AD_____

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

Annual Report

William O. Foye, Ph.D.

August 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3108

Massachusetts College of Pharmacy
and Allied Health Sciences
179 Longwood Avenue
Boston, Massachusetts 02115

DOD DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents

AD A 165798

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Massachusetts College of Pharmacy and Allied Health Sciences 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) 179 Longwood Avenue Boston, Massachusetts 02115	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-83-C-3108
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 62734A; PROJECT NO. 3M1-62734A875; TASK NO. AK; WORK UNIT ACCESSION N 094

11. TITLE (Include Security Classification)
Synthesis of Amino Derivatives of Dithio Acids as Potential Radiation Protective Agents

12. PERSONAL AUTHOR(S)
William O. Foye, Ph.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual Report	FROM 83/3/15 TO 83/8/31	1983 August	

16. SUPPLEMENTARY NOTATION

17 COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Radiation-protective compounds, dithio acid derivatives, aminopropenedithio acid esters, copper complex of bis-(methylthio) compound
07	03		
07	05		

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

The synthesis of several N-methylquinolinium-2-dithioacetic acid derivatives has been accomplished, and the compounds were submitted for radiation-protective screening. These included the zwitterion of the dithio acid, the bis(methylthio) derivative, and the methylthio N-morpholino and methylthio N-piperidino derivatives. Two of the compounds had 6-methyl substituents. Various attempts to prepare aliphatic amino dithio acid esters were made, including the reaction of an imino thio ester with H_2S, the reaction of an aldehyde with morpholine and sulfur, and the reaction of a protected thiol ester with Lawesson's reagent. None of these procedures gave pure, identifiable products.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Mrs. Virginia Miller	301/663-7325	SGRD-RMS

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE

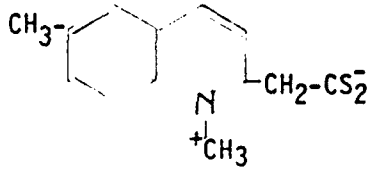
Summary

Dithio acids should be more effective agents for hydrogen atom transfer to effect repair of radiation-damaged DNA or other cellular substance than thiols since the pH for maximum rate of transfer for dithio acids (pH 4-6) is closer to cellular pH than the pH for maximum rate of H transfer from thiols (pH 10-11). Attempts to prepare dithio acids containing amino substituents included first the condensation of carbon disulfide with the active methyl of N-methylquinaldines. The resulting dithioacetic acid zwitterions were converted to the bis(methylthio) derivatives and methylthio amino derivatives to provide compounds with better solubility properties. Other attempts to prepare aliphatic dithio acids with amino substituents, to provide an analogy to the amino thiols, were not successful. These included the reaction of an imino thio ester with H_2S, the reaction of an aldehyde with morpholine and sulfur, and the reaction of a protected thiol ester with Lawesson's reagent. The inclusion of an amino or protected amino function in the target molecules prevented these procedures from being utilizable; no indication existed in the literature that amino-containing dithio acids or esters have been prepared by these methods.

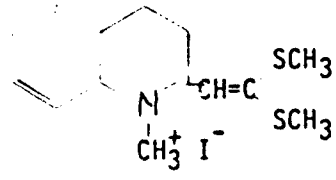
Table of Contents

Quinolinium-2-dithioacetic Acid Derivatives

Zwitterionic compound I has been synthesized previously (1), but has not been tested for radiation-protection activity. The compound has been re-prepared for this report in the same yield as earlier reported, though the higher melting point of the new material (196-197° vs 191-192°) may indicate a somewhat higher degree of purity. In the preparation of I, an apparent second crop of product can be obtained. Various attempts at purifying this material have met with failure. For example, washing with acetone, ether, or water improved the physical appearance of the material, but had little effect on melting point or TLC. Boiling with water, with subsequent drying in vacuo, gave a substance with a sharp melting point near that of the pure zwitterion, but TLC again indicated a complex mixture. Several derivatives of the quinolinium-2-dithioacetic acid zwitterion were also prepared which would not be capable of transferring H atoms to radiation-produced radicals, but which are subject to hydrolysis to the dithio acid in vivo. These compounds include the bis(S-methyl) derivative (II), the S-methyl-N-piperidyl derivative (IV), and the S-methyl-N-morpholinyl derivative (III) of the 6-methylquinoline. These compounds have been prepared previously (1a,1b). Compounds I - IV were submitted for screening (Table I).



I

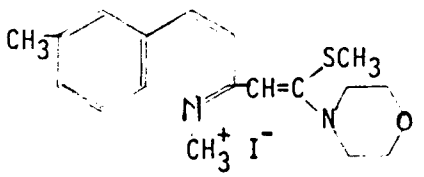


II

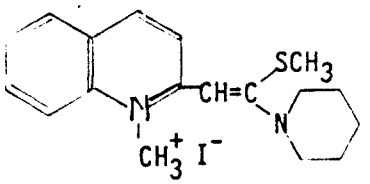
Table I. Compounds Submitted for Screening

Code No. 0942

Compound	Structure	Wt.g.	Reference
1,6-Dimethylquinolinium-2-dithioacetic acid zwitterion	I	2.2	Foye et.al., J. Pharm. Sci. 67, 962 (1978)
1-Methyl-2-bis(2-methylthio)-vinylquinolinium iodide	II	3.1	Foye and Kauffman, ibid., 68, 336 (1979).
1,6-Dimethyl-2-[2-methylthio-2-(1-morpholino)vinyl]quinolinium iodide	III	3.0	Foye and Kauffman, ibid., 69, 477 (1980)
1-Methyl-2-[2-methylthio-2-(1-piperidino)vinyl]quinolinium iodide	IV	2.3	This report



III

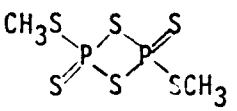


IV

Dithiocarboxylic Acid Esters

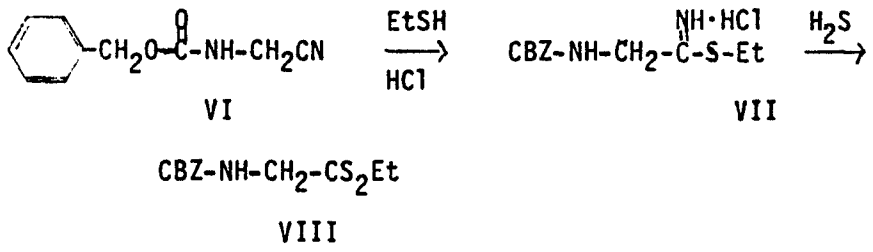
A number of methods are available for the preparation of dithiocarboxylic acids and their esters. Some of these are listed in Table I. Three methods were chosen for initial investigation in this project because they seem to be the least sensitive to the presence of an amino, or protected amino, group in the molecule.

Table II. Methods of Preparation of Dithioacids and -esters

Number	Reaction	Reference
1	$P_4S_{10}+CH_3OH \longrightarrow$  V $\xrightarrow{R\text{-}CO_2H}$ $R\text{-}CS_2CH_3$	2
2	$R\text{-}CN+R'\text{-}SH \xrightarrow{HCl}$ $R\text{-}\overset{NH\cdot HCl}{\overset{\|}{C}}\text{-}SR' \xrightarrow{H_2S}$ $R\text{-}CS_2R'$	3,4,5,6,7
3	$R\text{-}CHO+HN\!\!\bigcirc\!\!O+S_8 \longrightarrow R\text{-}\overset{S}{\overset{\|}{C}}\text{-}N\!\!\bigcirc\!\!O$ $CH_3I,\ \left[R\text{-}\overset{S\text{-}CH_3}{\overset{\|}{C}}\text{=}N^+\!\!\bigcirc\!\!O\ \ I^-\right] \xrightarrow{H_2S}$ $R\text{-}\overset{S}{\overset{\|}{C}}\text{-}SCH_3 \xrightarrow{NaSH} R\text{-}CS_2H$	5,8,9

Method 1 appeared especially promising since it offered a direct conversion of a carboxylic acid to a dithioester. Unfortunately, the requisite dithiadiphosphetane reagent (V) could not be prepared by the procedure reported (2). It is conceivable that the diethyl analog of the reagent is easier to prepare. If so, it could be used to form ethyl dithioesters.

The preparation of an N-protected amino dithioester (VII) from the corresponding nitrile (VI), an example of Method 2, has been reported (6). Although the intermediate iminothioester VII is formed in quantitative yield, it is unstable. Moreover, the yield of the dithioester (VIII) was only 22%. The S-phenyl analog of VII has been prepared (W.O. Foye and J.M. Kauffman, unpublished results), and has recently been purified. It appears to be quite stable.

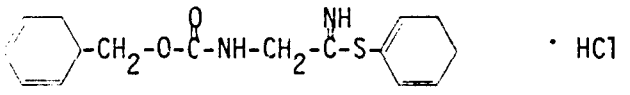


VI VII VIII

Investigation of Method 1 has been abandoned, at least for the time being, because of the difficulty experienced in obtaining the dithiadiphosphetane reagent (V). If work resumes in this area, it will probably entail the preparation and use of the diethyl or diphenyl analog of II.

The recently purified imino phenylthioester of Method 2 will be treated with H_2S using literature procedures (3-7) in an attempt to prepare the corresponding phenyl dithioester.

An investigation was then made of the reaction of benzyl N-(2-phenylthio-2-imino)-ethyl carbamate hydrochloride (IX) with H_2S. The reaction of an iminothioester with H_2S to afford the corresponding dithioester has been reported to take place in pyridine (4,5,7), acetonitrile (10), and ether (3). In the case of IX,

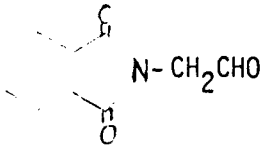


IX

however, no reaction took place, the starting material being the only isolatable product. It was thought that the addition of NaSH might facilitate the conversion, but again, used either alone or in combination with H_2S, no reaction occurred.

Dithioesters have been prepared from aldehydes through their treatment with morpholine and elemental sulfur, followed by reaction with CH_3I and H_2S (5,8,9) (eqn. 3). The preparation of the desired α-aminodithioesters by this method would require aminoacetaldehyde as starting material. Since this compound, and its N-methyl derivative, are available only as acetals, a small amount of p-toluene-sulfonic acid was added to the initial reaction mixture to produce the parent aldehyde. The crystalline product, however, was characterized not as the expected thiomorpholide, but as elemental sulfur. The same reaction proceeded well with cyclohexane carboxaldehyde, suggesting the starting material must already be in the aldehyde form.

If this is so, the nitrogen atom of the amino aldehyde must be masked to prevent polymerization. For this purpose the phthaloyl group was chosen, with phthaloylacetaldehyde (X) as the specific intermediate



X

target. This compound has been prepared by Foye et.al. (11) via Rosenmund reduction of phthaloylglycine, but it was decided to explore other methods for its synthesis, since not all of the materials necessary for Foye's procedure were on hand at the time. The first attempt involved heating to 160° a mixture of phthalic anhydride and aminoacetaldehyde diethylacetal, the product to be hydrolyzed to X. Although the condensation may have taken place, a low yield was obtained, and the crude reaction product appeared to also contain the intermediate phthalic monoamide and unidentified decomposition products. The reaction was repeated at a lower temperature (steam bath), with approximately the same results.

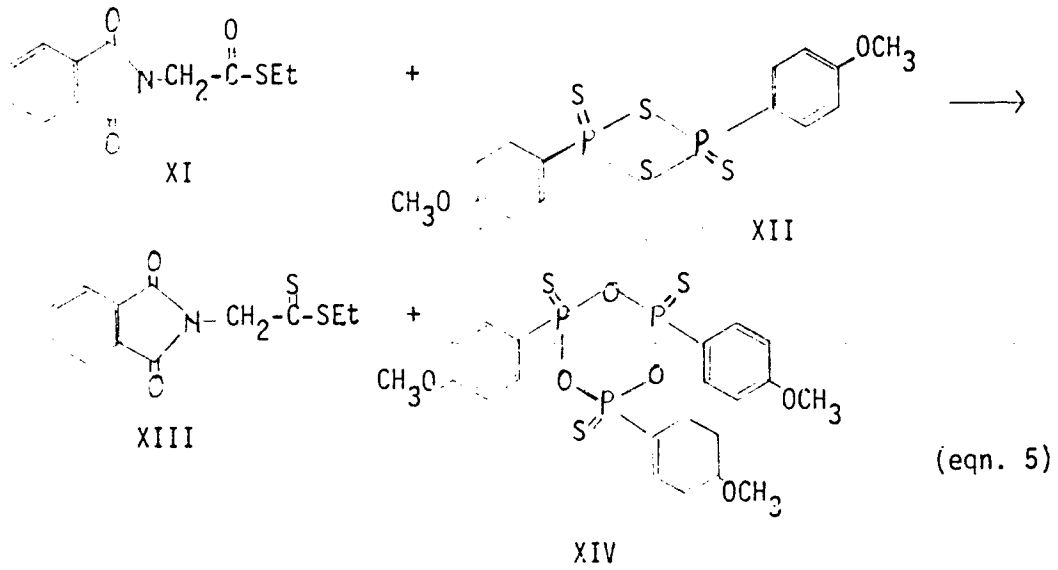
A method for the selective reduction of carboxylic acids to aldehydes, using dimethylchloromethyleniminium chloride, under mild conditions has recently been published (12). Application of this procedure to phthaloylglycine gave a product whose spectral properties are not those of starting material nor of those expected for the product aldehyde, or even the related alcohol. In addition, the melting point of the product is some 20° below that reported (11) for phthalimidoacetaldehyde. Other routes to X involve the condensation of potassium phthalimide with chloroacetaldehyde diethylacetal and the reaction of aminoacetaldehyde diethylacetal with N-carboethoxyphthalimide (13).

Another approach taken toward the preparation of aminodithioesters and acids has involved the conversion of a carbonyl group to a thiocarbonyl moiety. Thus, phthaloylthioglycine S-ethyl ester (XI) was prepared in 81% yield (eqn. 4).

(eqn. 4)

Treatment of this material with phosphorus pentasulfide and $NaHCO_3$ (14) gave a product devoid of the aromatic group according to its NMR spectrum. This spectrum is also inconsistent with the structure $H_2N\text{-}CH_2\text{-}CS_2Et$ (6).

Lawesson's reagent, XII (15), has recently become used for carbonyl-to-thiocarbonyl conversions. Indeed, treatment of XI with XII (eqn. 5) does seem to have

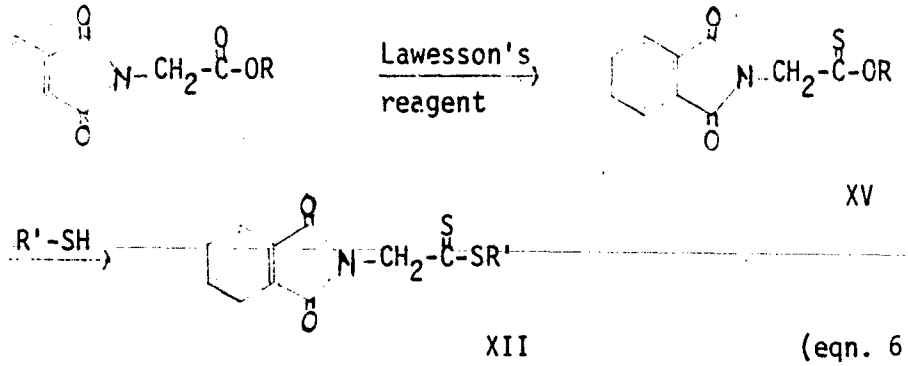


XI + XII → XIII + XIV (eqn. 5)

produced the desired phthalimido dithioester, XIII, though the NMR spectrum is not in exact agreement. In addition, the chromatographic properties of XIII and by-product XIV are very similar, making separation and purification difficult.

Future Work

Plans for the immediate future include a closer look at the use of Lawesson's reagent. If its reaction with thiolester XI was indeed successful, and if the dithioester can be satisfactorily purified from the reaction mixture, it would prove a useful tool in the preparation of the target compounds of this project. A closely related procedure will also be examined. Thus, an ester of phthaloylglycine would be converted to the thionoester (XV), which may be more easily

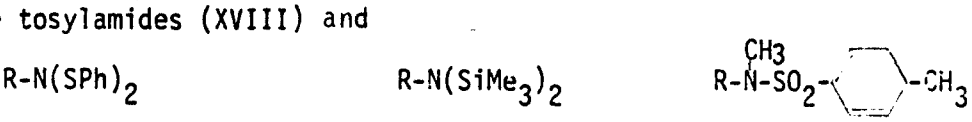


XV

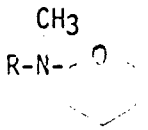
XII (eqn. 6)

isolated than thiolester XI, and thence converted to the dithioester (eqn 6).

Some of the reactions described in this report, e.g., the thiomorpholide route to dithioesters, will be explored further, examining the effects of modified conditions. The application of other N-protecting groups may also be investigated. N-Alkyl bisbenzenesulfenimides (XVI) (16) and N,N-bis (trimethylsilyl) amines (XVII) (17) are possibilities for the primary amines, while tosylamides (XVIII) and



XVI XVII XVIII



XIX

tetrahydropyranyl derivatives (XIX) could be used for secondary amines. The use of these or other protective groups may improve reactivity and facilitate isolation of reaction products.

Experimental

1,6-Dimethylquinolinium-2-dithioacetic acid zwitterion (I). To a stirring solution of 7.80g (26.1 mmole) of 1,6-dimethylquinaldinium iodide in 20ml of water, 40ml of dioxane, and 20ml (330 mmole) of carbon disulfide, was added 60ml of 30% sodium hydroxide (450 mmole) in one portion. A red precipitate formed a few seconds later, and more water (10ml) was added. After stirring 18 hr at room temperature, the mixture was filtered, and the solid product was washed with 50ml of hot water, two 50-ml portions of carbon disulfide, and another 50-ml portion of hot water. Drying in vacuo afforded 3.81g (59.0%) of a brown powder, mp 196-197° (lit. (1) 60% yield, mp 191-192°). IR (KBr): 1310 cm^{-1} (C=S).

Anal.- Calcd- for $C_{13}H_{13}NS_2$: C, 63.15; H, 4.7; N, 5.5; S, 25.9. Found: C, 62.9; H, 5.0; N, 5.5; S, 25.5.

1-Methyl-2-bis(2-methylthio)vinylquinolinium Iodide (II). A mixture of 1-methylquinolinium-2-dithioacetic acid zwitterion (6.81g, 0.021 mole), iodomethane (10ml), and dimethylformamide (40ml) was allowed to stand at room temperature, with occasional shaking, for 17 hr. The dark yellow solid was filtered, washed with ether, recrystallized from water, and dried at 25° (1.5 torr), giving a 15.5% yield of brown crystals; mp 198-201° (dec). NMR (dimethylsulfoxide-d6): δ 2.50(s,3H, SCH_3), 2.70 (s, 3H, SCH_3), 440 (s,3H, NCH_3), 6.80 (s, 1H, vinyl H), and 8.3-9.0 (m,6H, ring H) ppm.

Anal.- Calc. for $C_{14}H_{16}INS_2$: C, 43.19; H, 4.14; N, 3.60. Found: C, 43.31; H, 4.19; N, 3.56.

1,6-Dimethyl-2-[2-methylthio-2-(1-morpholino) vinyl]quinolinium Iodide (III). A flask was charged with 7.26g (0.018 mole) of 2-(bis(2-methylthio) vinyl-1,6-dimethylquinolinium iodide, 80ml of dimethylformamide, and 1.74g (0.020 mole) of morpholine (redistilled after drying with a 3-A^0 molecular sieve). A drying tube containing 10g of indicating Drierite was attached, and the reaction was stirred at 35^0 for 5.5 days. The reaction was followed by the progression of brown coloration on the Drierite and the detection of the odor of methanethiol. Toluene (80ml) was added, and the mixture was stored at 25^0 for 4 hr.

Following filtration, the filtrate was diluted with 350 ml of toluene and kept at -20^0 to give a first crop of 6.78g (85% yield); mp 198-199^0(dec). A second crop was obtained by heating the filtrate to 90^0, diluting with 250 ml of toluene, and cooling to -20^0; 0.44g (6% yield) was obtained; mp 197-199^0 (dec). NMR (dimethylsulfoxide-d6): δ 2.51 (s,3H,SCH_3), 2.57 (s, 3H,6-CH_3), 3.71 (s,br,8H, morpholine), 4.09 (s,3H,NCH_3), 5.59 (s, 1H, vinyl), and 7.65-8.20 (m,5H, aromatic) ppm.

Anal.- Calc. for $C_{18}H_{23}IN_2OS$: C, 48.87; H, 5.24; N, 6.33.
Found: C, 48.77; H, 5.04; N, 5.93.

1-Methyl-2-[2-methylthio-2-(1-piperidino)vinyl]quinolinium Iodide (IV). To a suspension of 2-bis(2-methylthio)vinyl-1-methylquinolinium iodide (2.72g, 0.007 mole) in 25ml of dimethylsulfoxide was added freshly distilled piperidine (1.0g, 0.012 mole), and the mixture was stirred at 30^0 for 5 days. The reaction was monitored by TLC on silica gel plates (developed with chloroform-methanol 9:1). It was diluted with anhydrous ether (200ml) and stored at 0^0 for 2 hr. The crude precipitate was dissolved in 1-propanol (300ml), treated

with charcoal, and filtered hot. This procedure was repeated thrice, and the combined filtrates were evaporated to dryness under reduced pressure. The residue was recrystallized from 2-propanol to give 2.70g (90%) of orange crystals; mp 195-196°, NMR (dimethylsulfoxide-d6): δ 1.75 (s, 6H, piperidine), 2.63 (s,3H,SCH_3), 3.81 (s,4H, piperidine), 4.10 (s,3H,NCH_3), 5.55 (s,1H,vinyl), and 7.6-8.2 (m,6H,aromatic) ppm.

Anal.- Calc. for $C_{18}H_{23}IN_2S$: C, 50.70; H, 5.43; N, 6.57.
Found: C, 50.93; H, 5.23; N, 6.38.

Benzyl N-(2-phenylthio-2-imino)ethyl carbamate hydrochloride. Hydrogen chloride was slowly passed into a cooled (4°) mixture of 9.5g (50 mmole) of benzyl cyanomethylcarbamate(6) and 6.0g (55 mmole) of thiophenol in 250 ml of ether for 1 hr. The mixture was then stored at 4° overnight. The precipitate was filtered, washed with ether, and dried over sodium hydroxide and sulfuric acid at 0.2 torr, to afford 13.9g (82%) of a grayish-tan solid, mp 130-190°d. Some of this material (4.99g) was recrystallized from 25ml of boiling 95% ethanol. Washing the product with 20ml of ether produced 2.40g of off-white plates; mp 135-137°. IR (KBr): 3380, 3320 ($=NH_2^+$), 1685 (C=O), 1645 (C=N) cm^{-1}.

Phthaloylthioglycine S-ethyl ester (XI). To a stirring suspension of 1.00g (4.87 mmol) of phthaloylglycine in 3 ml of benzene was added 2.25ml (30.8 mmol) of thionyl chloride. After the mixture was refluxed overnight, most of the thionyl chloride was boiled off, and the rest was removed by adding 4 ml of benzene, removing this by boiling, and repeating this three more times. Ethyl mercaptan (5 ml, 67.5 mmol) was added to the residue, and the suspension was allowed to stir overnight at room temperature. The solvent was removed, and the residue was treated with benzene as above. Recrystallization of the crude product from ether produced 0.75g of white plates, mp 122.5-123.5°. A second crop of crystals was obtained from the mother liquor, affording a total yield of 0.99g (81%). NMR ($CDCl_3$): δ 1.27 (t, J = 3.5 Hz, 3H, CH_3), 2.95 (q, J = 3.5 Hz, 2H, S-CH_2), 4.60 (s, 2H, N-CH_2), 7.80 (m, 4H, aromatic H). IR (KBr): 1780, 1720 (imide CO), 1680 (thioester CO) cm^{-1}.

Reaction of XI with Lawesson's Reagent. A mixture of 0.20g (0.81 mmol) of thiolester XI and 0.20g (0.49 mmol) of Lawesson's reagent in 4 ml of toluene was held at reflux for 5 hr, then allowed to stir overnight at room temperature. Subsequent addition of another 0.20g portion of Lawesson's reagent, followed by 5 hr. of refluxing, 2 days stirring at room temperature, and evaporation of the solvent in vacuo gave a very viscous, brown oil. The NMR spectrum of this material indicated the presence of trioxatriphosphane XIV and perhaps an approximately equimolar amount of dithioester XIII. In addition, TLC showed two major spots, at r_f 0.62 and 0.53.

Cyclohexane thiomorpholide. A mixture of 1.01g (8.97 mmol) of cyclohexane carboxaldehyde, 1.18g (13.5 mmol) of morpholine, and 0.43g (13.5 mmol) of sulfur was heated on a steam bath for 3 hr. On cooling to room temperature, the product was taken up in 5 ml of chloroform, filtered, and stripped of solvent. Recrystallization from 95% ethanol gave 1.45g (76%) of light

orange plates, mp 124.5-126. NMR $(CDCl)_3$: δ 0.87-2.23 (m, 10H, $(CH_2)_5$), 2.40-2.93 (m, 1H, CH), 3.47-4.03 (m, 6H, morpholine), 4.10-4.53 (m, 2H, morpholine). IR (KBr): 1470, 1280 (C=S) cm^{-1}.

Methyl cyclohexanedithiocarboxylate. A solution of 0.41g (1.90 mmol) of cyclohexanethiomorpholide and 0.50ml (8.03 mmol) of methyl iodide in 5 ml of dry acetone was heated at reflux for 4.5 hr Another 0.50 ml of MeI was added, and the mixture was stirred at room temperature overnight. Dry pyridine (2 ml) was added to the resulting suspension, and H_2S was passed in for 6 hr. After standing overnight at room temperature, the mixture was filtered, and the solid was washed with acetone and absolute ethanol. Removal of solvent from the combined filtrate and washings under reduced pressure left a moist yellow solid. This was cooled in ice, taken up in 20 ml of ice-cold 4N HCl, and extracted with six 10-ml portions of ether. The combined ether solutions were washed with three 10-ml portions of water, and finally with 10 ml of saturated aqueous $NaHCO_3$. Drying ($MgSO_4$), filtration, and removal of solvent afforded 0.30g of a clear orange liquid with a sulfurous odor. The NMR spectrum indicated an approximately 3:1 molar ratio of the dithioester and thiomorpholide, although no attempt was made at purification.

References

1. a. W. O.Foye, Y.J. Lee, K.A. Shah, and J.M. Kauffman, J. Pharm. Sci., 67, 962 (1978). b. W.O. Foye and J.M. Kauffman, ibid., 68, 336 (1979). c. W.O. Foye and J.M. Kauffman, ibid. 69, 477 (1980).
2. H. Davy, J. Chem. Soc. Chem. Commun., 457 (1982).
3. S.A. Karjala and S.M. McElvain, J. Amer. Chem. Soc., 55, 2966 (1933).
4. C.S. Marvel, P. de Radzitsky, and J.J. Brader, ibid., 77, 5997 (1955).
5. R. Mayer, S. Scheithauer, and D Kunz, Chem. Ber., 99, 1393 (1966).
6. W.O. Foye and J. M. Kauffman, J. Pharm. Sci. 57, 1614 (1968).
7. P. Gosselin, S. Masson, and A Thullier, J. Org. Chem., 44, 2807 (1979).
8. D.A. Peak and S. Stansfield, J. Chem. Soc., 4067 (1952).
9. E.J. Hedgley and H.G. Fletcher, Jr., J. Org. Chem., 30, 1282 (1965).
10. P. Gosselin, S. Masson, and A. Thuillier, Tet. Lett., 2715 (1978).
11. W.O. Foye and JJ. Hefferren, J. Amer. Pharm. Assoc., 43, 124 (1954).
12. T. Fujisawa, T. Mori, S. Tsuge, and T. Sato, Tet. Lett., 24, 1543 (1983).
13. G. H. L. Nafkens, G.I. Tesser, and R.J.F. Nivard, Rec. Trav, Chim., 79, 688 (1960).
14. J. W. Scheeren, P.H.J. Ooms, and R.J.F. Nivard, Synthesis, 149, (1973).
15. B. Pedersen, S. Scheibye, K. Clausen, and S. Lawesson, Bull. Soc. Chim Belg., 87, 223 (1978).
16. T. Mukaiyama and T. Taguchi, Tet. Lett., 3411 (1970).
17. H.H. Hils, Chem. Ber., 99, 776 (1966).

DISTRIBUTION LIST

12 copies	Director Walter Reed Army Institute of Research Walter Reed Army Medical Center ATTN: SGRD-UWZ-C Washington, DC 20307-5100
4 copies	Commander US Army Medical Research and Development Command ATTN: SGRD-RMS Fort Detrick, Frederick, Maryland 21701-5012
12 copies	Defense Technical Information Center (DTIC) ATTN: DTIC-DDAC Cameron Station Alexandria, VA 22304-6145
1 copy	Dean School of Medicine Uniformed Services University of the Health Sciences 4301 Jones Bridge Road Bethesda, MD 20814-4799
1 copy	Commandant Academy of Health Sciences, US Army ATTN: AHS-CDM Fort Sam Houston, TX 78234-6100