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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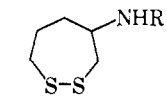
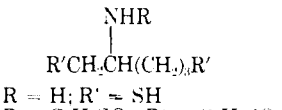
The conversion of aminodiols to N-benzenesulfonyl bis(benzenesulfonates), displacement of the sulfonate groups with S-containing nucleophiles, and reductive removal of the N-benzenesulfonyl group leads to aminodithiols which can be oxidized to cyclic disulfides. By such a sequence of reactions from (+)-(*S*)-glutamic 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]

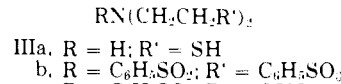
The synthesis of Ia by the method used for the preparation of 1,2-dithiepan-5-amine[1b] would require the use of a 4-halo-1-(halomethyl)butylamine. Such a substituted amine, as the free base, easily would undergo cyclization to a piperidine and/or an aziridine. Blocking groups such as the phthaloyl,[3a] 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.



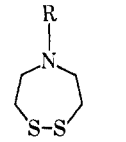
Ia, R = H
b, R = $C_6H_5SO_2$
c, R = CH_3SO_2



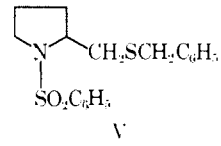
IIa, R = H; R′ = SH
b, R = $C_6H_5SO_2$; R′ = $C_6H_5SO_2$
c, R = CH_3SO_2; R′ = CH_3SO_2
d, R = $C_6H_5SO_2$; R′ = SCN
e, R = CH_3SO_2; R′ = SCN
f, R = CH_3SO_2; R′ = S_2O_3Na
g, R = $C_6H_5SO_2$; R′ = AcS
h, R = $C_6H_5SO_2$; R′ = SH
i, R = CH_3SO_2; R′ = SH



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).

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

(3) (a) V. A. Portnyagina, *Tiolovye Soedin. v Med., Ukr. Nauchn.-Issled. Sanit.-Khim. Inst., Tr Nauchn. Konf., Kiev, 1957*, 31 (1959); *Chem. Abstr.*, **54**, 24508*b* (1960); (b) V. A. Portnyagina, *Ukr. Khim. Zh.*, **25**, 102 (1959); *Chem. Abstr.*, **53**, 19953*c* (1959).

(4) G. R. Handrick and E. R. Atkinson, *J. Med. Chem.*, **9**, 558 (1966).

(5) J. Harley-Mason, *J. Chem. Soc.*, 320 (1947).

(6) L. F. Semenov and E. A. Prokudina, *Med. Radiol.*, **1**, 70 (1956); *Chem. Abstr.*, **52**, 6612*f* (1958).

zenesulfonate[7] (IIIb) was converted to the dithiocyanate[8] IIIc in essentially a quantitative yield. The rate in boiling 95% EtOH, followed by titration of unreacted thiocyanate ion with standard $Hg(NO_3)_2$, was $3.3 \times 10^{-4}\ M^{-1}\ sec^{-1}$; an excellent second-order plot was obtained for more than 90% of the reaction. With alcoholic alkali the dithiocyanate yielded 70% N-benzenesulfonyl-1,2-dithia-5-azepane[12] (IVa) which on reduction with Zn–HCl[13] gave 2,2′-iminodiethanethiol (IIIa) isolated through its Hg salt as the hydrochloride. Alternatively, hydrolysis of the N-benzenesulfonyl group by H_2SO_4[13] gave a very low yield of 1,2-dithia-5-azepane (IVb).[14] Removal of the benzenesulfonyl group with 30% HBr–AcOH and phenol[13] was unsuccessful.

Because of the difficulties which were encountered in removal of the blocking benzenesulfonyl group from the nitrogen by methods that left the cyclic disulfide ring intact, use of the mesyl blocking group[15] was explored since it has been claimed[15a] that methanesulfonamides are hydrolyzed more readily than are arenesulfonamides. N,N-Bis(2-hydroxyethyl)methanesulfonamide dimethanesulfonate (IIId), from diethanolamine and methanesulfonyl chloride, reacted with NaSCN in boiling 95% EtOH with a second-order rate constant of $8.8 \times 10^{-4}\ M^{-1}\ sec^{-1}$, the reaction being followed for over 90% of its course. With alcoholic alkali the resulting dithiocyanate (IIIe) gave N-methanesulfonyl-1,2-dithia-5-azepane (IVc) from which the methanesulfonyl group could not be removed by hydrolysis with H_2SO_4 or HBr and phenol nor by reduction with Zn or $SnCl_2$ and acid.

The 2-amino-1,5-pentanediol necessary for the synthesis of 4-amino-1,2-dithiepane was obtained from the LAH reduction of diethyl (+)-(*S*)-glutamate hydrochloride. The isolation procedure for the water-soluble aminodiol, a modification[16] of methods developed by Karrer, *et al.*,[17] and by Brown and Van Gulick[18] resulted in a recovery of 56% (*S*)-2-amino-1,5-pentanediol and 23% 2-pyrrolidinemethanol, the latter undoubtedly resulting from reduction of 5-carbethoxy-2-pyrrolidone formed by cyclization of the amino ester in the basic solution.[17b] The amount of pyrrolidine formed was diminished when the reduction was carried out initially at 0° rather than at the boiling point of the solvent.

The aminodiol with benzenesulfonyl chloride and with methanesulfonyl chloride gave the benzenesulfonyl (IIb) and mesyl (IIc) derivatives which were converted to the dithiocyanates (IId and IIe) and cyclized with alkali to (−)-(*S*)-4-benzenesulfonamido-1,2-dithiepane (Ib) and (−)-(*S*)-4-methanesulfonamido-1,2-dithiepane (Ic). The dithiepane Ic also was obtained, in a 37% yield from IIc, by base hydrolysis of the bis-Bunte salt IIf. Reduction of the benzenesulfonamido derivative Ib with Na–liquid NH_3 gave the desired (*S*)-2-amino-1,5-pentanedithiol (IIa) isolated as its hydrochloride. The dithiol IIa was obtained also by conversion of IIb to (*S*)-2-benzenesulfonamido-1,5-pentanedithiol diacetate (IIg) and then either direct reduction of the dithiol diacetate with Na–liquid NH_3 or ammonolysis of the diacetate and reductive removal of the benzenesulfonyl protective group. Oxidation of the dithiol IIa to (−)-(*S*)-4-amino-1,2-dithiepane (Ia) was accomplished with aqueous I_2 in dilute solution.

The methanesulfonyl group of (−)-(*S*)-4-methanesulfonamido-1,2-dithiepane (Ic) was not removed by reduction either with Na–liquid NH_3 or with Zn and acid; from each of these reductions (*S*)-N-[4-mercapto-1-(mercaptomethyl)butyl]methanesulfonamide (IIh) resulted. That arenesulfonamides are reduced by Na–NH_3 and alkylsulfonamides are not indicates that the reduction, when it occurs, proceeds through an electron-transfer from the liquid NH_3 solution to the aromatic ring.[19]

Sodium benzylthiol with IIb gave an oily product that lacked the medium intensity N–H stretching vibration at 3390 cm^{-1} characteristic of secondary sulfonamides. The compound, which was not identified, may have been the pyrrolidine resulting from an intramolecular displacement of the benzenesulfonate anion by the sulfonamide anion.[8]

The dithiepane derivatives Ia (as the hydrochloride), Ic, and IVb (as the hydrochloride) absorb at wavelengths slightly higher in the uv than do ethyl disulfide[20] or cystamine, 2,2′-dithiobisethylamine.[21] Since electronegative substituents cause blue shifts of the disulfide absorption,[22] the red shifts observed for the dithiepane derivatives must not be a consequence of the fact that Ia and IVb are amine salts and Ic is an amide but may result from small distortions of the disulfide dihedral angle from ideality.[1b]

Neither (−)-(*S*)-4-amino-1,2-dithiepane (Ia) nor 2,2′-iminodiethanethiol (IIIa) provided significant protection from the effects of ionizing radiation.

Experimental Section[23]

N,N-Bis(2-hydroxyethyl)benzenesulfonamide Dithiocyanate (IIIc).—N,N-Bis(2-hydroxyethyl)benzenesulfonamide dibenzene-

(7) G. S. Skinner, H. R. Krysiak, and J. A. Perregrino, *J. Amer. Chem. Soc.*, **77**, 2248 (1955).

(8) Many S-containing nucleophiles other than CNS^- could be used provided the nucleophile is not more basic than the sulfonamide anion. If the nucleophile were more basic than the conjugate base of the sulfonamide, *e.g.*, the pK_a of benzylthiol (in H_2O–EtOH) is 11.8,[9] whereas that of benzenesulfonamide (in H_2O) is 10.00,[10] the sulfonamide anion itself could behave as a neighboring group and give rise to a 1-(benzenesulfonyl)-aziridine.[11]

(9) J. Maurin and R. A. Paris, *Compt. Rend.*, **232**, 2428 (1951).

(10) A. V. Willi, *Helv. Chim. Acta*, **39**, 46 (1956).

(11) M. S. Kharasch and H. M. Priestly, *J. Amer. Chem. Soc.*, **61**, 3425 (1939); W. J. Gensler, B. A. Brooks, and W. R. Koehler, *J. Org. Chem.*, **30**, 4365 (1965).

(12) No polymer appeared to be formed in this or other similar syntheses even though H. Brintzinger, M. Langheck, and H. E. Ellwanger, *Chem. Ber.*, **87**, 320 (1954), have stated that polymeric rather than cyclic disulfides result from attempts to synthesize from dithiocyanates disulfides with more than four carbons in the ring.

(13) S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959).

(14) W. H. H. Günther and H. G. Mautner, *J. Amer. Chem. Soc.*, **82**, 2762 (1960).

(15) (a) C. S. Marvel, M. D. Helfrick, and J. P. Belsley, *ibid.*, **51**, 1272 (1929); (b) R. Adams and W. P. Samuels, *ibid.*, **77**, 5375 (1955); (c) S. Hünig and J. Utermann, *Chem. Ber.*, **88**, 1485 (1955).

(16) D. Kruh, unpublished results.

(17) (a) P. Karrer, P. Portmann, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948); (b) P. Karrer and P. Portmann, *ibid.*, **31**, 2088 (1948).

(18) R. F. Brown and N. M. Van Gulick, *J. Amer. Chem. Soc.*, **77**, 1079 (1955).

(19) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson, and P. Wriede, *ibid.*, **89**, 5311 (1967).

(20) S. P. Glynn, J. Nag-Chaudhuri, and M. Good, *ibid.*, **84**, 9 (1962).

(21) N. A. Rosenthal and G. Oster, *ibid.*, **83**, 4445 (1961).

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

(23) Some experimental details are presented in Table I. All melting points are uncorrected. Uv absorption 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.

TABLE I

SUBSTITUTED 1,2-DITHIEPANES AND INTERMEDIATES

Compd	Mp, °C	Yield, %	Formula	Analyses
Ia[a]	229.5–230[b]	72	$C_9H_{12}ClNS_2$	C, H, Cl, N, S
Ib	105–105.5	43	$C_{11}H_{15}NO_2S_3$	C, H, N, S
Ic	122.5–123.5	24,[c] 37[d]	$C_6H_{13}NO_2S_3$	C, H, N, S
IIc	75.5–77	72	$C_8H_{19}NO_5S_3$	C, H, N, S
IIIc	71–72.5	99	$C_{12}H_{13}N_3O_2S_3$	C, H, N, S
IIId	114.5–115.2	99	$C_7H_{17}NO_8S_2$	C, H, N, S
IVa	109–110.5	72	$C_{10}H_{13}NO_2S_2$	C, H, N, S
IVc	99.5–100.2	49	$C_5H_{11}NO_2S_2$	C, H, N, S

[a] Hydrochloride. [b] With decomposition. [c] Dependent on rate of heating. [d] From IIe. [e] From IIc *via* IIf.

sulfonate[7] (80 g, 0.152 mole) and NaSCN (29.8 g, 0.375 mole) were brought to reflux in 400 ml of 95% EtOH. The progress of the reaction was followed by removing 5.00-ml samples by pipet, diluting with 50 ml of H_2O, adding 1 ml of a saturated solution of ferric ammonium sulfate, and titrating with standard $Hg(NO_3)_2$ solution. The reaction was 91% complete in 3 hr under these conditions; when 0.785 mole of NaSCN was used with 0.156 mole of the benzenesulfonate ester, the reaction was complete within 72 min. Plots of the data as a second-order reaction, treating each benzenesulfonate group as if it behaved independently of the substituent five atoms removed, gave good straight lines which led to the conclusion that the second-order rate constant under these conditions for the disappearance of thiocyanate ion was $3.3 \times 10^{-4} M^{-1}$ sec^{-1}. The dithiocyanate separated as an oil which gradually crystallized when the reaction mixture was poured into 3 l. of water. It crystallized from EtOAc–petroleum ether (bp 30–60°) as long needles; ir, 2130 (thiocyanate), 1320, 1160 cm^{-1} (sulfonamide).

N-Benzenesulfonyl-1,2-dithia-5-azepane (IVa).—To a 5% solution of KOH in 175 ml of deaerated 95% EtOH at 35° was added 3.0 g (0.09 mole) of IIIc. The solution was allowed to stand at room temperature for 24 hr after which it was diluted with a large amount of H_2O. Filtration gave 1.8 g of product which crystallized as rosettes from MeOH; ir, 1330 and 1160 cm^{-1} (sulfonamide). It was identical with a sample prepared from 1,2-dithia-5-azepane[14] with benzenesulfonyl chloride.

2,2′-Iminodiethanethiol (IIIa) Hydrochloride.—To IVa (24.8 g, 0.092 mole) in 200 ml of glacial HOAc and 50 ml of concentrated HCl at reflux was added 118 g (1.8 g-atoms) of Zn dust over a period of 4 hr. Three 50-ml quantities of concentrated HCl were added over the same period. Most of the thiophenol which was formed was removed by steam distillation, the trace of Zn that remained was removed by filtration, and the mercaptan was precipitated with 36 g (0.113 mole) of mercuric acetate. The precipitate was filtered, washed well (hot H_2O), and ground in a mortar. The Hg salt of thiophenol was removed by heating 10 g of the Hg salt twice with 75 ml of pyridine, dissolving in 60 ml of hot, concentrated HCl, and precipitating by dilution with H_2O. The dry, powdered Hg salt was then suspended in hot, absolute EtOH and treated with H_2S. Filtration, concentration of the filtrate, and dilution with dry Et_2O gave IIIa·HCl as very hygroscopic platelets, mp 151–156° (sealed capillary). After one recrystallization from absolute *i*-PrOH, the hydrochloride weighed 4.4 g (28%) and had mp 158–159° (sealed capillary, lit.[5] mp 161°); ir, 2490 and 2420 cm^{-1} (SH).

1,2-Dithia-5-azepane (IVb) Hydrochloride.—A mixture of 4.0 g of IVa in 20 ml of 90% H_2SO_4 was poured onto ice after standing for 3 days in the dark. The impure starting material which separated, 3.5 g, was removed by filtration, and the aqueous solution was made basic and extracted with Et_2O. After the Et_2O solution had been dried, gaseous HCl precipitated from it a small amount of material which, from its mp 182–185° (lit.[14] mp 178°, resolidified, 230° dec) and ir spectrum, was demonstrated to be 1,2-dithia-5-azepane hydrochloride.

N,N-Bis(2-hydroxyethyl)methanesulfonamide Dimethanesulfonate (IIId).—To a solution of 52.3 g (0.498 mole) of reagent grade diethanolamine in 375 ml of pyridine was added slowly, with stirring at a temperature below 0°, 215 g (1.87 moles) of $MeSO_2Cl$. The mixture was maintained at 0° for 10 hr and then poured onto a mixture of 400 cc of concentrated HCl and 1 kg of ice. More ice was added as needed to maintain the temperature below 0°. The crude product, after filtration and washing with H_2O, weighed 167 g. The analytical sample was recrystallized from EtOH, EtOH–$CHCl_3$, and finally from Me_2CO with charcoal.

N,N-Bis(2-hydroxyethyl)methanesulfonamide Dithiocyanate (IIIe).—The reaction was carried out in a manner similar to that used for the preparation of IIIc with 151 g (0.444 mole) of unrecrystallized IIId and 183 g (2.26 moles) of NaSCN in 1.2 l. of 95% EtOH. Samples of 2 ml were removed for titration. The reaction was complete within 75 min, and the data gave a good straight line for a second-order reaction with $k = 8.8 \times 10^{-4}$ M^{-1} sec^{-1}. Dilution of the reaction mixture to 4 l. with H_2O caused the product to separate as an oil. The oil and supernatant were used directly, without purification, for preparation of the 1,2-dithia-5-azepane IVc.

N-Methanesulfonyl-1,2-dithia-5-azepane (IVc).—To the aqueous phase which had been decanted from the oily IIIe was added 120 g of KOH. The oil was dissolved with warming in 1700 ml of 95% EtOH containing 135 g of KOH. Both solutions were allowed to stand at room temperature for 2 days, and then, after a small amount of black material had been removed from the EtOH solution by filtration, the aqueous and alcoholic solutions were combined and continuously extracted with Et_2O for 21 hr. The Et_2O and EtOH were removed from the extract by distillation to give 46.3 g of cream-colored solid. One recrystallization from 95% EtOH with charcoal and one recrystallization from MeOH gave colorless needles; ir, 1320 and 1150 cm^{-1} (sulfonamide).

Diethyl (+)-(*S*)-Glutamate Hydrochloride.—A suspension of 244 g (1.66 moles) of (+)-(*S*)-glutamic acid in 2.5 l. of absolute EtOH was saturated with dry HCl, 250 ml of thiophene-free dry C_6H_6 was added, and the solution was heated under reflux for about 1 week; H_2O formed in the reaction was removed by azeotropic distillation through a fractionating column and collection in a Dean–Stark trap. Solvent was removed at reduced pressure and crystallization of the solid residue once from absolute EtOAc gave 305.4 g (76.7%) of white solid, mp 105–110° dec and $[\alpha]^{27}D$ 19.5° (*c* 18.6, water). A sample was recrystallized three times from absolute EtOAc to constant mp 110.5–112° dec (lit.[24] mp 96–98°).

Monosodium (*S*)-glutamate monohydrate of 99% (min) purity (General Mills) was found to have $[\alpha]^{27}D$ −1.8° (*c* 23.5, H_2O). Esterification of this monosodium (*S*)-glutamate to diethyl (+)-(*S*)-glutamate hydrochloride gave a product which, after one recrystallization from EtOAc, had $[\alpha]^{27}D$ 20.6° (*c* 20.2, H_2O).

(*S*)-2-Amino-1,5-pentanediol and (+)-(*S*)-2-Pyrrolidinemethanol.—Diethyl (+)-(*S*)-glutamate hydrochloride (168 g, 0.678 mole) was added over a period of 2 hr to a suspension of 103 g (2.71 moles) of LAH in 1.5 l. of dry THF cooled to 0° in an ice–salt bath. The mixture was stirred at room temperature for 23 hr and then heated under reflux with stirring for 22 hr. It was cooled and decomposed by the addition of 830 ml of *i*-PrOH and then 675 ml of a saturated NaCl. The inorganic salts were removed by filtration and extracted with *i*-PrOH in a Soxhlet extractor for 15 hr. The extract was combined with the filtrate, and solvent was removed by distillation at reduced pressure and under N_2.

This preparation was repeated, starting with 152 g (0.634 mole) of diethyl (+)-(*S*)-glutamate hydrochloride. Distillation under N_2 of the combined product gave 30.8 g (23.3%) of 2-pyrrolidinemethanol, bp 120–143° (0.8 mm) [lit.[17b] bp 90–140° (10 mm)],

(24) H. M. Chiles and W. A. Noyes, *J. Amer. Chem. Soc.*, **44**, 1798 (1922).

$[\alpha]^{21}D$ +64° (neat; sp gr 1.05),[25] and 87.3 g (56%) of (*S*)-2-amino-1,5-pentanediol, bp 150–159° (1.5 mm) [lit.[17b] bp 125–135° (0.05 mm)].

(*S*)-2-Benzenesulfonamido-1,5-pentanediol Dibenzenesulfonate (IIb).—Benzenesulfonyl chloride (314 ml, 2.46 moles) was added dropwise over a period of 4 hr to a stirred solution of 78.2 g (0.656 mole) of (*S*)-2-amino-1,5-pentanediol in 492 ml of dry pyridine cooled to −2° in an ice–salt bath. The mixture was stirred at 5° for 36 hr and then at 10° for 8 hr, moisture being excluded, after which it was slowly poured into a stirred mixture of 525 ml of concentrated HCl and sufficient ice to maintain a temperature below 0°. The precipitated semisolid was taken up with CH_2Cl_2 and the layers were separated. The aqueous phase was extracted with three 150-ml portions of CH_2Cl_2 and the combined CH_2Cl_2 solution was washed with two 150-ml portions of H_2O and dried (Na_2SO_4). Removal of solvent by distillation left 312 g (76%) of a viscous amber oil: ir, 1350 and 1180 cm^{-1} (sulfonamide and sulfonate, broad).

(*S*)-2-Benzenesulfonamido-1,5-pentanediol Dithiocyanate (IId).—The synthesis, similar to that of IIe but accomplished by a 13-hr reflux of 61.5 g (0.750 mole) of NaSCN and 94.4 g (0.150 mole) of IIb in 385 ml of EtOH, gave an oil which was extracted into CH_2Cl_2, washed, and dried (Na_2SO_4). Removal of the solvent under reduced pressure left an amber oil: ir, 2140 and 2040 (thiocyanate) and at 1330 and 1160 cm^{-1} (sulfonamide).

(−)-(*S*)-4-Benzenesulfonamido-1,2-dithiepane (Ib).—IId, as prepared above, was treated with 145 g (2.25 moles) of KOH in 3 l. of 95% EtOH as in the synthesis of IVa. Acidification to a pH of 1 with 210 ml of concentrated HCl, removal of the KCl by filtration, and evaporation of the solvent under reduced pressure gave a residue which was extracted into CH_2Cl_2, washed, and dried (Na_2SO_4). Removal of the CH_2Cl_2 by distillation left 42.5 g (97.8%) of a viscous dark amber oil. The oil was stirred thoroughly with five 500-ml portions of warm Et_2O. Removal of the Et_2O from the combined extract left a light yellow oil which crystallized to an oily yellow solid (27.5 g). Crystallization of the solid once from aqueous EtOH gave 18.8 g of a yellow solid. Five additional recrystallizations from aqueous EtOH, treating the product twice with Norit, gave the analytical sample as white plates: $[\alpha]^{25}D$ −5° (*c* 3.36, $CHCl_3$); λ_{max}^{EtOH} 272 mμ (ε 803), 265 (960), and 259 (818); ir, 1320 and 1160 cm^{-1} (sulfonamide).

(*S*)-2-Benzenesulfonamido-1,5-pentanedithiol Diacetate (IIg).—Thiolacetic acid (65.7 g, 0.863 mole) was cooled in an ice bath and neutralized with 338 ml of 2.5 *N* NaOEt to a phenolphthalein end point determined by dissolving a small aliquot of the solution in distilled H_2O containing a few drops of phenolphthalein at 1-ml intervals near the end point. Evaporation of the solution in a vacuum desiccator left an orange syrup which crystallized on being stirred. Complete removal of solvent left 81.6 g (96.5%) of light yellow, solid sodium thiolacetate.

The sodium thiolacetate (81.6 g, 0.832 mole) was added to a solution of 174.5 g (0.277 mole) of IIb in 1.5 l. of dry THF and the stirred mixture was refluxed under N_2 for 3 hr, moisture being excluded. After the mixture had stood for 12 hr (N_2 atmosphere) the precipitated solid was removed by filtration and washed with THF. Solvent was removed under N_2 and at reduced pressure until *ca.* 100 ml remained. CH_2Cl_2 (300 ml) and 300 ml of H_2O were added, and the layers were separated. The aqueous phase was extracted with four 75-ml portions of CH_2Cl_2 and the combined extract was washed with two 100-ml portions of H_2O. The solid which had previously been removed by filtration was dissolved in 500 ml of H_2O, the solution was extracted with four 75-ml portions of CH_2Cl_2, and the combined extract was washed with two 50-ml portions of H_2O. The CH_2Cl_2 solution was combined with that previously obtained and dried over Na_2SO_4. Removal of solvent by distillation at reduced pressure and under N_2 left 11.5 g (107%) of a dark red-amber oil: ir, 1700 (carbonyl), 1330, and 1160 cm^{-1} (sulfonamide).

(*S*)-N-[4-Mercapto-1-(mercaptomethyl)butyl]benzenesulfonamide (IIh).—The method, with modifications, was based on that of Baddiley and Jamieson.[26] NH_3 was passed for 4 hr into a solution of 83 g (0.221 mole) of IIg in 200 ml of MeOH cooled in an ice bath. Removal of solvent by distillation at reduced pressure and under N_2 left a dark amber oil: ir, 2570 (thiol), 1330, and 1150 cm^{-1} (sulfonamide).

(*S*)-2-Amino-1,5-pentanedithiol (IIa) Hydrochloride.—Ib (20 g, 0.0692 mole) was dissolved in 600 ml of liquid NH_3 and Na (6.9 g, 0.300 g-atom) was added in small pieces over a period of 45 min to the stirred solution, moisture being excluded, until a permanent blue color was attained. An additional 0.6 g of Na was added and the solution was stirred for 0.5 hr, the blue color remaining during this time. The NH_3 was allowed to vaporize spontaneously in N_2. The yellow-green solid residue was cooled in an ice bath and treated with 100 ml of EtOH and then acidified to a pH of 1 with 400 ml of 6 *N* HCl. The solution was diluted with 200 ml of H_2O and extracted with three 75-ml portions of thiophene-free C_6H_6. A solution of 37.6 g (0.138 mole) of $HgCl_2$ in 60 ml of 4 *N* HCl was added to the aqueous solution and the mixture was allowed to stand overnight. The precipitated mercury mercaptide was removed by filtration and dried. The solid was suspended in 200 ml of absolute EtOH and H_2S was passed under pressure into the mixture for 2 hr. HgS was removed by filtration through Celite, the solid was resuspended in absolute EtOH, and the mixture was again treated with H_2S. After filtration, the combined filtrate was evaporated to dryness in a vacuum desiccator over NaOH pellets. A colorless oil (8.5 g, 65%), which could not be induced to crystallize, was obtained; ir, 2510 cm^{-1} (thiol).

The same dithiol, identical in its ir spectrum with the product obtained from the dithiepane, was obtained in a 41% yield by the Na–NH_3 reduction of IIh and in a 36% yield by the Na–NH_3 reduction of IIg.

(−)-(*S*)-1,2-Dithiepan-4-amine Hydrochloride (Ia·HCl).—A solution of IIa·HCl (5.5 g, 0.0292 mole) in 200 ml of distilled H_2O and a 0.05 *M* I_2–KI solution were added to 200 ml of efficiently stirred distilled H_2O. The I_2 solution was added in 5-ml portions and an excess of 1 to 5 ml was maintained while the dimercaptan solution was added dropwise. After the end point had been reached, 20 g of Na_2CO_3 was added and the solution was extracted continuously with thiophene-free C_6H_6 for 48 hr. The extract was dried over Na_2SO_4 and then treated with dry HCl gas in slight excess. The white solid (3.9 g, 72%) which precipitated was removed by filtration, washed with C_6H_6, and dried. Three recrystallizations from absolute EtOH gave the analytical sample, $[\alpha]^{26}D$ −35° (*c* 0.744, H_2O), λ_{max}^{EtOH} 256 mμ (ε 412), $\lambda_{max}^{H_2O}$ 255 mμ (ε 394).

(−)-(*S*)-2-Methanesulfonamido-1,5-pentanediol Dimethanesulfonate (IIc).—Prepared from 87 ml (1.13 moles) of $MeSO_2Cl$ and 35.9 g (0.301 mole) of (*S*)-2-amino-1,5-pentanediol by the method used for the synthesis of IId, the product separated as a gum when poured onto concentrated HCl and ice. CH_2Cl_2 was added to take up the gum and the layers were separated. Dilution of the CH_2Cl_2 solution with Et_2O caused the precipitation of 50.1 g of orange solid that was removed by filtration. The aqueous phase was extracted with five 100-ml portions of CH_2Cl_2 and solvent was distilled from the combined extract until *ca.* 100 ml remained. Dilution with Et_2O caused the precipitation of 26.2 g of solid, giving a total yield of 76.3 g (72%) of product. An amber oil consisting chiefly of mesyl chloride was recovered from the filtrates. The analytical sample, $[\alpha]^{26}D$ −12° (*c* 2.70, Me_2CO), was obtained after one crystallization from Me_2CO–Et_2O, four crystallizations from MeOH, and two crystallizations from Me_2CO–Et_2O, including several treatments with Norit; ir, 1350, 1340, 1180, and 1150 cm^{-1} (sulfonamide and sulfonate).

(*S*)-2-Methanesulfonamido-1,5-pentanediol Dithiocyanate (IIe).—IIc (8.8 g, 0.025 mole) and 10.3 g (0.125 mole) of NaSCN in 200 ml of MeOH were treated as in the synthesis of IIIc. By following the decrease in CNS^- concentration, it was determined that the reaction was complete in about 4 hr. The product was isolated as an oil which was extracted into CH_2Cl_2, washed, and dried (Na_2SO_4). Distillation of the solvent under reduced pressure left 5.3 g, 76% (83% corrected for removal of 9% of the reaction mixture for titration), of a light amber viscous oil; ir, 2130 (thiocyanate), 1330, and 1150 cm^{-1} (sulfonamide).

Disodium (*S*)-2-Methanesulfonamido-1,5-pentanediol Dithiosulfate (IIf).—IIc (61.6 g, 0.174 mole) was added to a solution of 216 g (0.870 mole) of $Na_2S_2O_3 \cdot 5H_2O$ in 450 ml of distilled H_2O and the mixture was heated with stirring on a steam bath for 2 hr under N_2. The solution of the bis-Bunte salt was used directly for the preparation of Ic.

(−)-(*S*)-4-Methanesulfonamido-1,2-dithiepane (Ic). a. From the Dithiocyanate IIe.—A solution of 18.4 g (0.285 mole) of 85% KOH in 200 ml of MeOH was added dropwise over a period of 50 min to a stirred solution of 5.3 g (0.019 mole) of IIe in 200 ml of MeOH cooled in an ice bath. The stirred solution was heated at 50° for 0.5 hr and then was cooled in an ice bath and stirred for 3

(25) Kindly determined by Mr. Stephen B. Silbering.

(26) J. Baddiley and G. A. Jamieson, *J. Chem. Soc.*, 1085 (1955).

hr. It was acidified to pH 1 with 60 ml of 6 *N* HCl and the precipitated KCl (18.3 g) was removed by filtration. MeOH was distilled from the filtrate at reduced pressure, the remaining aqueous mixture was extracted with three 50-ml portions of CH_2Cl_2, and the combined extract was dried (Na_2SO_4). Distillation of solvent from the extract left 3.3 g of an amber oil which crystallized to an oily tan solid. One recrystallization from aqueous EtOH gave 1.0 g of white solid, mp 109–113°. Recrystallization of the product once again from aqueous EtOH and three times from 95% EtOH gave the analytical sample: $[\alpha]^{25}D$ −31° (c 3.99, $CHCl_3$); λ_{max}^{EtOH} 259 mμ (ε 403), $\lambda_{max}^{CHCl_3}$ 261 mμ (ε 506); ir, 1300 (broad), 1160, and 1140 cm^{-1} (sulfonamide).

b. From the Bis-Bunte Salt IIf.—The solution of the bis-Bunte salt IIf, prepared as described above, was added dropwise over a period of 35 min to a stirred solution of 159 g (2.41 moles) of 85% KOH in 3 l. of distilled H_2O, N_2 being bubbled through during this time. The solution was allowed to stand for 19 hr at room temperature and then stirred and heated at 85° under N_2 for 4 hr. After standing for 6 hr at room temperature, the solution was extracted with five 100-ml portions of CH_2Cl_2 and the combined extract was dried (Na_2SO_4). Distillation of solvent from the extract left 3 g of an orange solid, mp 99–110°. The aqueous phase was saturated with NaCl and extracted continuously with Et_2O for 5 days. After the extract had been dried over Na_2SO_4, distillation of solvent left 11.2 g of a white solid, mp 107–115°, giving a combined yield of 14.2 g. An ir spectrum of the crude solid obtained by Et_2O extraction was identical with that of authentic Ic prepared from IIe.

(*S*)-[4-Mercapto-1-(mercaptomethyl)butyl]methanesulfonamide (IIi). a.—Na (1.0 g, 0.0435 g-atom) was added in small pieces to a solution of 3.0 g (0.0132 mole) of Ic in 200 ml of liquid NH_3 until a permanent deep blue color was attained. The solution was stirred for 45 min, the blue color remaining during this time, and then solvent was removed at reduced pressure. EtOH (50 ml) was added to the gray solid residue and the mixture was stirred thoroughly. It was cooled in an ice bath and acidified to pH 1 with 125 ml of 6 *N* HCl. A solution of 8.4 g (0.026 mole) of $Hg(OAc)_2$ in 100 ml of distilled H_2O was added to the faintly yellow solution and the precipitated white mercury mercaptide was removed by filtration, washed (EtOH), and dried. A suspension of the mercaptide in 50 ml of absolute EtOH was treated with H_2S for 1 hr. The HgS precipitate was removed by filtration through Celite and washed with EtOH. Evaporation of the colorless filtrate to dryness in a vacuum desiccator left 2.2 g (73.4%) of a colorless oil: ir, 2560 (thiol), 1290, and 1150 cm^{-1} (sulfonamide).

b.—Concentrated HCl (28 ml) was added dropwise over a period of 1 hr to a stirred mixture of 5.1 g (0.0224 mole) of Ic, 30.4 g (0.465 g-atom) of Zn powder, and 84 ml of glacial HOAc. The mixture was heated under reflux with stirring for 12.5 hr. At the end of this time 84 ml of concentrated HCl was added over a period of 1.5 hr, and the mixture was heated under reflux for 1 hr until nearly all the Zn had dissolved. The solution was cooled and diluted with 200 ml of H_2O. A solution of 10.6 g of $Hg(OAc)_2$ in 100 ml of distilled H_2O was added and the precipitated mercury mercaptide was coagulated by warming on a steam bath, removed by filtration, and washed with EtOH. The mercaptide was dissolved in 100 ml of hot concentrated HCl and reprecipitated by dilution with 200 ml of H_2O. It was reprecipitated a second time from concentrated HCl, removed by filtration, washed with EtOH, and dried. A suspension of the solid in 50 ml of absolute EtOH was treated with H_2S for 0.5 hr. The precipitated HgS was removed by filtration through Celite, resuspended in 20 ml of absolute EtOH, and again treated with H_2S for 10 min. After filtration, the combined filtrate was evaporated to dryness in a vacuum desiccator and 3.5 g (68%) of a colorless oil was obtained. An ir spectrum of the oil was identical with that obtained from the Na–NH_3 reduction of Ic.

Biologically Oriented Organic Sulfur Chemistry. II. Formation of Hemimercaptals or Hemimercaptoles as a Means of Latentiating Thiols[1]

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Reactions of thiols with carbonyl compounds that form isolable hydrates led to hemimercaptals and hemimercaptoles. Hemimercaptals (**3** and **7**) of 2-aminoethanethiol hydrochloride (**1**), containing the groups Cl_3C-CH(OH), or $F_3CCH(OH)$, respectively, were active as antiradiation drugs, suggesting that these two groups (and similar ones) deserve a broader trial as latentiating groups for medicinally promising thiols. The hemimercaptal **3** reduced the titer of the rheumatoid factor *in vitro* but not the skin-tensile strength of rats *in vivo*.

The biochemical significance of the SH group and of moieties related to it is so well known as to require no comment. Medicinally, thiols have been of interest in a number of situations, among which the following may be mentioned illustratively: rheumatoid arthritis[2a–c,e] and rheumatoid lung disease,[2d] leprosy,[3a] Wilson's disease,[3b,c] heavy-metal antagonism,[3b] macroglobulinemia,[4] inflammation,[5] cystinuria[6a,b] and cystinosis,[6c] scleroderma,[7] idiopathic pulmonary fibrosis,[8] as a mucolytic agent,[9] and for protection against ionizing radiation.[10] Two of these applications particularly interest us: rheumatoid arthritis and protection against ionizing radiation.

In respect to the first, penicillamine (β,β-dimethylcysteine) produces a fall in titer of the rheumatoid factor, as well as a favorable effect on other parameters

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