of Southern Research Institute for biological data; to Mrs. Luverne Mattil for assistance in the compilation of the data in Table IV; to Mr. W. E. Fitzgibbon, Jr., and his staff (Mrs. Sarah Jo Clayton, Mr. Francis Chen, Mrs. Lucy Rose, Mrs. Anita Shortnacy) for preparation of some of the intermediates and products in large amounts; and to Dr. W. J. Barrett, Dr. P. D. Sternglanz, and members of the Analytical Chemistry Section of Southern Research Institute who performed the microanalytical and spectral determinations.

The Use of α-Amino Acids in the Synthesis of Derivatives of 2-Aminoethanethiol as Potential Antiradiation Agents[1]

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The utility of α-amino acids as intermediates in multistep syntheses of derivatives of 2-aminoethanethiol as potential antiradiation agents has been further demonstrated; the types of compounds synthesized included S-substituted derivatives of 2-aminoalkanethiols, 2-amino-2-methylalkanethiols, and 1-aminocycloalkanemethanethiols—chiefly inner Bunte salts and phosphorothioates—and cyclic dithiocarbamates, in addition to a number of the aminothiols themselves. A convenient method for the preparation of amino acid esters from 2-alkanones and cycloalkanones was developed by combining a modified Strecker amino acid synthesis with the Fischer amino acid esterification. Applied to 1,4-cyclohexanedione, this method led to the synthesis of a novel bisaziridine, 1,7-diazaspiro[2.2.2.2]decane (**37**), and to a novel synthesis of 1,4-diamino-1,4-cyclohexanedimethanethiol diphosphate (**40**), which involved hydrolysis of the corresponding bis(phosphorothioic acid) **39b** in 1 *M* phosphoric acid. The following products so derived afforded mice good protection against lethal radiation in a standard test: sodium hydrogen S-2-amino-3-methylbutylphosphorothioate (**5d**), S-2-amino-2-methylpropylthiosulfuric acid (**16b**), S-2-amino-2-methylpropylphosphorothioic acid (**16c**), and tetrahydro-1H,3H-thiazolo[4,3-*c*][1,4]thiazine-3-thione (**29**).

The lithium aluminum hydride reduction of α-amino acid esters by Karrer, *et al.*,[2] provided a synthetic route to 2-substituted 2-aminoethanols that is particularly useful if the desired substituent is contained in a readily available amino acid. Vogl and Pöhm demonstrated later that a direct reduction of amino acids could be achieved similarly.[3] Thus, in the present work, 2-amino-1-pentanol (**1**, R = n-C_3H_7) was obtained by the reduction of both ethyl DL-norvalinate and DL-norvaline. Conversion of the resultant 2-aminoalkanols **1** to the corresponding 2-bromoethylamine hydrobromides **3** was accomplished either directly by the action of (1) phosphorus tribromide on the preformed hydrobromide [as with 2-amino-3-phenyl-1-propanol[4] (**1**, R = $C_6H_5CH_2$) from DL-phenylalanine] and (2) refluxing 48% hydrobromic acid[5] [as with L-leucinol (**1**, R = i-C_4H_9) from L-leucine], or indirectly by the hydrobromic acid ring opening of the aziridine derived by the Wenker method[6,7] [as with DL-valinol (**1**, R = i-C_3H_7) from DL-valine *via* 2-isopropylaziridine (**2**)]. These examples, then, typify the amino acid derived intermediates that led to the preparation of a number of S-substituted 2-aminoalkanethiols, chiefly inner Bunte salts and phosphorothioates, which were desired as analogs of known radioprotective compounds.[8] The syntheses outlined in Chart I were based on 2-aminoalkanols derived from common amino acids; a subsequent synthesis based on commercially available 2-amino-2-methylbutyric acid (**7**) is shown in Chart II. Some examples of the utility of amino acids in the synthesis of potential antiradiation compounds have recently been reported.[12]

Commercially available 2-amino-2-methyl-1-propanol (**12**) and later 2,2-dimethylaziridine (**13**, R = CH_3) were used as starting materials for the synthesis of 2-amino-2-methylpropanethiol (**16a**) and several of its S-substituted derivatives by the route outlined in Chart II. The radioprotective activity shown by S-2-amino-2-methylpropylthiosulfuric acid (**16b**) in an initial test inspired the synthesis of a series of S-2-amino-2-methylalkylthiosulfuric acids in which one of the methyl groups of **16b** is replaced by other alkyl groups as in the route **7** → **16e** already mentioned. Development of practical methods for the preparation of the intermediate amino acid esters **10** was requisite since neither these esters nor the corresponding amino acids (except **7**) were readily available. The general procedure that evolved, as applied to 2-alkanones (**8**), combines a modified Strecker amino acid synthesis

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) P. Karrer, P. Portmann, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

(3) O. Vogl and M. Pöhm, *Monatsh. Chem.*, **83**, 541 (1952).

(4) W. J. Gensler and J. C. Rockett, *J. Am. Chem. Soc.*, **74**, 4451 (1952).

(5) F. Cortese, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 91.

(6) (a) H. Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935); (b) P. E. Fanta, "Heterocyclic Compounds with Three- and Four-membered Rings," Part One, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 528–532.

(7) T. L. Cairns, *J. Am. Chem. Soc.*, **63**, 871 (1941).

(8) For example: 2-amino-1-propanethiol,[9] S-2-aminoethylthiosulfuric acid,[10] and S-2-aminoethylphosphorothioic acid.[11]

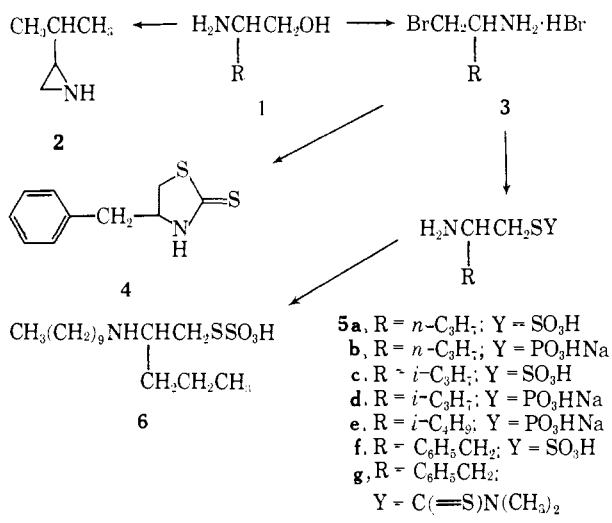
(9) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, p 66.

(10) B. Holmberg and B. Sörbo, *Nature*, **183**, 832 (1959).

(11) (a) B. Hansen and B. Sörbo, *Acta Radiol.*, **56**, 141 (1961); (b) S. Åkerfeldt, *Acta Radiol., Therapy, Phys. Biol.*, **1**, 465 (1963); *Chem. Abstr.*, **60**, 13534 (1964).

(12) (a) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963); (b) D. L. Klayman, J. W. Lown, and T. R. Sweeney, *ibid.*, **30**, 2275 (1965); (c) G. R. Handrick, E. R. Atkinson, F. E. Granchelli, and R. J. Bruni, *J. Med. Chem.*, **8**, 762 (1965); (d) H. Gershon and R. Rodin, *ibid.*, **8**, 864 (1965).

CHART I



modeled after that described by Steiger[13] with the amino acid esterification described by Fischer,[14] but the tedious isolation of intermediate amino acids was avoided by use of the dried Strecker reaction mixtures, which contained ammonium chloride and sodium chloride, in the esterification step. The first attempt to prepare ethyl 2-amino-2,3-dimethylbutyrate (**10**, R = *i*-C_3H_7) from 3-methyl-2-butanone (**8**, R = *i*-C_3H_7) by this method, however, led to the isolation of 2-amino-2,3-dimethylbutyronitrile (**9**), which is apparently sterically hindered toward hydrolysis and imino ester formation. This difficulty was subsequently overcome by a rigorous protraction of the hydrolysis step. The remaining sequential steps followed the pattern already established for the more accessible amino acid esters with the exception that conversions of the 2-amino-2-methylalkanols **11**, which have tertiary branching next to the amino group, were effected only by way of the 2-alkyl-2-methylaziridines **13**, direct conversions under prolonged Cortese conditions[5] having failed. The over-all scheme has a molecular weight limitation as illustrated by the sequence beginning with 2-tridecanone; the attempted conversion of 2-amino-2-methyl-1-tridecanol (**11**, R = *n*-$C_{11}H_{23}$) to 2-methyl-2-undecylaziridine by the Wenker method failed because charring occurred under reaction conditions too mild for the formation of the intermediate hydrogen sulfate ester.

The hydrobromic acid ring opening of the aziridines **13** encountered in this work is presumed to give amines having tertiary α-carbons by the same SN2 mechanism that was previously demonstrated for 2,2-dimethylaziridine.[15] Cortese conversion of the 2-aminoalkanols **1** to the 1-(bromomethyl)alkylamines **3** circumvented the preparation of intermediate 2-alkylaziridines, but does not preclude possible product ambiguity in the reaction of **3** with nucleophiles such as thiosulfate and phosphorothioate ions *via* aziridine intermediates.[16] The Bunte salt obtained from 1-(bromomethyl)-2-methylpropylamine hydrobromide (**3**, R = *i*-C_3H_7) was indicated to be S-2-amino-3-methylbutylthiosulfuric acid (**5c**) by a pmr study based on the method of Lown and Klayman;[12b,17] in D_2O the absorption peaks attributed to the CH proton broadened on acidification indicating spin-spin coupling with the NH_3^+ protons while the CH_2 peaks remained sharp, although the spectral changes due to acidification were not as pronounced as in the cited example[17] and were hardly observable in the case of isomeric S-2-aminopentylthiosulfuric acid (**5a**). In the sequence leading to **5c** and the corresponding monosodium phosphorothioate **5d** vigorous Cortese treatment of **1** (R = *i*-C_3H_7) gave impure **3** (R = *i*-C_3H_7); but pure **3** (R = *i*-C_3H_7) was obtained *via* 2-isopropylaziridine (**2**), and both the pure and impure bromoamines produced identical samples of **5c**. The identity of the Bunte salt derived from 1-(bromomethyl)ethylamine hydrobromide and from 2-methylaziridine has been recently and clearly established as S-2-aminopropyl thiosulfuric acid;[12b] these findings lend support to the structures assigned to products of nucleophilic displacements depicted in Charts I and II.

The general sequence of reactions used for the conversion of 2-alkanones to S-2-amino-2-methylalkylthiosulfuric acids **16** (**b**, **e**, **g**, and **i**-**l**) was found applicable to the conversion of the cycloalkanones **19** (**a** and **b**) to the corresponding S-1-aminocycloalkanemethylthiosulfuric acids **26a1** and **26b** according to the route outlined in Chart III. In addition, the known[18] intermediate 1-azaspiro[2,5]octane (**22b**) was utilized in a ring opening with H_2S under conditions described by Bestian[19] for opening of ethyleneimine itself, and the resultant 1-aminocyclohexanemethanethiol (**23b**) was characterized as such and as the hydrochloride. The structure of **23b** was proved by a comparison of the physical constants of the derived 1-[(benzylthio)methyl]cyclohexylamine (**24**) and its hydrochloride with those of the isomeric 1-(benzylthio)-cyclohexanemethylamine reported by Carroll, *et al.*[20] Subsequently the aziridine ring of **22b** was opened with thiosulfate ion in cold water, and the S-1-aminocyclohexanemethylthiosulfuric acid (**26b**) so obtained was identical with that prepared from 1-(bromomethyl)-cyclohexylamine hydrobromide (**25b**). 1-Aminocyclopentanemethanethiol (**23a**) was prepared from 1-azaspiro[2,4]heptane (**22a**), and S-1-aminocyclopentanemethylphosphorothioic acid (**26a2**) from 1-(bromomethyl)cyclopentylamine hydrobromide (**25a**) by the conventional Åkerfeldt procedure.[21] Potassium car-

(13) (a) R. E. Steiger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 68.

(14) (a) E. Fischer, *Ber.*, **34**, 433 (1901); (b) E. Fischer and Y. Suzuki, *ibid.*, **38**, 4173 (1905).

(15) J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and R. C. Lawes, *J. Am. Chem. Soc.*, **80**, 3158 (1958).

(16) For discussions of neighboring-group participation in the reactions of haloalkylamines see, for example: (a) E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1954, pp 356–359; (b) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, pp 570–571; (c) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp 121–129; (d) W. J. C. Ross, "Biological Alkylating Agents," Butterworth and Co. (Publishers) Ltd., London, 1962, pp 11–13.

(17) J. W. Lown and D. L. Klayman, quoted in No. 00 NMR at Work Series by Varian Associates, Analytical Instrument Division, Palo Alto 38, Calif.

(18) (a) P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, **24**, 526 (1959); (b) H. Najer, R. Giudicelli, and J. Sette, *Bull. Soc. Chim. France*, 2572 (1964).

(19) H. Bestian, *Ann. Chem.*, **566**, 210 (1950).

(20) F. I. Carroll, J. H. White, and M. E. Wall, *J. Org. Chem.*, **28**, 1240 (1963).

(21) (a) S. Åkerfeldt, *Acta Chem. Scand.*, **13**, 1179 (1959); (b) *ibid.*, **14**, 1980 (1960); (c) *ibid.*, **16**, 1897 (1962).

Chart II

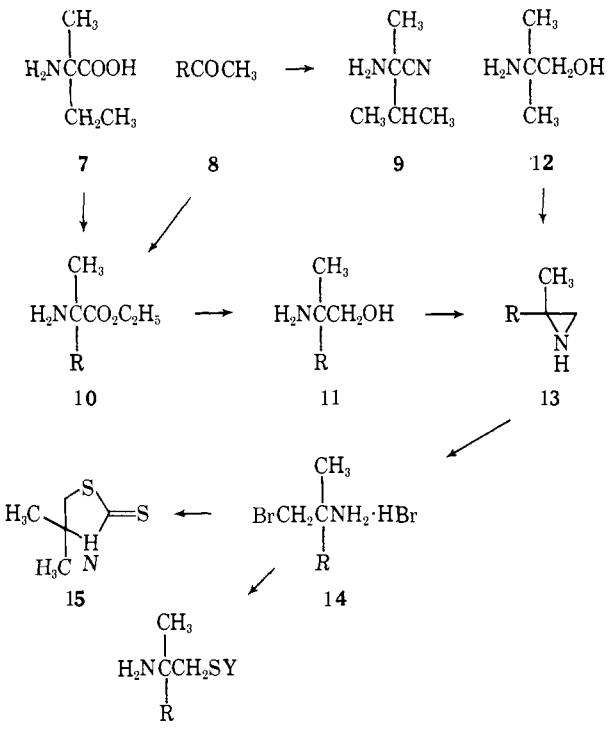
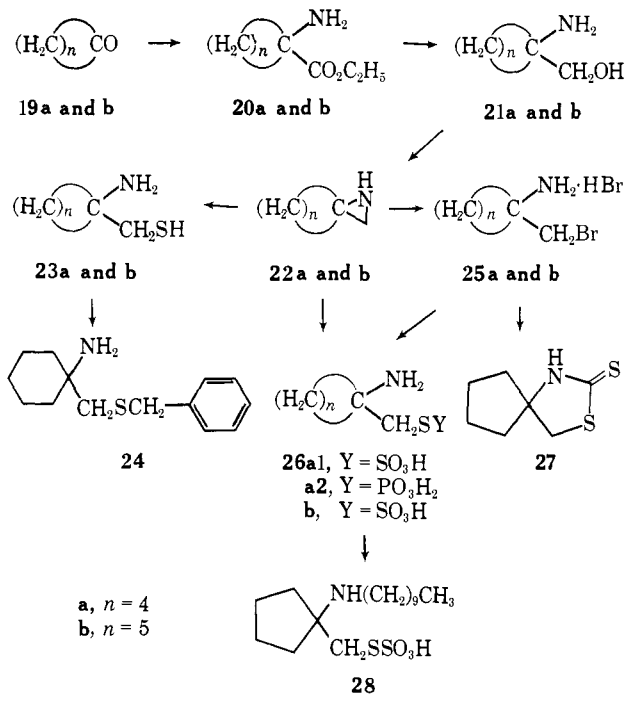


Chart III



bonate effected ring closure of **25a** with CS_2 in dimethylformamide (DMF) to give 3-thia-1-azaspiro[4.4]nonane-2-thione (**27**). 4-Benzyl-2-thiazolidinethione (**4**) and 4,4-dimethyl-2-thiazolidinethione (**15**) were obtained by similar, respective cyclizations of **3** (R = $C_6H_5CH_2$) and **14** (R = CH_3). These cyclizations extended the method previously applied to 2-(chloromethyl)pyrrolidine and 2-(2-chloroethyl)piperidine;[12a] 3-(bromomethyl)thiomorpholine hydrobromide,[12a] which was also derived from an amino acid ester, was cyclized similarly to give tetrahydro-1H,3H-thiazolo[4,3-*c*]-[1,4]thiazin-3-one (**29**) and was also converted to sodium hydrogen S-3-thiomorpholinylmethylphosphorothioate (**30**).[22] S-1-Decylaminocyclopentanemethylthiosulfuric acid (**28**) was prepared by decylation with 1-bromodecane of the potassium salt of compound **26a1**, formed *in situ* in DMF with potassium bicarbonate. S-2-Decylaminopentylthiosulfuric acid (**6**) and S-2-decylamino-2-methylpropylthiosulfuric acid (**17**) were similarly prepared from compounds **5a** and **16b**, respectively. This method, which is applicable to DMF-soluble potassium Bunte salts and is a variation of the recently described N-alkylations of sodium S-2-aminoethylthiosulfate in aqueous ethanol,[23] was also adapted to the preparation of the N,N′-alkylenebis(S-2-amino-2-methylpropylthiosulfuric acids) **18** (**a** and **b**); the yields were low, and the method was not successful when the alkylene group was tetramethylene (from 1,4-diiodobutane) probably because of preferential pyrrolidine ring formation.

The synthesis of S,S′-1,4-diamino-1,4-cyclohexylenedimethylenebis(thiosulfuric acid) (**39a**), the corresponding bis(phosphorothioic acid) **39b**, and 1,4-diamino-1,4-cyclohexanedimethanethiol as the diphosphate salt **40** from 1,4-cyclohexanedione (**31**) was adapted from the conversions of cycloalkanones described above and is outlined in Chart IV. The intermediate 1,4-diamino-1,4-cyclohexanedicarboxylic acid (**33**), a known amino acid derived from 1,4-diamino-1,4-cyclohexanedicarbonitrile (**32**),[24] underwent slow esterification with methanol saturated with HCl to give the dimethyl ester **34**, whose reduction in tetrahydrofuran with lithium aluminum hydride afforded a low yield of 1,4-diamino-1,4-cyclohexanedimethanol (**35**). It was subsequently found that **35** was more easily isolated as the dihydrobromide than as the free base with a consequent increase in yield. Although earlier conversions of amino alcohols structurally related to **35** involved aziridine formation followed by

(22) The corresponding Bunte salt was described previously.[12a]
(23) D. L. Klayman and W. F. Gilmore, *J. Med. Chem.*, **7**, 823 (1964).
(24) N. Zelinsky and N. Schlesinger, *Ber.*, **40**, 2888 (1907).

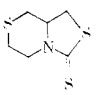
Table I

Antiradiation Protection of Mice against Lethal Radiation[a]

R_1

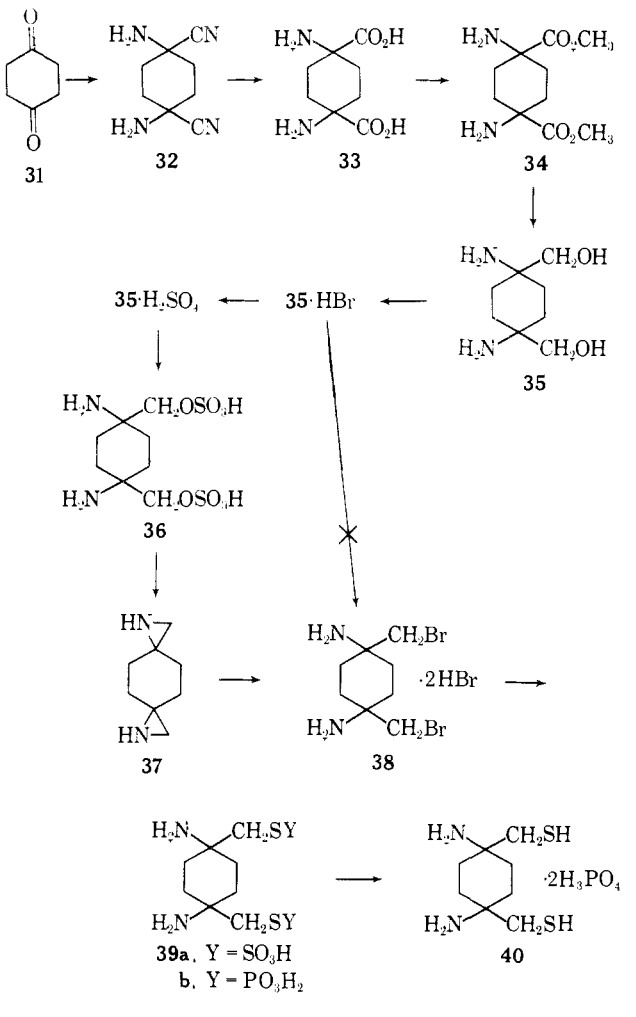
H_2NCCH_2SY

R_2

No.	R_1	R_2	Y	Approx LD_{50}, mg/kg	Drug dose, mg/kg	Vehicle of administration	pH of prepn	% survival
5b	*n*-C_3H_7	H	PO_3HNa	375	125	Water	7.1	27
5d·$3H_2O$	*i*-C_3H_7	H	PO_3HNa	600	300	Saline	8.1	67
					150			40
16b	CH_3	CH_3	SO_3H	800	600	Water	7.1	80
16c	CH_3	CH_3	PO_3H_2	750	600	Water	7.2	95
26a1	$-(CH_2)_5-$		SO_3H	900	300	Saline	5.5	87
					150			47
26a2	$-(CH_2)_5-$		PO_3H_2	300	200	Saline	6.0	13
26b	$-(CH_2)_6-$		SO_3H	300	200	MC-Tw[b]	6.2	40
29				140	100	MC-Tw[b]	7.1	83
					75			100
					37.5			67

[a] 825 r (X-rays), 1000 r (γ rays). [b] MC-Tw, compound suspended in physiological saline solution containing 0.2% methylcellulose (4000 cp) and 0.4% Tween 80.

Chart IV



ring opening with hydrobromic acid, efforts were made to convert **35**·2HBr to 1,4-bis(bromomethyl)-1,4-cyclohexanediamine dihydrobromide (**38**) directly. Refluxing mixtures of **35**·2HBr and pure phosphorus tribromide or a solution of PBr_3 in *o*-dichlorobenzene produced no reaction, a result possibly due to insolubility of **35**·2HBr in both media. Heating a mixture of **35**·2HBr and a 30% solution of HBr in acetic acid in a sealed tube at 150–155° for 12 hr also failed to produce **38**. Attention was then directed to the preparation of 1,7-diazaspiro[2.2.2.2]decane (**37**) by the Wenker method. Preparation of the requisite 1,4-cyclohexanedimethanol bis(hydrogen sulfate) (**36**) involved conversion of **35**·2HBr to **36**·H_2SO_4 with silver sulfate[25] followed by esterification with a slight excess of sulfuric acid. The product of the Wenker ring closure was purified by sublimation and then converted to **38** by ring opening with hydrobromic acid. Loss in yield due to purification of **37** was subsequently circumvented by addition of the aqueous distillate from the Wenker ring closure to cold hydrobromic acid, thus justifying the preparation of **38** as an intermediate for the final step even though the bisaziridine **37** could possibly have been converted directly to **39a** and the free dithiol corresponding to **40**. The actual route to **40**, however, involved the hydrolysis of **39b** in refluxing 1 *M* phosphoric acid, which promises to be representative of a general method. The stereochemical aspects of this series of reactions have not been considered.

Biological Results.—End products of the reaction sequences described above were tested as radioprotectors of mice exposed to lethal radiation; the tests were performed at the Walter Reed Army Institute of Research,[26] Washington, D. C., essentially according to a previously reported procedure.[27] Results are presented in Table I for only those compounds that showed fair or good protection (fair, 26–44% survival; good, 45–100% survival). Both S-2-amino-2-methylpropylthiosulfuric acid (**16b**) and S-2-amino-2-methylpropylphosphorothioic acid (**16c**)

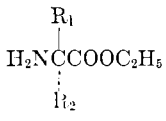
(25) C. G. W. Kohler and H. McKennis, Jr., *J. Biol. Chem.*, **152**, 103 (1944).

(26) Data made available to us by Drs. D. P. Jacobus and T. R. Sweeney.

(27) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

TABLE II

ETHYL ESTERS **10**, **20a**, AND **20b** FROM 2-ALKANONES AND CYCLOALKANONES



R_1	R_2	Ketone reaction time, hr	Nitrile hydrolysis time, hr	Method of neutralization[a]	Yield, %	Bp, °C (mm)	n_D (t, °C)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH_3	n-C_3H_7	20	18	B	67	86-88 (23)	1.4233 (23)	$C_8H_{17}NO_2$	60.34	10.76	8.80	60.29	10.96	8.22
CH_3	i-C_3H_7	17	30	B	22	101-107 (17)	1.4273 (27)	$C_8H_{17}NO_2$	60.34	10.76	8.80	60.42	10.95	8.75
CH_3	n-C_4H_9	7	2.5	A	15	84-86 (11)	1.4283 (25)	$C_9H_{19}NO_2$	62.39	11.05	...	62.75	11.10	...
CH_3	i-C_4H_9	5	2.5	A	48	80 (12)[b,c]	1.4288 (20)	$C_9H_{19}NO_2$	...	...	...	...	...	...
CH_3	n-C_8H_{13}	5	6	B	52	115-118 (14)	1.4360 (20)	$C_{11}H_{23}NO_2$	65.63	11.52	6.92	65.79	11.50	6.80
CH_3	n-$C_{11}H_{23}$	6	7	B	48	106-108 (0.1)	1.4457 (20)	$C_{16}H_{33}NO_2$	70.80	12.25	5.16	70.99	12.29	5.25
-$(CH_2)_4$-		20	4	B	67	84-87 (10)[b,d]	1.4528 (25)	$C_8H_{15}NO_2$	...	...	...	...	...	...
-$(CH_2)_5$-		18	7	B	47	78 (4)[b,e]	1.4628 (20)	$C_9H_{17}NO_2$	...	...	...	...	...	...

[a] See text for details. [b] Prepared earlier[33] from amino acids obtained from hydantoins. [c] Lit.[33] bp 78–80° (12 mm), $n^{20}D$ 1.4200. [d] Lit.[33] bp 110–112° (36 mm), $n^{20}D$ 1.4535. [e] Lit.[33] bp 78–79° (4 mm), $n^{20}D$ 1.4603.

gave good protection, whereas the corresponding thiol (**16a**) hydrochloride was recently reported[12c] to give no protection.

S-2-Amino-2-methylpropyl thioacetate hydrobromide (**16d**) and S-2-decylamino-2-methylpropylthiosulfuric acid (**17**) provided good protection against sublethal radiation (750 r, γ rays), but were not tested against lethal radiation (1000 r, γ rays). Modification of the tertiary branch by replacement of one methyl group with another alkyl group resulted in either no protection or slight protection (5–25% survival). (Screening data for the cyclohexylenedimethylene derivatives **39a**, **39b**, and **40** were not available for this comparison.)

The products of the reaction scheme outlined in Chart I, which resulted in secondary branching, parallel a recently reported series of 2-amino-1-alkanethiol hydrochlorides[12c] and S-2-aminoalkyl Bunte salts[12d] in which 2-amino-1-pentanethiol, 2-amino-3-methyl-1-butanethiol, and S-2-aminobutylthiosulfuric acid were rated as good protectors. In the present work sodium hydrogen S-2-amino-3-methylbutylphosphorothioate (**5d**) provided good protection, and sodium hydrogen S-2-aminopentylphosphorothioate (**5b**), fair protection.

Of the cyclic dithiocarbamates tested, tetrahydro-1H,3H-thiazolo[4,3-*c*][1,4]thiazine-3-thione (**29**) gave good protection, and 3-thia-1-azaspiro[4.4]nonane-2-thione (**27**) was exceptionally toxic (approximate LD_{50}, 5 mg/kg).

Experimental Section[28]

Ethyl Norvalinate.—A solution of norvaline (50.0 g, 0.427 mole) in absolute ethanol (300 ml) saturated with anhydrous HCl was refluxed for 8 hr. Removal of the solvent by evaporation under reduced pressure (water pump) on a rotary evaporator at a temperature not exceeding 35° left a clear syrup, which was dissolved in cold water (40 ml). Ether (200 ml) was added, and the stirred, chilled mixture was treated with aqueous K_2CO_3 (30 g dissolved in 25 ml of water). The ether layer, to which was added several ether extracts of the aqueous phase, was dried ($MgSO_4$); fractionation under reduced pressure afforded the ester, bp 65–66° (8 mm) [lit.[29] bp 68.5° (8 mm)], in 50% yield (30.7 g).

Ethyl L-Leucinate, Ethyl Valinate, and Ethyl 2-Amino-2-methylbutyrate.—A solution of the appropriate commercially available amino acid (0.761 mole) in absolute ethanol (1 l.) saturated with anhydrous HCl was refluxed for 2 hr. Benzene (200 ml) was added, and the resultant solution was distilled through a 30-cm Vigreux column until the distillation temperature reached 80° (approximately 500 ml of distillate was collected during 4 hr). Remaining solvent was removed under reduced pressure (water pump) on a rotary evaporator with the aid of a warm (40–45°) water bath. The resultant crystalline residue was stirred thoroughly with a cold (0–5°), saturated solution (prepared at 0°) of anhydrous NH_3 in ethanol (150 ml). The mixture was then diluted with ether (600 ml) and filtered. Fractionation of the filtrate under reduced pressure afforded the indicated ester with yield, boiling point [lit. boiling point] as follows: ethyl L-leucinate, 77%, 81–82° (12 mm) [83.5° (12 mm)[30]]; ethyl valinate, 76%, 83–84° (22 mm) [82.5° (23 mm)[31]]; ethyl 2-amino-2-methylbutyrate, 72%, 71–72° (24 mm) [65–66 (20 mm)[29]].

Ethyl Phenylalaninate, bp 76–78° (0.02 mm), was similarly obtained in 43% yield from its **hydrochloride,** mp 122.5–124.5°, which was prepared in 76% yield by the procedure of Murakashi.[32]

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.38; H, 7.82. Found: C, 68.20; H, 7.78.

Ethyl Esters 10, 20a, and 20b from 2-Alkanones and Cycloalkanones *via* the Strecker Synthesis.—Intermediate aminonitriles were prepared *in situ* on 1.0-mole scales by the procedure of Steiger;[13] variation of the reaction period during which the stirred mixtures were maintained at 55–60° is reflected in the ketone reaction times listed in Table II. Subsequent HCl hydrolysis was carried out as described by Steiger; the various reflux periods used are listed in Table II (see nitrile hydrolysis time). The mixtures were then evaporated *in vacuo* to thorough dryness, and the resultant amino acid hydrochlorides were esterified in the presence of residual inorganic salts; a general procedure follows. The dry solid mixture was stirred in ethanol (500 ml) saturated with anhydrous HCl, and the resultant mixture was refluxed 5–7 hr. Benzene (100 ml) was added, and the mixture was distilled until the distillation temperature reached 78°. Remaining solvent was removed under reduced pressure (water pump) with the aid of a warm (40–45°) water bath. The pure ethyl esters were isolated by one of the two following methods, and the results are summarized in Table II.

Method A.—The residue was stirred with ether (600 ml) with external ice-bath cooling while cold 50% NaOH solution was gradually added until the mixture was basic. The ethereal phase, to which was added several ether extracts of the aqueous phase, was dried ($MgSO_4$) and fractionated under reduced pressure.

(28) Melting points not designated as having been taken on a Kofler Heizbank were taken on a Mel-Temp apparatus.

(29) M. D. Stimmer, *Ber.*, **35**, 400 (1902).

(30) E. Fischer, *ibid.*, **34**, 433 (1901).

(31) E. Krause, *Monatsh. Chem.*, **29**, 1119 (1908).

(32) I. Murakashi, *J. Pharm. Soc. Japan*, **76**, 1139 (1956).

TABLE III

2-AMINOALKANOLS (**1**), 2-AMINO-2-METHYL-1-ALKANOLS (**11**), AND 1-AMINOCYCLOALKANEMETHANOLS (**21a** AND **21b**)

		Yield,				Calcd, %		Found, %	
R₁	R₂	%	Bp, °C (mm)	$n^{20}D$	Formula	C	H	C	H
H	*n*-C_3H_7	84[a]	84–85 (8)	1.4531	$C_5H_{13}NO$	58.23	12.70	58.23	12.70
H	*i*-C_3H_7	70	86–88 (11)[b]	...	$C_5H_{13}NO$	...	...	...	...
H	*i*-C_4H_9	69	65 (1.5)[c]	...	$C_6H_{15}NO$	...	...	...	...
H	$C_6H_5CH_2$	55[d]	...	...	$C_9H_{13}NO$	...	...	...	...
CH_3	C_2H_5	86	91–93 (20)	1.4553	$C_5H_{13}NO$	58.23	12.70	58.16	12.90
CH_3	*n*-C_3H_7	86	101–103 (20)	1.4547	$C_6H_{15}NO$	61.49	12.90	61.69	12.75
CH_3	*i*-C_3H_7	72	100–102 (20)[e]	...	$C_6H_{15}NO$	61.49	12.90	61.29	12.85
CH_3	*n*-C_4H_9	86	101–103 (12)	1.4557	$C_7H_{17}NO$	64.03	13.05	64.20	13.09
CH_3	*i*-C_4H_9	84	97–99 (12)[f]	1.4549	$C_7H_{17}NO$	...	...	...	...
CH_3	*n*-C_8H_{17}	59	121–125 (9)	1.4600	$C_9H_{21}NO$	67.86	13.35	68.02	13.28
CH_3	*n*-$C_{10}H_{21}$	81	141 (0.15)[g]	...	$C_{11}H_{25}NO$	73.29	13.62	73.14	13.86
-$(CH_2)_4$-		68	72–74 (0.3)[h]	1.4931	$C_6H_{13}NO$	...	...	...	...
-$(CH_2)_5$-		76	76 (0.4)[i]	1.4977	$C_7H_{15}NO$	...	...	...	...

[a] Also prepared in 41% yield by direct reduction of norvaline (see text); *cf.* ref 12c. [b] Lit.[3] bp 95–100° (air bath, 10 mm). [c] E. Segal [*J. Am. Chem. Soc.*, **74**, 1096 (1952)] used catalytic reduction and reported bp 73–74° (1.4 mm) for the L form. [d] Yield of hydrobromide, mp 149–152° (lit.[4] mp 148–149°), which was prepared from the crude free base in a manner similar to that described previously.[4] [e] Distillate crystallized, mp 47–49°. [f] Detailed preparation of this compound given in text as a typical example. [g] Distillate crystallized, mp 30–31°. [h] Adkins and Billica[33] used catalytic reduction and reported bp 68–69° (1 mm) and $n^{20}D$ 1.4899. [i] Adkins and Billica[33] used catalytic reduction and reported bp 117–118° (27 mm) and $n^{20}D$ 1.4970.

Method B.—Anhydrous NH_3 was passed into a vigorously stirred, externally cooled mixture of the residue in ethanol (100 ml) and ether (1000 ml) until the mixture was saturated with NH_3. The solids were removed by filtration, and the filtrate was fractionated under reduced pressure.

2-Amino-2,3-dimethylbutyronitrile (9).—In the initial effort to prepare **10** (R = *i*-C_3H_8) from 3-methyl-2-butanone *via* the steps described in the preceding procedure, the reflux period allowed for nitrile hydrolysis was 3 hr. The remaining operations were carried out as described above in the general method in expectation of obtaining the ester **10** (R = *i*-C_3H_7). The isolated material, bp 71° (13 mm) and $n^{23}D$ 1.4365, proved to be **9**, the product of the initial reaction, in 48% yield.

Anal. Calcd for $C_6H_{12}N_2$: C, 64.25; H, 10.78. Found: C, 64.24; H, 10.80.

A sample of **9** was prepared for comparison purposes by ether extraction of the aminonitrile reaction mixture. Fractionation of the ether solution gave a colorless liquid, bp 70–71° (13 mm) and $n^{20}D$ 1.4361.

Dimethyl 1,4-Diamino-1,4-cyclohexanedicarboxylate (34).—A mixture of **33**[24] (48 g, 0.24 mole) and methanol (750 ml) saturated with anhydrous HCl was refluxed with stirring for 5 days or until virtually complete solution occurred. The solution was evaporated to dryness under reduced pressure, and the crystalline residue was stirred in the cold (0–5°) for 15 min with a saturated solution (prepared at 25°) of anhydrous NH_3 in methanol (200 ml). Ether (400 ml) was added, and the mixture was filtered. Removal of the solvents from the filtrate by evaporation under reduced pressure afforded a solid residue from which pure **34**, mp 122° (Kofler Heizbank), was obtained in 71% yield (38.8 g) following recrystallization from benzene.

Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.15; H, 7.88; N, 12.17. Found: C, 52.28; H, 7.75; N, 12.18.

2-Amino-2,4-dimethyl-1-pentanol (11, R = *i*-C_4H_9).—The following description is typical of the method used for preparing the amino alcohols listed in Table III. A solution of **10** (R = *i*-C_4H_9) (47.8 g, 0.276 mole) in ether (340 ml) was added dropwise during 2 hr to a mechanically stirred suspension of $LiAlH_4$ (16.0 g, 0.422 mole) in ether (340 ml). The mixture was refluxed for 30 min after completion of the addition and was then allowed to cool. More ether (600 ml) was added, and the diluted mixture was chilled to 0°. Water (57 ml) was then gradually added dropwise with vigorous stirring, the first few milliliters being added cautiously at the rate of only 3 or 4 drops/min. Stirring was continued for 15 min after all of the water had been added. The mixture was then filtered, and the insoluble matter was washed thoroughly with four 200-ml portions of ether. The total filtrate was dried ($MgSO_4$), and fractionation afforded pure **11** (R = *i*-C_4H_9) in 84% yield (30.3 g), bp 97–99° (12 mm) and $n^{20}D$ 1.4549 [lit.[33] bp 98–98.5° (12 mm) and $n^{20}D$ 1.4563 of product from catalytic reduction of the same ester].

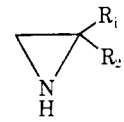
2-Amino-1-pentanol (1, R = *n*-C_3H_7).—Powdered norvaline (36.0 g, 0.308 mole) was gradually added during 1.5–2 hr through an addition sleeve to a vigorously stirred suspension of $LiAlH_4$ (18.0 g, 0.474 mole) in ether (1 l.). The resultant mixture was refluxed 6 hr and left standing at room temperature overnight. The mixture was then chilled to 0° and was carefully treated with water (64 ml) in the manner described above in the preparation of **11** (R = *i*-C_4H_9). Work-up afforded pure **1** (R = *n*-C_3H_7) in 41% (13.0 g) yield, bp 84–85° (8 mm) (identical with the sample prepared from ethyl norvalinate).

1,4-Diamino-1,4-cyclohexanedimethanol (35) Dihydrobromide.—A solution **34** (4.60 g, 20.0 mmoles) in sodium-dried tetrahydrofuran (THF) (100 ml) was added dropwise during 1 hr to a refluxing, mechanically stirred mixture of $LiAlH_4$ (2.32 g, 61.2 mmoles) in THF (75 ml). Refluxing with stirring was continued 2 hr longer. More THF (200 ml) was added, and the stirred mixture was chilled in an ice–water bath while a solution of water (2.5 ml) in THF (25 ml) was cautiously added dropwise; another solution of water (5.8 ml) in THF (15 ml) was then added more rapidly. NaOH solution (12 ml of 10%) was added, and the stirred mixture was allowed to warm to room temperature. The mixture was filtered, and the solid on the funnel was pressed as dry as possible. The filter cake was stirred into boiling ethanol (250 ml), and the mixture was filtered. The ethanol filtrate was combined with a small orange residue that remained following removal of the solvent from the original filtrate from the reaction mixture. The resultant solution was concentrated to about 100 ml, and the solution was treated with Norit and filtered through Celite. Hydrobromic acid (8 ml of 48% HBr) was added to the filtrate, and the crystalline precipitate of crude **35**·2HBr that separated was collected. Dilution of the filtrate with ether afforded a small second crop of dark solid that became white on being triturated with warm ethanol. The first and second crops (3.55 g and 0.60 g) were combined and recrystallized from 48% HBr; the recrystallized material was then reprecipitated from aqueous solution by addition of ethanol. Pure **35**·2HBr, mp 288–289° dec, was obtained in

[33] H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 3121 (1948).

Table IV

Substituted Aziridines **2, 13, 22a,** and **22b**



R_1	R_2	Yield, %	Bp, °C (mm)	n_D (t, °C)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	*i*-C_3H_7	34	100–103 (atm)	1.4199 (25)	$C_5H_{11}N$	...	...	16.45	...	...	16.11
CH_3	C_2H_5	38	97–98 (atm)	1.4174 (26)	$C_5H_{11}N$	70.57	13.02	16.45	70.07	13.27	16.15
CH_3	*n*-C_3H_7	47	120–125 (atm)	1.4258 (20)	$C_6H_{13}N$	72.64	13.21	14.12	71.84	13.43	14.01
CH_3	*i*-C_3H_7	39	111–116 (atm)	1.4261 (20)	$C_6H_{13}N$	72.64	13.21	14.12	72.66	13.41	13.93
CH_3	*n*-C_4H_9	53	60 (30)[a]	1.4307 (20)	$C_7H_{15}N$	74.27	13.36	12.38	73.90	13.33	12.23
CH_3	*i*-C_4H_9	31	56 (34)	1.4310 (20)	$C_7H_{15}N$	...	...	12.38	...	...	12.26
CH_3	*n*-C_6H_{13}	51	88 (22)	1.4407 (20)	$C_9H_{19}N$	76.52	13.56	9.92	76.30	13.61	9.69
$-(CH_2)_4-$		63	66–69 (51)	1.4704 (20)	$C_6H_{11}N$	74.17	11.41	14.42	74.08	11.53	14.32
$-(CH_2)_5-$		68	68 (23)	1.4762 (27)	$C_7H_{13}N$	75.62	11.78	12.60	75.79	11.98	12.4

[a] H. R. Heuze and W. D. Compton [*J. Org. Chem.*, **22**, 1036 (1957)] report bp 60–70° (30 mm) and $n^{20}D$ 1.4341 for product from reaction of *n*-butylmagnesium bromide and acetoxime.

51% yield (3.40 g). A larger run (0.104 mole of **34**) gave **35**·2HBr in 50% yield.

Anal. Calcd for $C_5H_{13}N_2O_2$·2HBr: C, 28.59; H, 6.00. Found: C, 28.46; H, 6.09.

In an earlier run pure **35** (free base), mp 215–217°, was isolated in 21% yield following the ethanol extraction of the insoluble solid matter. Removal of the solvent from the filtered solution left a solid residue, which was recrystallized from ethanol.

Anal. Calcd for $C_5H_{12}N_2O_2$: C, 55.16; H, 10.41; N, 16.08. Found: C, 55.01; H, 10.18; N, 16.06.

Treatment of **35**·2HBr with Ag_2SO_4 according to the method of Kilmer and McKennis[25] effected conversion to the sulfate (**35**·H_2SO_4), mp ~300° dec, which was obtained in 97% yield.

Anal. Calcd for $C_5H_{12}N_2O_2$·H_2SO_4: C, 35.27; H, 7.40. Found: C, 35.18; H, 7.36.

Substituted aziridines [**2**(R = *i*-C_3H_7), **13** (R = C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *i*-C_4H_9, *n*-C_6H_{13}), **22a**, and **22b**] listed in Table IV were prepared by the Wenker method as described by Cairns[7] for the preparation of **13** (R = CH_3) from **12** (R = CH_3) with slight modifications. (1) The formation under reduced pressure of the hydrogen sulfate esters was done on a rotary evaporator to facilitate degassing. (2) Some of the crude hydrogen sulfate esters lacked sufficient hardness to be pulverized. This type was dissolved in the minimum volume of warm (50–60°) water prior to use in the ring-closure step. (3) Following addition of KOH to the aqueous distillates containing the substituted aziridines, the upper layers were extracted with ether; the ether solutions were dried successively over KOH pellets, $MgSO_4$, and finally small chips of Na. Fractionation of the dried solutions afforded the aziridines (Table IV) as colorless liquids.

1,4-Diamino-1,4-cyclohexanedimethanol Bis(hydrogen sulfate) (36) Dihydrate.—Powdered **35**·H_2SO_4 (13.3 g, 48.9 mmoles) was dissolved in a boiling solution of H_2SO_4 (5.02 g of 96% H_2SO_4) in water (100 ml). The solution was distilled at atmospheric pressure until 70 ml of distillate had been collected. The flask containing the residual solution was then transferred to a rotary evaporator, and remaining water was removed under reduced pressure (water pump) with the aid of an oil bath at 50–60°. The oil bath temperature was then increased, and the grayish white residue was heated at 170–180° under reduced pressure for 1 hr. The gray solid formed was allowed to cool and was stirred with 1 *N* NaOH solution (100 ml). The resultant mixture, which contained a small amount of insoluble matter, was treated with Norit and filtered through Celite. Addition of 3 *N* HCl (34 ml) to the clear filtrate caused rapid precipitation of white crystals. The mixture was chilled, and the precipitate was collected and washed successively with cold water and ethanol. The product was dried to constant weight (12.80 g) *in vacuo* (P_2O_5) at room temperature, but initial analytical results were erratic because of hygroscopicity. After the sample had been allowed to equilibrate at 58% relative humidity (weight increased to 12.91 g), the material analyzed fairly satisfactorily for **36**·$2H_2O$, yield 71%, mp >300° dec.

Anal Calcd for $C_8H_{18}N_2O_8S_2$·$2H_2O$: C, 25.93; H, 5.99. Found: C, 25.82; H, 6.37.

1,7-Diazaspiro[2.2.2.2]decane (37).—A solution of **36**·$2H_2O$ (1.00 g, 2.70 mmoles) in 40% NaOH solution (5 ml) was heated to boiling under a distillation head equipped with a dropping funnel. The solution was distilled while water was added intermittently to maintain the volume in the distillation flask fairly constant. A total of 11 ml of water was added while two separate 6-ml portions of distillate were collected successively. KOH pellets were stirred into the separate portions until saturation was achieved. The white solid precipitate that formed in each was collected and dried *in vacuo* at room temperature. The two portions of crude solid thus obtained (0.33 and 0.07 g, respectively) were combined and sublimed at 70° and 0.3 mm to give pure **37**, mp 150–151°, in 46% yield (0.17 g).

Anal. Calcd for $C_8H_{14}N_2$: C, 69.51; H, 10.21; N, 20.27. Found: C, 69.57; H, 10.27; N, 20.23.

1-(Bromomethyl)butylamine hydrobromide (3, R = *n*-C_3H_7) **and 1-(bromomethyl)-3-methylbutylamine hydrobromide (3,** R = *i*-C_4H_9) were prepared from the appropriate 2-aminoalkanols (1, R = *n*-C_3H_7, *i*-C_4H_9) by the Cortese[5] method. The HBr remaining after the reaction period was removed under reduced pressure; the residue was dissolved in ethanol, and the solution was treated with Norit and filtered through Celite. Removal of the ethanol left a white residue, which was purified by recrystallization from acetonitrile. The results are included in Table V.

α-(Bromomethyl)phenethylamine Hydrobromide (3, R = $C_6H_5CH_2$).—A magnetically stirred mixture of 2-amino-3-phenyl-1-propanol (1, R = $C_6H_5CH_2$) hydrobromide[4] (14.0 g) in PBr_3 (28 ml) was refluxed for 10 min. The cooled mixture was stirred with ether (50 ml), and the solid material was collected. Dissolution in boiling ethanol followed by Norit treatment and filtration through Celite afforded a colorless filtrate from which the pure product was precipitated by addition of ether. The results are included in Table V.

2-Bromo-1,1-dimethylethylamine hydrobromide (14, R = CH_3) was prepared in 60% yield by HBr ring opening of **13** (R = CH_3) according to the instructions of Earley, *et al.*,[15] but an adaptation of the procedure described by Masters and Bogert[34] for the conversion of aziridine to 2-bromoethylamine hydrobromide proved more convenient. Use of the latter method gave **14** (R = CH_3), mp 185–186° (lit.[15] mp 185–186°), in 80% yield following recrystallization from acetonitrile.

1-(Bromomethyl)-2-methylpropylamine hydrobromide (3, R = *i*-(C_3H_7), **1-(bromomethyl)-1-methylalkylamine hydrobromides (14,** R = C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *i*-C_4H_9, *n*-C_6H_{13}), and **1-(bromomethyl)cycloalkylamine hydrobromides (25a** and **25b)** were also prepared by HBr ring opening of the appropriate aziridines (Table IV). The clear reaction solutions were evaporated to dryness under reduced pressure, and the crystalline residues were purified by recrystallization from ethyl acetate. Results are listed in Table V.

1,4-Bis(bromomethyl)-1,4-cyclohexanediamine Dihydrobromide (38).—A mixture of **36**·$2H_2O$ (10.7 g, 28.8 mmoles) and 50%

(34) E. J. Masters and M. T. Bogert, *J. Am. Chem. Soc.*, **64**, 2709 (1942).

Table V

1-(Bromomethyl)alkylamine (**3**), 1-(Bromomethyl)-1-methylalkylamine (**14**), and 1-(Bromomethyl)cycloalkylamine (**25a** and **25b**) Hydrobromides

$$R_1 \quad R_2$$
$$H_2NC(CH_2Br)\cdot HBr$$

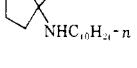
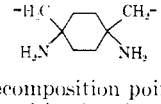
R_1	R_2	Yield, %	Mp, °C dec	Formula[a]	Calcd, % C	Calcd, % H	Calcd, % Br	Found, % C	Found, % H	Found, % Br
H	*n*-C_3H_7[c]	70	206–208[b]	$C_4H_{11}Br_2N$	24.31	5.31	64.71	24.10	5.19	64.7
H	*i*-C_3H_7[c]	59	214–216[d]	$C_4H_{11}Br_2N$	24.31	5.31	64.71	24.61	5.31	64.7
H	*i*-C_4H_9[c]	65	185[b]	$C_5H_{13}Br_2N$	27.61	5.79	61.24	27.86	5.67	61.0
H	$C_6H_5CH_2$	87	175[b,e]	$C_8H_{11}Br_2N$	...	...	...	...	...	...
CH_3	C_2H_5	78	156–157[f]	$C_4H_{11}Br_2N$	24.31	5.31	64.71	24.51	5.38	64.7
CH_3	*n*-C_3H_7	86	212–214[b]	$C_5H_{13}Br_2N$	27.61	5.79	61.24	27.54	5.99	61.3
CH_3	*i*-C_3H_7	62	218[b]	$C_5H_{13}Br_2N$	27.61	5.79	61.24	28.71	5.75	61.4
CH_3	*n*-C_4H_9	82	210–212[b]	$C_6H_{15}Br_2N$	30.67	5.86	58.10	30.62	6.27	57.9
CH_3	*i*-C_4H_9	77	214–216[f]	$C_6H_{15}Br_2N$	30.67	5.86	58.10	30.41	5.61	58.0
CH_3	*n*-C_5H_{11}	93	200[b]	$C_7H_{17}Br_2N$	35.66	6.65	52.73	36.00	7.00	52.8
$(CH_2)_4$		72	185–187	$C_5H_{11}Br_2N$	27.82	5.06	61.71	27.93	5.08	61.9
$(CH_2)_5$		77	214–216	$C_6H_{13}Br_2N$	30.79	5.17	58.54	30.95	5.28	58.5

[a] Previously prepared in apparently impure form.[24] [b] Observed on Kofler Heizbank. [c] D and L forms with widely different melting points have been reported.[24] [d] F. Barrow and G. W. Ferguson [*J. Chem. Soc.*, 410 (1935)] report mp 211–212°. [e] Lit.[3] mp 174–175°.

Table VI

S-Substituted Thiosulfuric Acids

$$RSSO_3H$$

No.	R	Yield, %	Approx mp, °C dec[a]	Recrystn solvent[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
5a	*a*-$C_3H_7CH(NH_2)CH_2$	81	240		$C_5H_{13}NO_3S_2$	30.14	6.57	...	...	29.93	6.35	...	...
5e[c]	*i*-$C_3H_7CH(NH_2)CH_2$	34	199–201	A	$C_5H_{13}NO_3S_2$	30.14	6.57	7.03	32.18	30.23	6.79	6.93	32.4
5f	$C_6H_5CH_2CH(NH_2)CH_2$	92	>260		$C_9H_{13}NO_3S_2$	43.71	5.30	...	25.93	43.84	5.41	...	26.1
6	*n*-$C_{10}H_{20}NHCHCH_2$ (*n*-C_3H_7)	52	252–254	B	$C_{15}H_{33}NO_3S_2$	53.05	9.79	...	18.88	53.23	9.62	...	18.9
16b[d]	$H_2NC(CH_3)_2CH_2$	70	240–245		$C_4H_{11}NO_3S_2$	25.92	5.98	...	34.61	25.85	5.84	...	34.6
16e	$H_2NC(CH_3)(C_2H_5)CH_2$	65	235–240	B	$C_5H_{13}NO_3S_2$	30.14	6.57	...	32.18	30.33	6.52	...	32.3
16g	$H_2NC(CH_3)(n\text{-}C_3H_7)CH_2$	57	218–223	C	$C_6H_{15}NO_3S_2$	33.78	7.09	...	30.07	33.67	6.85	...	29.9
16i	$H_2NC(CH_3)(i\text{-}C_3H_7)CH_2$	81	270	D	$C_6H_{15}NO_3S_2$	33.78	7.09	...	30.07	33.94	6.97	...	29.9
16j	$H_2NC(CH_3)(n\text{-}C_4H_9)CH_2$	76	216–220	A	$C_7H_{17}NO_3S_2$	36.97	7.54	...	28.20	37.05	7.56	...	28.2
16k	$H_2NC(CH_3)(i\text{-}C_4H_9)CH_2$	56	236–239	A	$C_7H_{17}NO_3S_2$	36.97	7.54	...	28.20	36.95	7.52	...	28.2
16l	$H_2NC(CH_3)(n\text{-}C_6H_{13})CH_2$	52	188–192	A	$C_9H_{21}NO_3S_2$	42.71	8.29	...	25.11	42.57	8.21	...	25.5
17	*n*-$C_{10}H_{21}NHC(CH_3)_2CH_2$	60	177–178	E	$C_{14}H_{29}NO_3S_2$	51.66	9.60	...	19.70	51.55	9.47	...	19.8
18a	$(CH_2)_2NHC[(CH_3)_2]CH_2$–NHC$[(CH_3)_2]CH_2$–	26	260	F	$C_{10}H_{24}N_2O_6S_2$	30.28	6.10	7.06	32.34	30.59	5.97	6.87	32.0
18b	$(CH_2)_3NHC[(CH_3)_2]CH_2$–NHC$[(CH_3)_2]CH_2$–	11	200–240	F	$C_{11}H_{26}N_2O_6S_2\cdot H_2O$	30.82	6.58	6.54	29.93	30.88	6.64	6.39	29.7
26a1		67	197		$C_6H_{13}NO_3S_2$	34.10	6.20	6.63	...	34.10	6.07	6.39	...
26b		74	230–234		$C_7H_{15}NO_3S_2$	37.40	6.71	...	28.46	37.68	6.77	...	28.5
28		50	217–219	E	$C_{16}H_{33}NO_3S_2$	54.65	9.46	3.98	18.24	54.59	9.34	3.86	18.5
39a		95	>260	F	$C_8H_{18}N_2O_6S_4$	21.26	4.95	7.64	34.99	26.55	5.11	7.60	34.9

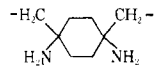
[a] Decomposition point is indefinite and dependent on rate of heating; measurements listed are approximate points or ranges where decomposition is evident on a Kofler Heizbank. [b] A, water; B, ethanol; C, methanol; D, methanol–ether; E, acetonitrile–methanol (9:1 by volume); F, reprecipitated from water solution of its sodium salt by addition of acetic acid. [c] Previously prepared by a different method, lit.[24d] mp 204.5°. [d] D. L. Klayman, W. F. Gilmore, and T. R. Sweeney [(*Chem. Ind.* (London), 1632 (1965)] used a different method and reported mp 250–252° dec.

NaOH solution (55 ml) was simply refluxed for 10 min in an apparatus arranged for distillation. Water (200 ml) was added, and the solution was distilled until a volume of distillate equal to that of the added water had been collected. More water (120 ml) was added, and distillation was continued until the total volume of distillate corresponded to that of water added. The distillate (320 ml) was added dropwise to rapidly stirred 48% HBr solution (300 ml) maintained at −5 to 0°. Stirring in the cold was continued 1 hr longer; during this time separation of **38** commenced. The mixture was allowed to stand overnight at room temperature, and the crystalline product that separated was collected and washed with ethanol. The yield of pure **38**, mp >260° dec, was 68% (9.02 g). The infrared spectrum of this material is identical with that of an

TABLE VII

S-SUBSTITUTED DERIVATIVES OF PHOSPHOROTHIOIC ACID

$RSPO_3HM \cdot xH_2O$

No.	R	M	x	Mp, °C dec	Yield, %	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
5b	n-$C_3H_7CH(NH_2)CH_2$	Na	0		93	$C_5H_{13}NNaO_3PS$	27.15	5.92	6.33	14.50	26.97	5.90	6.05	14.5
5d	i-$C_3H_7CH(NH_2)CH_2$	Na	3		85	$C_5H_{13}NNaO_3PS \cdot 3H_2O$	21.82	6.96	5.09	11.65	21.52	6.42	4.	11.8
5e	i-$C_4H_9CH(NH_2)CH_2$	Na	1		81	$C_6H_{15}NNaO_3PS \cdot H_2O$	28.46	6.77	...	12.66	28.40	6.54	...	12.9
16c	$H_2NC[(CH_3)_2]CH_2$	H	0	200	31	$C_4H_{12}NO_3PS$	25.94	6.53	7.56	17.31	25.71	6.48	7.35	17.6
16h	$H_2NC(CH_3)(n\text{-}C_3H_7)CH_2$	H	0	156–157	16	$C_6H_{16}NO_3PS$	33.79	7.56	6.57	...	33.77	7.56	6.22	...
26a2		H	1	235	23	$C_6H_{14}NO_3PS \cdot H_2O$	31.44	7.03	6.11	13.99	31.57	6.71	6.06	14.1
30		Na	4		94	$C_5H_{11}NNaO_3PS_2 \cdot 4H_2O$	18.57	5.92	4.33	19.84	18.72	5.96	4.37	19.5
39b		H	0	260	89	$C_8H_{20}N_2O_6P_2S_2$	26.23	5.50	7.65	17.50	26.53	5.88	7.59	17.1

analytical sample of **38** prepared by slow addition of powdered **37** to cold 48% HBr.

Anal. Calcd for $C_8H_{16}Br_2N_2 \cdot 2HBr$: C, 20.80; H, 3.93; Br, 69.19; N, 6.06. Found: C, 20.98; H, 4.03; Br, 68.5; N, 6.15.

S-2-Aminoalkyl- (5a, c, and f), S-2-Amino-2-methylalkyl- (16b, e, g, and i–l), and S-1-Aminocycloalkanemethylthiosulfuric Acids (26a1 and 26b).—Solutions of the bromoalkylamine hydrobromides **3** (R = n-C_3H_7, i-C_3H_7, $C_6H_5CH_2$), **14** (R = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9, i-C_4H_9, n-C_6H_{13}), **25a**, and **25b** and equimolar amounts of sodium thiosulfate in water (50 ml/0.10 mole of $Na_2S_2O_3$) were heated at 90–95° for 1 hr. The crystalline precipitates that separated from the chilled reaction solutions were collected, and some were recrystallized from appropriate solvents; others, however, were simply washed on the funnel with a little ice-cold water (see Table VI). The products were dried *in vacuo* (P_2O_5) at 80–110°.

S-1-Aminocyclohexanemethylthiosulfuric acid (26b) was also prepared directly from **22b**. A cold (0°), stirred solution of sodium thiosulfate pentahydrate (4.47 g, 18.0 mmoles) in water (7 ml) was treated dropwise with **22b** (2.00 g, 18.0 mmoles), and the mixture was stirred at 0° for 1 hr. Acetic acid (1.03 ml, 18.0 mmoles) was added, and the resulting solution was stirred at 0° for 30 min. Acetic acid (1.03 ml) was again added, and stirring was continued for 30 min. The solid that formed was collected, and concentration of the filtrate afforded a second crop. The dried (*in vacuo* over P_2O_5) first (1.68 g) and second (1.26 g) crops were combined and recrystallized from water to give pure **26b**, mp 231–233° (identical with the sample prepared from **25b**), in 28% yield (1.13 g).

Anal. Calcd for $C_7H_{15}NO_3S_2$: C, 37.40; H, 6.71; N, 6.23. Found: C, 37.54; H, 6.73; N, 6.10.

S-2-Decylaminopentyl- (6), S-2-Decylamino-2-methylpropyl- (17), and S-1-Decylaminocyclopentanemethylthiosulfuric Acids (28).—A stirred mixture of the appropriate S-substituted thiosulfuric acid (**5a**, **16b**, or **26a1**) (40.0 mmoles) and $KHCO_3$ (4.00 g, 40.0 mmoles) in DMF (40 ml) was heated during 1.5–2 hr to 80–85°. The resultant clear solution was treated dropwise during 0.5 hr with a solution of 1-bromodecane (9.30 g, 42.0 mmoles) in DMF (25 ml). Stirring and heating at 80–85° were contined for 4 hr. The mixture was then poured into water (330 ml), and the white precipitate that formed was purified by recrystallization from an appropriate solvent (see Table VI).

N,N′-Ethylenebis(S-2-amino-2-methylpropyl Thiosulfuric Acid) (18a).—A solution of the potassium salt of **16b** (64.8 mmoles), prepared in DMF (75 ml) in the manner described in the preceding general procedure, was maintained at 80–85° while a solution of 1,2-dibromoethane (32.4 mmoles) in DMF (25 ml) was added dropwise during 1 hr. Stirring and heating at about 85° was continued for 24 hr. The solvent was then removed by distillation *in vacuo* (0.5 mm, final bath temperature 65°). The residual syrup was dissolved in hot water (35 ml), and the solution was treated with Norit and filtered. The refrigerated filtrate deposited **18a** as a white crystalline precipitate, which was collected and dried *in vacuo* (P_2O_5) at 110°. The material obtained (3.86 g, 30% yield) was stirred into 1 N NaOH (10 ml), and the solution was treated with glacial acetic acid (2 ml). The mixture was refrigerated overnight, and the reprecipitated product was collected and dried as above. Results are listed in Table VI.

N,N′-Trimethylenebis(S-2-amino-2-methylpropylthiosulfuric acid) (18b) monohydrate was similarly prepared from the potassium salt of **16b** and 1,3-dibromopropane. Following removal of the solvent the residual syrup was stirred with warm water (50 ml), and the white solid that formed was purified by reprecipitation in the manner described for **18a**. Pure **18b** was obtained as a monohydrate after the reprecipitated product had been dried *in vacuo* (P_2O_5) at 80°.

S,S′-1,4-Diamino-1,4-cyclohexylenedimethylenebis(thiosulfuric acid) (39a).—A stirred mixture of **38** (3.79 g, 8.20 mmoles), $Na_2S_2O_3 \cdot 5H_2O$ (4.07 g, 16.4 mmoles), and water (15 ml) was heated at 95° for 2.5 hr. The white solid filtered from the cooled mixture was stirred into 1 N NaOH (16.5 ml), and the solution was filtered. Addition of glacial acetic acid (1.0 ml) to the filtrate caused separation of crystalline **39a**, which was dried *in vacuo* (P_2O_5) at 77°. Results are listed in Table VI.

Sodium hydrogen S-2-aminopentylphosphorothioate (5b) was prepared from **3** (R = n-C_3H_7) and trisodium phosphorothioate by the procedure described by Åkerfeldt[21a] for preparation of the S-2-aminoethyl homolog.

Sodium hydrogen S-2-amino-3-methylbutylphosphorothioate (5d) trihydrate, sodium hydrogen S-2-amino-4-methylpentylphosphorothioate (5e) monohydrate, and sodium hydrogen S-3-thiomorpholinylmethylphosphorothioate tetrahydrate (30)[22] were also prepared by the Åkerfeldt[21a] procedure. Following the dehydration step in which hydrated **5e** was stirred with anhydrous methanol, erratic analytical results were obtained because of hygroscopicity. After equilibration with ambient conditions in the laboratory **5e** analyzed as a monohydrate. In the preparations of **5d** and **30** that followed, the dehydration step was omitted, and the hydrated products were allowed to equilibrate at constant 58% relative humidity[35] to give **5d**·$3H_2O$ and **30**·$4H_2O$.

S-2-Amino-2-methylpentylphosphorothioic Acid (16h).—The sodium salt obtained by treatment of **14** (R = n-C_3H_7) with trisodium phosphorothioate as described above unexpectedly dissolved when stirred with methanol during attempted dehydration. Dilution of the methanol solution with ether caused precipitation of crude sodium salt of **16h**, which was converted to **16h** by dissolving it in glacial acetic acid and diluting the solution with ether.

S-2-Amino-2-methylpropylphosphorothioic Acid (16c) and **S-1-Aminocyclopentanemethylphosphorothioic Acid (26a2) Monohydrate.**—Following respective treatments of **14** (R = CH_3) and **25a** with trisodium phosphorothioate in the manner referred to above the sodium salts obtained were converted to **16c** and **26a2** monohydrate by adaptations of the procedure of Åkerfeldt for preparation of S-2-aminoethylphosphorothioic acid.[21b]

S,S′-1,4-Diamino-1,4-cyclohexylenedimethylenebis(phosphorothioic acid) (39b).—Powdered **38** (4.62 g, 10.0 mmoles) was added

(35) "Handbook of Chemistry," N. A. Lange, Ed., 9th ed, Handbook Publishers, Inc., Sandusky, Ohio, 1956, p. 1420.

TABLE VIII
AMINOTHIOLS
HSH

No.	R	Yield, %	Sublm pressure, mm[a]	Mp, °C	Formula	Calcd, % C	H	N	SH	Found, % C	H	N	SH
16a[b]	$H_2NC[(CH_3)_2]CH_2$	78	15	93–100	$C_4H_{11}NS$[c]	45.66	10.54	13.32	31.11	45.53	10.51	13.41	30.7
16f	$H_2NC(CH_3)(n\text{-}C_4H_9)CH_2$	62	32	30–31	$C_6H_{15}NS$	54.03	11.31	10.51	24.82	54.19	11.47	10.52	24.5
16f·HCl		58		264–266	$C_6H_{16}NS{\cdot}HCl$[d]	42.46	9.50			42.70	9.24		
23a		90	0.1	63–65	$C_6H_{13}NS$	54.90	9.98	10.67		55.05	10.02	10.53	
23a·HCl		83		172–174	$C_6H_{14}NS{\cdot}HCl$	42.97	7.81	8.35	19.72	43.02	7.80	8.30	19.8
23b		88	2.5	44–46	$C_7H_{15}NS$	57.87	10.01	9.64		58.09	10.24	9.50	
23b·HCl		87		223–227	$C_7H_{16}NS{\cdot}HCl$	42.26	8.32	7.71		46.61	8.76	7.68	

[a] Conducted with the aid of a warm-oil bath over a temperature range that afforded sublimation at a convenient rate. [b] **16a**·HCl prepared by another route, has been reported previously.[12b] [c] *Anal.* Calcd: S, 30.48. Found: S, 30.6. [d] *Anal.* Calcd: Cl, 20.90. Found: Cl, 20.9.

to a solution of trilithium phosphorothioate hexahydrate[20c,36] (4.80 g, 20.0 mmoles) in water (40 ml) contained in a 100-ml Morton (pleated) flask. The mixture was stirred for 1.5 hr, and DMF (20 ml) was added. Stirring was continued for 2 hr; complete solution did not occur. The mixture was diluted with ethanol (200 ml), and the white solid was collected and washed with ethanol. The solid was then dissolved in water (100 ml), and addition of glacial acetic acid (3 ml) caused immediate separation of crystalline **39b**. The product was collected, washed with water followed by ethanol, and dried *in vacuo* (P_2O_5) at room temperature. The material obtained (3.50 g) gave unsatisfactory analytical results at this point (*Anal.* Found: C, 27.51; H, 5.92; N, 7.60.); reprecipitation was necessary. The product (3.45 g) was stirred with NaOH solution (157 ml of 0.1206 *N*, 18.9 meqiv). The resultant solution was treated with Norit, filtered through Celite, and treated with glacial acetic acid (1.5 ml). Reprecipitated **39b** was collected, washed with water, and dried as above. The results are included in Table VII.

2-Amino-2-methylpropanethiol (16a) was prepared by treatment of **14** (R = CH_3) with NaSH in methanol solution in the manner described earlier in the preparation of 2-piperidineethanethiol.[12a] Following removal of the reaction solvent, pure **16a** was readily obtained by sublimation under reduced pressure. The results are included in Table VIII.

2-Amino-2-methylpentanethiol (16f), 1-aminocyclopentanemethanethiol (23a), and 1-aminocyclohexanemethanethiol (23b) were prepared by ring opening of the appropriate substituted aziridine [**13** (R = *n*-C_3H_7), **22a**, and **22b**] with H_2S in cold methanol solution according to the procedure of Bestian[19] for preparation of 2-aminoethanethiol from aziridine. Following removal of the solvent, the residue was sublimed under reduced pressure (see Table VIII).

1,4-Diamino-1,4-cyclohexanedimethanethiol Diphosphate (40).—A stirred mixture of **39b** (1.08 g, 2.95 mmoles) and 1 *M* phosphoric acid solution (20 ml) was refluxed for 30 min; solution occurred during this time. Dilution of the cooled solution with ethanol gave crystalline **40**, which was collected under nitrogen. The sample was redissolved in water (20 ml) containing 1 *M* H_3PO_4 (2 ml), and reprecipitation by dilution with ethanol afforded pure **40**, mp 265–267° dec, in 84% yield (1.00 g) [dried *in vacuo* (P_2O_5) at 77°], σ^{KBr} 2560 cm^{-1} (w, SH).

Anal. Calcd for $C_8H_{18}N_2S_2{\cdot}2H_3PO_4$: C, 23.88; H, 6.01; N, 6.96; SH, 16.44. Found: C, 23.87; H, 6.04; N, 6.93; SH, 15.6.

1-[(Benzylthio)methyl]cyclohexylamine (24) Hydrochloride.—Benzylation of **23b** by the procedure described for the preparation of 2-(benzylthio)ethylamine[37] gave **24**, bp 130–132° (0.5 mm) and $n^{25}D$ 1.5623, in 65% yield. Treatment of an ether solution of the free base with ethereal HCl followed by recrystallization from 2-propanol gave **24**·HCl, mp 204–205°, in 78% yield.

Anal. Calcd for $C_{14}H_{22}NS{\cdot}HCl$: C, 61.81; H, 8.16; Cl, 13.05. Found: C, 62.04; H, 8.09; Cl, 12.9.

2-Amino-3-phenylpropyl dimethyldithiocarbamate hydrobromide (5g), mp 178° (Kofler Heizbank), was prepared from **3** (R = $C_6H_5CH_2$) and sodium dimethyldithiocarbamate in 58% yield by the procedure used in the preparation of 2-(2-piperidyl)ethyl dimethyldithiocarbamate hydrobromide.[12a]

Anal. Calcd for $C_{12}H_{18}N_2S_2{\cdot}HBr$: C, 43.10; H, 5.73; N, 8.38; S, 19.18. Found: C, 43.35; H, 5.91; N, 8.47; S, 19.3.

S-2-Amino-2-methylpropyl thioacetate hydrobromide (16d) was prepared from **14** (R = CH_3) and an *in situ* preparation of potassium thioacetate in DMF in the manner described earlier for the S-2-(2-piperidyl)ethyl analog.[12a] Pure **16d**, mp 158° (Kofler Heizbank), was obtained in 51% yield.

Anal. Calcd for $C_6H_{13}NOS{\cdot}HBr$: C, 31.58; H, 6.19; N, 6.14; S, 14.05. Found: C, 31.53; H, 5.94; N, 6.20; S, 13.8.

4,4-Dimethyl-2-thiazolidinethione (15).—Anhydrous K_2CO_3 (10.0 g, 72.4 mmoles) was gradually added during 1 hr to a stirred mixture of **14** (R = CH_3) (7.50 g, 32.2 mmoles), CS_2 (6.3 g, 83 mmoles), and DMF (50 ml). Stirring at room temperature was continued overnight. The mixture was diluted with water (200 ml) and then extracted three times with ether (100-ml portions). Removal of the solvent from the water-washed and dried (Na_2SO_4) ether solution left crude **15** as a waxy solid. Two recrystallizations from benzene–ligroin (bp 30–60°) gave pure **15**, mp 94°, in 38% yield (1.80 g).

Anal. Calcd for $C_5H_9NS_2$: C, 40.77; H, 6.16; S, 43.54. Found: C, 40.85; H, 6.25; S, 43.5.

4-Benzyl-2-thiazolidinethione (4), 3-thia-1-azaspiro 4,4]nonane-2-thione (27), and tetrahydro-1H,3H-thiazolo[4,3-c][1,4]-thiazine-3-thione (29) were prepared by reaction of the appropriate intermediates [**3** (R = $C_6H_5CH_2$), **25a**, and 3-(bromomethyl)thiomorpholine hydrobromide,[12a] respectively] with CS_2 and K_2CO_3 in DMF using the procedure described for the preparation of hexahydropyrrolo[1,2-*c*]thiazole-3-thione.[12a] Pure **4**, mp 108° (Kofler Heizbank), was obtained in 87% yield and was recrystallized from ethanol with melting point unchanged; pure **27**, mp 136–137°, was obtained in 25% yield following thorough washing with ether; **29**, mp 98–100°, was obtained pure in 42% yield following recrystallization from ethanol.

Anal. Calcd for $C_{10}H_{11}NS_2$ (**4**): C, 57.38; H, 5.30. Found: C, 57.41; H, 5.24. Calcd for $C_7H_{11}NS_2$ (**27**): C, 48.52; H, 6.40; S, 37.01. Found: C, 48.37; H, 6.45; S, 36.8. Calcd for $C_6H_9NS_3$ (**29**): C, 37.66; H, 4.74; N, 7.32; S, 50.28. Found: C, 37.89; H, 4.47; N, 7.09; S, 50.3.

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(36) J. R. Piper, C. R. Stringfellow, and T. P. Johnston, *J. Med. Chem.*, **9**, 563 (1966).

(37) T. P. Johnston and V. Gallagher, *J. Org. Chem.*, **28**, 1305 (1963).