To the extent that the solution of a substance in each phase can be considered regular, the activity coefficient for a not too highly polar nonelectrolytic solute, *i.e.*, one which is not highly associated with itself due to its charge characteristics, is given by Hildebrand–Scott solubility theory[7] as

$$\log \gamma_2 = \frac{\Phi_1^2 V_2}{2.303RT} (\delta_1 - \delta_2)^2 \quad (2)$$

where V_2 is the molal volume of solute in solution, Φ_1 is the volume fraction of solvent, and δ_1, δ_2 are the "internal pressures" of the solvent and solute, respectively. In dilute solution $\Phi_1 \approx 1$ and, if this condition applies to each of the phases for a distribution system, then since $\delta = F/V$ where F is the molar attraction constant equation 1 can be written[7c] (following substitution of eq 2 into eq 1, expansion and cancellation of terms, and factoring) as

$$\log P = \frac{(\delta_a - \delta_o)}{2.303RT} \times [(\delta_a + \delta_o)V_2 - 2F_2] \quad (3)$$

From eq 3 it can be said that a distribution system each of whose phases form a regular solution with a series of compounds should yield a linear relationship in a plot of log P *vs.* F when the molar volumes V_2 do not vary greatly from substance to substance or if they vary in the same direction as does F_2. Biological activities which are predominantly influenced by lipid–water partitioning should also be linearly related to F subject to the same restrictions. Equation 3 thus accounts for the relationship found by Ostrenga[3b] between the *in vitro* bacteriostatic activities of penicillins and the molar attraction constants for the side chain.

According to Hildebrand and Scott[8] the molar attraction constant F corresponds to the constant a in the van der Waals equation of state, or something very similar, and is related to this constant by the equation

$$F_2^2 = a_2 = -2\pi N^2 \int_d^\infty \epsilon \rho(r) r^2 dr \quad (4)$$

where ϵ is the bimolecular interaction energy, $\rho(r)$ is a distribution function giving the probability of having a center-to-center distance r between the molecules and N is Avagadro's number. The integration is carried out over all values of r beginning from the most favorable intermolecular separation d. Substitution of eq 4 into eq 3 provides a basis for the correlation reported by Wulf and Featherstone[9] between the narcotic potencies of gaseous anesthetics and their van der Waals a constants.

For simplicity the interaction energy between two not too highly polar molecules may be given by the Lennard-Jones "6–12" potential

$$\epsilon = -\frac{k}{r^6} + \frac{j}{r^{12}} \quad (5)$$

Under most conditions the repulsion part may be considered negligible in comparison with the attraction part in eq 5. With this understanding, and assuming that $\rho(r)$ can be taken as a constant, say unity, in first approximation, the substitution of eq 5 into eq 4 followed by integration leads to the relationship

$$F_2^2 = \frac{2\pi N^2}{3d^3} \times k \quad (6)$$

where k in eq 6 differs depending on the formalism used to express the intermolecular attraction energy. With only slightly polar molecules involved in an interaction the dispersion energy[10] will make the largest stabilizing contribution. The most widely used estimate of dispersion energy, that due to London,[10a] when substituted into eq 6 [*i.e.*, $k = {}^3/_4(\alpha^2 I)$] leads to the relationships

$$F_2^2 = \frac{\pi N^2}{2d^3} \alpha^2 I = \frac{9}{32\pi d^3} \times P_E^2 I \quad (7)$$

in which I is the ionization potential and α, P_E are the molecular and molar polarizabilities, respectively, for a substance [$P_E = {}^4/_3(\pi N \alpha)$]. To a good approximation the ionization potential can be considered essentially constant for a variety of molecules,[2a,c] hence the appropriate substitution of eq 7 into eq 3 can account for the distribution processes which are related to polarizability measures. This can be taken as a basis for the correlation often observed between anesthetic potencies and polarizability[2b,c,3a]

The finding[4] that experimental partition coefficients often provide better correlations with biological activities than do polarizabilities or molar attraction constant indicates the "solution" of drugs in biological phases is frequently not regular, *i.e.*, the solution process has identified with it a positive heat of mixing, a nonideal entropy of mixing, and/or an appreciable difference in the molal volumes of the associated substances. For those cases where regular solution theory does hold, however, the relations which have been developed can provide considerable insight into dissolution processes involving biological materials. Additional verification of the relations developed and explicit applications to biological systems will be reported in detail at a later date.

(7) (a) J. H. Hildebrand and R. L. Scott, "The Solubility of Nonelectrolytes," Dover Publications, New York, N. Y., 1964; (b) A. N. Martin, J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd ed., Lea and Febiger, Philadelphia, Pa., 1969, pp 299–303. (c) Equation 3 applies only if the molal volumes of solute in each phase are equal, *i.e.*, $V_a = V_o$. In the event that the molal volumes are not equal eq 3 may be written as log $P = 1/(2.303RT)\{(V_a\delta_a^2 - V_o\delta_o^2) - 2[V_a\delta_a - V_o\delta_o)/V]F + [(V_a - V_o)/V^2]F^2\}$ where V is the *molar* volume of pure solute. Parabolic fits of log P (or quantities related to log P) to F are thus predicted.

(8) J. H. Hildebrand and R. L. Scott, ref 7a, pp 94–96, 124–129.

(9) R. J. Wulf and R. M. Featherstone, *Anesthesiology*, **18**, 97 (1957).

(10) (a) F. London, *Z. Physik.*, **63**, 245 (1930); (b) J. G. Kirkwood, *Phys. Z.*, **33**, 57 (1932); (c) J. H. Van Vleck, "Electric and Magnetic Susceptibilities," Oxford University Press, New York, N. Y., 1932, p 91.

Further Evaluation of *N,N'*-Polymethylene-Bridged 2-Aminoethanethiol Derivatives and Related Compounds as Radioprotective Agents[1]

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Good radioprotective activity observed with two members (A, $n = 3, 4$) of a limited series of *N,N'*-poly-

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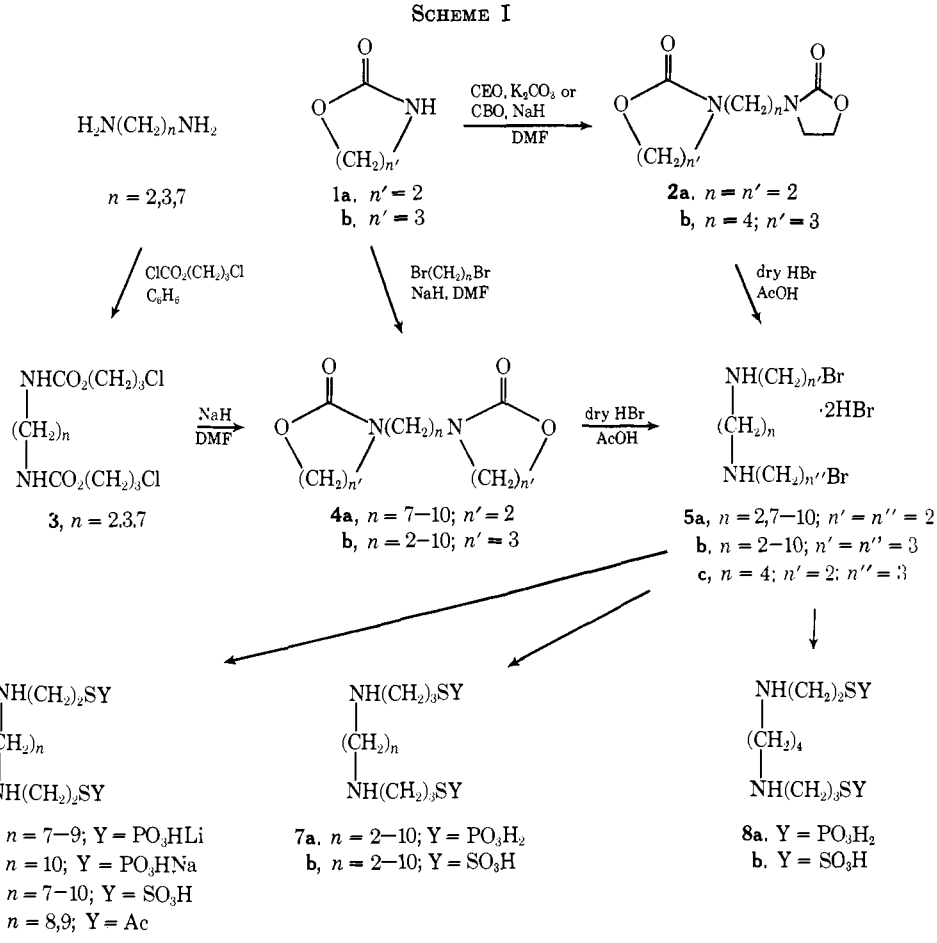
SCHEME I



methylene-bridged *S*-2-aminoethyl phosphorothioates and thiosulfates[2] prompted an expansion of the series

$$NaHO_3PS(CH_2)_2NH(CH_2)_nNH(CH_2)_2SPO_3HNa$$
A

and the synthesis of a number of related compounds. The approach originally followed,[2] *i. e.*, that based on the protection of amino groups as tosylamides, was eventually superseded by the dry HBr cleavage of appropriately substituted 2-oxazolidinones.[3] The superiority of the latter method was demonstrated by a resynthesis of the dibromide **5a** (n = 2) *via* the bis(2-oxazolidinone) **2a**, which was obtained by the alkylation of 2-oxazolidinone (**1a**) with 3-(2-chloroethyl)-2-oxazolidinone (CEO) (see Scheme I). The homologous bis(2-oxazolidinones) **4a** (n = 7–10) were obtained, however, by the alkylations of **1a** with α,ω-dibromoalkanes. The dibromides **5a** (n = 7–10) were converted to phosphorothioates (**6a,b**), thiosulfates (**6c**), and thioacetates (**6d**).

This approach was extended to a series of *N,N′*-polymethylenebis(*S*-3-aminopropyl dihydrogen phosphorothiates) (**7a**) and the corresponding thiosulfates (**7b**), which were derived from tetrahydro-2*H*-1,3-oxazin-2-one (**1b**) *via* the *N,N′*-polymethylenebis(tetrahydro-2*H*-1,3-oxazin-2-ones) (**4b**).[4] The low yield of the intermediate dibromide **5b** (n = 3) derived from **4b** (n = 3), an uncharacterizable oil, prompted the development of an effective alternative route that involved ring closure of bis(3-chloropropyl) α,ω-polymethylenedicarbamates as demonstrated by conversions of **3**. Analytical difficulties encountered in the characterization of phosphorothioates in this series as deliquescent hydrated Na and/or Li salts prompted their isolation as dihydrogen phosphorothioates.

Polymethylene bridging of unlike units was subsequently demonstrated in the synthesis of the unsymmetrical phosphorothioate **8a** and the thiosulfate **8b**. Preparation of the precursors **2b** and **5c** was enabled by the alkylation of **2b** with 3-(4-chlorobutyl)-2-oxazolidinone (CBO).

Variations in *N,N′*-polymethylene bridging were achieved in the synthesis of the cyclohexylene derivatives **12a,b** (n = 0) and similar derivatives [**12a,b** (n = 1) and **13a,b**] according to sequences depicted in Scheme II. The intermediate dicarbamates **9a,b** were derived, respectively, from 1,4-cyclohexanediamine dihydrochloride and commercial trans and cis forms of 1,4-cyclohexanebis(methylamine). The dicarbamate derived from the impure cis diamine was contaminated with **9a** (n = 1), but solubility differences permitted the isolation of pure **9b**. HCl hydrolysis of the phosphorothioates **12a** (n = 1) and **13a** produced the corresponding dithiol dihydrochlorides **14a,b**, but high solubility precluded the isolation of a dithiol salt following hydrolysis of **12a** (n = 0) in HCl, HBr, or H_3PO_4 solns.[5]

In tests conducted in mice at Walter Reed Army Institute of Research by a previously described proce-

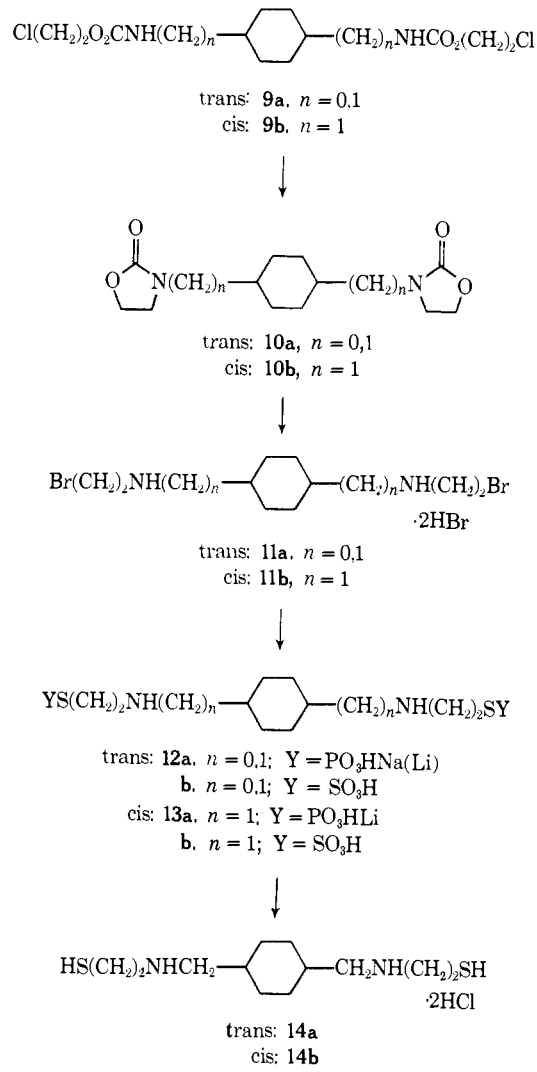
(2) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.* **9**, 563 (1966).

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

(4) The dry HBr cleavage of 3-substituted tetrahydro-2*H*-1,3-oxazin-2-ones was previously applied in the synthesis of *S*-3-(ω-aminoalkylamino)-propyl dihydrogen phosphorothioates [J. R. Piper, C. R. Stringfellow, Jr., R. D. Elliott, and T. P. Johnston, *J. Med. Chem.*, **12**, 236 (1969)].

(5) *Cf.* J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **32**, 1261 (1967).

SCHEME II



dure,[6] good radioprotection, *i. e.*, > 45% 30-day survival, was shown by none of the homologs and analogs of A (n = 3,4)[7] described above. Fair protection (27% survival) was observed with the bisthiosulfate **6c** (n = 9) and slight protection (13% survival) with the bisthiosulfate **6c** (n = 8); all other members of the **6** series were nonprotective. In contrast to A (n = 4), the unsymmetrical bisphosphorothioate **8a** was only slightly protective; and the bridged *S*-3-aminopropyl dihydrogen phosphorothioates **7a**, including n = 3,4 which correspond to A (n = 3,4), and thiosulfates **7b** were nonprotective. Except for the slightly protective **12b** (n = 0), the cyclohexane derivatives were also nonprotective.

Experimental Section[8]

3-(4-Chlorobutyl)-2-oxazolidinone (CBO).—Crude CBO (117 g from 0.700 mole of **1a**), prepd as previously described,[9] was dissolved in EtOAc (750 ml) (instead of EtOH), and the soln was clarified (Norit, Celite), then filtered through a compressed silica gel mat [silica gel H (Merck) 4-cm thick in a Buchner funnel 10 cm in diameter]. The undisturbed mat was then washed with EtOAc (750 ml). Removal of EtOAc from the filtrate gave the pure product as a limpid, nearly colorless oil in 88% yield (109 g); n^{25}D 1.4835, homogeneous by tlc. *Anal.* ($C_7H_{12}ClNO_2$) C, H, Cl, N.

3-[4-(2-Oxo-3-oxazolidinyl)butyl]tetrahydro-2*H*-1,3-oxazin-2-one (2b).—A soln of 0.281 mole each of **1b**[10] (28.4 g) and CBO (50.0 g) in DMF (250 ml) was added dropwise to a stirred mixt of NaH (11.3 g of 60% dispersion in oil, 0.282 mole) and DMF (250 ml), and the mixt was stirred at 25–30° for 18 hr. The DMF was then removed (H_2O aspirator, bath at ~70°), the residue was stirred with H_2O, and the aq mixt was extd several times with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ soln was evapd to give an oil, which crystd from EtOAc–Et_2O. The yield of pure **2b**, mp 74–75°, was 41% (28.1 g); ir (KBr) 1735 (2-oxazolidinone C=O) and 1675 cm^{-1} (tetrahydro-2*H*-1,3-oxazin-2-one C=O). *Anal.* ($C_{11}H_{18}N_2O_4$) C, H, N.

Bis(3-chloropropyl) α,ω-Polymethylenedicarbamates (3).—A soln of $ClCO_2(CH_2)_3Cl$ (0.100 mole) in C_6H_6 (60 ml) was added dropwise during 1 hr to a stirred soln of the appropriate α,ω-alkanediamine (0.100 mole) in C_6H_6 (60 ml) kept at 30–40°. The mixt was then refluxed 2 hr. Isolation procedures are described separately.

n = 2.—The cooled mixt was filtered, and the filtrate was evapd under reduced pressure while the air-dried solid on the funnel was stirred with H_2O. The H_2O-insol solid that remained was collected, dried *in vacuo* (25–30°, P_2O_5) to const wt (26.2 g from a 0.190-mole run), and combined with the small residue (2.3 g) obtd by evapn of the filtered reaction mixt. Recrystn of the combined samples from C_6H_6 gave pure **3** (n = 2), mp 106–107°, in 74% yield (21.4 g). *Anal.* ($C_{10}H_{18}Cl_2N_2O_4$) C, H, Cl, N.

n = 3.—The filtered reaction soln was concd (from 200 ml to ~75 ml); and pure **3** (n = 3), mp 71–73°, crystd in 77% yield (19.5 g from a 0.160-mole run). A sample recrystd from EtOH–H_2O had the same mp. *Anal.* ($C_{11}H_{20}Cl_2N_2O_4$) C, H, Cl.

n = 7.—A procedure like that described for the isolation of **3** (n = 2) but with EtOH as the recrystn solvent gave pure **3** (n = 7), mp 73–75°, in 77% yield (55.2 g from a 0.384-mole run). *Anal.* ($C_{15}H_{28}Cl_2N_2O_4$) C, H, Cl, N.

Bis(2-chloroethyl) *trans*-1,4-Cyclohexanedicarbamate (9a, n = 0).—$ClCO_2(CH_2)_2Cl$ (9.50 g, 66.4 mmoles) was added dropwise during 10 min to a rapidly stirred soln of *trans*-1,4-cyclohexanediamine·2HCl[11] (5.62 g, 30.0 mmoles) and NaOH (5.00 g, 0.125 mole) in H_2O (75 ml) kept at 30–35°. Stirring was contd 2 hr longer. Cryst **9a** (n = 0) sepd readily in 82% yield (8.08 g), mp 228–229° (identical with that of an anal. sample recrystd from EtOH). *Anal.* ($C_{12}H_{20}Cl_2N_2O_4$) C, H, Cl, N.

Bis(2-chloroethyl) (*trans*-1,4-Cyclohexylenedimethylene)dicarbamate (9a, n = 1).—A soln of $ClCO_2(CH_2)_2Cl$ (40.7 g, 0.285 mole) in Me_2CO (100 ml) was added dropwise to a stirred mixt of *trans*-1,4-cyclohexanebis(methylamine) (20.0 g, 0.142 mole), K_2CO_3 (59.2 g, 0.428 mole), and Me_2CO (1 l.). The resulting mixt was heated to boiling, refluxed 4 hr, and filtered while hot; solid on the funnel was washed with portions of warm Me_2CO (900 ml total). The filtrate and washings were combined and refrigd; a 16.3-g crop of **9a** (n = 1), mp 171–174°, was obtained. Concn of the filtrate gave two subsequent crops: 3.0 g, mp 169–171°, and 1.2 g, mp 165–167°. The crops were combined (total crude yield 40%) for use in the prepn of **10a** (n = 1). An anal. sample, recrystd from Me_2CO, had mp 174–175°. *Anal.* ($C_{14}H_{24}Cl_2N_2O_4$) C, H, N.

Bis(2-chloroethyl) (*cis*-1,4-Cyclohexylenedimethylene)dicarbamate (9b).—$ClCO_2(CH_2)_2Cl$ (83.9 g, 0.587 mole) was added dropwise to a stirred soln of commercial *cis*-1,4-cyclohexanebis(methylamine) (82.3 g, 0.587 mole) in DMF (500 ml) kept at 20–25°. The mixt was stirred at ~25° for 18 hr, filtered from pptd diamine·2HCl, and dild with H_2O (600 ml). The pptd oil soon solidified (dried wt 76.5 g). A refrigd soln of this material in MeCN (500 ml) deposited solid (11.5 g, mp 150–155°), which turned out to be crude **9a** (n = 1) (from the trans isomer present in the starting diamine). Concn of the filtrate to near dryness afforded nearly pure **9b** (57.8 g, mp 86–88°), which was further

(6) D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 723 (1969).

(7) Radioprotection of mice against 1000–1050 R (γ rays) after ip admin of A (n = 3) 15 min prior to irradiation: LD_{50} ~400 mg/kg, 93% survival at 250 mg/kg, 73% at 125; of A (n = 4) 30 min prior to irradiation: LD_{50} ~380 mg/kg, 73% survival at 200 mg/kg, 53% at 100.

(8) Melting points were taken on a Mel-Temp apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. Most of the analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

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

(10) B. L. Phillips and P. A. Argabright, *ibid.*, **3**, 84 (1966).

(11) P. A. S. Smith, *Org. React.*, **3**, 386 (1946); T. P. Johnston, G. S. McCaleb, P. A. Opliger, and J. A. Montgomery, *J. Med. Chem.*, **9**, 892 (1966).

purified by recrystn from the min vol of MeCN; yield 52% (53.9 g), mp 89–91°. A sample for anal. had mp 90–91° (from MeCN). *Anal.* ($C_{14}H_{24}Cl_2N_2O_4$) C, H, N.

3,3'-Polymethylenebis-2-oxazolidinones (4a, n = 7–10).—The following procedure for the prepn of **4a** (n = 7) is illustrative. A soln of 1,7-dibromoheptane[12] (44.4 g, 0.172 mole) and **1a** (29.9 g, 0.344 mole) in DMF (350 ml) was added dropwise to a stirred mixt of NaH (16.5 g of 50% dispersion in oil, 0.344 mole) in DMF (350 ml) at a rate so that the temp did not exceed 45°. The mixt was then stirred overnight at ~25°. Following removal of the solvent by distn *in vacuo* (H_2O aspirator, bath to 75°), the residue was stirred with H_2O (300 ml), and the mixt was extd with $CHCl_3$ (3 × 150 ml). Removal of solvent from the dried ($MgSO_4$) soln left **4a** (n = 7) as a yellow oil. The homologs **4a** (n = 8–10) were obtd similarly and each was used successfully as such for conversions to the corresponding **5a**.

3,3'-Polymethylenebis(tetrahydro-2*H*-1,3-oxazin-2-ones) (4b, Table I). n = 2, 3, 7 from 3.—The procedure for the prepn of **4b** (n = 2) is illustrative. A soln of **3** (n = 2) (21.0 g, 69.7 mmoles) in DMF (200 ml) was added dropwise to a stirred mixt of NaH (5.57 g of 60% dispersion in oil, 0.140 mole) and DMF (200 ml) at ~30°. The mixt was stirred 18 hr at 25–30°. Removal of the solvent from the filtered mixt by distn *in vacuo* (H_2O aspirator, bath to 75°) left crude **4b** (n = 2), which was purified as indicated in Table I.

TABLE I

3,3'-POLYMETHYLENEBIS(TETRAHYDRO-2*H*-1,3-OXAZIN-2-ONES) (**4b**)

n	Yield, %	Mp, °C	Formula	Analyses
2[a]	82	135–136	$C_{10}H_{16}N_2O_4$	C, H, N
3[a]	87	84–86	$C_{11}H_{18}N_2O_4$	C, H, N
4[a]	60	123–124	$C_{12}H_{20}N_2O_4$	C, H, N
5	65[b]	Oil[b]	$C_{13}H_{22}N_2O_4$	
6	82[b]	60–62[c]	$C_{14}H_{24}N_2O_4$	C, H, N
7	95[b]	Oil[b]	$C_{15}H_{26}N_2O_4$	
8	86[b]	Semisolid[b]	$C_{16}H_{28}N_2O_4$	
9	86[b]	Oil[b]	$C_{17}H_{30}N_2O_4$	
10[d]	58	82–83	$C_{18}H_{32}N_2O_4$	C, H, N

[a] Residual oil crystd when stirred with EtOAc and was recrystd from EtOAc. [b] Used without purification for conversion to corresponding **5b**. [c] A sample for anal. was obtained by stirring a portion of crude semisolid product with PhMe. [d] Cryst residue was recrystd from PhMe.

n = 4, 5, 6, 8, 9, 10 from 1b.—The alkylation of **1b** with α,ω-dibromoalkanes was carried out in the manner described above for the conversions of **1a** to **4a** (n = 7–10).

N,N'-Bis(2-bromoethyl)ethylenediamine Dihydrobromide (5a, n = 2).—3,3'-Ethylenebis-2-oxazolidinone[13] (**2a**) was obtd in crude form after a stirred mixt of 23.0 mmoles each of **1a** (2.00 g), K_2CO_3 (3.18 g), and 3-(2-chloroethyl)-2-oxazolidinone (3.45 g) in DMF (10 ml) had been heated at 110–120° for 18 hr, filtered, evapd, and extd with $CHCl_3$. Removal of the $CHCl_3$ left crude **2a**, which was treated with 30% dry HBr–AcOH soln in a manner like that described below for the prepn of **5a** (n = 9). Recrystn from H_2O–EtOH gave 1.96 g (20% overall yield) of pure **5a** (n = 2), mp 201–204° dec, identical (mp, mmp, and ir spectrum) with a sample prepd earlier by a reported procedure.[2]

N,N'-Bis(2-bromoethyl)-α,ω-alkanediamine Dihydrobromides (5a, n = 7–10; Table II).—Prepn of **5a** (n = 7) is given as a typical example. A soln of the sample of crude **4a** (n = 7) described above in 30% dry HBr–AcOH (600 ml) was stirred at ~25° for 24 hr, during which a crystn product sepd. Et_2O (600 ml) was added, and the collected ppt was recrystd from MeOH.

N,N'-Bis(3-bromopropyl)-α,ω-alkanediamine dihydrobromides (5b, n = 2–10; Table II) were prepd by the following general procedure. A stirred mixt of the appropriate **4b** in 30% dry HBr–AcOH soln (5–7 ml/1 g of **4b**) was gradually heated to boiling during 3–4 hr and was refluxed 1 hr. Sepn of product usually commenced before all **4b** had dissolved. The cooled mixt was thinned with Et_2O; the cryst ppt was collected, washed with Et_2O, and recrystd from MeOH.

TABLE II

N,N'-BIS(ω-BROMOALKYL)-α,ω-ALKANEDIAMINE DIHYDROBROMIDES (**5a, b**)

Compd	n	Yield, %	Mp, °C dec	Formula	Analyses
5a	7	62[a]	263–265	$C_{11}H_{24}Br_2N_2 \cdot 2HBr$	C, H, Br
	8	66[a]	265–267	$C_{12}H_{26}Br_2N_2 \cdot 2HBr$	C, H, Br, N
	9	64[a]	268–270	$C_{13}H_{28}Br_2N_2 \cdot 2HBr$	C, H, Br, N
	10	69[a]	259–261	$C_{14}H_{30}Br_2N_2 \cdot 2HBr$	C, H, Br, N
5b	2	92[b]	226–227	$C_8H_{18}Br_2N_2 \cdot 2HBr$	C, H, Br, N
	3	99[b]	265–266	$C_9H_{20}Br_2N_2 \cdot 2HBr$	C, H, Br
	4	95[b]	271–272	$C_{10}H_{22}Br_2N_2 \cdot 2HBr$	C, H, Br, N
	5	81[c]	260–262	$C_{11}H_{24}Br_2N_2 \cdot 2HBr$	C, H, Br
	6	39[c]	259–260	$C_{12}H_{26}Br_2N_2 \cdot 2HBr$	C, H, Br
	7	50[c]	249–251	$C_{13}H_{28}Br_2N_2 \cdot 2HBr$	C, H, Br, N
	8	58[c]	260–261	$C_{14}H_{30}Br_2N_2 \cdot 2HBr$	C, H, Br
	9	56[c]	270–271	$C_{15}H_{32}Br_2N_2 \cdot 2HBr$	C, H, Br, N
	10	56[b]	266–267	$C_{16}H_{34}Br_2N_2 \cdot 2HBr$	C, H, Br

[a] Overall yield from 2 steps. [b] From pure **4b** precursor. [c] Based on amt of crude **4b** used.

N-(2-Bromoethyl)-N'-(3-bromopropyl)-1,4-butanediamine dihydrobromide (5c) was prepd from **2b** by the method used for prepg the **5b** types and recrystd from MeOH–Et_2O; yield 72% (38.7 g from 0.113 mole of **2b**), mp 268–270° dec. *Anal.* $C_9H_{20}Br_2N_2 \cdot 2HBr$) C, H, N; Br: calcd, 66.88; found, 67.41.

3,3'-(*trans*-1,4-Cyclohexylene)bis-2-oxazolidinone (10a, n = 0).—A soln of **9a** (n = 0) (10.3 g, 31.4 mmoles) in DMF (200 ml) was added dropwise during 1 hr to a stirred suspension of NaH (2.51 g of 60% dispersion in oil, 62.9 mmoles) in DMF (100 ml) at 25°. The mixt was stirred at ~25° for 18 hr, heated at 100° for 30 min, cooled, and filtered. The solid residue that remained following removal of the DMF by distn *in vacuo* comprised most of the product, but a small amt was obtd by washing the solid filtered from the reaction mixt with H_2O. The 2 portions were combined and recrystd from EtOH to give pure **10a** (n = 0), mp 261–262°, in 83% yield (6.60 g). *Anal.* ($C_{12}H_{18}N_2O_4$) C, H, N.

3,3'-(*trans*-1,4-Cyclohexylenedimethylene)bis-2-oxazolidinone (10a, n = 1).—A soln of **9a** (n = 1) (20.5 g, 57.6 mmoles) in DMF (100 ml) was added dropwise to a stirred mixt of NaH (5.54 g of 50% dispersion in oil, 0.115 mole) and DMF (250 ml), and the mixt was stirred at ~25° for 20 hr. Solid material, which contd most of the product, was filtered from the mixt. Removal of DMF from the filtrate left a solid residue, which was stirred with cyclohexane, collected, and recrystd from $CHCl_3$–ligroin (bp 30–60°) to give 2.5 g of material with mp 205–210°. The solid matter filtered from the reaction mixt was extd with boiling $CHCl_3$ (500 ml), and the filtered $CHCl_3$ soln was dild with an equal vol of ligroin (bp 30–60°) to give cryst ppt (12.5 g), mp 212–214°. The crops were combined and recrystd from MeOH–Et_2O to give **10a** (n = 1), mp 213–216°, in 80% yield (13.0 g). An anal. sample from a trial run had mp 217–219°. *Anal.* ($C_{14}H_{22}N_2O_4$) C, H, N.

3,3'-(*cis*-1,4-Cyclohexylenedimethylene)bis-2-oxazolidinone (10b).—A soln of **9b** (47.0 g, 0.132 mole) in DMF (200 ml) was added dropwise to a stirred mixt of NaH (10.6 g of 60% dispersion in oil, 0.265 mole) and DMF (400 ml). The mixt was stirred at ~25° for 20 hr, filtered, and the solvent was removed by distn *in vacuo*. The yellow oil that remained crystd from $CHCl_3$ (200 ml) dild with ligroin (bp 30–60°, 100 ml), and crude **10b** thus obtd was purified by recrystn from MeCN; yield 59% (21.9 g), mp 109–110°. *Anal.* ($C_{14}H_{22}N_2O_4$) C, H, N.

N,N'-Bis(2-bromoethyl)-*trans*-1,4-cyclohexanediamine Dihydrobromide (11a, n = 0).—A mixt of **10a** (n = 0) (6.60 g, 25.9 mmoles) and 30% dry HBr–AcOH (130 ml) was stirred at ~25° for 20 hr. Soln did not occur, and the rate of CO_2 evoln (observed in a H_2O-charged gas absorption trap) was slow. The mixt was gradually heated during 2 hr to near boiling and was kept near reflux for 4 hr. The mixt, now contg insol **11a** (n = 0), was cooled. Et_2O (200 ml) was added, and the ppt was collected and washed with Et_2O and EtOH; yield 99% (12.6 g), mp > 260° indefinite (dec). *Anal.* ($C_{10}H_{20}Br_2N_2 \cdot 2HBr$) C, H, Br.

N,N'-Bis(2-bromoethyl)-*trans*-1,4-cyclohexanebis(methylamine) Dihydrobromide (11a, n = 1).—A soln of **10a** (n = 1)

(12) Prepd from com 1,7-heptanediol by the general procedure of W. L. McEwen ("Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 227); yield 76%, bp 123–125° (11 mm) [lit. bp 123° (11 mm); A. Mueller and W. Vanc, *Ber.*, **77B**, 669 (1944)].

(13) The prepn of pure cryst **2a** by another method has been reported [R. Delaby, P. Chabrier, and H. Nader, *C. R. Acad. Sci.*, **235**, 376 (1952)].

TABLE III

S-SUBSTITUTED HYDROGEN THIOSULFATES

Compd	n	Yield, %	Mp, °C dec	Formula[a]
6c	7	78	193–195	$C_{11}H_{26}N_2O_6S_4$
	8	83	192–194	$C_{12}H_{28}N_2O_6S_4$
	9	88	189–191	$C_{13}H_{28}N_2O_6S_4$
	10	94	196–197	$C_{14}H_{32}N_2O_6S_4$
7b	2	68	197–198	$C_8H_{20}N_2O_6S_4$
	3	95	205–207	$C_9H_{22}N_2O_6S_4$
	4	66	208–210	$C_{10}H_{24}N_2O_6S_4$
	5	79	220–222	$C_{11}H_{26}N_2O_6S_4$
	6	89	223–225	$C_{12}H_{28}N_2O_6S_4$
	7	42	197–198	$C_{13}H_{30}N_2O_6S_4$
	8	94	215–217	$C_{14}H_{32}N_2O_6S_4$
	9	58	193–195	$C_{15}H_{34}N_2O_6S_4$
	10	95	199–201	$C_{16}H_{36}N_2O_6S_4$
8b		54	205–208	$C_9H_{22}N_2O_6S_4$
12b	0	96	225–227	$C_{10}H_{22}N_2O_6S_4$
	1	88	215–220	$C_{12}H_{26}N_2O_6S_4$
13b		80	216–218	$C_{12}H_{26}N_2O_6S_4$

[a] *Anal.* C, H, N, S.

TABLE IV

S-SUBSTITUTED PHOSPHOROTHIOATES

Compd	n	Yield, %	Mp, °C dec	Formula[a]
6a	7	100		$C_{11}H_{26}Li_2N_2O_6P_2S_2\cdot 4H_2O$
	8	100		$C_{12}H_{28}Li_2N_2O_6P_2S_2\cdot 3.5H_2O$
	9	100		$C_{13}H_{30}Li_2N_2O_6P_2S_2\cdot 4H_2O$
6b		91		$C_{14}H_{32}N_2Na_2O_6P_2S_2\cdot 7H_2O$
7a	2	96	144–147	$C_8H_{22}N_2O_6P_2S_2$
	3	90	165–167	$C_9H_{24}N_2O_6P_2S_2$
	4	99	147–149	$C_{10}H_{26}N_2O_6P_2S_2\cdot 0.5H_2O$
	5	83	Indefinite[b]	$C_{11}H_{28}N_2O_6P_2S_2\cdot 0.5H_2O$
	6	75	162–164	$C_{12}H_{30}N_2O_6P_2S_2\cdot 0.5H_2O$
	7	98	138–140	$C_{13}H_{32}N_2O_6P_2S_2\cdot 0.5H_2O$
	8	91	155–157	$C_{14}H_{34}N_2O_6P_2S_2$
	9	89	123–125	$C_{15}H_{36}N_2O_6P_2S_2\cdot 0.5H_2O$
	10	87	Indefinite[c]	$C_{16}H_{38}N_2O_6P_2S_2$
8a		92	Indefinite[d]	$C_3H_{24}N_2O_6P_2S_2\cdot 1.5H_2O$
12a	0	89		$C_{10}H_{22}N_2Na_2O_6P_2S_2\cdot 5H_2O$
	1	96		$C_{12}H_{26}Li_2N_2O_6P_2S_2\cdot 5.5H_2O$
13a		96		$C_{12}H_{26}Li_2N_2O_6P_2S_2\cdot 4.5H_2O$

[a] *Anal.* C, H, N, P, S except for discrepancies in the following compds: **6a**, n = 9 (H: calcd, 7.34; found 6.80); **7a**, n = 3 (S: calcd, 16.77; found, 17.3); **7a**, n = 9 (P: calcd, 13.03; found, 12.47); **12a**, n = 1 (H: calcd, 6.99; found, 6.21). [b] Gradually formed opaque melt at ~130-140°; contd heating caused frothing and eventually a clear melt. [c] Formed opaque melt beginning at ~100°. [d] Formed opaque melt beginning at ~50°

(12.5 g, 44.3 mmoles) in 30% dry HBr–AcOH (100 ml) was stirred at ~25° for 48 hr (slow CO_2 evoln observed), then refluxed for 72 hr, cooled, and dild with Et_2O. The collected product, washed with Et_2O and air-dried, was recrystd from H_2O; yield 75% (17.2 g), mp ~300° dec. *Anal.* Calcd ($C_{12}H_{24}Br_2N_2\cdot 2HBr$) C, H, Br.

N,N'-**Bis(2-bromoethyl)**-*cis*-**1,4-cyclohexanebis(methylamine) Dihydrobromide** (**11b**).—A soln of **10b** (21.0 g, 74.4 mmoles) in 30% dry HBr–AcOH (150 ml) was gradually heated to boiling and refluxed for 72 hr; 25-ml addns of 30% dry HBr–AcOH were made at 24- and 48-hr intervals. The cooled, Et_2O-dild (500 ml) mixt gave cryst **11b**, mp 265–267° dec, in 98% yield (37.9 g). Recrystn from aq 98% EtOH afforded pure **11b**, mp 269–271° dec, in 88% yield (33.9 g). *Anal.* ($C_{12}H_{24}Br_2N_2\cdot 2HBr$) C, H, Br, N.

S-Substituted Hydrogen Thiosulfates (**6c, 7b, 8b, 12b, 13b**; **Table III**). **I.** *N,N'*-**Polymethylenebis(*S*-2-aminoethyl hydrogen thiosulfates)** (**6c**) were prepd by heating a soln of the appropriate **5a** with $Na_2S_2O_3\cdot 5H_2O$ (2 molar equivs) in H_2O (300 ml/0.1 mole of $Na_2S_2O_3$) at 90–95° for 1 hr. The pure products crystd directly from the reaction solns and were dried *in vacuo* (25–30°, P_2O_5).

II. *N,N'*-**Polymethylenebis(*S*-3-aminopropyl hydrogen thiosulfates)** (**7b**). n = **2, 5–10.**—The procedure used was like that described above for the prepn of **6c** (n = 7–10). Minimal vols of H_2O were used in the reaction soln. Compds **7b** (n = 2) and **7b** (n = 7) were obtd pure after 2 recrystns from H_2O; the other compds of this group did not require recrystn.

n = **3.**—The product sepd from the reaction soln after the addn of EtOH and was recrystd from H_2O–EtOH.

n = **4.**—A soln of **5a** (n = 4) (4.92 g, 10.0 mmoles) and $MgS_2O_3\cdot 6H_2O$ (4.89 g, 20.0 mmoles) in MeOH (100 ml) was refluxed (pptn commenced after ~5 min) with stirring for 3 hr. Product filtered from the cooled mixt was recrystd successively from H_2O and H_2O–EtOH.

III. *S,S'*-**3,8-Diazaundecamethylene Bis(hydrogen thiosulfate)** (**8b**).—A soln of **5c** (10.0 g, 20.8 mmoles) and $MgS_2O_3\cdot 6H_2O$ (10.16 g, 41.6 mmoles) in MeOH (50 ml) was refluxed 1 hr and cooled and the sepd solid was recrystd from H_2O–EtOH.

IV. *N,N'*-(*trans*-**1,4-Cyclohexylene)bis(*S*-2-aminoethyl hydrogen thiosulfate)** (**12b**, n = **0**).—Solid $Na_2S_2O_3\cdot 5H_2O$ (4.55 g, 18.3 mmoles) was added to a soln of **11a** (n = 0) (4.49 g, 9.16 mmoles) in H_2O (40 ml) at 90–95°. The resulting soln was boiled momentarily before cryst product began sepg. Solid filtered from the cooled mixt was washed successively with H_2O, EtOH, and Et_2O, then air-dried. This material (3.58 g) was stirred with H_2O (50 ml), NaOH soln (1 *N*, 18.2 ml; 2 molar equivs) was added, and the resulting soln was filtered before being treated with glac AcOH (1.2 ml). Cryst **12b** (n = 0) sepd readily.

N,N'-(*trans*-**1,4-Cyclohexylenedimethylene)bis(*S*-2-aminoethyl hydrogen thiosulfate)** (**12b**, n = 1) was prepd in essentially the same manner as **12b** (n = 0).

V. *N,N'*-(*cis*-**1,4-Cyclohexylenedimethylene)bis(*S*-2-aminoethyl hydrogen thiosulfate)** (**13b**).—A soln of $Na_2S_2O_3\cdot 5H_2O$ (4.97 g, 20.0 mmoles) in H_2O (25 ml) was added to a boiling soln of **11b** (5.18 g, 10.0 mmoles) in H_2O (50 ml), and the soln was refluxed briefly. Cryst **13b** sepd from the cooled soln and was recrystd from H_2O.

S-Substituted Phosphorothioates (**6a, 6b, 7a, 8a, 12a, 13a**; **Table IV**). **I.** *N,N'*-**Polymethylenebis(*S*-2-aminoethyl lithium hydrogen phosphorothioates)** (**6a**, n = **7–9.**).—$Li_3SPO_3\cdot 6H_2O$[2] (9.60 g, 40.0 mmoles) was dissolved in H_2O (80 ml) and *N,N*-dimethylacetamide (DMAC) (20 ml) was added. The appropriate **5a** (22.4 mmoles) was added in powd form followed by more DMAC (20 ml), and the mixt was stirred at ~25° for 2 hr. The nearly clear soln was clarified by filtration, then added dropwise during 30 min to rapidly stirred EtOH (600 ml). The ppt that formed was collected, washed with EtOH followed by Et_2O, kept *in vacuo* (no desiccant) for 30 min, and then allowed to equilibrate at const 58% relative humidity.

II. *N,N'*-**Decamethylenebis(*S*-2-aminoethyl sodium hydrogen phosphorothioate)** (**6b**).—Na_3SPO_3 (3.53 g, 19.6 mmoles) was dissolved in H_2O (20 ml) at 40–45°, and the stirred soln was cooled rapidly to 20° to cause partial sepn of Na_3SPO_3 as finely divided particles. DMF (10 ml) was added followed by the gradual addn during 30 min of powd **5a** (n = 10) (5.48 g, 10.0 mmoles). Sepn of product began just after the last addn, and the thick mixt was stirred 2 hr longer, then thinned with EtOH. The collected ppt was dissolved in H_2O (60 ml) and repptd by dropwise addn to stirred EtOH (600 ml). The white solid was collected, washed with EtOH, and dried *in vacuo* (25°, NaOH pellets). When the dried product (4.5 g) was exposed to ambient condns of the lab a continuous wt gain was noted for 8–9 hr. The material was then allowed to equilibrate at const 58% relative humidity.

III. *N,N'*-**Polymethylenebis(*S*-3-aminopropyl dihydrogen phosphorothioates)** (**7a**). n = **2, 4.**—The procedure for the reaction was like that described above for **6b**. Stirring for ~2 hr after the **5b** had been added gave a nearly clear soln, which was filtered and treated, successively, with glac AcOH (100 ml) and EtOH (750 ml). After the mixt had been stirred 30 min, the white solid was collected, washed with EtOH followed by Et_2O, and air-dried (50% relative humidity).

n = **3, 5, 6.**—The powd **5b** (12.0 mmoles) was added during 10 min to a stirred soln of $Li_3SPO_3\cdot 6H_2O$ (5.52 g, 23.0 mmoles) in H_2O (45 ml). Soln soon occurred, and DMAC (25 ml) was added. After 30 min, the soln was added dropwise to stirred EtOH (400 ml); the solid that sepd was collected, washed with EtOH followed by Et_2O, air-dried, and then dissolved in H_2O (25 ml). The soln was treated with glac AcOH (50 ml) followed by EtOH (80 ml), then refrigd for 1–2 days. The cryst ppt was collected, washed with EtOH and Et_2O, and dried *in vacuo* (25–30°, P_2O_5).

(n = **7–10**).—The procedure was essentially the same as that

described above for **7a** (n = 2, 4) except that the vols of H_2O and DMF were increased 2.5–3 times.

IV. *S,S'*-3,8-Diazaundecamethylenebis(dihydrogen phosphorothioate) (8a) was prepared by the procedure used for the prepn of **7a** (n = 2,4).

V. *N,N'*-(*trans*-1,4-Cyclohexylene)bis(*S*-2-aminoethyl sodium hydrogen phosphorothioate) (12a, n = 0).—Powd **11a** (n = 0) (4.90 g, 10.0 mmoles) was added in portions to a stirred partial soln of Na_3SPO_3 (3.60 g, 20.0 mmoles) in H_2O (20 ml). More H_2O (20 ml) was added, but soln had not occurred after 1 hr of stirring. Addnl H_2O (40 ml) caused complete soln. After 10 min the soln was treated with EtOH to cause pptn of cryst product, which was collected and repptd from H_2O soln with EtOH. The collected product, washed with EtOH and Et_2O, was air-dried.

***N,N'*-(*trans*-1,4-Cyclohexylenedimethylene)bis(*S*-2-aminoethyl lithium hydrogen phosphorothioate) (12a, n = 1).**—Gradual addn of powd **11a** (n = 1) (7.51 g, 14.5 mmoles) to a stirred soln of $Li_3SPO_3 \cdot 6H_2O$ (6.72 g, 28.0 mmoles) in H_2O (75 ml) and DMAC (50 ml) was followed by a 3-hr stirring period. The resulting nearly clear soln was filtered and added dropwise to stirred EtOH (600 ml) to ppt hydrated **12a** (n = 1) as white solid, which was collected, washed with EtOH, air-dried, and then equilibrated at const 58% relative humidity.

VI. *N,N'*-(*cis*-1,4-Cyclohexylenedimethylene)bis(*S*-2-aminoethyl lithium hydrogen phosphorothioate) (13a) was prepd in the manner described for **12a** (n = 1).

2,2'-[*trans*-1,4-Cyclohexylenebis(methyleneimino)]diethanethiol Dihydrochloride (14a).—A soln of **12a**(n = 1)$\cdot 5.5H_2O$ (4.00 g, 7.50 mmoles) in 3 *N* HCl (20 ml) was heated at 90–95° for 10 min. Diln with EtOH afforded cryst **14a**, which was collected under N_2, washed with EtOH followed by Et_2O, and dried *in vacuo* (25–30°, P_2O_5); yield 86% (2.16 g), mp indefinite (gradual decompn at elevated temp without melting). *Anal.* ($C_{12}H_{26}N_2S_2 \cdot 2HCl$) C, H, N, S, SH.

2,2'-[*cis*-1,4-Cyclohexylenebis(methyleneimino)]diethanethiol Dihydrochloride (14b).—Hydrolysis of **13a**$\cdot 4.5H_2O$ (5.00 g, 9.70 mmoles) in 3 *N* HCl (25 ml) at 90–95° for 15 min was followed by diln with EtOH (250 ml) followed by Et_2O (250 ml); cryst **14b** sepd gradually. After refrign (4 hr), the product was collected under N_2, washed successively with EtOH–Et_2O soln (1:1), cold EtOH, then Et_2O, and dried *in vacuo* (25–30°, P_2O_5); yield 63% (2.06 g), mp 232–233° dec. *Anal.* ($C_{12}H_{26}N_2S_2 \cdot 2HCl$) C, H, N, S.

***N,N'*-Polymethylenebis(*S*-2-aminoethyl thioacetate) dihydrobromides (6d; n = 8, 9)** were prepd by treatment of AcSNa (prepd *in situ* from freshly distd AcSH and $NaHCO_3$ or NaOMe) with **5a** (n = 8,9) in DMF in a manner similar to that described earlier for the prepn of *S*-2-(2-piperidyl)ethyl thioacetate$\cdot$2HBr.[14] The products were recrystd several times from EtOH. The yield of pure **6d** (n = 8), mp 209–210°, was 20%; that of pure **6d** (n = 9), mp 210–213°, was 29%. *Anal.* [$C_{16}H_{32}N_2O_2S_2 \cdot 2HBr$, **6d** ($n$ = 8)] C, H, Br, N, S. [$C_{17}H_{34}N_2O_2S_2 \cdot 2HBr$, **6d** ($n$ = 9)] C, H, Br, N, S.

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

2-Amino-5-nitroimidazoles

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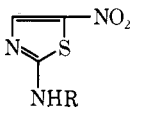
2-Amino-5-nitrothiazole[1] (**1**) and its *N*-acetyl derivative (**2**) are known to possess activity against turkey blackhead (histomoniasis). In connection with another problem on which we were working, it came to our attention that no imidazole analogs of **1** or **2** were known. Their synthesis was therefore undertaken.



1, R = H
2, R = Ac

Two routes appeared to offer possibilities of obtaining the desired analogs: (a) nitration of a 2-amino- or 2-acetamidoimidazole; and (b) reaction of a 2-bromo-5-nitroimidazole with an amine or amine derivative. Nitrations were attempted using H_2SO_4–HNO_3, HNO_3–BF_3, N_2O_5–BF_3, acetyl nitrate, trifluoroacetyl nitrate, and amyl nitrate. No evidence of the desired products could be found and reactions most often led to destruction of the imidazole ring.

The bromoimidazole used for the second route was 2-bromo-4(5)-methyl-5(4)-nitroimidazole[2] (**3**), which was more conveniently prepared than 2-bromo-4(5)-nitroimidazole, and could be expected to show similar reactivity. However, treatment of I with piperidine, hydrazine, and potassium phthalimide gave no evidence of reaction, even under forcing conditions.

Shortly after these reactions were attempted, Barlin[3] reported the preparation of 1-methyl-5-nitro-2-piperidinoimidazole by refluxing 2-bromo-1-methyl-5-nitroimidazole with piperidine in EtOH, a reaction which we had previously attempted with **3**. A sample of **3** was methylated with Me_2SO_4 to give 2-bromo-1,4-dimethyl-5-nitroimidazole[2] (**4**). Reaction of **4** with piperidine in refluxing EtOH proceeded smoothly to give a high yield of 1,4-dimethyl-5-nitro-2-piperidinoimidazole (**5**). Similarly, reaction of **4** with NH_3 in EtOH in a sealed tube at 75° gave 2-amino-1,4-dimethyl-5-nitroimidazole (**6**). Acetylation of **6** gave a low yield of 2-acetamido-1,4-dimethyl-5-nitroimidazole (**7**).

Biological Screening.—Compds **5, 6**, and **7** were screened for antiprotozoal activity against *Eimeria tenella* and *E. acervulina* in chickens[4] and *Histomonas meleagridis* in turkeys;[5] **6** was also tested for activity against *Trichomonas vaginalis*[6] at The National Drug Co. No antiprotozoal activity was found. Additional screening for anthelmintic and antibacterial activity[7] also gave negative results.

Experimental Section

Melting points were taken in open capillary tubes with a calibrated thermometer using a Thomas-Hoover melting point apparatus. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Compounds were analyzed for C, H, and N, and all values were within $\pm 0.2\%$ of theoretical. Solvents were removed under vacuum on a rotary evaporator. The prepns of 2-bromo-1,4-dimethyl-5-nitroimidazole[2] and its precursors [2-bromo-4(5)-methyl-5(4)-nitroimidazole,[2] 4(5)-methyl-5(4)-nitroimidazole,[8] and 4,(5)-methylimid-

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(1) Enheptin®.

(2) F. L. Pyman and G. M. Timmis, *J. Chem. Soc.*, **123**, 494 (1923).

(3) G. B. Barlin, *ibid.*, *B*, 641 (1967).

(4) C. A. Johnson and J. O'Connor, *Poultry Sci.*, **44**, 578 (1965).

(5) E. W. Berndt, H. Van Essen, and B. G. Held, *J. Med. Chem.*, **12**, 371 (1969).

(6) S. R. M. Bushby and F. C. Copp, *J. Pharm. Pharmacol.*, **7**, 112 (1955).

(7) H. K. Kim, H. K. Yaktin, and R. E. Bambury, *J. Med. Chem.*, **13**, 238 (1970).

(8) W. E. Allsebrook, J. M. Gulland, and L. F. Story, *J. Chem. Soc.*, 232 (1942).