was crystallized from ethanol to give 12.2 g (72%) of a reddish brown solid, mp 140–141°.

Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.15; H, 5.34; Cl, 10.44; N, 12.37. Found: C, 67.45; H, 5.55; Cl, 10.58; N, 12.26.

1-Chloro-2-methyl-3-(4-phenylazo-1-naphthylamino)-2-propanol.—Utilizing the procedure described above for the preparation of 1-chloro-3-(4-phenylazo-1-naphthylamino)-2-propanol, aniline (3.25 g, 0.035 mole) and 1-chloro-2-methyl-3-(1-naphthylamino)-2-propanol[29] (10.0 g, 0.035 mole) gave 7.8 g (63%) of maroon crystals, mp 130–131°.

Anal. Calcd for $C_{20}H_{20}ClN_3O$: C, 67.88; H, 5.70; N, 11.88. Found: C, 67.98; H, 5.67; N, 12.05.

Acknowledgments.—The authors wish to express their appreciation to Dr. Loren M. Long for encouragement in this investigation, to Dr. Paul E. Thompson, Mr. Jack E. Meisenhelder, and Dr. Haig Najarian for the antischistosome testing, and to Miss M. Virginia Dudley, Mrs. Zoe Gavrilis, Mrs. Mary K. Martin, Miss Joan D. Multhaup, Miss Josephine Rarity, Mrs. Doris R. Thomas, and Miss E. A. Weinstein for synthesizing several of the compounds described herein. We also thank Mr. William Pearlman for carrying out the hydrogenations, Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for determination of the infrared and ultraviolet absorption spectra.

Reactions of Mercaptoamines. III. Synthesis of N-Monosubstituted 2-Mercaptoethylamines[1,2]

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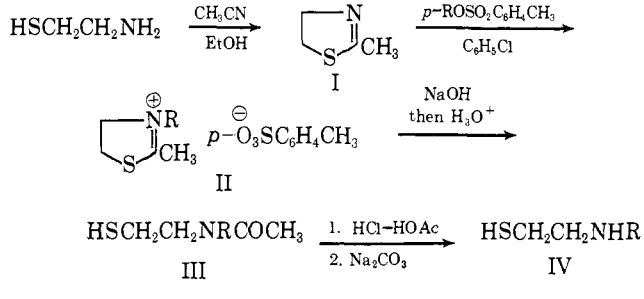
Received September 29, 1965

As part of a program on the synthesis of antiradiation drugs, a four-step novel synthesis of N-monosubstituted 2-mercaptoethylamines has been developed. The synthesis involves (1) conversion of 2-mercaptoethylamine by reaction with nitriles to 2-substituted 2-thiazolines (I), (2) quaternization of the thiazolines by tosylate esters to thiazolinium salts (II), (3) alkaline hydrolysis of the salts to an N-(2-mercaptoethyl)acetamide derivative (III), and (4) hydrolysis of the amides in concentrated HCl and glacial acetic acid to N-monosubstituted 2-mercaptoethylamines (IV).

Because of the potential use of 2-mercaptoethylamines as antiradiation drugs,[5–8] it has become imperative that additional synthetic routes to compounds of this class be devised.

Previous studies of the reactions of mercaptoamines have shown that many compounds capable of reacting with the amine function also react with the mercaptan function.[9,10] In the work reported here, a method was devised for protecting the mercaptan function in 2-mercaptoethylamine, allowing the amine function to react, and then regenerating the free mercaptan. N-Monosubstituted 2-mercaptoethylamines were thereby obtained.



Two recent investigations have independently shown that 2-mercaptoethylamine reacts with nitriles to give 2-substituted 2-thiazolines.[11,12] It had been shown earlier that 2-thiazolines are quaternized with alkyl iodides or *p*-toluenesulfonates.[13] It was found that low molecular weight alkyl iodides indeed gave good yields of solid quaternary thiazolinium iodides when heated with 2-methyl-2-thiazoline (I) in refluxing absolute ethanol. However, when more complex halides were used, the reaction appeared to be sluggish. Benzyl chloride and 2-bromoethylamine hydrobromide both gave ill-defined syrups with 2-methyl-2-thiazoline, and chloroacetone gave a tarry product. It became apparent that only active alkylating agents would serve to quaternize the thiazoline. Since esters of *p*-toluenesulfonic acid ("tosylates") are known to be more effective in displacement reactions than alkyl halides (*i.e.*, the tosylate anion is a better "leaving group" than any of the halide anions), they seemed a likely choice for the thiazoline quaternization. In the first experiments, refluxing absolute ethanol was used as solvent and ethyl and *n*-heptyl tosylates were the alkylating agents. The same solid product was obtained in both reactions, and it proved to be the simple tosylate salt of 2-methyl-2-thiazoline. From the reaction with heptyl tosylate, a liquid product was isolated and identified as ethyl *n*-heptyl ether. The isolation of this compound provided a basis for explaining what had happened in these reactions. The tosylate ester had alkylated the solvent in preference to the thiazoline, and the latter had acted merely as an acid acceptor. When refluxing dry acetonitrile

(1) This work was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-193-MD-2174.

(2) Presented in part at the Sixteenth Annual Midwest Chemistry Conference, Kansas City, Mo., Nov 19, 1964.

(3) Deceased.

(4) To whom requests for reprints should be addressed.

(5) *Cf.* Symposium on Radiation-Protective Agents, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962.

(6) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5130 (1961).

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(9) Paper I: A. F. Ferris and B. A. Schutz, *ibid.*, **28**, 3140 (1963).

(10) Paper II: A. F. Ferris and B. A. Schutz, *ibid.*, **29**, 201 (1964).

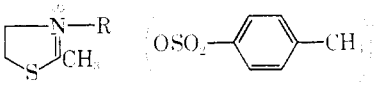
(11) R. Kuhn and F. Drawert, German Patent 937,231 (Dec 29, 1955); *Chem. Abstr.*, **53**, 409 (1959).

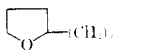
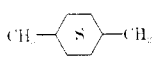
(12) T. Kurihava, K. Suzuki, and M. Okita, *Tohoku Yakka Daikago Kiyo*, **5**, 43 (1958); *Chem. Abstr.*, **53**, 10176 (1959).

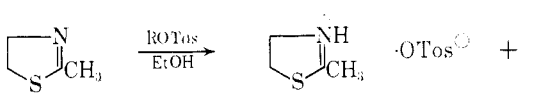
(13) L. G. S. Brocker, *J. Am. Chem. Soc.*, **58**, 662 (1936).

TABLE I

2-METHYL-3-SUBSTITUTED THIAZOLINIUM TOSYLATES



R	% yield: p-Toluenesulfonate ester	% yield: Salt	Salt mp, °C	Recrystn solvent	Calcd for salt, %: C	H	N	S	Found for salt, %: C	H	N	S
$CH_3(CH_2)_6$	81	54	152–154	Acetone	58.19	7.87	3.77	17.26	57.96	7.77	3.80	17.34
$CH_3(CH_2)_7$	84	62	158–160.5	Ethanol–ether	59.18	8.10	3.63	16.63	58.96	8.21	3.58	16.87
$CH_3(CH_2)_8$	88	62	154–156	Acetone–ethyl acetate	60.83	8.75	3.38	15.46	60.92	8.58	3.27	15.20
$C_6H_5CH_2CH_2$	85	53	126–128.5	Acetone	60.45	6.14	3.71	16.99	60.47	6.16	3.72	16.76
	71	58	144–146	Ethanol–ethyl acetate	56.07	7.06	3.63	16.63	55.96	6.88	3.43	16.78
	97	28	219–233	Ethanol–acetone	59.50	7.62	3.65	16.72	59.60	7.68	3.70	16.44
p-$(CH_3)_3CC_6H_4OCH_2CH_2$	100	50	145–150	Acetone	61.44	6.95	3.12	14.26	61.57	6.84	3.30	14.40
$C_6H_4CH_2OCH_2CH_2$	93	85	97–99	Acetone	58.94	6.18	3.44	15.73	58.70	6.24	3.47	15.90

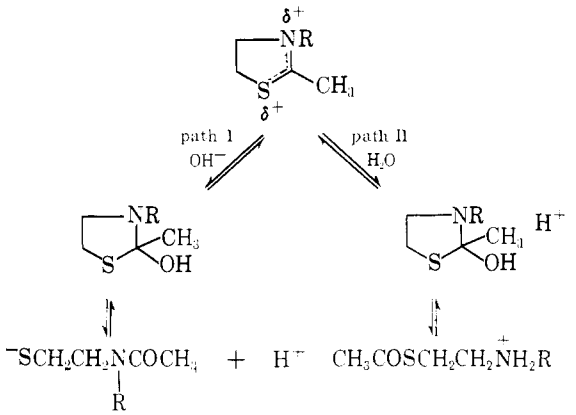


was used as the solvent, the desired thiazolinium salt was obtained in poor yields. From the reaction of heptyl tosylate and 2-methyl-2-thiazoline was obtained a 38% yield of 3-*n*-heptyl-2-methyl-2-thiazoline tosylate and considerable unidentified liquid by-product. Use of chlorobenzene solvent (as recommended by Lempert and Zauer[14] for the quaternization of nitrogen-containing heterocyclic molecules) in the quaternization of 2-methyl-2-thiazoline resulted in very marked improvement in yields over any other solvent tried. For example, the quaternization with heptyl tosylate gave a 54% yield of thiazolinium salt (II) *vs.* 38% in acetonitrile. With octyl and 2-benzyloxyethyl tosylates, yields of salt were 62 and 85%, respectively.

A recent study[15] has demonstrated that quaternized 2-oxazolines are cleaved to esters of amino alcohols on mild hydrolysis. Thus, hydrolysis of the quaternary salts to the N-2-(mercaptoethyl)acetamide derivatives (III) was carried out by adding a 3 *M* excess of alkali at 70° to the quaternary compound in a nitrogen atmosphere. For example, 2-methyl-3-(3-phenylpropyl)thiazolinium tosylate afforded an 88% yield of N-(2-mercaptoethyl)-N-(3-phenylpropyl)acetamide.

Attempts to hydrolyze the amide to the corresponding amine with excess alkali or 6 *N* HCl under reflux for 8 hr failed, the amide being recovered in each case. However, hydrolysis with a 1:1 mixture of concentrated HCl–glacial acetic acid under reflux for 24 hr in a nitrogen atmosphere did convert the amide to the desired amine (IV). In this way N-(2-mercaptoethyl)-N-(3-phenylpropyl)acetamide was converted to N-(2-mercaptoethyl)-3-phenylpropylamine in 64% yield.

Hydrolysis of the thiazolinium salts (II) very probably proceeds in a manner similar to that postulated by Martin[16] for hydrolysis of 2-alkylthiazolines. Base obviously shifts the equilibria so that the reaction proceeds according to path I, the driving force for C–S



cleavage being formation of the base-stable mercaptide ion. Consideration of path II leads to the conclusion that hydrolysis of the thiazolinium salts in neutral media should give a thiol ester. Refluxing 2-methyl-3-(3-phenylpropyl)thiazolinium tosylate in water gave a semisolid whose infrared spectrum was void of amide absorption but did reveal absorption at 1700 cm^{-1} (as does S-acetylmercaptoacetone) and bands at 810, 1005, and 1025 cm^{-1}, characteristics of tosylate anions.[17] Furthermore, hydrolysis of crude 2-methyl-3-(2-methoxyethyl)thiazolinium tosylate with water and then 6 *N* HCl gave a poor yield (13%) of N-(2-methoxyethyl)-2-mercaptoethylamine. The amine must almost certainly have been formed by path II, since the amides (path I) do not hydrolyze to the amines under these conditions.

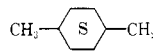
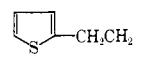
The thiazolinium salts were not all crystallizable solids. Those which were crystalline were characterized by melting point determination and analyzed. The infrared spectra of the thiazolinium salts all revealed intense bands at 1005 and 1020 cm^{-1}, characteristic of tosylate anion bands.[17] Results are reported in Table I. Not all the thiazolinium salts could be converted to N-monosubstituted 2-mercaptoethylamines. On the other hand, a number of thiazolinium salts which could not be crystallized underwent hydrolysis

(14) K. Lempert and K. Zauer, *Tetrahedron Letters*, 519 (1964).
(15) P. Allen, Jr., and J. Ginos, *J. Org. Chem.*, **28**, 2759 (1963).
(16) R. B. Martin, R. K. Hedrick, and A. Parcell, *ibid.*, **29**, 3197 (1964).
(17) A. F. Ferris and O. L. Salerni, *Inorg. Chem.*, **3**, 1721 (1964).

TABLE II

N-MONOSUBSTITUTED 2-MERCAPTOETHYLAMINES

$HSCH_2CH_2NHR$

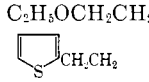
R	% yield Amide	% yield Amine	Overall[a] yield, %	Amine bp, °C (mm)	Amine $n^{25}D$	Calcd for amine, % C	H	N	S	Found for amine, % C	H	N	S
$C_6H_5(CH_2)_2$	68	60	18	81–82 (0.2)	1.5512	66.25	8.34	7.73	17.69	66.47	8.34	7.72	17.87
$C_6H_5(CH_2)_3$	88	64	23	107–110 (0.15)	1.5401	67.64	8.78	7.17	16.41	67.87	8.96	7.11	16.19
$C_2H_5OCH_2CH_2$	58	22	12	78–81 (4.4)	1.4690	48.28	10.13	9.39	21.48	48.18	9.97	9.24	21.63
$CH_3(CH_2)_3OCH_2CH_2$	73	51	29	97–100 (2.7)	1.4668	54.19	10.80	7.90	18.08	54.44	11.07	7.99	18.01
	64	38	7	70–73 (0.2)	1.4926	64.11	11.30	7.48	17.11	63.97	11.47	7.54	16.98
$CH_3(CH_2)_3O(CH_2)_2OCH_2CH_2$	56	18	10	99.5–100 (0.4)	1.4677	54.26	10.47	6.33	14.48	54.09	10.35	6.17	14.64
	54	46	22	95.5–96 (0.3)	1.5656	51.29	6.99	7.48	34.23	51.41	7.10	7.58	34.10
p-$(CH_3)_3CC_6H_4OCH_2CH_2$	100	40	20	143.5–144 (0.2)	1.5314	66.36	9.15	5.53	12.65	66.23	9.03	5.62	12.32
p-$ClC_6H_4OCH_2CH_2$[b]	92	42	17	136.5 (0.2)	1.5618	51.83	6.09	6.05	13.84	52.02	6.13	5.96	13.67

[a] Alcohol → amine. [b] *Anal.* Calcd: Cl, 15.30. Found: Cl, 15.10.

TABLE III

N-MONOSUBSTITUTED N-(2-MERCAPTOETHYL)ACETAMIDES

$CH_3CON<^{R}_{CH_2CH_2SH}$

R	% yield	Bp, °C (mm)	$n^{25}D$	Calcd, % C	H	N	S	Found, % C	H	N	S
$CH_3(CH_2)_9$	39	145–150 (0.04)	1.4815	64.81	11.27	5.40	12.36	64.91	11.25	5.46	12.15
$C_2H_5OCH_2CH_2$	58	102–103 (0.07)	1.4884	50.23	8.96	7.32	16.76	50.50	9.08	7.23	16.97
	54	150–155 (0.05)	1.5687	52.37	6.59	6.11	27.96	52.60	6.75	6.08	27.83
$CH_3(CH_2)_3OCH_2CH_2$	61	118–120 (0.10)	1.4830	54.76	9.65	6.39	14.62	54.91	9.74	6.37	14.57
$N{\equiv}CCH_2CH_2$	43	176–177 (0.05)	1.5169	48.81	7.02	16.27	18.62	49.00	7.19	16.50	18.38
$CH_3O(CH_2)_2OCH_2CH_2$	45	138–140 (0.5)	1.4906	48.84	8.65	6.33	14.49	48.59	8.47	6.46	14.63
$CH_3CH(OCH_3)CH_2CH_2$	19	108–110 (0.23)	1.4888	52.65	9.33	6.82	15.62	52.89	9.41	6.86	15.40
$C_2H_5OCH_2CH_2OCH_2CH_2$	18	128–132 (0.23)	1.4823	51.04	8.99	5.95	13.62	51.21	9.06	6.11	13.90

satisfactorily to give the appropriate N-monosubstituted 2-mercaptoethylamines. All the distillable monosubstituted mercaptoethylamine derivatives which were prepared are listed in Table II. The infrared spectra of these compounds all revealed mercaptan peaks at 2550 cm^{-1},[18] and were void of amide absorption. The properties of the amides which were isolated and distilled are listed separately in Table III. The infrared spectra of these substances were consistent with the desired structure and showed amide (1640 cm^{-1}) and mercaptan absorption (2550 cm^{-1}). For the reasons noted, the "R" groups do not necessarily correspond in the different tables.

Biological Activity.—The nine N-monosubstituted mercaptoethylamines listed in Table II have been examined for protective activity against radiation lethality in mice. The compound where R is phenethyl was found to have a protective effectiveness described as good. The compound where R is 2-(2-thienyl)-ethyl possessed activity described as fair. Slight activity was assigned to those compounds where R is *p*-*t*-butylphenoxyethyl, *p*-chlorophenoxyethyl, and 3-phenoxypropyl. The other N-monosubstituted mercaptoethylamines were inactive. The thiazolinium salts listed in Table I and the acetamide derivatives (Table III) were also examined for protective activity against lethal doses of radiation. All these compounds were inactive. The thiazolinium salts were tested on the premise that they may undergo *in vivo* hydrolysis to the corresponding N-monosubstituted mercaptoethylamine. The following dose levels were employed in testing the compounds for biological activity: 51–150 mg/kg for all the N-monosubstituted 2-mercaptoethylamines except those where R = 2-(*n*-butoxyethoxy)ethyl and phenethyl, which were tested at less than 50 mg/kg; 51–150 mg/kg for the acetamide derivatives except those where R = 2-(*n*-butoxyethoxy)-ethyl and 2-(2-methoxyethyl)ethyl, which were tested at 150–350 mg/kg; 51–150 mg/kg for the thiazolinium salts except the compound where R = decyl, which was tested at less than 50 mg/kg. The compounds were administered intraperitoneally to mice which were tested for 30-day survival against lethal radiation of 1000 r. Complete details are described by Field and co-workers.[19]

Experimental Section[20]

Only typical procedures are described here. All alcohols were converted to their tosylate esters by the method of Marvel and Sekera.[21]

2-Methyl-3-(2-phenethyl)thiazolinium Tosylate.—A solution of 55.2 g (0.20 mole) of crude phenethyl tosylate and 20.2 g (0.20

(18) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 350.

(19) L. Field, A. Ferretti, R. Crenshaw, and T. Owen, *J. Med. Chem.*, **7**, 42 (1964).

(20) Melting points are corrected and boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord recording spectrophotometer.

(21) C. S. Marvel and V. C. Sekera, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 366.

mole) of 2-methyl-2-thiazoline in 100 ml of chlorobenzene was refluxed for 4 hr. The solvent was then removed under reduced pressure, leaving a solid residue. After one recrystallization from acetone, 39.8 g (53%) of product was obtained, mp 122.5–127°. Two additional recrystallizations from acetone gave an analytical sample, mp 126.5–128.5°. See Table I for data on other thiazolinium salts.

Anal. Calcd for $C_{19}H_{23}NO_3S_2$: C, 60.45; H, 6.14; N, 3.71; S, 16.99. Found: C, 60.47; H, 6.16; N, 3.72; S, 16.76.

N-*n*-Decyl-N-(2-mercaptoethyl)acetamide.—Nitrogen was bubbled slowly through a solution of 24.0 g (0.6 mole) of NaOH in 250 ml of water for 10–15 min. All the following steps were carried out under nitrogen, whenever possible. With the solution at 50° and while stirring (magnetically), 2-methyl-3-*n*-decylthiazolinium tosylate (62.4 g, 0.2 mole) was added. The solution was allowed to stir for 1 hr, then chilled and made strongly acid with concentrated HCl. An oil separated which was extracted into three 50-ml portions of $CHCl_3$. The extracts were combined and washed with 10% Na_2CO_3 solution and water. The chloroform extracts were dried ($MgSO_4$); concentration under reduced pressure gave 10.1 g (39%) of product. A distillation *in vacuo* gave an analytical sample, bp 145–150° (0.04 mm), $n^{25}D$ 1.4815. See Table II for data on other purified amides.

Anal. Calcd for $C_{14}H_{29}NOS$: C, 64.81; H, 11.27; N, 5.40; S, 12.36. Found: C, 64.91; H, 11.25; N, 5.46; S, 12.15.

N-(2-Mercaptoethyl)-2-phenethylamine.—A solution of 16.6 g (0.074 mole) of crude N-(2-mercaptoethyl)phenethylacetamide (prepared as described above) in a mixture of 50 ml of concentrated HCl and 50 ml of glacial acetic acid was heated under reflux in a nitrogen atmosphere for 24 hr; then the solvent was evaporated under reduced pressure. The residue was taken up in 10% Na_2CO_3 solution with stirring and warming until the pH of the water layer was 8–9. An oil separated and, on cooling, was extracted into three 50-ml portions of ether. After drying the combined extracts ($MgSO_4$), the solvent was evaporated under reduced pressure. The remaining oil was distilled *in vacuo* and gave 8.1 g (60%) of product, bp 80–84° (0.2 mm). Another distillation *in vacuo* gave an analytical sample, bp 81–82° (0.2 mm), $n^{25}D$ 1.5512.

Anal. Calcd for $C_{10}H_{15}NS$: C, 66.25; H, 8.34; N, 7.73; S, 17.69. Found: C, 66.47; H, 8.34; N, 7.72; S, 17.87.

N-(2-Mercaptoethyl)(2-methoxyethyl)amine.—A solution of 52.8 g (0.16 mole) of 2-methyl-3-(2-methoxyethyl)thiazolinium tosylate in 150 ml of water was heated under reflux for 25 hr, with nitrogen bubbling through the solution. At this time, 150 ml of concentrated HCl was added, and the solution was heated under reflux for an additional 3 hr. The acid solution was evaporated *in vacuo*, and the residue was made alkaline with 180 ml of 10% Na_2CO_3. The solution was extracted into five 40-ml portions of chloroform, dried ($MgSO_4$), then concentrated *in vacuo*. The oily residue obtained in this way was distilled under reduced pressure. There was collected 3.7 g (13%) of amine, bp 70–72° (4.5 mm), $n^{26}D$ 1.4744.

Anal. Calcd for $C_5H_{13}NOS$: C, 44.41; H, 9.69; N, 10.36; S, 23.71. Found: C, 44.20; H, 9.69; N, 10.18; S, 23.90.

Radioprotective Activity of Triammonium 2-Dithiocarbamoyl-3-dithiocarbonylthiopropanoate

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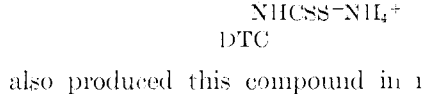
Received August 13, 1965

The synthesis of a water-soluble derivative of cysteine, the triammonium salt of the dithiocarbamate trithiocarbonate, is described. Toxicity studies show the compound to be two to three times less toxic than 2-aminoethylisothiouronium bromide hydrobromide (AET), and it provides good protection in mice against the lethal effect of ionizing radiation in the comparable order of activity as AET.

Trithiocarbonate zwitterions of 2-mercaptoethylamine, 2-mercaptoethylguanidine, and related compounds have shown good effectiveness as radiation protective agents.[1] These compounds show limited solubility in water and appreciable toxicity, so a compound having greater aqueous solubility and possibly lower toxicity was sought in the trithiocarbonate of cysteine. It was anticipated that both the mercapto and the amino function of cysteine would react with carbon disulfide to give either a dithiocarbamate trithiocarbonate or possibly a cyclization product. A dithiocarbamate of cystine has previously been prepared,[2] but no appreciable antiradiation properties have yet been reported for this compound.

Treatment of cysteine with carbon disulfide and ammonium hydroxide in the usual manner[1,2] gave only products of indefinite composition. Use of reaction conditions that avoided an excess of base did, however, provide the dithiocarbamate trithiocarbonate of cysteine as the triammonium salt, abbreviated hereafter as DTC. Use of ethanol as solvent with dry ammonia also produced this compound in much better yield. Infrared absorption at 1055 and 1105 cm^{-1} may be attributed to the C=S of the trithiocarbonate group,[3,4] and absorption at 995 cm^{-1} to the C=S of the dithiocarbamate group.[3] A strong absorption band at 1555 cm^{-1} may also be due to thioamide.[5]



DTC

The radiation protective ability and toxicity of DTC in mice have been determined and are reported herein. The comparative value of this compound with that of 2-aminoethylisothiouronium bromide hydrobromide (AET) is also presented.

Experimental Section

Analyses for carbon, hydrogen, and nitrogen were done by Weiler and Strauss, Oxford, England. Sulfur analysis was done

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(4) J. I. Jones, W. Kynaston, and J. L. Hales, *ibid.*, 614 (1957).

(5) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p 312.