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

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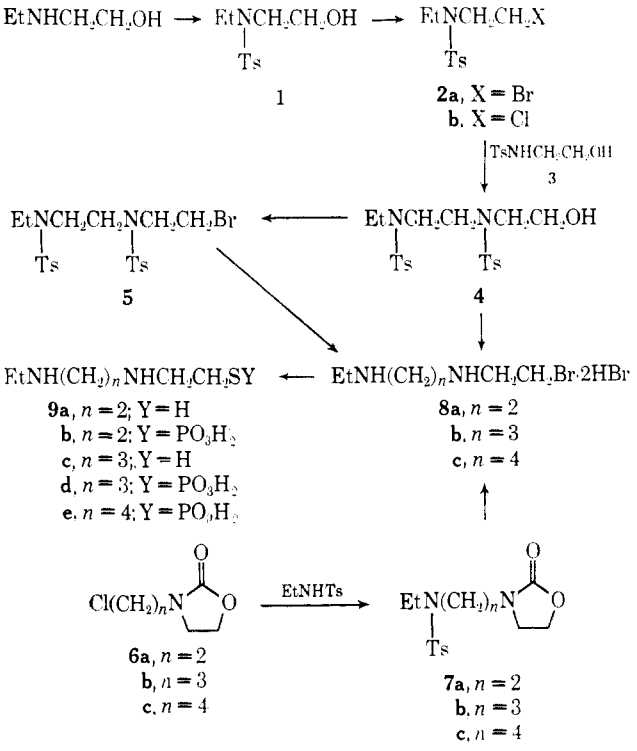
A number of terminal N-alkyl and N-aryl derivatives of S-2-(ω-aminoalkylamino)ethyl dihydrogen phosphorothioates and related compounds were prepared for evaluation as antiradiation agents. Several synthetic approaches were examined, and the generally preferred synthesis involved the concurrent detosylation and ring cleavage of 3-substituted 2-oxazolidinone intermediates containing a tosylated aminoalkyl side chain. Acetoxy group cleavage in conjunction with detosylation was also useful in the synthesis of N-alkyl derivatives. The last-step phosphorothioate displacements were generally successful in the N-alkyl series, but only thiosulfate displacements were successful in the N-aryl series. Among the congeners prepared, S-2-(3-ethylaminopropylamino)ethyl dihydrogen phosphorothioate (**9d**) and S-2-(3-methylaminopropylamino)ethyl dihydrogen phosphorothioate (**20b**) were the most effective in antiradiation screening tests in mice, their activities being comparable to the parent compound unsubstituted on the terminal amino group.

The high level of radioprotective activity shown in mice by a number of S-2-(ω-aminoalkylamino)ethyl dihydrogen phosphorothioates[2] prompted an interest in the effect of alkyl and aryl substitution on the terminal amino group in this series of compounds. Several approaches to this type of derivative have been investigated, but the most expedient and generally applicable approach incorporated steps that usually involved (1) protection of amino groups by prior tosylation and (2) concurrent detosylation and hydrogen bromide cleavage of 3-substituted 2-oxazolidinones.[3] A similar approach was followed, at least in part, in previously reported syntheses of related compounds,[4,5] and some general stoichiometrical aspects of displacements with thioanions in the last steps of such syntheses have been previously discussed in some detail.[5]

The synthesis of 2-(2-ethylaminoethylamino)ethanethiol (**9a**) and the corresponding phosphorothioate **9b** was accomplished *via* the two reaction sequences outlined in Scheme I, each proceeding through N-(2-bromoethyl)-N′-ethylethylenediamine dihydrobromide (**8a**) as a common intermediate. The longer and more tedious route consisted of a stepwise buildup from tosylated intermediates. The intermediate N-(2-chloroethyl)sulfonamide **2b** was more easily obtained in pure crystalline form and good yield than its more reactive bromo counterpart **2a**. Although N-ethyl-N′-(2-hydroxyethyl)-N,N′-ethylenebis-*p*-toluenesulfonamide (4) underwent both detosylation and bromodehydroxylation with HBr under Cortese conditions,[6] this direct conversion into **8a** was accompanied by considerable tar formation due to side reactions, which might have been minimized by the addition of phenol[7] as in similar detosylations.[4] This difficulty was circumvented conveniently, however, by the prior

SCHEME I



conversion of **4** into N-(2-bromoethyl)-N′-ethyl-N,N′-ethylenebis-*p*-toluenesulfonamide (**5**) with an over-all improvement in yield. The subsequent development of the hydrogen bromide cleavage of 3-substituted 2-oxazolidinones not only provided an expedient and superior route to **8a** and a number of related compounds but was easily adaptable to the preparation of the homologs **8b** and **8c**. Standard displacements afforded the thiols **9a**, **c** and the inner phosphorothioates **9b**, **d**, **e**, but thiosulfate displacements, as in the case of the unsubstituted analogs[2] and terminal N-methyl derivatives, failed to give crystalline inner Bunte salts.

The method of choice in the synthesis of the N-(2-bromoethyl)-N′-methyl-α,ω-alkanediamine dihydrobromides **19** and the S-2-(ω-methylaminoalkylamino)-ethyl dihydrogen phosphorothioates **20** derived from them (Scheme II) is again the one based on oxazol-

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

(2) J. R. Piper, C. R. Stringfellow, Jr., R. D. Elliott, and T. P. Johnston, *J. Med. Chem.*, **12**, 236 (1969).

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

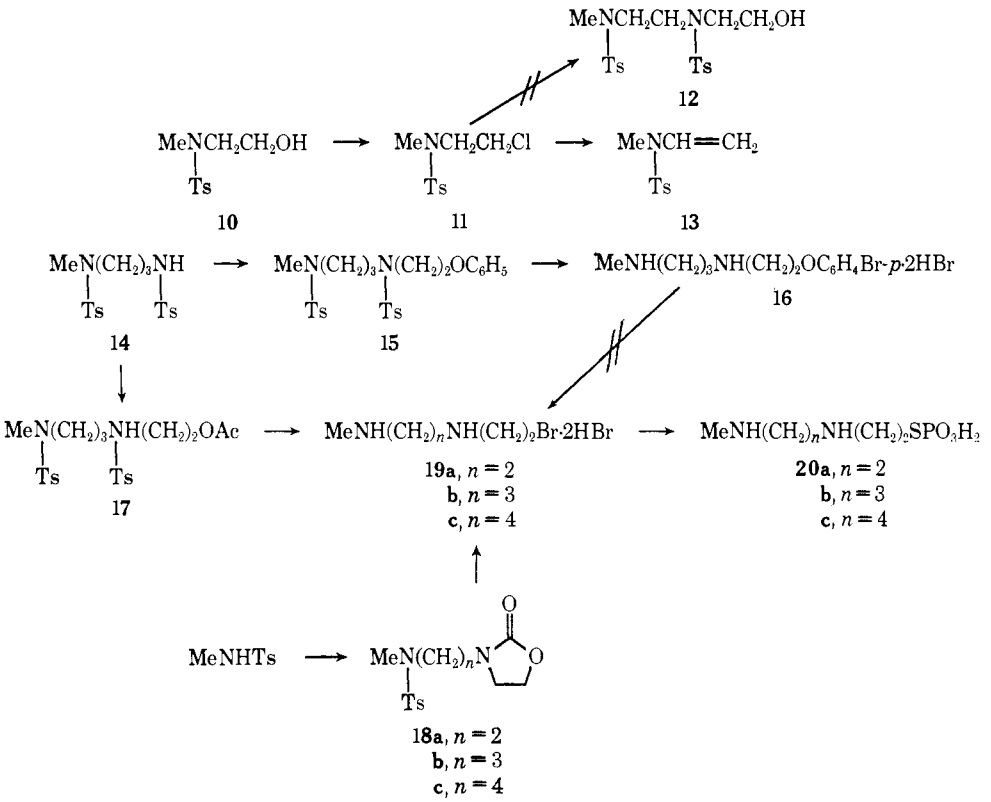
(4) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **9**, 563 (1966).

(5) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **33**, 636 (1968).

(6) 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.

(7) H. R. Snyder and R. E. Heckert, *J. Amer. Chem. Soc.*, **74**, 2006, 4864 (1952).

SCHEME II



idinone-ring cleavage. It was, in fact, in the conversion of the sulfonamide **18a** into **19a** that a 30% solution of dry HBr in HOAc containing phenol was found to be a more suitable reagent for simultaneous detosylation and decarboxylative ring cleavage and to require less vigorous conditions than aqueous 48% HBr. The use of phenol as a bromine scavenger in this type of reaction generally affords cleaner products, although good results are often obtained without it. Prior to the advent of the oxazolidinone method the synthesis of the intermediate **19a** was undertaken by a route based on the previous conversion of **1** into **8a** (Scheme I), but proceeded no further than the conversion of N-(2-hydroxyethyl)-N-methyl-*p*-toluenesulfonamide (**10**) into the 2-chloroethyl derivative **11**, the attempted condensation of which with **3** produced N-methyl-N-vinyl-*p*-toluenesulfonamide (**13**) instead of the desired bis-*p*-toluenesulfonamide **12**. Two schemes for the synthesis of **19b**, one of which was successful but was later superseded, were based on the substitution of N-methyl-N,N′-trimethylenebis-*p*-toluenesulfonamide (**14**) by a group that would cleave during subsequent detosylation. The protracted action of refluxing 48% HBr on the 2-phenoxyethyl derivative **15** apparently achieved both detosylation and ether cleavage, but the purple amorphous product could not be decolorized and recrystallized. The action of 30% dry HBr in HOAc on **15** effected detosylation, but not ether cleavage, and resulted in the isolation of a ring-brominated product, probably N-(2-*p*-bromophenoxyethyl)-N′-methyl-1,3-propanediamine dihydrobromide (**16**). That forcible cleavage of **16** with 48% HBr would produce an effect like that observed with **15** was indicated in a trial experiment. In contrast, the action of 48% HBr on the crude 2-acetoxyethyl derivative **17** afforded the desired **19b**. The cleavage of an acetoxy group in conjunction with oxazolidinone-ring cleavage with 30% dry HBr in HOAc was recently reported.[8] These examples involving the acetoxy blocking group illustrate a means whereby usually troublesome hydroxyethylations of primary amines with ethylene oxide can be circumvented when the end product is to be an N-substituted 2-bromoethylamine hydrobromide.

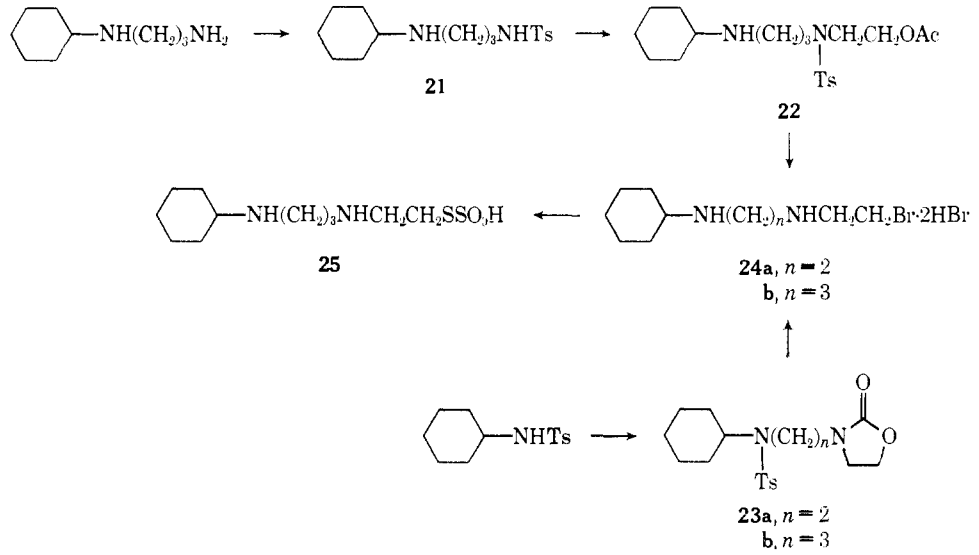
A reaction sequence based on the conversion of **14** into **19b** was chosen for the preparation of N-(2-bromoethyl)-N′-cyclohexyl-1,3-propanediamine dihydrobromide (**24b**), but steric hindrance unexpectedly altered the initial steps as indicated in Scheme III. The preparation of **14** by the addition of *p*-toluenesulfonyl chloride to N-methyl-1,3-propanediamine in DMF is represented by eq 1, but the product formed by a

$$2CH_3NH(CH_2)_3NH_2 + 2TsCl \longrightarrow \mathbf{14} + CH_3NH(CH_2)_3NH_2 \cdot 2HCl \quad (1)$$

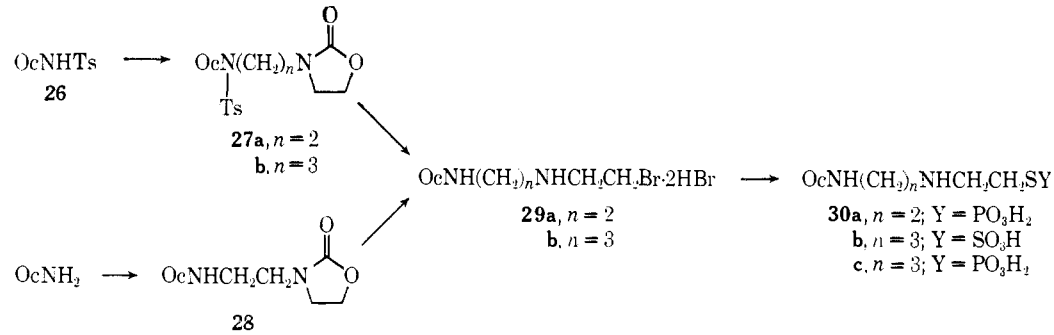
similar treatment of N-cyclohexyl-1,3-propanediamine was the H_2O-soluble hydrochloride of N-(3-cyclohexylaminopropyl)-*p*-toluenesulfonamide (**21**), which precipitated as the free base at pH 9 and whose structure was attested by high solubility in a strongly alkaline solution. In the alternative synthesis of **24b** and the lower homolog **24a** from the sulfonamides **23**, steric hindrance was evidenced by the requirement of more vigorous conditions for the alkylation of N-cyclohexyl-*p*-toluenesulfonamide with the 3-(ω-chloroalkyl)-

(8) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Heterocycl. Chem.*, **4**, 298 (1967).

SCHEME III



SCHEME IV

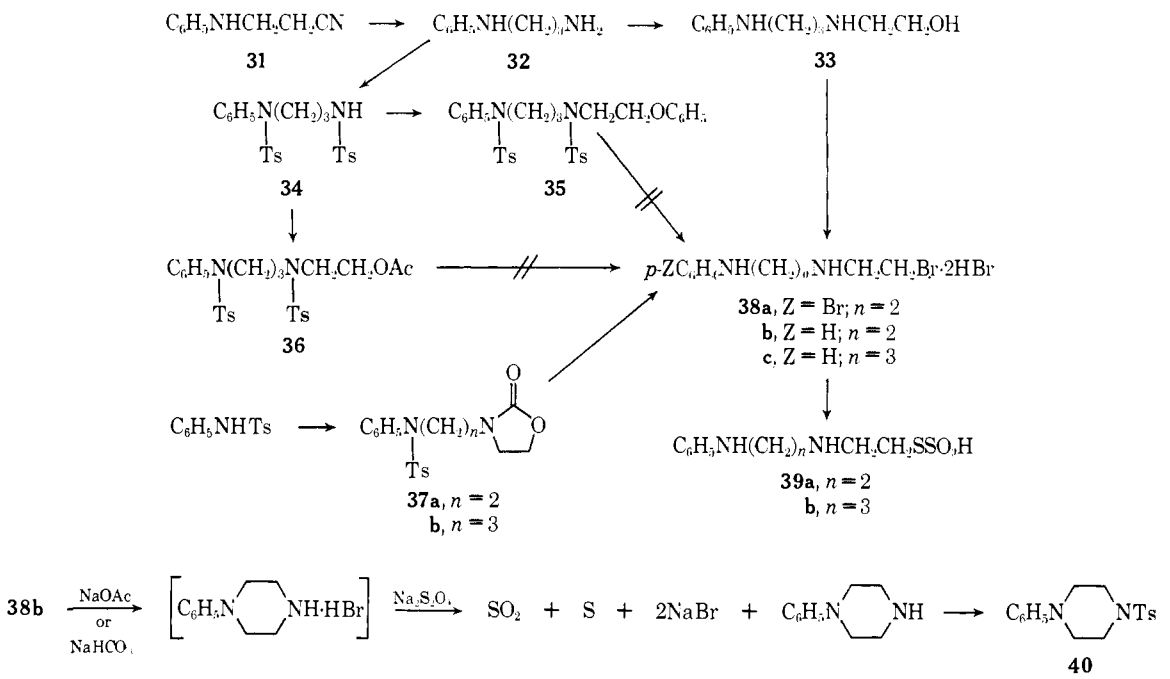


2-oxazolidinones **6a**, **b**; the alkylations were effected at 130–140° in dimethylacetamide (DMAC) after an attempted alkylation with **6a** at 115° in DMF had failed. In marked contrast to the methyl and ethyl analogs, **24b** gave a crystalline Bunte salt (**25**) hydrobromide (although in low yield) when treated with equimolar amounts of $Na_2S_2O_3$ and NaOAc. The preferred procedure, however, involved neutralization of the reaction mixture with $NaHCO_3$, which allowed the isolation of **25** as a crystalline hemihydrate in high yield. On the other hand, the displacement reaction of **24b** with trisodium phosphorothioate in H_2O–DMF at room temperature was incomplete after 2 days.

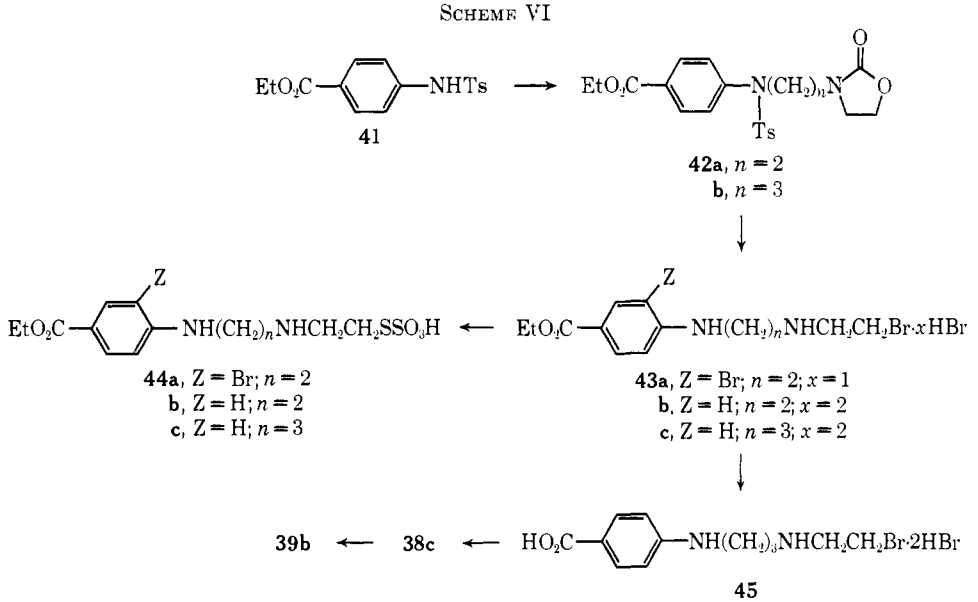
The N-(2-bromoethyl)-N′-octyl-α,ω-alkanediamine dihydrobromides **29** were prepared from the oily, uncharacterized sulfonamides **27** and converted into the corresponding phosphorothioates **30a**, **c** and the thiosulfate **30b** as outlined in Scheme IV. In a variation of this sequence, the preparation of N-octyl-*p*-toluenesulfonamide (**26**) was by-passed by the direct alkylation of octylamine with **6a** to give crude 3-(2-octylaminoethyl)-2-oxazolidinone (**28**). Trilithium phosphorothioate was the reagent used in the preparation of **30a**, **c**; the isolation of **30b** was effected by $NaHCO_3$ neutralization as in the preparation of **25**. The use of trilithium rather than trisodium phosphorothioate sometimes facilitates the isolation of crystalline derivatives as was the case with **20c**.

Several approaches to the synthesis of the N-(2-bromoethyl)-N′-phenyl-α,ω-alkanediamine dihydrobromides **38b**, **c**, from which the respective thiosulfates **39a**, **b** were derived, are delineated in Scheme V. The convenience of the sequence beginning with the reduction of 3-anilinopropionitrile (**31**) was limited by the troublesome separation of 2-(3-anilinopropylamino)ethanol (**33**) from the mixture of products that resulted from the treatment of N-phenyl-1,3-propanediamine (**32**) with ethylene oxide. In the search for an alternative route, **32** was converted into the bis-*p*-toluenesulfonanide **34**, from which both the 2-phenoxyethyl and 2-acetoxyethyl derivatives **35** and **36** were derived as crude oils, but neither could be converted into isolable **38c** by treatment with 48% HBr. The route *via* **33** was eventually outmoded by the hydrogen bromide cleavage of the N-ω-(2-oxo-3-oxazolidinyl)alkyl-*p*-toluenesulfonanilides (**37**). An initial cleavage of **37a** with 30% dry HBr in HOAc in the presence of slightly more than an equimolar amount of phenol and with a finishing reflux period, however, resulted in the isolation of an analytically pure ring-brominated product, probably N-(2-bromoethyl)-N′-(*p*-bromophenyl)ethylenediamine dihydrobromide (**38a**). Ring bromination was avoided by a threefold increase in the amount of phenol used and elimination of the reflux period. The treatment of **38c** with equimolar amounts of $Na_2S_2O_3$ and NaOAc in H_2O at 90° gave the Bunte salt **39b**, but the same treatment of **38b** resulted in the precipitation of elemental S and the evolution of SO_2. Several procedural variations designed to avoid the effects of acidity on $Na_2S_2O_3$ gave similar results, including the prior partial neutralization of **38b** with an equimolar amount of $NaHCO_3$. The formation of 1-phenylpiperazine in the latter variation as indicated in Scheme V was demonstrated by the isolation of the

SCHEME V



SCHEME VI



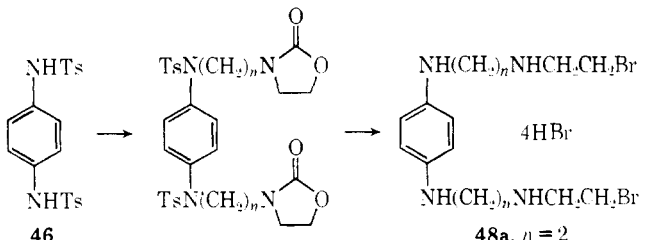
sulfonamide **40** following treatment of the reaction mixture with $NaHCO_3$ and *p*-toluenesulfonyl chloride. The preparation of **39a** was ultimately effected by the slow addition of powdered **38b** to a warm solution of an equivalent amount of $Na_2S_2O_3$ and 2 molar equiv of NaOAc in H_2O containing DMAC as a catalyst. Satisfactory procedures for the conversion of **38b**, **c** into the corresponding phosphorothioates were not devised.

The synthetic sequence shown in Scheme VI was followed in the preparation of the *p*-aminobenzoic acid derivatives **44**. Forcible conditions were also requisite to the conversion of ethyl *p*-(*p*-toluenesulfonamido)-benzoate (**41**) into the ethyl *p*-{N-[ω-(2-oxo-3-oxazolidinyl)alkyl]-*p*-toluenesulfonamido}benzoates **42**. Completion of the sequence leading to the thiosulfate **44c** was routine, but benzene-ring bromination was again encountered in the hydrogen bromide cleavage of **42a** in HOAc in the presence of an equimolar amount of phenol as bromine scavenger. On the basis of spectral evidence and Br^- analysis, the identity of the product was rationalized as the 3-bromobenzoate hydrobromide **43a**. The problem of ring bromination in the preparation of the benzoate dihydrobromide **43b** was subsequently overcome by doubling the molar ratio of phenol. Stoichiometric differences in the conversions of the monohydrobromide **43a** and the dihydrobromides **43b**, **c** permitted the preparation of the thiosulfate **44a** in the absence of NaOAc as buffer.

An initial effort to hydrolyze **43c** to *p*-[3-(2-bromoethylamino)propylamino]benzoic acid dihydrobromide (**45**) in refluxing 48% HBr resulted in decarboxylation, the product being identical with the previously prepared **38c**. Hydrolysis without appreciable decarboxylation was achieved on a pilot scale by refluxing a solution of **43c** in 10% HBr, but decarboxylation also occurred in a subsequent scale-up because of an inadvertent increase in reflux time but was not recognized until the derived Bunte salt was identified as **39b**.

The N,N′-bis[ω-(2-bromoethylamino)alkyl]-*p*-phenylenediamine tetrahydrobromides **48** were prepared according to Scheme VII, aromatic ring bromination in the hydrogen bromide cleavage step being inhibited by a 4:1 molar ratio of phenol. Attempts to prepare a Bunte derivative from **48b** by treatment with 2 molar equiv each of $Na_2S_2O_3$ and NaOAc in H_2O resulted in reaction mixtures that rapidly developed a red color and eventually became black. This behavior was probably due to the formation of quinonediimines by oxidation.

SCHEME VII



Although a comparison of thiols, Bunte salts, and phosphorothioates among these terminally substituted analogs is limited by discontinuity in their syntheses, the most effective radioprotectors among those compounds prepared, as judged by the results of antiradiation screening in mice at Walter Reed Army Institute of Research, Washington, D. C., were found among the methyl- and ethyl-substituted phosphorothioates (see Table I). The activities of **9d** and **20b**, which were sustained at a reduced dose level, compare favorably with those of the unsubstituted parent phosphorothioates.[2] On the other hand, none of the thiosulfates was active with the exception of the anilino analog **39b**, which was only slightly active. The two thiols, **9a** and **9c**, were both inactive even though **9c** corresponds to the highly active phosphorothioate **9d**.

Experimental Section[9]

N-Ethyl-N-(2-hydroxyethyl)-*p*-toluenesulfonamide (1).—A solution of *p*-toluenesulfonyl chloride (117.5 g, 0.617 mole) in DMF (400 ml) was added dropwise to a stirred mixture of 2-ethylaminoethanol (55.0 g, 0.617 mole), K_2CO_3 (85.3 g, 0.617 mole), and DMF (400 ml). The resultant mixture was then heated at 60–65° for 1 hr. The solvent was removed by distillation *in vacuo*, and the semisolid residue was extracted several times with C_6H_6 (900 ml total). Dilution of the filtered C_6H_6 solution with 30–60° ligroin led to separation of **1**, mp 60–62°, in 76% yield (113.6 g). *Anal.* ($C_{11}H_{17}NO_3S$) C, H, N.

N-(2-Bromoethyl)-N-ethyl-*p*-toluenesulfonamide (2a) was obtained from **1** in a manner similar to that previously described for the preparation of 2-(bromomethyl)-1,4-di(*p*-tolylsulfonyl)piperazine.[10] The crude product, obtained as a dark oil, was distilled *in vacuo*, and the pale yellow distillate, bp 158–168° (0.4 mm), solidified on standing. After being triturated in 30–60° ligroin, the product (62% yield) melted at 47–62°. Recrystallization from EtOH afforded a pure colorless sample, mp 64–66°. *Anal.* ($C_{11}H_{16}BrNO_2S$) C, H, Br.

N-(2-Chloroethyl)-N-ethyl-*p*-toluenesulfonamide (2b). A solution of **1** (50.0 g, 0.206 mole), $SOCl_2$ (25 ml, 0.34 mole), and PhMe (200 ml) was refluxed 3 hr. Evaporation under reduced pressure and subsequent recrystallization of the residue (from EtOH) gave pure **2b**, mp 64–65° (lit.[9] mp 67°), in 93% yield (49.6 g). *Anal.* ($C_{11}H_{16}ClNO_2S$) C, H, Cl.

N-Ethyl-N-(2-hydroxyethyl)-N,N′-ethylenebis-*p*-toluenesulfonamide (4).—After a stirred mixture of **3**[9] (39.4 g, 0.183 mole), K_2CO_3 (30.0 g, 0.217 mole), and DMF (150 ml) had been heated at 120° for 1 hr, a solution of **2b** (48.0 g, 0.183 mole) in DMF (100 ml) was added, and stirring and heating at 120–125° was continued for 5 hr. The cooled mixture was poured into ice water (1 l.), and the viscid oil that separated formed a waxy solid when the aqueous mixture was refrigerated. The collected, H_2O-washed solid was recrystallized from EtOH to give pure **4**, mp 163°, in 30% yield (24.5 g). *Anal.* ($C_{30}H_{38}N_2O_6S_2$) C, H, N.

N-(2-Bromoethyl)-N′-ethyl-N,N′-ethylenebis-*p*-toluenesulfonamide (5). A solution of **4** (24.0 g, 51.5 mmoles), $SOBr_2$ (19.4 g, 91.6 mmoles), and PhMe (225 ml) was refluxed 3 hr, clarified (Norit, Celite), and diluted with 30–60° ligroin. Crystalline **5** that separated was further purified by recrystallization from EtOH; the yield of pure **5**, mp 144°, was 80% (22.0 g). *Anal.* ($C_{30}H_{37}BrN_2O_6S_2$) C, H, Br.

N-(2-Bromoethyl)-N′-ethylethylenediamine Dihydrobromide (8a). From 5.—A stirred mixture of **5** (20.0 g, 39.7 mmoles) and 48% HBr (200 ml) was refluxed 6 hr and then evaporated under reduced pressure to near dryness. The residual dark oil was stirred with H_2O (150 ml), and the mixture was clarified (Norit, Celite). The colorless aqueous filtrate was evaporated to dryness under reduced pressure with the aid of several added portions of MeOH. The white crystalline residue was triturated in Me_2CO and then recrystallized from MeOH to give pure **8a**, mp ~195° dec, in 52% yield (7.43 g). *Anal.* ($C_6H_{15}BrN_2 \cdot 2HBr$).

From 4.—Treatment of **4** (10.0 g, 22.7 mmoles) with boiling 48% HBr (initially 300 ml) under Cortese-type conditions followed by a work-up procedure similar to that described above (for the conversion from **5**) afforded a 20% yield (1.65 g) of pure **8a** identical (melting point, mixture melting point, and ir spectrum) with the samples prepared from **5** and **7a**. *Anal.* ($C_6H_{15}BrN_2 \cdot 2HBr$) C, H, Br.

N-(2-Hydroxyethyl)-N-methyl-*p*-toluenesulfonamide (10) was prepared in 88% yield according to the procedure of Sloetz and Behnisch:[12] bp 167–168° (0.2 mm) [lit.[12] bp 250° (20 mm) and 180–185° (3.5 mm)].

N-(2-Chloroethyl)-N-methyl-*p*-toluenesulfonamide (11) was prepared from **10** in the manner described for the preparation of **2b**. The yield of pure **11**, mp 70–71° (from EtOH), was 77%. *Anal.* ($C_{10}H_{14}ClNO_2S$) Cl.

N-Methyl-N-vinyl-*p*-toluenesulfonamide (13) was the only product isolated from two attempted preparations of **12** (see Scheme II). A stirred mixture of equimolar amounts of **3** and NaOMe (4.64 mmoles each) in *n*-PrOH (15 ml) was refluxed for 1 hr; **11** (4.64 mmoles) was added, and the mixture was refluxed 15 hr. Dilution with H_2O (~100 ml) caused separation of **13**, mp 50–53° (lit.[13,14] mp 56–57.7° and 56–56.5°), in 94% yield. (Similar results were obtained from a run in which 2-methoxyethanol was used in place of *n*-PrOH.) *Anal.* ($C_9H_{11}NO_2S$) C, H, N.

N-Methyl-N′-(2-phenoxyethyl)-N,N′-trimethylenebis-*p*-toluenesulfonamide (15).—A stirred mixture of **14** (1.50 g, 3.78 mmoles) and K_2CO_3 (0.60 g, 4.35 mmoles) in DMF (10 ml) was heated during 1 hr to 120°. β-Bromophenetole[15] (0.76 g, 3.78 mmoles) was added, and the mixture was maintained at 120–125° for 3 hr. Dilution with H_2O (50 ml) caused separation of an oil, which was extracted with C_6H_6 (50 ml). Removal of the solvent from the H_2O-washed and dried ($MgSO_4$) C_6H_6 solution left a

(9) 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.

(10) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963); see also preparation of N,N′-tetramethylenebis-*p*-toluenesulfonamide.[3]

(11) H. H. Peacock and Y. S. Gwan, *J. Chem. Soc.*, 1468 (1937).

(12) K. H. Sloetz and R. Behnisch, *J. Prakt. Chem.*, **135**, 225 (1932).

(13) J. Furukawa, A. Onishi, and T. Tsuruta, *J. Org. Chem.*, **23**, 872 (1958).

(14) F. W. Stacey, J. C. Sauer, and B. C. McKusick, *J. Amer. Chem. Soc.*, **81**, 987 (1959).

(15) C. S. Marvel and A. L. Tanenbaum in "Organic Syntheses," Coll. Vol. I, 2nd ed, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, pp 435–436.

TABLE I

RADIOPROTECTIVE ACTIVITIES OF SOME TERMINALLY SUBSTITUTED S-2-(ω-AMINOALKYLAMINO)ETHYL DIHYDROGEN PHOSPHOROTHIOATES AND RELATED COMPOUNDS[a]

$RNH(CH_2)_nNHCH_2CH_2SY$

Compd	R	n	Y[b]	Approx LD_{50}, mg/kg	Drug dose, mg/kg[c]	Vehicle of admin	pH of prepn	30-day survival, %[d]
9a	Et	2	H(·2HCl)	>200	150	Water	5.7	0
					75	Water	5.7	0
9b	Et	2	$PO_3H_2(\cdot 2.5H_2O)$	850	400	Water	6.4	13
					200	Water	6.4	0
9c	Et	3	H(·2HCl)	350	75	Water	6.1	0
					37.5	Water	6.1	0
9d	Et	3	$PO_3H_2(\cdot 1.5H_2O)$	750	500	Water	6.6	100
					250	Water	6.6	100
					125	Saline[e]	6.6	7
20a	Me	2	$PO_3H_2(\cdot 2.5H_2O)$	900	400	PB[f]	6.9	73
					400	PB	6.9	47
					200	PB	6.9	20
20b	Me	3	$PO_3H_2(\cdot H_2O)$	800	400	PB	7.0	100
					200	PB	7.0	87
					100	PB	7.5	46
					50	PB	7.5	13
20c	Me	4	$PO_3H_2(\cdot 4H_2O)$	240	180	CMC-Tw[g]	7.5	33
					90	CMC-Tw	7.5	0
25	Cyclohexyl	3	$SO_3H(\cdot 0.5H_2O)$	250	150	PB	6.5	0
					150	CMC-Tw	8.5	0
					75	PB	6.5	0
					75	CMC-Tw	8.5	0
30a	Octyl	2	$PO_3H_2(\cdot 2H_2O)$	160	50	CMC-Tw	6.1	0
					25	CMC-Tw	6.1	0
30b	Octyl	3	$SO_3H(\cdot 0.5H_2O)$	50–150	<50	CMC-Tw	8.1	<5
30c	Octyl	3	$PO_3H_2(\cdot 1.5H_2O)$	175	125	Saline	6.6	20
					62.5	Saline	6.6	0
39a	Ph	2	SO_3H	225	50	CMC-Tw	6.4	0
					25	CMC-Tw	6.4	0
39b	Ph	3	SO_3H	300	200	CMC-Tw	6.6	13
					100	CMC-Tw	6.6	0
44b	p-$EtO_2CC_6H_4$	2	SO_3H	>1800	1000	CMC-Tw	5.5	0
					500	CMC-Tw	5.5	0
44c	p-$EtO_2CC_6H_4$	3	SO_3H	1800	1000	CMC-Tw	5.5	0
					500	CMC-Tw	5.5	0

[a] Antiradiation screening tests in mice against lethal radiation [825 R (X-rays) or 1000 R (γ rays)] were performed at Walter Reed Army Institute of Research, Washington, D. C., under the direction of Dr. D. P. Jacobus. [b] H_2O of crystallization and characterization as HCl salts indicated in parentheses. [c] Drug injected intraperitoneally as 0.5–5.0% solution or suspension 15–30 min before irradiation. [d] No 30-day survival among control mice. [e] Physiological saline. [f] Phosphate buffer. [g] Compound dissolved or suspended in physiological saline containing 0.3% sodium carboxymethylcellulose and 0.1% Tween 80.

yellow oil, which crystallized from warm EtOH to give pure **15**, mp 74°, in 73% yield (1.39 g). This sample proved to be identical (melting point and mixture melting point) with an analytical sample of **15** obtained in 60% yield *via* a NaOEt-promoted alkylation of **14** with β-bromophenetole in refluxing EtOH. *Anal.* ($C_{26}H_{32}N_2O_2S_2$) C, H.

N-(2-*p*-Bromophenoxyethyl)-N′-methyl-1,3-propanediamine Dihydrobromide (16).—A solution of **15** (0.60 g, 1.16 mmoles) in 30% dry HBr–HOAc (6 ml) was stirred at 25–30° for 24 hr, then gradually heated during 90 min to boiling, and refluxed for 4.5 hr. Solid that crystallized from the cooled solution was recrystallized from MeOH–Me_2CO; yield 77% (0.40 g). *Anal.* ($C_{12}H_{19}BrN_2O\cdot 2HBr$) C, H, Br, N.

N-Methyl-N,N′-trimethylenebis-*p*-toluenesulfonamide (14) was prepared from N-methyl-1,3-propanediamine[16] by an adaptation of a previously described procedure for the preparation of N,N′-tetramethylenebis-*p*-toluenesulfonamide.[5] The yield of pure **14**, mp 93° (from EtOH), was 79%. *Anal.* ($C_{18}H_{24}N_2O_4S_2$) C, H, S.

N-(2-Acetoxyethyl)-N′-methyltrimethylenebis-*p*-toluenesulfonamide (17).—A solution of **14** (120 g, 0.302 mole) in DMF (400 ml) was added dropwise during 1 hr to a stirred suspension of NaH (14.5 g of 50% oil dispersion, 0.302 mole of NaH) in DMF (100 ml) with the temperature being maintained at ~30°. Stirring at 25–30° was continued 1 hr longer, and a nearly clear solution resulted. A solution of freshly distilled 2-bromoethyl acetate (51.0 g, 0.305 mole) was added dropwise during 30 min; the resultant solution was left at 25–30° for 18 hr and then heated at 80–85° for 2 hr. Most of the solvent was removed by distillation *in vacuo*, and the residual red-orange syrup was dissolved in C_6H_6 (400 ml). The C_6H_6 solution was washed (H_2O, four 250-ml portions) and dried (Na_2SO_4). Removal of C_6H_6 by evaporation under reduced pressure left crude **17** as an orange oil, which was used as such for conversion to **19b**.

N-(2-Bromoethyl)-N′-methyl-1,3-propanediamine Dihydrobromide (19b). From 17.—A stirred mixture of the sample of crude **17** described above and 48% HBr (1 l.) was refluxed under a 30-cm Vigreux column for 16 hr. Heating was then increased to cause distillation, and 520 ml of distillate was collected during 2 hr. The solution was then caused to reflux. After 2 hr, distillation was again effected, and 90 ml of distillate was collected during 20 min. The dark red residual mixture was then refluxed 40 min longer, cooled, clarified (Norit, Celite), and evaporated to dryness under reduced pressure. The red, semisolid residue was dissolved in warm MeOH (~400 ml), and the solution was repeatedly decolorized (Norit) until a pale yellow filtrate was obtained. The MeOH was removed by evaporation under reduced pressure, and the residue, an orange semisolid, was triturated under EtOH (150 ml). Crystallization occurred, and the solid was collected and washed with EtOH. Addition of Et_2O to the

(16) Ames Laboratories, Inc., Milford, Conn.

filtrate gave a second crop. The dried crops (37.0 and 10.0 g, respectively) were combined and recrystallized from EtOH to give **19b**, mp 213–216° dec, in 38% over-all yield (41.0 g) from **14**. Recrystallization from MeOH afforded an analytical sample, but did not change the melting point. *Anal.* ($C_6H_{15}BrN_2 \cdot 2HBr$) C, H, Br.

N-(3-Cyclohexylaminopropyl)-*p*-toluenesulfonamide (21).—A solution of *p*-toluenesulfonyl chloride (85.4 g, 0.448 mole) in DMF (300 ml) was added dropwise to a stirred solution of N-cyclohexyl-1,3-propanediamine[17] (70.0 g, 0.448 mole) in DMF with the temperature being maintained at 15–20° by external cooling. The mixture was then stirred at 25–30° for 1 hr before being poured into H_2O (3 l.). The nearly clear solution was filtered, and the filtrate was made basic (pH 10) with 50% NaOH. The crystalline precipitate that formed was collected, dried, and recrystallized from C_6H_6–ligroin (bp 30–60°) to give pure **21**, mp 94–95°, in 66% yield (93.1 g). *Anal.* ($C_{16}H_{26}N_2O_2S$) C, H, N.

N-(2-Acetoxyethyl)-N′-(3-cyclohexylaminopropyl)-*p*-toluenesulfonamide (22).—The reaction procedure used (0.284-mole scale) was essentially the same as that described for **17**, but the DMF was not removed by distillation. The reaction solution was poured into H_2O (5 l.), and the orange oil that separated was extracted with C_6H_6. Removal of the C_6H_6 from the H_2O-washed and dried ($MgSO_4$) solution left crude **22** as an orange oil, which was used as such for conversion to **24b**.

N-(2-Bromoethyl)-N′-cyclohexyl-1,3-propanediamine Dihydrobromide (24b). From 22.—A mixture of the crude preparation of **22** described above (120 g) and 48% HBr (500 ml) was refluxed under a Claisen head for 18 hr. Heating was then increased to cause distillation, and 250 ml of distillate was collected. Simple refluxing was resumed, and, after 5 hr, an additional 80 ml of distillate was removed. Refluxing was then continued 18 hr longer. The remaining dark mixture was cooled, diluted with H_2O (300 ml), clarified by filtration, and evaporated to dryness. The solid residue was twice recrystallized from MeOH to give **24a**, mp 268–271° dec, in 37% over-all yield (45.4 g) based on the starting amount of **21**. *Anal.* ($C_{11}H_{23}BrN_2 \cdot 2HBr$) C, H, Br.

3-(2-Octylaminoethyl)-2-oxazolidinone (28).—A stirred mixture of octylamine (3.00 g, 23.2 mmoles), K_2CO_3 (3.53 g, 25.5 mmoles), and DMF (15 ml) was heated at 85–90° while a solution of **6a** (3.47 g, 25.5 mmoles) in DMF (15 ml) was added dropwise during 2 hr. Heating with stirring at 85–90° was continued for 18 hr. The solvent was then removed in an aspirator vacuum; the residue was stirred with H_2O (50 ml), and the aqueous mixture was extracted (C_6H_6, three 30-ml portions). Evaporation of the H_2O-washed and dried ($MgSO_4$) C_6H_6 solution left crude **28** as a viscous oil, which was used as such for conversion to **29a**.

N-(2-Bromoethyl)-N′-octylethylenediamine Dihydrobromide (29a). From 28.—A solution of the sample of crude **28** described above and 48% HBr (30 ml) was refluxed for 20 hr; H_2O (25 ml) was added, and the boiling solution was treated with Norit and filtered (Celite). Crystalline **29a** that separated from the cooled filtrate amounted to 28% over-all yield (2.90 g).

N-Phenyl-1,3-propanediamine (32).—A $LiAlH_4$ reduction of **31**[18] based on the general procedure of Nelson and Amundsen[19] afforded **32**, bp 128–132° (3.5–3.8 mm) and $n^{20}D$ 1.5761 [lit.[20] bp 134–135° (7 mm) and $n^{20}D$ 1.5747], in 88% yield.

2-(3-Anilinopropylamino)ethanol (33).—Following a hydroxyethylation of **32** (0.456 mole) that was adapted from the procedure of Steck, *et al.*, for the preparation of 2-(7-aminoheptylamino)-ethanol,[21] the crude reaction mixture was roughly fractionated by distillation *in vacuo*. The major portion (67.9 g), bp 132–202° (0.15 mm), was redistilled through an 18-cm Vigreux column, and the fraction (31.4 g) with bp 158–175° (0.9–1.3 mm) was distilled finally through a 30-cm Vigreux column to give **33**, bp 148–153° (0.2–0.45 mm), in 31% yield (27.3 g). *Anal.* Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 67.35; H, 9.48; N, 14.83.

N-Phenyl-N,N′-trimethylenebis-*p*-toluenesulfonamide (34). A solution of *p*-toluenesulfonyl chloride (162 g, 0.852 mole) in DMF (250 ml) was added dropwise to a mechanically stirred mixture of **32** (63.9 g, 0.426 mole), K_2CO_3 (118 g, 0.852 mole), and DMF (250 ml). Heat evolution occurred during addition of the first half of the TsCl–DMF solution, and moderate external cooling was applied so that the reaction mixture temperature did not exceed 60°. During the second half of the addition no heat evolution was observed, and the mixture was warmed with a 55–60° H_2O bath. After the addition had been completed, the stirred mixture was heated on a steam bath for 2 hr. It was cooled and poured into H_2O (3 l.), and the H_2O–DMF phase was decanted from the precipitated viscous oil. The oil was stirred twice with portions of H_2O (500 ml), each of which was removed by decantation. The remaining stiff gum was dissolved in C_6H_6, and the solution was washed (H_2O) and dried ($MgSO_4$). Removal of the C_6H_6 left a glass-like residue. Trituration of this material in 10% NaOH solution afforded an amorphous white solid, which was collected, washed (H_2O), and dried *in vacuo* (60°, P_2O_5). The yield of crude **34**, mp 212–214° dec, was 95% (186 g). *Anal.* ($C_{24}H_{28}N_2O_4S_2$) H, N; C: calcd, 57.62; found, 56.45.

N-(2-Bromoethyl)-N′-phenyl-1,3-propanediamine Dihydrobromide (38c). From 33.—A solution of **33** (27.2 g, 0.140 mole) in 48% HBr (300 ml) was distilled through a Claisen head until 150 ml of distillate had been collected. Heating was then diminished somewhat to cause reflux without distillation. The solution was refluxed overnight and was then subjected to Cortese-type conditions involving six distillation periods wherein 15-ml portions of distillate were collected at 1-hr intervals. The cooled semisolid residue was stirred with EtOH (50 ml), and the mixture was evaporated to dryness under reduced pressure. The dry residue was triturated in Me_2CO, collected, and recrystallized from MeOH to give **38c**, mp 217–219° dec, in 44% yield (26.1 g). *Anal.* ($C_{11}H_{17}BrN_2 \cdot 2HBr$) C, H, Br.

N-Methyl- and N-ethyl-*p*-toluenesulfonamides and *p*-toluenesulfonanilide were obtained from commercial sources.

N-Octyl-*p*-toluenesulfonamide (26), N-cyclohexyl-*p*-toluenesulfonamide, and ethyl *p*-(*p*-toluenesulfonamido)benzoate (41) were prepared conveniently by treatment of the appropriate amine with *p*-toluenesulfonyl chloride (2:1 *M* ratio) in DMF in a manner like that reported for N,N′-ethylenebis-*p*-toluenesulfonamide.[22] The yield of **26**, mp 53–54° (lit.[23] mp 50°), was 97% and that of the N-cyclohexyl analog, mp 85° (lit.[24] mp 86–87°), was 95%. Pure **41**, mp 206–208° (lit.[24] mp 206–207°), was obtained in 58% yield following recrystallization from EtOH.

N,N′-*p*-Phenylenebis-*p*-toluenesulfonamide (46) was prepared by practically the same procedure as that referred to above.[22] The yield of **46**, mp 274–276° dec (lit.[25] mp 276°), was 46%, following recrystallization from Me_2CO–H_2O.

N-Substituted N-[ω-(2-oxo-3-oxazolidinyl)alkyl]-*p*-toluenesulfonamides were prepared by alkylation of the corresponding N-substituted *p*-toluenesulfonamides with the appropriate **6**[26] as described below. Some were obtained in crystalline form; several others obtained as crude oils were used as such in conversions to the N-(2-bromoethyl)-N′-substituted α,ω-alkanediamine dihydrobromides.

7a–c.—A stirred mixture of N-ethyl-*p*-toluenesulfonamide (40.0 g, 0.200 mole), K_2CO_3 (30.0 g, 0.218 mole), **6a** (30.0 g, 0.209 mole), and DMF (300 ml) was maintained at 110–120° for 3 hr. Dilution with H_2O (1.2 l.) followed, and the orange oil that separated was extracted with two 500-ml portions of C_6H_6. The C_6H_6 solution was washed five times with 500-ml portions of H_2O, dried ($MgSO_4$), and evaporated under reduced pressure to give **7a** as a pale orange oil in 84% yield (52.5 g). Compounds **7b** and **7c** were similarly obtained as oils in respective yields of 90 and 98%.

18a and 18b. Treatment of N-methyl-*p*-toluenesulfonamide with the appropriate **6** as in the above description of **7a** was followed by dilution with H_2O and overnight refrigeration.[27] The

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(26) The weight of crude **6c**[8] used in these preparations corresponded to a 15% molar excess.

(27) *Cf.* the previously reported preparation of **18c**.[7]

crystalline products that formed were recrystallized from EtOH. The yield of **18a**, mp 111–113°, was 69% and that of **18b**, mp 68–69°, was 73%. *Anal.* ($C_{13}H_{18}N_2O_4S$, **18a**) C, H, S. ($C_{14}H_{20}N_2O_4S$, **18b**) C, H, N, S.

23a and **23b** were obtained as oils by the following procedure. A stirred mixture of N-cyclohexyl-*p*-toluenesulfonamide (33.4 g, 0.132 mole), K_2CO_3 (18.3 g, 0.132 mole), **6a** (21.7 g, 0.145 mole), and DMAC (200 ml) was maintained at 130–140° for 4 hr. The solvent was removed by distillation *in vacuo*, and the residue was distributed between H_2O (300 ml) and $CHCl_3$ (500 ml). Evaporation of the H_2O-washed and dried ($MgSO_4$) $CHCl_3$ solution afforded crude **23a**.

27a and 27b.—The procedure described for the preparation of **7a** with the heating period increased to 17 hr and $CHCl_3$ used as the extraction solvent afforded the oily crude products.

37a and 37b.—Treatment of *p*-toluenesulfonanilide with the appropriate **6** was carried out as described for the preparation of **7a**; the DMF was then removed by distillation *in vacuo*, and the residue was stirred with H_2O. The H_2O-insoluble solid was collected and recrystallized from MeOH. Pure **37a**, mp 138–140°, was obtained in 83% yield and **37b**, mp 135–136°, in 85% yield. *Anal.* ($C_{18}H_{20}N_2O_4S$, **37a**) C, H, N. ($C_{19}H_{22}N_2O_4S$, **37b**) C, H, N.

42a and 42b.—A mixture of equimolar amounts of **41**, **6b**, K_2CO_3 (0.100 mole each), and DMAC (150 ml) was stirred at 130–140° for 5 hr. The cooled mixture was poured into H_2O (900 ml), and the oil that separated was extracted with $CHCl_3$. Evaporation of the H_2O-washed and dried ($MgSO_4$) $CHCl_3$ solution left **42b** as a viscous oil. The same procedure using **6a** afforded crystalline **42a** when the mixture was diluted with H_2O. The collected solid was recrystallized from EtOH to give pure **42a**, mp 115–116°, in 51% yield. *Anal.* ($C_{21}H_{24}N_2O_6S$) C, H, N.

N-(2-Bromoethyl)-N′-substituted α,ω-alkanediamine dihydrobromides, which are listed in Table II, were prepared from the corresponding N-substituted N-[ω-(2-oxo-3-oxazolidinyl)-alkyl]-*p*-toluenesulfonamides, the procedures designated in the table being carried out essentially as described in the following typical examples.

8a (Procedure A).—A solution of **7a** (52.0 g, 0.166 mole) and phenol (16.0 g, 0.170 mole) in 30% dry HBr–HOAc (150 ml) was stirred at 25–30° for 3 days. More 30% dry HBr–HOAc (75 ml) was added, and the mixture was gradually heated to boiling and refluxed for 24 hr. The cooled mixture, which deposited crude **8a** as a purple crystalline precipitate, was diluted with Et_2O (1 l.). The precipitate was collected and washed alternately with Et_2O and Me_2CO until the purple color was removed. Recrystallization from MeOH gave pure **8a**.

19b (Procedure B).—Treatment of **18b** (41.0 g, 0.131 mole) with 30% dry HBr–HOAc (200 ml) for 4 days at 25–30° was followed by dilution with Et_2O (1.5 l.) containing Me_2CO (100 ml), and the precipitated product was recrystallized from MeOH.

38b (Procedure C).—A solution of **37a** (47.0 g, 0.130 mole) and phenol (40.2 g, 0.427 mole; molar ratio **37a**:phenol, 1:3.3) in 30% dry HBr–HOAc (350 ml) was stirred at 25–30° for 42 hr. The product that crystallized from the reaction mixture was collected with the aid of Et_2O, washed with Et_2O and Me_2CO, and recrystallized from MeOH.

N,N′-Bis[2-(2-oxo-3-oxazolidinyl)ethyl]-N,N′-*p*-phenylenebis-*p*-toluenesulfonamide (47a).—A stirred mixture of **46** (41.6 g, 0.100 mole), K_2CO_3 (29.0 g, 0.210 mole), **6a** (33.5 g, 0.210 mole), and DMF (250 ml) was maintained at 110–120° for 5 hr. Dilution with H_2O (1.5 l.) precipitated crude **47a**, which was purified by recrystallization from MeCN; yield 83% (53.2 g), mp 192–193°. An analytical sample had mp 193–194° (from MeCN). *Anal.* ($C_{30}H_{34}N_4O_8S_2$) C, H, N.

N,N′-Bis[2-(2-oxo-3-oxazolidinyl)propyl]-N,N′-*p*-phenylenebis-*p*-toluenesulfonamide (47b) was prepared from **46** and **6b** by the procedure described for homologous **47a**; yield 74%, mp 189–191° (from MeCN). *Anal.* ($C_{32}H_{38}N_4O_8S_2$) C, H, N.

N,N′-Bis[ω-(2-bromoethylamino)alkyl]-*p*-phenylenediamine Tetrahydrobromides (48a and 48b).—A solution of **47a** (53.2 g, 82.7 mmoles) and phenol (31.2 g, 0.331 mole) in 30% dry HBr–HOAc (300 ml) was stirred at 25–30° for 64 hr. Et_2O (300 ml) was added, and the precipitated solid was collected, washed (Et_2O, warm EtOH), and recrystallized from 48% HBr. The collected crystals were triturated in EtOH. The yield of **48a**, mp 290–300° dec (indefinite), was 35% (21.3 g). *Anal.* ($C_{14}H_{24}Br_2N_4 \cdot 4HBr$) C, H, Br, N. Homologous **48b** was prepared from **47b** in essentially the same manner. The yield of **48b**, mp 249–252° dec, was 71%. An analytical sample of **48b** obtained from a trial run had mp 255–260° dec. *Anal.* ($C_{16}H_{28}Br_2N_4 \cdot 4HBr$) C, H, Br, N.

TABLE II

N-(2-BROMOETHYL)-N′-SUBSTITUTED α,ω-ALKANEDIAMINE DIHYDROBROMIDES

Compd	Procedure[a]	Yield, %	Mp, °C dec	Formula	Analyses
8a	A	55	195–200	$C_6H_{15}BrN_2 \cdot 2HBr$	C, H, Br, N
8b	A	70	262–263	$C_7H_{17}BrN_2 \cdot 2HBr$	C, H, Br
8c	B[b]	44[c]	273–275	$C_8H_{19}BrN_2 \cdot 2HBr$	C, H, Br, N
19a	A	93	160–161	$C_5H_{13}BrN_2 \cdot 2HBr$	H, Br; C[d]
19b	B	66	212–216[e]	$C_6H_{15}BrN_2 \cdot 2HBr$	Br
19c	B[f]	79	217–219	$C_7H_{17}BrN_2 \cdot 2HBr$	C, H, Br, N
24a	B[g]	14[c]	232–234	$C_{10}H_{23}BrN_2 \cdot 2HBr$	C, H, Br
24b	B	24[c]	271–274[h]	$C_{11}H_{25}BrN_2 \cdot 2HBr$	
29a	B[i]	23[c]	218–220	$C_{12}H_{27}BrN_2 \cdot 2HBr$	C, H; Br[j]
29b	C[i,k]	44[c]	268–270	$C_{13}H_{29}BrN_2 \cdot 2HBr$	C, H, Br, N
38b	C	65	262–264	$C_{16}H_{15}BrN_2 \cdot 2HBr$	C, H, Br
38c	C	57	225–226[l]	$C_{11}H_{17}BrN_2 \cdot 2HBr$	Br
43b	C[m,n,o]	65	158–160	$C_{18}H_{19}BrN_2O_2 \cdot 2HBr$	C, H, Br
43c	C[i,n,o]	53	205–208	$C_{14}H_{21}BrN_2O_2 \cdot 2HBr$	C, H, Br, N

[a] Unless noted otherwise, MeOH was used as the recrystallization solvent. [b] Recrystallized from MeOH–Et_2O; sample for analysis recrystallized from EtOH. [c] Over-all yield based on starting N-substituted *p*-toluenesulfonamide. [d] C: calcd, 17.51; found, 17.96. [e] Melting point, mixture melting point, and ir spectrum identical with those of the sample prepared from **17**. [f] Recrystallized successively from EtOH, MeOH–Et_2O, and finally from EtOH. [g] Reaction mixture diluted with Et_2O–EtOAc (2:1 by vol) to precipitate crude product. [h] Ir spectrum identical with that of the analytical sample with mp 268–271° dec prepared from **22**; mixture melting point was undepressed. [i] Recrystallized from EtOH. [j] Br: calcd, 54.35; found, 53.6. [k] Molar ratio **27b**: phenol, 1:1. [l] Ir spectrum identical with that of the sample with mp 217–219° dec, prepared from **33**. [m] Recrystallized from EtOH–Et_2O. [n] Molar ratio **42**: phenol, 1:2. [o] Ir (KBr) 1720 cm^{-1} (C=O), NH band absent; *cf.* ir data on the unexpectedly obtained ring-brominated analog (**43c**) obtained as a monohydrobromide.

N-(2-Bromoethyl)-N′-(*p*-bromophenyl)ethylenediamine dihydrobromide (38a) was an unexpected product of the initial effort to prepare **38b**. A solution of **37a** (1.40 g, 3.89 mmoles) and phenol (0.40 g, 4.3 mmoles) in 30% dry HBr–HOAc (5 ml) was stirred at 25–30° for 18 hr. More 30% dry HBr–HOAc (5 ml) was added, and the solution was slowly heated to boiling and refluxed 2 hr. The cooled mixture was treated with Et_2O and the precipitate present was collected, washed with Et_2O and MeOH, and recrystallized from MeOH to give pure **38a**, mp 194–197° dec, in 27% yield (0.51 g). *Anal.* ($C_{10}H_{14}Br_2N_2 \cdot 2HBr$) C, H, Br.

Ethyl 3-bromo-4-[2-(2-bromoethylamino)ethylamino]benzoate hydrobromide (43a) resulted from the initial effort to prepare **43b**. A solution of **42a** (27.3 g, 63.1 mmoles), phenol (6.0 g, 63 mmoles), and 30% dry HBr–HOAc (300 ml) was stirred at 25–30° for 5 days. The mixture was then stirred with Et_2O (300 ml), and the crystalline precipitate present was collected and washed with Et_2O and Me_2CO. Two recrystallizations from EtOH followed by a final recrystallization from H_2O afforded pure **43a**: 48% yield (14.3 g); mp 160–161° dec; ir (KBr), 3290 (NH) and 1670 cm^{-1} (C=O). *Anal.* ($C_{14}H_{18}Br_2N_2O_2 \cdot HBr$) C, H, Br; Br^-: calcd, 16.82; found, 17.8. (Br^- content was determined by titration in H_2O with standard NaOH at 0°. The high value found is probably indicative of partial displacement of the reactive Br attached to the aliphatic carbon, most likely through piperazine ring formation. Complete displacement occurred when the titration was carried out in H_2O–EtOH at room temperature, Br^-: calcd, 33.64; found, 33.5.)

***p*-[3-(2-Bromoethylamino)propylamino]benzoic Acid Dihydrobromide (45).**—A solution of **43c** (1.00 g) in 10% HBr (10 ml) was refluxed for 4 hr and then evaporated to dryness. The solid residue was stirred with MeCN, and the insoluble portion was collected and dried *in vacuo* to give nearly pure **45**, mp 216–218° dec, in 24% yield (0.23 g). *Anal.* Calcd for $C_{12}H_{17}BrN_2O_2 \cdot 2HBr$: C, 31.13; H, 4.13. Found: C, 31.75; H, 4.59.

2-(2-Ethylaminoethylamino)ethanethiol (9a) dihydrochloride was prepared by an adaptation of the reported procedure for the preparation of 2-[3-(4-aminobutylamino)propylamino]ethane-

(hiol trihydrochloride.[5] The crude product from treatment of **8a** (43.4 mmoles) with *in situ* prepared NaSH (0.130 mole) was fractionally distilled. An uncharacterized low-boiling fraction [bp 47° (10 mm), probably 1-ethylpiperazine] preceded the desired **9a**, which was obtained as a colorless oil, bp 102–103° (10 mm) and $n^{25}D$ 1.5038, in 38% yield (2.23 g). A solution of **9a** (2.12 g) in EtOH (25 ml) was treated with a solution of dry HCl in EtOH to give crystalline, EtOH-insoluble **9a**·2HCl (3.04 g, 96% yield from **9a**), mp 215–217° dec. *Anal.* ($C_6H_{16}N_2S$·2HCl) C, H, N, S, SH.

2-(3-Ethylaminopropylamino)ethanethiol (9c) Dihydrochloride.—An adaptation of the procedure referred to above for the preparation of **9a** afforded homologous **9c** as a colorless oil, bp 114–115° (10 mm) and $n^{25}D$ 1.5112, in 60% yield (3.68 g, from 37.7 mmoles of **8b** and 0.113 mole of NaSH). Treatment of **9c** (3.56 g) with HCl in EtOH afforded pure **9c**·2HCl (5.09 g, 99% yield from **9c**), mp 243–245° dec. *Anal.* ($C_7H_{18}N_2S$·2HCl) C, H, N, S, SH.

S-2-(2-Anilinoethylamino)ethyl Hydrogen Thiosulfate (39a).—Pulverized **38b** (8.10 g, 20.0 mmoles) was added during 5 min to a stirred solution of $Na_2S_2O_3$·$5H_2O$ (20.0 mmoles), NaOAc·$3H_2O$ (20.0 mmoles), DMAC (10 ml), and H_2O (10 ml) at 60–65°. The resultant solution was then heated at 90–95° for 1.5 hr. The solution was cooled, diluted with EtOH (100 ml), and filtered. Solvents were removed from the filtrate by evaporation under reduced pressure, and the residual solid was recrystallized three times from H_2O to give pure **39a**, mp 173–175°, in 39% yield (2.18 g). *Anal.* ($C_{10}H_{16}N_2O_3S_2$) C, H, N, S.

1-Phenyl-4-(*p*-tolylsulfonyl)piperazine (40).—$NaHCO_3$ (0.415 g, 4.94 mmoles) was added to a stirred solution of **38b** (2.00 g, 4.94 mmoles) in H_2O (15 ml). CO_2 evolution was observed along with formation of a white crystalline precipitate presumed to be the monohydrobromide corresponding to **38b**. A solution of $Na_2S_2O_3$·$5H_2O$ (1.23 g, 4.94 mmoles) in H_2O (15 ml) was added dropwise. The white solid present dissolved, but cloudiness soon developed and a yellow solid precipitated. The mixture was stirred overnight at 25–30°. A small amount of elemental S was removed by filtration. The filtrate was made slightly basic (pH 8) by addition of 10% NaOH, and the resultant solution was evaporated to dryness with additional S being removed by filtration as concentration progressed. The residue was dissolved in H_2O (15 ml) containing enough $NaHCO_3$ to afford a solution of pH 9. *p*-Toluenesulfonyl chloride (0.38 g, 2.0 mmoles) was added, and the mixture was stirred overnight. The solid that formed was collected and recrystallized (EtOH) to give **40** as white needles, mp 195–197°, lit.[28] mp 199–200°. *Anal.* ($C_{17}H_{20}N_2O_2S$) C, H, N.

S-2-(3-Anilinopropylamino)ethyl Hydrogen Thiosulfate (39b).—A solution of **38c** (13.4 g, 32.0 mmoles) in H_2O (75 ml) at 80–90° was combined with a solution of $Na_2S_2O_3$·$5H_2O$ and NaOAc·$3H_2O$ (32.0 mmoles each) in hot H_2O (75 ml). The cooled solution deposited crystalline **39b** in 63% yield (5.89 g), mp 182–185° dec. An analytical sample from a trial run had mp 181–182° dec. *Anal.* ($C_{11}H_{18}N_2O_3S_2$) C, H, N; S: calcd, 22.08; found, 21.6.

S-2-[2-(2-Bromo-4-ethoxycarbonylanilino)ethylamino]ethyl Hydrogen Thiosulfate (44a).—A solution of **43a** (3.50 g, 7.37 mmoles) in hot H_2O (150 ml) was combined with a solution of $Na_2S_2O_3$·$5H_2O$ (1.83 g, 7.37 mmoles) in H_2O (10 ml), and the mixture was stirred at 60–70° for 30 min. The oil that separated crystallized when the mixture was cooled. The solid was collected and dried *in vacuo* (P_2O_5). Purification was effected by dissolving the material (2.82 g) in the calculated minimum volume of 0.1 *N* NaOH and reprecipitating it from the filtered solution by acidification with HOAc. The yield of pure **44a**, mp 179–181° dec, was 50% (1.57 g). *Anal.* ($C_{13}H_{19}BrN_2O_5S_2$) C, H, Br, N, S.

S-2-[2-(*p*-Ethoxycarbonylanilino)ethylamino]ethyl Hydrogen Thiosulfate (44b).—Solid **43b** (10.0 g, 21.0 mmoles) was added in portions to a stirred solution of $Na_2S_2O_3$·$5H_2O$ (21.0 mmoles), NaOAc·$3H_2O$ (42.0 mmoles), DMAC (10 ml), and H_2O (10 ml). The resultant solution was heated and stirred at 85–90° for 1.5 hr while crystalline **44b** separated. The mixture was cooled, and the product was collected, washed with H_2O, and dried *in vacuo* (P_2O_5); 4.79 g, mp 210–212° dec. Recrystallization from H_2O (700 ml) afforded pure **44b**, mp 212–213° dec, in 54% yield (3.98 g). *Anal.* ($C_{13}H_{20}N_2O_5S_2$) C, H, N, S.

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TABLE III

S-2-(ω-ALKYLAMINOALKYLAMINO)ETHYL DIHYDROGEN PHOSPHOROTHIOATES

Compd	Yield, %	Mp, °C	Formula[a]	Analyses
9b	82	~115 (indef)	$C_8H_{17}N_2O_3PS$·$2.5H_2O$	C, H, N, S
9d	91	143–145	$C_{12}H_{29}N_2O_3PS$·$1.5H_2O$	C, H, N, P, S
9e	100	~25 (indef)	$C_{13}H_{29}N_2O_3PS$·$1.8H_2O$	C, H, N, P, S
20a	81	111–113[b]	$C_3H_{25}N_2O_3PS$·$2.5H_2O$	C, H, N, S
20b	91	140–142	$C_6H_{17}N_2O_3PS$·H_2O	C, H, N, S
20c	85	~100 (indef)	$C_7H_{19}N_2O_3PS$·$4H_2O$	C, N, S; H[c]
30a	66	134–135	$C_{12}H_{29}N_2O_3PS$·$2H_2O$	C, H, N, P, S
30c	86	125–127	$C_{18}H_{39}N_2O_3PS$·$1.5H_2O$	C, H, N, P, S

[a] Except for **9e** each compound was equilibrated at constant 58% relative humidity[4] prior to analysis. [b] Observed on a Kofler Heizbank. [c] H: calcd, 8.66; found, 7.78.

S-2-[2-(*p*-Ethoxycarbonylanilino)propylamino]ethyl Hydrogen Thiosulfate (44c).—A solution of **43c** (4.00 g, 8.38 mmoles) in hot H_2O (120 ml) was combined with a solution of $Na_2S_2O_3$·$5H_2O$ and NaOAc·$3H_2O$ (8.38 mmoles each) in H_2O (20 ml). The oil that immediately formed solidified while the stirred mixture was heated at 90–95° for 30 min. Crude **44c** was filtered from the cooled mixture and dried *in vacuo* (P_2O_5). The dried crude product (2.71 g) was reprecipitated from a solution of its Na salt by acidification with HOAc (in the manner described above for purification of **44a**) to give pure **44c**, mp 183–185° dec, in 84% yield (2.54 g). *Anal.* ($C_{14}H_{22}N_2O_5S_2$) C, H, N, S.

S-2-(3-Octylaminopropylamino)ethyl Hydrogen Thiosulfate (30b) Hemihydrate.—A solution of equimolar amounts of **29b**, $Na_2S_2O_3$·$5H_2O$, and NaOAc·$3H_2O$ (10.0 mmoles each) in H_2O (75 ml) was refluxed for 1 hr. The solution was allowed to cool somewhat, and $NaHCO_3$ (10.0 mmoles) was added. White solid began forming immediately, and the mixture was stirred while being allowed to cool to 25–30°. The solid was collected, washed (H_2O), and dried *in vacuo* (77°, P_2O_5). The material obtained (mp 94–98°, 3.0 g) was twice recrystallized from MeCN, but the melting point was unchanged. After the recrystallizations from MeCN, the product was dried to constant weight (2.42 g) *in vacuo* (25–30°, P_2O_5). The material obtained, which underwent weight increase on exposure to ambient conditions, was then allowed to equilibrate at constant 58% relative humidity. Pure **30b** hemihydrate was thus obtained in 74% yield (2.49 g). *Anal.* ($C_{19}H_{39}N_2O_3S_2$·$0.5H_2O$) C, H, N, S, H_2O (by glpc).

S-2-(3-Cyclohexylaminopropylamino)ethyl Hydrogen Thiosulfate (25) Hemihydrate.—A solution of equimolar amounts of **24b**, $Na_2S_2O_3$·$5H_2O$, and NaOAc·$3H_2O$ (10.0 mmoles each) in H_2O (25 ml) was heated at 90–95° for 1 hr. The solution was allowed to cool, and $NaHCO_3$ (10.0 mmoles) was added. The solution was stirred until CO_2 evolution had ceased and was then evaporated to dryness under reduced pressure. The white residual solid was twice recrystallized from MeCN to give pure **25**, as a hemihydrate, melting point indefinite from 125°, in 83% yield (2.54 g) after being dried *in vacuo* (P_2O_5). *Anal.* ($C_{13}H_{29}N_2O_3S_2$·$0.5H_2O$) C, H, N, S, H_2O (by glpc).

S-2-(ω-Alkylaminoalkylamino)ethyl dihydrogen phosphorothioates 9b, 9d, 9e, 20a, and 20b, which are listed in Table III, were prepared from Na_3PSO_3 and the appropriate **8** or **19** by a standard reaction procedure[2,29] consisting of adding the *N*-(2-bromoethyl)diamine dihydrobromide to a stirred partial solution of Na_3PSO_3 in H_2O (1 ml/mmole of Na_3PSO_3), stirring until solution occurred, then adding DMF (one-half volume of H_2O used), and keeping the solution at 25–30° for 1–2 hr or until the $AgNO_3$ test for unchanged PSO_3^{3-} [29] was negative. Compound **9b** (from Na_3PSO_3 and **8a**, 20 mmoles each) was caused to precipitate from the reaction solution by addition of EtOH (100 ml), and the collected solid was reprecipitated from H_2O–EtOH (20:100 ml). The same isolation method sufficed for obtaining **20a**. Both **9d** and **20b** were precipitated from the reaction solution by addition of DMF (100 ml) for a 40-mmole run, and the solid was collected with the aid of EtOH, washed (EtOH), then reprecipitated from H_2O–EtOH. Highly deliquescent **9e** was precipitated from the reaction solution by dropwise addition to DMF (175 ml for a 10-mmole run), collected, washed (DMF, Et_2O) under N_2, and then dried *in vacuo* (P_2O_5).

[29] S. Åkerfeldt, *Acta Chem. Scand.*, **16**, 1897 (1962).

Homologous **20c** was prepared by a different procedure. DMAC (7.5 ml) was added to a stirred solution of $Li_3PSO_3 \cdot 6H_2O$[4,29] (3.60 g, 15.0 mmoles) in H_2O (15 ml) followed by crystalline **19c** (5.57 g, 15.0 mmoles). The resultant solution was kept at 25–30° for 2 hr, chilled in an ice–water bath, and DMAC (15 ml) was added dropwise to the rapidly stirred solution. The white gum that separated initially soon solidified. EtOH (300 ml) was added, and after a few minutes of continued stirring, the white solid was collected, washed thoroughly with EtOH, and air dried (see Table III).

S-2-(ω-Octylaminoalkylamino)ethyl Dihydrogen Phosphorothioates (30a and 30c).—DMF (20 ml) was added to a stirred solution of $Li_3PSO_3 \cdot 6H_2O$ (4.80 g, 20.0 mmoles) in H_2O (40 ml). To the resultant solution the appropriate **29** (22.0 mmoles, pulverized to a fine powder) was added in portions during 15–20 min. In each preparation the corresponding **30** commenced separation before all the **29** had been added. Stirring was continued 2–3 hr. **30a** was isolated by the addition of EtOH (100 ml), and the white solid that formed was collected, washed with EtOH, and suction dried on the funnel. **30c** was isolated by adding more DMF (40 ml) to the stirred mixture containing precipitated **30c** as a semisolid. EtOH (100 ml) was also added, and continued stirring led to complete solidification of the precipitate. The solid was collected, washed (EtOH, 30–60° ligroin), and air dried (see Table III).

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Synthesis of Potential Antiradiation Agents from 3-Substituted 2-Oxazolidinones Derived from Phenol, Benzenethiol, and Related Compounds[1]

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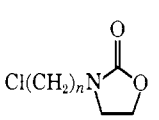
The HBr cleavage of 3-substituted 2-oxazolidinones was effectively applied in the synthesis of N-substituted and N,S-disubstituted derivatives of 2-aminoethanethiol in which the N substituent is a 2-phenoxy-, (phenylthio)-, (phenylsulfonyl)-, or (2-pyridylthio)ethyl or a correspondingly 3-substituted propyl group. None of these modifications of the amino group led to radioprotective activity approaching that of the parent compounds. Among the thiols, disulfides, thiosulfates, and phosphorothioates prepared, the following were slightly radioprotective in mice: sodium S-2-(2-phenoxyethylamino)ethyl hydrogen phosphorothioate (**4c**), S-2-[2-(phenylthio)-ethylamino]ethyl hydrogen thiosulfate (**4g**), S-2-[3-(phenylthio)propylamino]ethyl hydrogen thiosulfate (**4j**), N,N′-(dithiodiethylene)bis[3-(phenylthio)propylamine] dihydrochloride (**5c**), and lithium S-2-[3-(phenylsulfonyl)propylamino]ethyl hydrogen phosphorothioate (**10c**). N,N′-(Sulfonyldiethylene)bis(S-2-aminoethyl hydrogen thiosulfate) (**7b**), which was prepared by an aziridine ring-opening reaction, showed fair radioprotection.

The general utility of the hydrogen bromide cleavage of 3-substituted 2-oxazolidinones in the synthesis of uniquely substituted N-(2-bromoethyl)amines has been described in a preliminary communication,[2] and its subsequent application in the synthesis of potentially radioprotective derivatives of 2-aminoethanethiol (thiols, thiosulfates, and phosphorothioates), in which the N substituent is some type of aminoalkyl group, has recently been reported.[3] This paper describes the introduction of other types of substituents through the use of nucleophiles other than amines and amine derivatives in the preparation of suitable 2-oxazolidinone intermediates.

The 3-substituted 2-oxazolidinones **2**, which were derived by the alkylation of phenol and benzenethiol with the commerically available 3-(ω-chloroalkyl)-2-oxazolidinones **1**, proved to be suitable starting points



1a, $n = 2$
b, $n = 3$

for the conversions depicted in Scheme I. The hydrogen chloride cleavage of **2c** in refluxing 1-propanol[4] in an initial experiment was eventually superseded by the milder, more convenient and productive hydrogen bromide cleavage in AcOH. The halides **3c** and **3d** afforded the same thiosulfate, **4g**, but, apparently because of the reaction rate difference between **3c** and **3d**, a phosphorothioate could not be derived from **3c**, the required longer reaction time allowing extensive decomposition of the reagent Na_3PSO_3. Attempted purifications of the impure, hygroscopic sodium hydrogen phosphorothioates derived from **3d** and **3e** succeeded only in the case of **4k**, but the reaction of **3d** with the more soluble Li_3PSO_3 proceeded smoothly in aqueous DMF and produced the hydrated crystalline Li salt **4h**.

Three methods for the synthesis of N-substituted S-2-aminoethyl hydrogen thiosulfates in which the N substituent is an ω-(alkylsulfonyl)alkyl or ω-(arylsulfonyl)alkyl group were described recently.[5] Another method, which is shown in Scheme II, has been demonstrated by the preparation of N,N′-(sulfonyldiethylene)bis(S-2-aminoethyl hydrogen thiosulfate) (**7b**) by ring opening of the bisaziridine **6** with $Na_2S_2O_3$ and AcOH.[6] The generality of this method, however, is

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