

Novel Schistosomicides. *S*-2-{[2-(2-Thiazolylcarbamoyl)ethyl]amino}ethyl Hydrogen Thiosulfate and Related Compounds¹

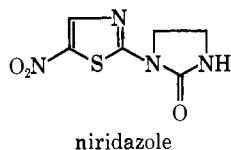
ROGER D. WESTLAND,* LESLIE M. WERBEL, JOHN R. DICE, JOYCE L. HOLMES, AND BARBARA G. ZAHM

Chemistry Department, Division of Medical and Scientific Affairs, Parke, Davis and Company, Ann Arbor, Michigan 48106

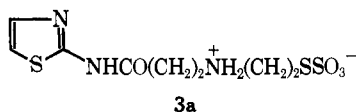
Received October 17, 1970

S-2-{[2-(2-Thiazolylcarbamoyl)ethyl]amino}ethyl hydrogen thiosulfate (**3a**), prepared by alkylation of *S*-2-aminoethyl hydrogen thiosulfate with 3-chloro-*N*-2-thiazolylpropionamide (**1**) has been found to be highly effective against infections of *Schistosoma mansoni* in mice and monkeys. The thiol, 3-[(2-mercaptoethyl)amino]-*N*-2-thiazolylpropionamide·HCl (**8**), prepared from *N*-2-thiazolyl-1-aziridinepropionamide (**5a**) and H₂S, had about the same potency as the Bunte salt **3a**. The corresponding disulfide, 3,3'-[dithiobis(ethyleneimino)]bis-(*N*-2-thiazolylpropionamide) (**7**), was also highly active. The 5-nitro derivative of **3a**, *S*-2-[(2-[(5-nitro-2-thiazolyl)carbamoyl]ethyl]amino)ethyl hydrogen thiosulfate (**3i**), in mice was approximately 0.5 as active as **3a**. This observation is in striking contrast to results with niridazole wherein the nitro group is essential to activity. The many other analogs and homologs prepared were devoid of activity.

Derivatives of 2-amino-5-nitrothiazole have shown activity against a variety of parasitic infections.² The most potent of these, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (niridazole), has proved particularly effective



against schistosomiasis in man and is also effective against various other human parasites.^{3,4} Activity among derivatives of aminonitrothiazole is extremely sensitive to structure. Very minor modifications in the niridazole molecule, for example, serve to eliminate antischistosome activity completely.⁵ Generally, the NO₂ group in the 5 position must be present for activity. Thus the desnitro derivative of niridazole is completely devoid of activity against *Schistosoma mansoni* when administered in the diet at 0.25%, a level at which niridazole kills 98% of the worms.⁶



It was indeed surprising to find the structurally unique *S*-2-{[2-(2-thiazolylcarbamoyl)ethyl]amino}ethyl hydrogen thiosulfate (**3a**) to be extremely potent against *S. mansoni* infections. Neither unnitrated 2-aminothiazole derivatives nor Bunte salts in general have in the past been demonstrated to be active against this parasite. The results reported herein represent studies with this potent schistosomicide and closely related compounds.

(1) This investigation was supported in part by the U.S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2306. We appreciate the interest and support of Dr. D. P. Jacobus, Dr. T. R. Sweeney, and Dr. E. A. Steck of Walter Reed Army Institute of Research.

(2) For a summary see L. M. Werbel, E. F. Elslager, A. A. Phillips, D. F. Worth, P. J. Islip, and M. C. Neville, *J. Med. Chem.*, **12**, 521 (1969).

(3) C. R. Lambert, M. Wilhelm, H. Striebel, F. Kradolfer, and P. Schmidt, *Experientia*, **20**, 452 (1964).

(4) C. R. Lambert, *Ann. Trop. Med. Parasitol.*, **58**, 292 (1964).

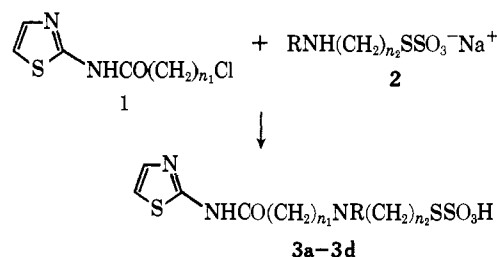
(5) L. M. Werbel and J. R. Battaglia, *J. Med. Chem.*, **14**, 10 (1970).

(6) P. E. Thompson and R. E. Voigtman, Parke, Davis and Company, unpublished results, 1968.

Chemically, **3a** is an internal Bunte salt having the characteristic zwitterionic structure. The first acid dissociation constant ($pK_a' = 8$) in 67% aq DMF represents ionization of the amine salt, and the second dissociation constant ($pK_a' > 11.5$) results from ionization of the amide H.⁷

Alkylation of sodium *S*-2-aminoethyl thiosulfate (**2**, R = H; $n_2 = 2$) with 3-chloro-*N*-2-thiazolylpropionamide (**1**, $n_1 = 2$) as shown in Scheme I resulted in a

SCHEME I



convenient synthesis of **3a**. This method allowed preparation of homolog **3b** (R = H; $n_1 = 2$; $n_2 = 3$) from *S*-3-aminopropyl hydrogen thiosulfate,⁸ and homolog **3c** (R = H; $n_1 = 5$; $n_2 = 2$), a derivative of 6-amino-*N*-2-thiazolylhexanamide (Table I). The *N*-Et derivative (**3d**) (R = C₂H₅; $n_1 = n_2 = 2$) was prepared similarly from *S*-2-ethylaminoethyl hydrogen thiosulfate.⁹ Additionally, the method shown in Scheme I was used to prepare analogs in which the 2-thiazolyl group was replaced by 5-methyl-1,3,4-thiadiazol-2-yl, phenyl, 2-benzothiazolyl, and 6-methoxy-8-quinolyl groups (Table I, **13-16**).

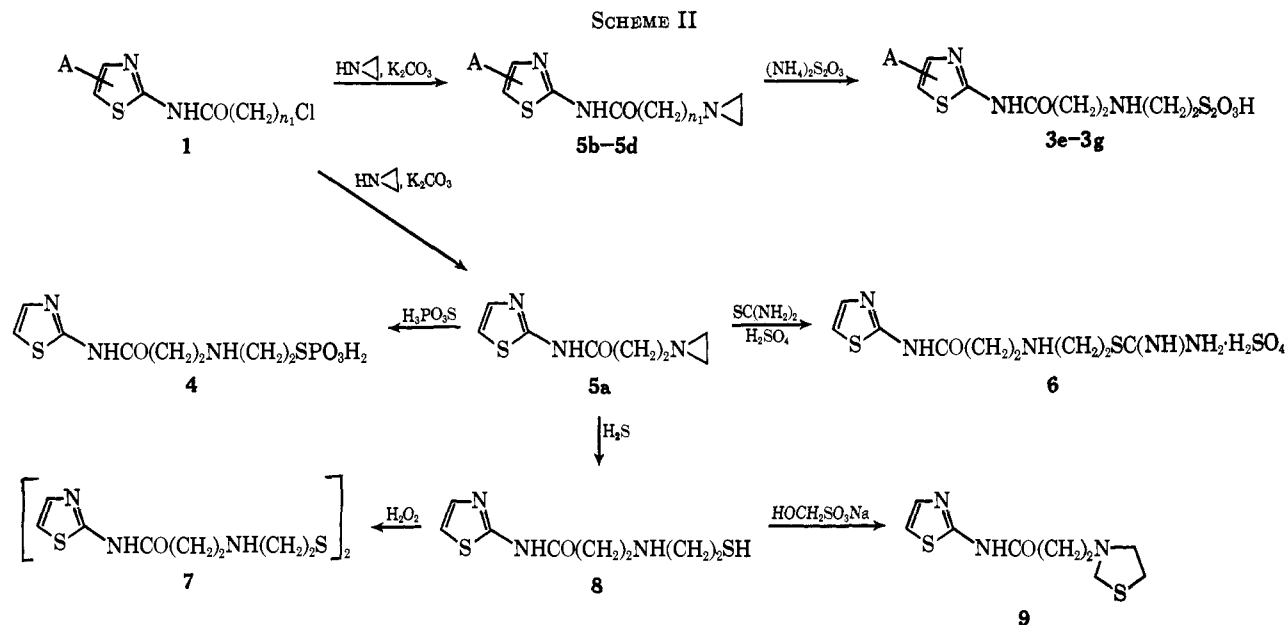
On the other hand homologs (Scheme I, $n_1 = 3,4$) from 4-chloro-*N*-2-thiazolylbutyramide and 5-chloro-*N*-2-thiazolylvaleramide were not obtained using reaction conditions found in Schemes I, II, or III because of facile base-catalyzed conversion of the chloroamides to the corresponding lactams **17**.¹⁰ Reasonable effort

(7) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 612 (1954).

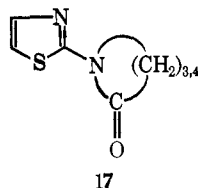
(8) A. Kaluszyner, P. Czerniak, and E. D. Bergmann, *Radiat. Res.*, **14**, 23 (1961).

(9) D. L. Klayman and W. F. Gilmore, *J. Med. Chem.*, **7**, 823 (1964).

(10) Cyclization reactions involving 5-nitrothiazole compounds are described in a patent: D. B. Capps, U. S. Patent 3,311,614 (1967); *Chem. Abstr.*, **67**, 43809 (1967).



given to other approaches also failed to provide these analogs.



The 1-substituted aziridines **5** prepared from the haloamides **1** proved to be very useful intermediates in this series (Scheme II). Good yields of **5** were obtained by using ethylenimine as solvent for the displacement in the presence of powdered anhyd K_2CO_3 . The exothermic reaction was allowed to proceed at a temp no higher than 40° . Displacement of halogen under these conditions would be expected to proceed easily in the case of the chloroacetyl derivative, 2-chloro-*N*-2-thiazolylacetamide. However, displacement of unactivated halide requires special reaction conditions,¹¹ and in the present work successful reactions involving chloropropionamides and ethylenimine no doubt de-

pend on dehydrohalogenation followed by addition of ethylenimine to the substituted acrylamide. The chemical shifts in the nmr spectrum for the aziridine protons of the 1-aziridinepropionamide **5a** were found downfield about 0.3 ppm from shifts usually seen¹² for 1-substituted aziridines. In this manner were obtained **5b** ($A = H$; $n_1 = 1$), **5c** ($A = 4-CH_3$; $n_1 = 2$), and **5d** ($A = 5-Br$; $n_1 = 2$).

Reaction of the 1-substituted aziridines (**5b,c,d**) with $(NH_4)_2S_2O_3$ in a manner first described by Klayman, *et al.*,¹³ effectively produced the corresponding Bunte salts (**3e,f,g**) (Table I). The phosphorothioate **4** analogous to the biologically active thiosulfate **3a** was prepared from **5a** by reaction with methanolic phosphorothioic acid. The preparation of free phosphorothioic acid in MeOH has been described by Brois.¹⁴ Aziridine ring opening of **5a** by thiourea in the presence of H_2SO_4 gave the substituted 2-thiopseudourea **6**.

The thiol **8** and disulfide **7** corresponding to the active Bunte salt **3a** were considered important analogs because they are likely biological degradation products of **3a**. Friedman and coworkers¹⁵ have demonstrated *in vivo* conversion of *S*-2-aminoethyl hydrogen thiosulfate to 2-aminoethanethiol. Preparation of pure samples of **7** and **8**, however, proved challenging. The aziridine **5a** was readily cleaved with H_2S to give a solid product either as the free base or HCl salt. Both forms were very difficult to purify by recrystallization because of rapid deterioration of the samples in solution. Presumably this thiol is especially sensitive to oxidation. The thiol **8** was successfully prepared by mixing **5a** and H_2S in abs MeOH below -65° , and allowing the mixture to warm gradually to room temperature. The HCl salt prepared in *i*-PrOH was rapidly recrystallized from MeOH. Several attempts to prepare the disulfide **7** by oxidation of the thiol **8** resulted in impure products. This compound also deteriorated rapidly in polar solvents giving recrystallized material of very poor quality.

(12) S. J. Brois and G. P. Beardsley, *Tetrahedron Lett.*, 5113 (1966).

(13) D. L. Klayman, W. F. Gilmore, and T. R. Sweeney, *Chem. Ind. (London)*, 1632 (1965).

(14) S. J. Brois, *Chem. Commun.*, 1237 (1967).

(15) J. J. Kelley, K. A. Herrington, S. P. Ward, A. Meister, and O. M. Friedman, *Cancer Res.*, **27**, 137 (1967).

(11) R. D. Westland, R. A. Cooley, Jr., M. L. Mouk, and J. L. Holmes, Abstracts, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967, No. 74.

TABLE I
S-2-{[2-(SUBSTITUTED CARBAMOYL)ALKYL]AMINO}ALKYL HYDROGEN THIOSULFATES
ArNHCO(CH₂)_mNR(CH₂)_nSSO₃H

No.	Ar	n ₁	n ₂	R	Method ^a	Recrystn solvent	Yield, %	Mp, °C ^b	Formula	Analyses
3a	2-Thiazolyl	2	2	H	I	H ₂ O	28	224-226 ^c	C ₉ H ₁₃ N ₃ O ₃ S ₃	C, H, N, S
3a, K salt	2-Thiazolyl	2	2	H	I	EtOH-Et ₂ O	25	166-169	C ₉ H ₁₂ N ₃ O ₃ S ₃ K	C, H, N
3b	2-Thiazolyl	2	3	H	I	H ₂ O	60	203	C ₉ H ₁₃ N ₃ O ₄ S ₃	C, H, N
3c	2-Thiazolyl	5	2	H	I	H ₂ O, DMF-EtOH	23	202-204	C ₁₁ H ₁₆ N ₃ O ₄ S ₃	C, H, N, S
3d	2-Thiazolyl	2	2	Et	I	H ₂ O	55	185-189	C ₁₀ H ₁₇ N ₃ O ₄ S ₃	C, H, N
3e	2-Thiazolyl	1	2	H	II	MeOH	23	193-195	C ₇ H ₁₁ N ₃ O ₄ S ₃	C, H, N, S
3f	4-Methyl-2-thiazolyl	2	2	H	II	MeOH	28	196-197	C ₈ H ₁₃ N ₃ O ₄ S ₃	C, H, N
3g	5-Bromo-2-thiazolyl	2	2	H	II	EtOH-Et ₂ O, MeOH	9	199-200	C ₈ H ₁₂ BrN ₃ O ₄ S ₃	C, H, N
3h	4-Phenyl-2-thiazolyl	2	2	H	III	H ₂ O	24	199-204	C ₁₄ H ₁₇ N ₃ O ₄ S ₃	C, H, N
3i	5-Nitro-2-thiazolyl	2	2	H	III	H ₂ O	17	228-230	C ₉ H ₁₂ N ₄ O ₆ S ₃	C, H, N, S
13	5-Methyl-1,3,4-thiadiazol-2-yl	2	2	H	I ^d	H ₂ O, MeOH-H ₂ O	5	209-211	C ₈ H ₁₄ N ₄ O ₄ S ₂	C, H, N
14	Phenyl	2	2	H	I ^d	H ₂ O, DMF-H ₂ O, DMF-EtOAc	16	192-199	C ₁₁ H ₁₆ N ₂ O ₄ S ₂	H, N, C ^e
15	2-Benzothiazolyl	2	2	H	I ^d	H ₂ O, DMF-EtOH	50	231-232	C ₁₂ H ₁₃ N ₃ O ₄ S ₃	C, H, N, S
16	6-Methoxy-8-quinolyl	2	2	H	I ^d	DMF-EtOH	28	219-220	C ₁₅ H ₁₉ N ₃ O ₅ S ₂	C, H, N, S

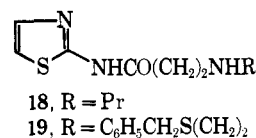
^a Schemes I, II, and III. ^b Decompn points. ^c Repeated recrystn gave mp 232° dec. ^d N-Aryl-3-chloropropionamides substituted for structure I. ^e C: calcd, 43.40; found 43.94. / S: calcd, 26.61; found, 25.72.

Even though **7** as the free base appeared relatively stable in weakly polar solvents, a pure sample was prepared only by using very mild conditions for the ring-opening reaction and the oxidation with H₂O₂. The related thiazolidine **9** prepared from thiol **8** by treatment with sodium formaldehyde bisulfite was stable and easily purified by recrystallization.

The versatile 3-chloropropionamides **1** of 2-aminothiazole and substituted 2-aminothiazoles are intermediates which led to analogs of **3a** by yet another route (Scheme III). Alkylation of 2-aminoethanol with the appropriate 3-chloropropionamides **1** afforded the N-substituted 2-aminoethanols **10a,b**, which were treated with SOCl₂ to give the corresponding N-substituted 2-chloroethylamines **11a,b**. Displacement¹⁶ of chloride by thiosulfate yielded the corresponding Bunte salt **3h** from **11b**.

3-[(2-Chloroethyl)amino]-N-2-thiazolylpropionamide·HCl (**11a**) was used to prepare the 5-nitrothiazole analog of **3a**. The NO₂ compound was considered to be a very important analog because of the requirement of the NO₂ group for biological activity in the niridazole series. Nitration of **11a** gave 3-[(2-chloroethyl)amino]-N-(5-nitro-2-thiazolyl)propionamide hemisulfate (**12**), which in turn was converted to the thiosulfate ester **3i** (Table I) by reaction with Na₂S₂O₃. Insertion of the NO₂ group at this late stage in the synthesis proved to be most convenient because of the instability of certain of the nitrothiazole intermediates.

3-Chloro-N-2-thiazolylpropionamide (**1**) was used additionally to alkylate propylamine and 2-(benzylthio)ethylamine, giving **18** and **19**, in order to explore the effects of other structural variations on biological activity.



S-2-{[2-(2-Thiazolylcarbonyl)ethyl]amino}ethyl hydrogen thiosulfate (**3a**) and related derivatives described in this communication were supplied to Dr. Paul E. Thompson and coworkers of these laboratories for evaluation against a Puerto Rican strain of *S. mansoni* in mice.¹⁷ As in previous work, drugs were administered in a powdered diet for 7 or 14 days or by gavage in 10 ml/kg per day of aqueous 1% hydroxyethyl- or carboxymethylcellulose for 3 to 10 days. At drug-diet doses of 338 mg/kg per day and greater for 14 days the internal Bunte salt **3a** was well tolerated and left only an occasional live worm (96% reduction in live worm burden). Treatment by gavage in doses of 400 mg/kg per day for 5 days resulted in only a 29% reduction in the worm burden.

The activity in this series proved to be extremely structure specific. Thus substitution in the thiazole ring (**3f-3h**) provided compounds devoid of schistosomocidal activity at doses of 154-243 mg/kg per day for 14 days, except for the 5-nitro derivative **3i** which in mice was approximately 0.5 as active as **3a** (63% reduction

(16) H. Bretschneider, *Monatsh. Chem.*, **81**, 372 (1950).

(17) For descriptions of test procedures used for both mice and monkeys, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Amer. J. Trop. Med. Hyg.*, **11**, 31 (1962).

in live worm burden at 354 mg/kg per day for 14 days). This observation is in striking contrast to the results with niridazole wherein the NO₂ group is essential to activity.

Replacement of the thiazole ring with other heterocycles (**13**, **15**, **16**) or Ph (**14**) also provided inactive compounds. Homologs **3b,c,e** and the *N*-Et derivative **3d** were also devoid of activity.

Modification of the S-covering function with the thiazolidine ring (**9**), the 2-thiopseudourea (**6**), and a thioether (**19**) likewise resulted in complete loss of activity. The thiol **8** and disulfide **7**, however, were essentially as effective as **3a** when administered to mice. Thiol **8** in the diet caused 76% reduction in live worm burden at 296 mg/kg per day for 14 days, and by gavage it was more active than **3a**, giving 90% reduction at 400 mg/kg per day for 5 days. The disulfide **7** caused 92% reduction at 400 mg/kg per day by gavage for 5 days. Surprisingly the phosphorothioate **4** with its labile S-P bond retained only minimal activity resulting in 22% of worm reduction when administered in the diet at 345 mg/kg per day for 14 days.

In an effort to improve absorption of the drug, **3a** was examined as its K and Na salts. The K salt of **3a** administered by gavage for 5 days at 400 mg/kg per day in mice reduced the worm burden 60%. Furthermore, gavage administration of **3a** in sufficient aq Na₂CO₃ to form the Na salt and to temporarily buffer the stomach of the mice, at 800 mg/kg per day for 10 days was curative (100% reduction in live worm burden) and for 5 days reduced the worm burden 98%.

Compound **3a** was also examined against the Puerto Rican strain of *S. mansoni* in Rhesus monkeys. At 400 mg/kg per day for 5 days **3a** strongly suppressed egg production but was not curative. When the drug was solubilized in aq Na₂CO₃ containing sufficient Na₂CO₃ to buffer the stomach, 400 mg/kg per day for 5 or 10 days was curative but caused diarrhea in the monkeys. The disulfide **7** given as a suspension in 1% hydroxyethylcellulose without any buffer was curative in the monkey when administered at 400 mg/kg per day for 5 days.

Thus, S-2-[[2-(2-thiazolylcarbamoyl)ethyl]amino]-ethyl hydrogen thiosulfate is a potent schistosomicide of unique structure, and the benign nature of its known side effects encourages clinical evaluation in man.

Experimental Section^{18,19}

S-2-[[2-(2-Thiazolylcarbamoyl)ethyl]amino]ethyl Hydrogen Thiosulfate (3a).—A refluxing mixt containing 54 g (0.30 mole) of sodium S-2-aminoethyl thiosulfate¹⁶ (**2**), 1 g of KI, and 300 ml of abs EtOH was treated in portions over about 3 hr with 30 g (0.16 mole) of 3-chloro-*N*-2-thiazolylpropionamide²⁰ (**1**). The mixt was heated under reflux for 2 days, neutralized to pH 7 with glacial AcOH, and concd nearly to dryness under vacuum. A slurry of the residue in H₂O was filtered and the water-insol solid was washed with Et₂O and dried to give 24.5 g of crude material, mp 196–200°. Three recrystns from H₂O resulted in 13.7 g (28%) of **3a**: mp 224–226° dec;²¹ p*K*_a' = 8, >11.5 (67% aq

DMF); solubility in mg/ml (pH), 29.5 (0.3), 11.9 (0.5), 4.3 (1.1), 1.54 (2.0), 1.31 (4.3), 1.34 (5.9), 1.51 (6.9), 2.12 (7.6), 4.7 (8.3), 21.7 (8.8), 39.0 (9.2), 149 (9.5).

Potassium S-2-[[2-(2-Thiazolylcarbamoyl)ethyl]amino]ethyl Thiosulfate.—A suspension of 15.6 g (0.50 mole) of **3a** in 200 ml of H₂O was treated with 50.5 ml of 0.99 *N* KOH. The Bunte salt was solubilized by stirring the mixt for 2 hr at room temp. The solvent was removed under vacuum and the dry residue was washed with Me₂CO and dried giving 10.8 g of solid, mp 165–170° dec. Pptn from EtOH–Et₂O resulted in 4.4 g (25%) of the K salt of **3a**, mp 166–169° dec.

***N*-2-Thiazolyl-1-aziridinepropionamide (5a).**—To a mixt of 36.2 g (0.26 mole) of powdered anhyd K₂CO₃ and 500 ml of ethylenimine cooled in an ice bath was added 50 g (0.26 mole) of 3-chloro-*N*-2-thiazolylpropionamide (**1**). The cooling bath was removed until the reaction temp had risen spontaneously to 30°. After 10 min at 25–30°, the mixt was concd, and the solid residue was extd 3 times with boiling Me₂CO and 2 times with boiling C₆H₆. The combined exts were filtered through Celite, and the filtrate was concd to 500–600 ml and chilled. The crude solid was recrystd from Me₂CO to give 38 g (74%) of **5a**: mp 145–147.5°; ir (KBr) 1673 cm⁻¹ (C=O); nmr (CDCl₃) δ 2.67 (m, 4, CO(CH₂)₂N), 1.83 and 1.24 ppm (2 m, 4, N(CH₂)₂). Anal. (C₈H₁₁N₃OS) C, H, N.

S-2-[[2-(2-Thiazolylcarbamoyl)ethyl]amino]ethyl Dihydrogen Phosphorothioate (4).—A soln of 5.0 g (0.025 mole) of **5a** in 400 ml of MeOH was cooled to –40° and added slowly with stirring to 30 ml of ca. 0.8 *M* methanolic H₃PO₃S¹⁴ which had been dild with 100 ml of MeOH and cooled to –40°. The temp had increased to –5° by the end of the addn. The mixt was filtered giving 0.4 g of solid. The filtrate immediately became cloudy and it was refiltered through Celite. This filtrate was allowed to stand at room temp for 0.5 hr before being refiltered to give 1.8 g of white solid, mp 130–135° dec. The resulting filtrate was allowed to stand for an addl 0.5 hr giving 1.1 g of **4**, mp 130–135°. Anal. (C₈H₁₄N₃O₄PS₂) Calcd: C, 30.86; H, 4.53; N, 13.50. Found: C, 30.38; H, 4.82; N, 12.46.

2-[[2-(2-Thiazolylcarbamoyl)ethyl]amino]ethyl-2-thiopseudourea Sulfate (6).—To a soln of 3.0 g (0.015 mole) of *N*-2-thiazolyl-1-aziridinepropionamide and 1.1 g (0.015 mole) of thiourea in 40 ml of MeOH at 0–5° was added dropwise a soln of 0.8 ml of concd H₂SO₄ in 10 ml of MeOH. The white ppt which sepd was filtered and dried to give 4.7 g of crude product, mp 160–170° dec. The solid was very sparingly sol and resisted attempts to recryst it. After washing the solid with hot DMF followed by hot EtOH, and then Et₂O there remained 1.6 g (30%) of **6**, mp 166–168°. Anal. (C₈H₁₅N₃OS₂·H₂SO₄) C, H, N; S: calcd, 25.90; found, 24.95.

3-[[2-(2-Mercaptoethyl)amino]-*N*-2-thiazolylpropionamide·HCl (8).—To a mixt of 5.0 g (0.025 mole) of **5a** and 20 ml of abs EtOH cooled in a Dry Ice–Me₂CO bath was added a soln of approx 2.5 g of H₂S in 30 ml of abs EtOH cooled to –65°. The reaction mixt was allowed to warm to room temp, kept at that temp for 3 hr, and then evapd under reduced pressure below 25° to give a solid residue of 3-[[2-(2-mercaptoethyl)amino]-*N*-2-thiazolylpropionamide. This was dissolved in *i*-PrOH, treated with 6.2 ml of a soln of HCl in *i*-PrOH (4 *N*), and the solid that pptd was isolated and purified by crstn twice from 250 ml of MeOH giving 2.5 g (37%) of **8**, mp 200–201° dec. Anal. (C₈H₁₃N₃OS₂·HCl) C, H, N; SH: calcd, 12.35; found, 11.54.

3,3'-[Dithiobis(ethyleneimino)]bis(*N*-2-thiazolylpropionamide) (7).—To a mixt of 10 g (0.048 mole) of **5a** and 50 ml of anhyd MeOH cooled in a Dry Ice–Me₂CO bath was added a soln of approx 5 g of H₂S in 100 ml of MeOH cooled to –45°. The mixt was allowed to warm to room temp and filtered to remove any insol material. The filtrate was concd under reduced pressure for 15 min without external heating, and the conc was filtered by gravity to remove the pptd solid. To the clear filtrate was added 2.5 ml of 30% H₂O₂, and the resulting mixt was kept undisturbed at room temp for 30 min. After decantation, the crst product was collected, washed with MeOH, and dried under reduced pressure over P₂O₅ to give 3.2 g (29%) of **7**, mp 67–75°. Anal. (C₁₆H₂₄N₆O₂S₄) C, H, N, S.

***N*-2-Thiazolyl-3-thiazolidinepropionamide (9).**—The thiol **8** as the free base was prepd from 9.8 g (0.05 mole) of **5a**. To a soln of **8** in 50 ml of MeOH was added a slurry of 67 g (0.5 mole) of sodium formaldehyde bisulfite in 50 ml of H₂O. The mixt

slightly exothermic reaction had subsided the mixt was heated for 2 hr at 50°, giving 75% of **9a**, mp 225° dec, or 53% of **9a**, mp 229–230° dec.

(18) Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected.

(19) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions are within ±0.4% of the theoretical values.

(20) A. H. Schlesinger and E. J. Prill, *J. Amer. Chem. Soc.*, **78**, 6123 (1956).

(21) Mr. H. D. Troutman and Mr. D. R. Johnson (Parke-Davis) have scaled up this prepn by adding at one time **1**, **2**, and KI to DMA. When the

was heated under reflux for 3 hr and then concd to dryness under vacuum. A soln of the residue in 600 ml of H₂O was extd with two 300-ml portions of EtOAc. The combined exts were dried (MgSO₄) and concd to give 5.4 g of solid residue which was recrystd from a mixt of 80 ml of EtOAc and 80 ml of 2,2,3-trimethylpentane to give 3.8 g (31%) of **9**: mp 132.5–135° (softened at 119° and then resolidified before melting); nmr (CDCl₃) δ 4.08 ppm (s, 2, NCH₂S). *Anal.* (C₉H₁₃N₃O₂) C, H, N, S.

3-Chloro-N-2-(substituted thiazolyl)propionamides (1) (Method, Ref 20). **3-Chloropropionamide.**²²—3-Chloro-*N*-(6-methoxy-8-quinolyl)propionamide, mp 101–103° (lit.²³ mp 104°). 3-Chloro-*N*-(4-methyl-2-thiazolyl)propionamide was obtained in 35% crude yield using 0.88 mole of 2-amino-4-methylthiazole; the recrystd (EtOH) material melted at 147.5–151.5°. *Anal.* (C₇H₉ClN₂OS) C, H, N. *N*-(5-Bromo-2-thiazolyl)-3-chloropropionamide was obtained in 44% crude yield from 0.1 mole of amine; the recrystd (EtOH) material melted at 223–225° dec. *Anal.* (C₆H₈BrClN₂OS) C, H, N. 3-Chloro-*N*-(4-phenyl-2-thiazolyl)propionamide was obtained in 43% yield using 0.4 mole of amine, mp 165–168°. *Anal.* (C₁₂H₁₁ClN₂OS) C, H, N. 3-Chloro-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)propionamide was obtained in 75% yield using 0.1 mole of amine, mp 195–196°. *Anal.* (C₈H₈ClN₃OS) C, H, N. Crude 6-chloro-*N*-2-thiazolylhexanamide, mp 120–123°, and *N*-2-benzothiazolyl-3-chloropropionamide, mp 182–184°, were used.

2-[(1-Aziridinyl)acylamino]thiazole (5) (Method, See 5a).—*N*-2-Thiazolyl-1-aziridineacetamide (**5b**) was obtained in 48% yield from 17.7 g (0.1 mole) of 2-chloro-*N*-2-thiazolylacetamide,²⁴ mp 147–150°. *Anal.* (C₇H₉N₃OS) C, H, N. *N*-(4-Methyl-2-thiazolyl)-1-aziridinepropionamide (**5c**) was obtained in 78% yield from 10.2 g (0.05 mole) of 3-chloro-*N*-(4-methyl-2-thiazolyl)propionamide, mp 140–143°. *Anal.* (C₉H₁₃N₃OS) C, H, N. *N*-(5-Bromo-2-thiazolyl)-1-aziridinepropionamide (**5d**) was obtained in 38% yield using 10.8 g (0.04 mole) of *N*-(5-bromo-2-thiazolyl)-3-chloropropionamide, mp 149–156°. *Anal.* (C₈H₁₀BrN₃OS) C, H, N.

3-[(2-Hydroxyethyl)amino]-*N*-2-thiazolylpropionamide (10a).—A mixt of 38 g (0.20 mole) of 3-chloro-*N*-2-thiazolylpropionamide (**1**) and 160 ml of 2-aminoethanol was stirred at 50–60° for 4 hr. The chilled mixt was filtered and the solid was recrystd from *i*-PrOH to give 19.6 g (45%) of **10a**, mp 139–142°. The ir, nmr, and uv spectra were as expected. *Anal.* (C₈H₁₃N₃O₂S) C, H, N.

3-[(2-Chloroethyl)amino]-*N*-2-thiazolylpropionamide·HCl (11a).—To 250 ml of cold (0–10°) SOCl₂ was added slowly 25 g (0.12 mole) of **10a**. The mixt was stirred at 25° for 18 hr and then at 50–60° for 1 hr. Concn and two recrystns of the residue from EtOH gave 15 g (48%) of **11a**, mp 222–224°. *Anal.* (C₈H₁₂ClN₃OS·HCl) C, H, N.

3-[(2-Chloroethyl)amino]-*N*-(5-nitro-2-thiazolyl)propionamide

(22) F. Mayer, L. van Zutphen, and H. Philipps, *Chem. Ber.*, **60**, 858 (1927).

(23) F. Bergmann and D. Schapiro, *J. Org. Chem.*, **7**, 419 (1942).

(24) K. C. Kauer, U.S. Patent 2,780,631 (1957); *Chem. Abstr.*, **51**, 10587 (1957).

Hemisulfate (12).—Solid **11a** (15 g, 0.55 mole) was added portionwise with stirring at –10 to 0° to 45 ml of concd H₂SO₄. The mixt was allowed to warm to 15° whereupon soln of the solid was effected. Red fuming HNO₃ (3 ml) was then added dropwise with vigorous stirring while maintaining the temp below 5°. The clear amber soln was allowed to warm to 25° under ambient conditions and was slowly heated to 55° and maintained at 50–60° for 3 hr. The cooled soln was poured onto 200 g of ice, and the resulting finely divided solid was sepd and washed with a small portion of cold H₂O. A soln of 22 g (two-thirds of crude solid) in hot H₂O was treated with charcoal and chilled to give 9.8 g (50%) of glistening pale yellow crystals, mp 165–167°. A 3-g portion was recrystd from 65 ml of H₂O giving 1.9 g of **12**, mp 170–172°. The uv spectrum was as expected. *Anal.* (C₈H₁₁ClN₄O₃S·0.5H₂SO₄) C, H, Cl, N.

3-[(2-Hydroxyethyl)amino]-*N*-(4-phenyl-2-thiazolyl)propionamide (10b).—Reaction of 8 g (0.03 mole) of 3-chloro-*N*-(4-phenyl-2-thiazolyl)propionamide (**1**) with 2-aminoethanol as in the prepn of **10a**, gave a 49% yield of **10b** after recrystn from C₆H₆, mp 131–135°. *Anal.* (C₁₁H₁₇N₃O₂S) C, H, N.

S-2-[(2-[(4-Phenyl-2-thiazolyl)carbamoyl]ethyl)amino]ethyl Hydrogen Thiosulfate (3h).—A 1.5-g lot of **3h** was obtained by reaction⁹ in 125 ml of 80% aq EtOH of 6.5 g of Na₂S₂O₃·5H₂O with 5.5 g (0.16 mole) of crude 3-[(2-chloroethyl)amino]-*N*-(4-phenyl-2-thiazolyl)propionamide·HCl (**11b**) (2.9 g of **10b** and 1.2 g of SOCl₂ in 50 ml of DMF gave 1 g of **11b**, mp 207–210°).

3-[(2-Benzylthio)ethyl]amino]-*N*-2-thiazolylpropionamide·HCl (19).—A mixt contg 9.5 g (0.05 mole) of 3-chloro-*N*-2-thiazolylpropionamide (**1**) and 16.7 g (0.1 mole) of 2-(benzylthio)ethylamine²⁵ in 500 ml of MeOH was heated under reflux for 4 hr and was then concd to dryness. The residue was washed with H₂O and twice recrystd from *i*-PrOH to give 2.4 g (13%) of the secondary amine·HCl, mp 181–184°. *Anal.* (C₁₅H₁₉N₃O₂S·HCl·0.67H₂O) C, H, Cl, N, H₂O.

3-(Propylamino)-*N*-2-thiazolylpropionamide·HCl (18).—A mixt of 20 g (0.11 mole) of 3-chloro-*N*-2-thiazolylpropionamide (**1**) in *ca.* 100 ml of PrNH₂ was heated under reflux for 3 hr. The excess PrNH₂ was removed under reduced pressure and the residue was recrystd from H₂O–Me₂CO to give 13 g (50%) of the secondary amine·HCl, mp 233–235°. *Anal.* (C₈H₁₅N₃OS·HCl) C, H, N.

Acknowledgment.—We are indebted to Dr. P. E. Thompson and Mr. R. E. Voigtman for antischistosomal evaluations, and to Josephine Battaglia, Margaret Deguan, Gail Harger, Eva R. Karger, and Mary Frisinger for assistance at various stages of the chemical work. We thank Dr. J. M. Vandenberg and coworkers for spectral studies and pK_a and solubility determinations, Mr. C. E. Childs and coworkers for microanalytical data, and Dr. E. F. Elslager for advice and encouragement.

(25) D. B. Reisner, *J. Amer. Chem. Soc.*, **78**, 5102 (1956).