1-methyl-2-bis(2-methylthio)vinylquinolinium

iodide gave only a little less protection than the uncomplexed compound, suggesting that the bis(methylthio) and methylthio amino derivatives may be acting as copper complexes and not by H atom transfer.

Table of Contents

Quinolinium-2-dithioacetic Acid Derivatives

Appreciable radioprotective properties were found with several N-methylquinolinium-2-dithioacetic acid derivatives (I-III), previously prepared (1-4). Modifications of the dithio acid function were accordingly made both in the heterocyclic ring and in the nature of the amine moiety in III. The quinolinium ring was substituted in the 6-position by a methoxy group, and a sizeable number of derivatives of the N-methylpyridine dithioacetic acid analog were also prepared. Modification of the amine function in both the quinoline and pyridine series included the introduction of both cyclic and open chain amines and the incorporation of additional amino, hydroxy and alkoxy groups. The methylthio function was also converted to the ethylthio group to check the possibility that a methylation reaction may be involved in radiation protection. The compounds synthesized are listed in Table I. The method of preparation is shown in the following scheme.

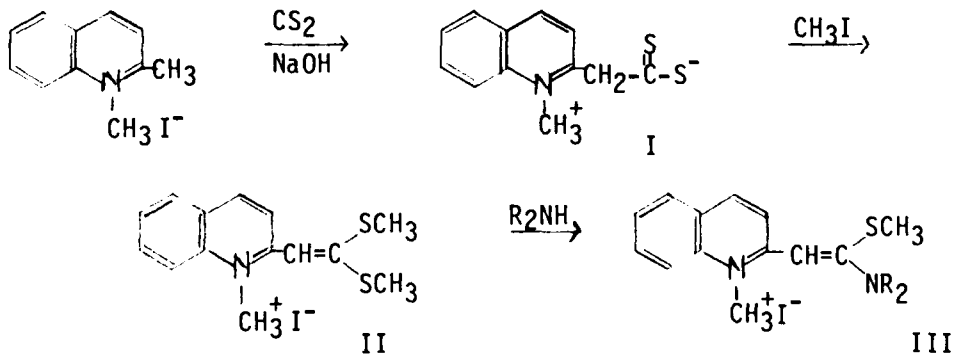
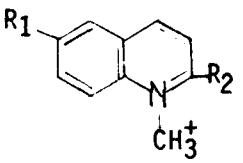
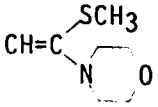
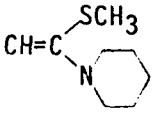
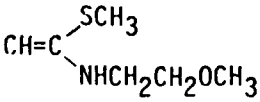
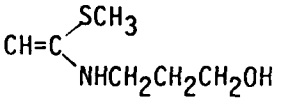
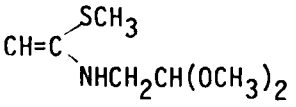
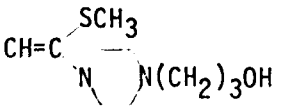
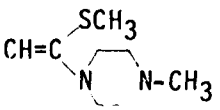


Table I. 1-Methylquinolinium-2-dithioacetic Acid Derivatives[a]

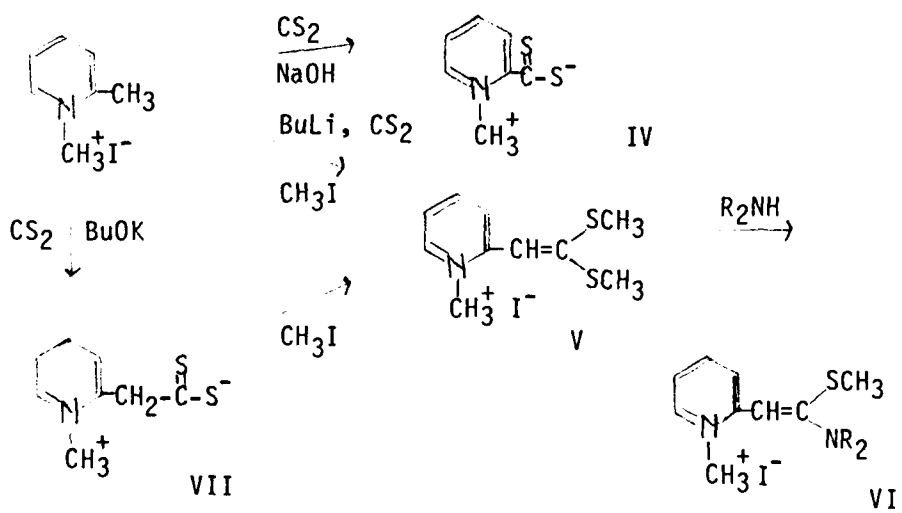


R_1	R_2	M.p.	Formula	Code No.	BN	Ref.
CH_3	$CH_2CS_2^-$	196-197°	$C_{13}H_{13}NS_2$	RWJ-I-7	BK63818	4
H	$CH{=}C(SCH_3)_2$	198-201°	$C_{14}H_{16}INS_2$	JK-B-62	BK63836	1
CH_3		200-201°	$C_{18}H_{23}IN_2OS$	JK-D-8-3	BK63827	2
H		195-196°	$C_{18}H_{23}IN_2S$	YHK-I-3	BK63845	3
H		143-145°	$C_{16}H_{20}IN_2OS$	BA-202	BK75256	12
H	$CH{=}C[NHCH_2CH_2N(CH_3)_2]_2$	148-150°	$C_{20}H_{32}IN_5$	BA-201	BK84308	12
H		135-138°	$C_{16}H_{21}IN_2OS$	BA-203	BK84282	12
CH_3O	$CH{=}C(SCH_3)_2$	212-214°	$C_{15}H_{18}INOS_2$	RWJ-II-46	BK94500	12
H		142-143°	$C_{17}H_{23}IN_2O_2S$	BA-206	BK98455	13
H		173-174°	$C_{20}H_{28}IN_3OS$	RWJ-IV-6	BL05688	13
H		125-126°	$C_{18}H_{24}IN_3S$	RWJ-III-54		3
	2-Methylisoquinolinium-1-dithioacetic Acid Derivative					
H	$CH{=}C(SCH_3)_2$	204-205°	$C_{14}H_{16}INS_2$	PG-28	BK95990	13

a. Elemental analyses are within 0.5% of theoretical values.

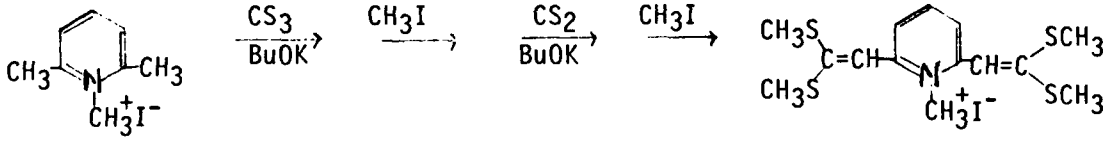
Pyridinium-2-dithioacetic Acid Derivatives

The same procedure that was successful for the preparation of the N-methylquinolinium-2-dithioacetic acid derivatives did not work for the corresponding pyridine derivatives. Aqueous alkali resulted in the replacement of the 2-methyl function to give the pyrdinium 2-dithiocarboxylic acid (IV)(4). One example of this type of compound was previously found to provide no radiation protection. With the use of butyl lithium as base, however, the bis(methylthio) derivative of the dithioacetic acid (V) was obtained. Further conversion of the bis(methylthio) derivatives to the methylthio amino derivatives (VI) took place as usual, however. Use of t-butoxide as base for the condensation of carbon disulfide with N-methylpicolinium iodide did give a dithioacetic acid derivative (VII), which was converted to the bis(methylthio) derivative (V) with methyl iodide. These reactions are shown in the following scheme.



Further modification of these derivatives was made to increase the lipophilicity of both the bis(methylthio) and methylthio amino derivatives. The thiomethyl functions were replaced by thioethyl, thiobutyl, and thiohexyl groups, and the amine functions included both cyclic and open chain amines, with the inclusion of additional amino and alkoxy functions.

One derivative having two of the bis(methylthio) functions (VIII) was prepared (4), since lutidine has two active methyls. Methyl groups in the 4-position of both N-methylquinolinium iodide and N-methylpyridinium iodide were not found sufficiently active for condensation with carbon disulfide using the available bases. The use of a two step procedure, using t-butoxide as base, provided a more complete conversion to the bis(methylthio) compound VIII.



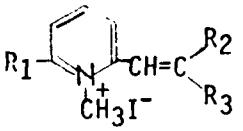
VIII

The pyridinium dithioacetic acid derivatives prepared are listed in Table II.

Aminocyclopentenedithio Acids

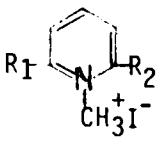
A convenient method for obtaining compounds having a dithio acid function located two carbons from an amino function was found in the condensation of carbon disulfide and ammonia with cyclopentanone (5). The resulting ammonium salt (IX) was obtained in poor yield and attempts at recrystallization resulted in decomposition. Conversion to the zwitterion (X) and the morpholinium salt (XI) gave more stable products, which were submitted for screening. Testing data for XI revealed no protection to mice vs. 1000 rad. The method of synthesis is shown in the following scheme.

Table II. 1-Methylpyridinium-2-dithioacetic Acid Derivatives[a]



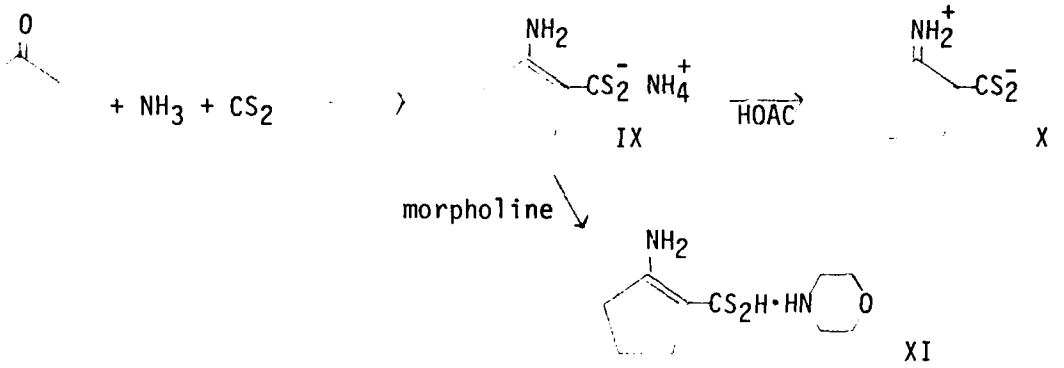
R_1	R_2	R_3	M.p.	Formula	Code No.	BN	Ref.
H	SCH_3	SCH_3	134-135°	$C_{10}H_{14}INS_2$	PG-7	BK95954	13
CH_3	SCH_3	SCH_3	165-166°	$C_{11}H_{16}INS_2$	PG-14	BK95972	13
H	SC_2H_5	SC_2H_5	143-145°	$C_{12}H_{18}INS_2$	PG-21	BK95981	13
H	SCH_3	N⟨⟩	143-144°	$C_{14}H_{21}IN_2S$	BA-401	BK96004	13
H	SCH_3	N⟨⟩O	154-157°	$C_{13}H_{19}IN_2OS$	BA-402	BK96013	13
H	SC_4H_9	SC_4H_9	105-106°	$C_{16}H_{26}INS_2$	PG-23	BK98482	13
H	SC_6H_{13}	SC_6H_{13}	86-88°	$C_{20}H_{34}INS_2$	PG-25	BK98473	13
H	SCH_3	N⟨⟩N-CH_3	173-174°	$C_{14}H_{22}IN_3S$	BA-403	BK98464	13
H	SCH_3	N⟨⟩-C_6H_5	189-190°	$C_{20}H_{25}IN_2S$	BA-II-65	BL01475	13

1-Methylpyridinium-2,6-bis(dithioacetic acid) Derivatives



R_1	R_2					
$^-S_2CCH_2$	$CH_2CS_2^-Na^+$	232-236°	$C_{10}H_{10}NNaS_4$	RWJ-I-54	BK71847	12
$(CH_3S)_2C{=}CH$	$CH{=}C(SCH_3)_2$	205-206°	$C_{14}H_{20}INS_4$	PG-18	BK95963	13

a. Elemental analyses are within 0.5% of theoretical values.



Compound XI showed a strong peak for SH absorption in the infrared spectrum at 2500 cm^{-1}, so it is believed to exist mainly as the free acid hydrogen-bonded to morpholine. The imino dithio acid X, however, gave no peak for SH absorption, so is considered to exist mainly as the zwitterionic immonium dithio acid. The compounds prepared in this series are listed in Table III.

3-Amino-2-aryldithiopropenoates

The preparation of several 3-dialkylamino-2-aryldithiopropenoates (XIV) from 1,2-dithiole-3-thiones has been reported (6). This reaction has been utilized to prepare both primary and secondary amine derivatives of the 2-aryldithiopropenoate ester resulting from ring opening of the 1,2-dithiole-4-phenyl-3-thione on reaction with amines.

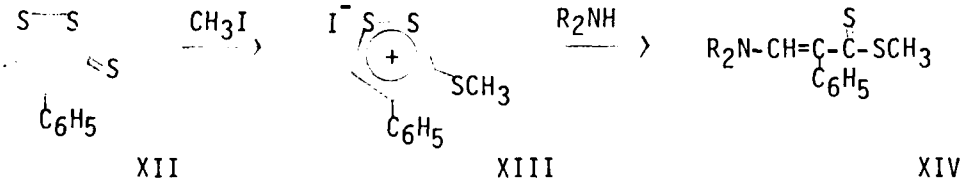
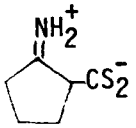
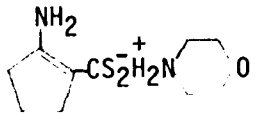


Table III. Aminocyclopentenedithio Acids[a]

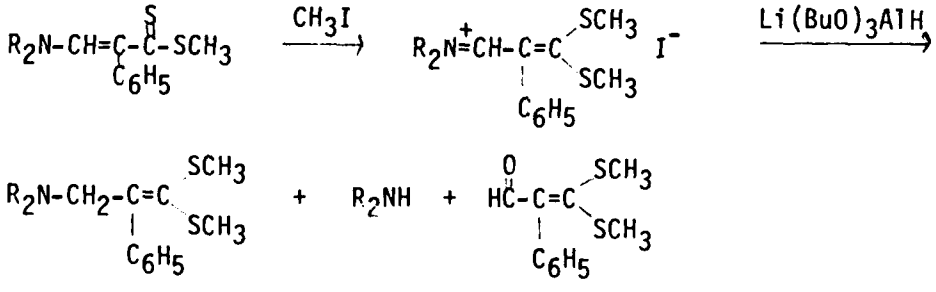
Compound	M.p.	Formula	Code No.	BN	Ref.
	98-99°	$C_6H_9NS_2$	RWJ-I-39	BK70466	12
	154-155°	$C_{10}H_{18}N_2OS_2$	RWJ-I-66	BK73074	12

a. Elemental analyses are within 0.5% of theoretical values.

The amine adduct from ammonia (R=H) was too unstable for testing, but primary amino derivatives where R=CH_3 and cyclohexyl have been isolated. Secondary amine adducts gave stable products, and a product was also isolated using N-aminomorpholine. The use of guanidine and alkyl-substituted guanidines did not produce characterizable compounds.

Precursors XII and XIII were submitted for screening, along with several of the amino derivatives XIV, since aryl dithiole-3-thiones have been found to raise glutathione levels in animal cells (5). Increased glutathione levels have been shown to provide protection in mice against hepatotoxic agents, and have been postulated to be of value in radiation protection (7). It is possible that the dithiole-3-thiones may act in vivo as the amine adducts, since they form under mild conditions.

A method of reducing the 3-amino-2-phenyldithiopropenoate esters was found in the use of $Li(t\text{-}BuO)_3AlH$. The reduction is carried out on the bis-(methylthio) derivative of the propenedithio acid and gives the 3-amino-2-phenylpropanedithio acid as the bis(methylthio) derivative XV, along with an aldehyde derivative (XVI).



XV XVI

Repeated chromatography on silica has given an analytically pure sample of XV

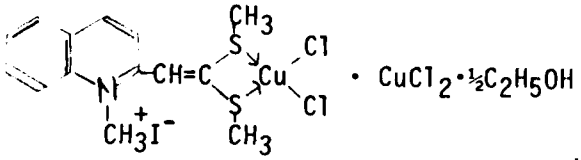
where R_2N = morpholine.

Antiradiation testing of one of the 3-amino-2-phenyldithiopropenoate esters, the methylamino derivative, gave 40% survival of mice vs. 1000 rad.

The 1,2-dithiole-4-phenyl-3-thiones synthesized in this series are listed in Table IV, and the 3-amino-2-phenyldithiopropenoate esters are listed in Table V.

Copper Complexes of the N-Methylquinolinium-2-dithioacetic Acid Derivatives

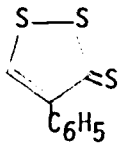
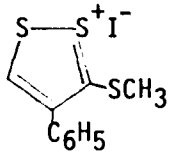
Dithio acids and derivatives are potentially strong complexing agents for copper ion, and as copper complexes, they may have the ability to act as mimics of superoxide dismutase, a copper-containing enzyme. A relatively simple copper complex, of 3,5-diisopropylsalicylic acid, has been shown to catalyze the disproportionation of superoxide (8), and was later found to have some radiation-protective activity (9). To test this possibility, several copper (II) complexes of the N-methylquinolinium dithioacetic acid derivatives were prepared and characterized. One of them was submitted for screening. The following structure XVII was proposed, based on infrared and elemental analysis.



XVII

One of the methylthio amino derivatives gave essentially the same copper complex. A log Ks value of 13.66 for the formation constant of XVII indicates

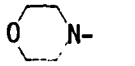
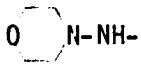
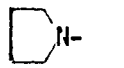
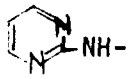
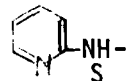
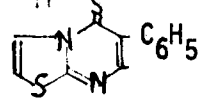
Table IV. 1,2-Dithiole-4-phenyl-3-thiones[a]

Compound	M.p.	Formula	Code No.	BN	Ref.
	121-123°	$C_9H_6S_3$	RWJ-I-47	BK75247	11
	177-178°	$C_{10}H_9IS_3$	RWJ-I-55	BK75238	12

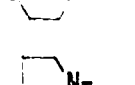
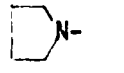
a. Elemental analyses are within 0.5% of theoretical values.

Table V. 3-Amino-2-phenyldithiopropenoates[a]

$R_2N-CH=C(C_6H_5)-C(=S)-SCH_3$

R_2N	M.p.	Formula	Code No.	BN	Ref.
CH_3NH-	134-136°	$C_{11}H_{13}NS_2$	RWJ-I-57	BK73065	12
$(CH_3)_2N-$	149-151°	$C_{12}H_{15}NS_2$	RWJ-II-13	BK85556	6
	120-126°	$C_{14}H_{17}NOS_2$	RWJ-II-6	BK75229	12
	135-136.5°	$C_{14}H_{18}N_2OS_2$	RWJ-III-36	BL01466	13
	145-149°	$C_{14}H_{17}NS_2$	PG-9	BL09088	13
	134-139°	$C_{14}H_{13}N_3S_2$	PG-10	BL09079	13
	170-175°	$C_{15}H_{14}N_2S_2$	PG-11	BL09097	13
	152-154°	$C_{12}H_8N_2S_2$	PG-12	BL09104	13

$R_2N-CH_2-C(C_6H_5)=C(SCH_3)_2$

	oil	$C_{15}H_{21}NOS_2$	RWJ-III-70	BL05697	13
	oil	$C_{15}H_{21}NS_2$	PG-13	BL09113	13
	98-100°	$C_{14}H_{15}N_3S_2$	PG-15	BL09122	13

a. Elemental analyses are within 0.5% of theoretical values.

that this complex is capable of existence under cellular conditions (10). The copper complexes prepared are listed in Table VI.

Discussion

With the assumption that dithio acids should theoretically perform more effectively as H atom transfer agents, to repair oxidized lesions of macromolecules resulting from ionizing radiation, than the aminoalkanethiols, the synthesis of amino-containing dithio acids was attempted. Compounds of this type that were obtained include the following:

N-Methylquinolinium-2-dithioacetic acids

2-Bis-(2-methylthio)vinyl-1-methylquinolinium iodides

2-(2-Amino-2-methylthio)vinyl-1-methylquinolinium iodides

2-Bis-(2-methylthio)vinyl-1-methylpyridinium iodides

2-(2-Amino-2-methylthio)vinyl-1-methylpyridinium iodides

Copper complexes of 2-bis-(2-methylthio)vinyl-1-methylquinolinium iodides

Copper complex of a 2-(2-amino-2-methylthio)vinyl-1-methylquinolinium iodide

Aminocyclopentenedithio acids

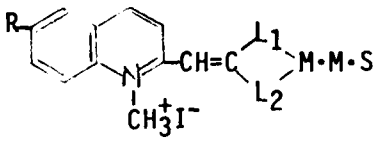
3-Amino-2-phenyldithiopropenoate esters

3-Amino-2-phenyl-bis(methylthio)-1-propenes

3-Heterocyclicamino-2-phenyldithiopropenoate esters

Radiation-protective activities have been received for only a few of the compounds submitted. In the series of N-methylquinolinium dithioacetic acids and derivatives, the bis(methylthio) and methylthio amino derivatives proved to be more protective vs. 1000 rad. in mice than the dithio acids. These two derivatives were also protective at exceptionally low dosage levels, e.g., less

Table VI. Copper Complexes of 1-Methylquinolinium-2-dithioacetic Acid Derivatives[a]



R	L_1	L_2	M	S	Formula	Code No.	BN	Ref.
H	SCH_3	SCH_3	$CuCl_2$	$\frac{1}{2}C_2H_5OH$	$C_{14}H_{16}INS_2 \cdot Cu_2Cl_4 \cdot \frac{1}{2}C_2H_5OH$	SSR-CII2C	BK85565	13
CH_3	SCH_3	SCH_3	$CuCl_2$	$\frac{1}{2}C_2H_5OH$	$C_{15}H_{18}INS_2 \cdot Cu_3Cl_6 \cdot \frac{1}{2}C_2H_5OH$	SSRCIII2C		13
CH_3	SCH_3	N O	$CuCl_2$	C_2H_5OH	$C_{18}H_{23}INS_2 \cdot Cu_3Cl_6 \cdot C_2H_5OH$	SSRCIV2C		13

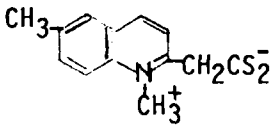
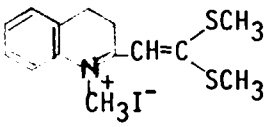
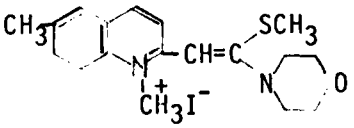
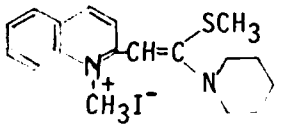
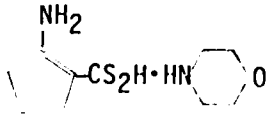
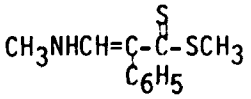
a. Elemental analyses are within 0.5% of theoretical values.

than 10 mg/kg. One of the aminocyclopentenedithio acids was found to give no protection, but one of the 3-amino-2-phenylpropenoate esters gave up to 40% protection. The only pyridinium compound for which testing results have been received, the compound having two bis(methylthio) functions, was inactive.

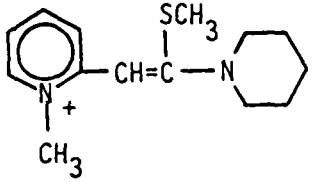
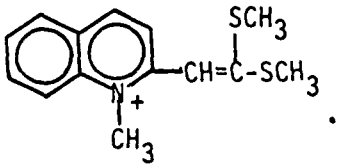
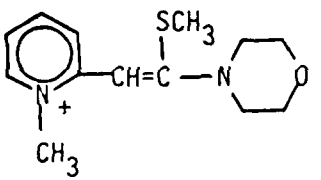
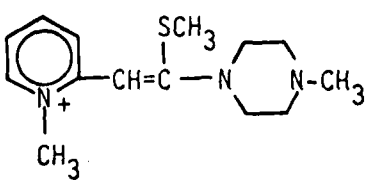
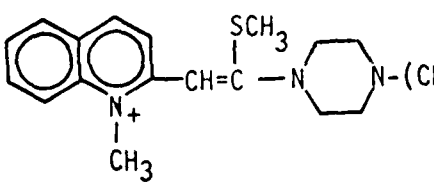
From the very limited amount of testing data received, it is apparent that the bis(methylthio) and methylthio amino derivatives are more active than the dithio acid salts. This suggests that these compounds may be acting either as superoxide dismutase mimics, by complexing copper ion, or by causing increased levels of glutathione in the cells. Radioprotector screening data received are tabulated in Table VII.

Table VII. Radioprotector Screening Data

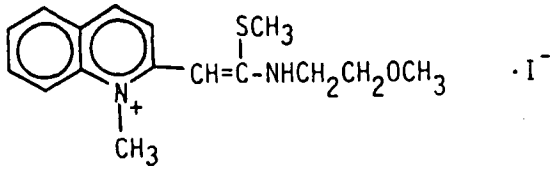
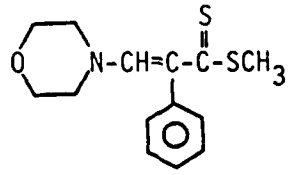
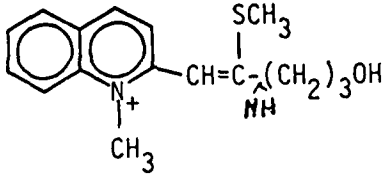
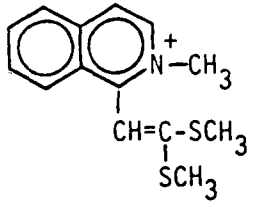
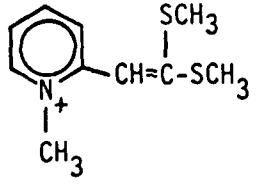
Code Number 0942

Compound	Route	Dose, mg/kg	LD_{50}/10d	Toxic deaths	Per cent survival[a]
	IP	150	~ 225	0/10	10
		75		0/10	20
		37.5		0/10	10
	PO	1200		0/10	0
		600		0/10	0
		300		0/10	0
	IP	150	~ 300	0/10	60
		75		0/10	0
		37.5		0/10	0
	PO	300		1/10	0
		150		2/10	10
		75		0/10	10
	IP	9.38	~ 15	0/10	60
		4.69		0/10	0
		2.34		0/10	0
	PO	75	~ 75	0/ 5	0
		37.5		0/ 5	0
		18.75		0/ 5	0
		9.38		0/ 5	0
	IP	4.69	~ 5	8/10	10
		2.34		0/10	70
		1.17		0/10	30
	PO	18.75		0/10	0
		9.37		0/10	0
		4.69		0/10	0
		2.34		0/10	0
	IP	300	~ 450	0/10	0
		150		0/10	0
		75		0/10	0
	IP	600	> 600	0/10	10
		300		0/10	40
		150		0/10	20

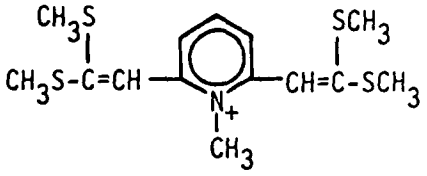
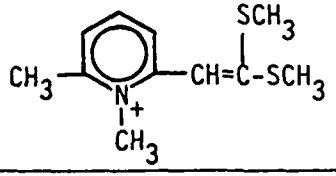
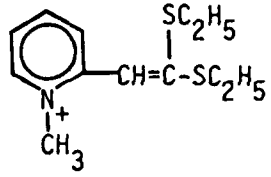
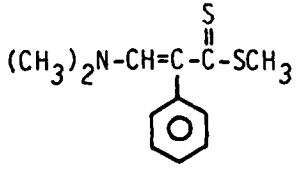
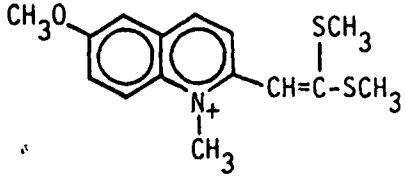
THIO ACIDS

WR		LD_{50} (mg/kg)	ROUTE	DOSE (mg/kg)	% SURVIVAL
252231 (FOYE)	 $\cdot I^-$	25	IP (30 min)	9.4 4.7 2.4 0	80 20 30 0
252485 (FOYE)	 $\cdot I^-$ $\cdot 2CuCl_2 \cdot 1/2 C_2H_5OH$	~25	IP (30 min)	37.5 18.8 9.4 0	40 (3 tox) 10 (5 tox) 20 0
252579 (FOYE)	 $\cdot I^-$	~50	IP (30 min)	18.8 9.4 4.7 0	0 0 0 0
253751 (FOYE)	 $\cdot I^-$	~60	IP (30 min)	18.8 9.4 4.7 0	10 0 0 0
254404 (FOYE)	 $\cdot I^-$	>10	IP (30 min)	9.4 4.7 2.3 0	30 0 0 0

THIO ACIDS

WR		LD_{50} (mg/kg)	ROUTE	DOSE (mg/kg)	% SURVIVAL
252187 (FOYE)		~50	IP (30 min)	37.5 18.8 9.4 0	0 (9 tox) 0 0 0
252188 (FOYE)		>1200	IP (30 min)	1200 600 300 0	0 0 0 0
252222 (FOYE)		~50	IP (30 min)	37.5 18.8 9.4 0	0 0 0 0
252245 (FOYE)		~15	IP (30 min)	9.4 4.7 2.3 0	20 0 0 0
252342 (FOYE)		~30	IP (30 min)	18.8 9.4 4.7 0	50 0 0 0

THIO ACIDS

WR		LD_{50} (mg/kg)	ROUTE	DOSE (mg/kg)	% SURVIVAL
252343 (FOYE)		~25	IP (30 min)	9.4 4.7 2.3 0	30 10 10 0
252344 (FOYE)		~50	IP (30 min)	18.8 9.4 4.7 0	40 (1 tox) 0 0 0
252457 (FOYE)		~20	IP (30 min)	9.4 4.7 0	20 0 0
252484 (FOYE)		>1200	IP (30 min)	1200 600 300 0	0 (3 tox) 20 0 0
253184 (FOYE)		~30	IP (30 min)	9.4 4.7 2.3 0	0 0 0 0

THIO ACIDS

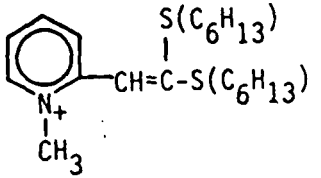
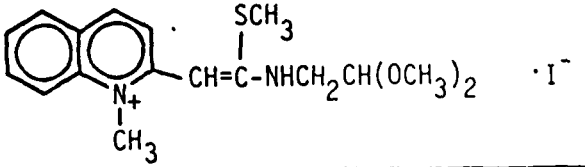
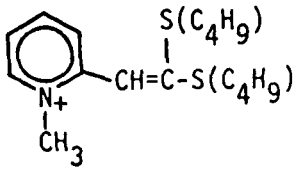
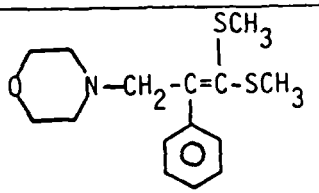
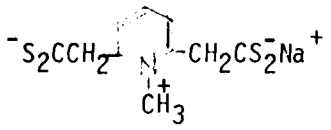
WR		LD_{50} (mg/kg)	ROUTE	DOSE (mg/kg)	% SURVIVAL
253748 (FOYE)		~ 5	IP (30 min)	4.7 2.3 1.2 0	0 (8 tox) 0 (4 tox) 0 0
253749 (FOYE)		~ 30	IP (30 min)	18.8 9.4 4.7 0	30 0 0 0
253750 (FOYE)		~ 3	IP (30 min)	2.3 1.2 0.6 0	30 (3 tox) 10 (1 tox) 0 0
254403 (FOYE)		>1200	IP (30 min)	1200 600 300 0	0 0 0 0

Table VII continued

Compound	Route	Dose, mg/kg	LD_{50}/10d	Toxic deaths	Per cent survival[a]
	IP	1200	> 600	2/10	0
		600		0/10	0
		300		0/10	0
	PO	1200	>1200	0/ 5	0
		600		0/ 5	0
		300		0/ 5	0

a. A radiation dose of 1000 rads was used 30 minutes after dosing. Animals were observed for 30 days to determine survival.

Experimental

1-Methylquinolinium-2-dithioacetic acid derivatives. Procedures for preparation of these compounds are found in refs. 1-4 and the Annual Progress Report dated August 1984. Several derivatives made since that Report follow.

1-Methyl-2-[2-methylthio-2-(2-{bis(methoxy)ethyl}amino)vinyl]-quinolinium iodide. Compound II (4.0g, 0.01 mol) and 1.05g (0.01 mol) of aminoacetaldehyde dimethyl acetal were added to 40 mL of DMSO. The solution was stirred at room temperature for 4 days and mixed with 300 mL of ether, and the ethereal layer was decanted. After the solvent was evaporated, 50 mL of 2-propanol was added and mixed. A solid was filtered and recrystallized from 2-propanol, yielding 2.48 g (58%); mp 142-143°.

IR(KBr); ν 3200 (NH),1610 (C=C).

Anal. Calcd. for $C_{17}H_{23}IN_2O_2S$: C, 45.74; H, 5.19: N, 6.25.

Found: C, 45.32; H, 4.97; N, 5.92.

1-Methyl-2-[2-methylthio-2-(4-{3-hydroxypropyl}-1-piperazinyl)vinyl]-quinolinium iodide. A mixture of 0.5g (1.28 mmol) of II, 0.19g (1.32 mmol) of 1-piperazinepropanol, and 5 mL of DMF was stirred at room temperature for 3 days. After the solvent was evaporated, 5 mL of ethyl acetate was added to the residue, followed by small portions of DMF until the product solidified. This was filtered and washed with ethyl acetate to give 0.40g of green solid; mp 175-178°. Recrystallization from 5 mL of water with charcoal, and then from 5 mL of n-propanol afforded 0.2g (31.2%) of orange powder; mp 175-176.5°.

IR(KBr): ν 3360 (OH), 1610 (C=C).

Calcd. for $C_{20}H_{28}IN_3OS \cdot \frac{1}{2}H_2O$: C, 48.58; H, 5.91; N, 8.50.

Found: C, 48.35; H, 5.67; N, 8.39.

2-Methyl-1-bis(2-methylthio)vinylisoquinolinium iodide. To a suspension of 1,2-dimethylisoquinolinium iodide (2.5g, 8.8 mmol) in toluene (50 mL) was added 1g of K tertiary butoxide and 5-10 drops of 95% ethyl alcohol. The mixture was stirred 20 min, and the clear supernate was decanted. To the residue was added toluene (35 mL), K tertiary butoxide (0.5g), and 95% ethyl alcohol (5-10 drops). The mixture was stirred 20 min, and the clear supernate was decanted. This process was repeated once more. To the combined toluene solutions was added carbon disulfide (3 mL), and the solution was stirred at room temperature 30 min. Methyl iodide (3 mL) was then added, and the mixture was stirred overnight. Toluene was removed in a rotavap at 50-60°, and the residue was crystallized from water, giving 2.4 (70%) of yellow needles, mp 204-205°.

IR(KBr): ν 1630 (C=C), 1155 (CH_2S), 815 (C=C).

^{1}HNMR ($CDCl_3$): δ 2.37 (3H, s, SCH_3), 2.80 (3H, s, SCH_3), 4.63 (3H, s, NCH_3), 7.03 (1H, s, CH=C), 7.80-9.10 (6H, m, arom H).

Anal. Calcd. for $C_{14}H_{16}INS_2$: C, 43.19; H, 4.14; N, 3.59.

Found: C, 43.11; H, 4.15; N, 3.57.

1-Methylpyridinium-2-dithioacetic acid derivatives. Compound VII and 1-methylpyridinium-2,6-bis(dithioacetate) sodium salt are found in the Annual Progress Report dated August, 1984. Preparations for examples of compounds V, VI, and VIII follow.

1-Methyl-2-bis(2-methylthio)vinylpyridinium iodide (V). To a stirring solution of picoline (0.97g, 0.01 mol) in dry THF (20 mL) under N_2 at -5° to -10°C was added n-BuLi (4.4 mL, 2.5 M) in hexane dropwise. To the resulting red solution carbon disulfide (1.2 mL, 0.02 mol) in THF (5 mL) was added

dropwise at -5° to -10°. After the mixture was stirred for 30 min at this temperature, an excess of methyl iodide (4 mL, 0.064 mol) was added. The solution was stirred overnight at room temperature, and filtered. The residue was washed with methylene chloride, and the combined filtrates were concentrated in a rotavap. The residue was taken up in methylene chloride (40 mL) and washed repeatedly with water until the water layer was colorless. The combined washings were concentrated to 10-15 mL in a rotavap at 50-60°. The solution was stored at 0°, and the resulting crystals were filtered and recrystallized from water, giving 1.8g (53%); mp 134-135°.

IR(KBr): ν 1630 (C=C), 1175 (CH_2S), 800 (C=C).

^{1}HNMR ($CDCl_3$): δ 2.57 (3H, s, SCH_3), 2.67 (3H, s, SCH_3), 4.57 (3H, s, NCH_3), 6.53 (1H, s, CH=C), 7.63-9.0 (4H, m, arom H).

Anal. Calcd. for $C_{10}H_{14}INS_2$: C, 35.40; H, 4.16; N, 4.12.

Found: C, 35.26; H, 4.11; N, 4.19.

1,6-Dimethyl-2-bis(2-methylthio)vinylpyridinium iodide. To a suspension of 2,6-dimethylpyridinium methiodide (7.5g, 0.03 mol) in toluene (50 mL) was added K t-butoxide (3.5g) in one portion. The mixture was stirred at room temperature and 95% ethyl alcohol (10-15 drops) was added. The yellow solution was stirred 20 min, and the supernatant solution was decanted. To the residue was added toluene (50 mL), followed by K t-butoxide (1g) and 95% ethyl alcohol (10-15 drops). The mixture was stirred 20 min, and the clear supernate was decanted. This process was repeated three more times using the same amounts of reagents. To the combined toluene solutions was added an excess of carbon disulfide (7.2 mL, 0.12 mol), and the mixture was stirred 30 min. A red solid was filtered, suspended in methylene chloride (100 mL), and methyl iodide

(7.4 mL, 0.12 mol) was added. The mixture was stirred overnight at room temperature, and was filtered. The residue was washed with methylene chloride, and the combined organic layers were evaporated to dryness. The yellow solid was recrystallized from water to give 7.3g (68%) of yellow needles; mp 165-166°.

IR(KBr): ν 1620 (C=C), 1190 (CH_2S), 830 (C=C).

^{1}HNMR ($CDCl_3$): δ 2.53 (3H, s, SCH_3), 2.67 (3H, s, SCH_3), 3.00 (3H, s, CH_3), 4.35 (3H, s, NCH_3), 6.63 (1H, s, CH=C), 7.67-8.41 (3H, m, arom H).

Anal. Calcd. for $C_{11}H_{16}INS_2$: C, 37.40; H, 4.57; N, 3.96.

Found: C, 37.28; H, 4.57; N, 3.89.

1-Methyl-2,6-bis[2-bis-(2-methylthio)vinyl]pyridinium iodide (VIII). The same procedure was repeated on the previous compound, and an 82% yield of yellow crystals was obtained; mp 205-206°.

IR(KBr): ν 1605 (C=C), 1190 (CH_2S), 820 (C=C).

^{1}HNMR ($CDCl_3$): δ 2.53 (6H, s, SCH_3), 2.68 (6H, s, SCH_3), 4.33 (3H, s, NCH_3), 6.55 (2H, brs, CH=C), 7.73-8.33 (3H, m, arom H).

Anal. Calcd. for $C_{14}H_{20}INS_4$: C, 36.75; H, 4.37; N, 3.06.

Found: C, 36.77; H, 4.42; N, 3.00.

1-Methyl-2-bis(2-ethylthio)vinylpyridinium iodide. To a stirred suspension of picolinium methiodide (3.5g, 0.015 mol) in toluene (100 mL) was added K t-butoxide (2g) followed by 95% ethyl alcohol (10-15 drops). The mixture was stirred 20 min, and the clear supernate was decanted. This process was repeated five times using 50 mL of toluene, 0.5g of K t-butoxide, and 5-10 drops of 95% ethyl alcohol. To the combined toluene solutions was added carbon disulfide (5 mL, 0.083 mol), and the mixture was stirred 30 min at room temperature. It was filtered, and the residue was taken up in DMF (20 mL). An excess of

ethyl iodide (6 mL, 0.075 mol) was added, and the mixture was stirred overnight. The solvent was removed in vacuo at 60-70°, and the residue was recrystallized from water, giving 4.2g (77%) of yellow needles; mp 143-145°.

IR(KBr): ν 1620 (C=C), 1165-75 (CH_2S), 800 (C=C).

^{1}HNMR ($CDCl_3$): δ 1.10-1.60 (6H, m, C_2H_5), 2.77-3.43 (4H, m, C_2H_5), 4.50 (3H, s, NCH_3), 6.67 (1H, s, CH=C), 7.63-9.07 (4H, m, arom H).

Anal. Calcd. for $C_{12}H_{18}INS_2$: C, 39.24; H, 4.94; N, 3.81.

Found: C, 39.10; H, 4.87; N, 3.72.

1-Methyl-2-[2-methylthio-2-(N-piperidino)vinyl]pyridinium iodide (VI). 2-Bis(2-methylthio)vinyl-1-methylpyridinium iodide (3.0, 0.009 mol) and 1.53g (0.018 mol) of piperidine were added to DMF (20 mL) and heated at 70° for 2 hr and 50° for 4 days with stirring. After being cooled, the solution was added to 150 mL of ether, and the ethereal layer was decanted. Ethyl acetate (150 mL) was added to the remaining syrup, and after chilling, yellow crystals appeared which were filtered and recrystallized from 1:1 ethanol/2-propanol. The product weighed 2.19g (66%); mp 143-144°.

IR(KBr): ν 1630 (C=C), 1160-70 (CH_2S), 780 (C=C).

^{1}HNMR ($CDCl_3$): δ 1:40-1.70 (6H, m, piperidine), 2.40 (3H, s, SCH_3), 320-3.60 (4H, d, CH_2N), 4.0 (3H, s, NCH_3), 5.2 (1H, s, CH=C), 7.2-8.6 (4H, m, arom H).

Anal. Calcd. for $C_{14}H_{21}IN_2S$: C, 44.92; H, 5.65; N, 7.48.

Found: C, 44.60; H, 5.59; N, 7.32.

1-Aminocyclopentene-2-dithio acids. Procedures for the preparation of these compounds are found in the Annual Progress Report dated August 1984.

Methyl 3-Amino-2-aryldithiopropenoates. Procedures for the preparation of these compounds are found in the Annual Progress Report dated Aug. 1984. The 1,2-dithiole-4-phenyl-3-thione and its methiodide were prepared by E.K. Fields (11). A reduced 1-bis(methylthio)-3-amino-2-phenylpropene and examples of recently prepared derivatives follow.

Methyl 3-pyrrolidino-2-phenyl-2-propenedithiocarboxylate. To a stirred suspension of XIII (5.0g, 0.14 mol) in benzene (150 mL) was added pyrrolidine (2.0g, 0.28 mol) dropwise during 5 min. The red solution was stirred for 0.5 hr at room temperature, and the solid was filtered and washed with benzene. The benzene layer was washed with water (3 x 50 mL), dried, and concentrated. The yellow solid was recrystallized from ethyl acetate-heptane, giving 4.06g; mp 148-149.5°.

^{1}HNMR ($CDCl_3$): δ 1.53-1.97 (4H, m, pyrrolidine), 2.57 (3H, s, SCH_3), 2.76-3.40 (4H, br m, pyrrolidine), 7.33 (5H, s, C_6H_5), 8.73 (1H, s, CH=C).

Anal. Calcd. for $C_{14}H_{17}NS_2$: C, 63.83; H, 6.51; N, 5.32.

Found: C, 64.14; H, 6.57; N, 5.34.

Methyl 3-(N-morpholinylamino)-2-phenyl-2-propenedithiocarboxylate. To a suspension of 1.00g (2.84 mmol) of XIII in 20 mL of benzene was added 0.40 mL (2.87 mmol) of Et_3N and 0.30g (2.94 mmol) of N-aminomorpholine. The mixture was stirred 45 min at room temperature and filtered; the residue was washed with benzene. Evaporation of the combined filtrates gave 1.02g of an orange solid which was chromatographed on silica and recrystallized from benzene-hexane, giving 0.37g (44%) of brown crystals, mp 132-135°.

IR (KBr): ν 1605 (C=C), 955 (C=S).

^{1}HNMR ($CDCl_3$): δ 2.47 (3H, s, SCH_3), 2.77-3.00 (4H, m, $N(CH_2)_2$), 3.53-3.80 (4H, m, $O(CH_2)_2$), 7.03-7.33 (6H, m, C_6H_5 + CH=C), 13.05 (1H, NH, J=11 Hz).

Anal. Calcd. for $C_{14}H_{18}N_2OS_2$: C, 57.11; H, 6.16; N, 9.51.

Found: C, 57.23; H, 6.19; N, 9.41.

1-Bis(methylthio)-3-(1-morpholinyl)-2-phenylpropene (XV). To a stirred solution of 1.00g (2.37 mmol) of 1,1-bis(methylthio)-3-(1-morpholinylidene)-2-phenyl-1-propene in 20 mL of methylene chloride was added a solution of 0.61g (2.40 mmol) of $Li(t\text{-}BuO)_3AlH$ in 24 mL of dry THF over 20 min. Evaporation of the solvents after 18 hrs of stirring at room temperature gave an orange paste. This was taken up in 50 mL of 1N HCl and extracted with three 20-mL portions of ethyl acetate (discarded). The aqueous phase was made alkaline with 50% KOH solution and extracted with two 20-mL portions of ethyl acetate. Drying (Na_2SO_4), filtering, and evaporating the combined extracts provided 0.44gof a clear yellow oil. Chromatography on silica afforded 0.08g of aldehyde XVI and 0.34g (48.6%) of XV, as a yellow oil.

IR (neat): ν 1590 (C=C), 1110 (CH_2O).

^{1}HNMR ($CDCl_3$): δ 2.18 (3H, s, SCH_3), 2.22-2.53 (7H, m, SCH_3 + N $(CH_2)_2$), 3.40-3.67 (6H, m, $O(CH_2)_2$ + NCH_2), 7.25 (5H, s, C_6H_5).

Anal. Calcd. for $C_{15}H_{21}NOS_2$: C, 60.98; H, 7.16; N, 4.74.

Found: C, 60.76; H, 7.12; N, 4.73.

Copper complex of 2-bis(2-methylthio)vinyl-1-methylquinolinium iodide (XVII). A mixture of 3.5g (8.99 mmol) of II in 150 ml of 95% ethyl alcohol was warmed gently with stirring until the solid dissolved, and the solution was allowed to stand at 30°. Anhydrous $CuCl_2$ (2.41g, 18 mmol) in 95% ethyl alcohol was slowly added dropwise with continuous stirring. A brown precipitate formed at once, and the mixture was stirred overnight. The precipitate was filtered and washed with small amounts of absolute ethanol, water, and ether. It was dried in a desiccator to give 2.66g (43.5%) of brown solid; mp >300°.

IR (KBr): ν 575,500 (Cu-S), 405 (Cu-Cl).

^{1}HNMR (DMSO-d_6): δ 2.50 (3H, s, SCH_3), 2.70 (3H, s, SCH_3), 4.40 (3H, s, NCH_3), 6.75 (1H, s, CH=C), 8.0-8.6 (6H, m, arom H).

Anal. Calcd. for $C_{14}H_{16}INS_2 \cdot 2\ CuCl_2 \cdot \frac{1}{2}C_2H_5OH$: C, 26.45; H, 2.81; N, 2.06; S, 9.41.

Found: C, 26.53; H, 2.55; N, 2.15; S, 9.13.

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