compound solidified in the condenser. The products were purified by recrystallization: **18** ($CHCl_3$–CCl_4), **19** and **21** (CCl_4–hexane), and **20** (CCl_4). Compounds **18** and **21** were further purified by recrystallization from diethyl ether.

With the exception of **22**, all of the compounds prepared in this study are stable at room temperature; on standing, **22** becomes highly viscous and eventually sets to a semisolid. With two exceptions, the products also appear to be photolytically stable. The low yields obtained in the syntheses of the heteroarylphosphonates **26** and **27** are apparently a result of their photolytic instability. The photolysis of 50-mg samples of these compounds at 0° for 24 hr results in approximately 50% decomposition to polymeric materials. Additionally, the low yield of the furylphosphonate **27** can be attributed in part to the purity of the reactant, 2-iodofuran. The iodofuran, prepared by the method of Gilman and Wright,[20] is apparently unstable since, upon distillation, the pure compound turned black and tarry almost immediately. As a consequence, impure (*ca.* 80–90% by pmr analysis) 2-iodofuran was used in synthetic reactions.

Photoinitiated Reactions of Nitroarenes with Trialkyl Phosphites.—Similar procedures were employed in all reactions; the reaction with *o*-iodonitrobenzene will be cited as an example. A mixture of 7.47 g (0.03 mole) of the arene and 18.60 g (0.15 mole) of trimethyl phosphite was irradiated at −8° for 24 hr. Glpc analysis of the reaction mixture showed it to contain trimethyl phosphite, trimethyl phosphate, and the arene.[21] Careful distillation (pot temperature <50° until all phosphite had been removed) gave these fractions: (1) bp 26–35° (20 mm), 14.66 g; (2) bp 27–84° (0.13 mm), 0.48 g; (3) bp 84–87° (0.13 mm), 5.85 g. Fractions 1 and 2 were identified as the phosphite and phosphate, respectively, by glpc comparisons with authentic samples. Fraction 3 solidified to a yellow material which was identified as the starting arene by melting point and infrared spectral comparisons with an authentic sample.

Pmr Spectra.—In addition to the ester and aromatic proton resonances cited in the text, resonances attributable to nuclear substituents were observed for most of the arylphosphonates prepared in this study. Unless otherwise noted, all spectra were recorded on solutions of the phosphonate in CCl_4. The following resonances were observed: **5** (CH_3, τ 7.50); **6** (CH_3, 7.48); **7** (CH_3, 7.62); **8** (CH_3, 7.60); **9** (CH_3, 7.95); **10** (CH_3, 7.93); **11** (C-CH_2, 6.87, C-C-CH_3, 8.75); **12** (OCH_3, 6.17); **13** (OCH_3, 6.32); **14** (OCH_3, 6.20); **15** (OCH_3, 6.12); **16** (OCH_3, 6.23); **17** (NH_2, 4.38); **18** (NH_2, 5.50 ($CDCl_3$)); **19** (OH, 0.32 ($CDCl_3$)); **20** (OH, 0.48 ($CDCl_3$)); **21** (OH, 0.57 ($CDCl_3$)); **22** (CHO, −0.60); **23** (CH_3, 7.43, J_{PH} = 1.7 Hz); **24** (OCH_3, 6.22 ppm).

Registry No.—**5**, 6840-23-9; **6**, 15286-11-0; **7**, 15286-12-1; **8**, 15286-13-2; **9**, 6840-25-1; **10**, 1754-46-7; **11**, 15286-15-4; **12**, 15286-16-5; **13**, 15286-17-6; **14**, 15286-18-7; **15**, 15286-19-8; **16**, 3762-33-2; **17**, 15286-21-2; **18**, 15286-22-3; **19**, 15286-23-4; **20**, 15286-24-5; **21**, 15286-25-6; **22**, 15286-26-7; **23**, 15286-27-8; **24**, 15286-28-9; **25**, 15286-29-0; **26**, 13640-94-3; **27**, 13640-97-6.

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(20) H. Gilman and F. Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).

(21) Glpc analyses were carried out on an F & M Model 300 chromatograph using a 6-ft stainless steel 20% silicone oil 710 on 60–80 mesh Chromosorb P column. The injection port was maintained at 160° and the column temperature was programmed as follows: 75° (0 min), 150° (22 min). A helium flow rate of 50 cc/min was used. Under these conditions, trimethyl phosphate and *o*-iodonitrobenzene had retention times of 13.5 and 42.0 min, respectively.

Derivatives of 2-Aminoethanethiol Related to Spermine and Spermidine[1]

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The development of methods involving hydrogen bromide cleavage of 3-substituted 2-oxazolidinones and concomitant detosylation of tosylamide functions in the substituent made possible the synthesis of N-(2-bromoethyl)amine hydrobromides from which potentially radioprotective compounds related to spermine and spermidine were derived. Thus, the method applied to N,N′-bis[3-(2-oxo-3-oxazolidinyl)propyl]-N,N′-tetramethylenebis-*p*-toluenesulfonamide (**3**) provided the spermine-related N,N′-bis[3-(2-bromoethylamino)propyl]-1,4-butanediamine tetrahydrobromide (**4**), which was converted into the corresponding bis Bunte salt **5a**, bisphosphorothioate **5b**, and dithiol **5c**. Synthesis of the spermidine-related N-[3-(2-bromoethylamino)propyl]-1,4-butanediamine trihydrobromide (**11**) involved acetyl protection of the terminal amino group. Retention of acetamido and phthalimido groups during oxazolidinone ring cleavage enabled the synthesis of the spermidine-related S-2-[3-(4-acetamidobutylamino)propylamino]ethylphosphorothioic acid (**13**) and the analogous phthalimido-substituted Bunte salt **22a** and phosphorothioate **22b**. Special problems of stoichiometry encountered in displacement reactions of polyfunctional N-(2-bromoethyl)amine hydrobromides with acid-labile thio anions are exemplified by the conversion of **11** into the corresponding Bunte salt **12a** and phosphorothioate **12b**; the thiol **12c**, as well as the thiol **5c**, were conveniently prepared by acid hydrolysis of the corresponding phosphorothioates.

In a preliminary report,[2] we briefly described syntheses of uniquely substituted N-(2-bromoethyl)amines by sequences consisting of preparations of 3-substituted 2-oxazolidinones and their facile ring cleavage with hydrogen bromide. Thus, syntheses beginning with 3-(3-chloropropyl)-2-oxazolidinone[3] (**2**) and derivatives of 1,4-butanediamine (**6**) afforded spermine- and spermidine-related N,N′-bis[3-(2-bromoethylamino)propyl]-1,4-butanediamine tetrahydrobromide (**4**) and N-[3-(2-bromoethylamino)propyl]-1,4-butanediamine trihydrobromide (**11**). These examples typify a versatile route to otherwise difficultly accessible intermediates that are convertible into analogs of 2-aminoethanethiol and related radioprotective agents containing multiple amine functions. In this report we describe development of these methods and conversions of the N-(2-bromoethyl)amines thus obtained into potential radioprotectors.

The initial step in the synthesis of **4**, which is outlined in Scheme I, was the alkylation of N,N′-tetramethyl-

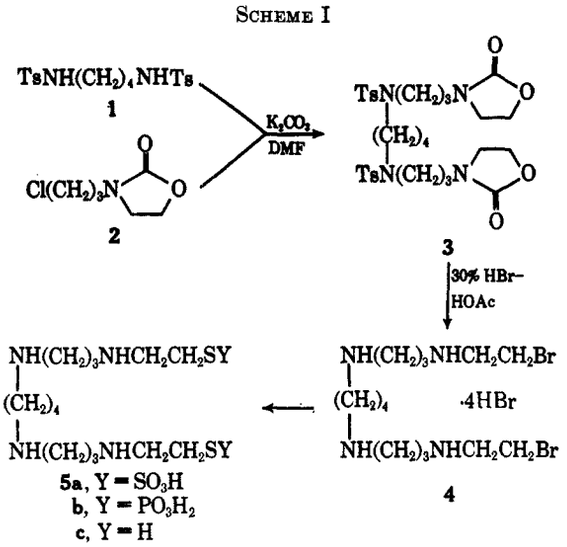
(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

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

(3) Asta-Werke AG, Brackwede (Westf.), Germany.

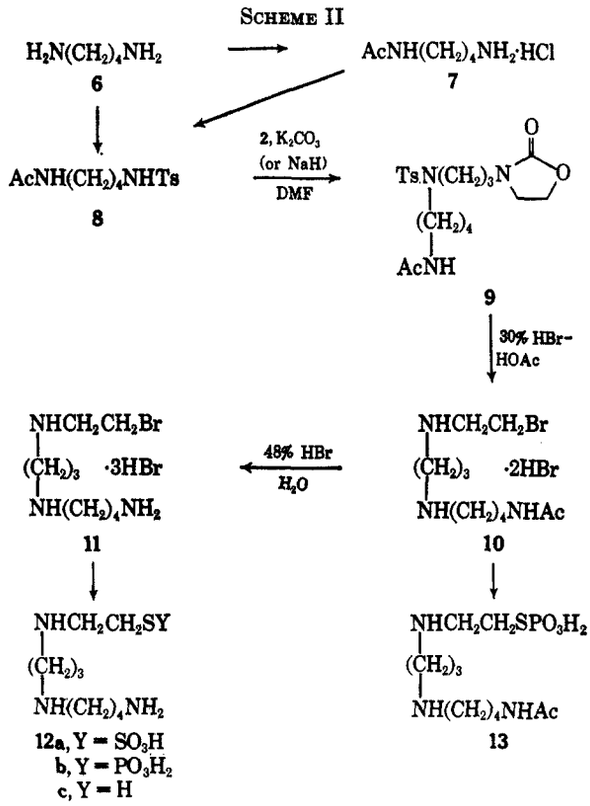
enebis-*p*-toluenesulfonamide (**1**) with **2** in N,N-dimethylformamide (DMF) containing potassium carbonate to give N,N′-bis[3-(2-oxo-3-oxazolidinyl)propyl]-N,N′-tetramethylenebis-*p*-toluenesulfonamide (**3**). Although earlier reported examples of ring cleavages of 2-oxazolidinones with hydrogen bromide were carried out at elevated temperatures,[4] it seemed likely that treatment of **3** with 30% hydrogen bromide–acetic acid solution (30% HBr–HOAc), a reagent often favored for reductive detosylation,[5] would also effect the desired decarboxylative ring cleavage.[6] These reactions did indeed occur concomitantly at room temperature, readily affording **4**.

SCHEME I



Since spermidine-related **11** is characterized by a single 2-bromoethylamino group and a terminal primary amino group, its synthesis by these methods required intermediates in which the terminal amino group-to-be is protected during the alkylation step (see Schemes II and III). N-(4-Acetamidobutyl)-*p*-toluenesulfonamide (**8**, Scheme II) and N-(4-phthalimidobutyl)-*p*-toluenesulfonamde (**18**, Scheme III) were prepared for this purpose. The initial preparation of **8** by tosylation of N-(4-aminobutyl)acetamide hydrochloride[7] (**7**) in 10% sodium carbonate solution was eventually supplanted by a more convenient method consisting of sequential treatment of an aqueous solution of **6** dihydrochloride with sodium acetate, acetic anhydride, sodium carbonate, and *p*-toluenesulfonyl chloride; **6** was thus acetylated and tosylated in one reaction mixture to give **8**. The corresponding phthaloyl derivative **18** was prepared by two routes. Alkylation of the potassium salt of ethyl *p*-tolylsulfonylcarbamate[8] (**15**), prepared *in situ* with potassium carbonate, with N-(4-bromobutyl)phthalimide (**14**) in DMF produced ethyl (4-phthalimidobutyl)(*p*-tolylsulfonyl)carbamate (**16**). Prolonged treatment of **16** with 30% HBr–HOAc containing phenol as a bromine scavenger effected removal of both the tosyl group and the ethoxycarbonyl group.[9] The resulting N-(4-aminobutyl)phthalimide hydrobromide (**17**) was then tosylated to give the desired N-(4-phthalimidobutyl)-*p*-toluenesulfonamide (**18**). At this point the alkylation of the sodium derivative of *p*-toluenesulfonamide with **14** was developed as an alternative, more direct route to **18**, which was made attractive by a facile separation of the expected coproduct, N,N-di(4-phthalimidobutyl)-*p*-toluenesulfonamide (**19**).[10] The DMF-soluble sodium salts of **8** and **18**, prepared *in situ* with sodium hydride, were readily alkylated with **2** to give, respectively, N-(4-acetamidobutyl)-N-[3-(2-oxo-3-oxazolidinyl)propyl]-*p*-toluenesulfonamide (**9**) and the phthalimido analog **20**. Use of potassium carbonate instead of sodium hydride in the conversion of **8** into **9** was also effective, though **9** was not obtained in crystalline form by either method. Treatment of **9** with 30% HBr–HOAc in the presence of phenol effected oxazolidinone-ring cleavage and detosylation while allowing retention of the terminal amide function and afforded N-{4-[3-(2-bromoethylamino)propylamino]butyl}acetamide dihydrobromide (**10**). Preparation of **11** was conveniently achieved in two steps by treatment of **9** with 30% HBr–HOAc, with or without added phenol, followed by hydrolysis of partially purified **10** by 48% hydrobromic acid. Retention of the phthalimido group similarly accompanied the 30% HBr–HOAc treatment (with added phenol) of **20**, which gave N-{4-[3-(2-bromoethylamino)propylamino]butyl}phthalimide dihydrobromide (**21**).

SCHEME II



(4) T. F. Wood, U. S. Patent 2,617,825 (1952); M. J. Viard, British Patent 693,325 (1953); H. Arnold and H. Bekel, *Arzneimittel-Forsch.*, **14**, 750 (1964); see also M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

(5) (a) D. I. Weisblat, B. J. Magerlein, and D. R. Myers, *J. Am. Chem. Soc.*, **75**, 3630 (1953); (b) G. R. Pettit and R. L. Smith, *Can. J. Chem.*, **42**, 572 (1964); (c) G. R. Pettit and R. E. Kadunce, *ibid.*, **41**, 2695 (1963).

(6) Benzyl carbamates are analogously cleaved under similar conditions: D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

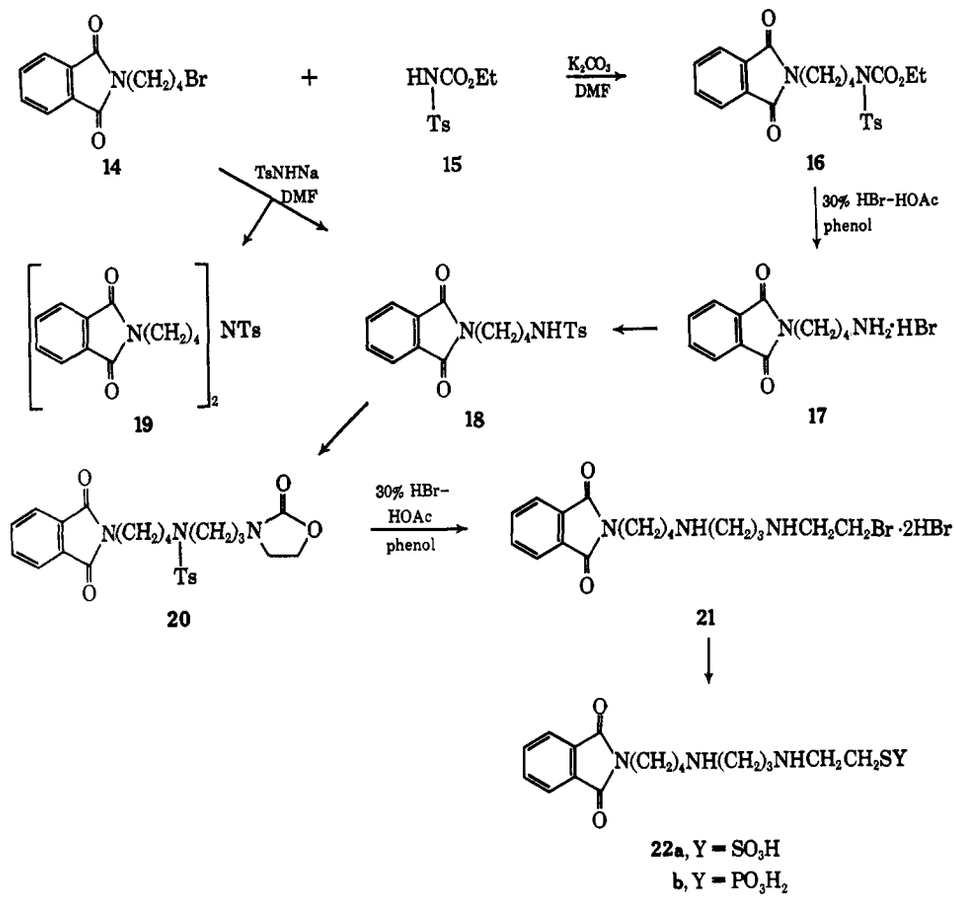
(7) C. W. Tabor, H. Tabor, and U. Bachrach, *J. Biol. Chem.*, **239**, 2194 (1964).

(8) K. Lanyi and Z. Szabo, *Magy. Tud. Akad. Kem. Tud. Oszt. Közlemén.*, **15**, 45 (1961); *Chem. Abstr.*, **55**, 17560 (1961).

(9) Reference 5c describes a similar conversion.

(10) *Cf.* A. E. Kretov, E. A. Abrashanova, S. I. Zlotchenko, and V. P. Kukhar, *J. Gen. Chem. USSR*, **33**, 2294 (1963); see also D. Klamann G. Hofbauer, and F. Drahowzal, *Monatsh. Chem.*, **83**, 870 (1952).

SCHEME III



Special problems of stoichiometry are encountered in the conversions of polyfunctional N-(2-bromoethyl)-amine hydrobromides, *e.g.*, **4**, **10**, **11**, and **21** into the corresponding internal Bunte salts and S-phosphorothioates by reactions with the divalent thiosulfate and trivalent phosphorothioate anions. Since N-(2-bromoethyl)amine hydrobromides are acidic and the reagents, sodium thiosulfate and trisodium (or trilithium) phosphorothioate, are acid labile, the ratio of covalent Br to the number of protonated amino groups (equivalent to ionic Br) must be considered with respect to the valency of the thio anion. In the preparation of Bunte salts with sodium thiosulfate, the ideal ratio of covalent Br to ionic Br ($RBr:Br^-$) is 1:1 as in the conversion of 2-bromoethylamine hydrobromide.[11] In some instances in which the $RBr:Br^-$ ratio is 1:2 or >2, the buffering action of sodium acetate is advantageous. As was demonstrated in the earlier conversion of 2-(bromomethyl)piperazine dihydrobromide into S-2-piperazinylmethylthiosulfuric acid hydrobromide,[12] sodium acetate did not neutralize the aliphatic amine hydrobromide, but protected sodium thiosulfate against decomposition (as evidenced by an immediate precipitation of sulfur in its absence). On the other hand, the S-phosphorothioates derived from trisodium phosphorothioate can be directly isolated either as the monosodium salt (the ideal $RBr:Br^-$ ratio being 1:1 as in $BrCH_2CH_2NH_2 \cdot HBr$)[13a,b] or the internal salt (the ideal $RBr:Br^-$ ratio being 1:2 as in **4**, **10**, and **21**). Acidity-increasing deviations from these ideal ratios necessitate buffering or partial neutralization. Furthermore, the isolation and characterization of S-phosphorothioates containing multiple amine functions are complicated by a propensity for solvation and deliquescence aside from their acute lability in acid. Hydrolysis of these compounds in neutral and basic media is, fortunately, relatively slow—an observation that is in accord with the pH profiles of certain S-phosphorothioates as determined by Åkerfeldt.[13c]

The following inner Bunte salts were prepared in the presence of sodium acetate and all were isolated as hydrobromide salts: (1) S,S′-3,7,12,16-tetraazaoctadecamethylenebis(thiosulfuric acid) (**5a**) dihydrobromide, from **4**; (2) S-2-[3-(4-aminobutylamino)propylamino]-ethylthiosulfuric acid (**12a**) dihydrobromide, from **11**; and (3) S-2-[3-(4-phthalimidobutylamino)propylamino]ethylthiosulfuric acid (**22a**) hydrobromide, from **21**. An ideal $RBr:Br^-$ ratio permitted the conversions of **4**, **10**, and **21** into S,S′-3,7,12,16-tetraazaoctadecamethylenebis(phosphorothioic acid) (**5b**), S-2-[3-(4-acetamidobutylamino)propylamino]ethylphosphorothioic acid (**13**), and S-2-[3-(4-phthalimidobutylamino)propylamino]ethylphosphorothioic acid (**22b**), respectively, in the absence of sodium acetate. Although the isolation of **13** and **22b** and their characterization as hydrates were exceptionally easy, the isolation and characterization of **5b** (from both trisodium and trilithium phosphorothioates) were complicated by deliquescence. The composition of a sample of **5b** that was prepared from trilithium phosphorothioate, reprecipitated from water with ethanol, collected under nitrogen, dried to constant weight *in vacuo* over

(11) H. Bretschneider, *Monatsh. Chem.*, **81**, 372 (1950).
(12) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963).
(13) (a) S. Åkerfeldt, *Acta Chem. Scand.*, **13**, 1479 (1959); (b) *ibid.*, **14**, 1980 (1960); (c) *ibid.*, **15**, 575 (1961); (d) *ibid.*, **16**, 1897 (1962).

P_2O_5, and stored under nitrogen, was established as an ethanolate dihydrate, the ethanol content being confirmed by gas–liquid partition chromatography.

An attempt to convert **11**, which has a 1:3 RBr:Br^- ratio, into S-2-[3-(4-aminobutylamino)propylamino]ethylphosphorothioic acid (**12b**) involved partial neutralization of **11** with an equimolar amount of sodium hydroxide (from standard 1 *N* solution) prior to introduction of trilithium phosphorothioate; however, the extreme deliquescence of the isolated product frustrated meaningful characterization. Results of elemental analysis of this product were inconsistent and not clearly indicative of **12b** or a possible solvate. Ample evidence was obtained to indicate that treatment of **11** with trisodium phosphorothioate in the presence of sodium acetate did indeed allow formation of **12b** hydrobromide, but the greater acid lability of S-phosphorothioates relative to S-thiosulfates precluded its isolation by techniques similar to those used in the isolation of **12a** dihydrobromide: ethanol-precipitated material presumed to be **12b** hydrobromide was initially nearly thiolfree (faintly nitroprusside positive) but rapidly became intensely nitroprusside positive during attempted work-up. This observation led to are markably facile preparation of 2-[3-(4-aminobutylamino)propylamino]ethanethiol (**12c**); the material presumed to be **12b** hydrobromide was hydrolyzed in phosphoric acid solution and pure **12c** triphosphate was readily obtained.[14] In an earlier preparation, **12c** (characterized as its trihydrochloride) had been much less conveniently prepared by treatment of **11** with sodium hydrosulfide (4 molar equiv).

The phosphorothioate hydrolysis method for preparing thiols proved particularly advantageous for preparing spermine-related 3,7,12,16-tetraazaoctadecane-1,18-dithiol (**5c**). Although **5c** could undoubtedly be formed by treatment of **4** with sodium hydrosulfide, it is quite likely that the methods of purification usually required in connection with this method (distillation or sublimation *in vacuo*) would not be conveniently applicable to **5c**. Phosphoric acid hydrolysis of **5b**, either as the material isolated as previously described or simply prepared *in situ* (from **4** and trilithium phosphorothioate), readily afforded **5c** tetraphosphate.

Experimental Section[15]

N,N′-Tetramethylenebis-*p*-toluenesulfonamide (1).—A solution of *p*-toluenesulfonyl chloride (76.8 g, 0.403 mole) in DMF (160 ml) was added dropwise during 20 min to a stirred solution of **6** (35.5 g, 0.403 mole) in DMF (100 ml) with the temperature maintained below 50°. The mixture was stirred at 25–30° for 1 hr and then poured into water (1.5 l.). The solid that precipitated was recrystallized from ethanol to give pure **1**, mp 124–125°, in 84% yield (67.4 g). Repeated recrystallizations from ethanol did not affect the melting point (lit.[16] mp 140°).

Anal. Calcd for $C_{18}H_{24}N_2O_4S_2$: C, 54.52; H, 6.10; N, 7.07; S, 16.17. Found: C, 54.66; H, 6.17; N, 6.96; S, 16.3.

N,N′-Bis[3-(2-oxo-3-oxazolidinyl)propyl]-N,N′-tetramethylenebis-*p*-toluenesulfonamide (3).—A stirred mixture of **1** (39.7 g, 0.100 mole), K_2CO_3 (30.4 g, 0.220 mole), and DMF (200 ml) was heated during 1 hr to 120°. A solution of **2**[3] (36.0 g, 0.220 mole) in DMF (100 ml) was added during 10–15 min and the resultant mixture was stirred at 115–120° for 4 hr. The cooled mixture was diluted with water (1 l.), the precipitated oil extracted with $CHCl_3$ (600 ml total), and the CH_3Cl_2 solution washed with four 500-ml portions of water. Removal of solvent from the dried ($MgSO_4$) $CHCl_3$ solution left crude **3** as a viscous orange oil. The oil was dissolved in boiling ethanol (100 ml) and, as the magnetically stirred solution was allowed to cool, crude **3** separated as a gum that gradually solidified. The solid, collected with the aid of water and dried *in vacuo* (P_2O_5), had mp 112–124° and amounted to 92% crude yield (60.0 g). Recrystallization from methanol afforded 66% yield (43.2 g) of **3**, mp 124–130°, suitable for use in the preparation of **4**. A sample was recrystallized twice more from methanol to give an analytical sample: mp 128–131°; ν_{max}^{KBr}, cm^{-1}, 3000–2800 (aliphatic CH), 1740 (C=O), 1330, 1155 (SO_2N).

Anal. Calcd for $C_{30}H_{42}N_4O_8S_2$: C, 55.37; H, 6.50; N, 8.61; S, 9.86. Found: C, 55.47; H, 6.34; N, 8.45; S, 9.9.

N,N′-Bis[3-(2-bromoethylamino)propyl]-1,4-butanediamine Tetrahydrobromide (4).—Pulverized **3** (42.2 g, 65.0 mmoles) was dissolved in 30% HBr–HOAc (300 ml) and the solution was stirred at room temperature for 4 days. The orange mixture was poured into a solution of ether (2 l.) and acetone (100 ml) and, after 2 hr, the white precipitate was collected and washed successively with acetone, ethanol, and ether. The crude product (29.0 g) was recrystallized from water–ethanol to give pure **4** in 54% yield (26.1 g), mp 271–272° dec with prior darkening.

Anal. Calcd for $C_{14}H_{32}Br_2N_4 \cdot 4HBr$: C, 22.72; H, 4.90; Br, 64.81; N, 7.57. Found C, 23.02; H, 4.97; Br, 64.7; N, 7.33.

N-(4-Acetamidobutyl)-*p*-toluenesulfonamide (8). Method A.—*p*-Toluenesulfonyl chloride (114 g, 0.598 mole) was added in portions during 30 min to a mechanically stirred solution of **7**[7] (98.0 g, 0.588 mole) and $Na_2CO_3 \cdot H_2O$ (150 g, 1.21 moles) in water (1.35 l.) at 60°. Stirring at 60° was continued for 2 hr. The mixture was allowed to cool and stirring was continued until the oily product crystallized (145 g, mp 124–127°). Recrystallization from ethyl acetate gave pure **8**, mp 125–126°, in 81% yield (136 g); ν_{max}^{KBr}, cm^{-1}, 3365 (carboxamide NH), 3145 (sulfonamide NH), 3000–2800 (aliphatic CH), 1655 (amide I), 1545 (amide II), 1310, 1155 (SO_2N).

Anal. Calcd for $C_{13}H_{20}N_2O_3S$: C, 54.90; H, 7.09; N, 9.85; S, 11.27. Found: C, 55.11; H, 7.16; N, 9.62; S, 11.3.

Method B.—Acetic anhydride (11.0 g, 0.108 mole) was added dropwise during 15 min to a mechanically stirred solution of **6**·2HCl (16.1 g, 0.100 mole) and NaOAc·$3H_2O$ (28.0 g, 0.206 mole) in water (200 ml) maintained at 55–60°. Solid $Na_2CO_3 \cdot H_2O$ (50 g, 0.40 mole) was then carefully added in portions. Gradual addition during 15 min of *p*-toluenesulfonyl chloride (19.1 g, 0.100 mole) followed and heating with stirring at 55–60° was continued for 3.5 hr. Solid filtered from the cooled reaction mixture was stirred with boiling ethanol (200 ml) and the mixture was cooled and filtered. Removal of the ethanol from the clear filtrate left an orange oil, which crystallized when stirred with warm ethyl acetate (100 ml). Two more recrystallizations from ethyl acetate afforded **8**, mp 123–126°, in 35% yield (10.0 g); the infrared spectrum of this sample is identical with that of the sample prepared by method A; the mixture melting point of the two samples was undepressed.

N-(4-Acetamidobutyl)-N-[3-(2-oxo-3-oxazolidinyl)propyl]-*p*-toluenesulfonamide (9). Method A.—A stirred mixture of **8** (136 g, 0.478 mole), K_2CO_3 (69.2 g, 0.500 mole), and DMF (380 ml) was heated during 1 hr to 120°. A solution of **2** (82.0 g, 0.501 mole) in DMF (190 ml) was added during 20 min and the resultant mixture was maintained at 115–120° for 4 hr. Solvent was removed by distillation *in vacuo*, the residue stirred with water (500 ml), and the suspended oil extracted with $CHCl_3$ (700 ml). Removal of the solvent from the water-washed and dried ($MgSO_4$) $CHCl_3$ solution left crude **9** (194 g) as an orange oil: ν_{max}^{film}, cm^{-1}, 3395, 3305 (broad doublet, NH), 3080 (aromatic CH), 3000–2800 (aliphatic CH), 1745 (2-oxazolidinone C=O), 1660 (amide I), 1545 (amide II), 1335, 1155 (SO_2N).

Method B.—A solution of **8** (50.0 g, 0.176 mole) in DMF (400 ml) was added during 20 min to a stirred suspension of NaH (8.45 g of 50% NaH in oil dispersion, 0.176 mole) in DMF (100 ml). Stirring was continued until a clear solution resulted (~30 min). A solution of **2** (28.8 g, 0.176 mole) in DMF (100 ml) was added; the resultant solution was gradually heated during 1.5 hr to 110° and maintained at 110° for 3 hr. The same isolation procedure as described in method A above afforded crude **9** (75 g) as an orange oil.

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

(15) Melting points were taken on a Mel-Temp apparatus. Infrared spectra were determined with a Perkin-Elmer Model 521 spectrophotometer.

(16) K. Wiesner and D. E. Orr, *Tetrahedron Letters*, No. 16, 11 (1960).

Method C.—A solution of **8** (10.0 g, 35.2 mmoles) and **2** (5.76 g, 35.2 mmoles) in DMF (80 ml) was added dropwise during 1 hr to a magnetically stirred and moderately cooled (20–25° water bath) suspension of NaH (1.41 g of 60% NaH in oil dispersion, 35.2 mmoles) in DMF (25 ml). The resultant mixture was stirred 48 hr at 25–30°, heated at 95° for 2.5 hr, cooled, and filtered from NaCl. The filtrate was washed twice with ligroin (bp 30–60°, 50-ml portions) and the hydrocarbon layer was discarded. Removal of the DMF by distillation *in vacuo* left **9** as a yellow-orange oil, which was used as such for preparation of **10**.

N-4-{[3-(2-Bromoethylamino)propylamino]butyl}acetamide Dihydrobromide (10).—Crude **9** from method C was dissolved along with phenol (10 g) in 30% HBr–HOAc (50 ml) and the mixture was stirred at 25–30° for 10 days while crystalline solid separated. Pink solid collected from the ether-diluted mixture was dissolved in methanol and the filtrate from the Norit-treated solution was diluted with ether to reprecipitate **10**, which was collected, washed with acetone, and recrystallized twice from ethanol: mp 168–169°; yield 31% over-all (4.92 g) for the conversion from **8**; ν_{max}^{KBr}, cm^{-1}, 3320 (NH), 1640 (amide I), 1530 (amide II).

Anal. Calcd for $C_{11}H_{24}BrN_3O \cdot 2HBr$: C, 28.97; H, 5.74; Br, 52.56; N, 9.21. Found: C, 29.00; H, 5.69; Br, 52.0; N, 9.02.

N-[3-(2-Bromoethylamino)propyl]-1,4-butanediamine Trihydrobromide (11).—After a solution of crude **9** (194 g, from method A) in 30% HBr–HOAc (1 l.) had been stirred at 25–30° for 7 days, ether (5 l.) was added and the precipitated material was collected and washed thoroughly with ether followed by acetone. Crude **10** thus obtained (87 g, dried *in vacuo*) was dissolved in 48% HBr (265 ml) and the solution was refluxed 1.5 hr. The cooled, Norit-treated and filtered (Celite) solution was diluted with ethanol (3 l.) to precipitate crystalline **11**. The mixture was refrigerated and the product collected, washed with ethanol, and dried *in vacuo* (80°, P_2O_5): yield ~23% (55.0 g); mp 252–255° dec. An analytical sample has mp 254–257° dec (from water–ethanol).

Anal. Calcd for $C_9H_{22}BrN_3 \cdot 3HBr$: C, 21.84; H, 5.09; Br, 64.58; N, 8.49. Found: C, 21.99; H, 5.05; Br, 64.49; N, 8.44.

In another run crude **9** (75 g, from method B) was dissolved along with phenol (35 g) in 30% HBr–HOAc (350 ml). The solution was stirred at 25–30° for 68 hr, gradually heated to boiling, and refluxed for 2.5 hr. The dark solution was cooled and diluted with ether (1 l.); the pink precipitate was collected, washed with ether, and suction dried under N_2. The crude solid was dissolved in 48% HBr (200 ml) and the solution was refluxed 1 hr. The hot (~80°), Norit-treated, and filtered (Celite) solution was diluted with boiling ethanol (1 l.) and pure **11**, mp 253–256° dec, separated from the cooled solution as lustrous platelets in ~40% yield (36.2 g).

N-(4-Bromobutyl)phthalimide (14).[17]—A stirred mixture of potassium phthalimide (41.3 g, 0.223 mole), 1,4-dibromobutane (193 g, 0.893 mole), and DMF (10 ml) was maintained at 150–155° for 2 hr. Excess 1,4-dibromobutane was removed by distillation *in vacuo* and the semisolid residue was extracted with boiling ethanol. The filtered ethanol solution afforded **14**, mp 75–76° (lit.[18] mp 77–80°), in three crops totalling 35.3 g (56% yield).

Ethyl (4-Phthalimidobutyl)(*p*-tolylsulfonyl)carbamate (16).—Anhydrous K_2CO_3 (80 g, 0.58 mole) was added to a magnetically stirred solution of **15**[8] (78.0 g, 0.321 mole) in DMF (320 ml). Following a period of CO_2 evolution, **14** (90.6 g, 0.321 mole) was added followed by more DMF (80 ml). The stirred mixture was heated at 70–75° for 2.5 hr, cooled, and poured into water (4 l.). Precipitated **16** was collected, pulverized, washed with water, and dried *in vacuo* (80°, P_2O_5): crude yield, 92% (131 g); mp 109–116°. This material proved suitable for use in the preparation of **17**. An analytical sample has mp 119–120° (from ethanol); ν_{max}^{KBr}, cm^{-1}, 3120–3000 (aromatic CH), 3000–2800 (aliphatic CH), 1735 (ester C=O), 1760 (m), 1710 (s) (imide C=O), 1260 (ester CO-).

Anal. Calcd for $C_{22}H_{24}N_2O_6S$: C, 59.44; H, 5.44; N, 6.30. Found: C, 59.72; H, 5.38; N, 6.11.

N-(4-Aminobutyl)phthalimide Hydrobromide (17).—A solution of **16** (131 g, 0.294 mole) and phenol (131 g) in 30% HBr–HOAc (1 l.) was stirred at 25–30° for 18 days, progress of the reaction being followed by observation of CO_2 evolution. Dilution with ether (8 l.) afforded crystalline **17**, which was collected, washed thoroughly with ether, and dried *in vacuo:* yield 88% (77.3 g); mp 212–215° dec (melting point unchanged by recrystallization from ethanol); ν_{max}^{KBr}, cm^{-1}, 2400–3250 (NH_3^+), 1770 (w), 1710 (s) (imide C=O).

Anal. Calcd for $C_{12}H_{14}N_2O_2 \cdot HBr$: C, 48.17; H, 5.06; N, 9.36. Found: C, 48.02; H, 5.12; N, 9.27.

N-(4-Phthalimidobutyl)-*p*-toluenesulfonamide (18). Method A. From 17.—A solution of *p*-toluenesulfonyl chloride (42.0 g, 0.220 mole) in DMF (50 ml) was added dropwise during 15 min to a mechanically stirred mixture of **17** (63.3 g, 0.212 mole), K_2CO_3 (70.0 g, 0.507 mole), water (10 ml), and DMF (200 ml) while the temperature was maintained at 25–30°. Following a 2-hr stirring period at 30°, the mixture was poured into water, neutralized by concentrated HCl, and refrigerated for 18 hr. The collected, water-washed precipitate was recrystallized from ethanol to give pure **18**: mp 126–129°; 15% yield (11.8 g); ν_{max}^{KBr}, cm^{-1}, 3300, 3280 (sh) (NH), 3000–2800 (aliphatic CH), 1760 (w-m), 1695 (s) (imide C=O), 1315, 1145 (SO_2N).

Anal. Calcd for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.61; H, 5.23; N, 7.27.

Method B. From Sodium *p*-Toluenesulfonamide and 14 with Accompanying Formation of N,N-Di-(4-phthalimidobutyl)-*p*-toluenesulfonamide (19).—A mixture of **14** (28.2 g, 0.100 mole) and sodium *p*-toluenesulfonamide[19] (19.3 g, 0.100 mole) in DMF (300 ml) was stirred at room temperature for 64 hr. Solvent was removed from the resultant solution by distillation *in vacuo*.

Isolation of 19.—The residue was dissolved in boiling ethanol (1 l.) and the resultant solution was kept at room temperature for 5 hr while crude **19** crystallized readily. The collected precipitate was pressed as dry as possible and the filtrate was set aside for isolation of **18**. Purification of crude **19** (14.7 g, mp 103–115°) was effected by recrystallization from ethanol (500 ml): yield, 11.9 g (equivalent to 41% of **14** used); mp 152–153°; ν_{max}^{KBr}, cm^{-1}, 3100–3000 (aromatic CH), 3000–2800 (aliphatic CH), 1770 (m), 1700 (s) (imide C=O), 1335, 1150 (SO_2N).

Anal. Calcd for $C_{31}H_{31}N_3O_6S$: C, 64.90; H, 5.45; N, 7.32. Found: C, 64.76; H, 5.40; N, 7.34.

Isolation of 18.—Solid remaining following removal of ethanol from the filtrate from crude **19** was stirred with boiling toluene (250 ml), the mixture was filtered, and the cooled filtrate was diluted with 30–60° ligroin (250 ml). Crude **18** separated and was reprecipitated once more from toluene–ligroin before being recrystallized from ethanol (200 ml) to give pure **18**: mp 127–130°; yield, 36% (13.5 g). Mixture melting point with the sample prepared by method A was undepressed.

N-(4-Phthalimidobutyl)-N-[3-(2-oxo-3-oxazolidinyl)propyl]-*p*-toluenesulfonamide (20).—A solution of **18** (13.0 g, 34.9 mmoles) in DMF (120 ml) was added dropwise during 30 min to a stirred suspension of NaH (1.40 g of 60% NaH in oil dispersion, 35.0 mmoles) in DMF (50 ml) with the temperature maintained at 20–25°. Stirring was continued 30 min longer until gas evolution had ceased and a clear solution remained. A solution of **2** (6.00 g, 36.7 mmoles) in DMF (25 ml) was added and the resultant solution was kept at about 25° for 72 hr while NaCl gradually separated. The mixture was then heated at 95° for 2 hr, cooled, and filtered. Removal of DMF from the filtrate by distillation *in vacuo* left an orange oil, which was dissolved in boiling methanol (100 ml). The Norit-treated and filtered (Celite) methanol solution was refrigerated overnight and pure **20**, mp 91–93°, crystallized readily in 64% yield (11.2 g): ν_{max}^{KBr}, cm^{-1}, 3140–3000 (aromatic CH), 3000–2800 (aliphatic CH), 1730 (2-oxazolidinone C=O), 1765 (w), 1695 (s) (imide C=O), 1335, 1150 (SO_2N).

Anal. Calcd for $C_{25}H_{29}N_3O_6S$: C, 60.10; H, 5.85; N, 8.41. Found: C, 60.03; H, 5.90; N, 8.47.

N-{4-[3-(2-Bromoethylamino)propylamino]butyl}phthalimide Dihydrobromide (21).—A mixture of **20** (11.0 g, 22.0 mmoles), phenol (11.0 g), and 30% HBr–HOAc (110 ml) was stirred at about 25° for 10 days. Following a 90-min period of gradual heating and a 30-min reflux, the cooled mixture was stirred with ether (500 ml). Crystalline product was collected, washed with

(17) *Cf.* H. B. Donahoe, R. J. Seiwald, M. M. C. Neuman, and K. K. Kimura, *J. Org. Chem.*, **22**, 68 (1957).

(18) W. Keller-Schierlein, P. Mertens, V. Prelog, and A. Walser, *Helv. Chim. Acta*, **48**, 710 (1965).

(19) Prepared in 86% yield by combining ethanol solutions of equimolar amounts of *p*-toluenesulfonamide and sodium methoxide; the ethanol-washed crystalline precipitate was dried *in vacuo* (77°, P_2O_5).

ether, and recrystallized from methanol to give pure **21**: mp ~235° dec; 87% yield (10.4 g); ν_{max}^{KBr}, cm^{-1}, 3150–2300 (NH_2^+), 1765 (m), 1705 (s) (imide C=O).

Anal. Calcd for $C_{17}H_{24}BrN_3O_2 \cdot 2HBr$: C, 37.53; H, 4.82; Br, 44.06; N, 7.72. Found: C, 37.75; H, 4.88; Br, 44.0; N, 7.58.

S,S'-3,7,12-16-Tetraazaoctadecamethylenebis(thiosulfuric acid) (5a) Dihydrobromide.—A solution of **4** (7.40 g, 10.0 mmoles), $NaOAc \cdot 3H_2O$ (2.72 g, 20.0 mmoles), and $Na_2S_2O_3 \cdot 5H_2O$ (4.96 g, 20.0 mmoles) in water (10 ml) was heated at 90–95° for 1.5 hr. The cooled solution was poured into methanol (200 ml), giving gummy precipitate that solidified during refrigeration. The collected solid was dissolved in water (40 ml), the solution filtered, and the vigorously stirred filtrate treated dropwise with methanol (300 ml) to reprecipitate **5a** 2HBr in 82% yield (5.30 g, dried *in vacuo* at 25–30° over P_2O_5): mp indefinite with decomposition above 190°; ν_{max}^{KBr}, cm^{-1}, 1210, 1190, 1020, 625 ($-SSO_3^-$).

Anal. Calcd for $C_{14}H_{34}N_4O_6S_4 \cdot 2HBr$: C, 26.09; H, 5.57; N, 8.70; S, 19.90. Found: C, 26.27; H, 5.81; N, 8.74; S, 20.2.

S,S'-3,7,12,16-Tetraazaoctadecamethylenebis(phosphorothioic acid) (5b) Ethanolate Dihydrate.—A solution of $Li_3SPO_3 \cdot 6H_2O$[13d,20] (4.80 g, 20.0 mmoles) and **4** (7.40 g, 10.0 mmoles) in water (45 ml) was treated with DMF (20 ml), stirred at room temperature for 2 hr, then added dropwise to rapidly stirred ethanol (600 ml). White solid separated initially, but ultimately became opaque gum. The supernatant was removed by decantation and the residue solidified readily when stirred with ethanol (600 ml). The deliquescent product was collected under N_2 and dissolved in water (40 ml), and the Norit-treated and filtered (Celite) solution was added dropwise to vigorously stirred ethanol (600 ml). Subsequent handling was carried out under N_2. The precipitate was collected, washed with ethanol followed by ether, and transferred without delay to a desiccator where it was dried overnight (18 hr) *in vacuo* (P_2O_5) at 25–30°. The yield was 84% (4.80 g) of deliquescent, solvated **5b** as a white powder lacking a definite melting point: ν_{max}^{KBr}, cm^{-1}, 1060 (broad, with shoulder at 1105), 950, 570 (SPO_3^{2-}).

Anal. Calcd for $C_{14}H_{36}N_4O_6P_2S_2 \cdot 1.1C_2H_5OH \cdot 2H_2O$: C, 34.18; H, 8.25; N, 9.84; P, 10.88; S, 11.27; C_2H_5OH, 8.90. Found: C, 33.97; H, 7.96; N, 9.57; P, 10.6; S, 11.2; C_2H_5OH, 9.1 (by glpc).

3,7,12,16-Tetraazaoctadecane-1,18-dithiol (5c) Tetraphosphate Monohydrate. Method A.—A solution of $Li_3SPO_3 \cdot 6H_2O$ (4.80 g, 20.0 mmoles), **4** (7.77 g, 10.5 mmoles), water (52 ml), and DMF (20 ml) was kept at room temperature for 2 hr. The solution was added dropwise to stirred ethanol (750 ml) and the precipitate that formed was collected under N_2, washed with ethanol, and suction dried under N_2 pressure. The precipitate was dissolved in 17% H_3PO_4 (90 ml), and the solution was refluxed under N_2 for 15 min. The cooled solution was added to ethanol (750 ml) and the crystalline precipitate that formed was recrystallized from water–ethanol to give solvated **5c**·$4H_3PO_4$ (dried *in vacuo* at 25–30° over P_2O_5) in 80% yield (6.18 g).

Anal. Calcd for $C_{14}H_{34}N_4S_2 \cdot 4H_3PO_4 \cdot C_2H_5OH \cdot H_2O$: C, 24.68; H, 6.99; N, 7.19; SH, 8.49. Found: C, 24.84; H, 6.77; N, 7.24; SH, 8.2.

Drying the above material at 77 and 110°, successively, *in vacuo* (P_2O_5) caused weight loss corresponding to the apparent ethanol content and gave pure **5c**·$4H_3PO_4$ monohydrate: mp 209–213° dec; ν_{max}^{KBr}, cm^{-1}, 1110–1070 (broad doublet), 960, 500 ($H_2PO_4^-$).

Anal. Calcd for $C_{14}H_{34}N_4S_2 \cdot 4H_3PO_4 \cdot H_2O$: C, 22.95; H, 6.60; N, 7.64; S, 8.75; SH, 9.03. Found: C, 23.12; H, 6.55; N, 7.65; S, 8.6; SH, 8.6.

Method B.—A solution of **4** (7.70 g, 10.5 mmoles) and $Li_3SPO_3 \cdot 6H_2O$ (4.80 g, 20.0 mmoles) in water (40 ml) was kept at room temperature for 2 hr. A solution of H_3PO_4 (18.5 g of 85%) in water (60 ml) was added and the resultant solution was refluxed under N_2 for 15 min. The hot solution was then added to boiling ethanol (250 ml). The solution was cooled and the crystalline precipitate was recrystallized from water–ethanol, then dried *in vacuo* (P_2O_5) at successive temperatures of 28, 77, and 110° to give pure **5c**·$4H_3PO_4$ monohydrate, mp 209–213° dec, in 91% yield (6.69 g).

Anal. Calcd for $C_{14}H_{34}N_4S_2 \cdot 4H_3PO_4 \cdot H_2O$: C, 22.95; H, 6.60; N, 7.64; P, 16.90; S, 8.75; SH, 9.03. Found: C, 23.10; H, 6.68; N, 7.76; P, 16.7; S, 8.6; SH, 9.0.

S-2-[3-(4-Acetamidobutylamino)propylamino]ethylphosphorothioic Acid (13) Hydrate.—Solid **10** (4.42 g, 9.70 mmoles) was added to a stirred partial solution of Na_3SPO_3[13b,14] (1.74 g, 9.67 mmoles) in water (10 ml); after complete solution had occurred, DMF (5 ml) was added. The solution was kept at 25–30° for 2.5 hr, diluted with ethanol (150 ml), and refrigerated for 2 days. Hydrated **13** that gradually crystallized as a first crop was collected, washed with ethanol, and air dried. The filtrate from the first crop was diluted with ether to give white solid precipitate, which was collected, washed with ethanol, dissolved in water (2 ml), and reprecipitated by addition of ethanol (70 ml). The reprecipitated second crop was collected, air dried, and then placed along with the first crop in a 58% relative humidity hygrostat for hydration equilibration.[20b] The two samples of hydrated **13** (1.34 and 1.04 g, respectively; 69% yield) thus obtained are identical: mp 128–129°; ν_{max}^{KBr}, cm^{-1}, 1670 (amide I), 1540 (amide II), 1115, 1070, 955, 580 ($-SPO_3^{2-}$).

Anal. Calcd for $C_{11}H_{26}N_3O_4PS \cdot 1.5H_2O$: C, 37.28; H, 8.25; N, 11.86; P, 8.74; S, 9.05. Found: C, 37.27; H, 8.15; N, 11.85; P, 9.01; S, 9.2.

S-2-[3-(4-Aminobutylamino)propylamino]ethylthiosulfuric Acid (12a) Dihydrobromide.—A solution of $Na_2S_2O_3 \cdot 5H_2O$ (4.96 g, 20.0 mmoles), $NaOAc \cdot 3H_2O$ (5.44 g, 40.0 mmoles), and **11** (9.90 g, 20.0 mmoles) in water (25 ml) was heated at 90–95° for 2 hr. Evaporation to dryness gave a semisolid residue, which, after being stirred with refluxing ethanol for several hours, ultimately afforded crude **12a**·2HBr as ethanol-insoluble, deliquescent solid. The collected (under N_2) ethanol-washed and dried (*in vacuo*, P_2O_5) crude product (5.56 g) was stirred with boiling methanol (~200 ml). Nearly complete solution occurred and the cloudy mixture was filtered (Celite). Removal of the methanol gave an opaque gum, which was again dissolved in boiling methanol (175 ml). The solution was filtered (Celite) and diluted with ethanol (400 ml). The mixture was kept 6 days at 25–30°, and the granular crystalline precipitate that formed was collected under N_2 and dried *in vacuo* (P_2O_5) at successive temperatures of 28, 58, and 77° to give **12a**·2HBr, melting point indefinite with decomposition from 160°, in 29% yield (2.64 g): ν_{max}^{KBr}, cm^{-1}, 1225–1180 (broad overlapping doublet), 1020, 630 ($-SSO_3^-$).

Anal. Calcd for $C_9H_{23}N_3O_3S_2 \cdot 2HBr$: C, 24.17; H, 5.63; Br, 35.73; N, 9.39; S, 14.34. Found: C, 24.64; H, 5.77; Br, 35.72; N, 9.45; S, 14.4.

2-[3-(4-Aminobutylamino)propylamino]ethanethiol (12c) Triphosphate.—The solution resulting from adding pulverized **11** (4.95 g 10.0 mmoles) followed by DMF (10 ml) to a stirred mixture of Na_3SPO_3 (1.80 g, 10.0 mmoles) and $NaOAc \cdot 3H_2O$ (1.36 g, 10.0 mmoles) in water (20 ml) was kept 1 hr at 25–30°, then added dropwise to rapidly stirred ethanol (150 ml). Supernatant was decanted from the white gum precipitate (presumably **12b**·HBr), which was washed by decantation several times with ethanol and then hydrolyzed under N_2 in 17% H_3PO_4 solution (30 ml) at 90–95° for 15 min. The cooled solution was diluted with ethanol (300 ml) and the crystalline precipitate, collected under N_2 and washed with ethanol, was twice reprecipitated from minimal volumes of 17% H_3PO_4 solution by addition of ethanol. Pure **12c**·$3H_3PO_4$, melting point indefinite from 135°, dried *in vacuo* (P_2O_5) at successively increasing temperatures up to 110°, was obtained in 74% yield (3.67 g): ν_{max}^{KBr}, cm^{-1}, 1040–950 (broad overlapping doublet), 490 ($H_2PO_4^-$).

Anal. Calcd for $C_9H_{23}N_3S \cdot 3H_3PO_4$: C, 21.65; H, 6.46; N, 8.42; S, 6.43; SH, 6.61. Found: C, 21.41; H, 6.81; N, 8.37; S, 6.30; SH, 6.50.

2-[3-(4-Aminobutylamino)propylamino]ethanethiol (12c) Trihydrochloride.—A solution of sodium methoxide (from 0.184 g-atom of Na metal) in methanol (300 ml) was saturated at 0–5° with H_2S. With a slow flow of H_2S being maintained, pulverized **11** (22.7 g, 45.9 mmoles) was added in portions during 1 hr. The mixture was stirred at 0° for 1 hr, allowed to warm during 1.5 hr to 25°, and kept at 25–30° for 2 hr. The H_2S flow was replaced with a slow current of N_2 and the solution was gradually heated to boiling and refluxed for 1 hr (50% NaOH and 5% NaOCl solutions served as gas-absorption traps.) Following removal of methanol by evaporation *in vacuo*, the product was extracted by warm $CHCl_3$ (150 ml) and removal of the $CHCl_3$ gave a yellow oil. Distillation *in vacuo* gave a crude product, boiling range 70–118° (0.06 mm); fractional distillation *in vacuo*

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

through a short (10 × 1 cm) Vigreux column gave **12c** as a colorless oil, bp 115–117° (0.1 mm), in 27% yield (2.53 g). This sample was dissolved in ethanol (25 ml) and treated with an ethanol solution of dry HCl to give crystalline, ethanol-insoluble **12c**·3HCl (3.68 g), which was reprecipitated from concentrated HCl (36 ml) by addition of ethanol (380 ml). The collected, ethanol-washed product was suction dried under N_2 and dried *in vacuo* (77°, P_2O_5) to give pure **12c**·HCl, mp 262–264° dec, in 84% conversion (3.26 g) from the free base: ν_{max}^{KBr}, cm^{-1}, 1455 (CH bend, strongest band in fingerprint region).

Anal. Calcd for $C_9H_{23}N_3S \cdot 3HCl$: C, 34.31; H, 8.33; Cl, 33.79; N, 13.35; S, 10.20; SH, 10.51. Found: C, 34.25; H, 8.05; Cl, 33.92; N, 13.36; S, 10.17; SH, 10.35.

S-2-[3-[4-Phthalimidobutylamino]propylamino]ethylthiosulfuric Acid (22a) Hydrobromide.—A solution of **21** (4.38 g, 8.05 mmoles), $NaOAc \cdot 3H_2O$ (1.10 g, 8.08 mmoles), and $Na_2S_2O_3 \cdot 5H_2O$ (2.00 g, 8.05 mmoles) in water (8 ml) was heated at 90–95° for 1 hr. The cooled solution deposited a colorless syrup that solidified on refrigeration. The collected, ethanol-washed, and dried (*in vacuo* at 25–30° over P_2O_5) solid (2.84 g) was dissolved in boiling methanol (350 ml). The Norit-treated and filtered (Celite) solution was concentrated on a rotary evaporator to 50 ml while an opaque white gum separated. Ethanol (150 ml) was added and rapid magnetic stirring soon caused the gum to solidify. The collected solid was dried *in vacuo* (25–30°, P_2O_5) to constant weight (2.47 g). Elemental analysis indicated this product to be a monoethanolate of **22a**·HBr.

Anal. Calcd for $C_{17}H_{25}N_3O_5S_2 \cdot HBr \cdot C_2H_5OH$: C, 42.07; H, 5.95; N, 7.75. Found: C, 42.26; H, 5.93; N, 7.79.

Further drying *in vacuo* (P_2O_5) at successive temperatures of 58, 77, and 100° caused a weight loss of ~11% (2.43 to 2.17 g) and afforded **22a**·HBr: yield, 54%; melting point indefinite range above 170°; ν_{max}^{KBr}, cm^{-1}, 1760 (m), 1700 (s) (imide C=O), 1230, 1180, 1010, 615 ($-SSO_3^-$).

Anal. Calcd for $C_{17}H_{25}N_3O_5S_2 \cdot HBr$: C, 41.13; H, 5.28; Br, 16.10; N, 8.46; S, 12.92. Found: C, 40.89; H, 5.20; Br, 15.80; N, 8.59; S, 12.98.

S-2-[3-(4-Phthalimidobutylamino)propylamino]ethylphosphorothioic Acid (22b) Dihydrate.—Pulverized **21** (6.00 g, 11.0 mmoles) was added in portions during 15 min to a stirred suspension of Na_3SPO_3 (1.98 g, 11.0 mmoles) in water (18 ml) and DMF (6 ml). Complete solution resulted and stirring was continued for 1 hr while crystalline product separated. The mixture was stirred with ethanol (180 ml) and the collected, ethanol-washed precipitate was dried *in vacuo* (P_2O_5) at 25–30°: yield 96% (4.79 g); melting point indefinite range above 120°; ν_{max}^{KBr}, cm^{-1}, 1760 (m), 1705 (s) (imide C=O), 1120, 1065, 945, 575 ($-SPO_3^{2-}$).

Anal. Calcd for $C_{17}H_{26}N_3O_5PS \cdot 2H_2O$: C, 45.23; H, 6.70; N, 9.31; P, 6.86; S, 7.10. Found: C, 44.87; H, 6.69; N, 9.21; P, 6.83; S, 6.97.

Registry No.—**1**, 15544-47-5; **3**, 13621-89-1; **4**, 13621-90-4; **5a**·2HBr, 15440-80-9; **5b**, 15440-81-0; **5c**·$4H_3PO_4$, 15544-48-6; **8**, 15440-82-1; **9**, 15440-95-6; **10**, 15440-83-2; **11**, 13621-88-0; **12a**·2HBr, 15440-85-4; **12c**·$3H_3PO_4$, 15440-96-7; **12c**·3HCl, 15440-86-5; **13**, 15440-87-6; **16**, 15440-88-1; **17**, 15440-89-8; **18**, 15544-49-7; **19**, 15440-90-1; **20**, 15440-91-2; **21**, 15544-50-0; **22a**·HBr, 15440-92-3; **22b**, 15440-93-4; 2-aminoethanethiol, 60-23-1; spermine, 71-44-3; spermidine, 124-20-9.

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Synthesis of Adenine and 4,5-Dicyanoimidazole from Hydrogen Cyanide in Liquid Ammonia[1]

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Adenine and 4,5-dicyanoimidazole were formed simultaneously in 22 and 21% yields, respectively, on heating a solution of hydrogen cyanide in excess liquid ammonia. Diaminomaleonitrile was also detected in the reaction mixture at the initial stage. When the reaction mixture was heated with aqueous acid, the hydrolysis products glycine and formamide were isolated. Furthermore, when anhydrous hydrogen cyanide and acetamidine were heated in liquid ammonia, 2-methyl-, 8-methyl-, and 2,8-dimethyladenine and 2-methyl-4,5-dicyanoimidazole, as well as adenine and 4,5-dicyanoimidazole, were formed. Anhydrous hydrogen cyanide was also allowed to react with liquid methylamine and yielded N,N'-dimethylformamidine, 1-methyl-4-methylamino-5-cyanoimidazole and its methylamidino derivative, and 7- and 9-methyl-6-methylaminopurine. From these results, a suggested mechanism by which adenine and 4,5-dicyanoimidazole might be derived is discussed.

Adenine has been synthesized from malononitrile and thiourea,[2] from malononitrile *via* its amidine derivatives,[3] or from hypoxanthine.[4] Oró and Kimball[5] have reported that small amounts of adenine accompany a large quantity of resinous substances when a solution of hydrogen cyanide is heated in excess aqueous ammonia and that, concurrently, formamidine, 4-amino-5-imidazolecarboxamidine, and 4-amino-5-imidazolecarboxamide can be detected as key intermediates leading to the formation of adenine. However, hydrogen cyanide and the postulated intermediate amidines are quite unstable under these conditions. A previous report[1] described the improved synthesis of adenine and the formation of 4,5-dicyanoimidazole under anhydrous conditions. In the present paper we describe our efforts to study this reaction further and to shed light on the route by which these compounds are formed.

Results

Reaction of Hydrogen Cyanide with Ammonia.—Either liquid hydrogen cyanide or a mixture of sodium cyanide and ammonium chloride was heated in liquid ammonia under various conditions in a pressure vessel.

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