N-Acrylyl-4-carbomethoxy-2,2-dimethylthiazolidine (VIII).—The procedure described for the preparation of II was used. Treatment of 15.3 g. (0.09 mole) of VII with 8.1 g. (0.09 mole) of acrylyl chloride in the presence of 9.1 g. (0.09 mole) of triethylamine afforded a yellow solid which was recrystallized from ether to give 12.5 g. (60%) of white prisms, m.p. 87.5–88.5°, $[\alpha]^{25}D$ −71.70° (*c* 5.54, $CHCl_3$).

Anal. Calcd. for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11; S, 13.99. Found: C, 52.36; H, 6.53; N, 6.20; S, 13.74.

Poly(N-acrylyl-4-carbomethoxy-2,2-dimethylthiazolidine) (IX).—A polymerization tube was charged with 8.0 g. of VIII and 29 mg. of α,α'-azobisisobutyronitrile dissolved in 15 ml. of dry benzene. The polymerization tube was alternately evacuated and flushed with dry nitrogen three times and then sealed under vacuum. The solution was heated at 60° for 2 hr. An additional 25 ml. of benzene was added to the polymer mass and the polymer was precipitated by adding dropwise to a 10:1 excess of cold pentane. The polymer was purified by repeating this procedure. The reprecipitated polymer weighed 6.9 g. (86.3%) and softened at 215–225°, $[\eta]$ 0.63 determined in benzene at 29.2°.

Anal. Calcd. for $(C_{10}H_{15}NO_3S)_n$: C, 52.38; H, 6.59. Found: C, 52.19; H, 6.63.

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Substituted 2-Aminothiosulfuric Acids Derived from α-Amino Acids[1]

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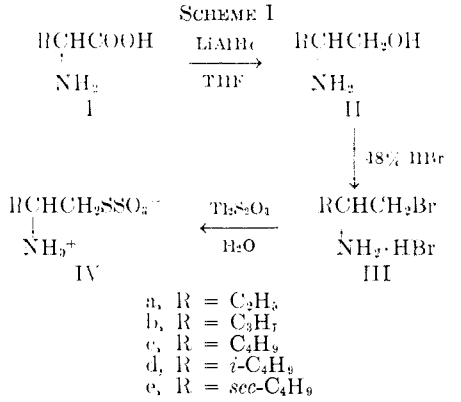
The discovery[3] of the protective effect of cysteine against acute radiation toxicity has led to the examination of simple mercaptoalkylamines and their derivatives, some of which are more effective than cysteine in reducing the toxic effect of radiation.[4] The most promising compounds contain a basic group and a free or potential sulfhydryl group separated by two or three carbon atoms.[5]

The replacement of the carboxylate function of α-amino acids by the methylenethiosulfonate group ($CH_2SSO_3^-$) would yield products having an amino group and a potential sulfhydrly group separated by two carbons. This transformation has been carried out on a number of racemic amino acids.

Scheme I presents the synthetic approach to the amino thiosulfuric acids derived from the neutral aliphatic amino acids. The reduction of this group of amino acids to amino alcohols (II) was accomplished by means of $LiAlH_4$ in tetrahydrofuran (THF) in 58–97% yields by the methods of Vogl and Pöhm.[6,7]

SCHEME I



a, R = C_2H_5
b, R = C_3H_7
c, R = C_4H_9
d, R = *i*-C_4H_9
e, R = *sec*-C_4H_9

The corresponding amino bromide hydrobromides (III) were prepared by treating the amino alcohols with 48% HBr.[8] In a number of cases, the products obtained were mixtures of the amino bromide hydrobromides and amino alcohol hydrobromides. Since a method of separation could not be worked out, the composition of the mixtures was determined from the bromine content, and the crude products were employed in the succeeding step without further purification. The mixtures contained from 80–95% bromide hydrobromide (58–82% yield). Upon treatment of III with thallous thiosulfate according to Lecher and Hardy,[9] the thiosulfuric acids (IV) were obtained in 60–83% yields.

The amino alcohols derived from the basic amino acids, ornithine and histidine, and the aromatic amino acid, tyrosine, could not be obtained directly by reduction with $LiAlH_4$. The preparation of L-tyrosinol from L-tyrosine was reported by Dornow, *et al.*,[10] but could not be reproduced.

The reactions employed in synthesizing the aminothiosulfuric acids from the basic and aromatic amino acids are summarized in Scheme II. L-Histidinol had been previously prepared[11] by reducing the ethyl ester of benzoyl-L-histidine with a large excess (18:1 mole) of $LiAlH_4$ in ethyl ether. In THF, an excess of $LiAlH_4$ reduced both the ester and amide functions and yielded benzylhistidinol (XIh). It seems that the reduction of the amide was temperature dependent since THF boils considerably higher than ether. When the ratio of $LiAlH_4$ to benzamido ester was 1:1 mole, a good yield of benzamido alcohol was obtained. To overcome the problem of nonselectivity during the reduction of the benzamido esters, the method of Stewart[12] was employed which depended on the selective reduction of ester functions by $LiBH_4$. The remainder of the synthetic sequence was similar to that of the aliphatic aminothiosulfuric acids, and the yield of Xf was 48%.

The infrared spectra of the thiosulfuric acids were characterized by peaks and bands at 1016–1040, 1065–1130, and 1180–1240 $cm.^{-1}$. These were in general agreement with the data reported by Simon and Kunath[13] for the sulfonate ion in alkylthiosulfates, and the crystal structure of compound IVa was de-

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TABLE I

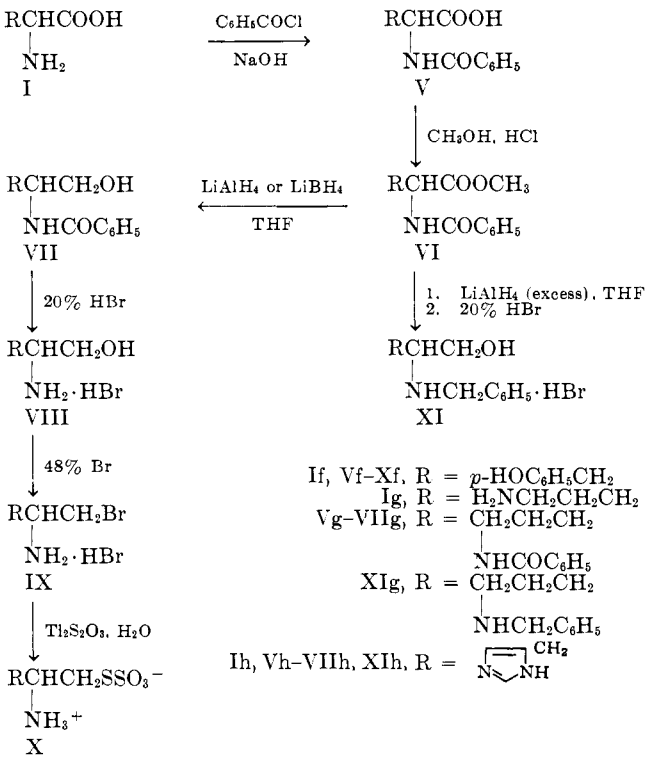
2-SUBSTITUTED 2-AMINOETHYLTHIOSULFURIC ACIDS

$RCHCH_2SSO_3^-$
|
NH_3^+

Compd.[a]	R	Yield, %	M.p., °C. dec.[b]	Formula	Calcd., % N	Calcd., % S	Found, % N	Found, % S
IVa	C_2H_5	68	206	$C_4H_{11}NO_3S_2$	7.56	34.62	7.82	34.45
IVb	C_3H_7	85	204.5	$C_5H_{13}NO_3S_2$	7.03	32.18	7.03	31.98
IVb (D)	C_3H_7	60	188	$C_5H_{13}NO_3S_2$	7.03	32.18	7.05	32.25
IVb (L)	C_3H_7	82	210.5	$C_5H_{13}NO_3S_2$	7.03	32.18	7.04	32.31
IVc	C_4H_9	83	204–204.5	$C_6H_{15}NO_3S_2$	6.57	30.08	6.69	30.32
IVd	*i*-C_4H_9	61	209.5	$C_6H_{15}NO_3S_2$	6.57	30.08	6.21	29.93
IVe	*sec*-C_4H_9	69	194.5	$C_6H_{15}NO_3S_2$	6.57	30.08	6.51	29.56
Xf	*p*-$HOC_6H_4CH_2$	48	213	$C_9H_{13}NO_4S_2$	5.32	24.35	5.51	24.85

[a] All compounds were DL except those indicated. [b] All were analytical samples and were crystallized from methyl alcohol.

SCHEME II



termined by X-ray diffraction.[14] It was confirmed that the assigned structure is correct. Table I contains a summary of the data on the aminothiosulfuric acids. These compounds were submitted to the Walter Reed Army Institute of Research for screening as potential radiation protective agents. Compound IVa showed good protective action in mice, whereas the remaining compounds were ineffective. The tests were carried out according to the methods described by Field, *et al.*[15] These results are summarized in Table II.

TABLE II

RADIATION PROTECTIVE DATA ON BUNTE SALTS[a]

$RCHCH_2SSO_3^-$
|
NH_3^+

Compd.[b]	R	Dose range, mg./kg.[c]	Protection[d]
IVa	C_2H_5	151–350	Good
IVb	C_3H_7	51–150	None
IVb (D)	C_3H_7	Not tested	
IVb (L)	C_3H_7	51–150	None
IVc	C_4H_9	51–150	None
IVd	*i*-C_4H_9	51–150	None
IVe	*sec*-C_4H_9	750 or more	None
Xf	*p*-HOC_6H_4	51–150	None

[a] We are indebted to Drs. D. Jacobus and T. R. Sweeney, Walter Reed Army Institute of Research, Washington 12, D. C., for making these data available to us. The details of the screening procedure can be found in ref. 15. [b] All compounds are DL except those indicated. [c] All compounds were administered intraperitoneally to mice in water solution. [d] The activity scale is based on cysteamine which is rated good against fully lethal loses of X-radiation (800 r.) in 30-day survival tests in mice.

Experimental Section[16]

D-Valinol (IIb).—A suspension of 33 g. (0.87 mole) of $LiAlH_4$ in 700 ml. of THF (dried over $LiAlH_4$) was prepared under anhydrous conditions and cooled to 10°. To the agitated mixture was added 44.6 g. (0.38 mole) of D-valine during the course of 45 min. The temperature of the reaction mixture was maintained at 10° for 30 min. after completion of addition of the valine and was then allowed to come to room temperature. The mixture was kept under reflux for 2 hr. on a water bath, and the excess hydride was decomposed by dropwise addition of water. The solid materials were removed by filtration, slurried three times in methylene chloride and once in benzene. The combined filtrates were washed twice with water, dried (Na_2SO_4), and evaporated. The residue was distilled and collected at 80–90° (0.2 mm.), m.p. 39–40° [lit.[4] b.p. 95–100° (10 mm.) for the DL isomer].

D-Valinyl Bromide Hydrobromide (IIIb).—To 128 ml. of 48% HBr, cooled to 5–10°, was added 31 g. (0.3 mole) of D-valinol dropwise with agitation and continued cooling. The temperature was raised to boiling during the course of 1 hr., and 34.8 ml. of liquid was distilled through a Vigreux column. The heat input to the flask was reduced so that the liquid continued to reflux in the column but did not distil. At the end of 1 hr., an additional 12.8 ml. was distilled. Following is the distillation schedule observed with intermittent hourly reflux periods: 34.8 ml., 12.8 ml., 10.4 ml., 5.2 ml., 4.6 ml., 3.3 ml., 1.8 ml., 0.9 ml., and after refluxing for 3 hr. 42.1 ml. was removed during a final distillation. The residue was allowed to cool to about 80–90° and was dissolved in 100 ml. of methyl alcohol. The solution was treated with decolorizing carbon, filtered, and evaporated to a syrup. Isopropyl ether was added, and the syrupy product crystallized. It was filtered, and the crystals were washed with additional isopropyl ether until no more color was removed. The yield of product was 82%, m.p. 150–155° dec. An analytical sample was crystallized from methyl alcohol; m.p. 154–156° dec.

Anal. Calcd. for $C_5H_{13}Br_2N$: Br, 64.71; N, 5.67. Found: Br, 64.90; N, 5.95.

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(16) This work was completed several years ago, and the melting points were then taken in a Hershberg melting point apparatus and are uncorrected. Infrared data were obtained with a Perkin-Elmer Infracord. The methods of synthesis of the analogous compounds are similar, and the particular derivatives described in detail are for illustrative purposes.

D-Valinyl bromide hydrobromide (IIIb) was prepared as above (yield 78%, m.p. 195–202° dec.). An analytical sample was crystallized from methyl alcohol; m.p. 203.5–204° dec.

Anal. Calcd. for $C_5H_{13}Br_2N$: Br, 64.71; N, 5.67. Found: Br, 64.50; N, 5.71.

D-Valinylthiosulfuric Acid (IVb).—A mixture of 29.6 g. (0.12 mole) of D-valinyl bromide hydrobromide, 90 g. (0.12 mole) of thallous thiosulfate,[9] and 240 ml. of water was agitated by means of a magnetic stirrer for 6 hr. The aqueous phase was removed by filtration, and the filter cake was washed twice with water at 50° and with 2 vol. of boiling methyl alcohol. The combined filtrates were evaporated in a flash evaporator below 50°, and the residue was slurried in acetone. The yield of product was 9.4 g., m.p. 178–182° dec. An additional 3.4 g. (m.p. 175–177° dec.) of product was recovered from the wash liquids. An analytical sample was crystallized from methyl alcohol; m.p. 188° dec.

Benzoyl-DL-tyrosine Methyl Ester (VIf).—To a solution of 184 g. (0.66 mole) of benzoyl-DL-tyrosine[17] in 1500 ml. of dry methyl alcohol was added with agitation a stream of dry HCl to saturation at room temperature. Agitation was continued overnight, after which the excess solvent was flash evaporated. The residue was dissolved twice in methyl alcohol and evaporated to remove the excess HCl. The syrupy product was then dissolved in water, made slightly ammoniacal, and refrigerated overnight. The ester was removed by filtration, ground, washed free of chloride with water, and dried under vacuum (H_2SO_4) at 50° overnight. The yield of product was 156 g. (79%), m.p. 155–159°. An analytical sample was prepared by recrystallization from a mixture of methyl alcohol and isopropyl alcohol; m.p. 159.5–160.5°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.54; H, 5.73; N, 4.78.

Dibenzoyl-DL-ornithine methyl ester (VIg) was prepared from benzoyl-DL-ornithine[18] by the method described for the preparation of VIf. The yield of product was 80%, m.p. 144–147°. An analytical sample was crystallized from isopropyl alcohol; m.p. 145–146°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.86; H, 6.70; N, 7.34.

Benzoyl-DL-tyrosinol (VIIf).—To a solution of 75 g. (0.25 mole) of VIf in 750 ml. of THF was added 7.1 g. (0.275 mole, 84.6% assay) of $LiBH_4$. The mixture was agitated and kept under reflux for 6 hr. After evaporation of the THF, the boron was removed by boiling a methyl alcoholic solution of the residue in the presence of 10 ml. of concentrated HCl to a reduced volume. This procedure was repeated twice with the addition of methyl alcohol. The crude product, dissolved in a small volume of methyl alcohol, was precipitated by addition of water. It was washed free of lithium salts with water and dried at 70° overnight. The yield of VIIf was 90%, m.p. 160-164°. An analytical sample was obtained by recrystallization from water, m.p. 164–165°.

Anal. Calcd. for $C_{16}H_{18}NO_3$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.83; H, 6.50; N, 5.22.

Dibenzoyl-DL-ornithinol (VIIg) was prepared as above for VIIf. The yield of product was 36%, and an analytical sample was crystallized from a mixture of isopropyl alcohol and isopropyl ether; m.p. 153–154°.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.46; H, 6.67; N, 8.93.

DL-Tyrosinol Hydrobromide (VIIIf).—Sixty grams (0.21 mole) of VIIf was heated under reflux with 720 ml. of 24% HBr overnight. After cooling to 5°, benzoic acid was removed by filtration, and the filtrate was extracted several times with ether. The filtrate was evaporated to near dryness under reduced pressure, and the residue was further dried under vacuum over H_2SO_4 for several days. The yield of product was 53.5 g. (97%), m.p. 167–172°. An analytical sample could not be prepared.

Benzyl-DL-histidinol Dihydrobromide (XIh).—To 1500 ml. of THF was added 76.6 g. (0.28 mole) of benzoyl-DL-histidine methyl ester (VIh),[11] and the solution was cooled to 10°. Lithium aluminum hydride (25.2 g., 0.67 mole) was added in small portions with agitation and continued cooling. Upon completion of addition of the hydride, the mixture was allowed to come to room temperature and was then heated under reflux for 2 hr. It was allowed to cool to room temperature with stirring overnight. The excess hydride was decomposed with water at 10° and the aqueous THF was removed by filtration. The filter cake was extracted twice with THF, and the combined filtrates were treated with charcoal and flash evaporated to yield a syrupy product. To 51 g. of this product was added 450 ml. of 20% HBr, and the mixture was warmed with intermittent shaking until a clear solution was obtained. It was treated several times with decolorizing carbon and evaporated to dryness under reduced pressure. The solid residue was slurried in acetone, filtered, and dried at 70° overnight. The product was obtained in 90% yield (78 g.), and an analytical sample was prepared by crystallization from isopropyl alcohol; m.p. 187–188°.

Anal. Calcd. for $C_{13}H_{19}Br_2N_3O$: C, 39.72; H, 4.87; N, 10.69. Found: C, 39.32; H, 4.80; N, 10.38.

Dibenzyl-DL-ornithinol dihydrobromide (XIg) was prepared in the same manner as XIh. The yield of product was 31%, m.p. 235.5–236.5° (analytical sample).

Anal. Calcd. for $C_{19}H_{29}Br_2N_2O$: C, 49.46; H, 6.35; N, 6.07. Found: C, 49.43; H, 6.22; N, 5.96.

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2-Trifluoromethyladenosine

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A number of 2-substituted adenosines, in particular 2-chloroadenosine, has been shown to inhibit the adenosine diphosphate induced aggregation of platelets[1] and to possess vasodilator properties.[2] 2-Trifluoromethyladenosine has been synthesized for evaluation of its vasodilator and antiagglutination effects.

Fusion[3] of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[4] with 2-trifluoromethyl-6-chloropurine[5] in the presence of *p*-toluenesulfonic acid followed by simultaneous removal of the blocking groups and amination with methanolic ammonia gave a gel-like crude product from which pure 2-trifluoromethyladenosine was isolated by crystallization first from 1-propanol and then from water.

Preliminary pharmacological evaluation of 2-trifluoromethyladenosine in this department[6] has shown

TABLE I
RELATIVE POTENCY

Compd.	Inhibition of ADP[a]-induced aggregation	Vasodilator effect
Adenosine	1	1
2-Chloroadenosine	4	4
2-Trifluoromethyladenosine	0.025	0.05

[a] ADP = adenosine diphosphate.

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(6) By courtesy of Miss D. Radford and Mr. F. Michal of this Department.