Hydroxy Derivatives of S-2-(3-Aminopropylamino)ethyl Dihydrogen Phosphorothioate and Related Compounds as Antiradiation Agents

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The high antiradiation activity and low toxicity of sodium 3-amino-2-hydroxypropyl hydrogen phosphorothioate (1) suggested the introduction of hydroxyl groups into other types of radioprotective phosphorothioates. A number of such compounds were synthesized, including *S*-3-(3-aminopropylamino)-2-hydroxypropyl dihydrogen phosphorothioate (11, $n = 3$), *S*-2-(3-amino-2-hydroxypropylamino)ethyl dihydrogen phosphorothioate (**20**) and its propyl homolog **26**, *N,N'*-(2-hydroxytrimethylene)bis(*S*-2-aminoethyl dihydrogen phosphorothioate) (**40**), *S*-2-[3-(2-hydroxyethylamino)propylamino]ethyl dihydrogen phosphorothioate (**44**), and sodium *S*-2-amino-2-(hydroxymethyl)-3-hydroxypropyl hydrogen phosphorothioate (**49**). Compounds 11 ($n = 3$), **20**, **26**, and **49** were highly protective when administered intraperitoneally but were generally ineffective when given perorally, as were the other hydroxylated phosphorothioates prepared. The introduction of hydroxyl groups significantly enhanced the radioprotective properties of nonhydroxylated parent compounds, however, only in the case of intraperitoneally administered 1.

The antiradiation evaluation of sodium *S*-3-amino-2-hydroxypropyl hydrogen phosphorothioate (1) in mice revealed high activity and low toxicity, an especially interesting result when viewed in comparison with the parent *S*-3-aminopropyl dihydrogen phosphorothioate, which was only slightly radioprotective and relatively toxic in earlier tests.[1] This observation suggested that favorable effects might be achieved by the introduction of hydroxyl groups into other types of radioprotective phosphorothioates. Synthetic routes to a number of such compounds were investigated, each type requiring an individual multistep approach to the formation and reaction of multifunctional intermediates. The types that received first attention and accounted for much method development were hydroxy derivatives of *S*-2-(3-aminopropylamino)ethyl dihydrogen phosphorothioate and its homologs, an uncommonly broad series of antiradiation compounds.[1]

$$\underset{\text{OH}}{\overset{|}{\text{H}_2\text{NCH}_2\text{CHCH}_2\text{SPO}_3\text{HNa}}} \cdot 4\text{H}_2\text{O}$$

1

Chemistry. A practical route developed for the synthesis of the hydroxy derivative 11 ($n = 3$) of *S*-3-(3-aminopropylamino)propyl dihydrogen phosphorothioate and later adapted to the synthesis of $n = 4,5$ homologs (Scheme I) involved the epoxidation of *N*-allyl-*N*-(3-phthalimidopropyl)-*p*-toluenesulfonamide (**5**, $n = 3$) and avoided the separation of di- and monoalkylated sulfonamides **3** and **4**. The conversion of the intermediate bromide **9** ($n = 3$) to 11 ($n = 3$), however, was fraught with setbacks attributable to solvation, hygroscopicity, and incomplete reaction. The product was eventually obtained as a crystalline solvate containing both methanol and water as confirmed by ^{1}H NMR spectroscopy. In the refined route to 11 ($n = 3$), purification of **9** ($n = 3$) as the acetate **10** was unnecessary. Incomplete reaction was overcome by the use of a 10% excess of **9** ($n = 3$), and the key to the isolation of crystalline, characterizable **11** ($n = 3$) was the use of methanol for precipitations instead of ethanol.

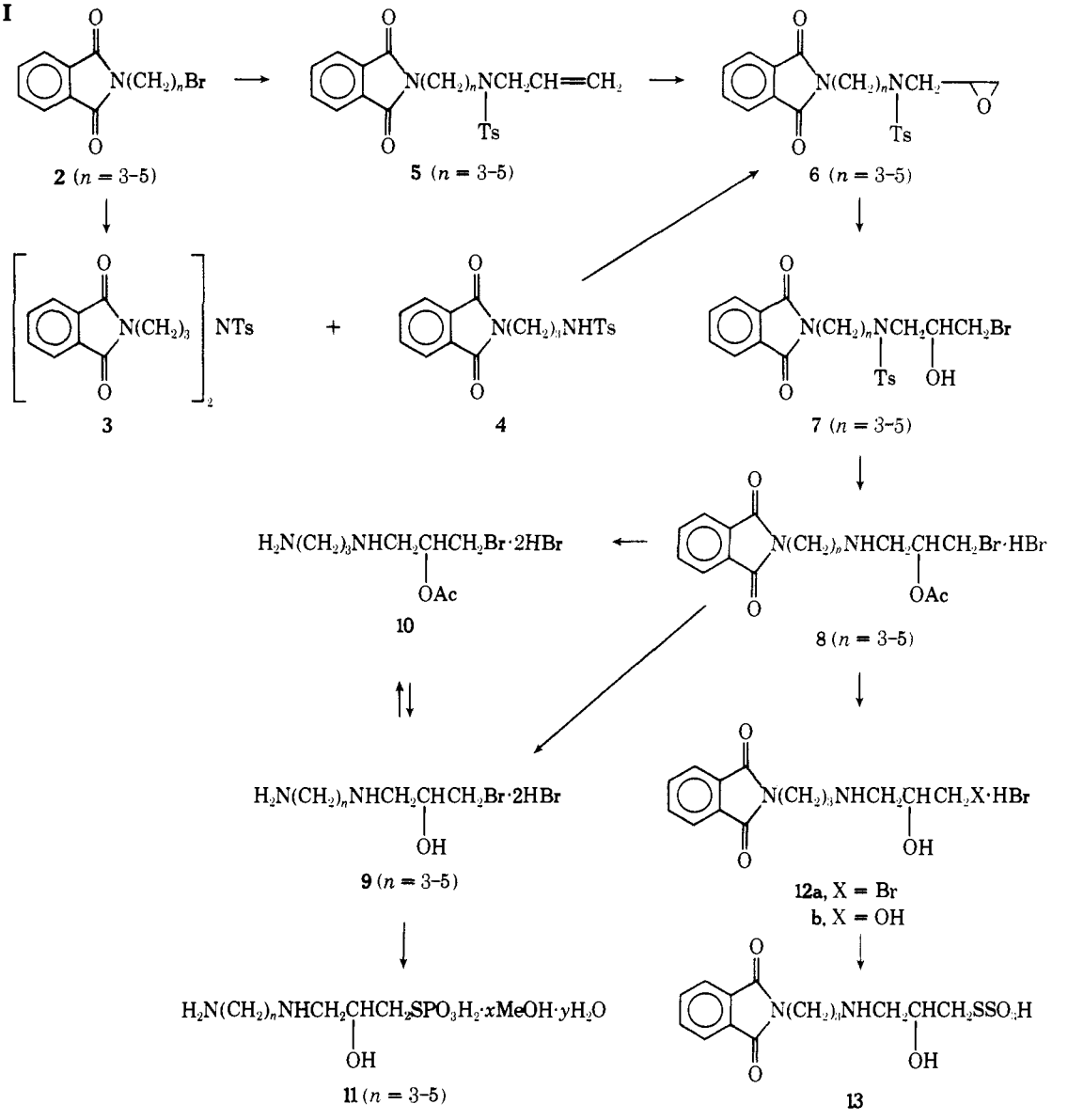
Selective hydrolysis of the phthalimido acetate **8** ($n = 3$) with 48% HBr enabled preparation of the phthalimido bromohydrin **12a**, which was purer than that prepared by transesterification; hydrolysis in boiling water produced the unwanted glycol **12b**. The thiosulfate **13** was prepared in the presence of NaOAc; in its absence sulfur dioxide was evolved and elemental sulfur was precipitated as a result of acidic decomposition of $Na_2S_2O_3$. Attempted reactions of the acetates **8** ($n = 3$) and **10** with Na_3SPO_3 in water containing DMF were surprisingly slow and incomplete after prolonged reaction periods.

The alkylation of 2-oxazolidinone with *N*-(2-acetoxy-3-chloropropyl)phthalimide having failed, the fusion of 2-oxazolidinone with *N*-(2,3-epoxypropyl)phthalimide (**14**) provided the phthalimido oxazolidinone **16** as a critical intermediate[2] in the synthesis of the hydroxy derivative **20** of *S*-2-(3-aminopropylamino)ethyl dihydrogen phosphorothioate (Scheme II). An earlier approach was abandoned when polymerization thwarted the preparation of the phthalimido aziridine **15** on a useful scale. Dephthaloylation and hydrolysis of the phthalimido acetate **17** was effected in boiling 48% HBr, a somewhat surprising result in view of the possibility of bromodehydroxylation of the secondary hydroxyl group. The final step of the sequence, in contrast to that in the synthesis of 11 ($n = 3$–5), was uncomplicated. The facile conversion of **17** to the phthaloylated and acetylated thiosulfate **18a** and phosphorothioate **18b** and that of the acetylated bromide **21** to the corresponding phosphorothioate **22** contrasted with the relative inactivity observed in attempted similar conversions of acetylated intermediates in the synthesis of 11 ($n = 3$). The acetate **22** was prepared in order to determine the effect of esterification on the oral effectiveness of **20**. The hydroxyalkylation of 2-oxazolidinone with *N*-(4,5-epoxypentyl)-phthalimide (as in the model conversion **14** → **16**) and the fusion of **14** with tetrahydro-2*H*-1,3-oxazin-2-one (as with 2-oxazolidinone and with several variations) failed in attempted extensions of the synthesis of **20** to higher homologs.

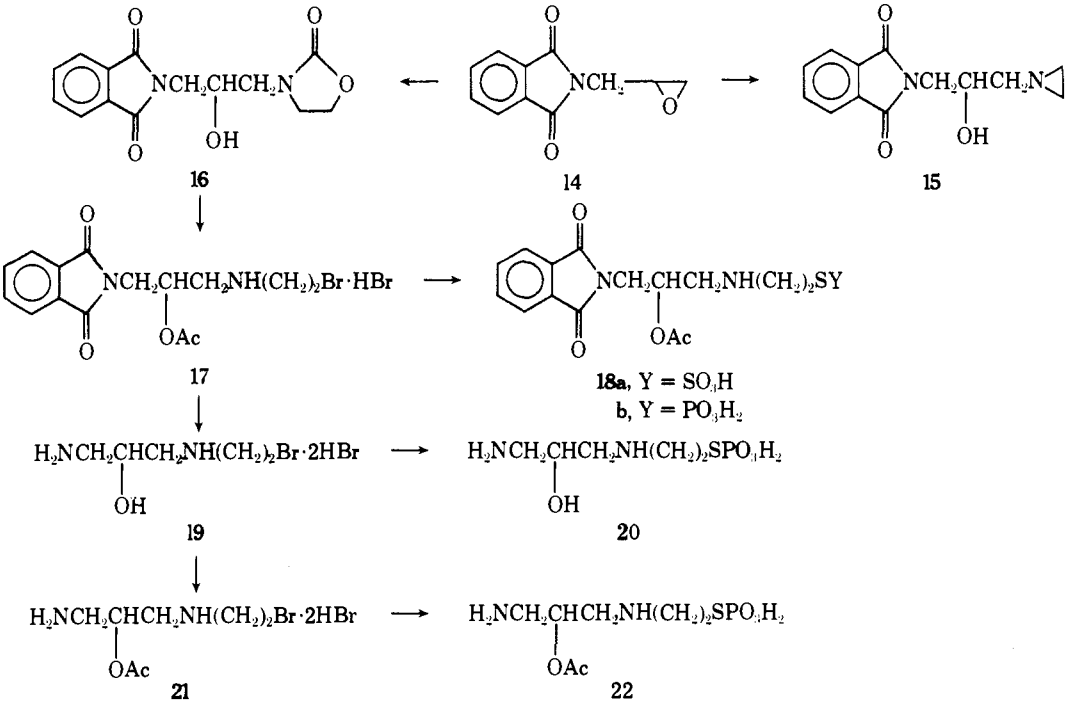
Failure of the fusion method led to an alternative synthesis (Scheme III) of *S*-3-(3-amino-2-hydroxypropylamino)propyl dihydrogen phosphorothioate (**26**), which involved hydroxypropylation of 1,3-diamino-2-propanol (**23**) and a subsequent Cortese-type[3] bromodehydroxylation of the preformed 3-(3-amino-2-hydroxypropylamino)-1-propanol (**24**) dihydrobromide. (Instability of **24** during attempted redistillation prompted purification as the dihydrobromide.) Prolonged drying in vacuo did not give **26** free of solvents (water and ethanol); the ethanol content estimated by the relative intensity of the CH_3 signal (^{1}H NMR) was in good agreement with that indicated by elemental analysis.

The reaction of epichlorohydrin with the dianion gener-

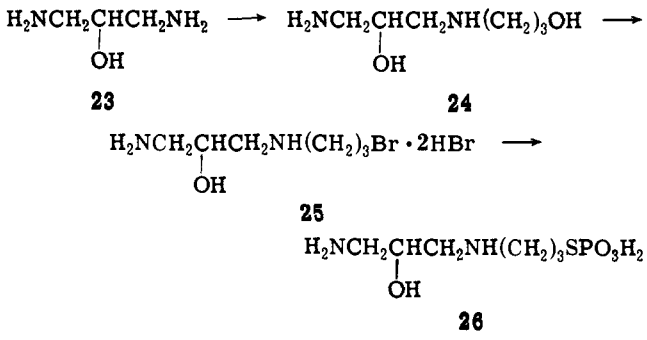
Scheme I



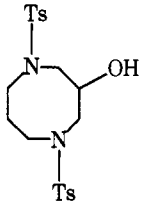
Scheme II



Scheme III



ated from *N,N'*-trimethylenebis(*p*-toluenesulfonamide) was rejected as the first step in a proposed synthesis of an *N,N'*-polymethylene-bridged derivative of **1** because of an unexpected ring closure. Octahydro-1,5-bis(*p*-tolylsulfonyl)-1,5-diazocin-3-ol (**27**) was recognized as the product after treatment with 48% HBr. A similar formation of the 3,7-diol corresponding to **27** has been reported.[4] *N,N'*-



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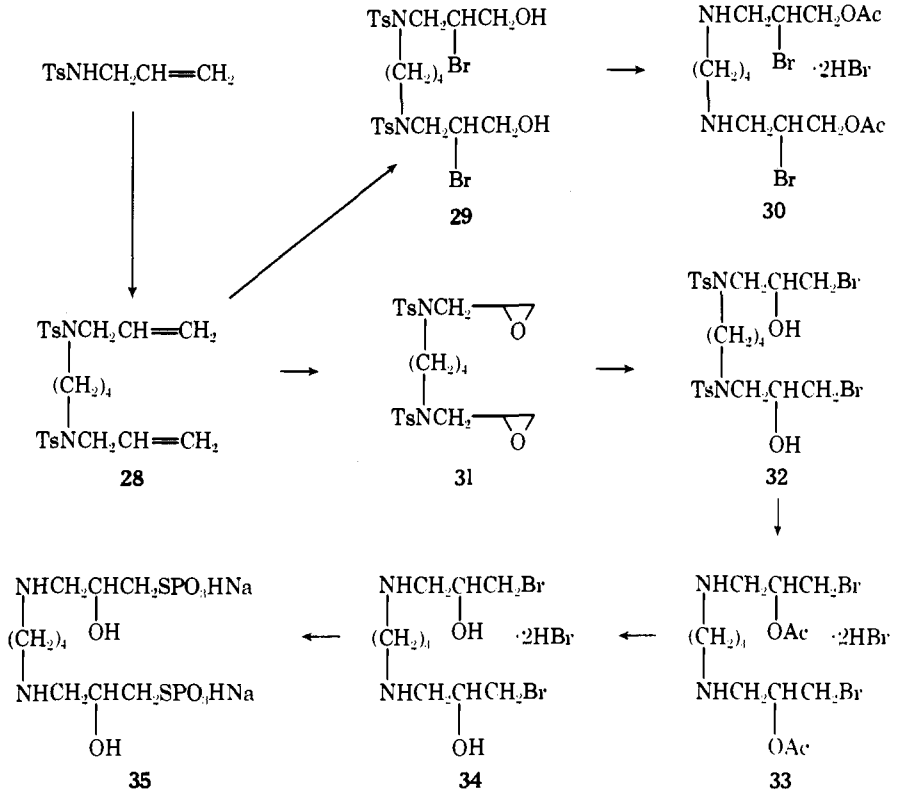
Polymethylene bridging had previously produced two derivatives of *S*-2-aminoethyl sodium hydrogen phosphorothioate that showed good radioprotection, the trimethylene- and tetramethylene-bridged members of the series,[5] but *N,N'*-polymethylene-bridged derivatives (n = 2–10) of *S*-3-aminopropyl dihydrogen phosphorothioate were nonprotective.[6]

The synthesis of the *N,N'*-tetramethylene-bridged derivative **35** as shown in Scheme IV was marked by confusion during development of initial steps. Failure of attempts to diepoxidize *N,N'*-diallyl-*N,N'*-tetramethylenebis(*p*-toluenesulfonamide) (**28**) with *m*-chloroperoxybenzoic acid was indicated by an undepressed mixture melting point. The alternative direct conversion of **28** to a bis(bromohydrin) with HOBr generated from *N*-bromosuccinimide[7] gave an impractical yield, which forced a reexamination of the diepoxidation. The material isolated in good yield analyzed correctly for the diepoxide **31**, even though a mixture melting point with **28** was still undepressed. A ^{1}H NMR spectral comparison showed that the bis(bromohydrin) derived from **31** by ring opening with HBr had the desired structure **32** and that the bis(bromohydrin) derived directly from **28** had the isomeric structure **29**. These assignments were further supported by the isomeric diacetates **30** and **33** obtained by detosylation with dry HBr in AcOH containing phenol, although incorrect structures for **29** and **30** were assumed until **32** and **33** became available for comparison. Hydrolysis of **33** with 48% HBr provided the bis(bromohydrin) **34** from which the target **35** solvated by both water and ethanol was derived.

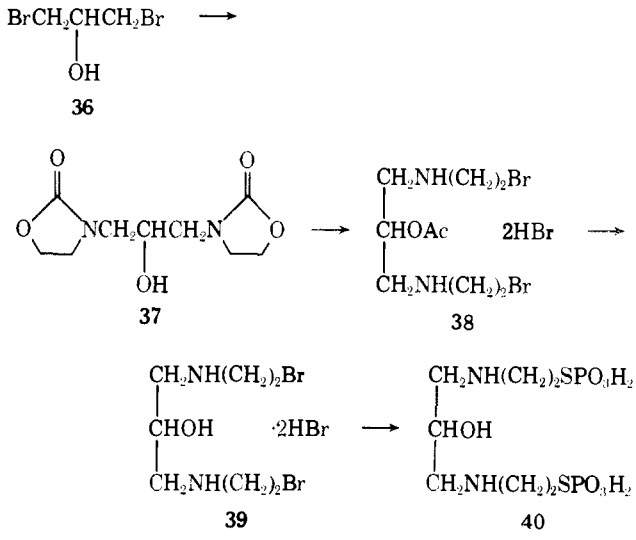
Substitution of the *N,N'*-trimethylene bridge by a hydroxyl group was accomplished according to Scheme V. Ring opening of the bis(2-oxazolidinone) **37** with dry HBr in AcOH[2] did not give the expected *O*-acetate **38** in pure form, but hydrolysis of crude **38** in boiling 48% HBr gave the hydroxy dibromide **39** in low overall yield from **37**. Pure samples of both **38** and **39** were isolated in low yields after a pilot hydrolysis that was incomplete. The dilithium salt of the target compound, much less deliquescent than the disodium salt, was prepared and converted to the inner salt **40**.

An oxazolidinone intermediate **41** was also the key to the synthesis (Scheme VI) of the terminal hydroxy derivative **44** of *S*-2-(3-ethylaminopropylamino)ethyl dihydrogen phosphorothioate,[8] whose radioprotective properties were comparable to those of the parent compound[1] with an un-

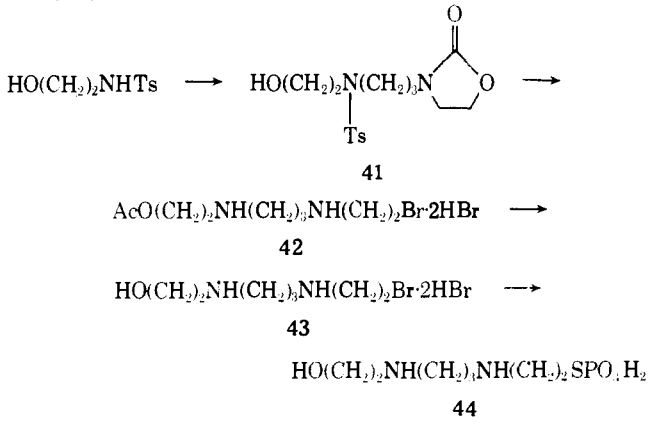
Scheme IV



Scheme V



Scheme VI



substituted terminal amino group. The isolated crude, oily **41** was the precursor of crystalline intermediates **42** and **43** in subsequent steps of the sequence. The last step eventually yielded **44** as a deliquescent solvate after trials with both Na_3SPO_3 and Li_3SPO_3 and tedious reprecipitations from aqueous solution by addition to ethanol. The deliquescent, unstable phosphorothioate derived from the acetoxy bromide **42** was not characterizable.

S-2-Amino-2-methylpropyl dihydrogen phosphorothioate showed good radioprotection in mice;[9] its dihydroxy analog **49** was synthesized according to Scheme VII. Urea[10] was found superior to diethyl carbonate[11] in the ring closure of 2-amino-2-(hydroxymethyl)-1,3-propanediol (**45**) to the intermediate oxazolidinone **46**. Dry HBr cleavage of **46** in AcOH, exceedingly slow at room temperature and accelerated at 100°, presumably gave the diacetate **47**, which required further treatment with 48% HBr (at ~75°) for conversion to the requisite bromide **48**; the products of each step, however, were impure oils. Direct transformation of **46** to **48** with refluxing HBr was attempted notwithstanding previous observations of resistance of 2-amino-2-methylalkanols (tertiary-branched primary amines) to Cortese conversion;[9] although mixtures with **45**·HBr were invariably produced, separation was effected to a practical degree by recrystallization and extraction. A slight excess of **48** compensated for impurities in the conversion to **49**.

Access to α-phenyl-1-aziridineethanol[12] (**50**) rather than radioprotective properties of parent compounds suggested the synthesis (Scheme VIII) of *N*-(β-hydroxyphenethyl)-substituted target compounds (**52a,b**, **53**). The thiosulfate **52a** was prepared with MgS_2O_3 in methanol.[13] Vacuum distillation of the thiol **53**, the product of H_2S ring opening of **50**, unexpectedly resulted in apparent thermal elimination of ethylene sulfide; the distillate was characterized as α-(aminomethyl)benzyl alcohol (**54**) hydrochloride. Purification of **53** was effected by extraction of the hydrochloride, but the yield of **53**·HCl was low.

Antiradiation Evaluation. Results of antiradiation testing of **1** and related hydroxy target compounds that gave a survival rate of at least 50% when administered intraperitoneally (ip) are summarized in Table I. The tests were carried out as previously described;[14] the source of radiation for tests with **22**, **40**, **44**, and **49** was ^{137}Cs (dose rate 141.5 rads/min). Compounds **11** (n = 5) and **18b** showed fair protection (27 and 40% survival, respectively) with ip administration; all others not listed in the table [**11** (n = 4), **13**, **18a**, **35**, **52a,b**, **53**] were either slightly protective (up to 24% survival) or nonprotective. Pertinent data for selected, previously tested parent compounds (A–E) are tabulated for comparison with the corresponding hydroxy derivatives.

The protective superiority of **1** over its parent *S*-3-aminopropyl dihydrogen phosphorothioate in ip tests was mentioned earlier; **1** was only slightly protective, however, in peroral (po) tests, whereas the parent was not tested po. Compounds **11** (n = 3), **20**, **22**, and **26** were highly protective in ip tests, but, in terms of protective index, only **11** (n = 3) and **20** were comparable to the parent *S*-ω-(3-aminopropylamino)alkyl dihydrogen phosphorothioates (A, B). These compounds, except for **20** at a preirradiation interval of 60 min, were either nonprotective or slightly protective in po tests, whereas the parent compounds were highly protective. The acetate **22** did not show a favorable effect on po activity. Compound **40** approached the parent *N,N'*-trimethylenebis(sodium *S*-2-aminoethyl hydrogen phosphorothioate) (C) in ip activity and was nonprotective in po tests (the parent compound was not tested po). The terminal *N*-(2-hydroxyethyl) derivative **44** was less active than the parent *S*-2-(3-ethylaminopropylamino)ethyl dihydrogen phosphorothioate (D) in ip tests and was nonprotective in po tests. The dihydroxylated **49** was as active as and less toxic than the parent *S*-2-amino-2-methylpropyl dihydrogen phosphorothioate (E) in ip tests; neither was much more than slightly protective in po tests.

Scheme VII

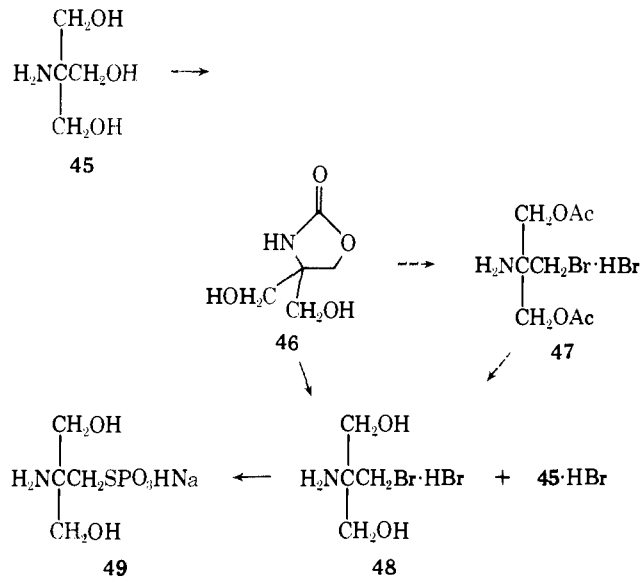
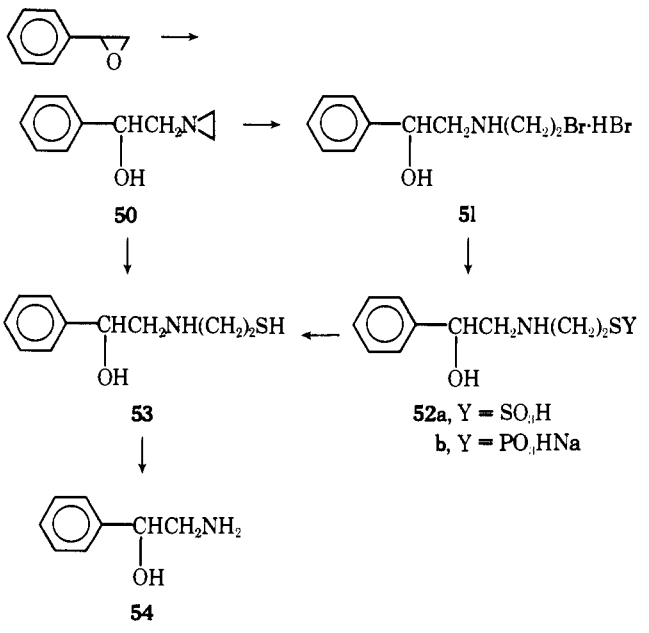


Table I. Radioprotective Activity[a] of Sodium *S*-3-Amino-2-hydroxypropyl Hydrogen Phosphorothioate and Selected Related Compounds, $RSPO_3H_2$ or $RSPO_3HNa$

No.	R	Admin route	Approx LD_{50}, mg/kg	Drug dose, mg/kg[b]	Preirradn interval, min[c]	30-Day survival, %[d]	Approx ED_{50}, mg/kg[e]	Approx PI at ED_{50}[f]
1	$H_2NCH_2CHOHCH_2$	ip	2200	400	30	100	200	17
		po	2500	750	30	20		
11, $n = 3$	$H_2N(CH_2)_3NHCH_2CHOHCH_2$	ip	875	200	15	100	100	13
		po	1200	600	60	7		
20	$H_2NCH_2CHOHCH_2NH(CH_2)_2$	ip	825	300	30	93	115	11
		po	>1800	750	60	53	700	>3.9
					30	0		
22	$H_2NCH_2CH(OAc)CH_2NH(CH_2)_2$	ip	>1250	500	15	100	250	>7.5
		po	>1000	1000	30	0		
26	$H_2NCH_2CHOHCH_2NH(CH_2)_3$	ip	>700	600	15	100	325	>3.2
		po	>700	500	60	7		
40	$CHOH[CH_2NH(CH_2)_2]_2$	ip	475	250	15	70	235	3.0
		po	>1500	800	30	0		
44	$HO(CH_2)_2NH(CH_2)_3NH(CH_2)_2$	ip	200	100	15	60	88	3.4
		po	400	150	30	10		
49	$H_2NC(CH_2OH)_2CH_2$	ip	>1250	250	15	100, 30	150	>13
		po	>1500	1034	60	20		
A	$H_2N(CH_2)_3NH(CH_2)_2$[g]	ip	1020	300		100	140	11
		po	1500	600	60	100		
B	$H_2N(CH_2)_3NH(CH_2)_3$[g]	ip	560	100	15	100	50	17
		po	>1200	700	60	100		
C	$(CH_2)_3[NH(CH_2)_2]_2$[h]	ip	400	250	15	93	92	6.5
D	$EtNH(CH_2)_3NH(CH_2)_2$[i]	ip	750	250	30	100	165	6.8
		po	1500	500	60	26		
E	$H_2NC(CH_3)_2CH_2$[j]	ip	750	600[k]	30	95		
		po	2800	1500[k]	30	27		

[a] Antiradiation tests in mice against a measured lethal dose of γ radiation [950–975 rads (^{60}Co) or 849 rads (^{137}Cs)]. [b] Lowest dose (ip) that gave the highest survival rate, administered as a solution in water or physiological saline (ip, 1–6%; po, 3–7.5%), pH usually 6–7.5. [c] Time between drug administration and irradiation. [d] No survival among control mice. [e] Dose for 50% survival estimated from a semilog dose–response curve. [f] The protective index (PI) approximated for the ED_{50} dose to provide a common basis for comparison of test compounds: $\sim LD_{50}$ (mg/kg) × 1.5/ED_{50} (mg/kg). [g] Reference 1. [h] Reference 5. [i] Reference 8. [j] Reference 9. [k] Only dose tested, hence no ED_{50}.

Scheme VIII



Thus, the introduction of hydroxyl groups into structurally varied radioprotective phosphorothioates had significantly favorable effects on radioprotective properties in only one instance, that of **1** vs. *S*-3-aminopropyl dihydrogen phosphorothioate when administered ip. Moreover, the hydroxylated compounds generally gave little or no protection when administered po.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Ir spectra were determined on all target compounds and many intermediates with Perkin-Elmer 521 and 621 spectrometers and were consistent with assigned structures; ^1H NMR spectra were determined with a Varian A-60A spectrometer. Analytical results indicated by element or function symbols were within ±0.4% of the theoretical values. Microanalyses were performed, for the most part, by Galbraith Laboratories, Knoxville, Tenn. Spectral determinations and some of the C, H, and N analyses were performed in the Molecular Spectroscopy Section of Southern Research Institute under the direction of Dr. W. C. Coburn, Jr. Evaporations under reduced pressure were carried out with a rotary evaporator and, unless indicated otherwise, a water aspirator. Products were dried in vacuo (oil pump) at room temperature over P_2O_5 unless other conditions are specified. Phosphorothioates described as deliquescent were handled under dry N_2; they were transferred in a plastic glove bag filled with dry N_2 to vials that were then hermetically sealed and stored in desiccated (Drierite) containers. In prolonged storage phosphorothioates were routinely kept in a freezer.

***S*-3-Amino-2-hydroxypropyl Sodium Hydrogen Phosphorothioate Tetrahydrate**[15] (1). Powdered 1-amino-3-bromo-2-propanol hydrobromide[16] (4.59 g, 19.5 mmol) was added during 10 min to a stirred partial solution of Na_3SPO_3[17] (3.20 g, 17.8 mmol) in H_2O (18 ml). The resulting solution was kept at 25° for 2 hr, chilled (ice bath), treated with DMF (9 ml), and stirred in the cold for 30 min. The crystalline product that had formed was collected after the addition of EtOH, reprecipitated from a filtered H_2O so-

lution by addition of EtOH with refrigeration, and air-dried: yield 4.69 g (94%); mp indefinite. Anal. ($C_3H_9NNaO_4PS\cdot4H_2O$) C, H, N, P, S.

***N,N*-Bis(3-phthalimidopropyl)-*p*-toluenesulfonamide (3) and *N*-(3-Phthalimidopropyl)-*p*-toluenesulfonamide (4).** A mixture of 0.414 mol each of **2** (n = 3, 111 g; Aldrich) and sodium *p*-toluenesulfonamide[18] (80.0 g) in DMF (1 l.) was stirred for 64 hr. (Solution occurred within 2 hr, and separation of **3** began after 3 hr.) Crystalline **3** (56.8 g) was filtered from the reaction mixture and dried in vacuo: mp 219–221°. A sample recrystallized from 2-methoxyethanol melted at 220–222°. Anal. ($C_{29}H_{27}N_3O_6S$) C, H, N. DMF was distilled from the filtrate in vacuo (<1 mm, bath to 60°); the solid that remained was pulverized under H_2O and recrystallized from EtOH (3.5 l.) to give 56.4 g (38%) of **4**, mp 166–168°. Anal. ($C_{18}H_{18}N_2O_4S$) C, H, N. A small amount of **3** (2.7 g) was removed when the hot solution was filtered: total yield of **3**, 53%.

***N*-Allyl-*p*-toluenesulfonamide.** A solution (prepared immediately before use) of *p*-toluenesulfonyl chloride (19.1 g, 0.100 mol) in DMF (50 ml) was added dropwise to a stirred solution of allylamine (11.4 g, 0.200 mol) in DMF (50 ml) kept at 25° by external cooling. After 30 min at 25–30°, the resulting solution was warmed at 40–45° for 5 min, cooled, and poured into H_2O (400 ml). The precipitate was collected, washed with H_2O, dried, and reprecipitated from a Norit-treated and Celite-filtered solution in 6% NaOH (50 ml) by dropwise addition of 25% H_2SO_4: yield 12.0 g (58%); mp 61–63° (lit.[19] mp 64–65°).

***N*-Allyl-*N*-(ω-phthalimidoalkyl)-*p*-toluenesulfonamides (5, n = 3–5).** A solution of equimolar amounts of *N*-allyl-*p*-toluenesulfonamide and the appropriate **2** in DMF (135 ml/0.1 mol) was added dropwise during 1 hr to a stirred mixture of NaH (equimolar amount as 60% dispersion in oil; Ventron) and DMF (40 ml/0.1 mol) kept at 20–25°. The mixture was stirred at 25–30° for 2 hr, then heated to 75°, kept at 70–75° for 2 hr, cooled, and poured into H_2O (10 × volume of DMF). Crude **5** separated immediately as a viscous oil and was purified as follows. n = 3. The precipitate solidified after 2–3 days in a refrigerator and was recrystallized from EtOH: yield 68%; mp 102–104°. Anal. ($C_{21}H_{22}N_2O_4S$) C, H, N. n = 4. After overnight refrigeration, the aqueous phase was removed by decantation, and the viscous gum solidified in EtOH and was recrystallized from EtOH: yield 62%; mp 93–94°. Anal. ($C_{22}H_{24}N_2O_4S$) C, H, N. n = 5. Extraction of the crude product into Et_2O and evaporation left a viscous, cloudy oil, which was clarified by dissolution in CH_2Cl_2, filtration through silica gel, and evaporation. The clear oil crystallized from EtOH–ligroine: yield 58%; mp 57–59°. Anal. ($C_{23}H_{26}N_2O_4S$) C, H, N.

***N*-(2,3-Epoxypropyl)-*N*-(ω-phthalimidoalkyl)-*p*-toluenesulfonamides 6 (n = 3–5). A. From 5 (n = 3–5).** A solution of *m*-chloroperoxybenzoic acid (85%, 25.0 g, 0.123 mol; Aldrich) in $CHCl_3$ (250 ml) was added dropwise to a stirred solution of **5** (0.113 mol) in $CHCl_3$ (450 ml). The solution was kept at 25–30° for 20 hr, then refluxed 3.5 hr, cooled, and washed successively with 5% Na_2CO_3, 5% Na_2SO_3, and H_2O. Removal of $CHCl_3$ from the dried ($MgSO_4$) solution left a viscous oil, which, when stirred with EtOH, crystallized readily to give a product suitable for bromohydrin formation: yields, **6** (n = 3, mp 87–89°) 87%, **6** (n = 4, mp 74–78°) 79%, **6** (n = 5, mp 64–69°) 78%. Samples for analysis were recrystallized from EtOH: **6** (n = 3), mp 90–92° [Anal. ($C_{21}H_{22}N_2O_5S$) C, H, N]; **6** (n = 4), mp 77–78.5° [Anal. ($C_{22}H_{24}N_2O_5S$) C, H, N]; **6** (n = 5), mp 65–69° [Anal. ($C_{23}H_{26}N_2O_5S$) C, H, N].

B. 6 (n = 3) from 4. A stirred mixture of the sodium derivative of **4** (0.137 mol, from 49.2 g of **4** and 7.42 g of NaOMe) and DMF (400 ml) was treated with epichlorohydrin (59 g, 0.64 mol), heated gradually to 90°, kept at 90–95° for 1 hr, cooled, diluted with PhH (300 ml), and filtered. Solvents and excess epichlorohydrin were removed by distillation in vacuo (final conditions: 0.2 mm, bath 80–85°). Oily **6** that remained (58.5 g) was suitable for use in the preparation of the bromohydrin **7** (n = 3) described below. Preparation of **6** (n = 3) by this procedure preceded the epoxidation of **5** (n = 3) described above, which led to crystalline **6** (n = 3).

***N*-(3-Bromo-2-hydroxypropyl)-*N*-(ω-phthalimidoalkyl)-*p*-toluenesulfonamides (7, n = 3–5).** A boiling solution of the epoxide **6** in EtOH (200 ml/0.1 mol) was treated dropwise during 10 min with 48% HBr (20 ml/0.1 mol of epoxide). The crystalline bromohydrin separated from the cooled solution and was recrystallized from EtOH: **7** (n = 3), yield 88%, mp 136–138° [Anal. ($C_{21}H_{23}BrN_2O_5S$) C, H, N]; **7** (n = 4), yield 52%, mp 94–95° [Anal. ($C_{22}H_{25}BrN_2O_5S$) C, H, N]; **7** (n = 5), yield 74%, mp 84–85° [Anal. ($C_{23}H_{27}BrN_2O_5S$) C, H].

***N*-[ω-(2-Acetoxy-3-bromopropylamino)alkyl]phthalimide Hydrobromides (8, n = 3–5).** A solution of **7** and an equal weight of PhOH in 30% dry HBr–AcOH (10 ml/g of **7**) was kept at 25–30° for 5 days and then combined with Et_2O (~100 ml/g of **7**). The precipitated product was washed with Et_2O and recrystallized from EtOH (**8**, n = 3, 4) or MeOH (**8**, n = 5): **8** (n = 3), yield 72%, mp 185–187° [Anal. ($C_{16}H_{19}BrN_2O_4\cdot HBr$) C, H, N]; **8** ($n$ = 4), yield 64%, mp 175–176° [Anal. ($C_{17}H_{21}BrN_2O_4\cdot HBr$) C, H, Br, N]; **8** ($n$ = 5), yield 58%, mp 196–198° [Anal. ($C_{18}H_{23}BrN_2O_4\cdot HBr$) C, H, Br, N].

1-(ω-Aminoalkylamino)-3-bromo-2-propanol Dihydrobromides (9, n = 3–5). A solution of **8** in 48% HBr (5 ml/g) was refluxed 5 hr, refrigerated several hours, filtered from phthalic acid, and then evaporated to dryness in vacuo with the aid of added portions of MeOH. Compounds **9** (n = 4, 5) remained as solid residues and were purified by recrystallization from EtOH: **9** (n = 4), yield 68%, mp 127–130° [Anal. ($C_7H_{17}BrN_2O\cdot2HBr$) C, H, Br, N]; **9** (n = 5), yield 58%, mp 129–135° [Anal. ($C_8H_{19}BrN_2O\cdot2HBr$) C, H, Br, N]. Residual crude **9** (n = 3) from 37.2 g (80.1 mmol) of **8** (n = 3) was an oil, a clarified solution of which in EtOH (200 ml) gradually deposited deliquescent solid (24.6 g, mp 110–130°). Recrystallization from EtOH was repeated, but the melting point was unchanged. A solution of this material (15.0 g) in *n*-PrOH (390 ml)–MeOH (130 ml) was distilled until nearly all the MeOH had been removed (vapor line temperature 96°). Pure **9** (n = 3) separated from the cooled residual solution as granular crystals (dried in vacuo at 78°): yield 11.0 g (37%); mp 130–135°. Anal. ($C_6H_{15}BrN_2O\cdot2HBr$) C, H, Br.

Purification of 9 (n = 3) via 1-(3-Aminopropylamino)-3-bromo-2-propanol *O*-Acetate Dihydrobromide (10). Crude **9** (n = 3) that remained after the evaporation of 48% HBr following dephthaloylation of **8** (n = 3) was treated with 30% dry HBr–AcOH for 64 hr. Addition of Et_2O gave a gummy precipitate that solidified when stirred with EtOH. Recrystallization from MeOH–Et_2O gave **10**, mp 157–160°, in 47% yield from **8** (n = 3). Anal. ($C_8H_{17}BrN_2O_2\cdot2HBr$) C, H, N. A solution of **10** (15.0 g, 36.1 mmol) in a solution (500 ml) of dry HBr (~60 g) in EtOH was refluxed 7 hr, kept at 25° for 64 hr, and diluted with Et_2O (1.6 l.). The precipitated **9** (n = 3), collected after refrigeration, was dissolved in EtOH and reprecipitated with Et_2O: yield 12.3 g (91%); mp 130–135°. Anal. ($C_6H_{15}BrN_2O\cdot2HBr$) C, H, N.

***S*-3-(ω-Aminoalkylamino)-2-hydroxypropyl Dihydrogen Phosphorothioates (11, n = 3–5).** A mixture of Na_3SPO_3 (2.70 g, 15.0 mmol) and **9** (16.5 mmol) in H_2O (15 ml) was stirred until solution was complete, chilled (ice bath), treated with DMF (7 ml), kept at 25° for 5 hr, left overnight in a refrigerator, and then slowly added dropwise to rapidly stirred MeOH (500 ml). The deliquescent precipitate was collected under N_2, washed with MeOH, and suction dried under N_2 pressure. The solid was redissolved in H_2O (15 ml total) and the solution filtered; precipitation by dropwise addition to stirred MeOH was repeated as before. Then the reprecipitation process was carried out once more. The precipitate was finally stirred with anhydrous methanol (100 ml) for 4 hr, collected, washed with Et_2O, suction dried under N_2, and transferred quickly to a desiccator where it was dried in vacuo (~0.1 mm) for 4 days. Each of the deliquescent products (**11**, n = 3–5) was solvated by both MeOH and H_2O and had indefinite melting points. Their ^1H NMR spectra were determined in D_2O, and estimates of the MeOH and H_2O content derived from the integrated spectra (with reference to a blank solvent integral) compared favorably with the solvate compositions indicated by elemental analysis: **11** (n = 3), yield 75% [Anal. ($C_6H_{17}N_2O_4PS\cdot CH_3OH\cdot0.5H_2O$) C, H, N, P, S]; **11** (n = 4), yield 52% [Anal. ($C_7H_{19}N_2O_4PS\cdot0.5CH_3OH\cdot H_2O$) C, H, N, P, S]; **11** (n = 5), yield 44% [Anal. ($C_8H_{21}N_2O_4PS\cdot0.5CH_3OH\cdot0.5H_2O$) C, H, N, P, S].

***N*-[3-(3-Bromo-2-hydroxypropylamino)propyl]phthalimide Hydrobromide (12a).** A solution of **8** (n = 3, 22.0 g, 47.4 mmol) in 48% HBr (110 ml) was kept at 60° for 16 hr. Crystalline **12a** separated from the cooled solution and was recrystallized from EtOH: yield 14.9 g (74%); mp 170–172°. Anal. ($C_{14}H_{17}BrN_2O_3\cdot HBr$) C, H, Br, N.

***S*-2-Hydroxy-3-(3-phthalimidopropylamino)propyl Hydrogen Thiosulfate (13).** Solid $Na_2S_2O_3\cdot5H_2O$ (2.48 g, 10.0 mmol) was added to a solution of 10.0 mmol each of **12a** (4.22 g) and $NaOAc\cdot3H_2O$ (1.36 g) in H_2O (100 ml) at 95°. The solution was boiled 10 min and filtered while hot with the aid of more hot H_2O (50 ml). Pure **13** crystallized from the filtrate: yield 1.85 g (49%); mp 222–223°. Anal. ($C_{14}H_{18}N_2O_6S_2$) C, H, N, S.

***N*-[3-(1-Aziridinyl)-2-hydroxypropyl]phthalimide (15).** A solution of ethylenimine (7.50 g, 0.174 mol; Matheson) and **14**[16,20]

(10.2 g, 50.0 mmol) in DMF (25 ml) was kept at 55° for 18 hr. The solvent and excess ethylenimine were removed by evaporation under reduced pressure (bath to 80°), and the yellow semisolid that remained was stirred with boiling *n*-BuOH (50 ml). The insoluble part was collected and recrystallized from MeCN to give **15**, mp 117–125°, in 18% yield (2.2 g). Anal. ($C_{13}H_{14}N_2O_3$) C, H, N.

3-(2-Hydroxy-3-phthalimidopropyl)-2-oxazolidinone (16). A mixture of 1.46 mol each of **14** (296.5 g) and 2-oxazolidinone (127.1 g; Aldrich) was kept at 130° for 48 hr. The viscous pale-red melt, allowed to cool somewhat, was dissolved in boiling EtOH (500 ml). The solution was kept at 25–30° for 4 days while crystalline **16** gradually separated: yield 43% (180 g); mp 120–122°. Anal. ($C_{14}H_{14}N_2O_5$) C, H, N.

***N*-[2-Acetoxy-3-(2-bromoethylamino)propyl]phthalimide Hydrobromide (17).** A solution of **16** (80.3 g, 0.276 mol) in 30% dry HBr–AcOH (400 ml) was kept at 25–30° for 4 days. Et_2O (800 ml) was added, and the precipitate that formed was recrystallized from EtOH to give pure **17**, mp 200–202°, in 29% yield (36.0 g). Anal. $C_{15}H_{17}BrN_2O_4$·HBr) C, H, Br, N.

***S*-2-(2-Acetoxy-3-phthalimidopropylamino)ethyl Hydrogen Thiosulfate (18a).** A solution of 10.0 mmol each of **17** (4.50 g) and MgS_2O_3·$6H_2O$ (2.44 g) in MeOH (25 ml) was refluxed 10 min. Crystalline **18a** that separated from the cooled solution was recrystallized from EtOH–H_2O (3:1, v/v): yield 67% (2.7 g); mp 210–211° dec. Anal. ($C_{15}H_{18}N_2O_7S_2$) C, H, N, S.

***S*-2-(2-Acetoxy-3-phthalimidopropylamino)ethyl Dihydrogen Phosphorothioate (18b) Dihydrate.** DMF (20 ml) was added to a solution of Na_3SPO_3 (1.80 g, 10.0 mmol) in H_2O (40 ml), and then pulverized **17** (4.95 g, 11.0 mmol) was gradually added. The mixture, which eventually became thick, was stirred for 1.5 hr. EtOH (250 ml) was added, and the precipitated sodium salt of **18b** was collected, washed with EtOH, air-dried, and redissolved in H_2O (25 ml). The filtered solution was treated with glacial AcOH (1 ml), and the resulting thick mixture was thinned with EtOH (150 ml). The precipitate (**18b**) was washed with EtOH and then Et_2O and dried in vacuo: yield 63% (2.76 g); mp 123–126°. Anal. ($C_{15}H_{19}N_2O_7PS$·$2H_2O$) C, H, N, P, S.

1-Amino-3-(2-bromoethylamino)-2-propanol Dihydrobromide (19). A solution of **17** (30.0 g, 66.6 mmol) in 48% HBr (150 ml) was refluxed 3.5 hr, cooled, refrigerated overnight, filtered from phthalic acid, and evaporated to dryness (oil pump) with the aid of several added portions of MeOH. The residue was precipitated from MeOH (Norit, Celite) by the addition of Et_2O to give an 83% yield (19.8 g) of **19**, mp 179° with prior sintering, of satisfactory purity for use in the preparation of **20**. From another run, pure **19**, mp 179–182°, was obtained in 62% yield after recrystallization from EtOH. Anal. ($C_5H_{13}BrN_2O$·2HBr) C, H, Br, N.

***S*-2-(3-Amino-2-hydroxypropylamino)ethyl Dihydrogen Phosphorothioate (20) Sesquihydrate.** Solid **19** (11.2 g, 31.0 mmol) was added to a stirred partial solution of Na_3SPO_3 (5.40 g, 30.0 mmol) in H_2O (30 ml). DMF (5 ml) was added to the resultant solution, and, after 2.5 hr, the solution was added dropwise to rapidly stirred MeOH (300 ml). Crystalline **20** that precipitated was collected, redissolved in H_2O (70 ml), and reprecipitated by addition to MeOH (700 ml) as before. The product was washed with MeOH, air dried, and then kept in a 50% relative humidity hygrostat for 24 hr: yield 86% (6.66 g); mp 134–139° dec (indefinite). Anal. ($C_5H_{15}N_2O_4PS$·$1.5H_2O$) C, H, N, P, S.

2-Acetoxy-*N*-(2-bromoethyl)-1,3-propanediamine Dihydrobromide (21). A mixture of **19** (18.0 g, 50.0 mmol), 30% dry HBr–AcOH (90 ml), and Ac_2O (45 ml) was stirred at 25–30° for 22 hr and then heated at 80–85° for 30 min. Solution occurred during the heating period, and the cooled mixture deposited crystalline **21**, which was purified by two reprecipitations from EtOH with Et_2O and a final recrystallization from EtOH: yield 57% (11.3 g); mp 126–130° dec. Anal. ($C_7H_{15}BrN_2O_2$·HBr) C, H, N.

***S*-2-(3-Amino-2-acetoxypropylamino)ethyl Dihydrogen Phosphorothioate (22) Sesquihydrate.** DMF (10 ml) was added to a cooled (~10°) partial solution of Na_3SPO_3 (4.39 g, 24.4 mmol) in H_2O (24 ml). Pulverized **21** (10.9 g, 27.1 mmol) was added in portions, and the resulting solution was stirred at 25–30° for 2 hr while three 5-ml portions of DMF were added at 30-min intervals. The product was precipitated by dropwise addition of the reaction solution to stirred EtOH (600 ml) and was reprecipitated from H_2O (25 ml) by addition to EtOH (800 ml): yield 50% (3.63 g) (dried in vacuo); mp 83–85° dec. Anal. ($C_7H_{17}N_2O_5PS$·$1.5H_2O$) C, H, N, P, S.

3-(3-Amino-2-hydroxypropylamino)-1-propanol (24) Dihydrobromide. A mixture of **23** (39.6 g, 0.440 mol; Aldrich), trimethylene oxide (25.0 g, 0.430 mol; Aldrich), and H_2O (20 ml) was heated in a glass-lined pressure vessel at 130–140° for 20 hr. The resulting viscous mixture was roughly fractionated in vacuo, and the fraction boiling at 139–159° (0.6 mm) was collected for redistillation. The second distillation was discontinued during collection of a fraction boiling at 110–114° (0.1 mm) because of apparent decomposition. Elemental analyses indicated that **24** was concentrated mainly in the residuum and not in the fractions collected before distillation was stopped. A test portion (0.5 g) of the residuum provided an analytically pure sample of **24**·2HBr, mp 160–161°, by treatment in EtOH with 48% HBr and recrystallization of the precipitate from EtOH–Et_2O: ^1H NMR (D_2O–DSS) δ 4.3 (complex m, 1, $CH_2CHOHCH_2$). Anal. ($C_6H_{16}N_2O_2$·2HBr) C, H, N. The remainder (18.7 g) was dissolved in EtOH (40 ml) and treated at 10–20° with 1:1 48% HBr–EtOH (v/v). The crystalline precipitate, collected after 2 hr at 0–5°, was washed first with EtOH and then Et_2O and dried in vacuo: yield 14.6 g (11% from **23**); mp 159–161°.

1-Amino-3-(3-bromopropylamino)-2-propanol Dihydrobromide (25). A solution of **24**·2HBr (14.6 g, 47.0 mmol) in 48% HBr (400 ml) was refluxed overnight (19 hr) and then slowly distilled during 8 hr while 175 ml of distillate was collected. The residual solution was again left at reflux overnight and then distilled to remove 25 ml of distillate during 3 hr. The solution was refluxed 2 hr longer (total boiling time 48 hr), cooled, and evaporated to dryness. The residue was dissolved in MeOH (200 ml), the Norit-treated and filtered solution was evaporated, and the residue was recrystallized from EtOH–Et_2O to give **25**, mp 228–230°, in 61% yield (10.7 g). Anal. ($C_6H_{15}BrN_2O$·2HBr) C, H, N; Br: calcd, 64.28; found, 62.63.

***S*-3-(3-Amino-2-hydroxypropylamino)propyl Dihydrogen Phosphorothioate (26) Ethanolate Monohydrate.** Na_3SPO_3 (3.14 g, 17.4 mmol) was dissolved in H_2O (17.5 ml) at 40–45°, the stirred solution was chilled (ice bath) until finely divided particles began separating, and DMF (8.7 ml) was added. The stirred mixture was allowed to warm to 25°, and solid **25** (6.70 g, 18.0 mmol) was added in portions. Solution occurred readily, and stirring was continued for 2 hr. The solution was kept in a refrigerator overnight and then added dropwise to stirred EtOH (~900 ml). The precipitated **26** was collected, washed with EtOH followed by Et_2O, and dried in vacuo to give 4.32 g of product solvated by EtOH as indicated by elemental analysis. Efforts to free the material of EtOH by stirring with anhydrous Et_2O and drying for 5 days in vacuo were only partially successful. The EtOH content estimated by the CH_3 signal in the integrated ^1H NMR spectrum in D_2O was in good agreement with that indicated by elemental analysis; the near identity of the methine proton ($CH_2CHOHCH_2$) absorption and that of **24**·2HBr provided additional support for the assigned structure. The yield of solvated **26** was 80% (3.86 g). Anal. ($C_6H_{17}N_2O_4PS$·$0.35C_2H_5OH$·H_2O) C, N, P, S; H: calcd, 7.64; found, 7.20.

Octahydro-1,5-bis(*p*-tolylsulfonyl)-1,5-diazocin-3-ol (27). A stirred solution of *N,N'*-trimethylenebis(*p*-toluenesulfonamide)[21] (10.0 g, 26.2 mmol) in DMF (75 ml) was treated with NaOMe (2.83 g, 52.3 mmol); solution occurred readily, but after a few minutes the expected disodium salt separated. Epichlorohydrin (19.5 g, 0.210 mol) was then added. The mixture was heated at 90–95° for 1 hr, cooled, diluted with PhH (75 ml), and filtered from NaCl. Solvents were removed under reduced pressure (H_2O aspirator followed by oil pump, bath to 75°). The residual oil was dissolved in boiling EtOH (60 ml) and the hot solution treated dropwise with 48% HBr (6.3 ml). The refrigerated solution deposited a crystalline product (3.04 g), which was recrystallized from EtOH to give **27**, mp 204–206°, in 18% yield (2.07 g). A sample recrystallized once more for analysis had mp 206–208°. Anal. ($C_{20}H_{26}N_2O_5S_2$) C, N, N, S.

Octahydro-1,5-bis(*p*-tolylsulfonyl)-1,5-diazocin-3-ol *p*-Toluenesulfonic Ester. A solution of 2.73 mmol each of **27** (1.20 g) and *p*-toluenesulfonyl chloride (0.520 g) in pyridine (10 ml) was kept at 25–30° overnight and then poured into cold H_2O (100 ml). After refrigeration, the product was collected, washed with H_2O, dried in vacuo, and recrystallized from EtOH: yield 0.32 g (20%); mp 185–188°. Anal. ($C_{27}H_{32}N_2O_7S_3$) C, H, N.

***N,N'*-Diallyl-*N,N'*-tetramethylenebis(*p*-toluenesulfonamide) (28).** A solution of *N*-allyl-*p*-toluenesulfonamide (4.22 g, 20.0 mmol) and 1,4-dibromobutane (2.16 g, 10.0 mmol) in DMF (20 ml) was added dropwise to a stirred suspension of NaH (0.80 g of 60% dispersion in oil, 20 mmol; Ventron) in DMF (7 ml) maintained at 20–25°. The mixture was stirred at 25–30° for 3 hr and then at 70–80° for 1 hr, cooled, and poured into cold H_2O (200 ml). The precipitated crude **28** was collected after refrigeration and recrystallized from EtOH: yield 66% (3.16 g); mp 80–82°. Anal.

($C_{24}H_{32}N_2O_4S_2$) C, H, N. A 5.70-fold run gave **28** in 75% yield (40.6 g).

***N,N'*-Tetramethylenebis[*N*-(2-bromo-3-hydroxypropyl)-*p*-toluenesulfonamide] (29).** *N*-Bromosuccinimide (48.4 g, 0.272 mol) was added in portions to a solution of **28** (32.5 g, 68.4 mmol) and H_2O (6.10 g, 0.338 mol) in DMSO (700 ml) kept at 20° under N_2. After 2 hr at 20–25°, the solution was poured into H_2O (2.5 l.) and the mixture refrigerated overnight. The oily precipitate was extracted with Et_2O, and the H_2O-washed Et_2O solution was dried ($MgSO_4$), filtered, and evaporated to give an orange oil (47.0 g). TLC (silica gel, PhH, I_2) showed a major spot just above the origin and several others that moved farther and close together. A PhH solution of a portion (1.2 g) of the crude product was applied to a silica gel column, and the column was eluted with PhH and 9:1 PhH–EtOAc until the faster-moving components were removed (as indicated by TLC). The column was then extruded and extracted with EtOAc. Evaporation of the extract gave a small sample (0.12 g) of pure **29**, mp 95–98°. Anal. ($C_{24}H_{34}Br_2N_2O_6S_2$) C, H, N. The remainder of the crude product was dissolved in PhH and the solution filtered through a silica gel mat (~6.5 cm thick) on a Büchner funnel (10-cm diameter). The undisturbed mat was washed with PhH (3 × 200 ml) and EtOAc (2 × 200 ml). TLC showed that the EtOAc solution contained **29** and small amounts of some of the components detected in the PhH solution. Evaporation of the EtOAc left a pale-orange oil, which was dissolved in EtOH and seeded with pure **29**. The white solid that slowly separated was recrystallized from PhH to give more TLC-homogeneous **29**: mp 95–97°; total yield 4.49 g (10%). The identity of **29** was supported (^1H NMR, $CDCl_3$) by a typical CH_2OH triplet centered at δ 2.75, which disappeared when D_2O was added.

3,3'-(Tetramethylenediimino)bis(2-bromo-1-propanol) *O,O'*-Diacetate Dihydrobromide (30). A mixture of **29** (3.35 g, 5.00 mmol) and 30% dry HBr–AcOH (25 ml) containing PhOH (3.4 g, 36 mmol) was stirred at 25–30° for 5 days (solution occurred after 4 days). Crude orange-colored **30** was precipitated by the addition of Et_2O, and successive reprecipitations from Norit-treated EtOH and MeOH solutions by the addition of Et_2O gave white, crystalline **30**, mp 134–138°, in 58% yield (1.77 g). Anal. ($C_{14}H_{26}Br_2N_2O_4 \cdot 2HBr$) H, N; C: calcd, 27.66; found, 27.25.

***N,N'*-Bis(2,3-epoxypropyl)-*N,N'*-tetramethylenebis(*p*-toluenesulfonamide) (31).** A solution of *m*-chloroperoxybenzoic acid (85%, 80.0 g, 0.394 mol) in PhH (1.5 l.) was added to a solution of **28** (69.5 g, 0.146 mol) in PhH (400 ml), and the solution was kept at 25–30° for 24 hr, then refluxed 1 hr, cooled, and filtered from *m*-$ClC_6H_4CO_2H$. The filtrate was washed successively with 5% Na_2CO_3, 5% Na_2SO_3, and H_2O. Evaporation of the PhH from the dried ($MgSO_4$) solution gave **31** as a clear oil, which crystallized readily from EtOH: yield 88% (65.0 g); mp 75–78°. An analytical sample obtained from a pilot run had mp 78–80°. Anal. ($C_{24}H_{32}N_2O_6S_2$) C, H, N.

***N,N'*-Bis(3-bromo-2-hydroxypropyl)-*N,N'*-tetramethylenebis(*p*-toluenesulfonamide) (32).** A solution of **31** (64.0 g, 0.126 mol) in EtOH (225 ml) at ~75° was treated dropwise with 48% HBr (35 ml, 0.307 mol), refluxed 10–15 min, and refrigerated 2 days. Solid **32** separated and was recrystallized from EtOH: yield 71% (60.5 g); mp 74–76°. Anal. ($C_{24}H_{34}Br_2N_2O_6S_2$) C, H, N. A comparison of the ^1H NMR spectra of **32** and **29** revealed a distinguishing feature described under **29**.

1,1'-(Tetramethylenediimino)bis(3-bromo-2-propanol) *O,O'*-Diacetate Dihydrobromide (33). **32** (60.5 g, 90.2 mmol) was treated for 5 days with 30% dry HBr–AcOH (450 ml) containing PhOH (60 g, 0.64 mol) (as described for the preparation of **30**). Et_2O was added, and the solid that separated (45.0 g) was washed on the collection funnel with EtOH (~500 ml) and then MeOH (~300 ml) to give pure **33**, mp 180–183°, in 56% yield (31.0 g). Anal. ($C_{14}H_{26}Br_2N_2O_4 \cdot 2HBr$) C, H, N.

1,1'-(Tetramethylenediimino)bis(3-bromo-2-propanol) Dihydrobromide (34). A solution of **33** (25.0 g, 41.1 mmol) in 48% HBr (125 ml) was kept at 60° for 2 hr, allowed to stand overnight at 25–30°, and evaporated to dryness under reduced pressure with the aid of added portions of MeOH. The residue was suspended in cold MeOH, collected, and reprecipitated from warm, Norit-treated MeOH solution by addition of Et_2O to give **34**, mp 211–213°, in 57% yield (12.3 g). Anal. ($C_{10}H_{22}Br_2N_2O_2 \cdot 2HBr$) C, H, N.

***N,N'*-Tetramethylenebis[(*S*-3-amino-2-hydroxypropyl) sodium hydrogen phosphorothioate] (35) Ethanolate Hydrate.** Na_3SPO_3 (6.84 g, 38.0 mmol) was added in portions to stirred H_2O (76 ml) at 25–30°; the mixture was warmed at 40–45° until solution occurred and then chilled to ~10°. DMF (38 ml) was added, and then **34** (11.0 g, 21.0 mmol) was added in portions to the stirred mixture at ~25°. Stirring at 25–30° was continued for 2 hr, but the oily phase that had soon formed did not dissolve, even after the addition of more H_2O (4 ml). The mixture was refrigerated ovenight before it was added to rapidly stirred EtOH (2.2 l.). The resulting mixture was refrigerated 36 hr, and the cloudy supernatant was decanted from the crystalline precipitate that had formed. The deliquescent precipitate was stirred with EtOH, collected under N_2, dissolved in H_2O (80 ml), and reprecipitated by addition to EtOH (2.1 l.) as before. After refrigeration (~17 hr), the precipitate was collected as before with the aid of EtOH, washed with EtOH followed by Et_2O, suction dried under N_2 pressure, and then dried in vacuo for 3 days. The yield of solvated **35** was 76% (7.69 g). Anal. ($C_{10}H_{24}N_2Na_2O_8P_2S_2 \cdot C_2H_5OH \cdot 0.5H_2O$) C, H, N, P, S. The ^1H NMR spectrum of this sample showed the prominent CH_3 triplet (δ 1.16) and CH_2 quartet (δ 3.63) due to EtOH.

1,3-Dibromo-2-propanol (36). A solution of epibromohydrin (87.5 g, 0.639 mol) in EtOH (85 ml) at 65–70° was treated dropwise with 48% HBr (79 ml, 0.69 mol), kept at 60–70° for 30 min, and evaporated under reduced pressure until the EtOH had been removed. The residue was stirred with Et_2O (600 ml), and the Et_2O solution was washed successively with H_2O, 1% $NaHCO_3$, and H_2O, then dried ($MgSO_4$), and evaporated. The residual oil was distilled to give **36**, bp 82° (6 mm) [lit.[22] bp 87° (8.5 mm)], in 78% yield (109 g).

3,3'-(2-Hydroxytrimethylene)bis(2-oxazolidinone) (37). A solution of **36** (43.1 g, 0.198 mol) and 2-oxazolidinone (34.5 g, 0.396 mol) in DMF (200 ml) was added dropwise to a stirred mixture of oil-free[23] NaH (from 16.7 g of 57% dispersion in oil, 0.396 mol) in DMF (200 ml) at 20–25°. The mixture was kept at ~25° by moderate cooling for 2 hr and then left overnight. The dark solution was treated with Norit and filtered (Celite); most of the DMF was removed by distillation in vacuo (<1 mm, bath to 60°). The residue, a mixture of oil and solid, was dissolved in H_2O (100 ml) and the solution repeatedly extracted with $CHCl_3$. Evaporation of the dried ($MgSO_4$) extract left an oil (14.1 g), whose equally strong ir absorptions at 1740 and 1660 cm^{-1} indicated a mixture of **37** and DMF. Evaporation of the aqueous phase left a semisolid mixture, which was extracted with $CHCl_3$; evaporation of the extract left 17.1 g (37%) of crude **37**, an oil, which was free of DMF as indicated by ir transparency at 1660 cm^{-1}. Anal. ($C_9H_{14}N_2O_5$) H, N; C: calcd, 46.96; found, 45.02.

The latter material was used without further purification in a trial run that resulted in the isolation of both ***N,N'*-bis(2-bromoethyl)-1,3-diamino-2-propanol *O*-acetate dihydrobromide (38)** and the desired deacetylated product **39**. This **37** (12.6 g) was treated with 30% dry HBr–AcOH (65 ml) for 24 hr. The solution was evaporated under reduced pressure; a solution of the residue in 48% HBr (65 ml) was refluxed 30 min, allowed to stand overnight, and evaporated under reduced pressure with the aid of added portions of MeOH. Addition of Et_2O to a solution of the residue in MeOH gave a solid (9.2 g), which was fractionated by recrystallization from EtOH. The less soluble **39** was filtered from the boiling EtOH: yield 1.14 g (4.5%); mp 247–249°. Anal. ($C_7H_{16}Br_2N_2O \cdot 2HBr$) C, H, N. Pure **38** crystallized from the cooled filtrate: yield 3.88 g (12.5%); mp 195–205° dec; ir (KBr) 1760 cm^{-1} (ester C=O). Anal. ($C_9H_{18}Br_2N_2O_2 \cdot 2HBr$) C, H, N.

***N,N'*-(2-Bromoethyl)-1,3-diamino-2-propanol Dihydrobromide (39).** Preparation of **37**, the above-described intermediate, was repeated on a larger scale (0.500 mol of **36**, 1.00 mol each of 2-oxazolidinone and NaH), but the residue from DMF evaporation was extracted directly with $CHCl_3$. The filtered extract was evaporated and the residue redissolved in $CHCl_3$. Repeated filtration and evaporation left crude **37** (102 g) as a clear oil, which (86.4 g) was treated with 30% dry HBr–AcOH (450 ml) at 25–30° for 20 hr. [Attempted purification of crude **37** (5 g) by vacuum distillation failed.] The solution was evaporated under reduced pressure and the residue treated with boiling 48% HBr (450 ml) for 1.5 hr. Evaporation gave a thick oil, which was stirred with warm EtOH (~200 ml). The resulting suspension or partial solution soon deposited a solid, which, after refrigeration (~18 hr), was collected and recrystallized from EtOH (~2.5 l.) to give **39**, mp 250–253°, in an overall yield from **36** of 10% (20 g). Anal. ($C_7H_{16}Br_2N_2O \cdot 2HBr$) C, H, N; Br: calcd, 68.61; found, 68.09.

***N,N'*-(2-Hydroxytrimethylene)bis(*S*-2-aminoethyl dihydrogen phosphorothioate) (40).** **39** (9.50 g, 20.4 mmol) was added in portions during 10–15 min to a stirred solution of $Li_3SPO_3 \cdot 6H_2O$[5] (9.60 g, 40.0 mmol) in H_2O (80 ml). The resulting solution was treated with $AcNMe_2$ (25 ml), kept at 25–30° for 30 min, and then added dropwise to rapidly stirred EtOH (700 ml). The deli-

quescent precipitate (dilithium salt of **40**) was collected, washed with EtOH followed by Et_2O, and suction dried under N_2, and then dried in vacuo over NaOH pellets. A solution of the salt (8.63 g) in H_2O (40 ml) was treated with glacial AcOH (85 ml), and the resulting solution was added dropwise to stirred EtOH (700 ml). The precipitated **40** was collected and stirred with EtOH (200 ml) to ensure removal of AcOH; the suspension was refrigerated overnight and the deliquescent product collected under N_2, washed with Et_2O, and dried in vacuo over NaOH pellets and P_2O_5: yield 7.28 g (98%); mp >100° dec (indefinite). Anal. ($C_7H_{20}N_2O_7P_2S_2$) C, H, N, P, S.

***N*-(2-Hydroxyethyl)-*N*-[3-(2-oxo-3-oxazolidinyl)propyl]-*p*-toluenesulfonamide (41).** A mixture of *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide[24] (47.4 g, 0.220 mol), 3-(3-chloropropyl)-2-oxazolidinone (36.0 g, 0.220 mol; Asta-Werke AG, Brackwede, West Germany), anhydrous K_2CO_3 (33.3 g, 0.240 mol; dried in vacuo at 110°), and DMF (325 ml) was heated with stirring at 115° for 6 hr, treated with Norit, filtered (Celite mat), and distilled in vacuo (<1 mm, bath to 60°) to remove the DMF. The red, oily residue was dissolved in EtOAc and the clarified (Norit, Celite) solution evaporated in vacuo (<1 mm, bath to 60°) to give crude **41** (77 g, theoretical yield 75.5 g) as an orange oil. Another run on this scale gave essentially the same results (74.7 g), and these samples were used without further purification for conversion to **42**.

2-[3-(2-Bromoethylamino)propylamino]ethanol *O*-Acetate Dihydrobromide (42). Crude **41** (77 g) was dissolved in 30% dry HBr–AcOH (390 ml), and the solution was stirred at 25–30° for 6 days and poured into Et_2O (4 l.) containing Me_2CO (40 ml). The white precipitate was washed with Et_2O and reprecipitated from MeOH with Et_2O to give **42**, mp 209–215° dec, in 38% yield (36.5 g). Anal. ($C_9H_{19}BrN_2O_2 \cdot 2HBr$) C, H, N. Similar treatment of the second sample of crude **41** (74.3 g) gave **42**, mp 210–214°, in 27% yield (26.4 g). Anal. C, H, N.

2-[3-(2-Bromoethylamino)propylamino]ethanol Dihydrobromide (43). A solution of **42** (62.0 g, 0.145 mol) in 48% HBr (145 ml)–H_2O (145 ml) was refluxed 1 hr and then evaporated to dryness under reduced pressure with the aid of added portions of MeOH. The residue was recrystallized twice from MeOH–Et_2O to give **43**, mp 190–194° dec, in 82% yield (45.8 g). Anal. ($C_7H_{17}BrN_2O \cdot 2HBr$) C, H, Br, N.

***S*-2-[3-(2-Hydroxyethylamino)propylamino]ethyl Dihydrogen Phosphorothioate (44) Ethanolate Hydrate.** A solution of $Li_3SPO_3 \cdot 6H_2O$ (7.20 g, 30.0 mmol) and **43** (12.7 g, 32.8 mmol) in H_2O (30 ml) was kept at 25–30° for 3 hr, filtered, and added dropwise to stirred EtOH (1.5 l.). The white precipitate was collected under N_2. Four reprecipitations from H_2O by addition to EtOH afforded a deliquescent, solvated product, which was dried in vacuo for several days, in 68% yield (6.2 g). The EtOH content was confirmed by ^1H NMR. Anal. ($C_7H_{19}N_2O_4PS \cdot 0.5C_2H_5OH \cdot 1.3H_2O$) C, N, P, S; H: calcd, 8.14; found, 7.33.

4,4-Bis(hydroxymethyl)-2-oxazolidinone[10] (46). A stirred mixture of 2.00 mol each of **45** (242 g; MC/B) and urea (120 g) in $AcNMe_2$ (500 ml) was refluxed 5 hr. The $AcNMe_2$ was removed by distillation in vacuo and the residue recrystallized from EtOH to give a first crop (99.3 g) of **46**, mp 108–110° (lit.[10] mp 107–109°). Two later crops (30.3 and 13.1 g) each had mp 107–109°; total yield 48%.

2-Amino-2-(bromomethyl)-1,3-propanediol Hydrobromide (48). A solution of **46** (50.0 g, 0.340 mol) in 48% HBr (1 l.) was refluxed 17 hr. Evaporation followed by crystallization from EtOH–Et_2O gave a mixture (76 g) of **45**·HBr and the desired **48**. [After 2 days, a small crop (3.0 g) of nearly pure **48**, mp 100–102°, had separated from the EtOH–Et_2O filtrate. Anal. ($C_4H_{10}BrNO_2 \cdot HBr$) C, H, N; Br: calcd, 60.32; found, 57.65.] The 76-g mixture was recrystallized from EtOH, and 27.4 g of **45**·HBr separated. EtOH was evaporated from the filtrate, the residue was extracted with THF, and the filtered solution was evaporated. The syrup that remained was dissolved in EtOH (150 ml), and Et_2O (1 l.) was slowly added with stirring. The solid obtained (42.7 g, mp 95–100°) was recrystallized from EtOH (minimum volume) to give 14.2 g of material, which, on further work-up, did not afford usable product. Addition of Et_2O to the EtOH filtrate gave 26.3 g of solid with mp 94–96° (with sintering from 90°). The latter fraction was dissolved in boiling THF (minimum volume) and the solution kept at 25° for 18 hr. The still-clear solution was concentrated under reduced pressure to one-half volume, kept several hr at 25°, filtered from a small amount of solid, and evaporated. The clear syrup that remained was dissolved in EtOH, and slow addition of Et_2O led to crystallization of 17.1 g of **48**: mp ~90–100°; ir (KBr) identical with the 3.0-g sample. Anal. ($C_4H_{10}BrNO_2 \cdot HBr$) C, H, Br, N. The total yield was 22%.

***S*-2-Amino-2-(hydroxymethyl)-3-hydroxypropyl Sodium Hydrogen Phosphorothioate (49) Ethanolate Hydrate.** **48** (8.75 g, 33.0 mmol) was added in portions during 10–15 min to a stirred partial solution of Na_3SPO_3 (5.40 g, 30.0 mmol) in H_2O (30 ml). After complete solution had occurred (10 min), DMF (15 ml) was added with external cooling (bath at 10–15°). An $AgNO_3$–dilute HNO_3 test for unchanged Na_3SPO_3[25] was negative after 20 min. The pale-yellow solution was then treated with Norit and filtered through a Celite mat. The colorless filtrate was added dropwise to rapidly stirred EtOH (650 ml) to give a white precipitate, which was collected under N_2, redissolved in H_2O (20 ml), and reprecipitated by addition to stirred EtOH (650 ml) as before. The deliquescent product was collected under N_2, washed with EtOH followed by Et_2O, suction dried under positive N_2 pressure, and then dried in vacuo: yield of solvated **49** 8.23 g (89%); melting point indefinite. The ratio of **49** to EtOH as estimated from the integrated ^1H NMR spectrum was in agreement with that indicated by elemental analysis. Anal. ($C_4H_{11}NNaO_5PS \cdot 0.7C_2H_5OH \cdot 2H_2O$) C, H, N, P, S.

α-Phenyl-1-aziridineethanol (50) was prepared from 1,2-epoxyethylbenzene and ethylenimine by a reported procedure.[12] The yield of **50**, mp 74–75° (lit. mp 74–75°), was 53% (132 g from 1.55 mol of ethylenimine).

α-[(2-Bromoethylamino)methyl]benzyl Alcohol Hydrobromide (51). A solution of **50** (50.0 g, 0.306 mol) in EtOH (150 ml) was added dropwise during 30 min to stirred 48% HBr (100 ml) at 0–5°. The resultant solution was evaporated to dryness under reduced pressure (bath to 74°) and the crystalline residue recrystallized from EtOH–Et_2O to give **51**, mp 153–154°, in 84% yield (84.0 g). Anal. ($C_{10}H_{14}BrNO \cdot HBr$) C, H, Br, N.

***S*-2-(β-Hydroxyphenethylamino)ethyl Hydrogen Thiosulfate (52a).** A solution of 15.0 mmol each of **51** (4.88 g) and $MgS_2O_3 \cdot 6H_2O$ (3.67 g) in MeOH (30 ml) was refluxed 75 min, cooled, filtered from faint turbidity, and evaporated under reduced pressure to a colorless, thick syrup. The residue was dissolved in warm EtOH (25 ml) and the solution diluted with Et_2O to produce incipient cloudiness. Crystalline **52a** that precipitated from the refrigerated mixture was recrystallized from EtOH: yield 58% (2.41 g); mp 98–101°. Anal. ($C_{10}H_{15}NO_4S_2$) C, H, N, S.

***S*-2-(β-Hydroxyphenethylamino)ethyl Sodium Hydrogen Phosphorothioate (52b) Trihydrate.** Na_3SPO_3 (9.00 g, 50.0 mmol) was dissolved in H_2O (75 ml) at 40–45°, the solution was chilled (ice bath), and DMF (40 ml) was added. The stirred suspension was allowed to warm to 25–30°, and **51** (16.3 g, 50.2 mmol) was added in portions during 10 min. The rapidly stirred mixture became nearly clear before crystalline product began to precipitate. After 40 min the mixture was poured into EtOH (500 ml). The collected, EtOH-washed, and suction-dried product was redissolved in H_2O (80 ml) and reprecipitated by addition of EtOH (400 ml). After overnight refrigeration, crystalline **52b** was collected, washed with EtOH followed by Et_2O, and air-dried: yield 71% (12.6 g). Anal. ($C_{10}H_{15}NNaO_4PS \cdot 3H_2O$) C, H, N, P.

α-[(2-Mercaptoethylamino)methyl]benzyl Alcohol (53) Hydrochloride. H_2S gas was introduced into a solution of **50** (10.0 g, 61.3 mmol) in MeOH (75 ml) at −60° until the weight gain was 4.0 g (0.118 mol). The solution was kept at −30° for 3 hr and then the solvent was removed under reduced pressure. The oily residue, which solidified on standing, was dissolved in EtOH (50 ml), the cloudy solution was clarified by filtration, and the EtOH was removed under reduced pressure. The residue was dissolved in MeOH (50 ml) and the solution treated with 3 *N* dry HCl–EtOH (21 ml). Addition of Et_2O gave a crystalline precipitate, which was reprecipitated from EtOH with Et_2O. This material (12.0 g, mp 108°) was repeatedly extracted with portions of boiling PhH and each extract filtered separately. Pure **53**·HCl, mp 119–120°, crystallized in 10% yield (1.36 g) from only the first filtrate. Anal. ($C_{10}H_{15}NOS \cdot HCl$) C, H, N, S, SH. Efforts to obtain more pure **53**·HCl from the other filtrates and from the sizable PhH-insoluble residue failed.

α-(Aminomethyl)benzyl Alcohol (54) Hydrochloride. The treatment of **50** with H_2S (as described above) in the initial effort to prepare **53** appeared to give crude **53** as a low-melting crystalline solid in theoretical yield. Anal. ($C_{10}H_{15}NOS$) H, N; C: calcd, 60.88; found, 61.84. Attempted purification by distillation in vacuo led to the following observations. The heated sample formed an opaque melt that did not become clear until after it had frothed vigorously at ~80° (bath temperature); the clear liquid then distilled readily. The colorless distillate [bp 140–150° (1.4 mm)] amounting to 66% of the weight of the crude solid would not crys-

tallize but was readily converted to a crystalline hydrochloride, which had unusual melting properties: it sintered at 135–136° and remained opaque until it formed a clear melt at 210–215°. The melting properties and elemental analysis suggested identity as 54·HCl (lit.[26] mp 211° with sintering at 135°), which was supported by ^{1}H NMR analysis. Anal. ($C_8H_{11}NO$·HCl) C, H, N.

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Antitumor Agents. 16.[1] Steroidal α-Methylene-γ-lactones

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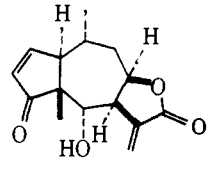
Several novel steroidal α-methylene-γ-lactones and related derivatives have been synthesized as potential steroid alkylating antitumor agents. The synthesis of these compounds involved the convenient Reformatsky-type reaction between ethyl α-(bromomethyl)acrylate and the proper steroidal ketones. In vitro assay for the cytotoxicity of these compounds against the growth of tissue culture cells originating from human epidermoid carcinoma of the larynx (H.Ep.-2) has shown significant activity. Cytotoxicity was improved at least sixfold with the introduction of lipophilic steroidal character. Preliminary in vivo tumor assay also indicated that these compounds were active against Walker 256 carcinosarcoma in rats and were inactive against both L1210 lymphoid leukemia and Ehrlich ascites carcinoma in mice. However, the simple α-methylene-β,β-dicarbethoxy-γ-butyrolactone significantly inhibited Ehrlich ascites tumor growth.

Steroidal alkylating agents, such as phenesterin,[2,3] estradiol mustard,[4–6] and some homoaza steroid mustards,[7] are known for their significant inhibitory activity on growth of various experimental tumors[8] and are currently undergoing clinical trials. During the course of an investigation of the relationship between the sesquiterpene lactone structure and the cytotoxic and antitumor activities, it was found that one of the structural requirements for significant cytotoxicity was an O=C—C=CH_2 system as part of an ester as well as a ketone or lactone.[9–12] This type of system has been observed, for example, in the cytotoxic antitumor agent helenalin (1). The ability of the latter system, i.e., an α-methylene-γ-lactone, to act as an alkylating center for the cytotoxic and antitumor sesquiterpene lactones, such as elephantopin, euparotin acetate, and vernolepin, has been demonstrated and ascribed to a rapid Michael-type addition reaction of the biological nucleophiles, such as L-cysteine[13] or sulfhydryl-bearing enzymes, e.g., phosphofructokinase[14] and glycogen synthase.[15] Although syntheses of certain simple α-methylene-γ-lactones and related derivatives as potential antitumor agents have recently been reported,[11,16,17] a survey of the literature[18] revealed no record of any investigation on the synthetic α-methylene-γ-lactone bearing steroids or hormones as alkylating anticancer agents.



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We decided to combine chemically this α-methylene-γ-