(11) S. Kit, W.-C. Leung, D. Trkula, and G. Jorgensen, *Int. J. Cancer*, **13**, 203 (1974).
(12) W. E. Rawls, G. Cashon, E. Adam, T. Ogino, R. Duff, and F. Rapp, *Cancer Res.*, **34**, 362 (1974).
(13) T. Y. Shen, J. F. McPhenson, and B. O. Linn, *J. Med. Chem.*, **9**, 366 (1966).
(14) J. Zemlicka and F. Sorm, *Collect. Czech. Chem. Commun.*, **30**, 1880 (1965).
(15) J. F. B. Mercer and R. H. Symons, *Biochim. Biophys. Acta*, **238**, 27 (1971).
(16) A. M. Michelson, *Synth. Proced. Nucleic Acid Chem. 1968–1973*, 1, 491 (1968).
(17) A. M. Michelson, *Biochim. Biophys. Acta*, **91**, 1 (1964).
(18) D. E. Hoard and D. G. Ott, *J. Am. Chem. Soc.*, **87**, 1785 (1965).
(19) R. C. Bleackley, A. S. Jones, and R. T. Walker, *Nucleic Acids Res.*, **2**, 683 (1975).
(20) P. F. Torrence, B. Bhooshan, J. Descamps, and E. DeClercq, *J. Med. Chem.*, **20**, 974 (1977).
(21) M. Freifelder, *J. Am. Chem. Soc.*, **82**, 2386 (1960).
(22) H. Vorbruggen, K. Krolikiewicz, and U. Niedballa, *Ann. Chem.*, **988** (1975).
(23) I. Wempen, R. Duschinsky, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 4755 (1961).
(24) B. R. Baker, T. J. Schwan, and D. V. Santi, *J. Med. Chem.*, **9**, 66 (1966).
(25) R. T. Markiw and E. S. Canellakis, *J. Org. Chem.*, **34**, 3707 (1969).
(26) F. Kappler and A. Hampton, *J. Carbohydr., Nucleosides, Nucleotides*, **2**, 109 (1975).
(27) J. P. Horwitz, A. J. Tomson, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962).
(28) E. J. Reist, A. Benitez, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).
(29) I. Nakagawa and T. Hata, *Tetrahedron Lett.*, 1409 (1975).
(30) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).
(31) N. Miller and J. J. Fox, *J. Org. Chem.*, **29**, 1772 (1964).
(32) J. P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, **29**, 2076 (1964).
(33) R. P. Glinski, M. S. Khan, and R. L. Kalamas, *J. Org. Chem.*, **38**, 4299 (1973).
(34) R. Teoule, B. Fouque, and J. Cadet, *Nucleic Acids Res.*, **2**, 487 (1975).
(35) J. S. Roth in "Protein Metabolism and Biological Function", C. P. Bianchi and R. Hilf, Eds., Rutgers University Press, New Brunswick, N.J., 1970, p 141.
(36) E. Bresnick, U. B. Thompson, and K. Lyman, *Arch. Biochem. Biophys.*, **114**, 352 (1966).
(37) H. G. Klemperer, G. R. Haynes, W. I. H. Shedden, and D. H. Watson, *Virology*, **31**, 120 (1967).
(38) E. P. Anderson, *Enzymes, 3rd Ed.*, **9**, 69–74 (1973).
(39) J. P. Neenan and W. Rohde, *J. Med. Chem.*, **16**, 580 (1973).
(40) Y.-C. Cheng and W. H. Prusoff, *Biochemistry*, **13**, 1179 (1974).
(41) B. R. Baker and J. P. Neenan, *J. Med. Chem.*, **15**, 940 (1972).
(42) E. P. Kowal and G. Markus, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **34**, 700 (1975).
(43) B. Fouque and R. Teoule, *Chemotherapy*, **20**, 221 (1974).
(44) J. G. Moffatt and H. G. Khorana, *J. Am. Chem. Soc.*, **83**, 649 (1961).
(45) O. H. Lowry and J. A. Lopez, *J. Biol. Chem.*, **162**, 421 (1946).
(46) H. Inoue and T. Ueda, *Chem. Pharm. Bull.*, **19**, 1743 (1971).
(47) A. T. Jamieson and J. H. Subak-Sharpe, *J. Gen. Virol.*, **24**, 481 (1974).
(48) S. Kit, W.-C. Leung, D. Trkula, and D. R. Dubbs, *Arch. Biochem. Biophys.*, **169**, 66 (1975).

S-2,ω-Diaminoalkyl Dihydrogen Phosphorothioates as Antiradiation Agents

James R. Piper,* Lucy M. Rose, Thomas P. Johnston,

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

and Marie M. Grenan

Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C. 20012. *Received December 18, 1978*

To enable further structure–activity comparisons among radioprotective phosphorothioates, *S*-2,ω-diaminoalkyl dihydrogen phosphorothioates were synthesized from L-2,4-diaminobutyric acid, L-ornithine, L-lysine, and DL-2,7-diaminoheptanoic acid as homologues of *S*-2,3-diaminopropyl dihydrogen phosphorothioate (**4**) and as isomeric analogues of *S*-2-[(ω-aminoalkyl)amino]ethyl dihydrogen phosphorothioates (e.g., **1**). The preferred route that evolved from exploratory trials retained optical activity and involved the reduction of methyl 2,ω-bis(benzoylamino)alkanoates with lithium borohydride, debenzoylation–bromodehydroxylation, and reaction of the resulting 1-(bromomethyl)-1,ω-alkanediamine dihydrobromides with trisodium phosphorothioate. The products of an alternative route that involved the reduction of phthaloylated intermediates with sodium borohydride were racemic. Exploratory conversions of *N*-(ω-alkenyl)phthalimides failed to provide suitable precursors of the target compounds. In terms of a protective index, these homologues were significantly more radioprotective than the parent phosphorothioate **4** when administered intraperitoneally to mice prior to whole-body γ irradiation. The homologues derived from L-lysine also showed good peroral activity. No apparent difference was observed in the protection afforded by optically active homologues and the corresponding racemates.

In the search for effective structural modifications of radioprotective phosphorothioates, *S*-2,3-diaminopropyl dihydrogen phosphorothioate (**4**) was prepared[1] and its structure proved by desulfurization of the derived thiol (Scheme I). The observed radioprotective properties of **4** suggested the synthesis of a homologous series, which would be isomeric with a group of radioprotective *S*-2-[(ω-aminoalkyl)amino]ethyl dihydrogen phosphorothioates.[2] One of these, *S*-2-[(3-aminopropyl)amino]ethyl dihydrogen phosphorothioate (**1**), is being considered for

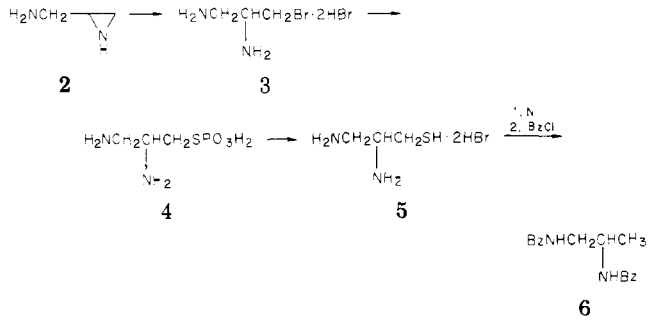
$$H_2N(CH_2)_3NH(CH_2)_2SPO_3H_2$$
1

use as a possible adjuvant to the radiotherapy of solid tumors because of observed selective protection of normal tissues and favorable toxicity.[3]

Chemistry. The structure assigned to the intermediate bromide **3** resulting from a possibly ambiguous opening

0022-2623/79/1822-0631$01.00/0

Scheme I

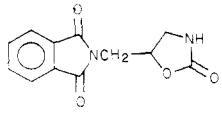


of 2-(aminomethyl)aziridine (**2**) was supported by NMR data; its structure could also be rationalized as primary in view of the sluggish and unsatisfactory reactions of the subsequently prepared secondary bromides **16a,b** with trisodium phosphorothioate.

Suitable precursors of homologues of **4** were sought in conversions of the *N*-(ω-alkenyl)phthalimides **7a–c** (see Scheme II). The addition of iodine isocyanate[4] to **7a,b** in methanol did not provide the expected methyl [1-(iodomethyl)-ω-phthalimidoalkyl]carbamates for conversion to the corresponding 4-(ω-phthalimidoalkyl)-2-oxazolidinones; trials with **7a** gave 1-iodo-4-phthalimido-2-butanol (**9**) in some instances, and an anhydrous workup gave the condensed heterocycle **8** in another instance. Spectral studies of **8** established the molecular weight (mass), alteration of the phthalimido group (IR), and structural features such as the angular methoxy group (NMR). Other examples of this ring system have been described[5] and explanation of the cyclization in terms of an iodonium ion with subsequent nucleophilic participation of methanol parallels previously reported observations made without spectral support.[5a] Infrared spectral changes indicated a partial transformation of **8** to **9** in storage, presumably by hydrolysis.

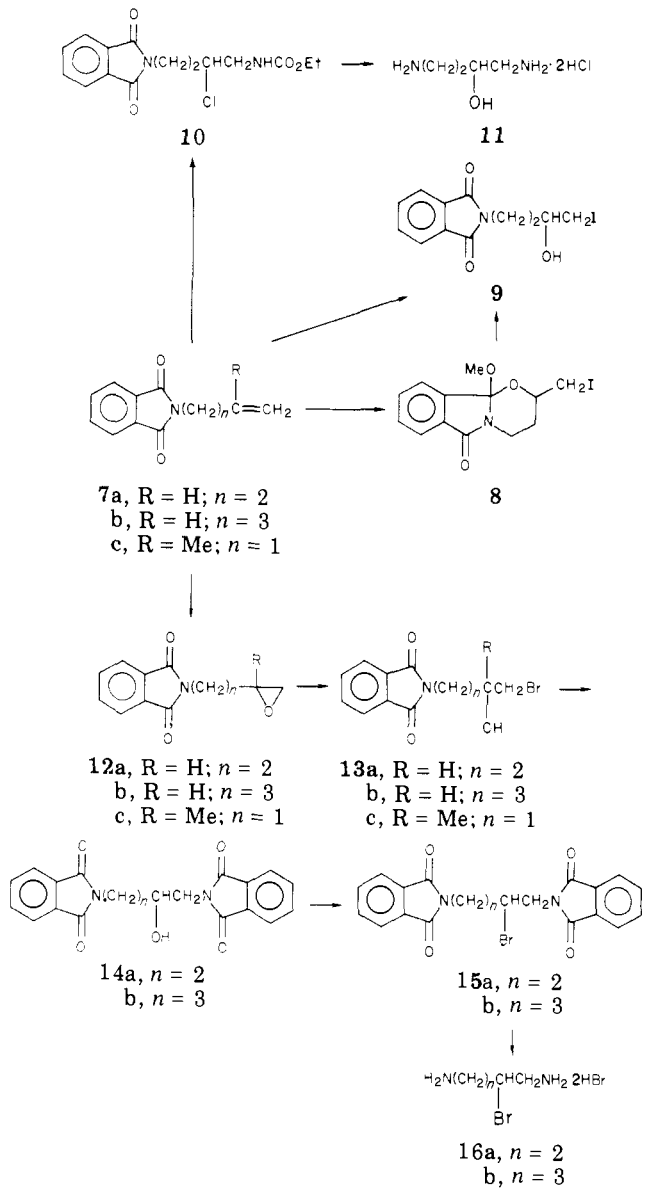
The addition of *N,N*-dichlorourethane[6] to **7a** gave ethyl (2-chloro-4-phthalimidobutyl)carbamate (**10**) and seemed a way to circumvent the problems of iodine isocyanate addition. Hydrolysis of **10** with hydrochloric acid in acetic acid, however, gave 1,4-diamino-2-butanol dihydrochloride (**11**) instead of the expected 2-chloro-1,4-butanediamine dihydrochloride, which would have been a potential precursor of 2-(2-aminoethyl)aziridine. The planned direct conversion of the secondary chloride to the primary phosphorothioate involving an aziridinium ion rearrangement became an unattractive approach when 2-chloro-1,3-propanediamine dihydrochloride[7] was observed not to react with trisodium phosphorothioate.

The bromohydrins **13a,b**, derived via epoxidation of **7a,b**, were intermediates for Gabriel syntheses of the secondary diamino bromides **16a,b**. Although dephthaloylations of **15a,b** were troublesome, the scheme faltered owing to the above-mentioned slow and incomplete reactions of **16a,b**. Attempts to convert **16a** to 2-(2-aminoethyl)aziridine for possible conversion to the more reactive primary bromide were also unsuccessful. An alternative approach to secondary bromides, which was suggested by the productive intermediacy of 3-substituted 2-oxazolidinones in the synthesis of radioprotective compounds,[8] was also abandoned when 5-(phthalimidomethyl)-2-oxazolidinone (**17**) was prepared as a model and



17

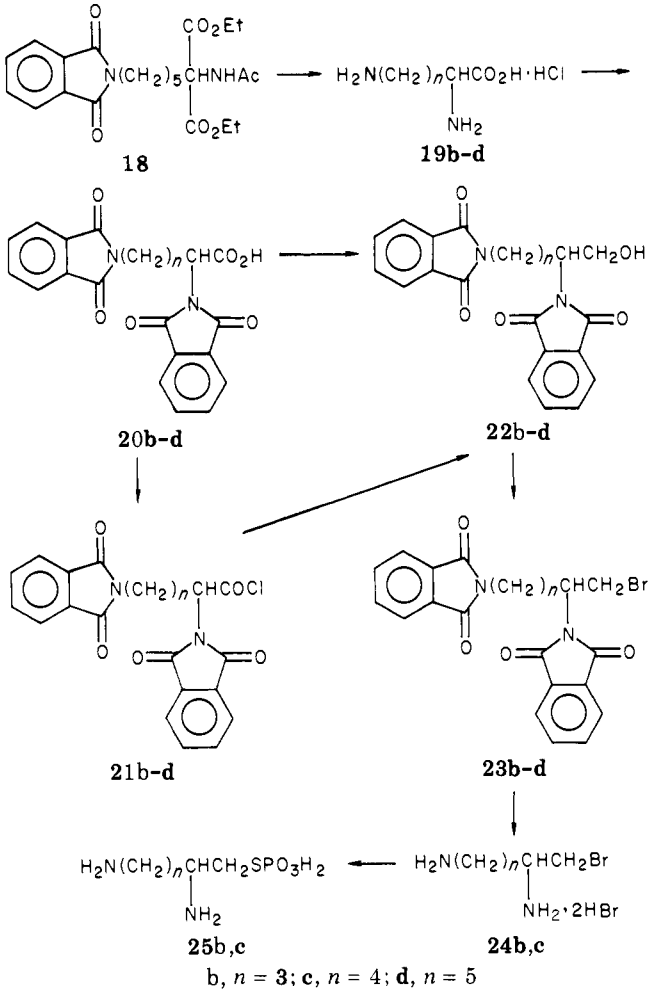
Scheme II



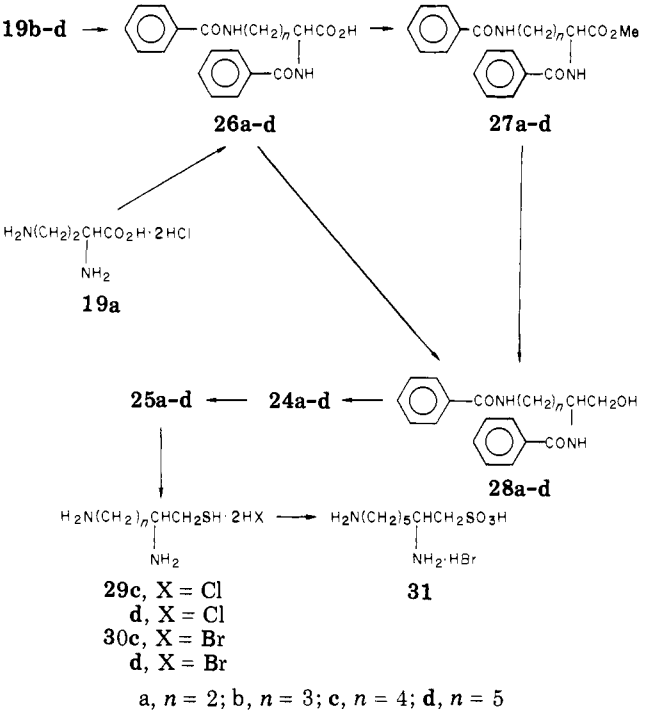
found surprisingly stable to ring opening with hydrogen bromide in acetic acid, even at elevated temperatures. A proposed synthesis of a branched homologue of **4** from *N*-(2-methyl-2-propenyl)phthalimide (**7c**) failed when an attempted Ritter conversion[9] of *N*-(3-bromo-2-hydroxy-2-methylpropyl)phthalimide (**13c**) did not provide the requisite phthalimidoacetamide as a precursor of 3-bromo-2-methyl-1,2-propanediamine dihydrobromide.

Approaches based on conversions of **7a–c** were at last abandoned in favor of an alternative approach involving the reduction of protected 2,ω-diaminoalkanoic acids. The lithium aluminum hydride reduction of methyl lysinate and of lysine itself had proved to be an unsatisfactory method for the preparation of "lysinol" (2,6-diamino-1-hexanol).[2a] The lithium aluminum hydride reduction of ethyl N^2,N^6-dibenzoyllysinate, however, was reported as the first step in an indirect preparation of uncharacterized lysinol.[10] The potential utility of acylated derivatives therefore prompted exploratory efforts that led to the reaction sequences shown in Schemes III and IV. The following contrasting results of pilot experiments directed attention initially to phthalimido intermediates: a reduction of L-N^2,N^6-dibenzoyllysine (L-**26c**) with diborane[11] in tetrahydrofuran gave a low yield of L-N^2,N^6-dibenzoyllysinol (L-**28c**), whereas a reduction of N^2,N^6-di-

Scheme III



Scheme IV



phthaloyllysyl chloride (**21c**) with sodium borohydride in bis(2-methoxyethyl) ether gave a good yield of N^2,N^6-diphthalimidolysinol (**22c**).

Scheme III was first followed in the synthesis of *S*-2,6-diaminohexyl dihydrogen phosphorothioate (**25c**). It was not surprising that phthaloylation of L-lysine hydrochloride in boiling *N*,*N*-dimethylacetamide containing sodium acetate resulted in racemization, which apparently occurred also in boiling acetic acid containing sodium acetate.[12] The preparation of **21c** with a slight excess of thionyl chloride and catalysis by *N*,*N*-dimethylformamide[13] was effective and more convenient than the previously reported procedure.[14] Several conversions of N^2,N^6-diphthalimidolysine (**20c**) to **22c** involving sodium borohydride reductions of **21c** gave a best overall yield of 30%; the yield given by a direct reduction of **20c** with diborane in tetrahydrofuran was only 13% after an involved workup. No problems were encountered in the remaining steps, which included bromodehydroxylation of **22c** with dibromotriphenylphosphorane[15] and dephthaloylation of **23c** with 48% hydrobromic acid in acetic acid.[2]

When the above methods were applied to the synthesis of a racemic lower homologue from L-ornithine dihydrochloride, difficulties encountered in the dephthaloylation step were surmounted by omitting acetic acid and increasing the reaction time. For synthesis of the $n = 5$ homologue, racemic 2,7-diaminoheptanoic acid hydrochloride (**19d**) was prepared in high yield by adaptation of a reported synthesis of 2,6-diamino-4-hexynoic acid.[16] But completion of the synthesis via phthaloylated intermediates was discouraged by low yields in the reduction step: 26% from **20d** and an overall 7% via uncharacterized **21d**. Attempts to overcome the yield problem included the reduction of the ethyl ester of **20c**, as a model, with lithium borohydride, which gave a mixture of products shown by TLC to contain neither starting ester nor desired product. These and other low yields and difficult isolations in the series may be related to reported examples of reductive alteration and hydrolysis of the imide moiety in the sodium borohydride reduction of N-substituted phthalimides.[17]

These results compelled a reexamination of the benzoyl blocking group, which culminated in the general utility of Scheme IV. The reduction of methyl L-N^2,N^6-dibenzoyllysinate (L-**27c**) with lithium borohydride afforded purer L-**28c** than the reduction of L-**26c** with diborane. High yields in the two-step conversion of L-**26c** to L-**28c** prompted a retrieval of **19d** by hydrazinolysis of **20d** so that the poor yield of **22d** could be redeemed via benzoylated intermediates. In the conversion of **28d** to the corresponding bromide **24d**, both hydrolysis and bromodehydroxylation were accomplished with 48% hydrobromic acid, benzoic acid being removed by extraction with carbon tetrachloride prior to completing the process under Cortese conditions.[18]

The phosphorothioate **25d** was derived from racemic intermediates, but Scheme IV offered, in addition to good yields and general applicability, an opportunity to obtain optically active target compounds from L-**19a–c**. Dibenzoylation did not cause racemization, and specific rotations of the methyl esters L-**27b,c** prepared by acid-catalyzed esterification agreed with values reported for the corresponding esters prepared with diazomethane.[19] A similar reaction scheme in which **27b** was reduced with lithium borohydride has been described.[20] Variations in the IR spectra (in KBr disks) of different crops of the bromides L-**24b,c** were ascribable to crystalline form, but the IR spectra of the derived phosphorothioates were identical with those of the corresponding racemates.

Appropriate acid hydrolysis of L-**25c** produced L-2,6-diaminohexanethiol dihydrohalides L-**29c** and L-**30c**. Attempts to prepare disulfides by oxidizing the di-

Table I. Radioprotective Activity of *S*-2,ω-Diaminoalkyl Dihydrogen Phosphorothioates and Thiols[a]

$H_2N(CH_2)_nCHCH_2SY$
NH_2

			ip						po			
compd	n	Y	approx LD_{50}, mg/kg	dose, mg/kg[b]	pre-irradn interval, min[c]	30-day surv, %[d]	ED_{50}, mg/kg[e]	PI at ED_{50}[f]	approx LD_{50}, mg/kg	dose, mg/kg[b]	pre-irradn interval, min[c]	survival, %[d]
4	1	PO_3H_2	>900	400	30	87, 80	230	>5.9	1600	800	30, 60	0
5	1	H(·2HBr)	800	200	30	20						
L-**25a**	2	PO_3H_2	>1250	250	15	100, 90	83	>23	>1500	1000	30	0
25b	3	PO_3H_2	>1000	250	15	100, 100	100	>15	>1500	1000	30	0
L-**25b**	3	PO_3H_2	>800	200	15	100	54	>22	>1000	1000	30	0
25c	4	PO_3H_2	450	250	15	90	24	29	900	500	30	60
										500	60	20
L-**25c**	4	PO_3H_2	325	62.5	15	89, 70	25	20	750	500	30	80
										500	60	10
25d	5	PO_3H_2	500	200	15	100	94	8.0	>1000	800	30	0
										400	60	30
L·**29c**	4	H(·2HCl)	88	25	15	90, 80	10	13	450	75	30	90, 50

[a] Antiradiation tests in mice against lethal γ radiation: 950 rd (^{60}Co) with **4** and **5**; 849 rd (^{137}Cs) with all other compounds tested. [b] Lowest dose that gave highest survival rate, administered as solution in water (**5** and L-**25a**,b) or physiological saline (L-**29c**) containing 0.3% methylcellulose and 0.1% Tween 80 (**4**, **25c**,**d**, and L-**25c**), pH usually 5–7 (L-**29c**, pH 3–4). [c] Time between drug administration and irradiation. [d] No survival among control mice. [e] Dose for 50% survival estimated from log dose-probit survival plots. [f] Protective index approximated for the ED_{50} dose to provide common basis for comparison of test compounds: $\sim LD_{50}$ (mg/kg) × 1.5/ED_{50} (mg/kg).

hydrochloride L-**29c** with trichloromethanesulfenyl chloride,[21] the dihydrobromide L-**30c** with cyanogen bromide,[22] and the in situ prepared dihydrochloride **29d** with iodine–potassium iodide gave uncharacterizable, deliquescent gums. The isolated thiol dihydrohalides **29d** and **30d** and the corresponding products of oxidation with the above reagents were also gums. A final effort to oxidize in situ prepared **30d** with bromine–water resulted in overoxidation and the isolation of 2,7-diaminoheptanesulfonic acid (**31**).

Antiradiation Evaluation. Antiradiation test results for the phosphorothioates described above and for two corresponding thiols (**5** and L-**29c**) are summarized in Table I. The tests were performed as previously described,[23] except that ^{137}Cs (dose rate 141.5 rd/min) was the radiation source instead of ^{60}Co. *S*-2,3-Diaminopropyl dihydrogen phosphorothioate (**4**) and its homologues **25b**–d and L-**25a**–**c** were all highly radioprotective when administered intraperitoneally (ip). In terms of the protective index (PI), however, the n = 2–4 homologues were significantly more protective than **4**; that is, 50% survival was effected with smaller fractions of the LD_{50} dose. Some of these homologues (for example, L-**25a**,**b** and **25c**) appeared by these comparisons to be more protective than *S*-2-[(3-aminopropyl)amino]ethyl dihydrogen phosphorothioate (**1**), a model radioprotective agent and an isomer of **25b**, whose PI at the calculated dose for 50% survival (ED_{50}) was reported[24] to be 11. The n = 4 homologues **25c** and L-**25c** and the corresponding thiol L-**29c** showed the only good peroral (po) activity in the series. Optically active homologues L-**25b**,**c** showed no apparent advantage over the corresponding racemates **25b**,**c**.

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. NMR spectra were determined with Varian A-60A and XL-100-15 spectrometers and specific rotations with a Rudolph 80 precision polarimeter. Analytical results indicated by element 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. Solutions were clarified, when so indicated, by treatment with Norit and filtration through Celite. Unless other conditions are specified, evaporations were performed with a rotary evaporator and a water aspirator, and products were dried in vacuo (oil pump) over P_2O_5 at room temperature. Phosphorothioates, which are acid sensitive, were dried in vacuo over both P_2O_5 and NaOH and were kept cold and dry in prolonged storage. Products having a chiral center are racemic unless indicated otherwise.

2-(Aminomethyl)aziridine (2). The following alternative to the reported procedure[25] was, as in related examples,[26] advantageous for making the intermediate hydrogen sulfate for ring closure. Fifty-percent aqueous solutions of 1,3-diamino-2-propanol (27.2 g, 0.300 mol) and H_2SO_4 (0.604 mol) were mixed by dropwise addition of the latter, concentrated by distillation (pot up to 115 °C), and evaporated to dryness with heating up to 105 °C for 1 h. An aqueous solution of the glassy residue was clarified (Norit, Celite) and evaporated to dryness. The residue was triturated in 1:1 2-PrOH–H_2O and dried, yield of $H_2NCH_2CH(OSO_3H)$-$CH_2NH_2 \cdot H_2SO_4$ 36.7 g (45%). Ring closure with NaOH gave a 14% yield of **2**, bp 64–67 °C (18 mm) [lit.[25] bp 54–56 °C (11 mm)].

3-Bromo-1,2-propanediamine Dihydrobromide (3). Ring opening of **2** with 48% HBr as described for related examples[26] gave **3**, mp 221–224 °C dec, in 75% yield after recrystallization from MeOH–Et_2O: NMR (Me_2SO-d_6) δ 3.18 (m, 2, CH_2N), 3.92 (m, 3, CHN and CH_2Br), 8.46 (s, 6, NH_3^+). The NMR spectrum was like that reported for 3-chloro-1,2-propanediamine dihydrobromide,[27] with the expected downfield shift for CH_2Cl (δ 4.08) relative to CH_2Br of **3**. Anal. ($C_3H_9BrN_2 \cdot 2HBr$) C, H, Br, N.

***S*-2,3-Diaminopropyl Dihydrogen Phosphorothioate (4).** Addition of **3** (6.30 g, 20.0 mmol) to a stirred partial solution of Na_3SPO_3[28] (3.60 g, 20.0 mmol) in H_2O (20 mL) gave a clear solution, which deposited crystalline **4** after 1 h. The mixture was stirred with EtOH (100 mL) before the product was collected: yield 3.71 g (100%); mp 191–192 °C dec. Anal. ($C_3H_{11}N_5O_3PS$) C, H, N, P, S.

2,3-Diamino-1-propanethiol Dihydrobromide (5). A solution of **4** (4.60 g, 24.7 mmol) in 3 N HBr (50 mL) was refluxed under N_2 for 10 min, cooled, and diluted with EtOH (100 mL) and enough Et_2O to produce incipient cloudiness. Crystalline **5** separated over a 2-h period: yield 5.61 g (85%); mp 210–215 °C dec. Anal. ($C_3H_{10}N_2S \cdot 2HBr$) C, H, Br, N, S.

Proof of Structure of 4. Conversion to *N*,*N*′-(1-Methyl-1,2-ethanediyl)bisbenzamide (6). A mixture of **4** (550

mg, 2.95 mmol) and H_2O (20 mL), adjusted to pH 4 with 1 N HCl, was refluxed for 10 min, cooled, and neutralized. An excess of wet Raney nickel was added to the solution, and the stirred mixture was refluxed for 5 h, cooled, and filtered. A solution of NaOH (2 g) in the filtrate was shaken with benzoyl chloride (1 mL) for 30 min, heated at 100 °C for 5 min, and chilled. The product was recrystallized from benzene–ligroin and from benzene, mp 196 °C after sintering and changing crystalline form at 186–187 °C. This sample was identical (mp, mmp, and IR) with authentic **6** prepared from 1,2-propanediamine (lit.[29] mp 192–193 °C). Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

***N*-(2-Methyl-2-propenyl)phthalimide (7c).** A stirred mixture of potassium phthalimide (74.1 g, 0.400 mol) and *N*,*N*-dimethylformamide (75 mL) was treated with 3-chloro-2-methyl-1-propene (36.2 g, 0.400 mol; Aldrich), gradually heated to 90 °C, kept at 90–100 °C for 3 h, cooled, and poured into cold H_2O (1 L). The precipitate was recrystallized from MeOH: yield 56.8 g (71%); mp 85–87 °C (lit.[30] mp 88.5–90 °C).

3,4-Dihydro-2-(iodomethyl)-10b-methoxy-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(10b*H*)-one (8). I_2 (2.06 g, 8.11 mmol) was added to a cold (−15 °C), stirred mixture of *N*-(3-butenyl)-phthalimide[31] (**7a**; 1.63 g, 8.11 mmol), silver cyanate[32] (3.65 g, 24.4 mmol), and dry Et_2O (25 mL). The mixture was stirred at −15 °C for 2 h and allowed to warm to 25 °C. The trace of color due to remaining I_2 was dissipated in ~10 min after the addition of dry tetrahydrofuran (5 mL). The mixture was diluted with MeOH (25 mL), refluxed 30 min, filtered, and concentrated in vacuo. The cloudy residual oil was clarified by dissolving in MeOH (10 mL), refluxing 30 min, and working up as above. The resultant pale-yellow oil (3.09 g) was kept at room temperature for 5 weeks, during which it partially crystallized, and was then refrigerated for 2 days. The solid was recrystallized from MeOH: yield of **8** 0.60 g (21%); mp 93–95 °C; NMR ($CDCl_3$) δ 1.0–2.3 (broad complex m, 2, CH_2CH_2CH), 2.9–3.6 [complex m, 3, $OCH(CH_2)(CH_2I)$], 3.14 (s, 3, OCH_3), 4.1–4.7 (complex m, 2, NCH_2CH_2), 7.3–8.0 (complex m, 4, C_6H_4); MS *m/e* 359 (M^+), 328 ($M^+ - OCH_3$), 232 ($M^+ - I$), 201 ($M^+ - OCH_3 - I$). Anal. ($C_{13}H_{14}INO_3$) C, H, N.

1-Iodo-4-phthalimido-2-butanol (9). A mixture of silver cyanate[32] (1.00 g, 6.66 mmol), I_2 (1.27 g, 5.00 mmol), and dry Et_2O (10 mL) was stirred 40 min, **7a**[31] (1.00 g, 5.00 mmol) was added in three equal portions at 10-min intervals, and the whole was stirred overnight and filtered. MeOH (10 mL) was added to the filtrate, and the dark solution was refluxed 2 h, concentrated to remove Et_2O, and poured into cold H_2O (50 mL) containing Na_2SO_3 (0.1 g). The supernatant was decanted from the dark gummy precipitate, which was stirred with a little MeOH and recrystallized from MeOH (Norit) by addition of H_2O to cloudiness. The orange precipitate was washed with cold MeOH and Et_2O, leaving white crystalline **9**: yield 0.68 g (34%); mp 98–100 °C. A sample was recrystallized from benzene–ligroin: mp 101 °C; NMR ($CDCl_3$) δ 1.5–2.2 (complex m, 2, CH_2CH_2CHOH), 2.92 (d, 1, $CHOH$; disappeared with addition of D_2O), 3.2–3.4 (m, 2, CH_2I), 3.2–3.8 (complex m, 1, $CHOH$), 3.88 (t, 2, NCH_2), 7.6–8.0 (m, 4, C_6H_4; typical AA'BB' pattern); IR (KBr) 1760 (medium), 1685 (strong) cm^{-1} (imide C=O). Anal. ($C_{12}H_{12}IO_3$) C, H, N.

Ethyl (2-Chloro-4-phthalimidobutyl)carbamate (10). A solution of *N*,*N*-dichlorourethane (33.1 g, 0.209 mol; Aldrich) in benzene (75 mL) was added under N_2 during 30 min to a stirred solution of **7a**[31] (42.0 g, 0.209 mol) in benzene (100 mL) at 35–40 °C. The solution was heated at 75–79 °C for 3 h, cooled to 0–5 °C, and treated dropwise with a solution of $NaHSO_3$ (33.4 g) in H_2O (135 mL). The benzene layer combined with two benzene extracts of the aqueous layer and was washed with 20% NaCl (3 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. Recrystallization of the waxy residue from EtOH gave **10**, mp 129–130 °C in 54% yield (36.6 g). Anal. ($C_{15}H_{17}ClN_2O_4$) C, H, N.

Dephthaloylation of 10. 1,4-Diamino-2-butanol Dihydrochloride (11). A stirred solution of **10** (1.00 g, 3.08 mmol) in AcOH (5 mL) and 12 N HCl (5 mL) was refluxed 21 h, cooled while phthalic acid crystallized, filtered, and evaporated to dryness. The residue was stirred with EtOH and washed with EtOH and then with Et_2O: yield 0.26 g (48% of **11** instead of the expected 2-chloro-1,4-butanediamine·2HCl); mp 223 °C dec. Anal. ($C_4H_{12}N_2O$·2HCl) C, H, N. A sample recrystallized from H_2O–EtOH melted at 228–231 °C dec (lit.[33] mp 231 °C dec).

Epoxides 12a–c. A solution of 3-chloroperoxybenzoic acid (85%; 31.7 g, 0.156 mol) in $CHCl_3$ (215 mL) was added dropwise to a stirred solution of **7a**[31] (28.8 g, 0.143 mol) in $CHCl_3$ (215 mL). The solution was kept overnight at room temperature, refluxed 1 h, cooled, and washed successively with 5% Na_2CO_3, H_2O, 5% Na_2SO_3, and H_2O. Evaporation of the dried ($MgSO_4$) and filtered solution left ***N*-(3,4-epoxybutyl)phthalimide (12a)** as a crystalline residue: yield 30.5 g (98%); mp 81–83 °C. A sample recrystallized from EtOH had mp 84–85 °C. Anal. ($C_{12}H_{11}NO_3$) C, H, N. Respective similar treatments of **7b**[34] and **7c** gave ***N*-(4,5-epoxypentyl)phthalimide (12b)** as a colorless oil in 97% yield and ***N*-(2,3-epoxy-2-methylpropyl)phthalimide (12c)**, mp 98–100 °C, in 79% yield after recrystallization from EtOH. Anal. **12b** ($C_{13}H_{13}NO_3$) C, H, N. Anal. **12c** ($C_{12}H_{11}NO_3$) C, H, N.

Bromohydrins 13a–c. A solution of **12a** (35.0 g, 0.161 mol) in EtOH (85 mL) was treated dropwise at 60–70 °C with 48% HBr (21 mL). The mixture left overnight at room temperature deposited ***N*-(4-bromo-3-hydroxybutyl)phthalimide (13a)**, mp 88–90 °C, in 60% yield (30.1 g). Anal. ($C_{12}H_{12}BrNO_3$) C, H, N. Respective similar treatments of **12b** and **12c** afforded ***N*-(5-bromo-4-hydroxypentyl)phthalimide (13b)**, mp 103–105 °C, in 61% yield and ***N*-(3-bromo-2-hydroxy-2-methylpropyl)-phthalimide (13c)**, mp 88–89 °C, in 63% yield. Anal. **13b** ($C_{13}H_{14}BrNO_3$) C, H, N. Anal. **13c** ($C_{12}H_{12}BrNO_3$) C, H, N.

***N*,*N*'-(2-Hydroxy-1,ω-alkanediyl)diphthalimides 14a,b.** A stirred mixture of 90.0 mmol each of **13a** (28.1 g) and potassium phthalimide (16.7 g) in *N*,*N*-dimethylformamide (100 mL) was heated at 100–114 °C for 4 h, cooled, and poured into cold H_2O (500 mL). The precipitated **14a** was recrystallized from MeCN: yield 13.3 g (40%); mp 246–248 °C. Anal. ($C_{20}H_{16}N_2O_5$) C, H, N. A similar treatment of **13b** (35.6 g, 0.114 mol) gave 23.0 g (53%) of **14b**, mp 213–215 °C. Anal. ($C_{21}H_{18}N_2O_5$) H, N; C: calcd, 66.66; found, 66.22.

***N*,*N*'-(2-Bromo-1,ω-alkanediyl)diphthalimides 15a,b.** A solution of Br_2 (6.77 g, 42.3 mmol) in MeCN (25 mL) was added dropwise to a stirred partial solution of triphenylphosphine (11.2 g, 42.7 mmol) in MeCN (150 mL). **14a** (13.2 g, 36.2 mmol) was added to the solution, and the mixture was stirred overnight, refluxed 2 h, and cooled. The precipitate was recrystallized from EtOH, giving 10.0 g of **15a**, mp 178–180 °C. Anal. ($C_{20}H_{15}BrN_2O_4$) C, H, N. Recrystallization of the residue obtained by evaporation of the filtrate gave an additional 2.2 g of product: total yield 79%. A similar treatment of **14b** (23.0 g, 60.8 mmol) gave, after removal of solvent, a gummy residue, which was stirred with EtOH (300 mL) and recrystallized from EtOH: yield of **15b** 18.1 g (68%); mp 142–144 °C. Anal. ($C_{21}H_{17}BrN_2O_4$) C, H, N.

2-Bromo-1,ω-alkanediamine Dihydrobromides 16a,b. A solution of **15a** (11.2 g, 26.2 mmol) in AcOH (55 mL) and 48% HBr (55 mL) was refluxed 4 h, chilled, filtered from phthalic acid, and evaporated to dryness. The residual **16a** was recrystallized twice from EtOH–Et_2O: yield 6.28 g (73%); mp 182–185 °C. Anal. ($C_4H_{11}BrN_2$·2HBr) H, N; C: calcd, 14.61; found, 15.22. A similar treatment of **15b** (3.00 g, 6.79 mmol) in 5 mL each of AcOH and 48% HBr gave a gummy residue, an aqueous solution of which was clarified by filtration and evaporated (finally at <1 mm) with additions of EtOH and MeOH. A solution of the residual orange glass in EtOH was diluted with Et_2O; the oily product (**16b**) solidified during 3 days (0.52 g; mp 134–150 °C). Anal. ($C_5H_{13}BrN_2$·2HBr) C, H, N. Addition of more Et_2O to the filtrate gave a second crop (0.16 g; mp 150–170 °C), which was also analyzed. Anal. ($C_5H_{13}BrN_2$·2HBr) H, N; C: calcd, 17.51; found, 17.98. The IR spectra of the two crops were virtually identical. A lower-melting third crop (0.24 g) was not analyzed; the yield of analyzed product was 29%.

5-(Phthalimidomethyl)-2-oxazolidinone (17). A. From the Chlorohydrin. A mixture of *N*-(3-chloro-2-hydroxypropyl)-phthalimide[35] (6.00 g, 25.0 mmol; Aldrich), potassium cyanate (2.43 g, 30.0 mmol), NaI (0.1 g), and *N*,*N*-dimethylformamide (25 mL) was stirred at 100 °C for 24 h, cooled, filtered, and evaporated to dryness at 60–70 °C. The residual product was recrystallized successively from H_2O, EtOH, and H_2O: yield 1.42 g (23%); dimorphic mp 188, 205 °C. Anal. ($C_{12}H_{10}N_2O_4$) C, H, N.

B. From the Epoxide. A mixture of *N*-(2,3-epoxypropyl)-phthalimide[36] (20.3 g, 0.100 mol) and urethane (13.3 g, 0.150 mol)

was fused at 90 °C and, after the addition of NaOMe (0.2 g), heated with stirring under a distillation apparatus at 180–185 °C until EtOH ceased to distill (~5 mL collected during 45 min). The mixture was extracted with boiling MeCN (100 mL), and the extract was clarified (Norit, Celite) and evaporated to dryness. The residual product was recrystallized from H_2O–EtOH (4:1): yield 2.8 g (11%); mp 184–187 °C.

Diethyl (Acetylamino)(5-phthalimidopentyl)malonate (18). Diethyl (acetylamino)malonate (180 g, 0.830 mol; Aldrich) was added to a solution of sodium (19.0 g, 0.826 g-atom) in dry EtOH (1.2 L), stirred 10 min, and treated with *N*-(5-bromopentyl)phthalimide[37] (245 g, 0.828 mol). This solution was refluxed 40 h, cooled, filtered, and evaporated to dryness. The semisolid residue was stirred with $CHCl_3$ (750 mL) and H_2O (200 mL); enough NaCl was added to give a sharp separation of layers. The $CHCl_3$ layer was washed with H_2O (3 × 200 mL), dried ($MgSO_4$), and evaporated. The residual product was stirred with Et_2O (300 mL): yield 267 g (75%); mp 101–102 °C. Anal. ($C_{22}H_{28}N_2O_7$) C, H, N.

2,7-Diaminoheptanoic Acid Hydrochloride (19d). A. From 18. A mechanically stirred solution of **18** (266 g, 0.615 mol) and hydrazine (95%; 30.0 g, 0.890 mol) in EtOH (2.5 L) was gradually heated to boiling, refluxed 1 h, and cooled. The precipitate was collected and washed with EtOH; the filtrate and washings were evaporated to dryness. A stirred mixture of the precipitate and 6 N HCl (800 mL) was heated at 80 °C for 45 min, cooled, and filtered from phthalhydrazide with the aid of 6 N HCl (200 mL). This filtrate and the solid remaining after evaporation of the ethanolic filtrate were mixed and transferred with the aid of 6 N HCl (200 mL) to a 5-L three-neck flask equipped for mechanical stirring and distillation. The stirred mixture was heated at 90–95 °C for 2 h with frothing and codistillation of volatiles. Heating was increased until the pot temperature reached 109 °C, more 6 N HCl (200 mL) was added, and distillation was continued for 1.5 h. The evolution of CO_2 having ceased, the mixture was cooled to 5 °C and filtered; the filtrate was evaporated to dryness (finally at <1 mm, 60 °C). To remove remaining phthalhydrazide, the oily residue was dissolved in H_2O (200 mL), refrigerated (2 h), and filtered (Norit, Celite) with the aid of more H_2O (50 mL). The filtrate was added to EtOH (2.5 L), the solution was treated with pyridine (250 mL), and the product was collected as short, colorless needles after refrigeration, washed with EtOH, and dried in vacuo at 60 °C; yield 119 g (98%); mp 263–266 °C dec (lit.[38] mp 263 °C). Anal. ($C_7H_{16}N_2O_2$·HCl) C, H, N.

B. From 20d. A stirred solution of **20d** (120 g, 0.285 mol) and hydrazine (95%; 30.0 g, 0.830 mol) in EtOH (2.5 L) was refluxed 2 h, cooled, treated with concentrated HCl (100 mL), filtered after 30 min, and evaporated to dryness. The residual gum was stirred with H_2O (125 mL) and the mixture clarified (Norit, Celite). The product was isolated as above after addition of the filtrate to EtOH (1.5 L) and treatment with pyridine (125 mL): yield 43.2 g (77%); mp 263 °C dec (Kofler Heizbank).

2,ω-Diphthalimidoalkanoic Acids 20b–d. A stirred mixture of L-ornithine monohydrochloride (L-**19b**; 152 g, 0.900 mol; Aldrich), phthalic anhydride (297 g, 2.01 mol), anhydrous NaOAc (90.0 g, 1.10 mol), and *N*,*N*-dimethylacetamide (900 mL) was refluxed 3 h and the solvent removed in vacuo (finally at <1 mm, 70 °C). A solution of the residual oil in warm EtOH (675 mL)–H_2O (225 mL) was diluted with H_2O (3 L); the precipitated **N^2,N^5-diphthaloylornithine (20b)** was recrystallized from EtOH–H_2O and from MeCN: yield 224 g (63%); mp 191–194 °C (lit.[39] mp 192–149 °C); $[\alpha]^{24}_D$ 0.0° (*c* 0.48, EtOH). Phthaloylations of L-lysine monohydrochloride (L-**19c**; 54.8 g, 0.366 mol; Mann) and **19d** (80.0 g, 0.495 mol) were performed similarly. **N^2,N^6-Diphthaloyllysine (20c)** was recrystallized successively from EtOH–H_2O and MeCN: yield 93.6 g (77%); mp 170–172 °C (lit.[12] mp 171 °C). **2,7-Diphthalimidoheptanoic acid (20d)** was purified by crystallization of the oily residue from MeCN–H_2O: yield 138 g (81%); mp 155–158 °C. An analytical sample of **20d** had mp 156–158 °C (from MeCN). Anal. ($C_{23}H_{20}N_2O_6$) C, H, N.

Ethyl N^2,N^6-Diphthaloyllysinate. A solution of **20c** (12.0 g, 29.5 mmol) in EtOH (320 mL), benzene (65 mL), and concentrated H_2SO_4 (5 mL) was refluxed 2 h and then distilled (30-cm Vigreux column) until the vapor-line temperature reached 78 °C. The remaining solution was treated with 3% $NaHCO_3$, and the gummy precipitate that formed was extracted with benzene. The extract was washed with 3% $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated to an oily product, which crystallized from benzene (50 mL) after dilution with 30–60 °C ligroin (500 mL): yield 10.4 g (80%); mp 85–88 °C. A sample for analysis had mp 88–90 °C (from EtOH). Anal. ($C_{24}H_{22}N_2O_6$) C, H, N.

N^2,N^5-Diphthaloylornithyl Chloride (21b). A stirred mixture of **20b** (220 g, 0.561 mol) and freshly distilled $SOCl_2$ (650 mL) was gradually heated to boiling and refluxed 1 h. The excess $SOCl_2$ was removed by distillation in vacuo, and the residual crystalline **21b** was stirred with 30–60 °C ligroin: yield 226 g (98%); mp 173–175 °C. An analytical sample from a smaller run melted at 177–179 °C. Anal. ($C_{21}H_{15}ClN_2O_5$) C, H, N.

N^2,N^6-Diphthaloyllysyl chloride (21c) and 2,7-diphthalimidoheptanoyl chloride (21d) were obtained as viscous oils by refluxing respective solutions of **20c** (31.2 g, 76.9 mmol) and **20d** (34.0 g, 80.8 mmol) in freshly distilled $SOCl_2$ (100 mL) for 1.5 h, removing excess $SOCl_2$ in vacuo with warming to 55 °C, and repeatedly evaporating benzene solutions of the residue to dryness. They were kept in vacuo over NaOH pellets until used in the preparations of **22c,d**. **21c** was also prepared by heating a stirred mixture of powdered **20c** (40.6 g, 0.100 mol), $SOCl_2$ (13.1 g, 0.110 mol), and CCl_4 (350 mL) containing *N*,*N*-dimethylformamide (1 mL) under reflux until solution occurred and then evaporating to dryness. The orange oily product of each method was used with similar results in conversions to **22c**.

***N*,*N*′-[1-(Hydroxymethyl)-1,4-butanediyl]diphthalimide (22b).** **21b** (226 g, 0.549 mol) was added in portions to a stirred solution of $NaBH_4$ (12.6 g, 0.33 mol) in bis(2-methoxyethyl) ether (1.35 L) kept at 30–35 °C. The mixture was stirred 1 h at ~30 °C, treated with more $NaBH_4$ (9.84 g, 0.260 mol), stirred 1 h at 35–40 °C, cooled, and filtered. The filtrate was diluted with H_2O (1.5 L) and the mixture left overnight. The crude product that precipitated was stirred 45 min with enough boiling MeOH to enable magnetic stirring; the mixture was then stirred overnight at room temperature before the product was collected and dried: yield 116 g (56%); mp 152–155 °C. The IR spectrum of this sample was identical with that of an analytical sample, mp 157–160 °C, obtained by chromatography on silica gel. Anal. ($C_{21}H_{18}N_2O_5$) C, H, N.

***N*,*N*′-[1-(Hydroxymethyl)-1,5-pentanediyl]diphthalimide (22c).** A solution of **21c** (the sample prepared above from 76.9 mmol of **20c**) in bis(2-methoxyethyl) ether (125 mL) was added during 15 min to a stirred solution of $NABH_4$ (3.20 g, 82.7 mmol) in the same solvent (75 mL) with moderate cooling (~30 °C). The mixture was stirred 17 h, treated dropwise with H_2O (25 mL), and poured into 0.05 N HCl (1 L). After refrigeration, the aqueous phase was decanted from the gummy precipitate, which was dissolved in EtOH (200 mL). The solution was clarified (Norit, Celite) and treated at intervals with H_2O (800 mL total) to give a semisolid precipitate, which solidified when stirred 30 min with MeOH (35 mL) and was recrystallized from MeOH (~200 mL): overall yield of **22c** from **20c** 10.2 g (30%); mp 129–132 °C. A sample for analysis was recrystallized once more from MeOH (mp unchanged). Anal. ($C_{22}H_{20}N_2O_5$) C, H, N.

***N*,*N*′-[1-(Hydroxymethyl)-1,6-hexanediyl]diphthalimide (22d).** A solution of **20d** (5.04 g, 12.0 mmol) in anhydrous tetrahydrofuran (15 mL) kept at ~25 °C was treated dropwise with a solution of diborane in tetrahydrofuran (1 M as BH_3, 16 mL; Ventron). After 1 h, the solution was treated with MeOH (10 mL) and evaporated to dryness. A solution of the oily residue in MeOH was treated with H_2O to incipient cloudiness and let stand for several days. Precipitation was completed by refrigeration and the addition of more H_2O. The supernatant was decanted from the gummy product, which solidified when stirred with MeOH (20 mL), and was collected after refrigeration: yield 1.25 g (26%); wide-melting range beginning at 102 °C.

***N*,*N*′-[1-(Bromomethyl)-1,ω-alkanediyl]diphthalimides 23b–d.** The preparation of **23c** was typical. **22c** (3.92 g, 10.0 mmol) was added to dibromotriphenylphosphorane prepared in situ by the dropwise addition of Br_2 (1.92 g, 12.0 mmol) in MeCN (10 mL) to a stirred partial solution of triphenylphosphine (3.14 g, 12.0 mmol) in MeCN (40 mL) at 10–15 °C. The resulting solution was refluxed 2 h and then distilled until 25 mL of MeCN had been removed; the cooled solution deposited crystalline product. The oil recovered by evaporation of the filtrate crystallized from MeOH to give a small second crop. Separate re-

crystallizations from MeOH gave lustrous platelets (mp 122–123 °C with sintering at 89–90 °C and resolidifying), which became a nonlustrous powder after prolonged drying in vacuo at 65 °C: combined yield 3.83 g (84%); mp 122–123 °C. A scale-up gave similar results. An analytical sample was obtained from a pilot run. Anal. ($C_{22}H_{19}BrN_2O_4$) C, H, N. The treatment of **22b** (107 g, 0.283 mol) with dibromotriphenylphosphorane (0.388 mol, prepared in situ as above) in MeCN (1.2 L) gave **23b**, mp 178–180 °C (from MeCN), in 74% yield (91.6 g). Anal. ($C_{21}H_{17}BrN_2O_4$) C, H, N. Similarly, **22d** (1.00 g, 2.46 mmol) was converted to **23d**, which was recrystallized from EtOH: yield 0.95 g (80%); mp 118–122 °C. Anal. ($C_{23}H_{21}BrN_2O_4$) H, N; C: calcd, 58.86; found 59.36.

5-Bromo-1,4-pentanediamine Dihydrobromide (24b). A stirred mixture of **23b** (30.0 g, 68.0 mmol) and 48% HBr (350 mL) was refluxed 48 h, cooled, filtered, and evaporated to dryness. The semisolid residue was stirred in EtOH to give a solid product, which was recrystallized from EtOH: yield 14.4 g (64%); mp ~200 °C dec with sintering at ~120 °C and resolidifying. Anal. ($C_5H_{13}BrN_2$·2HBr) C, H, Br, N.

6-Bromo-1,5-hexanediamine Dihydrobromide (24c). A stirred mixture of **23c** (14.0 g, 30.8 mmol), 48% HBr (75 mL), and glacial AcOH (75 mL) was refluxed 8 h, cooled, filtered from phthalic acid, and evaporated to near dryness. The residue was stirred with H_2O (50 mL), the solution was clarified (Norit, Celite) and evaporated to dryness with additions of MeOH, and the residual product was recrystallized from EtOH (50 mL): yield 7.17 g (65%, including 0.8 g obtained by workup of the filtrate), mp 161–163 °C. Anal. ($C_6H_{15}BrN_2$·2HBr) C, H, N.

L-5-Bromo-1,4-pentanediamine Dihydrobromide (L-24b) and Homologues L-24a,c and 24d. The preparation of **L-24b** was typical. A solution of **L-28b** (45.0 g, 0.138 mol) in 48% HBr (500 mL) was refluxed 16 h and allowed to cool to ~60 °C; the benzoic acid that formed was extracted with warm CCl_4 (4 × 250 mL). The aqueous layer was filtered through spun glass with the aid of additional 48% HBr (50 mL) into a 1-L round-bottom flask. The clear solution was then heated to boiling under a 30-cm Vigreux column; after 50 mL of distillate had been removed, heating was diminished so as to cause simple refluxing. Boiling was continued for 72 h, and during three periods on succeeding days heating was increased to cause distillation: 140, 90, and 70 mL of distillate were collected. The remaining solution was evaporated to dryness with additions of MeOH. The residual product was precipitated from MeOH with Et_2O after treatment with Norit and was recrystallized from EtOH: yield 40.8 g (86%); mp indefinite with sintering from ~150 °C; $[\alpha]^{26}_D$ +15.5 (*c* 1.01, H_2O). Anal. ($C_5H_{13}BrN_2$·2HBr) C, H, Br, N.

The crude **L-24a** derived from **L-28a** (10.8 g, 34.6 mmol) by treatment similar to that above still contained unconverted 2,4-diamino-1-butanol dihydrobromide and was repeatedly treated with 48% HBr (24- and 36-h reflux periods) to effect complete conversion. The crude product was recrystallized from MeOH–Et_2O: yield 7.90 g (69%); mp ~175 °C dec; $[\alpha]^{25}_D$ +9.2 (*c* 0.67, H_2O). Anal. ($C_4H_{11}BrN_2$·2HBr) C, H, Br, N.

Crude **L-24c**, isolated after a typical treatment of **L-28c** (55.0 g, 0.162 mol) with 48% HBr (600 mL), was a viscous orange oil, a solution of which in MeOH was clarified (Norit, Celite) and evaporated to a pale-yellow oil. A solution of this oil in EtOH (200 mL) afforded two crops of product (33.2 g, 11.1 g) when seeded with crystals obtained as follows: a test portion of the solution was diluted with Et_2O, and the gum that precipitated was triturated in Me_2CO. Each crop was again recrystallized from EtOH: yield 34.9 g (60%); mp 161–163 °C; $[\alpha]^{26}_D$ +14.6° (*c* 1.04, H_2O). Anal. ($C_6H_{15}BrN_2$·2HBr) C, H, Br, N.

Crude **24d** was obtained from **28d** (30.0 g, 84.6 mmol) as a pale-orange syrup (30.5 g), which solidified during 1 week after seeding with crystals that formed in the oily product of a pilot run. The solid mass was triturated in Me_2CO, washed with Et_2O, dissolved in boiling EtOH (~100 mL), and diluted with MeCN (~400 mL). Long refrigeration and additional MeCN (~400 mL) gave a crystalline product, which was pulverized under MeCN: yield 22.6 g (72%); mp ~115 °C dec. Anal. ($C_7H_{17}BrN_2$·2HBr) C, H, Br, N.

***S*-2,ω-Diaminoalkyl Dihydrogen Phosphorothioates L-25a–c and 25b–d.** The simple isolation and quantitative yield of the prototype **4** described earlier were atypical of other members of the series. The reactions, in which a slight excess of bromodiamine dihydrobromide was usually used, were monitored by a test[40] for unchanged Na_3SPO_3, a potential source of contamination.[41] Precipitations were varied so as to give analyzable crystalline products, which were hygroscopic and sometimes deliquescent.

Addition of **L-24a** (7.85 g, 23.9 mmol) to a stirred partial solution of Na_3SPO_3[28] (4.12 g, 22.9 mmol) in H_2O (23 mL) gave a clear solution, which after 3 h was added to stirred MeOH (300 mL). The precipitate was collected under N_2, washed with MeOH and with Et_2O, suction dried under N_2, and twice reprecipitated from H_2O (20 mL) by addition to MeOH (400 mL). The deliquescent **L-*S*-2,4-diaminobutyl dihydrogen phosphorothioate (L-25a)** was stirred overnight with Et_2O, collected under N_2, and dried: yield 2.62 g (79%); mp ~130 °C dec; $[\alpha]^{25}_D$ +24° (*c* 0.65, H_2O). Anal. ($C_4H_{13}N_2O_3PS$) C, H, N, P, S.

A smooth suspension prepared by adding Na_3SPO_3 (19.6 g, 0.109 mol) in portions to stirred H_2O (100 mL), warming (40–45 °C), and rapid chilling was treated with **L-24b** (38.1 g, 0.111 mol), and the resulting solution was stirred for 2 h at room temperature and added dropwise to stirred EtOH (1 L). The precipitated **L-*S*-2,5-diaminopentyl dihydrogen phosphorothioate (L-25b)** was collected after 1 h and dissolved in H_2O (100 mL), the solution was filtered and added to stirred MeOH (1.3 L), and the precipitate was washed with MeOH and Et_2O, suction dried under N_2, and dried: yield 21.1 g (83%); mp 160–162 °C dec; $[\alpha]^{26}_D$ +24.1° (*c* 1.02, H_2O). Anal. ($C_5H_{15}N_2O_3PS$·H_2O) C, N, P, S; H: calcd, 7.38; found, 6.81. Racemic **25b** was similarly prepared from **24b** (10.8 g, 31.5 mmol) and Na_3SPO_3 (5.88 g, 31.0 mmol) and twice precipitated from H_2O (30 mL) by addition to MeOH (250 mL): yield 5.49 g (83%); mp 158–161 °C dec. Anal. ($C_5H_{15}N_2O_3PS$) C, H, N, P, S.

The solution resulting from the 20-min addition of **L-24c** (33.9 g, 95.0 mmol) to a partial solution of Na_3SPO_3 (16.7 g, 93.0 mmol) in H_2O (93 mL) was kept at room temperature for 2 h, refrigerated overnight, and stirred for 1 h with EtOH (1 L). The precipitate was dissolved in H_2O (~5 L), and the solution was filtered, combined with EtOH (~6 L), and refrigerated. The product, **L-*S*-2,6-diaminohexyl dihydrogen phosphorothioate (L-25c)**, was deposited as lustrous plates, which were washed with EtOH and Et_2O and dried: yield 22.7 g (92%); mp 148–150 °C dec; $[\alpha]^{26}_D$ +13.6° (*c* 1.04, 0.1 N NaOH). Anal. ($C_6H_{17}N_2O_3PS$·2H_2O) C, H, N, P, S. Racemic **25c** was prepared similarly from **24c** (11.2 g, 31.2 mmol) and Na_3SPO_3 (5.58 g, 31.0 mmol): yield 7.54 g (92%); mp 135–138 °C dec. Anal. ($C_6H_{17}N_2O_3PS$·2H_2O) C, H, N, P, S.

***S*-2,7-Diaminoheptyl dihydrogen phosphorothioate (25d)** precipitated when the solution resulting from the 20-min addition of **24d** (13.3 g, 35.8 mmol) to a stirred solution of Na_3SPO_3 (6.30 g, 35.0 mmol) in H_2O (100 mL) was poured into MeOH (500 mL) after 1 h. The precipitate was collected after 2 h, washed with MeOH, dried, and reprecipitated from H_2O (500 mL) by addition to EtOH (1.2 L): yield 6.08 g (72%); mp ~223 °C dec. Anal. ($C_7H_{19}N_2O_3PS$) C, H, N, P, S.

2,ω-Bis(benzoylamino)alkanoic Acids L-26a–c and 26d. The preparation of **L-N^2,N^6-dibenzoyllysine (L-26c)** was typical. A cold (5 °C) mechanically stirred solution of **L-19c** (41.1 g, 0.225 mol) in H_2O (150 mL) was treated dropwise with a solution of NaOH (36.0 g, 0.900 mol) in H_2O (225 mL) and then with a solution of Na_2CO_3 (47.7 g, 0.450 mol) in H_2O (375 mL). To the resulting solution kept at −5 to 5 °C in an ice–salt bath benzoyl chloride (73.0 g, 0.520 mol) was added dropwise, and the mixture was stirred for 2 h, allowed to warm gradually to 25 °C, and clarified (Norit, Celite). The filtrate was added in portions to swirled 3 N HCl (600 mL). The initially gummy product was collected after overnight refrigeration, stirred with Et_2O (1 L) to give a filterable suspension, and recrystallized from EtOH–H_2O: yield 74.0 g (93%); mp 148–150 °C (lit.[19] mp 149–150 °C). The molar ratio of NaOH was 5:1 instead of 4:1 in the conversion of **19a** (13.1 g, 68.6 mol; Sigma) to **L-2,4-bis(benzoylamino)butyric acid (L-26a)**; the acidification step gave a white gum, which crystallized when stirred with Et_2O after decantation of the aqueous phase: yield 19.4 g (87%); mp 146–148 °C (lit.[19] mp 149 °C). **L-N^2,N^6-Dibenzoylornithine (L-26b)** was prepared from **L-19b** (50.6 g, 0.300 mol) and recrystallized from EtOH: yield 75.5 g (74%); mp 186–188 °C (lit.[42] mp 185–186 °C). **2,7-Bis(benzoylamino)heptanoic acid (26d)**, prepared from **19d** (29.5 g,

0.150 mol), was reprecipitated from EtOH (~250 mL) with H_2O and stirred with Et_2O (500 mL): yield 50.8 g (92%); mp 151–154 °C (lit.[38] mp 154–155 °C).

Methyl 2,ω-Bis(benzoylamino)alkanoates L-27b,c and 27d. A solution of L-**26b** (73.0 g, 0.214 mol) in MeOH (1 L), benzene (217 mL), and concentrated H_2SO_4 (5 mL) was kept at room temperature overnight and then slowly distilled through a 30-cm fractionating column until 525 mL of distillate had been collected. The cooled residue was poured with stirring into 2% $NaHCO_3$ (1.5 L) and the mixture refrigerated. The precipitate, which solidified, was collected, dried (72.5 g), and recrystallized from EtOAc, giving a first crop of 47.8 g; mp 148–150 °C, $[\alpha]^{25.5}_D$ −12.7° (*c* 1.42, MeOH). Later crops of 6.9 and 10.6 g exhibited dimorphism, melting at 128–130 °C, resolidifying, and remelting at 148–150 °C. Resolidified samples no longer gave the lower melting point. The total yield of **methyl L-N^2,N^5-dibenzoylornithinate** (L-**27b**) was 85%. Previously reported L-**27b**, mp 145–146 °C, $[\alpha]^{17}_D$ −13.2° (*c* ~1.4, MeOH), was prepared with CH_2N_2.[19] L-**26c** (71.5 g, 0.202 mol) was esterified in MeOH (1.5 L), benzene (325 mL), and concentrated H_2SO_4 (10 mL) as above with a distillate volume of ~1 L, the remaining solvent being removed in vacuo. The concentrate was dissolved in benzene (500 mL) and treated with a solution of $NaHCO_3$ (35 g) in H_2O (500 mL) with the addition of more benzene (1.2 L) to effect a clean separation of the aqueous layer. The benzene layer was dried ($MgSO_4$), filtered, concentrated to ~300 mL, and diluted with 30–60 °C ligroin (~1.5 L), giving **methyl L-N^2,N^6-dibenzoyllysinate** (L-**27c**) as a white gum, which solidified wthin 3 days: yield 68.8 g (93%); mp 112–114 °C. A sample recrystallized from EtOH had mp 113–114 °C and $[\alpha]^{25.5}_D$ −18.3° (*c* 1.43, MeOH) [lit.[19] mp 114 °C; $[\alpha]^{17}_D$ −18.6° (*c* 1.4, MeOH)]. The esterification of **26d** (50.6 g, 0.137 mol) in MeOH (1 L), benzene (215 mL), and concentrated H_2SO_4 (5 mL) was performed similarly with removal of 560 mL of distillate. The cooled mixture was poured into a solution of $NaHCO_3$ (20 g) in H_2O (2.5 L), precipitating **methyl 2,7-bis(benzoylamino)heptanoate** (**27d**), which solidified when refrigerated and was recrystallized from EtOAc: yield 91% (two crops: 41.3 and 6.4 g); mp 138–140 °C. Anal. ($C_{22}H_{26}N_2O_4$) C, H, N.

***N*,*N*'-[1-(Hydroxymethyl)-1,ω-alkanediyl]bisbenzamides 28a–d.** The preparation of L-**28b** was typical. L-**27b** (45.0 g, 0.127 mol) was added in portions during 10–15 min to a mechanically stirred solution of $LiBH_4$ (3.90 g, 0.179 mol) in dry tetrahydrofuran (350 mL). The mixture was refluxed 2.5 h, let stand overnight, and with rapid stirring treated successively with H_2O (150 mL) in a thin stream and a solution of concentrated HCl (15 mL) in H_2O (150 mL) dropwise with moderate cooling. The solution was stirred 30 min longer and poured into H_2O (1.5 L). The product that separated was collected after refrigeration: yield 95% (39.4 g); mp 189–191 °C. A sample recrystallized from EtOH had mp 190–192 °C and $[\alpha]^{25.5}_D$ −35.2° (*c* 1.16, DMF). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N. Crude L-**28a** (14.1 g) obtained by the reduction of L-**27a** (16.3 g, 47.8 mmol) as above (but including some recovered by evaporation of the filtrate) was recrystallized from MeOH–H_2O: yield 72% (10.8 g); $[\alpha]^{22.5}_D$ −99.7° (*c* 1.26, DMF). Anal. ($C_{18}H_{20}N_2O_3$) C, H, N. The reduction of L-**27c** (66.0 g, 0.179 mol) gave 58.1 g (95%) of L-**28c**. A sample recrystallized from MeCN had mp 153–154 °C (lit.[10] mp 133–135 °C) and $[\alpha]^{25.5}_D$ −40.1° (*c* 0.97, DMF). Anal. ($C_{20}H_{24}N_2O_3$) C, H, N. Crude **28d**, obtained by the reduction of **27d** (28.7 g, 75.0 mmol), was also recrystallized from MeCN: yield 91% (24.2 g); mp 114–116 °C. Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

L-2,6-Diaminohexanethiol Dihydrohalides L-29c and L-30c. A solution of L-**25c**·$2H_2O$ (6.50 g, 23.6 mmol) in 3 N HCl (65 mL) was heated at ~90 °C for 10 min and evaporated to dryness. The residual oil was dissolved in EtOH (30 mL), treated with dry HCl–EtOH (~5 N, 5 mL), and refrigerated overnight. The crystalline dihydrochloride (L-**29c**) was collected under N_2 after the addition of Et_2O (~35 mL): yield 5.36 g (99%); mp 202–205 °C dec; $[\alpha]^{25}_D$ +15.9° (*c* 1.0, H_2O). Anal. ($C_6H_{16}N_2S$·2HCl) C, H, N, SH. The dihydrobromide (L-**30c**), mp 154–157 °C dec, was obtained in 92% yield (1.08 g) by a 10-min hydrolysis of L-**25c**·$2H_2O$ (1.00 g) in 3 N HBr at 90 °C, evaporation to dryness, and recrystallization from EtOH–Et_2O. Anal. ($C_6H_{16}N_2S$·2HBr) C, H, N.

2,7-Diaminoheptanesulfonic Acid Hydrobromide (**31**). A solution of **25d** (0.22 g, 0.091 mmol) in dilute HBr [48% HBr (0.5 mL) in H_2O (2 mL)] was treated with Br_2–H_2O until a yellow color persisted and was then evaporated to dryness. The residue was dissolved in boiling EtOH by the addition of a few drops of MeOH; the cooled solution deposited crystalline **31**: yield 0.15 g (57%); mp ~215 °C dec; NMR and IR spectra consistent with the assigned structure. Anal. ($C_7H_{18}N_2O_3S$·HBr) C, H, N; Br: calcd, 27.44; found, 26.84.

Acknowledgment. This investigation was supported by the U.S. Army Medical Research and Development Command through Contract DADA17-69-C-9033. The authors are indebted to Mrs. Martha C. Thorpe for interpretation of NMR spectra.

References and Notes

(1) The preparation of **4** from the corresponding bromoalkanamine hydrobromide has been reported previously by F. Yu. Rachinskii, N. M. Slavachevskaya, and L. V. Pavlova, *J. Gen. Chem. USSR*, **39**, 2592 (1969), but no other details were given.
(2) (a) J. R. Piper, C. R. Stringfellow, Jr., R. D. Elliott, and T. P. Johnston, *J. Med.* Chem., **12**, 236 (1969); (b) J. R. Piper and T. P. Johnston, U.S. Patent 3892824 (1975).
(3) T. L. Phillips, *Cancer*, **39**, 987 (1977).
(4) (a) T. A. Foglia and D. Swern, *J. Org. Chem.*, **32**, 540 (1967); (b) A. Hassner, M. E. Lorber, and C. Heathcock, *ibid.*, **32**, 540 (1967).
(5) (a) S. Huenig and L. Geldern, *J. Prakt. Chem.*, **24** (4), 246 (1964); (b) W. J. Houlihan, U.S. Patent 3408350 (1968), Division of U.S. Patent 3334113 (1967); (c) H. E. Zaugg, *Synthesis*, 49 (1970).
(6) T. A. Foglia and D. Swern, *J. Org. Chem.*, 31, 3625 (1966).
(7) (a) S. Gabriel and W. Michels, *Ber. Dtsch. Chem. Ges.*, **25**, 3056 (1892); (b) T. P. Johnston, G. S. McCaleb, P. S. Opliger, W. R. Laster, Jr., and J. A. Montgomery, *J. Med. Chem.*, 14, 600 (1971).
(8) (a) J. R. Piper, R. D. Elliott, C. R. Stringfellow, Jr., and T. P. Johnston, *Chem. Ind. (London)*, 2010 (1966); (b) R. D. Elliott, J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **15**, 595 (1972).
(9) R. M. Lusskin and J. J. Ritter, *J. Am. Chem. Soc.*, **72**, 5577 (1950).
(10) A. Schneider, E. Henson, O. O. Blumenfeld, and P. M. Gallop, *Biochem. Biophys. Res. Commun.*, **27**, 546 (1967).
(11) H. C. Brown, P. Helm, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970).
(12) G. Wanag and A. Veinbergs, *Ber. Dtsch. Chem. Ges.*, **75**, 1558 (1942).
(13) H. H. Boshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).
(14) N. Z. Stanacev and M. Prostenik, *Croat. Chem. Acta*, **28**, 291 (1956); *Chem. Abstr.*, **51**, 11995*d* (1957).
(15) G. A. Wiley, R. L. Hershkowitz, B. M. Reim, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).
(16) J. L. Neumeyer and W. Firshein, *J. Pharm. Sci.*, **55**, 441 (1966).
(17) (a) F. C. Uhle, *J. Org. Chem.*, **26**, 2998 (1961); (b) T. Watanabe, F. Hamaguchi, and S. Ohki, *Chem. Pharm. Bull.*, **26**, 530 (1978).
(18) F. Cortese in "Organic Syntheses", Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, 1943, pp 91–93.
(19) P. Karrer, K. Escher, and R. Widmer, *Helv. Chim. Acta*, **9**, 301 (1926).
(20) H. Gershon and R. Rodin, *J. Med. Chem.*, 8, 864 (1965).
(21) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **26**, 3780 (1961).
(22) W. O. Foye, A. B. Hebb, and J. Mickles, *J. Pharm. Sci.*, **56**, 292 (1967).
(23) D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 510 (1969).
(24) J. R. Piper, L. M. Rose, and T. P. Johnston, *J. Med. Chem.*, **18**, 803 (1975).
(25) J. D. Spivack, U.S. Patent 2931804 (1960).

(26) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **9**, 911 (1966).
(27) R. Paul, R. P. Williams, and E. Cohen, *J. Org. Chem.*, **40**, 1653 (1975).
(28) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **32**, 1261 (1967).
(29) H. Strache, *Ber. Dtsch. Chem. Ges.*, 2358 (1888).
(30) R. Adams and T. L. Cairns, *J. Am. Chem. Soc.*, **61**, 2464 (1939).
(31) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).
(32) A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).
(33) L. Macholan, *Collect. Czech. Chem. Commun.*, **30**, 2074 (1965).
(34) W. Kirmse and D. Grassmann, *Chem. Ber.*, **99**, 1746 (1966).
(35) S. Gabriel and H. Ohle, *Ber. Dtsh. Chem. Ges.*, **50**, 819 (1917).
(36) D. H. Ball, J. M. Williams, and L. Long, Jr., *J. Org. Chem.*, **28**, 1589 (1963).
(37) Prepared in DMF like *N*-(4-bromobutyl)phthalimide [J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **33**, 636 (1968)] and recrystallized from hexane, yield 57%.
(38) S. Takagi and K. Hayashi, *Chem. Pharm. Bull.*, **7**, 183 (1959).
(39) E. E. van Tamalen and E. E. Smissman, *J. Am. Chem. Soc.*, **75**, 2031 (1953).
(40) S. Akerfeldt, *Acta Chem. Scand.*, **16**, 1897 (1962).
(41) D. L. Klayman and E. S. Copeland, *Drug Des.*, **6**, 81 (1975).
(42) P. Karrer and M. Ehrenstein, *Helv. Chim. Acta*, **9**, 323 (1926).

Studies on Biologically Active Nucleosides and Nucleotides. 5. Synthesis and Antitumor Activity of Some 2,2′-Anhydro-1-(3′,5′-di-*O*-acyl-β-D-arabinofuranosyl)cytosine Salts and 2,2′-Anhydro-1-(3′-*O*-acyl-β-D-arabinofuranosyl)cytosine 5′-Phosphates

Kazuhiko Kondo, Takeo Nagura, Yoshihisa Arai, and Ichizo Inoue*

Research Laboratories of Tanabe Seiyaku Co., Ltd., 16-89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan.
Received September 21, 1978

A series of 3′,5′-diesters of a 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine salt bearing functional substituents on the ester side chains (**4–16**) have been synthesized. The synthesis of these diesters involved the reaction between cytidine and the corresponding acid anhydride or acid chloride in the presence of boron trifluoride etherate. Similar reaction of bis(cytidine 5′-)suberate (**21**) with pivaloyl chloride gave bis[2,2′-anhydro-1-(3′-*O*-pivaloyl-β-D-arabinofuranosyl)cytosine 5′-]suberate dihydrochloride (**22**). The reaction could also be extended to a one-step synthesis of 3′-esters of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine 5′-phosphate (**24**) from 5′-cytidylic acid. These compounds have been examined for antitumor activity against L1210 leukemia in BDF_1 mice. The diesters with a long-chain carboxylic acid (**4c**, **7c**, **12**, and **24d**) showed high activity when administered intraperitoneally. The compound **24d** exhibited moderate activity when administered orally.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)cytosine (anhydro-*ara*-C) hydrochloride, a depot form of 1-(β-D-arabinofuranosyl)cytosine (*ara*-C),[1] is a more effective and less toxic antitumor agent than is *ara*-C itself.[2] A number of analogues of anhydro-*ara*-C with modification in the base and/or sugar portions have been prepared in an attempt to find more potent antitumor agents. Kanai et al.[3] reported the synthesis of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine 5′-phosphate (anhydro-*ara*-C 5′-phosphate) by the reaction of 5′-cytidylic acid (**23**) with partially hydrolyzed phosphorus oxychloride in 46% yield. This compound has shown marked activity against L1210 leukemia in mice.[4] Very recently, Moffatt and co-workers[5] have synthesized 3′,5′-di-*O*-acyl derivatives of anhydro-*ara*-C with a homologous series of aliphatic saturated or unsaturated carboxylic acids by the acylation of anhydro-*ara*-C hydrochloride. They have also shown that these diesters have activity against L1210 leukemia in mice when administered intraperitoneally (ip). The degree of the activity was strongly influenced by the chain length; high activity was shown by the compound containing C_{12}–C_{14} saturated acyl groups and C_{18}–C_{22} unsaturated acyl groups.

In a previous study in this series, we have developed a simple and efficient method for the preparation of the diesters by the reaction of cytidine with carboxylic acid anhydrides or carboxylic acid chlorides in the presence of boron trifluoride etherate.[6] The mechanism for the formation of the diesters could be explained via the opening of the 2′,3′-*O*-acyloxonium ion intermediate **3** by C_2-carbonyl oxygen (Scheme I). Using this procedure, we have prepared a series of the diesters with simple aliphatic and aromatic carboxylic acids and have tested[7] them for antileukemic (L1210) activity in mice. Among the compounds tested, 2,2′-anhydro-1-(3′,5′-di-*O*-palmitoyl-β-D-arabinofuranosyl)cytosine hydrochloride was found to be highly active at 100 (mg/kg)/day (5 days), ip (see Table II). However, the therapeutic index could not be improved compared to anhydro-*ara*-C because of the increased toxicity, and it showed only slight activity when administered orally (po).

On the other hand, it has been shown that some 5′-*O*-acyl-*ara*-C compounds with low water solubility and susceptibility to the enzymatic hydrolysis exhibit high anti-L1210 activity in mice.[8] However, clinical phase 1 trials of such derivatives, 5′-*O*-palmitoyl- and 5′-*O*-benzoyl-*ara*-C, have given discouraging results, suggesting that somewhat increased water solubility would be necessary for the antileukemic activity in man.[9] In view of these facts that the biological activity of the esters of anhydro-*ara*-C and *ara*-C is markedly affected by the precise nature of the acyl group(s), it was of interest to investigate an extensive modification of the acyl groups of the 3′,5′-di-*O*-acyl-anhydro-*ara*-C compounds. We have synthesized a series of the diesters (**4–16**, **22**, and **24**) bearing a variety of functional substituents on the ester side chains. Such modification may affect the water solubility, rate of the enzymatic hydrolysis, and other properties of the diesters and bring about improvement of the therapeutic properties of anhydro-*ara*-C.

Chemistry. The diesters **4–16** synthesized in this study are listed in Table II. These diesters were prepared by the acid chloride and acid anhydride methods. The key intermediates in these methods are functionally substituted carboxylic acid anhydrides (**2a**) and carboxylic acid

0022-2623/79/1822-0639$01.00/0