It will be shown in a following publication that both C–O and C–C coupling in the present system are brought about by oxidized forms of the copper–amine catalytic system. It is well established that in a solution of a copper salt and a coördinating ligand, various complexes are capable of existence in equilibrium. These will differ in the number of ligand molecules coördinated with the metallic ion, and their relative concentrations will be governed by the stoichiometric concentrations of ligand and metal, and by the various associative equilibrium constants.[13] The results of the present investigation strongly indicate that such equilibria are important here, and constitute the key to catalytic specificity. It is proposed that two copper–amine complexes are catalytically active, differing in coördination number with respect to the amine ligand, and that the complex with the lower coördination number leads predominantly to C–C coupling, and the complex with the higher coördination number leads to C–O coupling. This situation can be represented schematically as in equation 2 where L represents the amine ligand, with these qualifications: the two complexes may actually differ in nuclearity, and the difference in coördination number is not necessarily unity.

$$\begin{array}{ccc} Cu^{II}L_n + L & \rightleftharpoons & Cu^{II}L_{n+1} \\ \downarrow + \text{ArOH} & & \downarrow + \text{ArOH} \\ \text{C—C} & & \text{C—O} \end{array} \qquad (2)$$

The other ligands involved in the complexes (chloride, oxide, or hydroxide ions) are omitted for the sake of clarity. Indeed, since both reactions are believed to involve intermediate complexes in which the anion derived from 2,6-dimethylphenol is coördinated with copper, this anion could be shown as a ligand on both sides of equation 2. In any event, this scheme accounts qualitatively for the observed effects of ligand ratio, catalyst concentration and steric hindrance in the ligand.[14] It is believed reasonable to expect that the predominant structures present in oxidized solutions of copper(I) chloride and amines in a noncoördinating solvent should change drastically as the stoichiometric ligand ratio is increased from a low value like 0.67 or 1.0. Succeeding papers will present evidence concerning the structure and role of the catalytic complexes, and the nature of the bond-forming processes in carbon–oxygen and carbon–carbon coupling.

Acknowledgment.—We are indebted to Miss Cynthia P. Lape and Mr. Barry Williams for technical assistance.

(13) For the formation constants of pyridine–copper ion complexes in aqueous media, see (a) J. Bjerrum, *et al.*, "Stability Constants of Metal-Ion Complexes," Part I, "Organic Ligands," The Chemical Society, London, 1957, p. 28; (b) B. R. James and R. J. P. Williams, *J. Chem. Soc.*, 2007 (1961).

(14) The decrease in oxidation rate observed with pyridine at high ligand ratio may be due to formation of catalytically inactive complexes of higher coördination number. Both valence states of the copper ion can achieve four-coördination with pyridine (ref. 13.)

The Synthesis of 2-Purin-6-ylaminoethanethiol and Some Related Compounds[1]

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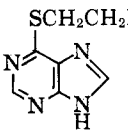
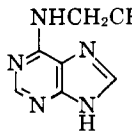
Syntheses of 2-purin-6-ylaminoethanethiol (II), 2-purin-8-ylaminoethanethiol (VI), and 2-(2-pyrimidinylamino)ethanethiol (VII) were achieved by the surprisingly facile catalytic hydrogenolysis of the corresponding disulfides in basic media. An N → S migration of the purin-6-yl group under acidic conditions and a novel formation of 7,8-dihydrothiazolo[2,3-*i*]purine (V) were encountered during development of the hydrogenolysis procedure for II. Compound II was also prepared from purine-6(1*H*)-thione in low yield *via* a rearrangement of the intermediate 6-(2-aminoethylthio)purine (I) under basic conditions.

As an extension of the previously reported series of *S*-substituted derivatives of purine-6-thiol,[2] the preparation of 6-(2-aminoethylthio)purine (I) was attempted by the reaction of purine-6(1*H*)-thione and 2-bromoethylamine hydrobromide in *N*,*N*-dimethylformamide containing potassium carbonate. This effort led to the isolation of pure 2-purin-6-ylaminoethanethiol (II) in low yield (5%), an equal yield of the impure disulfide III, unchanged purine-6(1*H*)-thione, but none of the intended product I. The thiol II reacted positively in the sodium nitroprusside test and showed ultraviolet absorption compatible with that of N^6-alkyladenines[3] and incompatible with that of 6-(alkylthio)-purines[2]; it obviously resulted from an intramolecular rearrangement of I. The limited preparative value of this procedure prompted an investigation of other synthetic routes to II and related *N*-(heteroaromatic-substituted) aminoethanethiols.





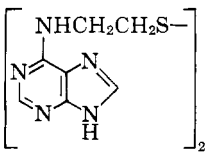
II. R = H
IV. R = $CH_2C_6H_5$

N^6-[2-(Benzylthio)ethyl]adenine (IV), prepared from 6-chloropurine and 2-(benzylthio)ethylamine, was debenzylated with sodium in liquid ammonia, but the product isolated was apparently a mixture of the desired thiol II and the disulfide III; a pure monohydrate of III was obtained in low yield by dilution of a 2-methoxyethanol solution of the crude product with an equal volume of water. Chu and Mautner[4] performed a

(1) This investigation was supported by the U. S. Army Medical Research and Development Command (contract no. DA-49-193-MD-2028) and, in part, by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health (contract no. SA-43-ph-1740).

(2) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, **80**, 6265 (1958).

(3) For example, *cf.* the spectra of N^6-methyladenine [S. F. Mason, *J. Chem. Soc.*, 2071 (1954)].

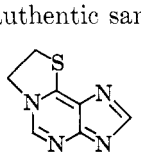


III

similar debenzylation of 6-amino-8-[2-(benzylthio)-ethylamino]purine and isolated the product as the corresponding disulfide after intentional peroxide oxidation. The disulfide III was more conveniently prepared from 6-chloropurine and 2,2′-dithiobisethylamine dihydrochloride in refluxing propanol in the presence of potassium carbonate. In the preparation of III a 2:1 molar ratio of diamine to 6-chloropurine gave an 87% yield; the ratios 1:1 and 0.5:1 gave 82 and 59% yields, respectively, with no attempted isolation of monosubstituted diamine as a probable by-product.[5]

Low pressure hydrogenolysis of III over palladium on charcoal was then investigated as a means of obtaining the thiol II in quantity. In 0.1 *N* sodium hydroxide solution the hydrogen uptake was surprisingly rapid, and the pure thiol II, identical with that prepared from purine-6(1*H*)-thione was isolated when normal precautions were taken to avoid air oxidation. (A reliable assay of II by iodometric titration could not be worked out.) Catalyst poisoning, which is usually associated with sulfur compounds, was apparently minimized by carrying out the hydrogenolysis in aqueous sodium hydroxide, a good solvent for both the starting material and the product.

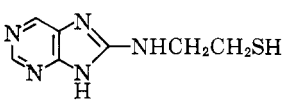
The hydrogenolysis of III in 0.3 *N* hydrochloric acid was slow, even with intermittent additions of fresh catalyst. The ultraviolet absorption spectrum of an aliquot of the reduction mixture indicated the product to be a hydrochloride of I (λ_{max} at pH 7, 285 mμ), which could have resulted from a rearrangement of II (λ_{max} at pH 7, 269 mμ) in acid solution. An analogous N → S migration of an acyl group has been previously described.[6] Refluxing an aliquot of the solution containing I in 0.1 *N* hydrochloric acid for three hours resulted in the formation as a major product not the expected hypoxanthine[2] but 7,8-dihydrothiazolo[2,3-*i*]-purine (V), which was identified by comparison of paper chromatograms and ultraviolet absorption spectra with those of an authentic sample.[7] These results



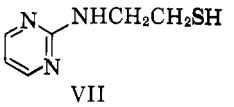
V

clearly show that I, which rearranged to II under basic conditions, underwent ring closure with loss of ammonia (as ammonium chloride) under acidic conditions to form the hydrochloride of V.

Catalytic hydrogenolysis under basic conditions was then applied to the preparation of 2-purin-8-ylamino-ethanethiol (VI) and 2-(2-pyrimidinylamino)ethanethiol (VII) from the corresponding disulfides, the latter reduction being carried out in 90% ethanol. The disulfides, 8,8′-[dithiobis(ethyleneimino)]dipurine and 2,2′-[dithiobis(ethyleneimino)]dipyrimidine, were obtained by displacement reactions of 2,2′-dithiobisethylamine with 8-(methylsulfonyl)purine and 2-chloropyrimidine, respectively.

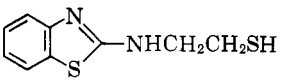


VI



VII

Several attempts to find the proper conditions for a similar catalytic reduction of 2,2′-[dithiobis(ethyleneimino)]bisbenzothiazole over palladium on charcoal were unsuccessful; this reduction was achieved, however, with sodium borohydride,[8] and near pure 2-(2-benzothiazolylamino)ethanethiol (VIII, 95% by iodometric titration) was isolated and subsequently characterized as the *S*-2,4-dinitrophenyl derivative. The intermediate disulfide was prepared in two ways: displacement by 2,2′-dithiobisethylamine of (1) the chlorine atom of 2-chlorobenzothiazole and (2) the phenylsulfonyl group of 2-(phenylsulfonyl)benzothiazole.



VIII

Experimental[9]

2-(Benzylthio)ethylamine.—To a stirred mixture of 96% 2-aminoethanethiol hydrochloride[10] (5.00 g., 42.4 mmoles), anhydrous potassium carbonate (12.3 g., 89.0 mmoles), and *N*,*N*-dimethylformamide (50 ml.) was added α-chlorotoluene (5.0 ml., 45 mmoles). After the exothermic reaction had ceased, the mixture was heated at 60° for 1 hr., then poured into water (375 ml.). The aqueous mixture was acidified (pH 3) with hydrochloric acid and washed with ether; it was then made basic (pH 11) with sodium hydroxide and extracted with ether. The ether layer, washed with water and dried over sodium sulfate, was evaporated to a colorless oil, which was further dried under reduced pressure at 60° for 2 hr.; yield 6.08 g. (86%), $n^{23}D$ 1.5770. Vacuum distillation of a portion of the crude product afforded analytically pure 2-(benzylthio)ethylamine, b.p. 92–96° (0.5–0.6 mm.), $n^{22}D$ 1.5763.[11] The product was stored under nitrogen (a small portion formed a solid carbonate when exposed to air).

Anal. Calcd. for $C_9H_{13}NS$: C, 64.56; H, 7.83; S, 19.17. Found: C, 64.89; H, 8.06; S, 18.96.

N⁶-[2-(Benzylthio)ethyl]adenine (IV).—A solution of crude 2-(benzylthio)ethylamine (4.00 g., 24.0 mmoles) and 6-chloropurine (1.48 g., 9.60 mmoles) in 1-propanol (15 ml.) was heated under reflux for 3 hr. The solution was evaporated under reduced pressure to near dryness and poured into water (100 ml.). The white solid that precipitated was washed with water and then ether and dried *in vacuo* over phosphorus pentoxide at 80°; yield of IV, 2.43 g. (89%); m.p. 175°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 275–276 (15.1) at pH 1, 269 (16.8) at pH 7, 275 (17.0) at pH 13.

A pilot run carried out in *N*,*N*-dimethylformamide at 105° produced the analytical sample (recrystallized from water and then benzene); m.p. 176° with softening from 163°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 276 (14.6) at pH 1, 269 (16.3) at pH 7,275 (16.8) at pH 13, 269 (18.7) in ethanol.

Anal. Calcd. for $C_{14}H_{15}N_5S$: C, 59.12; H, 5.32; S, 11.26. Found: C, 58.94; H, 5.32; S, 11.04.

N⁶,N⁶′-(Dithiodiethylene)diadenine (III).—To a stirred mix-

(4) S.-H. Chu and H. G. Mautner, *J. Org. Chem.*, **26**, 4498 (1961).

(5) *Cf.* H. Lettré and H. Ballweg, *Ann. Chem., Liebig's*, **649**, 124 (1961).

(6) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).

(7) R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).

(8) *Cf.* T. P. Johnston and A. Gallagher, *ibid.*, **27**, 2452 (1962).

(9) Melting points under 260° were determined on a Kofler Heizbank (unless otherwise noted); those above 260° were determined in a capillary and are uncorrected.

(10) Evans Chemetics, Inc., New York, N. Y.

(11) Chu and Mautner[4] reported b.p. 78–80° (0.15 mm.) and $n^{25.4}D$ 1.5740 for the product from aziridine and α-toluenethiol.

ture of 2,2′-dithiobisethylamine dihydrochloride[12] (10.3 g., 46.0 mmoles), anhydrous potassium carbonate (14.0 g., 101 mmoles), and 1-propanol (60 ml.) was added 6-chloropurine (7.10 g., 46.0 mmoles), and the resulting suspension was heated under reflux for 6 hr. The reaction mixture was evaporated *in vacuo* to 45 ml. and then poured into water (900 ml.). After the mixture was neutralized with hydrochloric acid, the off-white precipitate was washed with water and dissolved in boiling 1 *N* hydrochloric acid (1 l.), an insoluble tan solid being removed by filtration. The cooled filtrate was brought to pH 8 with concentrated ammonium hydroxide, and the resulting cream-colored precipitate was washed with water and dried *in vacuo* over phosphorus pentoxide at 100°; yield of III, 7.27 g. (81%); λ_{max} in mμ ($\epsilon \times 10^{-3}$): 275 (31.0) at pH 1, 265 (29.2) at pH 7,274 (32.5) at pH 13. For analysis, a sample was precipitated from *N*,*N*-dimethylformamide by the addition of water; m.p. 290° dec. (from 200°) with darkening from 285°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 276 (31.8) at pH 1, 266 (29.1) at pH 7, 275 (32.8) at pH 13.

Anal. Calcd. for $C_{14}H_{16}N_{10}S_2$: C, 43.28; H, 4.15; S, 16.51. Found: C, 43.11; H, 4.15; S, 16.54.

2-Purin-6-ylaminoethanethiol (II). (1) From Purin-6(1*H*)-thione.—2-Bromoethylamine hydrobromide (663 mg., 3.24 mmoles) was added to a well stirred mixture of purine-6(1*H*)-thione monohydrate (500 mg., 2.94 mmoles), anhydrous potassium carbonate (815 mg., 5.90 mmoles), and *N*,*N*-dimethylformamide (4 ml.). After the exothermic reaction had ceased, the mixture was heated at 50° for 2 hr. and then poured into water (20–25 ml.). Neutralization of the resulting solution with hydrochloric acid caused the precipitation of a light yellow solid, which was extracted with hot chlorobenzene; the residue (316 mg., 63%) was unchanged purine-6(1*H*)-thione (λ_{max} in mμ: 324 at pH 1, 321 at pH 7, 308 at pH 13). The aqueous *N*,*N*-dimethylformamide filtrate, adjusted to pH 6 and left overnight in a refrigerator, was filtered to remove a small additional precipitate of purine-6(1*H*)-thione and the filtrate evaporated to dryness under reduced pressure. The residue, triturated in water and dried *in vacuo*, was a pinkish white solid (45 mg., m.p. 234°), recrystallization of which from chlorobenzene afforded pure II as colorless crystals, which were dried *in vacuo* at 110°; yield 31 mg. (5%); m.p. 236°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 274 (16.2) at pH 1, 268 (17.2) at pH 7, 276 (17.4) at pH 13; strongly positive nitroprusside test.[13]

Anal. Calcd. for $C_7H_9N_5S$: C, 43.08; H, 4.65; N, 35.88. Found: C, 43.05; H, 4.42; N, 35.83.

The refrigerated aqueous filtrate from the trituration deposited an additional 30 mg. (5%) of white solid, which apparently was a mixture of II and III; m.p. 266° dec.; λ_{max} in mμ: 276 at pH 1, 267 at pH 7, 275 at pH 13; transitorily positive nitroprusside test.

(2) From N^6,N$'^{6'}$-(Dithiodiethylene)diadenine.—A solution of III (1.55 g., 4.00 mmoles) in 0.1 *N* sodium hydroxide (160 ml.) was hydrogenated at room temperature in a Parr shaker apparatus at an initial pressure of 45 p.s.i. over 5% palladium on charcoal (310 mg., 20% weight of disulfide). When the hydrogen uptake was complete (*ca.* 1 hr.), the catalyst was removed by filtration under nitrogen. The filtrate, carefully neutralized with 6 *N* hydrochloric acid with cooling, deposited II as a white crystalline solid, which was collected under nitrogen and dried *in vacuo* over phosphorus pentoxide; yield 990 mg. (64%); m.p. 236°; positive nitroprusside test; positive Rheinboldt test[14] (red in hydrochloric acid); λ_{max} in mμ ($\epsilon \times 10^{-3}$): 274 (16.3) at pH 1, 268 (17.4) at pH 7, 276 (18.3) at pH 13.

A similar 2-hr. hydrogenolysis of III on a 20-mmole scale gave an 80% yield of II, m.p. 238°.

8,8′-[Dithiobis(ethyleneimino)]dipurine.—8-(Methylsulfonyl/-purine[15] (3.96 g., 20.0 mmoles) was added to a solution of 2,2′-dithiobisethylamine[12] (3.35 g., 22.0 mmoles) in 1-propanol (30 ml.). The resulting mixture was refluxed for 5 hr. and evaporated to dryness under reduced pressure. A suspension of the residue in water (50 ml.) was brought to pH 7 with 1 *N* hydrochloric acid. The precipitated gum slowly solidified to a tan solid, which was collected and dried *in vacuo;* yield of crude disulfide, 2.78 g. (72%); λ_{max} in mμ ($\epsilon \times 10^{-3}$): 298 (31.4) at pH 1, 288–289 (25.4) at pH 7, 298 (25.4) at pH 13. For analysis, a small sample of the crude product was twice recrystallized from water; recovery of the product as a white microcrystalline powder, 18%; m.p. 282° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 296 (38.6) at pH 1, 286 (33.2) at pH 7, 296 (30.8) at pH 13.

Anal. Calcd. for $C_{14}H_{16}N_{10}S_2$: C, 43.28; H, 4.15; S, 16.50. Found: C, 43.51; H, 4.55; S, 16.22.

2-(Purin-8-ylamino)ethanethiol (VI).—A clarified 0.1 *N* sodium hydroxide solution (200 ml.) containing approximately 1.6 g. (4.1 mmoles) of 8,8′-[dithiobis(ethyleneimino)]dipurine was hydrogenated over 390 mg. of 5% palladium on charcoal at an initial pressure of 50 p.s.i. at room temperature in a Parr shaker apparatus; the calculated amount of hydrogen was absorbed within an hour. The catalyst was removed by filtration under nitrogen, and the filtrate was neutralized with 6 *N* hydrochloric acid and evaporated to dryness *in vacuo*. The residue was triturated in water (3 × 5 ml.) and dried *in vacuo* over phosphorus pentoxide; yield of crude VI, 1.0 g. (*ca.* 63%). A solution of the crude thiol in boiling ethanol (*ca.* 40 ml.) was treated with Norit, filtered under nitrogen, and evaporated to dryness under reduced pressure; recovery 96%; m.p. 209°; positive nitroprusside and Rheinboldt tests; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 297 (19.2) at pH 1, 289 (17.1) at pH 7, 299 (15.6) at pH 13.

Anal. Calcd. for $C_7H_9N_5S$: C, 43.05; H, 4.64; S, 16.42. Found: C, 43.20; H, 4.88; S, 16.31.

2,2′-[Dithiobis(ethyleneimino)]dipyrimidine.—A solution of 2-chloropyrimidine[16] (12.1 g., 0.106 mole) and 2,2′-dithiobisethylamine[12] (17.0 g., 0.111 mole) in 1-propanol (75 ml.) was refluxed for 5 hr. Dilution of the cooled reaction mixture with water (750 ml.) gave 13.4 g. of vacuum-dried product as a white powder, m.p. 166°. The aqueous filtrate yielded a second crop of 1.03 g., m.p. 165°. The total yield was 88%. [2,2′-Dithiobisethylamine dihydrochloride (10.3 g., 87%), m.p. 218° (lit.,[12] m.p. 216°), was isolated from the last filtrate.] For analysis, a small sample of the first crop was recrystallized from ethanol with Norit treatment. The white needles obtained melted at 166° after being dried *in vacuo* over phosphorous pentoxide at 80°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 230 (37.1), 315 (7.54) at pH 1; 235 (36.4), 305 (5.38) at pH 7; 235 (36.4), 305 (5.38) at pH 13.

Anal. Calcd. for $C_{12}H_{16}N_6S_2$: C, 46.42; H, 5.19; S, 20.66. Found: C, 46.76; H, 5.56; S, 20.91.

2-(2-Pyrimidinylamino)ethanethiol (VII).—A solution of 2,2′-[dithiobis(ethyleneimino)]dipyrimidine (1.55 g., 5.50 mmoles) in ethanol was treated with 0.903 *N* sodium hydroxide solution (11.1 ml.), and the resulting solution was diluted so that the final volume was 300 ml. and the medium was 90% ethanol (by volume). Hydrogenation was carried out in a Parr shaker apparatus over 310 mg. of 5% palladium on charcoal at an initial pressure of 50 p.s.i. for 2 hr. The catalyst was removed by filtration under nitrogen; the filtrate, after neutralization with the calculated volume of 1 *N* hydrochloric acid, was evaporated *in vacuo* to near dryness. The orange-colored oil that separated was extracted with ether (3 × 15 ml.); the ether extract, washed once with water (10 ml.) and dried over sodium sulfate, was evaporated to dryness under reduced pressure. The residual pale yellow semisolid was triturated in ethanol (5 ml.): the insoluble solid (78 mg., m.p. 165°) was identified as the starting disulfide, whereas evaporation of the ethanol solution *in vacuo* gave 1.15 g. (74%) of a pale yellow oil, which gave a positive nitroprusside test. The oil was distilled under reduced pressure. The distillate, b.p. 86° (0.3 mm.), solidified to a white crystalline solid having a pepper-like odor; m.p. 40–41° (capillary); λ_{max} in mμ ($\epsilon \times 10^{-3}$): 229 (17.9), 315 (3.62) at pH 1; 235 (18.5), 305 (2.74) at pH 7; 237 (22.8), 309 (2.50) at pH 13.

Anal. Calcd. for $C_6H_9N_3S$: C, 46.42; H, 5.84; S, 20.66; SH, 21.3. Found: C, 46.38; H, 5.84; S, 20.52; SH, 21.6, 21.3 (iodometric).

2-(Phenylsulfonyl)benzothiazole.—A stirred mixture of 2-chlorobenzothiazole (12.0 g., 71.5 mmoles), sodium benzenesulfinate (12.3 g., 75.0 mmoles), and *N*,*N*-dimethylformamide (50 ml.) was heated at 70–80° for 3 hr. Pouring the resulting mixture into water (500 ml.) caused the precipitation of a white solid, which was washed with water and dried *in vacuo* over phosphorus pentoxide; yield 18.6 g. (94%), m.p. 161–162° (lit.,[17] m.p. 161°).

2,2′-[Dithiobis(ethyleneimino)]bisbenzothiazole.—A mixture of 2-(phenylsulfonyl)benzothiazole (1.65 g., 6.00 mmoles), 2,2′-

(12) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **26**, 3780 (1961).

(13) R. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *Radiation Research*, **7**, 22 (1957).

(14) H. Rheinboldt, *Ber.*, **60**, 184 (1927).

(15) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957).

(16) I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Syn.*, **35**, 34 (1955).

(17) O. Bayer and H. Schindhelm, German Patent 609,025 (February 6, 1935); *Chem. Abstr.*, **29**, 3174 (1935).

dithiobisethylamine (930 mg., 6.10 mmoles), and 1-propanol (20 ml.) was refluxed for 3.5 hr. The resulting solution was cooled and poured into water (100 ml.), and the solid that precipitated was collected and dried *in vacuo;* yield 1.04 g., (83%), m.p. 180°. Recrystallization of a 150-mg. sample of the crude product from acetonitrile (45 ml.) gave 120 mg. of the disulfide as a white solid, which melted at 188° after being dried *in vacuo* over phosphorus pentoxide at 80°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 250 (20.7), 281 (17.9), 288 (18.7) at pH 1; λ_{max} at pH 7 and pH 13 unrecorded because solutions became cloudy.

Anal. Calcd. for $C_{18}H_{18}N_4S_4$: C, 51.64; H, 4.33; S, 30.64. Found: C, 51.73; H, 4.66; S, 30.72.

2-(2-Benzothiazolylamino)ethanethiol (VIII).—A 5% solution of 2,2′-[dithiobis(ethyleneimino)]bisbenzothiazole (2.09 g., 5.00 mmoles) in 2-methoxyethanol was added to a 5% solution of sodium borohydride (1.28 g., 30.0 mmoles) in methanol over a period of 5 min. The resulting solution was heated at 60° for 15 min. and then evaporated to dryness under reduced pressure. The semisolid residue was suspended in water (50 ml.) and the pH of the mixture adjusted to 8 with hydrochloric acid. The white solid was collected, washed with water, and extracted with ether (3 × 50 ml.). The ether solution, after being dried over magnesium sulfate and filtered, was evaporated to dryness under reduced pressure. The residual white solid was dried *in vacuo* over phosphorus pentoxide; yield 1.13 g. (54%); m.p. 85–86° with opaque melt (capillary); % VIII by iodometric titration 95. The ether-insoluble substance, m.p. 185°, was identified as the starting disulfide (recovery 23%).

The thiol VIII was further characterized as the *S*-2,4-dinitrophenyl derivative, which was prepared from VIII, 1-chloro-2,4-dinitrobenzene, and potassium carbonate in *N,N*-dimethylformamide. The crude 2-[2-(2,4-dinitrophenylthio)ethylamino] benzothiazole was recrystallized from an acetonitrile–water solvent pair as an orange solid, which decomposed without melting at 187–189° (capillary).

Anal. Calcd. for $C_{15}H_{12}N_4O_4S_2$: C, 47.86; H, 3.21; S, 17.04. Found: C, 47.54; H, 3.10; S, 16.68.

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Transoxazolination. Preparation of Disulfides of 2-(2-Mercaptoethylamino)-2-oxazolines

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The products obtained from the aminoethylation of several 2-thioöxazolidones underwent rearrangement in alkaline solution to 2-(2-mercaptoethylamino)-2-oxazolines, which were readily oxidized to the corresponding disulfides. The disulfides required for identification were prepared by the reaction of 2-methylthio-2-oxazolines with 2-mercaptoethylamine hydrochloride. An intermediate with anomalous properties was encountered in the latter reaction.

The rearrangement of *S*-(2-aminoethyl)isothiourea (AET), a radioprotective agent, to 2-mercaptoethylguanidine by transguanylation through a proposed cyclic intermediate in neutral or weakly alkaline solution has been described by Doherty, *et al.*[1,2] The study of this transformation was extended by these workers to a number of aminoalkylisothioureas and to 2-(2-aminoethylthio)-2-imidazoline.[3] We have recently reported the rearrangement of 2-(2-aminoethylthio)-2-thiazoline to 2-(2-mercaptoethylamino)-2-thiazolineby transthiazolination through a proposed bicyclic intermediate.[4]

In the case of the transthiazolination described, the similarity of the rings comprising the hypothetical bicyclic intermediate permitted the formation of only a single product. We have attempted to extend the rearrangement to 2-oxazoline derivatives, in which unsymmetrical bicyclic intermediates of type III would be involved.

From the reaction of 4,4-dimethyl-2-thioöxazolidone (Ia) and 2-bromoethylamine hydrobromide in refluxing isopropyl alcohol a crystalline hydrobromide of type II could not be isolated. However, when an aqueous solution of the reaction product was adjusted to pH 7.3, there was obtained, after standing, 2-(2-mercaptoethylamino)-4,4-dimethyl-2-oxazoline (IVa), isolated as the picrate, in 23% yield from the thioöxazolidone.[5] Adjustment of the solution of the reaction product to higher pH values, accompanied by aeration, resulted in the formation in 5–7% yield of the disulfide (Va) of the mercaptan.

Since sodium ethylate has been used effectively in the alkylation of 2-thioöxazolidones with alkyl halides,[6] the reaction of Ia and 2-bromoethylamine hydrobromide was carried out with this reagent. After aeration in alkaline solution, a 12% over-all yield of the disulfide dipicrate was obtained.

Similarly, the reaction of both 2-thioöxazolidone (Ib) and 4-methyl-5-phenyl-2-thioöxazolidone (Ic) with 2-bromoethylamine in the presence of sodium ethylate, followed by aeration in alkaline solution, afforded the rearranged disulfides. Bis[2-(2-oxazolin-2-ylamino)-ethyl] disulfide (Vb) and bis[2-(4-methyl-5-phenyl-2-oxazolin-2-ylamino)ethyl] disulfide (Vc), isolated as the dipicrates, were obtained in 10–15% yield.

The compounds required for identification of the rearrangement products were prepared by the reaction of the appropriate 2-methylthio-2-oxazoline with 2-mercaptoethylamine hydrochloride. The reaction of 2-methylthio-2-thiazoline with various amines[4,7] and an instance of the reaction of a 2-methylthio-2-oxazoline

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(2) J. X. Khym, R. Shapira, and D. G. Doherty, *ibid.*, **79**, 5663 (1957).

(3) J. X. Khym, D. G. Doherty, and R. Shapira, *ibid.*, **80**, 3342 (1958).

(4) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *J. Org. Chem.*, **26**, 1666 (1961).

(5) In the preparation of 2-(2-aminoethylthio)-2-thiazoline dihydrobromide from 2-thiothiazolidone and 2-bromoethylamine hydrobromide, a yield of 27% was obtained.[4] Thus the 23% over-all yield obtained here might indicate a rather high yield in the rearrangement step.

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