Cyclic Disulfides. II. 1,2-Dithiepan-5-amine[1]

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As part of a study of the effect of ring strain on the radiation-protective action provided by amino-1,2-dithiacyclanes and related compounds, the comparatively unstrained 1,2-dithiepan-5-amine was synthesized. 3-Bromo-1-(2-bromoethyl)propylamine was converted to 3-amino-1,5-pentanedithiol hydrochloride and to 3-amino-1,5-pentanebis(2-thiopseudourea) trihydrobromide. Although oxidation of the 3-amino-1,5-pentanedithiol by a number of methods gave polymeric disulfide, oxidation with iodine in high dilution gave 1,2-dithiepan-5-amine. None of the compounds tested, 1,2-dithiepan-5-amine hydrochloride, 3-amino-1,5-pentanedithiol hydrochloride, 3-amino-1,5-pentanebis(2-thiopseudourea) trihydrobromide, or tetrahydro-1-thiapyran-4-amine hydrobromide, provided significant protection from the effects of radiation.

Twisting of the dihedral S–S angle from the normal value of about 90–100°[2] to 27° as found for the five-membered cyclic disulfide 1,2-dithiolane-4-carboxylic acid[3] gives rise to ring strain which has prevented isolation in the pure state of the unsubstituted 1,2-dithiolane.[4-10] The six- and seven-membered ring disulfides, *o*-dithiane and 1,2-dithiepane, are more stable [11] as a consequence of diminished dihedral strain, but there is conflicting evidence concerning the relative reactivities of these two compounds to ring-opening reactions.[12]

Since numerous compounds that contain a thiol group or a potential thiol group β or γ to an amine function protect, to a degree, experimental animals from the effects of ionizing radiation,[13] it was of interest to synthesize amine-substituted cyclic disulfides and the related acyclic dithiols in order to determine the effect of ring size on protective action. Whatever may be the mechanism or mechanisms for the protection afforded by amino disulfides, variation in ring strain with ring size in cyclic amino disulfides might be reflected in the degree of protection provided by these compounds. Similarly, if oxidation of thiol to disulfide in any way were involved in the protective action of thiols, the degree of protection afforded by dithiols might be related to the ease of ring closure to the cyclic disulfides. Aminodithiols, furthermore, should form very stable chelates with numerous metal ions, a property of aminothiols which has been correlated with radiation-protective properties.[14] In this and subsequent papers we shall report on the synthesis and properties of a variety of amine-substituted five-, six-, and seven-membered ring disulfides and related compounds.

1,2-Dithiepan-5-amine (V) was prepared from 3-bromo-1-(2-bromoethyl) propylamine (I) according to Chart I. Prelog has used this amine[15] and the analogous 3-chloro-1-(2-chloroethyl)propylamine[16] in the preparation of 4-aminopiperidines, and our objective was to cyclize similarly the dibromo compound with insertion of the disulfide link. The reaction with sodium disulfide, paralleling Günther and Mautner's[17] synthesis of 1,2-dithia-5-azepane from 2,2′-dichlorodiethylamine, was unsuccessful yielding only tetrahydro-1-thiapyran-4-amine (II) and a large amount of polymer. Since the steam distillate from treatment of the polymer with CN^- contained an excellent yield of II, one can conclude that the polymer was a di- or polysulfide and the depolymerization to II was similar to other reactions which form dialkyl sulfides from the reaction of CN^- on dialkyl disulfides.[18]

The synthesis of 1,2-dithiepan-5-amine (V) was successfully accomplished through the intermediate 3-(benzylthio)-1-[2-(benzylthio)ethyl]propylamine (III) obtained by treatment of I with sodium benzyl sulfide in alcoholic solution. Although the half-life for ring closure of 3-bromopropylamine to azetidine in H_2O at 78° is only about 4 min,[19] no evidence was obtained that a comparable ring closure occurred with I during reaction with the sodium benzyl sulfide. Reduction of III with Na–liquid NH_3[20] containing added propylamine[21] gave 3-amino-1,5-pentanedithiol (IV), purified through its Hg salt. Isolation of the dimercaptan as its hydrochloride without prior conversion to the mercury mercaptide led to difficulties in purification.

(1) (a) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2058. (b) Part I: N. Isenberg and H. F. Herbrandson, *Tetrahedron*, **21**, 1067 (1965).

(2) G. Bergson, *Arkiv Kemi*, **16**, 315 (1961).

(3) O. Foss and O. Tjomsland, *Acta Chem. Scand.*, **12**, 1810 (1958).

(4) Calvin, *et al.*,[5] has isolated 1,2-dithiolane, the molecular weight of which he determined to be 104, as an unstable oil. On attempted purification the oil gave a polymeric disulfide. From the preparation also was isolated a colorless, crystalline solid of mp ≈73° which has been much studied and which has the same empirical formula as does 1,2-dithiolane. In spite of continuing doubts expressed in the literature, it seems clear that this compound of mp ≈73° is the cyclic dimer, $C_6H_{12}S_4$. Brintzinger[6] and Gagon[7] and their coworkers have reported a molecular weight essentially equal to that of the dimer although Yur'ev and Levi[8] reported the compound to be the monomer. Wallace[9] attributed the peak at *m/e* 106 in its mass spectrum to the parent ion and Moreau and Weiss[10] reported a uv spectrum which he considers to be that of the monomer.

(5) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954); see also L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969).

(6) H. Brintzinger, M. Langheck, and H. Ellwanger, *Chem. Ber.*, **87**, 320 (1954).

(7) P. E. Gagon, J. L. Boivin, and G. M. Brown, *Can. J. Chem.*, **37**, 1597 (1959).

(8) Yu. K. Yur'ev and I. S. Levi, *Dokl. Akad. Nauk SSSR*, **73**, 935 (1950).

(9) T. J. Wallace, *J. Amer. Chem. Soc.*, **86**, 2018 (1964).

(10) W. M. Moreau and K. Weiss, *ibid.*, **88**, 204 (1966).

(11) F. S. Dainton, K. J. Ivin, and D. A. G. Walmsley, *Trans. Faraday Soc.*, **56**, 1784 (1960).

(12) A. Schöberl and H. Gräfje, *Ann.*, **614**, 66 (1958); J. G. Affleck and G. Dougherty, *J. Org. Chem.*, **15**, 865 (1950).

(13) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962.

(14) E. C. Knoblock and W. C. Purdy, *Radiation Res.*, **15**, 94 (1961); *J. Electroanal. Chem.*, **2**, 493 (1961).

(15) E. Cerkovnikov and V. Prelog, *Ber.*, **74**, 1648 (1941).

(16) V. Hahn, E. Cerkovnikov, and V. Prelog, *Helv. Chim. Acta*, **26**, 1132 (1943).

(17) W. H. H. Günther and H. G. Mautner, *J. Amer. Chem. Soc.*, **82**, 2762 (1960); *cf.* also F. O. Davis, U. S. Patent 2,715,635 (Aug 16, 1955).

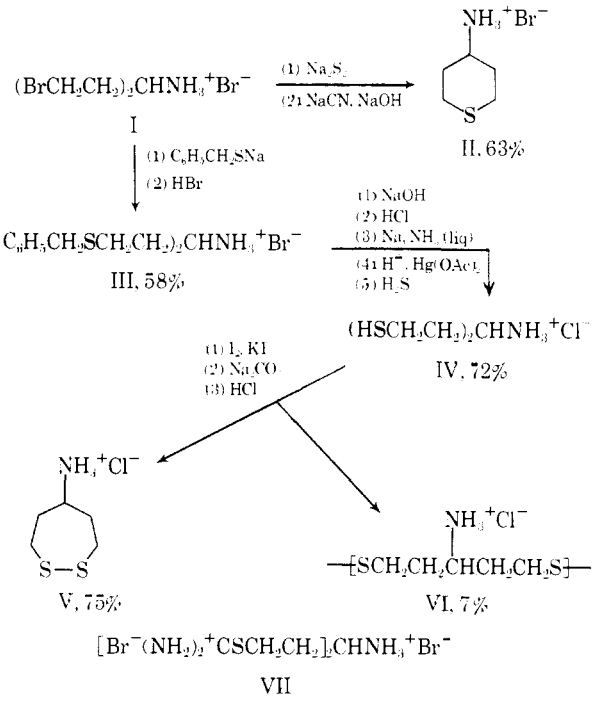
(18) R. G. Hiskey and F. I. Carroll, *J. Amer. Chem. Soc.*, **83**, 4647 (1961).

(19) Extrapolated from data given by G. Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933).

(20) R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

(21) C. G. Overberger and H. Aschkenasy, *J. Amer. Chem. Soc.*, **82**, 4357 (1960).

CHART I



The 1,2-dithiepan-5-amine (V) was obtained from oxidation of the dithiol with I_2 at high dilution. It was essential to extract the 1,2-dithiepan-5-amine from the aqueous solution with benzene rather than ether since use of the latter solvent resulted in complete polymerization of the product when gaseous HCl was passed into the dried extract. This may have been a consequence of cationic polymerization[11,12,22] in the more polar ethereal solvent or of free-radical polymerization[22,23] initiated by peroxides in Et_2O.

Polymeric disulfide VI was the major product when other methods were used for oxidation of the aminodithiol IV: oxidation with I_2 not under conditions of high dilution or oxidation by O_2 in basic solution. Oxidation by air in basic solution proceeded very slowly and oxidation by air or oxygen using $FeCl_3$ as a catalyst was unsuccessful. The polymer VI, as the hydrochloride, had a uv spectrum commensurate with that to be expected of a disulfide[24] polymer ($\lambda_{max}^{H_2O}$ 249 mμ, ε per S–S unit 393) and was soluble in H_2O, giving a solution of pH ≈5. In more basic solutions the polymer was insoluble as the free amine.

The uv spectra of cyclic disulfides reflect the change in the dihedral S–S angle. This has been attributed by Bergson[25] to the ground-state conformation being of lowest energy if the dihedral angle is 90° and the energy of the lowest excited state being independent of the dihedral angle. The observed shift of the uv maximum from about 250 mμ found for acyclic disulfides[24] and 1,2-dithiepanes[5] to about 290 mμ for *o*-dithianes[10,5] and about 330 mμ for 1,2-dithiolanes[26] is thus a consequence of an increase in energy of the ground state as the disulfide ring becomes smaller. 1,2-Dithiepan-5-amine hydrochloride with $\lambda_{max}^{H_2O}$ 257 mμ (ε 404) exhibits a slight bathochromic shift from typical acyclic disulfide absorption and from that of the polymeric amino disulfide VI, perhaps indicating a small deviation from the preferred dihedral angle for the disulfide link.

TABLE I

1,2-DITHIEPAN-5-AMINE HYDROCHLORIDE AND INTERMEDIATES

Compd	Mp, °C[a]	Yield, %	Formula	Analyses
II	217–220.5	64	$C_5H_{12}BrNS$	H, Br, N, S; C[b]
III	113.5–114	58	$C_{19}H_{26}BrNS_2$	C, H, Br, N, S
IV	128–132	72	$C_5H_{14}ClNS_2$	C, H, Cl, N, S
V	224–228[c]	75	$C_5H_{12}ClNS_2$	C, H, Cl, N, S
VII	206–209[c]	66	$C_7H_{20}Br_3N_5S_2$	C, H, Br, N, S

[a] All melting points were with decomposition. [b] C: calcd, 30.31; found, 30.93. [c] Dependent on rate of heating.

The availability of 3-bromo-1-(2-bromoethyl)propylamine (I) from this work and the fact that aminoisothiouronium salts provide protection from the effects of radiation[13] also led us to synthesize 3-amino-1,5-pentanebis(2-thiopseudourea) trihydrobromide (VII).

None of the compounds tested, II, IV, V, or VII, exhibited significant activity in the antiradiation test system.[27] The testing methods have been described.[28]

Experimental Section[29]

Tetrahydropyran-4-amine Hydrobromide.—Dry $CHCl_3$ (1.43 l.) was added to a solution of 162 g (1.24 moles) of tetrahydropyran-4-carboxylic acid[30] in 500 ml of concentrated H_2SO_4, and 121 g (1.86 moles) of powdered NaN_3 was added in small portions to the stirred mixture over a period of 3 hr, the rate of addition being such that the mixture remained below reflux temperature and no excessive foaming occurred. The mixture was stirred at room temperature for 15 hr. The $CHCl_3$ layer was decanted and discarded. The acid layer was cooled and then slowly poured on ice. *Safety precautions should be taken during this step.*[31] A single loud "pop" was heard in this preparation. The solution was covered with a layer of Et_2O, made basic to pH 12 with 10 *N* NaOH solution, and allowed to stand overnight. The supernatant liquid was decanted from the large amount of $Na_2SO_4 \cdot 10H_2O$ which had crystallized. The $Na_2SO_4 \cdot 10H_2O$ was dehydrated to small crystals by heating on a steam bath and was washed (H_2O). The H_2O solution and washings were extracted continuously with Et_2O for 72 hr. Removal of ether from the extract left the free amine as a yellow liquid. The amine was cooled in an ice bath and treated with excess 48% HBr. Removal of excess acid at reduced pressure left 145 g (64.5%) of tan solid amine hydrobromide. A sample decolorized with Norit and crystallized twice from absolute *i*-PrOH had mp 189.5–192° dec, lit.[32] mp 190–191° cor.

3-Bromo-1-(2-bromoethyl)propylamine Hydrobromide (I).—Crude tetrahydropyran-4-amine hydrobromide (77.0 g, 0.432 mole) was heated under reflux with 960 ml (8.42 moles) of 48%

(22) F. S. Dainton, J. A. Davies, P. P. Manning, and S. A. Zahir, *Trans. Faraday Soc.*, **53**, 813 (1957); A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(23) W. H. Stockmayer, R. D. Howard, and J. T. Clarke, *J. Amer. Chem. Soc.*, **75**, 1756 (1953); A. V. Tobolsky and B. Baysal, *ibid.*, **75**, 1757 (1953).

(24) Ethyl disulfide has $\lambda_{max}^{H_2O}$ 2451 Å: S. P. McGlynn, J. Nag-Chaudhuri, and M. Good, *ibid.*, **84**, 9 (1962).

(25) G. Bergson, *Arkiv Kemi*, **18**, 409 (1962); G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, **16**, 1159 (1962).

(26) G. Bergson and B. Anderson, *Arkiv Kemi*, **19**, 173 (1962).

(27) These determinations were made by Dr. J. P. Jacobus and his associates, Walter Reed Army Institute of Research, Washington, D. C. 20012.

(28) E. R. Atkinson, G. R. Handrick, R. J. Bruni, and F. E. Granchelli, *J. Med. Chem.*, **8**, 29 (1965).

(29) Some experimental details are presented in Table I. All melting points are uncorrected. Uv spectra were obtained on a Beckman Model DU spectrophotometer. Ir spectra were measured with a Perkin-Elmer Model 137 spectrophotometer. Analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(30) G. H. Harnest and A. Burger, *J. Amer. Chem. Soc.*, **65**, 370 (1943).

(31) Extremely brisant explosions occurred during two subsequent preparations in which the reaction scale was increased by one-third and a longer reaction time was used. It was found that the explosive mixtures became harmless after standing for 3 weeks in humid air.

(32) V. Prelog, E. Cerkovnikov, and G. Ustricev, *Ann.*, **535**, 37 (1938).

HBr for 47 hr. Distillation of the excess acid at reduced pressure left 119 g (86%) of solid residue. Crystallization of the solid from the minimum volume of EtOH–EtOAc and washing with Me_2CO gave 89.1 g (65%) of product. A sample crystallized five times from EtOH–EtOAc had mp 181–182.5° dec, lit.[32] mp 182–183° cor, and a neutralization equivalent of 325 (theory 326).[33] On the basis of results obtained in the preparation of 3-(benzylthio)-1-[2-(benzylthio)ethyl]propylamine hydrobromide, the product obtained after one crystallization from EtOH–EtOAc was a mixture consisting of about 70% 3-bromo-1-(2-bromoethyl)-propylamine hydrobromide (I) and 30% unreacted tetrahydropyran-4-amine hydrobromide. This mixture was used in subsequent reactions carried out on **I**, and separation of the tetrahydropyran derivative from the product was easily achieved in most cases.

3-(Benzylthio)-1-[2-(benzylthio)ethyl]propylamine Hydrobromide (III).—Benzyl mercaptan (99.2 g, 0.800 mole) was added to a NaOEt solution prepared from 27.6 g (1.20 g-atoms) of Na and 600 ml of absolute EtOH. The resulting solution was added to 130.4 g (0.400 mole) of I (containing about 30% tetrahydropyran-4-amine hydrobromide as a contaminant) dissolved in 600 ml of absolute EtOH; the stirred solution was heated under reflux for 18 hr under dry N_2. After the mixture had been cooled in an ice bath, 87.5 g of NaBr was removed and the filtrate was acidified to pH 1 with 120 ml of 48% HBr. Two-thirds of the solvent was removed by distillation at reduced pressure and under N_2. Dilution of the residue with H_2O to 1 l. caused the precipitation of an oil which rapidly crystallized to a white solid. The solid (104 g, 63% yield, 91% conversion, mp 108–112° dec) was removed by filtration and washed (H_2O, Et_2O). Tetrahydropyran-4-amine hydrobromide (40.5 g) was recovered by evaporation of the filtrate to dryness at reduced pressure and extraction of the residue with hot absolute *i*-PrOH. The bis(benzylsulfide) derivative was extracted (Et_2O, Soxhlet extractor) for 20 hr to remove $PhCH_2SH$. After the extraction, 96 g of undissolved product remained which had mp 112–113.5° dec. Crystallization once from H_2O and four times from absolute *i*-PrOH gave the analytical sample. Potentiometric titration in 63% EtOH with aqueous $AgNO_3$ solution gave equiv wt 413 (calcd 412).

3-(Benzylthio)-1-[2-(benzylthio)ethyl]propylamine Hydrochloride.—NaOH (500 ml, 3 *N*) was added to a suspension of 192 g (0.464 mole) of 3-(benzylthio)-1-[2-(benzylthio)ethyl]propylamine hydrobromide in 400 ml of H_2O and the stirred mixture was heated on a steam bath until all the solid had dissolved and the free amine separated as an oil. The mixture was cooled and extracted with five 100-ml portions of Et_2O. The combined Et_2O extract was washed with two 100-ml portions of H_2O and dried over Na_2SO_4. Passage of dry HCl into the extract caused a voluminous precipitation of product which, after addition of more Et_2O, was removed by filtration and washed thoroughly (Et_2O). The filtrate was treated repeatedly with dry HCl until no further precipitation of product occurred. A yield of 160 g (93.5%) of white solid, mp 117.5–118° dec, was obtained. A sample was recrystallized three times from absolute *i*-PrOH to constant mp 120–120.5° dec.

3-Amino-1,5-pentanedithiol Hydrochloride (IV).—3-(Benzylthio)-1-[2-(benzylthio)ethyl]propylamine hydrochloride (80.0 g, 0.217 mole) was dissolved in 250 ml of *n*-$PrNH_2$ and 2.1 l. of liquid NH_3 was added. Na (17.1 g, 0.743 g-atom) was added in small pieces to the stirred solution, moisture being excluded from the system, until a permanent blue color was attained. An additional 0.9 g of Na was added and the solution was stirred for 1 hr, the blue color remaining during this time. Solvent was completely removed at reduced pressure and under N_2. EtOH (150 ml) was added to the cream-colored solid residue and, after thorough stirring and cooling in an ice bath, the mixture was acidified to a pH of 1 with 650 ml of 6 *N* HCl. A solution of 103.8 g of $Hg(OAc)_2$ in 350 ml of H_2O was added to the cloudy, colorless solution which had a layer of PhMe floating on the surface. The mercury mercaptide precipitate was coagulated by warming on a steam bath and the mixture was allowed to stand overnight. The solid was removed by filtration and was extracted for 15 hr in a Soxhlet extractor with EtOH to remove bibenzyl. The dried mercury mercaptide (117.5 g) was suspended in 400 ml of absolute MeOH and decomposed by passage of H_2S into the mixture for 1 hr. HgS was removed by filtration through Celite, suspended in 75 ml of absolute MeOH, and again treated with H_2S. After filtration, the combined filtrate was evaporated to dryness in a vacuum desiccator over NaOH. The product was obtained as a white, crystalline solid (29.2 g, 71.8%), mp 128–132° dec. The solid was recrystallized three times from absolute *i*-PrOH; equiv wt 93.1 (calcd 93.9) by iodimetric titration; ir, 2620 and 2550 cm^{-1} (SH).

An attempt to prepare 3-amino-1,5-pentanedithiol hydrobromide by debenzylation of 3-(benzylthio)-1-[2-(benzylthio)-ethyl]propylamine hydrobromide and isolation of the dimercaptan *via* the mercury mercaptide was unsuccessful because the mercury mercaptide hydrobromide was much less soluble in MeOH than the hydrochloride and could not be decomposed with H_2S. The mercury mercaptide hydrobromide could be converted to the hydrochloride by repeated precipitation from concentrated HCl. Isolation of the dithiol hydrobromide without prior conversion to the mercury mercaptide was found to be unsatisfactory due to subsequent difficulties in purifying the product.

1,2-Dithiepan-5-amine Hydrochloride (V).—A solution of 2.15 g (0.0114 mole) of crude IV in 50 ml of distilled H_2O and a 0.1 *N* I_2–KI solution were added dropwise and simultaneously to 175 ml of distilled H_2O with efficient magnetic stirring. The dithiol was added at such a rate that it was always in excess and the solution remained colorless until the end point. IV was added over a period of 1.5 hr, and after 3.25 hr the end point was reached with the addition of *ca.* 200 ml of I_2 solution. The solution was made basic to pH 10 by the addition of 4 g (0.038 mole) of Na_2CO_3 and a small amount of polymer precipitated. More I_2 solution (18 ml) was added dropwise to the stirred solution until a faint yellow color seemed to persist for a few seconds. The solution was cooled in an ice bath and saturated with about 60 g of Na_2CO_3. The cold solution was extracted with five 50-ml portions of thiophene-free C_6H_6 and the combined extract was dried (Na_2SO_4). The C_6H_6 extract was deoxygenated by bubbling N_2 through the solution for 10 min and then dry HCl was slowly passed in until in slight excess. The white solid which precipitated was removed by filtration.

A second 2.15-g sample was oxidized as described above and a total of 3.2 g (75%) of product was obtained from both oxidations. The aqueous phases from the two oxidations were combined and extracted continuously for 3 days with C_6H_6. After the extract had been dried (Na_2SO_4) and deaerated with N_2, dry HCl gave an additional 0.3 g of product. A total of 3.5 g (82%) of product was thus obtained. Crystallization of the product once from N_2-saturated EtOH–EtOAc removed 0.3 g of insoluble polymeric material and three more crystallizations from boiled, N_2-saturated absolute EtOH gave the analytical sample; equiv wt 185 (calcd 186) by potentiometric titration with aqueous $AgNO_3$, λ_{max}^{EtOH} 258 mμ (ε 418), $\lambda_{max}^{H_2O}$ 257 mμ (ε 404).

The polymeric by-product, isolated in this preparation, in hot EtOH was an insoluble gum which hardened on cooling to a light yellow granular solid having $\lambda_{max}^{H_2O}$ 249 mμ (ε 393). The polymer was soluble in aqueous solutions of its own pH (*ca.* 5) but was insoluble in solutions more basic.

It was found essential to extract the free amino disulfide from aqueous solution with C_6H_6 rather than Et_2O since use of the latter resulted in complete polymerization of the product to a white rubbery mass when HCl was passed into the extract.

Tetrahydro-1-thiapyran-4-amine Hydrobromide (II).—The method of preparation was based on that used by Günther and Mautner[17] for the preparation of 1,2-dithia-5-azepane hydrochloride.

A mixture of 28.5 g (0.117 mole) of $Na_2S \cdot 9H_2O$ and 3.74 g (0.117 g-atom) of powdered S was heated under N_2 until a clear, dark red melt was obtained. A solution of Na_2CO_3 (17.8 g) in the minimum volume of H_2O was added to the hot melt, the solution was thoroughly mixed, and crushed ice was added until the total volume was 475 ml. The mixture was cooled to 0° in an ice–salt bath and a mixture of 32.6 g (0.100 mole) of I (containing tetrahydropyran-4-amine hydrobromide as a contaminant) in 30 ml of H_2O and 90 g of ice was added. The mixture was stirred thoroughly and then was allowed to stand, with occasional stirring, for 72 hr at 0°. A large amount of brown polymer had precipitated from solution after 2 hr. After 72 hr the mixture was steam distilled. A solution of 0.5 g of KCN in 60 ml of 6 *N* NaOH was added after 4 l. of distillate had been collected and the pH of the distillate had dropped from 9 to 8.5. The distillation was continued until a total of 8 l. had been collected. The polymer which had precipitated during the reaction slowly dissolved after the addition of CN^-. At the end of the distillation, 3.7 g of polymer remained undissolved. The distillate was acidified with

(33) Determined by titration of the sample in methanol-benzene with sodium methoxide–benzene by the method of J. S. Fritz and N. M. Lisicki, *Anal. Chem.*, **23**, 589 (1951).

excess 6 *N* HBr and solvent was removed at reduced pressure. The residue, consisting of a mixture of a brown gum and a tan crystalline solid, was triturated with warm absolute EtOH and filtered to remove insoluble gum. Removal of solvent from the filtrate left 12.6 g (63.6%) of a brown crystalline solid. Five crystallizations from absolute *i*-PrOH removed more insoluble gum and gave the analytical sample, a white solid which crystallized from *i*-PrOH in the form of rosettes.

3-Amino-1,5-pentanebis(2-thiopseudourea) Trihydrobromide (VII).—The preparation was based upon the method of Doherty, *et al.*[34] I (50.0 g, 0.153 mole; crystallized twice from EtOH–EtOAc and containing tetrahydropyran-4-amine hydrobromide as a contaminant) was added to a hot solution of 29.0 g (0.382 mole) of thiourea in 452 ml of absolute *i*-PrOH (containing 0.25% H_2O). After being stirred for 5 min at 85°, the solution became cloudy and a white semisolid began to precipitate. Heating was discontinued for a few minutes until the mild reaction subsided, and then the mixture was heated under reflux with stirring for 0.5 hr until the precipitate had solidfied and the supernatant liquid was clear. The mixture was cooled, the supernatant liquid was decanted, and the remaining solid was washed with *i*-PrOH and dried. The solid (48.5 g, 66%) had mp 168–194° dec and neut equiv 184 (calcd 159), determined by titration of a sample in 1:1 C_6H_6–MeOH with NaOMe–C_6H_6 solution by the method of Fritz and Lisicki.[34] Removal of solvent at reduced pressure from the decanted solution left a white solid, mp 88–130° dec.

The solid which precipitated during the reaction was crystallized three times from MeOH to give a product, mp 205–206° dec, and neut equiv 180–198. Three more crystallizations from MeOH gave the analytical sample.

(34) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Amer. Chem. Soc.*, **79**, 5667 (1957).

Cyclic Disulfides. III. (−)-(*S*)-1,2-Dithiepan-4-amine and Related Compounds[1]

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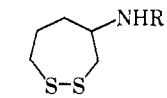
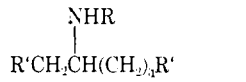
The conversion of aminodiols to N-benzenesulfonyl bis(benzenesulfonates), displacement of the sulfonate groups with S-containing nucleophiles, and reductive removal of the N-benzenesulfonyl group leads to aminodithiols which can be oxidized to cyclic disulfides. By such a sequence of reactions from (+)-(*S*)-glutamic acid through (*S*)-2-amino-1,5-pentanediol, (−)-(*S*)-1,2-dithiepan-5-amine (Ia) was synthesized. This compound and 2,2′-iminodiethanethiol (IIIa), prepared in a similar way, have been found to provide no significant protection from the effects of ionizing radiation.

In extending our study of the relatively unstrained amine-substituted seven-membered ring disulfides as possible radiation-protective drugs, it was of interest to prepare 1,2-dithiepan-4-amine (Ia) since this compound has the amine group β to one sulfur function and δ to the other. Little protective action apparently is provided if the sulfur and amine functions in monothiols are separated by more than three carbon atoms.[2]

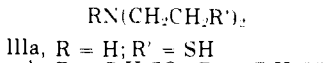
The synthesis of Ia by the method used for the preparation of 1,2-dithiepan-5-amine[1b] would require the use of a 4-halo-1-(halomethyl)butylamine. Such a substituted amine, as the free base, easily would undergo cyclization to a piperidine and/or an aziridine. Blocking groups such as the phthaloyl,[3a] benzoyl,[3] and arenesulfonyl[3,4] substituents on N have been used to diminish the basicity of the amine group and prevent its participation in neighboring-group reactions in the synthesis of aminothiols. Of particular interest was the use of arenesulfonyl and methanesulfonyl (mesyl) groups as blocking agents on amino alcohols, since the alcohol converted to its sulfonate ester could be subjected to a nucleophilic displacement by any of a variety of sulfur-containing nucleophiles to yield a mercaptan precursor. It was anticipated that the aminothiol then could be obtained in a single hydrolysis or reduction step that would remove the blocking group on the nitrogen and form the free thiol from its precursor.



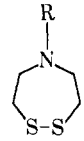
Ia, R = H
b, R = $C_6H_5SO_2$
c, R = CH_3SO_2



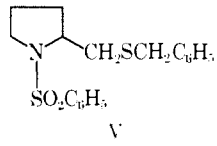
IIa, R = H; R′ = SH
b, R = $C_6H_5SO_2$; R′ = $C_6H_5SO_2$
c, R = CH_3SO_2; R′ = CH_3SO_2
d, R = $C_6H_5SO_2$; R′ = SCN
e, R = CH_3SO_2; R′ = SCN
f, R = CH_3SO_2; R′ = S_2O_3Na
g, R = $C_6H_5SO_2$; R′ = AcS
h, R = $C_6H_5SO_2$; R′ = SH
i, R = CH_3SO_2; R′ = SH



IIIa, R = H; R′ = SH
b, R = $C_6H_5SO_2$; R′ = $C_6H_5SO_2$
c, R = $C_6H_5SO_2$; R′ = SCN
d, R = CH_3SO_2; R′ = CH_3SO_2
e, R = CH_3SO_2; R′ = SCN



IVa, R = $C_6H_5SO_2$
b, R = H
c, R = CH_3SO_2



V

The behavior of diethanolamine, 2,2′-iminodiethanol, was studied as a model compound because of its availability and because the aminodithiol which would result, 2,2′-iminodiethanethiol (IIIa), had not been tested on this program although it had been prepared[5,6] and tested[6] elsewhere.

N,N-Bis(2-hydroxyethyl)benzenesulfonamide diben-

(1) (a) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2058. (b) Part II: H. F. Herbrandson and R. H. Wood, *J. Med. Chem.*, **12**, 617 (1969).

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