a previously heated mixture of 4-methyl-1-pentanol (4.4 g) and $NaNH_2$ (2.1 g) in PhMe (10 ml). The reaction was carried out as for Ve and afforded a white solid (2.45 g), mp 85–88°. Recrystallization from hexane gave pure Vd: mp 97–99°; ν_{max} 1115 cm^{-1} (COC); nmr peaks at 0.94 [doublet, J = 6 cps, $C(CH_3)_2$] and 4.15 ppm (triplet, J = 6.5 cps, OCH_2). *Anal.* ($C_{15}H_{18}INO$) C, H.

4-Dimethylamino-7-iodoquinoline (Ve).—Me_2NH was bubbled through an ice-cooled solution of IVb (2 g) in PhMe (20 ml) and MeCOEt (10 ml) for 3 hr in a pressure bottle. The bottle was tightly stoppered and placed in an oven at 50° for 10 days. The mixture was cooled and washed (H_2O). The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. Recrystallization of the solid residue gave pure Ve (1.1 g), mp 107–108°, and an nmr peak at 2.99 ppm (NCH_3). *Anal.* ($C_{11}H_{11}IN_2$) C, H.

4-Hydroxyethyoxy-7-iodoquinoline (Vf).—A solution of Ve (100 mg) in ethylene glycol (1.5 ml) was heated in an oil bath at 185° for 16 hr, cooled, and diluted with H_2O. The precipitate (70 mg), mp 153–155°, was recrystallized (Me_2CO–H_2O) to give pure Vf, mp 154–155°. The ir and nmr spectra were as expected. *Anal.* ($C_{11}H_{10}INO_2$) C, H.

Isotope Exchange. General Method.—A solution containing 1–3 mCi of $Na^{125}I$ was placed in a 10-ml round-bottom flask and evaporated to dryness at 100° under a gentle stream of N_2. The substituted 7-iodoquinoline (100 mg) dissolved in the appropriate solvent (2 ml) was added, a condenser was attached, and the bath temperature was raised. The mixture was stirred under N_2 for the specified time and allowed to cool. In the case of IVa, Vc, and Ve, H_2O was added and the product was collected by filtration and washed well (H_2O). For Vb, the solution was concentrated to approximately 0.5 ml under reduced pressure and treated with H_2O and NH_4OH, and the precipitate was collected as above. For Vd, the solvent was removed *in vacuo*, the residue was treated with H_2O containing a little Me_2CO, and the precipitate was collected. In all cases, the products were purified by recrystallization and the purity was established by (a) tlc and a radiochromatogram of the strip and (b) mixture melting point with authentic samples (see Table III).

Acknowledgment.—Support for this investigation was provided by Grants CA-08349 and CA-08429 from the National Cancer Institute, U. S. Public Health Service, Bethesda, Md., and PRA-18 from the American Cancer Society, New York, N. Y. The authors are also grateful to Mallinckrodt Chemical Works for furnishing the Va-^{125}I required for the preclinical animal studies.

S-2-(ω-Aminoalkylamino)ethyl Dihydrogen Phosphorothioates and Related Compounds as Potential Antiradiation Agents[1]

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Received August 5, 1968

A number of S-2-(ω-aminoalkylamino)ethyl and S-3-(ω-aminoalkylamino)propyl dihydrogen phosphorothioates (**3a–e**, **18a–c**) and some related compounds including the S-2-(ω-aminoalkylamino)ethyl hydrogen thiosulfates **10a–c** have been prepared and evaluated for radioprotective activity in mice. Intermediate N-(2-bromoethyl)-α,ω-alkanediamine dihydrobromides (**2a–e**) were prepared by the Cortese treatment of the 2-(ω-aminoalkylamino)ethanols **1a–e**; the potential of a Gabriel synthesis from the 3-(ω-phthalimidoalkyl)-2-oxazolidinones **7a–c** was demonstrated by the conversion of N-[3-(2-bromoethylamino)propyl]phthalimide hydrobromide (**8b**) into **2b**. The requisite N-(3-bromopropyl)-α,ω-alkanediamine dihydrobromides **17a–c** were prepared from the 3-(ω-aminoalkylamino)-1-propanols **16a** and **16b** and from the 3-(ω-phthalimidoalkyl)tetrahydro-1,3-oxazin-2-ones **14a** and **14b** in two steps involving selective cleavage of the tetrahydrooxazinone ring. Intermediates obtained by the addition of 2-methyl- and 2,2-dimethylaziridine to acrylonitrile led to several branched-chain analogs (**21a-d**, **23a**, and **23b**). Aziridine-ring opening by ammonium thiosulfate was employed in the preparation of the inner Bunte salts **10a**, **10b**, **21b**, and **21d** monohydrochlorides. The phosphorothioates, as a series of a novel type, exhibited an exceptionally high level of radioprotective activity, whereas the thiosulfates were essentially nonprotective.

Current interest in the radioprotective properties of N-substituted derivatives of 2-aminoethanethiol (with and without latentiating S-substitution) in which the N-substituent is a terminally and functionally substituted alkyl group is attested by a growing number of reported syntheses in this area.[2] This report concerns the synthesis and evaluation of N-(ω-aminoalkyl)-substituted derivatives (chiefly N and S disubstituted), a type that structurally resembles several recently described and more complex spermine and spermidine derivatives[3] and N,N′-polymethylene-bridged derivatives[4] in which some antiradiation activity has been observed.

Various modifications of 2-aminoethanethiol have been achieved by the use of α-amino acids as starting materials,[5] but the general reaction sequence was not successfully applied to L-lysine or its ethyl ester because of difficulties encountered in their reduction to the apparently as yet unknown L-lysinol [$H_2N(CH_2)_4CH(NH_2)CH_2OH$]. As a model for the planned conversion of L-lysinol the following sequence (eq 1)

$$\underset{\textbf{1a}}{H_2NCH_2CH_2NHCH_2CH_2OH} \xrightarrow{HBr} \underset{\textbf{2a}}{H_2NCH_2CH_2NHCH_2CH_2Br\cdot HBr} \xrightarrow{Na_2SPO_3} \underset{\textbf{3a}}{H_2NCH_2CH_2NHCH_2CH_2SPO_3H_2} \quad (1)$$

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

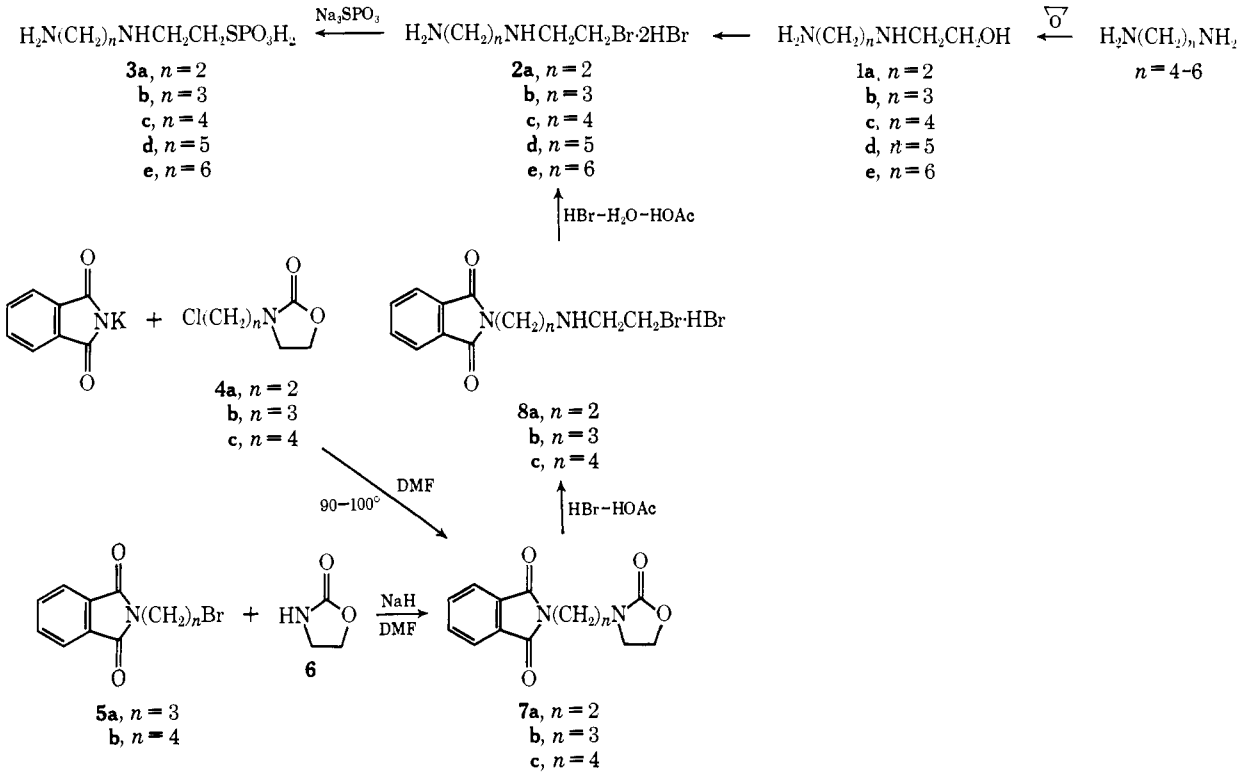
(2) E. Felder, F. Bonati, and S. Bianchi, *Experientia*, **15**, 32 (1959); R. J. Wineman, M. H. Gollis, J. C. James and A. M. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962); F. I. Carroll, H. M. Dickson, and M. E. Wall, *ibid.*, **30**, 33 (1965); O. L. Salerni, R. N. Clark, and B. E. Smart, *J. Chem. Soc., C*, 645 (1966); T. P. Johnston and C. R. Stringfellow, Jr., *J. Med. Chem.*, **9**, 921 (1966); T. P. Johnston and R. D. Elliott, *J. Org. Chem.*, **32**, 2344 (1967); S. F. Thames and L. H. Edwards, *J. Heterocycl. Chem.*, **5**, 155 (1968).

(3) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **33**, 536 (1968).

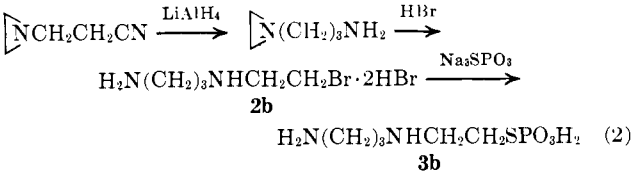
(4) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.* **9**, 563 (1966).

(5) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *ibid.*, **9**, 911 (1966).

SCHEME I



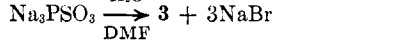
beginning with commercially available 2-(2-aminoethylamino)ethanol (**1a**) was carried out. The product **3a** was a unique example of a phosphorothioic acid ester in which the acidic function can be neutralized internally by two amino groups. Whether the internal zwitterionic neutralization is partial or complete as in $H_3\overset{+}{N}CH_2CH_2\overset{+}{N}H_2CH_2CH_2SPO_3^{2-}$ in the solid state or in solution is not known, but for convenience phosphorothioate structures in this paper are written in the nonzwitterionic form. The radioprotective activity of **3a** in initial screening tests encouraged the preparation of the homologous and also impressively active S-2-(3-aminopropylamino)ethyl dihydrogen phosphorothioate (**3b**) by the following route (eq 2) based



(2)

on known aziridine intermediates.[6] These beginnings, marked by a high level of activity, were then expanded into a series of homologs and analogs.

The two routes that led to the S-2-(ω-aminoalkylamino)ethyl dihydrogen phosphorothioates **3** are outlined in Scheme I; one involved the Cortese conversion[7] of hydroxyethylated α,ω-alkanediamines, and the other involved the Gabriel synthesis from intermediates made available by the recently developed hydrogen bromide cleavage of 3-substituted 2-oxazolidinones.[8] The last step of each approach was based on methods developed by Åkerfeldt,[9] but the favorable stoichiometry[10] of this particular application permitted the isolation of inner salts without additional acid (eq 3).



(3)

The stoichiometry of the conversion of the N-(2-bromoethyl)-α,ω-alkanediamine hydrobromides **2** into the corresponding inner Bunte salts requires that the reagent $Na_2S_2O_3$ be protected against acidity.[10] Buffering with NaOAc was effective in the analogous preparation of a Bunte salt from 2-(bromomethyl)-piperazine dihydrobromide, but neutralization did not occur and the product was isolated as a hydrobromide.[11] In the attempted conversion of **2** in the presence of NaOAc, however, only one member of the series, S-2-(6-aminohexylamino)ethyl hydrogen thiosulfate (**10c**), could be obtained in crystalline form; the others were obtained as solvated syrups, from which NaBr and NaOAc could not be separated. Two members of the series, **10a** and **10b**, were ultimately obtained, as indicated in Scheme II, by aziridine-ring openings with $(NH_4)_2S_2O_3$; other examples of the application of this method have been reported.[12]

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

(7) F. Cortese in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed. John Wiley and Sons, Inc., New York, N. Y., 1953, pp 91–93.

(8) J. R. Piper, R. D. Elliott, C. R. Stringfellow, Jr., and T. P Johnston, *Chem. Ind.* (London), 2010 (1966).

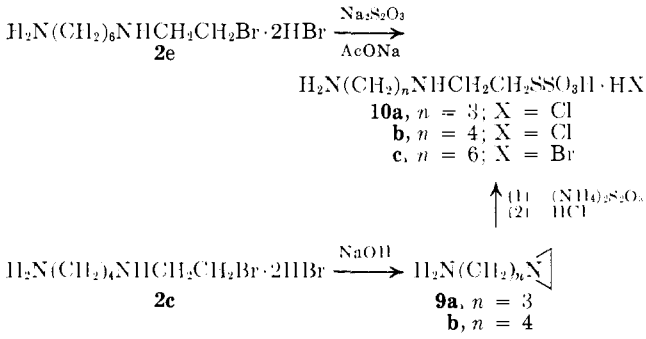
(9) (a) S. Åkerfeldt, *Acta Chem. Scand.*, **13**, 1479 (1959); (b) *ibid.*, **14**, 1980 (1960); (c) *ibid.*, **16**, 1897 (1962); (d) *ibid.*, **20**, 1783 (1966).

(10) *Cf.* ref 3.

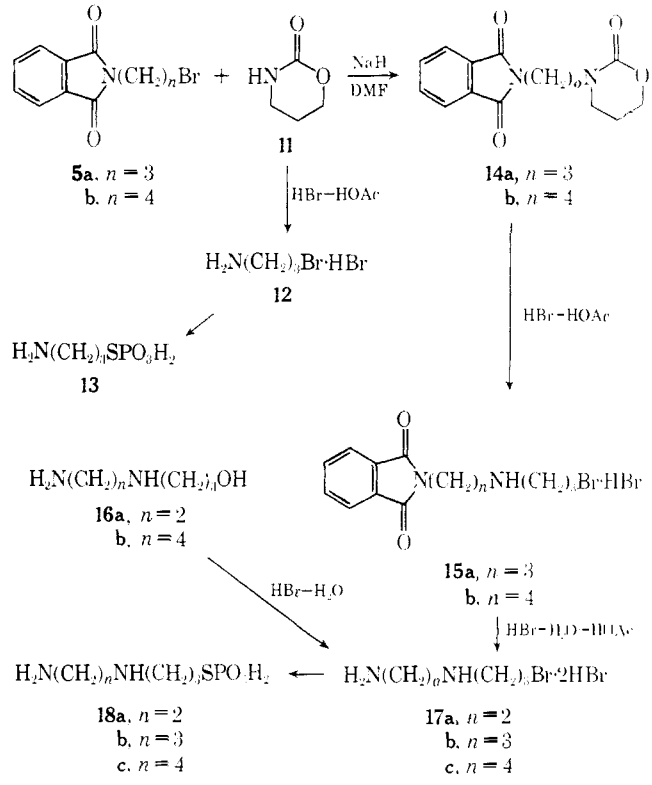
(11) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963).

(12) D. L. Klayman, W. F. Gilmore, and T. R. Sweeney, *Chem. Ind.* (London), 1632 (1965); D. L. Klayman, J. W. Lown, and T. R. Sweeney, *J. Org. Chem.*, **30**, 2275 (1965).

SCHEME II



SCHEME III



The feasibility of a synthetic route to the S-3-(ω-aminoalkylamino)propyl dihydrogen phosphorothioates **18** based on the hydrogen bromide cleavage of the 3-substituted tetrahydro-2H-1,3-oxazin-2-ones **14** (Scheme III) was initially demonstrated by the conversion of tetrahydro-2H-1,3-oxazin-2-one (**11**) itself into S-3-aminopropyl dihydrogen phosphorothioate (**13**) *via* 3-bromopropylamine hydrobromide (**12**). The cleavage of **11** was extremely slow at room temperature, but increased markedly with warming as evidenced by an accelerated evolution of CO_2. The preparation of the intermediate **14b** by the addition of a solution of N-(4-bromobutyl)phthalimide (**5b**) and **11** in DMF to a stirred slurry of NaH in the same solvent exemplified a technical refinement in this type of alkylation. The alternative route to **18a** and **c** provided by the Cortese treatment of the 3-(ω-aminoalkylamino)-1-propanols **16** and shown in Scheme III was developed because of difficulties encountered in the route involving phthalimido intermediates: (1) dehydrobromination occurred in the attempted alkylation of **11** with N-(2-bromoethyl)phthalimide to give N-vinylphthalimide instead of the expected 3-substituted tetrahydro-2H-1,3-oxazin-2-one, and (2) analyses of the phosphorothioate **18c** derived by the longer route were inconsistent. It should be pointed out that the phthalimido intermediates **8** and **15** were the source of a number of terminal phthalimido analogs, which will be described in a subsequent paper.

Several branched-chain congeners of the title compounds were synthesized by routes outlined in Scheme IV and based on the addition of 2-methylaziridine and 2,2-dimethylaziridine to acrylonitrile. The formation of 2-methyl-1-aziridinepropionitrile (**19a**) and 2,2-dimethyl-1-aziridinepropionitrile (**19b**) was promoted by heat, which was not required in the reported addition[6] of ethylenimine itself to acrylonitrile. The thiols (isolated as hydrochlorides) and thiosulfates were produced by appropriate aziridine-ring openings, but the product of the ring opening of **19a** with H_2S was not obtained in characterizable form.

The radioprotective activities of the phosphorothioates described above as judged by screening tests performed in mice at the Walter Reed Army Institute of Research, Washington, D. C., are expressed in Table I as per cent survival along with those of several of the corresponding Bunte salts among other compounds. The phosphorothioates, with the exception of **18c** (and **13**), showed good activity (50–100% survival), whereas the corresponding thiosulfates were nonprotective with the exception of the slightly protective branched-chain analog **21d**. The striking difference between the phosphorothioates and thiosulfates in this series is somewhat surprising in view of the reported good activity of both types of thioester when the substituent is simply a 2-aminoethyl group.[13] One of the outstanding phosphorothioates in this series, **18b**, is a structural relative of S-3-aminopropyl dihydrogen phosphorothioate (**13**), which, however, showed only slight activity. In fact, the structural requirements for the high level of radioprotective activity observed among the S-ω-(ω-aminoalkylamino)alkyl dihydrogen phosphorothioates examined here, including the branched-chain analogs **23a** and **23b**, appear to be unusually broad, even for a series of closely related compounds. The effect of substitution on terminal amino groups in this series will be explored in later papers.

Experimental Section[14]

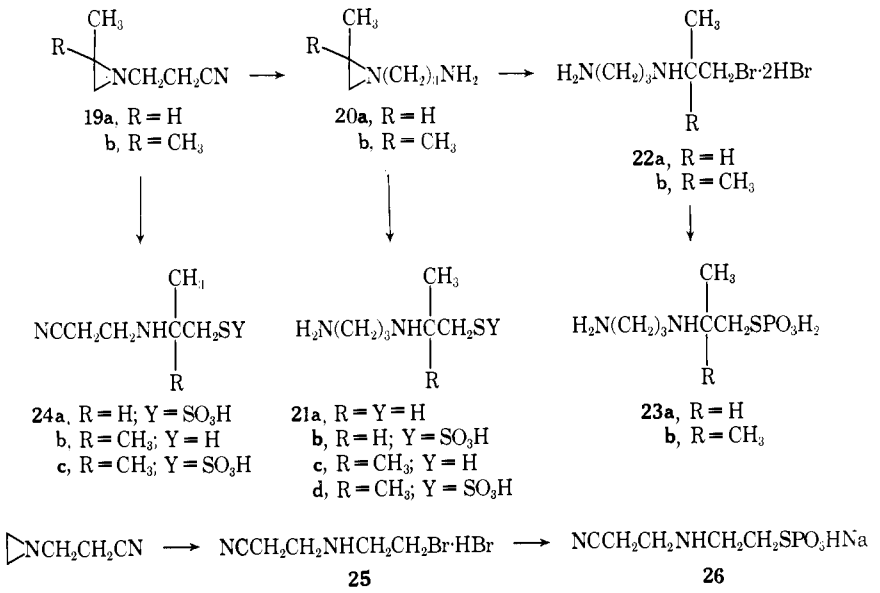
2-(ω-Aminoalkylamino)ethanols (1a–e).—Compounds **1a** and **1b** were obtained from commercial sources; **1c–e** were prepared from the corresponding α,ω-alkanediamines and ethylene oxide by an adaptation of the procedure of Steck, *et al.*[15] In each example the monohydroxyethylated product was isolated by fractional distillation *in vacuo;* results listed below refer to redistilled products. The yield of **1c**, bp 97–100° (0.10 mm) and $n^{25}D$ 1.4800, was 25%; **1d**, bp 107–110° (0.10 mm) and $n^{25}D$ 1.4806, 26%; and **1e**, bp 118–120° (0.15 mm) (partially solidified after second distillation), 30%. *Anal.* ($C_8H_{16}N_2O$, **1c**) C, H, N. ($C_7H_{18}N_2O$, **1d**) C, H, N. Although **1e** was not obtained analytically pure, it was converted into pure **2e**.

(13) B. Hansen and B. Sörbo, *Acta Radiol.*, **56**, 141 (1961).

(14) Unless noted otherwise, melting points with a range were determined with a Mel-Temp apparatus; those without a range, with a Kofler Heizbank. Ir spectra were determined with a Perkin-Elmer Model 521 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. Some of the analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(15) E. A. Steck, J. S. Buck, and L. T. Fletcher, *J. Amer. Chem. Soc.*, **79**, 4414 (1957).

SCHEME IV



3-(2-Aminoethylamino)-1-propanol (16a).—The procedure that follows is essentially that of Ishiguro and Matsumura.[16] A solution of ethylenediamine (26.4 g, 0.440 mole) and trimethylene oxide (25.0 g, 0.431 mole) in H_2O (20 ml) was heated in a glass-lined pressure vessel at 130–140° for 20 hr. The mixture was fractionated *in vacuo*, and the fraction with bp 130–136° (14 mm) (16.3 g) was redistilled to give **16a** as a colorless hygroscopic oil, bp 136–140° (14 mm), 25% yield (12.8 g) [lit.[16] bp 146–149° (14 mm)]. *Anal.* ($C_5H_{14}N_2O$) C, H; N: calcd, 23.70; found, 22.90.

3-(4-Aminobutylamino)-1-propanol (16b).—Adaptation of the procedure described for the preparation of **16a** led to **16b**, bp 128–130° (2 mm), in 29% yield. *Anal.* ($C_7H_{18}N_2O$) H; C: calcd, 57.51; found, 58.16.

3-(ω-Phthalimidoalkyl)-2-oxazolidinones (7a–c).—Compounds **7b** and **7c** were each prepared by two methods represented below by typical examples designated methods A and B; **7a** was prepared by method A only.

Method A. 7a.—A mixture of equimolar amounts of **4a** and potassium phthalimide (66.9 mmoles each) in DMF (10 ml) was stirred at 95–100° (bath temperature) for 2 hr, diluted (H_2O, 70 ml), and refrigerated overnight to give pure **7a**, mp 158°, in 94% yield (16.4 g). *Anal.* ($C_{13}H_{12}N_2O_4$) C, H, N.

7b.—Similar treatment of **4b** gave crude **7b** (93% yield); one recrystallization from EtOAc gave an 80% yield of **7b**, mp 101–103°, suitable for use in preparation of **8b**. An analytical sample of **7b** had mp 105–106° (from EtOAc). *Anal.* ($C_{14}H_{14}N_2O_4$) C, H, N.

7c.—The crude product (90% yield) was recrystallized from H_2O to give pure **7c**, mp 101–103°, in 67% yield. *Anal.* ($C_{15}H_{16}N_2O_4$) C, H, N.

Method B. 7b.—A solution of equimolar amounts of **5a** and **6** (81.1 mmoles each) in DMF (150 ml) was added dropwise during 30 min to a stirred mixture of NaH (3.24 g of 60% NaH in oil dispersion, 81.1 mmoles) in DMF (50 ml) maintained at 25°. The resultant mixture was stirred at 25–30° for 18 hr. Removal of the solvent by distillation *in vacuo* (aspirator, bath temperature 70–80°) left a solid residue, which, when stirred with H_2O (200 ml), afforded crude **7b** (76% yield). Recrystallization from EtOAc gave pure **7b** (melting point and mixture melting point identical with that of the analytical sample prepared by method A) in 50% yield (11.2 g).

7c.—Following removal of the DMF from alkylation of **6** with **5b** (69.0-mmole scale) essentially as described for **7b**, the residue was stirred with PhMe (200 ml), and the mixture was filtered from NaBr. The filtrate was concentrated under reduced pressure to about 100 ml, and the clarified (Norit, Celite) PhMe solution was diluted with 30–60° ligroin (400 ml) to precipitate crude **7c**; subsequent recrystallization (H_2O) gave **7c** (52%), mp 100–102° (ir spectrum identical with that of the sample prepared by method A).

Tetrahydro-2H-1,3-oxazin-2-one (11) was prepared from 3-chloro-1-propanol and KCNO using the reaction procedure of Phillips and Argabright.[17] Because of difficulties with the reported purification procedure (involving successive recrystallizations from cold Me_2CO) the crude oily product (from a run using 0.250 mole of 3-chloro-1-propanol) was distilled *in vacuo* (15-cm Vigreux column) to give a colorless oil (17.6 g), bp 126–128° (0.1 mm), which crystallized when cooled; recrystallization (EtOAc) gave 11, mp 80–83° (lit.[17] mp 82–83°), in 54% yield (13.6 g); ir (KBr), 3265 (NH) and 1690 cm^{-1} (C=O). In subsequent runs, 11 of satisfactory purity was obtained by simply allowing it to crystallize from clarified (Norit, Celite) EtOAc solutions of the crude undistilled oil.

3-(3-Phthalimidopropyl)tetrahydro-2H-1,3-oxazin-2-one (14a).—Alkylation of 11 with **5a** using the same procedure as described for the preparation of **7b** (method B) gave **14a**, mp 133–135° (recrystallized once from PhMe), in 62% yield. An analytical sample had mp 135–136° (from PhMe); ir (KBr), 1775 (w), 1710 (s) (imide C=O), and 1675 cm^{-1} (carbamate C=O). *Anal.* ($C_{15}H_{16}N_2O_4$) C, H, N.

3-(4-Phthalimidobutyl)tetrahydro-2H-1,3-oxazin-2-one (14b) was prepared from 11 and **5b** by the same procedure as indicated for the preparation of **14a**. Pure **14b**, mp 146–148° (from PhMe), was obtained in 68% yield; ir (KBr), 1760 (w), 1705 (s) (imide C=O), and 1680 cm^{-1} (carbamate C=O). *Anal.* ($C_{16}H_{18}N_2O_4$) C, H, N.

3-Bromopropylamine Hydrobromide (12).—A solution of 11 (1.00 g, 9.89 mmoles) in 30% HBr–HOAc (5 ml) was stirred at 25–30° for 4 hr while extremely slow reaction occurred as evidenced by evolved CO_2 bubbling from a H_2O-charged gas-absorption trap. Gentle warming caused a marked increase in the rate of CO_2 evolution. The solution was slowly heated to boiling during 1 hr and was maintained under reflux for 10 min. The cooled solution deposited crystalline **12**, which was collected with the aid of Et_2O and washed thoroughly with Et_2O before being dried *in vacuo* (77°, P_2O_5). The yield of **12**, mp 173–175° (lit. mp 169–172°[18] and 171°[9c]), was 100% (2.17 g). The melting point, mixture melting point, and ir spectrum of this sample were identical with those of a sample of **12** obtained from a commercial source and purified for use in the preparation of

(16) T. Ishiguro and M. Matsumura, *Yakugaku Zasshi*, **78**, 153 (1959); *Chem. Abstr.*, **53**, 13163*g* (1959).

(17) B. L. Phillips and P. A. Argabright, *J. Heterocycl. Chem.*, **3**, 84 (1966).

(18) F. C. Schaefer, *J. Amer. Chem. Soc.*, **77**, 5928 (1955).

TABLE I

RADIOPROTECTIVE ACTIVITIES OF S-ω-(ω-AMINOALKYLAMINO)ALKYL DIHYDROGEN PHOSPHOROTHIOATES AND RELATED COMPOUNDS[a]

Compd	n'	n	Y[b]	Approx LD_{50}, mg/kg	Drug dose, mg/kg[c]	Vehicle of admin	pH of prepn	30-day survival, %[d]
			A. $H_2N(CH_2)_{n'}NH(CH_2)_nSY$					
3a	2	2	$PO_3H_2(\cdot H_2O)$	1300	800	Water	6.1	100
					400	Water	6.1	100
					200	Saline[e]	6.5	27
					100	Saline	6.5	0
3b	3	2	$PO_3H_2(\cdot H_2O)$	700	600	Water	6.3	86
					300	Water	6.3	86
					150	Water	6.5	40
					75	Water	6.5	20
3c	4	2	PO_3H_2	800	400	Water	7.0	100
					200	Water	7.0	80
					100	Saline	7.6	13
3d	5	2	$PO_3H_2(\cdot H_2O)$	550	300	Water	6.9	100
					150	Water	6.9	100
					75	Saline	7.2	13
3e	6	2	$PO_3H_2(\cdot H_2O)$	550	300	Water	7.0	87
					200	Saline	7.2	40
					150	Water	7.0	93
					100	Saline	7.2	0
10a	3	2	$SO_3H(\cdot HCl)$	700–1000	350–700	Water	5.3	0
					150–350	Water	5.3	0
10b	4	2	$SO_3H(\cdot HCl)$	410	300			0
					150			0
10c	6	2	$SO_3H(\cdot HBr)$	400	200	Saline	6.9	0
					100	Saline	6.9	0
18a	2	3	PO_3H_2	1300	1000	CMC–Tw[f]	6.5	100
					800	CMC–Tw	6.5	83
					500	CMC–Tw	6.5	100
					400	CMC–Tw	6.5	67
					200	CMC–Tw	6.5	13
18b	3	3	$PO_3H_2(\cdot 2H_2O)$	560	320	CMC–Tw	5.5	100
					160	CMC–Tw	5.5	100
					100			100
					75			80
					38			10
18c	4	3	$PO_3H_2(\cdot 2H_2O)$	225	100	Saline	7.1	13
					50	Saline	7.1	0
			B. $H_2N(CH_2)_3NHCCH_2SY$ (R = CH₃)					
	R							
21a	H		$H(\cdot 2HCl)$	180	100			67
21b	H		$SO_3H(\cdot HCl)$	600	400	Water	6.9	0
					200	Water	6.9	0
21c	CH_3		$H(\cdot 2HCl)$	74	56	CMC–Tw	5.5	0
					28	CMC–Tw	5.5	0
21d	CH_3		$SO_3H(\cdot HCl)$	1300	1000	CMC–Tw	7.0	17
					500	CMC–Tw	7.0	0
23a	H		$PO_3H_2(\cdot 2.5H_2O)$	450	240	Water		50
23b	CH_3		$PO_3H_2(\cdot 2.5H_2O)$	900	600	Saline	6.5	87
					300	Water	5.5	80
					150	Saline	6.5	20
					75	Saline	6.5	7
			C. $NCCH_2CH_2NHCCH_2SY$ (R = CH₃)					
24a	H		SO_3H	1300	1000	CMC–Tw	5.5	0
					500	CMC–Tw	5.5	0
24b	CH_3		$H(\cdot HCl)$	320	180	CMC–Tw	5.5	0
					90	CMC–Tw	5.5	0
24c	CH_3		SO_3H	1800	1000	CMC–Tw	5.5	33
					500	CMC–Tw	5.5	17

TABLE I (*Continued*)

Compd	Structure	Approx LD_{50}, mg/kg	Drug dose, mg/kg[c]	Vehicle of admin	pH of prepn	30-day survival, %[d]
	D. Others					
13	$H_2N(CH_2)_3SPO_3H_2$	430	320	CMC–Tw	5.5	17
			160	Water	5.5	13
			125	CMC–Tw	5.7	13
			62.5	CMC–Tw	5.7	7
26	$NCCH_2CH_2NHCH_2CH_2SPO_3HNa$	500	200	CMC–Tw	6.7	0
			100	CMC–Tw	6.7	0

[a] Antiradiation screening tests in mice against lethal radiation [825 R (X-rays) or 950–1050 R (γ rays)] were performed at Walter Reed Army Institute of Research, Washington, D. C., under the direction of Dr. D. P. Jacobus. [b] Water of crystallization and characterization as hydrohalide salts indicated in parentheses. [c] Drug injected intraperitoneally as 0.3–5.0% solution or suspension 15–30 min before irradiation. [d] No 30-day survival among control mice. [e] Physiological saline solution. [f] Compound dissolved or suspended in physiological saline solution containing 0.3% sodium carboxymethylcellulose and 0.1% Tween 80.

13 by successive recrystallizations from MeCN and MeOH–Et_2O.

N-[ω-(ω-Bromoalkylamino)alkyl]phthalimide hydrobromides (8, 15) listed in Table II were prepared from the appropriate **7** or **14** as illustrated by the following procedures.

A. 8a and 8b.—A solution of **7a** (39.5 g, 0.152 mole) in 30% HBr–HOAc (200 ml) was stirred at 25–30° for 21 hr. Et_2O (700 ml) was added, and the collected precipitate was recrystallized from EtOH. Similar treatment of **7b** afforded **8b**, which was recrystallized from 95% EtOH.

B. 8c, 15a, and 15b.—A stirred mixture of **14b** (20.0 g, 66.2 mmoles) in 30% HBr–HOAc (125 ml) was gradually heated to reflux during 90 min. Following a 30-min reflux period, the mixture was allowed to cool, and Et_2O (500 ml) was added; and the product was recrystallized from EtOH. Similarly obtained **8c** and **15a** were recrystallized from MeOH and 95% EtOH, respectively.

N-(2-Bromoethyl)-α,ω-alkanediamine dihydrobromides (2) were prepared from **1** essentially by the Cortese method.[8] The HBr remaining after the reaction period was removed under reduced pressure, and the crystalline residue was stirred with Me_2CO, collected, and recrystallized from MeOH–Me_2CO. Results are given in Table III.

N-(3-Bromopropyl)-α,ω-alkanediamine dihydrobromides (17) were prepared as follows with yields and characterizations being recorded in Table III.

A. 17a.—A solution of **16a** (12.8 g, 0.108 mole) in 48% HBr (500 ml) was refluxed 1 hr, then slowly distilled during 12 hr until 400 ml of distillate had been collected. The remaining solution was evaporated to dryness under reduced pressure, and the solid residue was reprecipitated from MeOH solution by addition of Et_2O.

B. 17b.—A solution of **15a** (13.0 g, 32.0 mmoles) in 48% HBr (50 ml) and glacial AcOH (50 ml) was refluxed 17 hr, cooled while phthalic acid separated, and filtered. Removal of solvents from the filtrate by evaporation under reduced pressure left crystalline **17b**, which was purified by reprecipitation from MeOH solution by addition of Et_2O followed by recrystallization from EtOH.

C. 17c was obtained from **15b** by the same procedure as described for the preparation of **17b.**

1-(4-Aminobutyl)aziridine (9b).—Pulverized **1c** (100 g, 0.280 mole) was added in portions to stirred 20% NaOH solution (800 ml). The stirred mixture was refluxed for 1 hr and allowed to cool, and the two liquid layers were separated. The aqueous layer was extracted with three 100-ml portions of Et_2O; the dried ($MgSO_4$) Et_2O solution was evaporated to an oil, which was combined with the organic phase from the reaction mixture. The crude product was dried (KOH) and fractionally distilled (Vigreux column) to give **9b**, bp 79–80° (20 mm) and $n^{22}D$ 1.4587, in 70% yield (22.3 g); purity by glpc was >99%. *Anal.* Calcd for $C_6H_{14}N_2$: C, 63.11; H, 12.36; N, 24.53. Found: C, 61.72; H, 12.03; N, 24.09.

2-Methyl-1-aziridinepropionitrile (19a).—2-Methylaziridine (100 g, 1.75 moles) was added dropwise to stirred acrylonitrile (93.3 g, 1.76 moles) preheated to 65°; the temperature was maintained at 65–70° throughout the addition period and for about 1 hr afterward by moderate cooling. When heat ceased to be evolved, the mixture was heated at 70–75° for 2 hr. Fractionation (30-cm Vigreux column) afforded **19a**, bp 70–72° (10 mm) and $n^{24}D$ 1.4368, in 80% yield (155 g). *Anal.* ($C_6H_{10}N_2$) H, N; C: calcd, 65.42; found, 64.82.

2,2-Dimethyl-1-aziridinepropionitrile (19b).—A solution of 2,2-dimethylaziridine (100 g, 1.41 moles) and acrylonitrile (64.7 g, 1.20 moles) was refluxed for 12 hr, the reflux temperature gradually rising during this period from 78 to 138°. Fractionation (30-cm Vigreux column) afforded **19b**, bp 81–89° (11 mm) and $n^{25}D$ 1.4419, in 63% yield (94.2 g). An analytical sample, bp 78–81° (10 mm) and $n^{27}D$ 1.4406, was obtained in 19% yield employing the conditions described by Bestian for the preparation of 1-aziridinepropionitrile.[6] *Anal.* ($C_7H_{12}N_2$) C, H, N.

1-(3-Aminopropyl)aziridine (9a), 1-(3-Aminopropyl)-2-methylaziridine (20a), and 1-(3-Aminopropyl)-2,2-dimethylaziridine (20b).—$LiAlH_4$ reductions of the appropriate nitriles (1-aziridinepropionitrile,[6] **19a**, and **19b**) were performed according to a general procedure described by Amundsen and Nelson.[19] Pure **9a**,

TABLE II

N-[ω-(ω-BROMOALKYLAMINO)ALKYL]PHTHALIMIDE HYDROBROMIDES (8, 15)

No.	Yield, %	Mp, °C dec	Formula	Analyses
8a	82	190–192	$C_{12}H_{13}BrN_2O_2 \cdot HBr$	C, H, Br
8b	82	225–227	$C_{13}H_{15}BrN_2O_2 \cdot HBr$	C, H, Br
8c	94	229–231	$C_{14}H_{17}BrN_2O_2 \cdot HBr$	C, H, Br, N
15a	89	199–200	$C_{14}H_{17}BrN_2O_2 \cdot HBr$	C, H, Br, N
15b	91	192–196	$C_{15}H_{19}BrN_2O_2 \cdot HBr$	C, H, Br, N

TABLE III

N-(2-BROMOETHYL)-α,ω-ALKANEDIAMINE DIHYDROBROMIDES (2), N-(3-BROMOPROPYL)-α,ω-ALKANEDIAMINE DIHYDROBROMIDES (17), AND N-(2-BROMOALKYL)-1,3-PROPANEDIAMINE DIHYDROBROMIDES (22)

No.	Yield, %	Mp, °C	Formula	Analyses
2a	85	174–176[a]	$C_4H_{11}BrN_2 \cdot 2HBr$	C, H, Br[b]
2b[c]	80	205–206[a]	$C_5H_{13}BrN_2 \cdot 2HBr$	C, H, Br
2c	78	200–201[a]	$C_6H_{15}BrN_2 \cdot 2HBr$	C, H, Br
2d	86	183–185[a]	$C_7H_{17}BrN_2 \cdot 2HBr$	C, H, Br
2e	84	176–178[a]	$C_8H_{19}BrN_2 \cdot 2HBr$	C, H, Br
17a	81	144–145	$C_5H_{13}BrN_2 \cdot 2HBr$	C, H, Br, N
17b	83	243–245	$C_6H_{15}BrN_2 \cdot 2HBr$	C, H, Br, N
17c[d]	79	227–229	$C_7H_{17}BrN_2 \cdot 2HBr$	C, H, Br, N
22a	37	211–212	$C_6H_{15}BrN_2 \cdot 2HBr$	C, H, Br
22b	54	188–189	$C_7H_{17}BrN_2 \cdot 2HBr$	C, H, Br

[a] Determined on a Kofler Heizbank. [b] Br: calcd, 72.89; found, 73.5. [c] The sample prepared from **1b** was not analyzed; it is identical (melting point, mixture melting point) with an analytically pure sample prepared in nearly theoretical yield by ring opening of **9a** in the manner described for the preparation of **22b**. Pure **2b** was also prepared in 92% yield from **8b** using the procedure described for **17b**. [d] Also prepared from **16b** in 62% yield using the procedure described for **17a**.

(19) L. H. Amundsen and L. S. Nelson, *J. Amer. Chem. Soc.*, **73**, 242 (1951).

TABLE IV

S-2-(ω-AMINOALKYLAMINO)ETHYL HYDROGEN THIOSULFATE HYDROHALIDES (**10**), S-2-(3-AMINOPROPYLAMINO)ALKYL HYDROGEN THIOSULFATE HYDROCHLORIDES (**21b**·HCl, **21d**·HCl), AND S-2-(2-CYANOETHYLAMINO)ALKYL HYDROGEN THIOSULFATES (**24a**, **24c**)

No.	Yield, %	Mp, °C	Formula	Analyses
10a	95	87–90	$C_5H_{14}N_2O_3S_2$·HCl	C, H, N, S
10b	98	79–89	$C_6H_{16}N_2O_3S_2$·HCl	C, H, S; N[a]
10c	50	149[b]	$C_8H_{20}N_2O_3S_2$·HBr	C, H, Br, S
21b·HCl	88	[c]	$C_6H_{16}N_2O_3S_2$·HCl	C, H, N, S
21d·HCl	86	[c]	$C_7H_{18}N_2O_3S_2$·HCl	C, H, N, S
24a	51	214[b]	$C_6H_{12}N_2O_3S_2$	C, H, N, S
24c	46	240[b]	$C_7H_{14}N_2O_3S_2$	C, H, N, S

[a] N: calcd, 10.58; found, 10.16. [b] Determined on a Kofler Heizbank. [c] Indefinite.

TABLE V

S-2-(ω-AMINOALKYLAMINO)ETHYL DIHYDROGEN PHOSPHOROTHIOATES (**3a**–**3e**), S-3-(ω-AMINOALKYLAMINO)PROPYL DIHYDROGEN PHOSPHOROTHIOATES (**18a**–**18c**), AND S-2-(3-AMINOPROPYLAMINO)ALKYL DIHYDROGEN PHOSPHOROTHIOATES (**23a**, **23b**)

No.	Scale, mmoles of Na_3PSO_3	Yield, %	Mp, °C dec	Formula	Analyses
3a	50.0	82	139–141	$C_4H_{12}N_2O_3PS\cdot H_2O$	C, H, N, S
3b	38.5	21	160–161[c]	$C_5H_{14}N_2O_3PS\cdot H_2O$	C, H, N
3c	55.1	71	[b]	$C_6H_{16}N_2O_3PS$	C, H, N, S
3d	37.8	67	[b]	$C_7H_{18}N_2O_3PS\cdot H_2O$	C, H, N, S
3e	50.0	33	[b]	$C_8H_{22}N_2O_3PS\cdot 2H_2O$	C, H, N, S
18a	[c]	81	168–170	$C_6H_{15}N_2O_3PS$	C, H, N, P, S
18b		92	140–143	$C_8H_{17}N_2O_3PS\cdot 2H_2O$	C, H, N, P, S
18c		67	171–172	$C_7H_{19}N_2O_3PS\cdot 2H_2O$	C, H, N, P, S
23a		78	122–124	$C_6H_{17}N_2O_3PS\cdot 2.5H_2O$	C, H, N, P, S
23b		93	149–151	$C_7H_{19}N_2O_3PS\cdot 2.5H_2O$	C, H, N; P, S[d]

[a] Determined on a Kofler Heizbank. [b] Indefinite melting point with decomposition over wide range (starting about 170°) dependent on rate of heating. [c] For remaining entries molar scales are stated in the procedures. [d] *Anal.* Calcd: P, 10.79; S, 11.16. Found: P, 11.2; S, 11.6.

bp 58–60° (19 mm) [lit.[6] bp 61–62° (19 mm)], was obtained in 38% yield. The yield of **20a**, bp 72–75° (40 mm) and $n^{23}D$ 1.4466, was 68% and that of **20b**, bp 84–86° (30 mm) and $n^{25}D$ 1.4485, was 74%. *Anal.* ($C_5H_{14}N_2$, **20a**) C, H, N. ($C_7H_{16}N_2$, **20b**) C, H, N.

N-(2-Bromo-1-methylethyl)-1,3-propanediamine dihydrobromide (22a) was prepared by dropwise addition of **20a** (26.0 g, 0.236 mole) to stirred 48% HBr (105 ml) maintained at −5 to 0°. The clear solution was evaporated to dryness under reduced pressure with the aid of several added portions of MeOH. The residual gum was stirred with boiling EtOAc (1 l.) for 1 hr, and crystalline **22a** formed while the stirred mixture was allowed to cool. The crude material was collected, dried (*in vacuo*, 80°, P_2O_5), and recrystallized from *i*-PrOH (1.5 l.) to give pure **22a**. Results are recorded in Table III.

N-(2-Bromo-1,1-dimethylethyl)-1,3-propanediamine dihydrobromide (22b) (see Table III) was prepared by HBr ring opening of **20b** in the manner described for **22a** from **20a**. Following evaporation to dryness, the solid residue was stirred with Me_2CO. The collected, Me_2CO-insoluble solid was purified by one recrystallization (MeOH–Me_2CO) followed by two reprecipitations from MeOH solution by addition of Et_2O.

S-2-(ω-Aminoalkylamino)ethyl Hydrogen Thiosulfate Hydrochlorides (10a, 10b).—The following description of the preparation of **10b** is typical of the procedure used; results are recorded in Table IV. A solution of **9b** (1.90 g, 16.6 mmoles) and $(NH_4)_2S_2O_3$ (2.46 g, 16.6 mmoles) in H_2O (10 ml) was evaporated (aspirator) during 1 hr in a bath gradually heated to 90°. Last traces of volatile material were then removed *in vacuo* (1 mm) at 60° (30 min). The residual syrup was dissolved in H_2O (10 ml), and the solution was treated with 1 *N* HCl (16.6 mequiv). The resultant solution of **10b** was evaporated to dryness, final conditions being 1 mm, 60°. Drying was completed *in vacuo* at 25–30° over P_2O_5.

S-2-(6-Aminohexylamino)ethyl Hydrogen Thiosulfate Hydrobromide (10c).—A solution of equimolar amounts of $Na_2S_2O_3\cdot 5H_2O$, NaOAc·$3H_2O$, and **2e** (40.0 mmoles each) in H_2O (40 ml) and DMF (20 ml) was kept at 25–30° for 2 hr and then at 90–100° for 1 hr. Solvents were removed under reduced pressure, and the residue was dissolved in boiling EtOH (about 500 ml). Crystalline material that separated during a 4-day period was collected and recrystallized again from EtOH. The material obtained, now pale-yellow, was dissolved in boiling MeOH; the hot solution was decolorized (Norit, Celite), then evaporated under reduced pressure to a colorless syrup, which crystallized readily when stirred with warm (50°) EtOH (100 ml) to give pure **10c** (dried *in vacuo*, 25–30°, P_2O_5) (Table IV).

S-2-(3-Aminopropylamino)propyl Hydrogen Thiosulfate (21b) and S-2-(3-Aminopropylamino)-2-methylpropyl Hydrogen Thiosulfate (21d) Hydrochlorides.—The following procedure for the preparation of **21b**·HCl is illustrative; results are given in Table IV. A solution of **20a** (2.67 g, 23.4 mmoles) and $(NH_4)_2S_2O_3$ (3.30 g, 22.3 mmoles) in H_2O (15 ml) was evaporated during 1 hr (aspirator, 35° bath). The residual syrup was redissolved in H_2O (15 ml), and evaporation under the same conditions was repeated. The residue was then subjected to 0.2 mm, bath temperature 100°. The pasty residue was dissolved in H_2O (15 ml), and 1 *N* HCl (22.3 mequiv) was added; **21b**·HCl was then isolated in the same way as **10b** described above.

S-2-(2-Cyanoethylamino)propyl Hydrogen Thiosulfate (24a).—A solution of **19a** (2.89 g, 26.3 mmoles) and $(NH_4)_2S_2O_3$ (3.71 g, 25.0 mmoles) in H_2O (15 ml) was evaporated (aspirator, bath temperature 40°). A solution of the residue in H_2O (15 ml) was again evaporated to dryness, and the product was further purified by reprecipitation from H_2O with EtOH. Results are included in Table IV.

S-2-(2-Cyanoethylamino)-2-methylpropyl hydrogen thiosulfate (24c) (see Table IV) was prepared from **19b** by essentially the same procedure as described for **24a** except that **24c** was recrystallized from MeOH.

2-(3-Aminopropylamino)-1-propanethiol (21a), 2-(3-Aminopropylamino)-2-methyl-1-propanethiol (21c) Dihydrochlorides, and 3-(2-Mercapto-1,1-dimethylethylamino)propionitrile (24b) Hydrochloride.—Preparation of these compounds involved H_2S ring opening of the appropriate aziridine **20a**, **20b**, or **19b**. The procedure for preparing **21a**·2HCl is illustrative. MeOH (75 ml) was saturated with H_2S at −10°. A slow stream of H_2S was passed through the stirred solution while **20a** (3.00 g, 26.3 mmoles) was added dropwise. The resultant solution was kept at −5° for 30 min and then refrigerated (at about 4°) overnight in a securely stoppered flask. The solution was then concentrated under reduced pressure to 25 ml and treated with dry HCl in EtOH (9.5 ml of 6.35 *N*, 60 mequiv HCl). Addition of Et_2O (75 ml) afforded crystalline **21a**·2HCl, which was collected and dried *in vacuo* (25–30°, P_2O_5); yield 98% (5.69 g), mp ~156°. *Anal.* ($C_6H_{16}N_2S\cdot 2HCl$) C, H, N, S, SH. Similar treatment of **20b** afforded **21c**·2HCl, mp 182–183°, in 73% yield after recrystallization from EtOH. *Anal.* ($C_7H_{18}N_2S\cdot 2HCl$) C, H, N, S, SH. The yield of **24b**·HCl, mp 163°, was 72% (from 24.2 mmoles of **19b**, 25.4 mequiv of HCl being used). *Anal.* ($C_7H_{14}N_2S\cdot HCl$) C, H, N, S; SH: calcd, 16.98; found, 15.9.

S-2-(ω-Aminoalkylamino)ethyl Dihydrogen Phosphorothioates (3).—The general reaction procedure used is essentially that described by Åkerfeldt[9d] for the preparation of related compounds. A stirred partial solution of Na_3PSO_3 in H_2O (1 ml/mmole of Na_3PSO_3) was treated with the appropriate 2-(3-6)-one (5% excess). When solution was complete, DMF (one-half the volume of H_2O used) was added with external cooling; the resultant solution was kept at 25–30° until the $AgNO_3$ test for unchanged PSO_3^{3-}[9e] was negative. Isolation procedures used for the individual examples listed in Table V follow.

3a was the only member of the **3** series that crystallized directly from the reaction solution. The solid was collected, washed (MeOH–H_2O, 4:1 by vol), then dissolved (H_2O, 400 ml) and reprecipitated by addition of MeOH (1 l.). Following overnight refrigeration, crystalline **3a** was collected, washed (MeOH, Et_2O), and air dried.

3b.—Dilution of the reaction solution with MeOH (250 ml) caused precipitation of white solid; following overnight refrigeration, the solid was collected, dissolved (H_2O, 40 ml),

and reprecipitated with MeOH (250 ml). The collected solid was washed (MeOH, Et_2O), and air dried.

3c was precipitated by addition of MeOH (175 ml), reprecipitated from H_2O–MeOH, then dried *in vacuo* (P_2O_5) for about 5 min at 80° followed by several hours at 25–30°. This material showed no tendency to gain weight when exposed to ambient conditions.

3d.—MeOH (200 ml) was added to the reaction solution, but no precipitate formed. EtOH (200 ml) was then added, and a white, somewhat gelatinous solid formed. After overnight refrigeration the solid was collected, washed (MeOH), and then stirred with MeOH (200 ml) for 1.5 hr. The solid that remained was collected, dissolved in H_2O (20 ml), and reprecipitated by addition of MeOH (100 ml) followed by EtOH (100 ml). After refrigeration (18 hr), the solid was collected, washed (MeOH), and dried *in vacuo* (80°, P_2O_5). Marked shrinkage occurred before the sample came to constant weight (6.20 g). Equilibration with ambient conditions caused a weight increase (to 6.62 g).

3e.—Essentially the same procedure as used in the isolation of **3b** sufficed.

S-3-Aminopropyl dihydrogen phosphorothioate (13), mp 293–295° dec, was prepared in 36% over-all yield *via* its uncharacterized monosodium salt (from **12** and Na_3PSO_3) using the methods described for the S-2-aminoethyl homolog[9b] (Åkerfeldt[9c] has described preparation of the monolithium salt of **13**). *Anal.* ($C_3H_{10}NO_3PS$) C, H, N, P, S.

S-3-(ω-Aminoalkylamino)propyl dihydrogen phosphorothioates (18), which are included in Table V, were prepared as follows.

18a.—A stirred solution of Na_3PSO_3 (3.60 g, 20.0 mmoles) and **17a** (6.86 g, 20.0 mmoles) in H_2O (20 ml) was treated with DMF (10 ml), and stirring was continued 1.5 hr while crystalline **18a** separated. Addition of EtOH (200 ml) followed; the collected, EtOH-washed precipitate was redissolved in H_2O (50 ml), then reprecipitated by addition of MeOH (~35 ml to cause incipient cloudiness). Crystalline **18a** that separated during refrigeration was collected, washed (MeOH–H_2O, Et_2O), and air dried.

18b.—A solution of equimolar amounts of **17b** and Na_3PSO_3 (10.0 mmoles each) in H_2O (10 ml) was kept at 25–30° for 2 hr, then stored overnight in a refrigerator (~4°). The still-cold solution was stirred while DMF (5 ml) was added, and crystalline **18b** separated immediately. EtOH (100 ml) was added, and the solid was collected, washed (EtOH), redissolved in H_2O (60 ml), then reprecipitated by addition of EtOH (50 ml to cause incipient cloudiness). Following refrigeration, the lustrous platelets were collected, washed (EtOH), and dried *in vacuo* (25–30°, NaOH pellets).

18c.—A stirred solution of Na_3PSO_3 (2.70 g, 15.0 mmoles) and **17c** (5.60 g, 15.1 mmoles) in H_2O (15 ml) was treated with DMF (7.5 ml). The resultant solution was kept at 25–30° for 2 hr, then added dropwise to rapidly stirred EtOH (450 ml). The solid that separated was collected, washed (EtOH), then suspended in rapidly stirred MeOH (25 ml). H_2O (~15 ml) was added slowly until nearly all of the solid had dissolved. More MeOH (50 ml) was then added causing crystalline product to separate. The collected material was washed (MeOH) and dried *in vacuo* (25–30°, P_2O_5). Equilibration with ambient conditions (~50% relative humidity) caused a weight increase (from 2.60 to 2.81 g).

S-2-(3-Aminopropylamino)propyl Dihydrogen Phosphorothioate (23a).—Solid **22a** (5.25 g, 14.7 mmoles) was added to a stirred solution of $Li_3PSO_3 \cdot 6H_2O$ (3.36 g, 14.0 mmoles) in H_2O (28 ml), and, after solution was complete, DMF (14 ml) was added. The solution was kept at 25–30° for 40 min and then poured into EtOH (400 ml). Solvated **23a** separated as an opaque gum. The supernatant was removed by decantation, and the gum was dissolved in H_2O (50 ml). The solution was added dropwise to rapidly stirred EtOH (500 ml), but the solvated product again separated as white opaque gum. Following removal of the supernatant, the residue was dissolved in H_2O (20 ml); EtOH (50 ml) was added to the stirred solution. After a few minutes of rapid stirring, the cloudy mixture began depositing crystalline material. More EtOH (450 ml) was added, and stirring was continued 1 hr. The crystalline product was collected, washed with EtOH followed by Et_2O, air dried (3.04 g), and equilibrated at constant 58% relative humidity[4] (equilibrated weight, 2.97 g). Results are included in Table V.

S-2-(3-Aminopropylamino)-2-methylpropyl Hydrogen Phosphorothioate (23b).—A solution of **22b** (4.45 g, 12.0 mmoles) and $Li_3PSO_3 \cdot 6H_2O$ (2.88 g, 12.0 mmoles) in H_2O (12 ml) was stirred at 25–30° for 30 min. DMF (6 ml) was added, and, after 15–20 min, the solution began depositing crystalline product. The mixture was refrigerated overnight, EtOH (60 ml) was added, and the precipitate was collected, washed (EtOH), redissolved in H_2O (20 ml), then reprecipitated by addition of EtOH (100 ml). Hydrated **23b** was collected, washed (EtOH, Et_2O), air dried (3.18 g), and equilibrated at 58% relative humidity[4] (equilibrated weight, 3.21 g.). Results are included in Table V.

S-2-(2-Cyanoethylamino)ethyl Sodium Hydrogen Phosphorothioate (26) Tetrahydrate.—A mixture of equimolar amounts of **25** and Na_3PSO_3 (40.0 mmoles each) in H_2O (40 ml) was stirred until solution had occurred (20 min). DMF (20 ml) was added, and the solution was stirred at 25–30° for 1 hr. Dropwise addition of EtOH (150 ml) with chilling (ice–water bath) and continued stirring caused separation of hydrated **26** as a white solid, which was collected, redissolved in H_2O (40 ml), and reprecipitated by addition of EtOH. The collected product was washed (EtOH, Et_2O) and air dried; yield 81% (9.85 g). *Anal.* ($C_5H_{10}N_2NaO_3PS \cdot 4H_2O$) C, H, S; N: calcd, 9.21; found, 8.62; P: calcd, 10.18; found, 10.6.

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