1-Phenethyl-3-phenylpyrrolidine (II).—N-Phenethyl-2-phenylsuccinimide, mp 72–73° (23 g obtained by fusion of phenylsuccinic anhydride with phenethylamine), was reduced with $LiAlH_4$ (6 g) in dry ether to give 14 g, bp 172–174° (3 mm), $n^{26}D$ 1.5663. Since the hydrochloride salt appeared to be hygroscopic, the base was analyzed as the **picrate**, obtained as yellow needles from ethanol, mp 112.5–115°.

Anal. Calcd for $C_{24}H_{24}N_4O_7$: C, 60.00; H, 5.0; N, 11.7. Found: C, 59.2; H, 5.2; N, 11.7.

1-Phenyl-4-phenethylpiperazine (III).—A mixture of 1-phenylpiperazine (9 g, 0.055 mole), phenethyl bromide (10.3 g, 0.055 mole), and anhydrous Na_2CO_3 (8 g) were refluxed for 7 hr in 100 ml of absolute alcohol. After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The resulting semicrystalline mass was extracted three times with 100-ml portions of warm petroleum ether (bp 55–75°) which, on evaporation, gave 9 g (61%) of III. The hydrochloride was prepared by treating an ethereal solution of the base with gaseous HCl. Recrystallization from alcohol–ether gave prisms, mp 219–221°, lit.[15] mp 220–222°.

1,4-Diphenethylpiperazine (IV).—Ethylene dibromide (21.6 g, 0.115 mole), phenethylamine (12.1 g, 0.111 mole), and Na_2CO_3 (20 g) were refluxed in 100 ml of water for 3 hr. After cooling, the reaction mixture was extracted with four 100-ml portions of ether, the extracts were dried (Na_2SO_4), and the solvent was removed to leave a liquid that slowly crystallized. Recrystallization from petroleum ether gave colorless needles, mp 76–78°, lit.[16] mp 79–80°. The hydrochloride prepared in the manner above, was recrystallized from ethanol: mp 27 °.

(15) B. L. Hampton and C. B. Pollard, *J. Am. Chem. Soc.*, **59**, 2570 (1937).

4-Phenethyl-1,4-thiazane (V).—Thiodiglycollic acid anhydride (13 g, 0.1 mole) and phenethylamine (12.5 g, 0.103 mole) were cautiously mixed and then heated at 200° for 5 hr. Considerable decomposition occurred, but distillation of the fusion mixture and subsequent crystallization from benzene–petroleum ether gave 6 g (28%) of N-phenethylthiodiglycollic acid imide, bp 175–185° (3 mm), mp 56–59°. Reduction of this imide with $LiAlH_4$ (3 g) in ether gave 4.5 g of product, bp 145–152° (5 mm), $n^{28}D$ 1.5625. The hydrochloride was precipitated from an ethereal solution of the base by gaseous HCl and, after recrystallizations from water and ethanol, it was obtained as colorless flakes, mp 252–254° dec.

Anal. Calcd for $C_{12}H_{16}ClNS$: C, 59.1; H, 7.4; N, 5.7. Found: C, 59.6; H, 7.5; N, 5.4.

3-(3-Benzoylethyl)-3-azaspiro[5.5]undecane Hydrochloride.—3-Azaspiro[5.5]undecane hydrochloride (9.1 g, 0.048 mole), acetophenone (5.8 g, 0.048 mole), paraldehyde (3.2 g), and concentrated HCl (0.2 ml) were refluxed for 2 hr in 100 ml of absolute ethanol. The solution was then concentrated to 50 ml and the product precipitated with the addition of ether. Recrystallization from acetone–ethanol gave colorless plates (6.2 g, 35%), mp 190° dec.

Anal. Calcd for $C_{20}H_{28}ClNO$: C, 70.9; H, 8.8; N, 4.3. Found: C, 71.3; H, 8.7; N, 3.9.

Acknowledgment.—The authors wish to thank Dr. I. W. Parnell for his assistance in setting up the screening test. Thanks are also due to Messrs. A. E. Sibbing and M. L. Murray for their careful technical assistance.

(16) W. G. Barb, *J. Chem. Soc.*, 2577 (1955).

Potential Antiradiation Drugs. III.[1] 2-Amino-2-alkyl-1,3-propanedithiols and 3-Amino-4-mercapto-1-butanol[2]

G. RICHARD HANDRICK AND EDWARD R. ATKINSON

Arthur D. Little, Inc., Cambridge, Massachusetts 02140

Received February 28, 1966

Syntheses and radioprotective properties are described for 2-amino-2-methyl-1,3-propanedithiol, 2-amino-2-ethyl-1,3-propanedithiol, and L-(+)-3-amino-4-mercapto-1-butanol. The dithiols did not provide significant protection in rodents, but the aminothiol alcohol gave good protection.

In continuing our study[1] of pure organic compounds that might protect against the lethal effects of ionizing radiation it was of interest to examine simple aminothiols having more than one thiol function. The significance of aminodithiols as potential antiradiation drugs was recognized some time ago by Russian workers[3] who prepared a wide variety of N-substituted aminopropanedithiols; an evaluation of these substances as drugs has not been published. A closely similar group of compounds was also prepared by Japanese workers[4] who claimed only bactericidal and insecticidal activity for the substances. Both groups synthesized the dithiols by the sulfhydrylation of appropriate halogeno precursors.

Aminothiol alcohols were also of interest in our program. The synthesis of a series of Bunte salts derived from isomeric aminomercaptopropanols has been described, which involved the respective aminothiol alcohols as nonisolated intermediates.[5] More complex substances having two secondary hydroxyl groups, two secondary amino groups, and two thiol groups have also been prepared[6] but nothing is known about their radioprotective properties. The three compounds whose synthesis and radioprotective properties we describe here contain *primary* amino, primary thiol, and primary alcohol functions.

Chemistry.—The two aminodithiols were prepared from available amino alcohols by the route indicated in Chart I, in which the procedure of Owen and co-

(1) Paper II: G. R. Handrick, E. R. Atkinson, F. E. Granchelli, and R. J. Bruni, *J. Med. Chem.*, **8**, 762 (1965).

(2) This work was performed under contract DA-49-193-MD-2071 with the U. S. Army Medical Research and Development Command, Office of the Surgeon General, during the period 1961–1962.

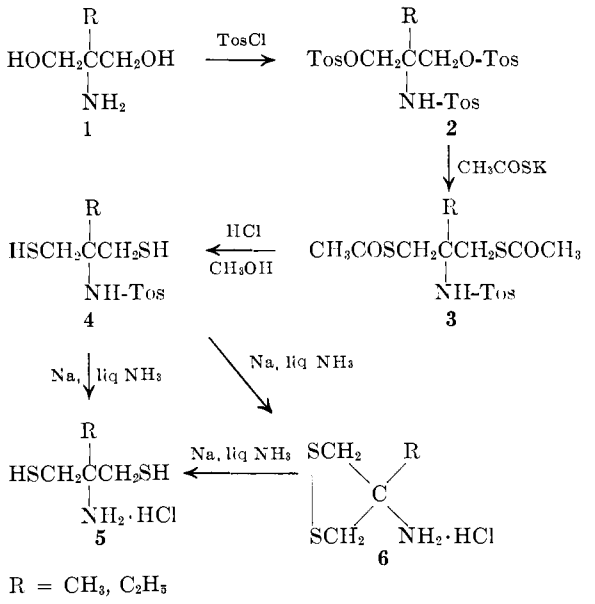
(3) (a) V. M. Fedoseev, A. G. Tarasenko, L. Mrazek, and A. B. Silaev, *Dokl. Akad. Nauk SSSR*, **148**, 871 (1963); (b) A. G. Tarasenko, V. M. Fedoseev, and A. B. Silaev, *J. Gen. Chem. USSR*, **34**, 1002 (1964); (c) *ibid.*, **34**, 2378 (1964); (d) V. A. Partnyagina, *Tiolovye Soedin. v Med., Ukr. Nauchn. Issled. Sanit. Khim. Inst., Trudy Nauchn. Konf., Kiev, 1957*, 31 (1959); *Chem. Abstr.*, **54**, 24508 (1960).

(4) (a) C. Harukawa, S. Yurugi, H. Hagiwara, and K. Konishi (to Takeda Chemical Industries, Ltd.), Japanese Patents 14,916 (1963), 18,012 (1964), 18,013 (1964).

(5) D. H. Ball, J. M. Williams, and L. Long, Jr., *J. Org. Chem.*, **28**, 1589 (1963).

(6) (a) J. E. Christensen and L. Goodman, *ibid.*, **28**, 847 (1963); (b) S. L. Holton, J. E. Christensen, O. P. Crews, and L. Goodman, *Can. J. Chem.*, **42**, 2147 (1964).

CHART I



R = CH_3, C_2H_5

workers[7] was appropriately modified by the use of the tosyl protective group on nitrogen.[8] The tritosyl compound **2** was obtained in 60–70% yields by tosylation of **1** in pyridine or mixtures of pyridine and halogenated solvents. Conversion to the bisthiolacetate **3** and to the N-tosyldithiol **4** also proceeded in high yield. The use of aqueous HCl for the hydrolysis of **3** to **4** gave unsatisfactory results, the only identifiable product being *p*-toluenesulfonamide. We made one conversion directly from **3** (R = CH_3) to **5** by reduction with sodium in liquid ammonia, but the yield of **5** was not sufficiently high for preparative purposes.

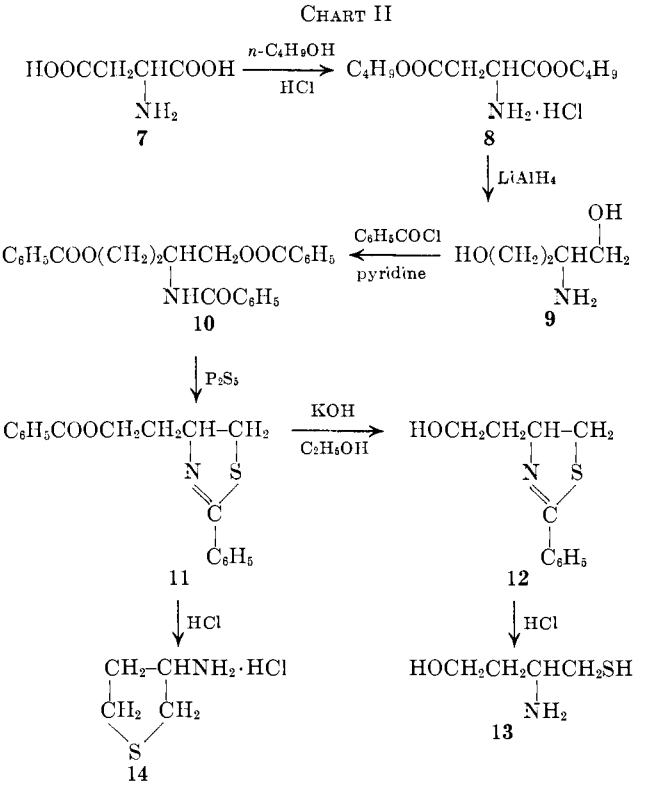
Before undertaking the removal of the N-tosyl group of **4** by cleavage with sodium in liquid ammonia, we attempted to remove it by the use of strong sulfuric acid[9] and HBr in phenol[10] but were unable to isolate the desired **5**. Refluxing alcoholic phenylhydrazine did not attack **4**, but refluxing 70% aqueous hydrazine gave a 70% yield of *p*-toluenesulfonamide, and no **5**. We also sought to avoid the use of an N-tosyl group altogether by attempting to prepare analogs of **2** in which the N-protective group was benzoyl or acetyl. The preparation of the ditosylate ester from N-2-(1,3-dihydroxy-2-ethylpropyl)benzamide by reaction with tosyl chloride under a variety of conditions failed. Similar difficulties were also experienced in attempts to tosylate N-2-(1,3-dihydroxy-2-methylpropyl)acetamide to form the N-acetyl analog of **2** (R = CH_3) (see Experimental Section).

When we studied the cleavage of **4** to **5** by sodium in liquid ammonia we did not have available a recent illuminating paper on this reaction[11] in which earlier work is reviewed. In developing a procedure that was satisfactory for preparative purposes, we isolated a number of intermediates and by-products described in the Experimental Section. Because we made no attempt to determine whether these substances were initially formed in the reaction, or were produced during subsequent work-up, and also because their formation might be a function of just how the sodium addition was carried out, we shall not speculate concerning the significance of these products to the mechanism of the reductive cleavage by sodium. As practiced by us the cleavage procedure usually gave a mixture of the desired aminodithiol (**5**) along with the dithiolane (**6**). The latter could be reduced to **5** in high yield by another reduction by sodium in liquid ammonia. The over-all yield of **5** from **4** was about 75%.

The Experimental Section describes the isolation of several intermediates and products in polymorphic forms. In every such case the forms had identical infrared spectra and were entirely equivalent when used in subsequent reactions.

3-Amino-4-mercapto-1-butanol (**13**) was prepared in 30% yield as shown in Chart II, in which the thiazoline route[1] was used effectively. The entire synthesis was carried out from both L-(+)- and racemic aspartic acids (**7**). In our hands 2-amino-1,4-butanediol (**9**) was prepared by the reduction of di-*n*-butyl aspartate (**8**) rather than by the reduction of the dimethyl or diethyl esters used by previous workers;[12] these latter esters, being much more water soluble and more prone to hydrolysis, were troublesome to prepare in the quantities needed. The tribenzoyl derivative (**10**) was much more readily obtained than the more water-soluble triacetyl analog; acylation in pyridine was definitely superior to the Schotten–Baumann technique. Ring closure with phosphorus pentasulfide gave the desired thiazoline **11**, rather than the less favored[13] isomeric

CHART II



(7) (a) J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 579 (1950); (b) P. Bladon and L. N. Owen, *ibid.*, 585 (1950).
(8) R. A. Boissonnas, *Advan. Org. Chem.*, **3**, 175 (1963).
(9) F. E. King, R. J. S. Beer, and S. G. Waley, *J. Chem. Soc.*, 92 (1946).
(10) H. R. Snyder and R. E. Heckert, *J. Am. Chem. Soc.*, **74**, 2006 (1952).
(11) J. Kovacs and U. R. Ghatak, *J. Org. Chem.*, **31**, 119 (1966).
(12) (a) P. Karrer, P. Portmann, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948); (b) M. Justisz, M. P. de Garilhe, M. Suquet, and C. Fromageot, *Bull. Soc. Chim. Biol.*, **36**, 117 (1954); (c) M. W. Rees, *Biochem. J.*, **68**, 118 (1958); (d) H. F. Herbrandson, personal communication.
(13) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, **83**, 4830 (1961).

dihydrothiazine. When we attempted the direct acid hydrolysis of **11** to **13** we obtained high yields of 3-aminothiophane (**14**). This result was in accord with a study of factors influencing thiophane ring formation made earlier.[14] The desired ring opening was obtained by a prior alkaline hydrolysis of **11** to **12** before proceeding to **13**. The final hydrolysis of **12** to **13** involved a complication not experienced in our earlier work with 2-methyl-2-thiazolines; the desired product **13** was invariably accompanied by varying amounts of its O,N-dibenzoyl and O,N,S-tribenzoyl derivatives. No study was made of the mechanism involved in these facile exchanges of benzoyl groups. It was believed that the isolation of the benzoyl derivatives was the result of their precipitation from the hydrolysis solution, but the quantities involved were not sufficiently great to warrant a study of their hydrolysis to **13**.

Radioprotective Activities.—The compounds were tested exactly as described previously.[15] Both 2-amino-2-alkyl-1,3-propanedithiol hydrochlorides (**5**) showed "good" protection toward bacteria, but when administered to mice at 50 mg/kg the protection was not significant against midlethal radiation. L-(+)-3-Amino-4-mercapto-1-butanol (L-**13**) showed no protection with bacteria but gave "good" protection to mice at 351–750 mg/kg. The 10 g of pure DL-**13** needed for biological evaluation was not available before the end of our work.

Experimental Section[16]

2-Ethyl-2-*p*-toluenesulfonylamino-1,3-propanediol Di-*p*-toluenesulfonate (2, R = C_2H_5).—Redistilled 2-amino-2-ethyl-1,3-propanediol (84.2 g, 0.7 mole; bp 117–119° (1.5 mm); Commercial Solvents Corporation) dissolved in 150 ml of pyridine was added during 30 min to a stirred solution of 410 g (2.11 moles) of *p*-toluenesulfonyl chloride in 500 ml of methylene chloride maintained at 14–18°. The reaction mixture was stored at 0° for 4 days, filtered free from pyridine hydrochloride, and washed well with dilute HCl and then with dilute $NaHCO_3$ solution. The solvent was removed by distillation and the viscous residue was warmed briefly under vacuum and then poured into vigorously stirred petroleum ether to precipitate 360 g (88%) of crystalline product. Recrystallization from isopropyl alcohol gave 275 g (67%) of material, mp 123.5–124.5°. An analytical sample had mp 124.5–125°.

Anal. Calcd for $C_{25}H_{31}NO_8S_3$: C, 53.68; H, 5.37. Found: C, 53.98; H, 5.28.

Approximately the same yields were obtained when pyridine–chloroform, or pyridine alone, was used as solvent. Yields decreased seriously when reflux temperatures were used in an effort to speed up the reaction.

2-Methyl-2-*p*-toluenesulfonylamino-1,3-propanediol Di-*p*-toluenesulfonate (2, R = CH_3).—Crude product (85% yield) was obtained from 2-amino-2-methyl-1,3-propanediol (Eastman P4792) by essentially the same procedure used for the ethyl homolog and was recrystallized twice from isopropyl alcohol to yield 322 g (57%) of a cream-colored granular solid, mp 133.5–134.5°.

Anal. Calcd for $C_{25}H_{29}NO_8S_3$: C, 52.89; H, 5.15; S, 16.94. Found: C, 52.26; H, 5.06; S, 17.17.

In two early experiments the product was obtained as a polymorph, mp 110–111°, whose analysis and infrared spectrum were the same as those of the higher melting material obtained subsequently.

2-Ethyl-2-*p*-toluenesulfonylamino-1,3-propanedithiol Diacetate (3, R = C_2H_5).—Potassium thiolacetate was prepared by neutralizing thiolacetic acid with KOH in alcohol solution, evaporating the solution almost to dryness, and precipitating the salt by addition of acetone. In a typical run this salt (12 g, 0.105 mole) was stirred with a solution of 23.2 g (0.04 mole) of **2** (R = C_2H_5) in 200 ml of acetone, and the mixture was then refluxed for 30 min. The mixture was cooled, potassium salts were removed by filtration, the filtrate was evaporated to dryness, and the residue was recrystallized from ethyl alcohol to give 12.7 g (81%) of cream-colored crystals, mp 83–84°.

Anal. Calcd for $C_{16}H_{21}NO_4S_3$: C, 49.33; H, 5.95; S, 24.69. Found: C, 49.56; H, 6.12; S, 25.07.

The procedure was also carried out on a scale ten times that specified above; on this scale the reaction was noticeably exothermic.

2-Methyl-2-*p*-toluenesulfonylamino-1,3-propanedithiol diacetate (3, R = CH_3) was prepared from both polymorphic forms of **2** (R = CH_3) by a procedure similar to that described above for the ethyl homolog. In runs involving up to 170 g of **2** the crude compound was obtained in almost quantitative yield; recrystallization from isopropyl alcohol gave 83% yields of colorless solid, mp 80–81°.

Anal. Calcd for $C_{15}H_{19}NO_4S_3$: C, 47.97; H, 5.64; S, 25.61. Found: C, 47.95; H, 5.34; S, 26.22.

N-2-(1,3-Dimercapto-2-ethylpropyl)-*p*-toluenesulfonamide (4, R = C_2H_5).—A solution of 156.4 g (0.4 mole) of **3** (R = C_2H_5) in 1100 ml of approximately 1 *N* methanolic HCl was refluxed for 17.5 hr. Solvent was distilled at atmospheric pressure and the residue was mixed with ice-cold isopropyl alcohol and filtered; some additional material was obtained by working up the filtrate. After recrystallization from isopropyl alcohol we obtained 101 g (83%) of colorless needles, mp 137–138°.

Anal. Calcd for $C_{12}H_{19}NO_2S_3$: C, 47.18; H, 6.27; N, 4.58; S, 32.35; SH, 21.65. Found: C, 46.81, H, 6.11; N, 4.57; S, 32.35; SH, 21.30.

N-2-(1,3-Dimercapto-2-methylpropyl)-*p*-toluenesulfonamide (4, R = CH_3) was prepared from **3** (R = CH_3) by the same process used for the ethyl homolog. The crude was recrystallized from ethyl alcohol to give almost quantitative yields of colorless cubes, mp 110–111°.

Anal. Calcd for $C_{11}H_{17}NO_2S_3$: C, 45.33; H, 5.88. Found: C, 45.44; H, 5.77.

2-Amino-2-ethyl-1,3-propanedithiol Hydrochloride (5, R = C_2H_5).—A solution of 61 g (0.2 mole) of **4** (R = C_2H_5) in 600 ml of liquid ammonia was stirred and cooled by Dry Ice while 25 g (1.09 g-atoms) of sodium was added in small pieces during 4.25 hr. During this time the color of the solution became successively yellow, green, brown, and black. The color was completely discharged by addition of 62 g of NH_4Cl and the mixture was allowed to evaporate to dryness under nitrogen. The colorless residue was dissolved in 250 ml of 7 *N* HCl and 12.5 g of an unidentified insoluble oil was removed by extraction with methylene chloride. The acid layer was evaporated to dryness under vacuum and the residue was further dried by azeotropic distillation with benzene. The product was then extracted from insoluble chlorides by 200 ml of boiling glacial acetic acid. On standing under nitrogen for 5 days at room temperature the extract deposited 11 g of solid from which 4 g of **5** having adequate purity was obtained by several recrystallizations from glacial acetic acid as almost colorless crystals, mp 275–276° dec (sealed capillary).

Anal. Calcd for $C_5H_{14}ClNS_2$: C, 31.98; H, 7.52; N, 7.46; SH, 35.23. Found: C, 31.63; H, 7.36; N, 7.90; SH, 34.84.

All the acetic acid filtrates were worked up to give additional **5** and also the more soluble **4-amino-4-ethyl-1,2-dithiolane hydrochloride (6)**, yellow plates from isopropyl alcohol, mp 198–199° (sealed capillary), which was not oxidized by iodine.

Anal. Calcd for $C_5H_{12}ClNS_2$: C, 32.33; H, 6.51; Cl, 19.09; N, 7.54; S, 34.53. Found: C, 32.30; H, 6.40; Cl, 19.00; N, 7.50; S, 34.30.

The dithiolane was cleanly reduced by 3 g-atoms of sodium in liquid ammonia to the desired dithiol in yields of 90%; this procedure for the reduction of dithiolanes has been described previously.[17] We conveniently reprocessed mixtures of **5** and **6** in this way so as to avoid a tedious separation of **5** from the mixture.

(14) J. S. Harding, L. W. C. Miles, and L. N. Owen, *Chem. Ind.* (London), 887 (1951).

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

(16) All melting points and boiling points are corrected; analyses were performed by S. M. Nagy (Massachusetts Institute of Technology) or by C. K. Fitz (Needham, Massachusetts).

(17) H. J. Backer and A. F. Tammena, *Rec. Trav. Chim.*, **57**, 1183 (1938).

2-Amino-2-methyl-1,3-propanedithiol Hydrochloride (5, R = CH_3).—In a procedure similar to that described above for the ethyl homolog, 64.5 g of 4 (R = CH_3) was reduced by sodium in liquid ammonia. In this case the acid-insoluble oil extracted into CH_2Cl_2 weighed 19.5 g. This oil was extracted by ether, leaving 2.5 g of insoluble solid, mp 177–181°, not identified. The ether extract was evaporated and the residue was triturated with petroleum ether to leave as a residue 10.7 g of *p*-tolyl *p*-toluenethiolsulfonate, mp 78° (ethyl alcohol); lit.[18] mp 78°. The petroleum ether extract gave 5.5 g of an oily solid from which was isolated 1.8 g of *p*-tolyl disulfide, mp 44–45°.

The acid-soluble products of the reaction were leached from the dry chloride salt mixture by boiling isopropyl alcohol and recovered as 37.1 g (98%) of bright yellow solid by evaporation of the solvent. Preliminary runs had shown that this solid contained not only the desired **5**, but also a considerable quantity of (presumably) **4-amino-4-methyl-1,2-dithiolane (6, R = CH_3)**, mp 189–192°, not otherwise characterized. The mixture was therefore processed once again with sodium in liquid ammonia. The dried crude hydrochloride salts were extracted by three 125-ml portions of boiling isopropyl alcohol to yield 29.6 g (78%) of **5**. Recrystallization from 200 ml of isopropyl alcohol containing a little HCl gave 21 g of colorless crystals of **5**, which underwent a phase change at 134.5° and melted again at 175–179°.

Anal. Calcd for $C_4H_{12}ClNS_2$: C, 27.65; H, 6.96; N, 8.06; SH, 38.07. Found: C, 27.84; H, 7.09; N, 8.09; SH, 35.83.

The first sample of **5** isolated by us consisted of colorless cubes and melted completely at 134–135°. All subsequent samples simply underwent the phase change described above; this was observed either in a capillary or on a microscope slide. We were unable to raise the thiol content above the 94% specified in the above analysis.

2-Amino-2-methyl-1,3-propanedithiol has been mentioned in the patent literature;[19] its preparation and properties were not described.

N-2-(1,3-Dihydroxy-2-ethylpropyl)benzamide.—By the use of conventional Schotten–Baumann conditions this substance was prepared from 1 (R = C_2H_5) in 50% yield, mp 99–99.5°.

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.66; H, 7.77; N, 6.36.

Tosylation of this substance by *p*-toluenesulfonyl chloride either in the melt or in pyridine solution gave intractable products. Oxazoline formation under the dehydrating action of the reagent is likely in this case.[20]

N-2-(1,3-Dihydroxy-2-methylpropyl)acetamide.—Although this substance has been prepared by the partial hydrolysis of the O,O,N-triacetyl derivative of 1 (R = CH_3),[21] we acetylated 1 with ethyl acetate.[1] Subsequent reaction with *p*-toluenesulfonyl chloride in pyridine gave poor yields of materials whose infrared spectra suggested that acyl migration had occurred during the reaction; oxazoline formation is also likely as in the case of the benzoyl analog cited above.

Di-*n*-butyl L-(+)-Aspartate Hydrochloride (L-8).[22]—L-(+)-Aspartic acid (L-**7**, 328 g, 2.54 moles; mp 344–350° dec, $[\alpha]^{22}D$ +27° (*c* 2, 1 *N* HCl); Mann Research Laboratories) was esterified by the Fischer technique, with azeotropic removal of water. The ester was isolated in 70% yield either as the free base, bp 110° (0.4 mm), $n^{23}D$ 1.4434, or as the hydrochloride salt, mp 113.5–114°, $[\alpha]^{22}D$ +8.2° (*c* 2, H_2O).

Anal. Calcd for $C_{12}H_{24}ClNO_4$: C, 51.15; H, 8.23. Found: C, 50.99; H, 8.40.

The hydrochloride was purified by recrystallization from benzene–petroleum ether (bp 30–60°); less pure material, mp 106–108°, was entirely suitable for the next step.

Di-*n*-butyl DL-aspartate hydrochloride (DL-8)[22] was prepared in a similar manner from racemic **7** (Mann Research Laboratories, mp 362–365° dec). The crude product was recrystallized twice from benzene–petroleum ether; mp 83–84°, neut equiv, 280. The infrared spectrum was identical with that of the L-isomer.

L-(−)-2-Amino-1,4-butanediol (L-9).—The reduction of **8** to **9** was carried out by a procedure which avoided high losses of **9** by absorption in inorganic salts.[12d] A solution of 281.8 g (1.0 mole) of **8** in 1 l. of dry tetrahydrofuran (THF) at 30° was added during 30 min to a stirred slurry of 113.7 g (3.0 moles) of $LiAlH_4$ in 1 l. of THF; some external cooling by ice was used to control excessive reflux. The mixture was refluxed for 30 min, cooled to 0°, and treated with 600 ml of isopropyl alcohol as fast as foaming would permit. Water (225 ml, 12.5 moles) was then stirred in and the fluid mixture was filtered. Despite careful washing of the solids, very little product could be isolated from the filtrates.

The solids were dried in air and then extracted in a Soxhlet device with isopropyl alcohol for 20 hr. Distillation of the extract gave 93.5 g (89%) of the aminodiol, bp 136–137° (1 mm), $n^{25}D$ 1.4920, $[\alpha]^{22}D$ −2.1° (*c* 2, H_2O); lit.[12d] bp 131–135° (0.6–0.8 mm), $n^{20}D$ 1.4910.

We were unable to prepare this substance by the reduction of L-aspartic acid with the activated $NaBH_4$ reagent[23] because of the insolubility of the acid. A reduction of the dibutyl ester by a modified Bouveault–Blanc technique[24] gave the desired aminodiol in just 22% yield.

DL-2-Amino-1,4-butanediol (DL-9) was prepared from racemic dibutyl ester in 95% yields by the $LiAlH_4$ reduction process described above; bp 134–137° (0.6 mm), $n^{25}D$ 1.4910; oxalate, mp 112–113° dec, lit.[12a] mp 114–116°.

L-(−)-2-Benzoylamino-1,4-butanediol Dibenzoate (L-10).—A solution of 392 g (2.79 moles) of benzoyl chloride in 324 ml of pyridine was added in a thin stream during 30 min to a vigorously stirred solution of 81.7 g (0.78 mole) of L-**9** in 500 ml of pyridine maintained at 15–20°. The thick reaction mixture was heated at 60° for 20 min, cooled, and poured into 4 l. of cold water. The oil that formed soon became crystalline. The solid product was washed well with water, then with 2 l. of ethyl alcohol, and finally with ether until the filtrates were no longer colored. The air-dried material, mp 152–153°, 270 g (83%), was sufficiently pure for use in the next step. A small portion was recrystallized from ethyl alcohol to give colorless needles, mp 153–154°, $[\alpha]^{22}D$ −44° (*c* 0.6, acetone). Its infrared spectrum was identical with that of the DL-isomer, whose analysis appears immediately below.

DL-2-Benzoylamino-1,4-butanediol dibenzoate (DL-10) was prepared similarly from DL-**9** in 95% yield as light tan needles, mp 148.5–149°, whose purity was adequate for use in the next step. Recrystallization from methyl alcohol gave colorless needles of unchanged melting point.

Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 72.18; H, 5.59; N, 3.58.

L-4-(2-Benzoyloxyethyl)-2-phenyl-2-thiazoline (L-11).—Although our previous experience with thiazoline synthesis had been restricted to the use of hydroxyalkylacetamides,[1] it was known[25] that the procedure could also be applied to O,N-dibenzoyl derivatives of amino alcohols.

A stirred slurry of 270 g (0.647 mole) of L-**10**, 72 g (0.324 mole) of P_2S_5, and 750 ml of mineral oil was heated to 152° during 75 min and held at 150–155° for an additional hour. In contrast with our previous experience, this reaction was not violently exothermic and did not evolve significant amounts of H_2S. Mineral oil was separated from the hot mixture by decantation. The residual tar was dissolved in 200 ml of 20% NaOH by stirring at 75–80°, the thiazoline was extracted from this solution by two 400-ml portions of ether, and the ether solution was combined with a similar extract of the cooled mineral oil. The combined ether extracts were washed with 10% NaOH and allowed to stand overnight. A small amount of solid that separated was filtered off and the thiazoline was then extracted into 550 ml of 6 *N* HCl. The acid solution was washed with ether, then stirred into aqueous Na_2CO_3 to produce 190 g (95%) of crude L-11 as an orange-colored syrup sufficiently pure for use in the next step. The thiazoline could be distilled at 198–200° (0.5 mm) as a stable yellow-orange syrup whose infrared spectrum was identical with that of the DL isomer described below.

DL-4-(2-Benzoyloxyethyl)-2-phenyl-2-thiazoline (DL-11) was prepared similarly in 85% yield from racemic **10**. A portion was distilled for analysis, bp 186–187° (0.2 mm), $n^{25}D$ 1.6050.

Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.42; H, 5.50; N, 4.50. Found: C, 69.48; H, 5.38; N, 4.87.

L-(−)-4-(2-Hydroxyethyl)-2-phenyl-2-thiazoline (L-12).—A warm solution of 50 g (0.89 mole) of KOH in 500 ml of ethyl

(18) I. Remsen and H. J. Turner, *Am. Chem. J.*, **25**, 199 (1901).
(19) P. J. Dasher (to B. F. Goodrich), U. S. Patent 2,304,551 (1942).
(20) R. N. Boyd and R. H. Hansen, *J. Am. Chem. Soc.*, **75**, 5896 (1953).
(21) J. Nys and J. Libeer, *Bull. Soc. Chim. Belges*, **65**, 377 (1956).
(22) A "dibutyl aspartate" is mentioned but not described by T. Uno and M. Yuasa (to T. Seiyaku Company, Ltd.), British Patent 939,154 (1963).
(23) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956).
(24) W. Enz, *Helv. Chim. Acta*, **44**, 206 (1961).
(25) G. Bach and M. Zahn, *J. Prakt. Chem.*, **8**, 68 (1959).

alcohol was added to a stirred solution of 190 g (0.612 mole) of crude L-11 in 300 ml of ethyl alcohol. A voluminous precipitation of potassium benzoate occurred after 5 min, but this was not removed until after refluxing the reaction mixture for 1 hr. The filtrate was concentrated under vacuum, the residue was mixed with benzene, and the remaining potassium salts were washed out with water. The organic layer was dried (Na_2SO_4) and distilled to give 120.4 g (95%) of a yellow syrup, bp 140–142° (0.2 mm), $n^{22}D$ 1.6066, $[\alpha]^{22}D$ −60° (*c* 3, 1 *M* HCl). An analytical sample was a colorless oil, bp 132–135° (0.1 mm).

Anal. Calcd for $C_6H_{13}NOS$: C, 63.73; H, 6.32; S, 15.47. Found: C, 63.24; H, 6.13; S, 15.67.

DL-**4-(2-Hydroxyethyl)-2-phenyl-2-thiazoline** (DL-**12**) was prepared similarly from DL-11. Its observed physical constants, including infrared spectrum, were the same as those of L-**12**.

L-(+)-**3-Amino-4-mercapto-1-butanol** (L-**13**).—All operations were conducted under nitrogen. In a typical run 31.5 g (0.15 mole) of L-**12** was refluxed in a mixture of 17 ml of concentrated HCl and 700 ml of water for 46 hr during which time a yellow oil had appeared and subsequently changed to a colorless solid (A). The mixture was cooled, filtered, and extracted with methylene chloride; both the filtered solid (A) and material (B) extracted into CH_2Cl_2 were subsequently indentified (see below).

The aqueous acid solution was evaporated to dryness under vacuum and the residual syrup (L-**13**·HCl, 26 g) was subjected to a variety of conventional procedures designed to permit isolation of crystalline material. We were not only unable to isolate a crystalline hydrochloride, but subsequently were unable to characterize crystalline salts of other acids even when using the pure base as a reactant. The crude L-**13**·HCl was then dissolved in 100 ml of isopropyl alcohol and the solution was raised to an apparent pH 11 (glass electrode) by addition of 20% ethanolic KOH. The resulting slurry was filtered at 60° to remove a theoretical yield of KCl, which was washed on the filter with 50 ml of warm isopropyl alcohol. The combined filtrates were stored at 0° and slowly deposited 12.4 g (68%) of colorless crystals of L-**13**, mp 101–103°, $[\alpha]^{22}D$ +37° (*c* 1.7, H_2O).

Anal. Calcd for $C_4H_{11}NOS$: C, 39.70; H, 9.15; N, 11.56; S, 26.46; SH, 27.29; neut equiv, 121.2. Found: C, 39.55; H, 8.92; N, 11.59; S, 26.31; SH, 26.86; neut equiv, 122.2 (in aqueous ethyl alcohol with 0.1 *N* HCl).

L-(+)-3-Amino-4-mercapto-1-butanol is not hygroscopic and is quite stable when stored under nitrogen at 0°. At room temperature deterioration to the disulfide occurs; this also occurs during recrystallization from hot isopropyl alcohol, so that repeated recrystallization cannot be used to raise the thiol value above the 98% of theoretical reported above. The disulfide component of grossly deteriorated samples was readily removed by trituration with cold isopropyl alcohol in which it is much more soluble than the aminothiol alcohol. This disulfide (characterized as a benzoyl derivative) could be reduced to the thiol by sodium in liquid ammonia in good yield.

L-(+)-**4,4′-Dithiobis(3-benzoylamino-1-butanol benzoate**) was obtained either from crude disulfide isolated from deteriorated samples of **13** by trituration, or from crude oily disulfide deliberately prepared by the oxidation of **13** in methyl alcohol by iodine. The disulfide reacted with excess benzoyl chloride in pyridine solution to give the colorless product, mp 183–185° (toluene), $[\alpha]^{22}D$ +45° (*c* 1, dimethylformamide).

Anal. Calcd for $C_{36}H_{36}N_2O_6S_2$: C, 65.83; H, 5.53; S, 9.76. Found: C, 65.41; H, 5.47; S, 9.73.

The by-products formed during the hydrolysis of L-**12** to L-**13** were identified as follows. The colorless solid (A) that had been filtered from the hydrolysis mixture was triturated with ether and then identified as L-(−)-**3-benzoylamino-4-benzoylmercapto-1-butanol benzoate**, 1.5 g, mp 187.5–188.5°, $[\alpha]^{23}D$ −25° (*c* 0.7, CH_2Cl_2), identical with an authentic sample prepared by the reaction between L-**13** and excess benzoyl chloride in pyridine solution.

Anal. Calcd for $C_{25}H_{23}NO_4S$: C, 69.26; H, 5.35; N, 3.23; S, 7.40. Found: C, 68.50; H, 4.98; N, 3.28; S, 7.19.

Material (B) that had been extracted from the hydrolysis solution by CH_2Cl_2 consisted of benzoic acid (74%) (removed by extraction with dilute aqueous carbonate) and 4.3 g of a solid obtained by evaporation of the dried solution. This latter solid was found to consist of a mixture of the O,N,S-tribenzoyl derivative described immediately above, and of L-(+)-4,4′-dithiobis(3-benzoylamino-1-butanol benzoate). We suspected that the latter compound was derived from a thiol precursor, **L-3-benzoylamino-4-mercapto-1-butanol benzoate**. To prove this, a typical hydrolysis of L-**12** was interrupted after 16 hr when 6 g of the dense yellow oil was still present. The oil was separated by decantation and dissolved in ether; 0.4 g of L-3-benzoylamino-4-benzoylmercapto-1-butanol benzoate remained undissolved and was removed by filtration. The ether solution was extracted by aqueous carbonate (to remove benzoic acid) and then was dried and evaporated to give 4.3 g of a water-insoluble neutral oil which slowly solidified during several months standing under nitrogen. This oil could not be characterized but was readily oxidized by iodine in methyl alcohol solution in high yield to L-4,4′-dithiobis(3-benzoylamino-1-butanol benzoate), mp 184°, identical with the authentic sample described above.

DL-**3-Amino-4-mercapto-1-butanol** (DL-**13**) was prepared from DL-**12** by the same procedure used for the preparation of L-**13**. As in the case of L-**13** the hydrochloride salt could not be obtained crystalline. The free base, DL-**13**, was obtained as a colorless solid, mp 92–94°, whose thiol assay indicated just 89% purity. The same two types of by-products were isolated as during the hydrolysis of L-**12**: DL-**3-benzoylamino-4-benzoylmercapto-1-butanol benzoate**, mp 164.5–166° (toluene), and the neutral oil DL-**3-benzoylamino-4-mercapto-1-butanol benzoate**, oxidized by iodine to DL-**4,4′-dithiobis(3-benzoylamino-1-butanol benzoate**), mp 122–124° (ethyl alcohol). The infrared spectra of these substances were identical with those of the higher melting analogs of the L series.

L-(−)-**3-Aminothiophane Hydrochloride** (L-**14**).—In an attempt to hydrolyze L-11 directly to L-**13** a solution of 32.6 g (0.105 mole) of L-**11** in 200 ml of 6 *N* HCl was refluxed for 18 hr. The mixture was cooled and benzoic acid (88%) was filtered off. The filtrate was evaporated and the crude residual L-**14** (12.6 g, 86%, mp 159–161°) was recrystallized from isopropyl alcohol to give colorless plates, mp 166.5–167°, $[\alpha]^{22}D$ −15° (*c* 2, H_2O).

Anal. Calcd for $C_4H_{10}ClNS$: C, 34.40; H, 7.22; N, 10.03; S, 22.96. Found: C, 34.89; H, 7.30; N, 10.37; S, 23.13.

A portion of this substance was benzoylated by the Schotten–Baumann technique to produce L-**3-(benzoylamino)thiophane** as colorless needles, mp 130–130.5° (methyl alcohol–water).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76; S, 15.47. Found: C, 63.51; H, 6.12; N, 6.94; S, 15.79.