Phenyl 2-Carbamyl-5-aminobenzenesulfonate (*11*).—The above nitro compound (3.5 g., 0.0109 mole) was dissolved in 200 ml. of ethyl acetate and reduced in the presence of palladium and carbon. The reaction proceeded very smoothly and at the end, the suspension was filtered and concentrated to give an oil which slowly solidified. The solid was recrystallized from isopropyl alcohol, m.p. 136–140°, 1.8 g. (57%).

Anal. Calcd. for $C_{13}H_{12}N_2O_4S$: C, 53.44; H, 4.14; N, 9.58. Found: C, 53.99; H, 4.51; N, 9.39.

N-(Heteroaromatic-Substituted Methyl) Derivatives of 2-Aminoethanethiol[1,2]

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Several methods for the preparation of *N*-(heteroaromatic-substituted methyl) derivatives of 2-aminoethanethiol have been investigated. The sodium borohydride reduction of Schiff bases derivable from cystamine and heteroaromatic aldehydes (for example, Ia and Ib) may have general utility for the preparation of this type of *N*-substituted 2-aminoethanethiols. The iodine oxidation of the thiazolidines IIa and IIb has been demonstrated to be an advantageous source of the corresponding Schiff bases. The direct aralkylation of cystamine with 8-(bromomethyl)quinoline was shown to be controllable so as to give as the predominant product either a tetra- or a disubstituted cystamine (IX and X, respectively). Sulfite cleavage of the disubstituted cystamines VIa and X afforded the corresponding intra Bunté salts.

Although simple 2-alkylaminoethanethiols have been reported to be less protective against radiation injury in experimental animals than 2-aminoethanethiol itself,[3] *N*-(heteroaromatic-substituted methyl) derivatives of 2-aminoethanethiol warrant antiradiation screening because their structure combines heteroaromatic nuclei of potential biological importance with 2-aminoethanethiol without profoundly affecting the basicity of the amino group and its relation to the thiol group. The compounds selected for synthesis are represented by the structure $ArCH_2NHCH_2CH_2SH$ where Ar is the heterocyclic groups 3-pyridyl, 2-thienyl, 3-indolyl, and 8-quinolyl.

Of the synthetic methods that we examined, one that appears to have general utility is the reduction of Schiff bases derivable from 2,2′-dithiobisethylamine (cystamine) and heteroaromatic aldehydes, a number of which are commercially available or readily prepared. 2,2′-Dithiobis[*N*-(3-pyridylmethylene)ethylamine] (IVa), the Schiff base from nicotinaldehyde (Ia), was obtained as a pure solid, whereas 2-thiophenecarboxaldehyde (Ib) afforded 2,2′-dithiobis[*N*-(2-thenylidine)ethylamine] (IVb) as a viscous oil, which was used in the subsequent reduction without further purification. The infrared absorption spectrum of each was characterized by strong absorption near 1640 cm.$^{-1}$ assigned to the conjugated exocyclic —CH=N— group,[4] which disappeared on subsequent reduction. Attempts to characterize the Schiff bases IVa and IVb as picrates resulted in hydrolysis, and in each case the dipicrate of 2,2′-dithiobisethylamine was obtained.

As an alternative procedure, the iodine oxidation of the thiazolidines IIa and IIb, prepared by the condensation of 2-aminoethanethiol with nicotinaldehyde and 2-thiophenecarboxaldehyde, respectively, in a manner modeled after previously described[5,6] general procedures, was demonstrated to produce conveniently the desired Schiff bases. That certain thiazolidines unsubstituted on the nitrogen atom undergo many reactions typical of thiols has previously been observed.[7] Thus, 2-(3-pyridyl)thiazolidine (IIa), isolated as an analytically pure water-soluble oil, gave a positive nitroprusside test for a thiol and consumed a nearly quantitative volume of standard iodine–potassium iodide solution to give a Schiff base that was identical with the authentic sample of 2,2′-dithiobis[*N*-(3-pyridylmethylene)ethylamine] (IVa). These results are in agreement with the proposed equilibrium between a thiazolidine and the corresponding methyleneaminoethanethiol (in this case, IIa⇌IIIa).[7,8] Significant antiradiation protection of rats by the intraperitoneal injection of 4-thiazolidinecarboxylic acid (in hydrolytic equilibrium with cysteine) has recently been reported.[9] The properties of the thiazolidine IIa, which showed a strong NH stretching band (3250 cm.$^{-1}$) in the infrared and formed a pure dipicrate, do not agree with those described recently[10] for the water-insoluble product obtained from a condensation of 2-aminoethanethiol and nicotinaldehyde carried

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(2) Presented at the Combined Southwest-Southeast Regional American Chemical Society Meeting, New Orleans, Louisiana, December 8, 1961.

(3) H. Langendorff and R. Koch, *Strahlentherapie*, **99**, 567 (1956).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 270.

(5) H. Bestian, *Ann.*, **566**, 210 (1950).

(6) R. Kuhn and F. Drawert, *ibid.*, **590**, 55 (1954).

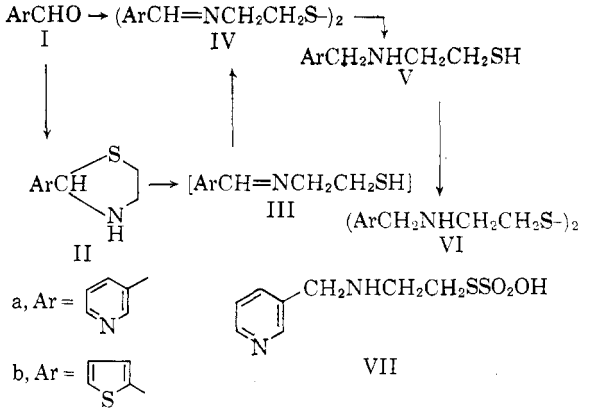
(7) G. Hesse and G. Ludwig, *ibid.*, **632**, 158 (1960).

(8) M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936).

(9) R. Riemschneider, *Z. Naturforsch.*, **16b**, 75 (1961).

(10) A. Banashek and M. N. Shchukina, *Zh. Obshchei Khim.*, **31**, 1483 (1961).

out in aqueous ethyl alcohol and followed by the disappearance of thiol by the nitroprusside test.



The condensation of 2-thiophenecarboxaldehyde and 2-aminoethanethiol afforded 2-(2-thienyl)-thiazolidine (IIb) as a pure crystalline solid, stable in storage and readily oxidizable with iodine to the corresponding Schiff base IVb. This and similar thiazolidines were recently described as unstable compounds, which decomposed quickly on standing.[11]

Many examples of the sodium borohydride reduction of Schiff bases to the corresponding secondary amines have been described,[12,13] but the preparative use of sodium borohydride as a reducing agent for disulfides has not been widely applied, the reduction of α-lipoic acid to 6,8-dimercaptooctanoic acid[14] and more recently the reduction of 2,2′-dithiobisbenzothiazole to 2-mercaptobenzothiazole[15] being exceptional examples. The dual reduction of the azomethine and disulfide linkages in the Schiff bases IVa and IVb has been accomplished by sodium borohydride in methanolic solution, and the respective products, 2-[(3-pyridylmethyl)amino]ethanethiol (Va) and 2-(2-thenylamino)ethanethiol (Vb), exhibited properties expected of the desired thiols: positive nitroprusside tests, high iodometric titers, and infrared absorption spectra showing NH and SH bands. The thiol Va was further characterized as a dipicrate. The properties of the thiol Vb were in relatively close agreement with those previously described for the 2-(2-thenylamino)ethanethiol obtained from ethylene sulfide and 2-thenylamine.[16] Each of the thiols Va and Vb was converted to the corresponding disulfides: (1) The air oxidation of Va in aqueous solution at *p*H 8–9 produced 2,2′-dithiobis[*N*-(3-pyridylmethyl)ethylamine] (VIa), a thick oil whose infrared absorption spectrum was identical with that of Va except for the absence of thiol absorption near 2500 cm.$^{-1}$. (2) The iodine oxidation of Vb gave the dihydroiodide of 2,2′-dithiobis[*N*-(2-thenyl)ethylamine] (VIb).

The disulfide VIa was characterized as the tetrapicrate, which was different from that prepared from Va, and as the dihydrochloride. When air was bubbled through the reaction mixture from the sodium borohydride reduction of IVa diluted with water and adjusted to pH 8–9, the isolated disulfide contained boron (methyl borate green flame test[17]) and showed the characteristic infrared absorption in the 2300–2500-cm.$^{-1}$ region that has been assigned to amine–borine complexes.[18,19] Further, the dihydrochloride of the disulfide VIa was cleaved in aqueous solution by sulfurous acid in the presence of sodium acetate, and *S*-2-[(3-pyridylmethyl)amino]ethyl thiosulfuric acid (VII), an intra Bunté salt, was isolated in 16% yield. The method employed is an adaptation of that described by Kaluszyner for the preparation of *S*-2-guanidinoethyl thiosulfuric acid.[20,21] Bunté salts of this type are of interest because of the reported antiradiation activity of *S*-2-aminoethyl thiosulfuric acid.[22] The infrared absorption spectrum of VII is characterized by a series of overlapping bands in the 1100–1300-cm.$^{-1}$ region with two strong peaks at 1170 and 1230 cm.$^{-1}$; in addition there are equally strong absorptions at 1020 cm.$^{-1}$ (sharp) and 630 cm.$^{-1}$. These absorptions, characteristic of the sulfonate ion,[23] are in general agreement with the values recently recorded for sodium and potassium *S*-alkyl thiosulfates.[24]

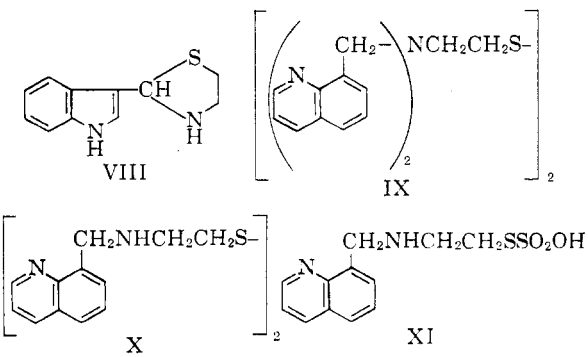
Applied to indole-3-carboxaldehyde, the methods described above were only partially successful. Recently the preparation of a number of 3-(alkylaminomethyl)indoles by the sodium borohydride reduction of the corresponding Schiff bases was reported.[25] 2-Indol-3-ylthiazolidine (VIII) was obtained in pure form, but the only product isolated from the attempted iodine oxidation of VIII was indole-3-carboxaldehyde, which presumably resulted from the hydrolysis of the desired Schiff base in the presence of water and the hydroiodic acid formed during the oxidation. The desired 2,2′-dithiobis[*N*-(indol-3-ylmethylene)ethylamine] was obtained as a crude oil directly from 2,2′-dithiobisethylamine. The reaction mixture from the sodium borohydride reduction of the Schiff base carried out under the conditions specified by Walker and Moore[25] gave a transitory nitroprusside test for thiol when tested immediately.

(11) Yu. K. Yur'ev, E. V. Dyatlovitskaya, and A. E. Sokol, *J. Gen. Chem. U.S.S.R.* (Eng. Transl.), **29**, 3844 (1959).
(12) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957).
(13) I. L. Finar and K. Utting, *J. Chem. Soc.*, 4015 (1959).
(14) I. C. Gunsalus, L. S. Barton, and W. Gruber, *J. Am. Chem. Soc.*, **78**, 1763 (1956).
(15) J. J. D'Amico, *J. Org. Chem.*, **26**, 3461 (1961).
(16) F. Yu Rachinskiĭ, N. M. Slavachevskaya, and D. V. Ioffe, *J. Gen. Chem. U.S.S.R.* (Eng. Transl.), **28**, 3027 (1958).
(17) F. Feigl, "Spot Tests," 4th Eng. ed., Vol. I, Elsevier Publishing Co., Amsterdam, 1954, p. 315.
(18) A. R. Katritzky, *J. Chem. Soc.*, 2049 (1959).
(19) R. Köster, G. Bruno, and P. Binger, *Ann.*, **644**, 1 (1961).
(20) A. Kaluszyner, *Bull. Res. Council Israel*, **9A**, 35 (1960).
(21) For a general discussion of the sulfite cleavage of disulfides, see A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).
(22) B. Holmberg and B. Sörbo, *Nature*, **183**, 832 (1959).
(23) Ref. 4, p. 364.
(24) A. Simon and D. Kunath, *Chem. Ber.*, **94**, 1980 (1961).
(25) G. N. Walker and M. A. Moore, *J. Org. Chem.*, **26**, 432 (1961).

The rapid disappearance of the thiol indicated concurrent disulfide formation, but a pure disulfide could not be isolated because of the stability of the borine complex in base and the decomposition of the indole ring in acid.

The direct aralkylation of cystamine, to be followed by reductive cleavage of the resulting disulfide, was also considered as a preparative route to [(heteroaromatic-substituted methyl)-amino]ethanethiols. The 8-quinolylmethylation of cystamine was found to be controllable so as to give as the major product either 2,2′-dithiobis-[*N*,*N*-di(8-quinolylmethyl)ethylamine] (IX) or 2,2′ - dithiobis[*N* - (8 - quinolylmethyl)ethylamine] (X). Thus the reaction of one mole of cystamine with two moles of 8-(bromomethyl)-quinoline in *N*,*N*-dimethylformamide at 60° in the presence of potassium carbonate gave 51% of the tetrasubstituted cystamine IX, characterized as the pure monohydrate. When cystamine was treated similarly with 8-(bromomethyl)quinoline in the molar ratio of 1.5:1, the latter being added at 80°, the product isolated in 87% yield was the oily disubstituted cystamine X, which was characterized as the tetrahydrochloride monohydrate. The attempted reduction of the disubstituted cystamine X with sodium borohydride was not successful; if reduction occurred, the product was rapidly re-oxidized to the starting disulfide. The cleavage of the disulfide, however, with sulfurous acid was achieved in two ways: the prolonged action of dilute sulfurous acid on either (1) the tetrahydrochloride in aqueous *p*-dioxane in the presence of sodium acetate or (2) the free base in *p*-dioxane. Both methods resulted in the precipitation of the desired *S*-2-[(8-quinolylmethyl)amino]ethyl thiosulfuric acid (XI, inner salt), which showed an infrared absorption typical of Bunté salts[24] and similar to that of VII.

Early in this work the use of *N*,*N*′-(dithiodiethylene)bis-*p*-toluenesulfonamide was investigated as a means of preventing the anticipated tetra-aralkylation of the type that led to the formation of IX. Thus 2-thenylation of the sulfonamide, carried out in *N*,*N*-dimethylformamide with potassium carbonate as the acid acceptor, gave *N*,*N*′-(dithiodiethylene)bis[*N* - (2 - thenyl) - *p* - toluenesulfonamide]; but this approach was abandoned when it was found that this compound underwent excessive decomposition in the attempted hydrolysis under various acidic conditions.[26]



Experimental

2-(3-Pyridyl)thiazolidine (IIa).[27]—A solution of 4.6 g. (0.060 mole) of 2-aminoethanethiol[28] and 6.4 g. (0.060 mole) of freshly distilled nicotinaldehyde in 12.5 ml. of benzene was refluxed over a Dean-Stark trap for 6 hr., but little, if any, water was formed. The benzene was evaporated under reduced pressure, and the residue heated at 60° *in vacuo* for 1 hr. The residual pale yellow oil, 9.6 g. (97%), $n^{25}D$ 1.6125, was twice-distilled *in vacuo* through a Claisen head; yield 6.7 g. of analytically pure thiazolidine as a straw-colored, slightly viscous, water-soluble oil, b.p. 107–113° (0.3 mm.), $n^{24}D$ 1.6123.

Anal. Calcd. for $C_8H_{10}N_2S$: C, 57.79; H, 6.06; S, 19.28. Found: C, 57.77; H, 6.03; S, 19.44.

A dipicrate was obtained from the thiazolidine in ethyl alcohol and was recrystallized from the same solvent as large yellow needles, m.p. 185° dec.,[29] 192° dec.[30]; nitroprusside test positive (in sodium hydroxide solution).

Anal. Calcd. for $C_{20}H_{16}N_8O_{14}S$: C, 38.46; H, 2.58; S, 5.14. Found: C, 38.58; H, 2.60; S, 4.85.

2,2′-Dithiobis[*N*-(3-pyridylmethylene)ethylamine] (IVa). 1. From 2,2′-Dithiobisethylamine.—A mixture of 6.85 g. (45.0 mmoles) of 2,2′-dithiobisethylamine[31] and 9.64 g. (90.0 mmoles) of freshly distilled nicotinaldehyde in 150 ml. of benzene was refluxed over a Dean-Stark trap for 1 hr. Within the first 20 min., the theoretical amount of water (1.6 ml.) was collected. The reaction mixture, filtered hot to remove a small amount of insoluble material, was evaporated to dryness under reduced pressure and the residue dried *in vacuo* at 60° for 1 hr. The remaining thick, yellow-red oil solidified when the side of the flask was scratched with a glass rod; yield of the Schiff base as an off-white crystalline solid was 15.0 g. (100%), m.p. 58–60°. For analysis, a small sample was recrystallized from ethyl ether–petroleum ether to give colorless crystals, m.p. 62–63°.

Anal. Calcd. for $C_{16}H_{18}N_4S_2$: C, 58.15; H, 5.49; S, 19.40. Found: C, 57.69; H, 5.51; S, 19.19.

The Schiff base IVa was also prepared by stirring an aqueous solution of 2,2′-dithiobisethylamine dihydrochloride[32] (14.3 g.), brought to pH 10–11 with sodium hydroxide solution, with an equivalent amount of nicotinaldehyde for 30 min., extracting the resulting mixture with benzene, and completing the procedure as described above; yield 18.0 g. (86%), m.p. 58–60°.

2. From 2-(3-Pyridyl)thiazolidine.—An aqueous solution of a sample of the thiazolidine IIa was treated with an equivalent amount of 1 *N* iodine–potassium iodide solution. After being made alkaline (pH 9) with sodium hydroxide, the solution was extracted with benzene. Evaporation of

(26) For a general discussion of the cleavage of sulfonamides, see S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959).

(27) *Cf.* ref. 11.

(28) 2-Aminoethanethiol, m.p. 96–98°, was freed from the commercially available hydrochloride in a manner similar to that described for 2,2′-dithiobisethylamine[31] although volatility reduced the recovery.

(29) Melting points (uncorrected) were determined in a capillary unless otherwise indicated.

(30) Determined on a Kofler Heizbank.

(31) Methanolic solutions of equivalent amounts of 2,2′-dithiobisethylamine dihydrochloride[32] and sodium methoxide were mixed and evaporated to dryness under reduced pressure. The resulting semisolid residue was extracted several times with chloroform and the combined chloroform solutions, evaporated to dryness under reduced pressure, gave 92–98% of 2,2′-dithiobisethylamine as a straw-colored oil, which was further dried *in vacuo* for 1 hr. at 60°.

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

the benzene under reduced pressure left an off-white solid, m.p. 60–61°, whose infrared absorption was identical with that of the Schiff base described above. A mixed melting point with the authentic sample was undepressed.

Attempts to prepare a dipicrate of IVa in ethyl alcohol resulted in the isolation of the dipicrate of 2,2′-dithiobisethylamine as yellow needles, m.p. 197–198° dec. (from glacial acetic acid).[33]

2-[(3-Pyridylmethyl)amino]ethanethiol (Va).—A 5% methanolic solution of 9.1 g. (240 mmoles) of sodium borohydride was added over a period of 20 min. to a 10% methanolic solution of 13.2 g. (40.0 mmoles) of crude Schiff base IVa, m.p. 58–60°. The resulting solution was refluxed for 30 min. and then evaporated to near dryness under reduced pressure. A solution of the gummy residue in 100 ml. of water was brought to pH 8 with hydrochloric acid, filtered to remove the precipitated inorganic salts, and extracted with chloroform (3 × 50 ml.). The chloroform layer, dried over magnesium sulfate, was evaporated to dryness *in vacuo*. The residual yellow oil gave a negative boron test[17] and a positive nitroprusside test; yield 11.5 g. (85%), $n^{28}D$ 1.5880.

A similarly prepared sample of crude thiol was twice distilled *in vacuo* through a Claisen head, but a pure distillate was not obtained because some thermal decomposition occurred during each distillation. A straw-colored fraction from the second distillation [b.p. 105–110° (0.25 mm.), $n^{28}D$ 1.5817, % thiol by iodometric titration 90%, ν_{max}^{film} 2400–2560 cm.$^{-1}$ (SH, weak), 3270 cm.$^{-1}$ (NH, medium)] gave a dipicrate, which crystallized from ethyl alcohol as golden microcrystalline powder, m.p. 173° dec., 182°,[30] nitroprusside test positive. Mixed melting points with the picrates of the corresponding disulfide and thiazolidine were depressed.

Anal. Calcd. for $C_{20}H_{18}N_8O_{14}S$: C, 38.34; H, 2.90; S, 5.12. Found: C, 38.49; H, 3.18; S, 4.76.

Flash distillation *in vacuo* of a small sample of the crude thiol gave a colorless distillate, b.p. 106–108° (0.5 mm.), $n^{28}D$ 1.5820.

Anal. Calcd. for $C_8H_{12}N_2S$: C, 57.10; H, 7.19; S, 19.05. Found: C, 57.50; H, 6.67; S, 19.33.

2,2′-Dithiobis[*N*-(3-pyridylmethyl)ethylamine] (VIa) Dihydrochloride.—Air was bubbled through a solution of 11.2 g. of crude thiol IVa in 50 ml. of water (pH 8–9) until a negative nitroprusside test was obtained (3 hr.). The thick yellow oil that had formed was extracted with chloroform (3 × 25 ml.), the extract dried over magnesium sulfate and evaporated to dryness under reduced pressure, and the oily residue further dried *in vacuo* 1 hr. at 60°; yield 10.0 g. (90%), $n^{20}D$ 1.6042. A solution of 5.02 g. (15.0 mmoles) of the disulfide in 33 ml. of 1 *N* hydrochloric acid was evaporated to dryness under reduced pressure. The residue was triturated in methyl alcohol (3 × 5 ml.) and dried *in vacuo* over phosphorus pentoxide; yield of white crystalline dihydrochloride 2.31 g. (46%), m.p. 262° dec.[30]

Anal. Calcd. for $C_{16}H_{22}N_4S_2 \cdot 2HCl$: C, 47.16; H, 5.94; S, 15.74. Found: C, 47.03; H, 5.99; S, 15.70.

The sodium borohydride reduction mixture from another run was poured into water, and the resulting solution was brought to pH 7 with hydrochloric acid and evaporated to dryness under reduced pressure. An aqueous solution of the solid residue, which had been extracted with methyl alcohol at room temperature to remove material that gave a positive nitroprusside test, deposited white crystals, m.p. 262° dec.[30] after being dried *in vacuo* over phosphorus pentoxide. The infrared absorption spectrum of this product was virtually identical with that of the dihydrochloride described above.

Anal. Calcd. for $C_{16}H_{22}N_4S_2 \cdot 2HCl \cdot H_2O$: C, 45.17; H, 6.16; S, 15.07. Found: C, 45.18; H, 5.61; S, 15.04.

A sample of the free disulfide VIa was also obtained by bringing an aqueous solution (pH 6) of the dihydrochloride monohydrate to pH 8–9 with sodium hydroxide, evaporating the aqueous mixture to dryness *in vacuo*, extracting the resulting residue with acetonitrile, removing the acetonitrile *in vacuo*, extracting the residue this time with chloroform and removing the chloroform *in vacuo*. The residual yellow oil, $n^{28}D$ 1.5982, gave a tetrapicrate, which after digestion in hot ethyl alcohol, melted at 234° dec. with darkening from 230° (capillary inserted in bath at 200°).

Anal. Calcd. for $C_{40}H_{34}N_{16}O_{28}S_2$: C, 38.40; H, 2.74; S, 5.13. Found: C, 38.55; H, 2.91; S, 4.95.

***S*-2-[(3-Pyridylmethyl)amino]ethyl Thiosulfuric Acid (VII).**—To a mixture of 2.04 g. (5.00 mmoles) of 2,2′-dithiobis[(3-pyridylmethyl)ethylamine] (VIa) dihydrochloride and 1.36 g. (10.0 mmoles) of sodium acetate trihydrate was added 7.5 ml. of 10% aqueous sulfur dioxide solution. The resulting solution was capped and allowed to stand at room temperature. After 10 days the solution was evaporated to dryness under reduced pressure. The residue, further dried by successive vacuum evaporations after being washed down several times with methyl alcohol, was triturated in 5 ml. of cold acetonitrile. The solid that formed was dried under nitrogen and extracted in a Soxhlet apparatus with 100 ml. of acetonitrile for 11 hr. The solid that deposited in the extract was dried *in vacuo* over phosphorus pentoxide at room temperature for 4 hr.; yield 393 mg. (16%). A solution of the crude product in 5 ml. of water after treatment with charcoal was diluted with 25 ml. of acetone. The small amount of precipitate that formed was discarded as inorganic salt. The filtrate was then evaporated to dryness, the residue redissolved in 1.5 ml. of water, 25 ml. of acetone added, and the white crystalline Bunté salt that precipitated dried *in vacuo* over phosphorus pentoxide; yield 153 mg., m.p. 210° dec.[30]

Anal. Calcd. for $C_8H_{12}N_2O_3S_2$: C, 38.69; H, 4.87; S, 25.82. Found: C, 38.80; H, 4.89; S, 25.70.

2-(2-Thienyl)thiazolidine (IIb).—A solution of 7.72 g. (0.100 mole) of 2-aminoethanethiol[28] and 11.2 g. (0.100 mole) of freshly distilled 2-thiophenecarboxaldehyde in 150 ml. of benzene was heated under reflux for 3 hr., during which time 1.5 ml. (83%) of water was collected in an attached Dean-Stark trap. The cooled mixture was filtered to remove insolubles and the filtrate evaporated to dryness under reduced pressure; yield 16.1 g. (94%) of a straw-colored, slightly viscous oil. Vacuum distillation of the crude product gave a colorless fraction boiling at 94–100° (0.35 mm.) that quickly solidified; yield 8.74 g. (51%), m.p. 42–46°. Recrystallization from cyclohexane gave long white needles, m.p. 47–48°.[34]

Anal. Calcd. for $C_7H_9NS_2$: C, 49.08; H, 5.30; S, 37.44. Found: C, 49.04; H, 5.17; S, 37.62.

The picrate prepared from the distilled thiazolidine melted at 128–130° dec., 158°,[30] after recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{12}H_{12}N_4O_7S_2$: C, 38.99; H, 3.02; S, 16.02. Found: 39.19; H, 3.04; S, 16.20.

2,2′-Dithiobis[*N*-(2-thenylidene)ethylamine] (IVb). 1. From 2,2′-Dithiobisethylamine.—A solution of 3.36 g. (30.0 mmoles) of 2-thiophenecarboxaldehyde in 10 ml. of benzene was added to a solution of 2.28 g. (15.0 mmoles) of 2,2′-dithiobisethylamine[31] in 50 ml. of benzene. A slightly exothermic reaction occurred and droplets of water precipitated. The mixture was evaporated to dryness under reduced pressure, and the residual oil heated at 60° *in vacuo* for 1 hr. The remaining viscous orange oil was extracted with hot benzene (2 × 25 ml.) to remove an insoluble brown solid. The filtrate, treated hot with Norit, was evaporated to dryness under reduced pressure. The residual viscous orange oil, 4.83 g. (94.5%), $n^{25}D$ 1.6648, ν_{max}^{film} 1630 cm.$^{-1}$ (C=N), was used without further purification in the preparation of 2-(2-thenylamino)ethanethiol (Vb).

(33) Lit., m.p. 198–200° [V. Coblentz, *Ber.*, **24**, 2131 (1891)].

(34) Lit.,[11] m.p. 41–42°.

An attempt to characterize the crude Schiff base as the dipicrate, which was prepared in ethyl alcohol and recrystallized from water, resulted in the isolation of the pure dipicrate of 2,2′-dithiobisethylamine as yellow needles, m.p. 206–207° dec.,[33] 210° dec.[30] An identical product, m.p. 206–207° dec., crystallized from ethyl alcohol–ethyl ether.

Anal. Calcd. for $C_{16}H_{18}N_8O_{14}S_2$: C, 31.48; H, 2.97; S, 10.50. Found: C, 31.23; H, 3.01; S, 10.62.

2. From 2-(2-Thienyl)thiazolidine.—A solution of the thiazolidine IIb (685 mg., 4.00 mmoles) in 5 ml. of ethyl alcohol was treated with 4 ml. of 1 *N* iodine–potassium iodide solution. The resulting solution was concentrated *in vacuo* to near dryness, water added, and the mixture made basic (pH 8–9) and extracted with benzene (3 × 10 ml.). The benzene solution, washed with water (2 × 5 ml.) and dried over magnesium sulfate, was evaporated to dryness under reduced pressure and then further dried *in vacuo* at 60° for 1 hr. The residue was an orange oil, $n^{25}D$ 1.6617, whose infrared absorption spectrum was identical to that of the Schiff base prepared from 2-thiophenecarboxaldehyde and 2,2′-dithiobisethylamine.

2-(2-Thenylamino)ethanethiol (Vb).—A solution of 2.99 g. (70.2 mmoles) of 90% sodium borohydride in 60 ml. of absolute methyl alcohol was added drop by drop to a solution of approximately 4.00 g. (11.7 mmoles) of 2,2′-dithiobis[*N*-(2-thenylidene)ethylamine] in 80 ml. of absolute methyl alcohol. The resulting solution was heated under reflux for 15 min., cooled under nitrogen, and then evaporated to dryness under reduced pressure. The gummy residue was suspended in 50 ml. of water, the pH of the mixture adjusted from 11 to 8–9 with 1 *N* hydrochloric acid, the mixture filtered to remove the inorganic salt that precipitated, and the filtrate extracted with benzene (3 × 25 ml.). The benzene extract, washed with water (2 × 5 ml.) and dried over magnesium sulfate, yielded on evaporation to dryness under reduced pressure 3.7 g. (93%) of an orange oil, $n^{24}D$ 1.6108, which gave a positive nitroprusside test. Two distillations *in vacuo* afforded a colorless oil, b.p. 82–84° (0.25 mm.),[35] $n^{24}D$ 1.5910,[35] $\tilde{\nu}_{max}^{film}$ 2480–2570 cm.$^{-1}$ (SH, weak), 3300 cm.$^{-1}$ (NH, medium). The thiol content by iodometric titration was 93% (after 1 month). A solid picrate was not isolated.

Anal. Calcd. for $C_7H_{11}NS_2$: C, 48.51; H, 6.40; S, 37.02. Found: C, 48.42; H, 6.00; S, 37.11.

2,2′-Dithiobis[*N*-(2-thenyl)ethylamine] (VIb) Dihydroiodide.—2-(2-Thenylamino)ethanethiol (440 mg., 2.5 mmoles), dissolved in 5 ml. of ethyl alcohol, was treated dropwise with 2.5 ml. of 1 *N* iodine–potassium iodide solution. The off-white solid that precipitated as plates was collected and dried *in vacuo* over phosphorus pentoxide; yield 354 mg. (47%),[36] m.p. 227° dec.[30] The crude product crystallized from ethyl alcohol as white, shiny plates, m.p. 230° dec.[30]

Anal. Calcd. for $C_{14}H_{20}N_2S_4 \cdot 2HI$: C, 28.00; H, 3.69; S, 21.36. Found: C, 28.22; H, 3.72; S, 21.25.

The dipicrate, recrystallized from ethyl alcohol–water as yellow needles, melted at 154–155°, 154°.[30]

Anal. Calcd. for $C_{26}H_{26}N_8O_{14}S_4$: C, 38.90; H, 3.26; S, 15.97. Found: C, 38.94; H, 3.30; S, 15.81.

An aqueous solution of a small sample of the crude dihydroiodide was made basic (pH 9) and extracted with benzene. Evaporation of the magnesium sulfate-dried extract to dryness under reduced pressure left an orange oil, $n^{25}D$ 1.6120, whose infrared absorption spectrum was identical with that of 2-(2-thenylamino)ethanethiol except for the lack of SH absorption in the 2500-cm.$^{-1}$ region.

***N,N′*-(Dithiodiethylene)bis-*p*-toluenesulfonamide.**—A solution of 381 mg. (2.00 mmoles) of *p*-toluenesulfonyl chloride in 5 ml. of chloroform was added dropwise to a cold (10°) vigorously agitated (by a Vibromixer) solution of 225 mg. (1.00 mmole) of 2,2′-dithiobisethylamine dihydrochloride[32] and 744 mg. (6.00 mmoles) of sodium carbonate monohydrate in 25 ml. of water. Vigorous agitation of the mixture was continued for 30 min. in the cold, and then the mixture was stirred for 16 hr. at room temperature. The white solid that had precipitated was collected, washed well with water, and dried *in vacuo* over phosphorus pentoxide; yield 368 mg. (80%), m.p. 83° with softening from 80°. Precipitated from a benzene solution (treated with Norit) with cyclohexane (5:1) in high recovery, the white crystalline product melted at 83°[30] after being dried *in vacuo* over phosphorus pentoxide at 80° for 4 hr.

Anal. Calcd. for $C_{18}H_{24}N_2O_4S_2$: C, 46.93; H, 5.25; S, 27.84. Found: C, 47.14; H, 5.21; S, 27.84.

***N,N′*-(Dithiodiethylene)bis[*N*-(2-thenyl)-*p*-toluenesulfonamide].**—2-(Chloromethyl)thiophene[37] (347 mg., 2.62 mmoles) was added to a well stirred mixture of 560 mg. (1.25 mmoles) of *N,N′*-(dithiodiethylene)bis-*p*-toluenesulfonamide, 362 mg. (2.62 mmoles) of anhydrous potassium carbonate, and 7 ml. of *N,N*-dimethylformamide. The resulting mixture was stirred and heated at 100° for 1.5 hr. Cooled to room temperature, the reddish reaction mixture was diluted with 50 ml. of water. The mother liquor was decanted from the gummy precipitate, which was first triturated in methyl alcohol (2 × 25 ml.) and then in water (5 × 5 ml.). The residual white solid, dried *in vacuo* over phosphorus pentoxide, melted at 125–126°; yield 485 mg. (60%). Recrystallization of the crude product from isopropyl alcohol afforded white needles, m.p. 127°.

Anal. Calcd. for $C_{28}H_{32}N_2O_4S_6$: C, 51.50; H, 4.94; S, 29.46. Found: C, 51.21; H, 5.32; S, 29.49.

2-Indol-3-ylthiazolidine (VIII).—A solution of 761 mg. (5.24 mmoles) of indole-3-carboxaldehyde and 404 mg. (5.24 mmoles) of 2-aminoethanethiol[28] in 15 ml. of ethyl alcohol was heated under reflux for 3 hr. The resulting orange solution was then evaporated to dryness under reduced pressure. The residue, a pale orange solid, was triturated in 5 ml. of ethyl alcohol and dried *in vacuo* over phosphorus pentoxide; yield 710 mg. (70%), m.p. 130°[30] with presoftening, nitroprusside test positive. Recrystallization of the crude thiazolidine from ethyl alcohol afforded long off-white needles, which melted at 128–130°.

Anal. Calcd. for $C_{11}H_{12}N_2S$: C, 64.66; H, 5.92; S, 15.70. Found: C, 64.57; H, 5.84; S, 15.55.

2,2′-Dithiobis[*N,N*-di(8-quinolylmethyl)ethylamine] (IX) Monohydrate.—A solution of 13.3 g. (60.0 mmoles) of 8-(bromomethyl)quinoline[38] in 25 ml. of *N,N*-dimethylformamide was added to a stirred mixture of 2.39 g. (15.7 mmoles) of 2,2′-dithiobisethylamine,[31] 8.29 g. (60.0 mmoles) of potassium carbonate, and 15 ml. of *N,N*-dimethylformamide. The mixture thus obtained was heated at 60° for 3 hr., then evaporated to near dryness under reduced pressure, leaving a semisolid residue, which was diluted with water. The pH of the aqueous mixture was adjusted from 10 to 7, and the slightly gummy solid was collected, washed with ethyl alcohol (2 × 5 ml.), and air-dried: yield 7.60 g. Recrystallization of the crude product from undried 2-methoxyethanol with the aid of Norit gave the product as an off-white solid, which was dried *in vacuo* over phosphorus pentoxide; yield 5.43 g. (51%), m.p. 160°.[30] For analysis, recrystallization of a small sample from the same solvent afforded the product as a white powder, m.p. 157–158°, 160°.[30] The infrared absorption spectrum showed no NH stretching band. A hydrochloride could also be isolated as white crystals by recrystallization of the free base from 1 *N* hydrochloric acid.

Anal. Calcd. for $C_{44}H_{36}N_6S_2 \cdot H_2O$: C, 72.30; H, 5.24; S, 8.77. Found: C, 72.39; H, 5.59; S, 9.00.

2,2′-Dithiobis[*N*-(8-quinolylmethyl)ethylamine] (X)

(35) Ref. 16 reported b.p. 138–140° (6 mm.) and $n^{20}D$ 1.5776.

(36) The crude yield obtained from 3.5 g. of the thiol in 50 ml. of ethyl alcohol was 89%, m.p. 226° dec.[30]; recrystallization gave a 73% yield of product that melted at 229° dec.[30]

(37) K. B. Wiberg and H. F. McShane, *Org. Syn.*, Vol. 29, J. Wiley & Sons, Inc., New York, N. Y., 1949, p. 31.

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Tetrahydrochloride Monohydrate.—To a stirred mixture of 15.5 g. (102 mmoles) of 2,2′-dithiobisethylamine,[31] 9.90 g. (73.4 mmoles) of potassium carbonate, and 25 ml. of *N,N*-dimethylformamide heated to 80° was added drop by drop over a period of 2 hr. a solution of 14.9 g. (67.0 mmoles) of 8-(bromomethyl)quinoline[38] in 50 ml. of *N,N*-dimethylformamide. The resulting mixture was heated at 80° for an additional 5 hr. and then cooled. The thick slurry thus obtained was poured into 750 ml. of water. The pH of the cloudy mixture was adjusted from 11 to 8–9 with concentrated hydrochloric acid, and the dark oil that separated was extracted from the mixture with benzene (3 × 250 ml.). The benzene extract was washed with water (3 × 50 ml.), treated with Norit, filtered through Celite, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The residual orange oil, washed down with ethyl alcohol (3 × 25 ml.), was dried for 1 hr. at 60° *in vacuo;* yield 12.6 g. (87%). A 7.7-g. sample of the oily free base was dissolved in 65 ml. of 1 *N* hydrochloric acid and the solution evaporated to dryness under reduced pressure. The solid residue, after trituration in ethyl alcohol (2 × 25 ml.), was collected and dried *in vacuo* over phosphorus pentoxide; yield of a crude hydrochloride 6.81 g. An analytically pure sample (740 mg.) of the tetrahydrochloride monohydrate was obtained in the following manner: A solution of 1.0 g. of the crude hydrochloride in 75 ml. of boiling methyl alcohol was filtered, cooled, and diluted with an equal volume of ethyl ether. The cream-colored solid that precipitated was dried *in vacuo* over phosphorus pentoxide; it decomposed without melting above 200°.

Anal. Calcd. for $C_{24}H_{28}N_4S_2 \cdot 4HCl \cdot H_2O$: C, 48.16; H, 5.39; S, 10.71; Cl, 23.70. Found: C, 47.78; H, 5.40; S, 10.64; Cl, 23.36.

***S*-2-[(8-Quinolylmethyl)amino]ethyl Thiosulfuric Acid (XI).** 1. **From the Disulfide Tetrahydrochloride Monohydrate.**—To a mixture of 600 mg. (1.00 mmole) of 2,2′-dithiobis[*N*-(8-quinolylmethyl)ethylamine] tetrahydrochloride monohydrate and 545 mg. (4.00 mmoles) of sodium acetate trihydrate was added 1.5 ml. of aqueous 10% solution of sulfur dioxide. *p*-Dioxane (0.5 ml.) was added to make the reaction mixture homogeneous. After 2 days the tan needles that had precipitated were collected and dried *in vacuo* over phosphorus pentoxide; yield 450 mg. (76%), m.p. 214° dec.[30] Two recrystallizations from water, followed by drying for 6 hr. at 100° *in vacuo* over phosphorus pentoxide, gave colorless crystals that melted at 193–194° dec.; yield 42%, $\bar{\nu}_{max}^{KBr}$ 1240, 1195, 1175, 1025, 635 cm.$^{-1}$ (SO_3^-).

Anal. Calcd. for $C_{12}H_{14}N_2O_3S_2 \cdot {}^1/_4H_2O$: C, 47.58; H, 4.82; S, 21.17. Found: C, 47.50; H, 4.57; S, 21.55.

2. **From the Disulfide Free Base.**—The free base X in *p*-dioxane was treated with aqueous sulfur dioxide in a manner similar to that described under 1. After 6 days the product had precipitated in 51% yield as pale yellow needles, m.p. 220° dec.[30] Recrystallization from water with the aid of Norit afforded colorless needles that melted at 197–198° dec. after being dried as described above; yield 43%.

Anal. Calcd. for $C_{12}H_{14}N_2O_3S_2$: C, 48.30; H, 4.73; S, 21.49. Found: C, 47.87; H, 4.73; S, 21.60.

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Investigations in Heterocycles. XI. Tetracyclic and Pentacyclic Indolo[2,3-*a*]quinolizines

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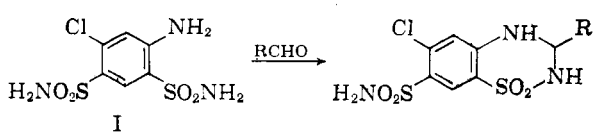
Various procedures have been developed for the synthesis of tetracyclic and pentacyclic indolo[2,3-*a*]quinolizines containing hetero atoms in ring D and ring E, respectively.

In several previous publications from our laboratories[1–4] it was demonstrated that some new and biologically interesting heterocycles could be prepared through application of an intramolecular Mannich reaction. In particular, 4-amino-6-chloro-1,3-benzenedisulfonamide (I) was allowed to react with a wide variety of aldehydes, acetals, and ketones to give rise to dihydrobenzothiadiazine 1,1-dioxides. The chemical and biological significance (*i.e.*, diuretics) of this class of compounds has recently been the subject of an extensive review.[5]



I

It had also been shown that the modified Mannich reaction was useful in the preparation of the new heterocyclic seven-membered ring system 1,2,4,5-tetrahydro-3-methyl-1,3-benzodiazepine.[4]

It was thus considered of interest to extend this investigation to other systems and, in particular, to the indoles. The indoles were selected primarily because of their teleological significance. Moreover, the pharmacological importance of indolic com-

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