butane-1,3-dicarboxamide; 1,1,5,5-tetrakis(dimethylamino)-1,4-pentadiene (VIII) from N,N,N′,N′-tetramethylglutaramide; and 2,2-difluorovinylidenebis(dimethylamine) (XX) from difluoroacetic acid.

2,5-Bis(dimethylamino)-2,4-hexadiene (V) was prepared by the $Ti(NMe_2)_4$ method from 2,5-hexanedione as a liquid, bp 79° (1.5 Torr) (it solidifies near 0°). It exhibits an nmr spectrum consisting of singlets at τ 4.8 (2 H), 7.4 (12 H), and 8.2 (6 H). Its mass spectrum includes a parent ion at *m/e* 168; an M + 1 peak equal to 12.1% of M^+ (expected for $C_{10}H_{20}N_2$: 11.9%); and fragment ions corresponding to $[M - (CH_3)_2NH]^+$ and $[M - (CH_3)_2NHCH_3]^+$, reasonable fragments for this structure.

2,3-Bis(dimethylamino)butadiene (XVIII) and 1-dimethylaminostyrene (XXI) were prepared by the $TiCl_4$–$HNMe_2$ method of White and Weingarten[27,31] from 2,3-butanedione and acetophenone, respectively. The preparation of 1-methyl-3-dimethylamino-2 butenylidenedimethylammonium fluoroborate (XXII) will be described elsewhere.[20]

Acknowledgments. We thank Professor W. H. Urry and Dr. S. S. Tseng of the University of Chicago for their gracious gifts of samples and Dr. Urry and the many others who have helped in discussions.

Thiazolothiazoles. II.[1a] The Parent Heterocycle and Its Carboxylic and Amino Derivatives[1b]

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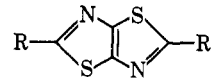
Abstract: Side chain oxidation of 2,5-bis-β-styryl and 2,5-bis-2-furylthiazolo[5,4-*d*]thiazole with permanganate furnished 2,5-thiazolothiazoledicarboxylic acid in good yields. The dicarboxylic acid has served as starting material for a variety of thiazolothiazole derivatives that are inaccessible by direct routes. Stepwise decarboxylation led to 2-thiazolothiazolecarboxylic acid and to the parent heterocycle. Thiazolothiazole is remarkably stable and does not undergo electrophilic substitution reactions. The nucleus is attacked by strong nucleophilic reagents and was converted by means of *n*-butyllithium to 2-thiazolothiazolyllithium. Experiments leading to 2,5-diamino and 2-aminothiazolothiazole and their derivatives are reported.

The reaction of dithiooxamide with aromatic aldehydes affords a general synthesis of 2,5-diarylthiazolo[5,4-*d*]thiazoles,[1a] but we have been unable to obtain directly the parent heterocycle or its alkyl derivatives by means of a similar condensation with formaldehyde or other simple aliphatic aldehydes.[2] The present paper describes the synthesis of a series of carboxylic and amino derivatives, and of the parent thiazolo[5,4-*d*]thiazole (**1**) by an indirect route from the readily available condensation products of dithiooxamide with cinnamaldehyde or furfural.

Owing to the high stability of the thiazolothiazole nucleus, 2,5-thiazolothiazoledicarboxylic acid (**2**) can be obtained in high yields by permanganate oxidation of either the 2,5-bis-β-styryl (**3**) or 2,5-bis-2-furyl (**4**) derivative of thiazolothiazole. The dicarboxylic acid (**2**) separated from aqueous media as a relatively stable dihydrate which can be converted to the anhydrous acid by prolonged drying over phosphorus pentoxide at low pressure. The strongly electrophilic character of the thiazolothiazole system is disclosed by the relatively high acidity of the dicarboxylic acid: pK_1 and pK_2, 2.52 and 3.05. The rather small diminution in acidity for the second acidic hydrogen, ΔpK 0.53, indicates that inductive electron release from the carboxylate anion is not effectively transmitted between the 2 and 5 positions of the bicyclic system (*cf.* terephthalic acid, ΔpK *ca.* 1.0; fumaric acid, ΔpK *ca.* 1.5).



1, R = R′ = H
2, R = R′ = COOH
3, R = R′ = CH=CHC$_6$H$_5$
4, R = R′ = C$_4$H$_3$O
5a, R = R′ = COOCH$_3$
b, R = R′ = COOC$_2$H$_5$
6a, R = COOH; R′ = COOCH$_3$
b, R = COOH; R′ = COOC$_2$H$_5$
7a, R = H; R′ = COOCH$_3$
b, R = H; R′ = COOC$_2$H$_5$
8, R = H; R′ = COOH
9, R = COOH; R′ = CONH$_2$
10, R = COOH; R′ = CON$_2$H$_3$
11, R = H; R′ = CONH$_2$
12, R = H; R′ = CON$_2$H$_3$
13, R = R′ = CONH$_2$
14, R = R′ = CON$_2$H$_3$
15, R = R′ = CON$_3$
16, R = R′ = NHCOOC$_3$H$_7$
17, R = R′ = N(CO)$_2$C$_6$H$_4$
18, R = R′ = NH$_2$
19, R = H; R′ = NHCOOC$_3$H$_7$
20, R = H; R′ = N(CO)$_2$C$_6$H$_4$
21, R = H; R′ = NH$_2$

The dibasic acid (**2**) was converted readily to the dimethyl ester (**5a**) by direct esterification with methanol in the presence of hydrogen chloride, or by diazomethane. The diethyl ester (**5b**) was prepared similarly from ethanol. Controlled saponification of the dimethyl and diethyl esters furnished the monoesters, *e.g.*, 5-carbomethoxy-2-thiazolothiazolecarboxylic acid (**6a**). Decarboxylation of these led to the corresponding esters of 2-thiazolothiazolecarboxylic acid (**7**) which upon hydrolysis gave 2-thiazolothiazolecarboxylic acid (**8**) in a pure state. Aminolysis and hydrazinolysis of the half-esters (**6**) afforded the monoamide (**9**) and the monohydrazide (**10**) of the dibasic acid which by decarboxylation afforded the amide (**11**) and the hydrazide (**12**) of the monocarboxylic acid

(1) (a) Part I: *J. Amer. Chem. Soc.*, 82, 2719 (1960); (b) abstracted from the Ph.D. Theses of D.H.R. (1960) and R.K. (1956); (c) Todd Fellow in Chemistry, 1956–1959; to whom inquiries may be directed, Esso Research and Engineering Company, Linden, N. J. 07036; (d) to whom inquiries may be directed, School of Pharmacy, University of California, San Francisco, Calif. 94122.

(2) A previously reported Mannich-type condensation of dithiooxamide with aliphatic and aromatic aldehydes in the presence of secondary amines (O. Wallach and J. Froelich, *Chem. Zentr.*, II, 1024 (1899)) has been reinvestigated in this laboratory by Dr. Hector Belmares-Sarabia, Ph.D. Thesis, Cornell University, 1963.

identical with the products obtained directly from the monocarboxylic acid.

While seeking a solvent suitable for crystallization of the dicarboxylic acid (**2**), we observed that decarboxylation occurred as the acid dissolved slowly in refluxing ethanol. If heating is stopped when 1 mol of carbon dioxide has been evolved the principal product is the monocarboxylic acid (**8**) (yield, *ca.* 90%). Prolonged refluxing in ethanol effects decarboxylation of the monocarboxylic acid and gives thiazolothiazole (**1**). The parent heterocycle was prepared first by thermal decarboxylation of the dicarboxylic acid (**2**), which loses 2 mol of carbon dioxide upon melting. 2-Thiazolothiazolecarboxylic acid (**8**) likewise loses carbon dioxide upon melting.

Thiazolo[5,4-*d*]thiazole (**1**), like other typical aromatic systems, exhibits broad general absorption in the ultraviolet region (220–280 mμ). The infrared spectrum is quite simple and consists of a small number of strong bands, reflecting the high symmetry of the molecule. The nucleus has the properties of a stable aromatic system of strong electrophilic character. It is resistant to attack by strong nitric or sulfuric acid at ordinary temperatures. Nitration could not be effected by a mixture of absolute nitric acid and fuming sulfuric acid (10% SO_3) at 20–25° but oxidative degradation occurred at higher temperatures. Attempts to effect direct bromination and Friedel–Crafts acylations also were unsuccessful. 2-Bromo- and 2,5-dibromothiazolothiazole (mp of the latter, 189–190°) were obtained eventually in low yields by the Hunsdiecker reaction of bromine and the silver salts of the mono- and dicarboxylic acids.[3]

The thiazolothiazole system is susceptible to attack by powerful nucleophiles but these reagents tend to bring about extensive decomposition. Attempts to obtain 2-aminothiazolothiazole (**21**) by direct amination with sodium amide were not successful. Metallation was effected by treatment with *n*-butyllithium at low temperature (−65°) to form 2-thiazolothiazolyllithium, which was characterized by carbonation to give 2-thiazolothiazolecarboxylic acid (**8**). The lithium derivative decomposes at temperatures above −20° and appears to have limited usefulness for synthetic purposes. Metallic sodium in the form of a thin mirror on glass reacts with thiazolothiazole vapor to form an unstable red compound of the composition $Na_2C_4H_2N_2S_2$.[4]

On warming with thionyl chloride in the presence of dimethylformamide as catalyst, the dicarboxylic acid (**2**) is converted quantitatively to the bisacid chloride. The acid chloride is hydrolyzed by water at room temperature much more rapidly than typical aroyl chlorides. 2,5-Thiazolothiazoledicarboxamide (**13**) was prepared by treating the acid chloride or the dimethyl ester (**5a**) with strong aqueous ammonia. Several attempts to obtain 2,5-diaminothiazolothiazole (**18**) or its derivatives from the diamide by reaction with sodium hypobromite under various conditions were unsuccessful. The Curtius synthesis, using the bishydrazide (**14**) and bisacid azide (**15**), affords a more promising route to the amino derivatives.

(3) Experiments of Mr. Lloyd Frauenglass.

(4) Private communication, Dr. Seymour Hochberg, Marshall Laboratory, E. I. du Pont de Nemours and Co., Philadelphia, Pa.

Treatment of the dimethyl ester (**5a**) with hydrazine hydrate at 0–20° gave bright yellow crystals of the bisacid hydrazide (**14**), one of the few derivatives of the dicarboxylic acid that exhibits absorption in the visible region (350–400 mμ). The hydrazide dissolves in aqueous base to form a yellow anion and in hydrochloric acid to form a colorless hydrazidium cation.[5]

The monocarboxylic acid hydrazide (**12**) is pale yellow in color and behaves in the same way as the bisacid hydrazide toward aqueous alkali and acid.

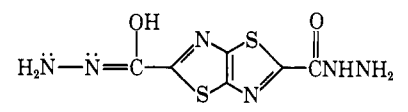
The 2,5-bisacid hydrazide (**14**) was converted by treating with nitrous acid to 2,5-thiazolothiazolebiscarbonyl azide (**15**), which was refluxed with 1-propanol to obtain N,N′-dicarbopropoxy-2,5-diaminothiazolothiazole (**16**). This compound dissolves in hot aqueous alkali to form a stable salt and is recovered unchanged upon acidification. It is also resistant to hydrolysis by warm aqueous hydrochloric acid but is decomposed by acids at elevated temperatures. The biscarbamate (**16**) was converted by fusion with phthalic anhydride to 2,5-bisphthalimidothiazolothiazole (**17**), which was deacylated with only limited success by means of hydrazine.[6] The crude 2,5-diaminothiazolothiazole (**18**) was converted to its dibenzoyl derivative which has also resisted purification.

The hydrazide of 2-thiazolothiazolecarboxylic acid (**12**) was converted by a similar series of reactions to the acid azide, various alkyl carbamates, and thence to 2-phthalimidothiazolothiazole (**20**). Treatment of the latter with hydrazine hydrate gave 2-aminothiazolothiazole (**21**). The amine dissolves in aqueous acids and *also* in aqueous alkalies. The solubility of the amine in alkali affords further evidence of the strongly electrophilic character of the thiazolothiazole nucleus.

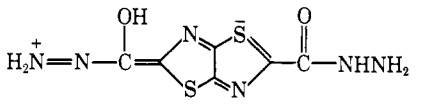
Experimental Section[7]

2,5-Thiazolo[5,4-*d*]thiazoledicarboxylic Acid (2). The preparation of the starting material, 2,5-bis(2-furyl)thiazolothiazole (**4**), was improved by addition of phenol to the reaction mixture. Dithiooxamide (20 g, 0.167 mol), 60 g of phenol, and 200 g (2.08 mol) of freshly distilled furfural were heated in an oil bath at 200–205° for 45 min after the dark solution had reached its boiling point. After standing overnight the dark crystalline product was collected with suction and washed with several portions of ethanol, ether, and hexane. The crude product was heated under reflux with chloroform (*ca.* 1 l.) and the filtered solution concentrated and

(5) This behavior suggests that the hydrazide exists in a tautomeric imidol form (i), in which conjugation with the strongly electrophilic heterocycle gives rise to an extended chromophore (as in ii). The



i



ii

bathochromic shift is enhanced by conversion to the anion (λ_{max} 362 mμ) but protonation of the hydrazide function (λ_{max} 323 mμ, with no absorption beyond 350 mμ) precludes its participation.

(6) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926); *J. Amer. Chem. Soc.*, **51**, 1202 (1929).

(7) Melting points are uncorrected. Uv spectra were determined on a Beckman DK 2 spectrophotometer in 95% ethanol. Ir spectra were measured on a Perkin-Elmer Model 21 spectrophotometer in KBr. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

allowed to cool. The first crop of greenish yellow needles weighed 15–16 g, mp 239–241°. Concentration of the mother liquor gave two further crops of crystals, mp 238–240° (total yield, 21–23 g; *ca.* 50%). This material is sufficiently pure for the subsequent oxidation step.

2,5-Bis(2-furyl)thiazolothiazole (**4**, 17 g, 0.062 mol) and 475 ml of pyridine were heated on a steam bath with rapid stirring until the solid had dissolved almost completely. After cooling to 70°, 75 ml of water was added to produce a uniform suspension of fine crystals. The mixture was cooled to 15–20° and held at this temperature while 104 g (0.66 mol) of finely powdered potassium permanganate and 70 ml of water were added, with continued rapid stirring. The amount of permanganate used was the theoretical quantity required for the oxidation: 10.67 mol/mole of **4**.

After the permanganate had been added, the temperature of the mixture was allowed to rise slowly to 40° and maintained there for 12 hr, with stirring. The mixture was cooled and 1 g of sodium bisulfite and 100 ml of water were introduced. The black precipitate, consisting of manganese dioxide and the potassium salt of the acid (**2**), was collected with suction on a large filter, washed sparingly with water, and squeezed dry with a filter dam. The filtrate may be discarded with little loss of product since the sparingly soluble potassium salt of the acid is effectively salted out by the high concentration of potassium ions in the system.

The filter cake was boiled with 1 l. of water and the extract filtered hot with suction. Two further extractions of the residual manganese dioxide were made with smaller volumes of hot water. The almost colorless filtrates were acidified with concentrated hydrochloric acid and the precipitated acid was collected. The product was washed thoroughly with water, with dioxane, and finally with ether. The air-dried material weighted 10.5–11 g (65%): mp 214° dec; neut equiv, 135 (calcd for $C_4N_2S_2(CO_2H)_2 + 2H_2O$, 133). This material was sufficiently pure for conversion to the esters and other derivatives. An analytical sample of the dihydrate was prepared by repeated precipitation of the potassium salt (ir λ_{max} 6.15 and 6.90 μ) and regeneration of the acid, followed by drying at 34° (20 mm) for 5 hr; mp 212° dec; neut equiv, 133; ir λ_{max} 2.90, 5.73 (m), 5.90 (s), 6.78, and 6.90 μ; broad peaks at 3.50, 4.0, and 5.0 μ. *Anal.* Calcd for $C_6H_2N_2O_4S_2 + 2H_2O$: C, 27.07; H, 2.27; N, 10.52. Found: C, 27.35; H, 2.33; N, 10.49.

The anhydrous acid was obtained by drying a pure sample of the dihydrate over phosphorus pentoxide in a drying pistol at 56° (0.1 mm) for 10 hr: colorless crystals, mp 211° dec; neut equiv, 116 (calcd 115); ir λ_{max} 5.76 (s), 5.88 (m), 6.91, and s 6.81 μ; broad peaks at 3.51 and 4.0 μ; uv λ_{max} 314 mμ (log ϵ = 4.20), s 288 mμ, s 278 mμ. *Anal.* Calcd for $C_6H_2N_2O_4S_2$: C, 31.30; H, 0.88; N, 12.17. Found: C, 31.75; H, 1.18; N, 12.60.

Ths bisbenzylthiuronium salt crystallized from aqueous ethanol in colorless needles, mp 211–211.5° dec. *Anal.* Calcd for $C_{22}H_{22}N_6O_4S_4$: C, 46.96; H, 3.94; N, 14.94. Found: C, 47.19; H, 4.16; N, 14.94.

Oxidation of 2,5-bis(β-styryl)thiazolothiazole (**3**) with potassium permanganate (using 5.7 mol/mol) under similar conditions furnished the same product in 65–70% yields but the overall yield from dithiooxamide was lower.

Dimethyl 2,5-Thiazolothiazoledicarboxylate (5a). A stirred suspension of 5.3 g (0.2 mol) of the dihydrate of 2,5-thiazolothiazoledicarboxylic acid (**2**) in 200 ml of methanol was saturated with anhydrous hydrogen chloride and maintained at its boiling point for 2 hr. The acid dissolved slowly and dense colorless crystals of the ester separated. After distilling off part of the excess methanol the mixture was cooled and neutralized with 80 ml of 20% aqueous sodium carbonate. Crystallization from dioxane gave 4.5 g (87% yield) of colorless needles: mp 249–250°; ir λ_{max} 3.42, 5.87, and 6.90 μ. *Anal.* Calcd for $C_8H_6N_2O_4S_2$: C, 37.20; H, 2.34; N, 10.85. Found: C, 37.73; H, 1.73; N, 10.98.

The dimethyl ester was prepared also by treating the dihydrate of the dicarboxylic acid, suspended in methanol and ether, with a large excess of ethereal diazomethane.

5-Carbomethoxy-2-thiazolothiazolecarboxylic Acid (6a). A stirred suspension of the dimethyl ester (**5a**, 4.12 g, 0.016 mol) in 150 ml of absolute methanol was treated with 45 ml of a methanolic solution of potassium hydroxide (0.016 mol) for 48 hr at 20°. Separation of the products furnished the monomethyl ester (*ca.* 45% yield) in an impure state admixed with 15–20% of the dicarboxylic acid, mp 168–178° dec. Recovered dimethyl ester and dicarboxylic acid accounted for about 45% of the starting material. The crude monomethyl ester (**6a**) was used for the preparation of other derivatives since the latter could be purified more easily.

Diethyl 2,5-Thiazolothiazoledicarboxylate (5b). This ester was prepared by direct esterification of the dicarboxylic acid in the same manner as the dimethyl ester. Crystallization from ethanol, followed by recrystallization from acetone, gave colorless needles: mp 140–141° (50% yield); ir λ_{max} 3.36, 3.42, 5.75, 6.75, 6.83, and 6.91 μ; uv λ_{max} 319 (log ϵ = 4.25), s 293, s 280 mμ. *Anal.* Calcd for $C_{10}H_{10}N_2O_4S_2$: C, 41.95; H, 3.52; N, 9.78. Found: C, 42.43; H, 3.59; N, 9.75.

Subsequent experiments disclosed that the dicarboxylic acid undergoes decarboxylation rapidly in boiling ethanol, which accounts for the relatively low yield of the diethyl ester. The yield could be improved by conducting the esterification at lower temperature or by use of the acid chloride.

5-Carboethoxy-2-thiazolothiazolecarboxylic Acid (6b). Partial saponification of the diethyl ester (**5b**, 700 mg, 2.5 mmol) with 25 ml of ethanolic potassium hydroxide (2.5 mmol) for 12 hr at 20° afforded colorless crystals (65% yield), mp 140° dec. This was used directly for the preparation of ethyl 2-thiazolothiazolecarboxylate (**7b**) (see below).

2,5-Thiazolothiazoledicarboxamide (13). (a) A sample of 520 mg (2 mmol) of the dimethyl ester (**5a**) was suspended in 55 ml of concentrated aqueous ammonia and stirred for 25 hr at 20°. The ester dissolved slowly and a fine colorless precipitate of the diamide was formed. After washing with water, ethanol, and ether the product was crystallized from dimethylformamide, yield 280 mg (60%). Further crystallizations from dimethylformamide and sublimation (220° (0.004 mm)) gave colorless crystals: dec pt ~350°; ir λ_{max} 2.90, 3.02, 3.13, 5.98, 6.28, and 6.83 μ; uv λ_{max} 316, s 292, s 278 mμ. *Anal.* Calcd for $C_6H_4N_4O_2S_2$: C, 31.57; H, 1.77; N, 24.55. Found: C, 31.66; H, 1.99; N, 24.32.

(b) A sample of 720 mg (2.7 mmol) of the dihydrate of 2,5-thiazolothiazoledicarboxylic acid (**2**) was refluxed with 3 ml of thionyl chloride without evidence of reaction. When 1 drop of dimethylformamide was added, rapid evolution of sulfur dioxide and hydrogen chloride occurred and the acid slowly dissolved. An additional 1.5 ml of thionyl chloride and a drop of dimethylformamide were added and heating was continued until all of the acid had dissolved. Part of the excess thionyl chloride was distilled and the cooled residual liquid was poured cautiously, with rapid stirring, into 60 ml of cold concentrated aqueous ammonia. The precipitated diamide was collected and washed with water, ethanol, acetone, and ether, yield 580 mg (93%).

5-Carbamyl-2-thiazolothiazolecarboxylic Acid (9). Five hundred milligrams (2 mmol) of the crude 5-carbomethoxy-2-thiazolothiazolecarboxylic acid (**6a**) were stirred rapidly with 20 ml of concentrated aqueous ammonia at 0° for 1 hr and then at 20° for 1 hr. The colorless precipitate of the ammonium salt of the amidic acid was collected and washed with absolute ethanol and ether: yield 380 mg (75%); mp 233° dec. Evaporation of the original aqueous filtrate gave 120 mg of diammonium 2,5-thiazolothiazoledicarboxylate (22% of the starting material).

The ammonium salt of the amidic acid was dissolved in warm dilute aqueous sodium bicarbonate and the filtered solution acidified with hydrochloric acid. The colorless precipitate of 5-carbamyl-2-thiazolothiazolecarboxylic acid (**9**) was washed with water, ethanol, and ether: yield 330 mg (75%); dec pt ~200° with evolution of carbon dioxide; ir λ_{max} 3.01, 3.15, 5.88, 6.04, 6.50, 6.88 μ.

2-Thiazolothiazolecarboxamide (11). Sublimation of 5-carbamyl-2-thiazolothiazolecarboxylic acid (**9**) at 190° (0.005 mm), crystallization from methanol, and a second sublimation at 100–140° (0.005 mm) gave colorless crystals of the carboxamide (**11**): mp 236–236.5°; uv λ_{max} 298 (log ϵ = 4.04), s 265 mμ; ir λ_{max} 2.92, 3.03, 3.14, 3.29, 5.92, 6.0, 6.20, 6.30, 6.81, and 10.61 μ. *Anal.* Calcd for $C_5H_3N_3OS_2$: C, 32.42; H, 1.63; N, 22.69. Found: C, 32.27; H, 1.96; N, 22.73.

2,5-Thiazolothiazoledicarbonyl Hydrazide (14). Dimethyl 2,5-thiazolothiazoledicarboxylate (**5a**, 2.6 g, 10 mmol) was suspended in 30 ml of 100% hydrazine hydrate and the mixture stirred rapidly at 0° for 3 hr, then at 20° for 2 hr. The colorless ester was converted gradually to a bright yellow solid. The crude product was dissolved in warm aqueous hydrochloric acid and unchanged ester removed by filtration. The purified hydrazide was reprecipitated by neutralization with sodium bicarbonate and washed with water, ethanol, and ether: yield 2.3 g (88%); dec pt ~325°. The analytical sample was purified by sublimation (230° (0.003 mm)): ir 2.98, 3.07, 3.18, 3.57, 5.94, 6.32, 6.41, 6.65, and 6.93 μ; uv λ_{max} 324, 267 mμ.

The bright yellow bisacid hydrazide forms a colorless solution in aqueous hydrochloric acid (λ_{max} 323 and 262 mμ, with no absorption beyond 350 mμ). It dissolves in aqueous or ethanolic sodium

hydroxide to form a yellow solution (λ_{max} 362 and 260 mμ, with diminisbing absorption 362–400 mμ). *Anal.* Calcd for $C_6H_6N_6O_2S_2$: C, 27.90; H, 2.34; N, 32.54. Found: C, 27.97; H, 2.52; N, 32.39.

5-Hydrazinocarbonyl-2-thiazolothiazolecarboxylic Acid (10). Crude 5-carbomethoxy-2-thiazolothiazolecarboxylic acid (**6a**, 920 mg, 3.77 mmol) was stirred for 1 hr at 0° with 16 ml of 1:1 absolute ethanol–100% hydrazine hydrate. A yellow precipitate formed rapidly. An additional 10 ml of the 1:1 solution was added and the mixture was stirred for 1.5 hr at 0° and for 15 min at 20°. The pale yellow impure hydrazinium 5-hydrazinocarbonyl-2-thiazolothiazolecarboxylate was collected and washed with ethanol and ether (1.01 g, dec pt 200–300°).

Acidification of a filtered aqueous solution with 5% hydrochloric acid afforded 230 mg of the hydrazide acid, mp 207–209° dec. Further cautious acidification gave 260 mg: mp 198–209° dec (total yield 490 mg, 53%); ir λ_{max} 3.01, 3.12, 3.30, 5.95, 6.14, 6.30, 6.52, 6.96 μ. Additional acidification gave 330 mg (36%) of the dibasic acid (**2**).

2-Thiazolothiazolecarbonyl Hydrazide (12). (a) 5-Hydrazinocarbonyl-2-thiazolothiazolecarboxylic acid (**10**, 300 mg, 1.23 mmol) was sublimed at 177–220° (0.01 mm) to give 210 mg of yellow sublimate, mp 210.5–212° dec. Crystallization from absolute ethanol gave 180 mg (72%) of product, mp 222.5–224° dec. Two further recrystallizations gave the analytical sample: mp 224–225° dec; uv λ_{max} 302 (log ε = 4.07), 263 mμ; in acid 305, s 270 mμ; in base 332, 260 mμ; ir λ_{max} 3.10, 3.32, s 6.00, 6.10, 6.56, 6.91, 10.31, and 10.66 μ. *Anal.* Calcd for $C_5H_4N_4OS_2$: C, 30.00; H, 2.01; N, 27.98. Found: C, 30.05; H, 2.18; N, 28.11.

(b) Methyl 2-thiazolothiazolecarboxylate (**7a**, 830 mg, 4.15 mmol, crude) suspended in 20 ml of methanol was stirred with 4.12 g (82.4 mmol) of cold 100% hydrazine hydrate at 0° for 2 hr. The yield of yellow hydrazide was 560 mg (68%), mp 217.5–218.5°. Recrystallization afforded material identical with that described above.

2-Thiazolothiazolecarboxylic Acid (8). (a) Methyl 2-thiazolothiazolecarboxylate (**7a**, 230 mg, 1.15 mmol) was stirred with 35 ml of 1% aqueous potassium hydroxide at 20° for 12 hr. The resulting colorless solution was diluted with 20 ml of water, filtered, and acidified with hydrochloric acid. The colorless precipitate was washed with water and ether, and vacuum dried. The yield of 2-thiazolothiazolecarboxylic acid, mp 178° dec, was 180 mg (86%): neut equiv, 189 (calcd 186); uv λ_{max} 296 (log ε = 3.99), s 273 mμ; ir λ_{max} 3.30, 5.89, 6.83, 6.98, and 10.40 μ; broad peaks at 3.70, 4.0–4.15, and 5.46 μ. *Anal.* Calcd for $C_5H_2N_2O_2S_2$: C, 32.25; H, 1.08; N, 15.05. Found: C, 32.49; H, 1.09; N, 14.77.

This acid (**8**) was prepared more conveniently but in a less pure state by controlled decarboxylation of 2,5-thiazolothiazoledicarboxylic acid (**2**), as described in part b. It was obtained also in 27% yield, from thiazolothiazole by conversion to the lithium derivative and carbonation.

(b) Absolute ethanol (250 ml) was heated in a flask equipped with an upright condenser connected to a simple mercury-filled gas collector. After the solvent was refluxing actively and the system had attained equilibrium, 1.55 g (5.8 mmol) of the dihydrate of 2,5-thiazolothiazoledicarboxylic acid (**2**) was introduced. The acid dissolved slowly in the refluxing solvent but decarboxylation occurred rapidly as dissolution took place. After 1–1.5 hr, when slightly more than 1 equiv of carbon dioxide (143 ml at 20°, 750 mm) had been evolved, the solution was cooled and the ethanol removed (40°, 10 mm). The residual solid was dissolved in aqueous bicarbonate, the solution filtered, and the acid reprecipitated with hydrochloric acid. The colorless product was washed with water, dioxane, and ether, and vacuum dried: mp 170–180° dec; yield, *ca.* 1.0 g (93%). The crude 2-thiazolothiazolecarboxylic acid (**8**) obtained in this way usually contains 5–15% of unaltered dicarboxylic acid, most of which can be removed by salting out its sparingly soluble dipotassium salt. The crude acid may be purified also by conversion to the methyl ester (**7a**) and separation from the dimethyl ester of the dicarboxylic acid by fractional crystallization (see below).

Methyl 2-Thiazolothiazolecarboxylate (7a). (a) Crude 5-methoxycarbonyl-2-thiazolothiazolecarboxylic acid (**6a**, 900 mg, 3.69 mmol) was sublimed at 150° (0.08 mm). The sublimate (620 mg, 89%) was fused for 1 min at 150° to complete the decarboxylation followed by crystallization from methanol to give two crops, 160 mg (23%), mp 135–139°, and 120 mg (18%), mp 129–134°. The first crop was recrystallized twice from methanol to give material of mp 138–140°, identical with that described below.

(b) Crude monocarboxylic acid (**8**, 1.02 g, 5.4 mmol) was powdered and suspended in 60 ml of 1:1 methanol–ethyl ether and treated portionwise with approximately 1.7 g (40.4 mmol) of diazomethane in 150 ml of ether (20 min). The mixture was diluted with ether to 300 ml and insoluble dimethyl thiazolothiazoledicarboxylate (**5a**, 170 mg, mp 246–248°) was removed. After concentration another 50 mg of the diester (**5a**), mp 240–247°, was removed. Evaporation of the remaining solvent gave 850 mg (77%) of crude monoester. Two further crystallizations from methanol followed by sublimation (40–55°, 0.02 mm) gave fine colorless needles: mp 135.5–137°; uv λ_{max} 303 (log ε = 4.06), s 276 mμ; ir λ_{max} 3.29, 3.46, 5.86, 6.89, and 10.39 μ. *Anal.* Calcd for $C_6H_4N_2O_2S_2$: C, 35.99; H, 2.01; N, 13.99. Found: C, 36.17; H, 2.01; N, 14.00.

Ethyl Thiazolothiazolecarboxylate (7b). Sublimation (160°, 0.88 mm) of the half ethyl ester (**6b**, 420 mg, 1.63 mmol) followed by fusion (120°) and crystallization from ethanol–water gave 140 mg (40%) of material, mp 106–107.5°. One more recrystallization followed by sublimation (50–70°, 2.5 mm) gave colorless crystals: mp 106–107°; uv λ_{max} 303 (log ε = 4.07), s 276 mμ; ir λ_{max} 3.27, 5.86, 6.01, 6.80, 6.90, and 10.50 μ. *Anal.* Calcd for $C_7H_6N_2O_2S_2$: C, 39.24; H, 2.82; N, 13.08. Found: C, 39.33; H, 2.98; N, 13.11.

Thiazolothiazole (1). (a) One hundred milligrams (0.38 mmol) of 2,5-thiazolothiazoledicarboxylic acid dihydrate (**2**) was heated in a vacuum sublimation apparatus at 225–230° (5 mm). The sublimate was fused in a small test tube, heated briefly to decompose traces of unchanged acid, and allowed to cool. Crystallization from 5 ml of 50% aqueous ethanol gave 500 mg (95% yield) of colorless crystals of thiazolothiazole, mp 150–151°. The analytical sample was purified by sublimation at 100° and 12 mm: uv 255 (log ε = 3.94), 260 mμ (log ε = 3.87); ir λ_{max} 3.31, 6.09, 7.10, 7.17, 7.65, 10.4, and 12.6 μ. *Anal.* Calcd for $C_4H_2N_2S_2$: C, 33.79; H, 1.42; N, 19.70. Found: C, 34.04; H, 1.35; N, 19.50.

(b) A sample of 600 mg (2.3 mmol) of 2,5-thiazolothiazoledicarboxylic acid dihydrate (**2**) was heated under reflux with 100 ml of absolute ethanol for 12 hr. The clear solution was cooled and the solvent removed (46°, 25 mm). There remained 260 mg (83% yield) of colorless crystals of thiazolothiazole, mp 150–152°.

Thiazolothiazolyllithium. Thiazolothiazole (**1**, 100 mg, 0.704 mmol) stirred in 9.5 ml of tetrahydrofuran at −70° in a nitrogen atmosphere was treated dropwise with 4 ml of 0.37 *N* butyllithium in pentane (1.48 mmol). After addition (10 min) the green yellow solution was treated with dry carbon dioxide gas (10 min) which produced an almost colorless precipitate. While still at −65°, 10 ml of 10% hydrochloric acid was added and the temperature was permitted to rise to 20°. The mixture was neutralized with solid sodium bicarbonate, washed with ether, and acidified with concentrated hydrochloric acid. The precipitate (35 mg, 27%, mp 172–173°) was identical with thiazolothiazolecarboxylic acid (**8**).

Di-*n*-propyl 2,5-Thiazolothiazoledicarbamate (16). The biscarbonyl hydrazide (**14**, 1 g, 3.87 mmol) in 350 ml of aqueous hydrochloric acid was treated while stirring at 10° with 720 mg (10.12 mmol) of sodium nitrite. After 8 min the precipitated dicarbonyl azide (**15**) was collected and washed with cold water, acetone, and ether. It exploded when placed in a flame or tapped with a hammer and decomposed violently at about 130° in a melting point tube: ir λ_{max} 4.34, 4.60, 6.00, and 7.00 μ.

The dicarbonyl azide (**15**) was heated under reflux with 150 ml of *n*-propyl alcohol for 1 hr. The solid slowly changed to a fine yellow suspension as nitrogen evolved. The volume was reduced to 25 ml and the solid dicarbamate (**16**) was collected and washed with ethanol and ether to give 730 mg (55%), mp 330–350° dec. The analytical sample was prepared by crystallization from dioxane followed by sublimation (218–223°, 0.008 mm) to give an almost colorless product: uv λ_{max} 310 (log ε = 4.27), 242 mμ; ir λ_{max} 3.17, 3.29, 3.42, 3.61, 5.87, 6.31, and 6.80–6.88 μ. *Anal.* Calcd for $C_{12}H_{16}N_4O_2S_2$: C, 41.85; H, 4.68; N, 16.27. Found: C, 41.93; H, 4.70; N, 16.83.

Treatment of this dicarbamate with 10% methanolic potassium hydroxide furnished the potassium salt: mp 300–400° dec; uv λ_{max} 308 (log ε = 4.29), 240 mμ; ir λ_{max} 2.80, 3.42, 6.30, and 6.80 μ. The dicarbamate was recovered quantitatively on treatment with dilute hydrohcloric acid.

2,5-Diphthalimidothiazolothiazole (17). The dicarbamate (**16**, 540 mg, 1.28 mmol) and 1.77 g (12 mmol) of phthalic anhydride were heated at 230° for 1 hr until bubbling ceased. The inhomogeneous paste was cooled, broken up, and stirred overnight with 10 ml of aqueous sodium bicarbonate. The solid diphthalimidothiazolothiazole (570 mg, 84%, mp ~340°) was crystallized three

times from cyclohexanone to give bright yellow needles: mp 375–377°; uv λ_{max} 330, 220 mμ; ir λ_{max} 3.30, 5.60, 5.69, 5.80, 6.23, and 6.81 μ. *Anal.* Calcd for $C_{20}H_8N_4O_4S_2$: C, 55.54; H, 1.86; N, 12.96. Found: C, 55.40; H, 1.78; N, 13.19.

This material did react with hydrazine to give an amino product (**18**) and subsequently a benzoyl derivative. However, neither of these has so far been purified or otherwise adequately characterized.

***n*-Propyl 2-Thiazolothiazolecarbamate (19).** To 2-thiazolothiazolecarbonyl hydrazide (**12**, 710 mg, 3.55 mmol) in 20 ml of aqueous hydrochloric acid, stirred with 400 ml of ether at 10°, was added 420 mg (5.9 mmol) of sodium nitrite. A precipitate of the azide was formed but was extracted by the ether as stirring was continued for 15 min. The ether phase and an ether extract of the aqueous phase was dried (magnesium sulfate and then Drierite) and then diluted with 100 ml of *n*-propyl alcohol. The ether was distilled and the alcohol solution was refluxed for 1 hr, concentrated to 10 ml, and allowed to stand at 20°. There was obtained 470 mg (55%) of the *n*-propyl carbamate (**19**), mp 185–192°. The material was dissolved in ether, the solution was filtered and diluted with propyl alcohol, and the ether distilled to give colorless crystals, mp 192–194°. This process was repeated twice followed by sublimation (115–123°, 0.01 mm) for the analytical sample: mp 198–200.5°; uv λ_{max} 289 (log ε = 4.22), 246 mμ (log ε = 3.78); ir λ_{max} 3.18, 3.30, 3.42, 3.62, 5.83, 6.39, 6.80, 6.96, 10.43 μ. *Anal.* Calcd for $C_8H_9N_3O_2S_2$: C, 39.49; H, 3.73; N, 17.27. Found: C, 39.71; H, 3.89; N, 17.37.

Allyl (26%, mp 190–192°) and *t*-amyl (26%, mp 230° dec) carbamates were prepared by similar procedures.

2-Phthalimidothiazolothiazole (20). The *n*-propyl carbamate (**19**, 465 mg, 1.93 mmol) and 610 mg (4.12 mmol) of phthalic anhydride were heated at 225° for 40 min to give a dark liquid melt. The reaction mixture was cooled, broken up, and stirred overnight with 60 ml of aqueous sodium bicarbonate. The solid phthalimide derivative was collected, washed with water, and dried to give 440 mg (80%) of dark beige solid, mp 275–278°. Crystallization from chloroform–cyclohexane gave bright yellow needles: mp 279–280°; uv λ_{max} 300 (log ε = 4.26), 230 mμ; ir λ_{max} 3.30, 3.35, 5.60 (m), 5.69 (m), 5.80 (s), 6.26, 6.78, 7.00, and 10.50 μ. *Anal.* Calcd for $C_{12}H_5N_3O_2S_2$: C, 50.16; H, 1.75; N, 14.63. Found: C, 50.38; H, 1.85; N, 14.80.

2-Aminothiazolothiazole (21). 2-Phthalimidothiazolothiazole (**20**, 127 mg, 0.44 mmol), 1 ml of 95% ethanol, and 0.026 ml (27 mg, 0.54 mmol) of 100% hydrazine hydrate were stirred at room temperature for 1.5 hr. The yellow solid dissolved slowly and a white precipitate formed. Addition of 5 ml of 5% hydrochloric acid dissolved most of the suspended matter. Filtration removed 40 mg of unidentified material. Removal of ethanol and some water precipitated 12 mg (17%) of phthalhydrazide which was removed by filtration. The acidic filtrate was washed with ether, neutralized with solid sodium bicarbonate, and extracted with ether. Concentration of the ether solution afforded crops of 20 mg (29%, mp 213–214° dec) and 12 mg (17%, mp 203–207° dec). Crystallization of the first crop from chloroform gave rhombic crystals: mp 215–215.5° dec; uv λ_{max} 297 (log ε = 3.97), 235; in acid 225, 283 mμ; ir λ_{max} 3.10, 3.28, 3.70, 6.09, 6.58, 6.92, and 10.42 μ. *Anal.* Calcd for $C_4H_3N_3S_2$: C, 30.56; H, 1.92; N, 26.73. Found: C, 30.30; H, 2.36; N, 26.72.

The Effect of Substituents on the Rate of Pyramidal Inversion of 1-Aryl-2,2-dimethylaziridines[1]

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Abstract: The influence of electronic effects on the barrier to pyramidal inversion in *meta*- and *para*-substituted N-phenyl-2,2-dimethylaziridines has been investigated by an examination of the temperature-dependent nmr spectrum. Rate constants and free energies of activation at the coalescence temperature have been determined. The inversion barrier shows a linear correlation with the Hammett substituent constant σ^- (ρ = 2.8–3.3 at −60°). The direction of the substituent effect parallels that previously found for pyramidal inversion at sulfur in sulfoxides and at phosphorus in phosphines, but the magnitude of the effect is greatest in the aziridines. These results are ascribed to conjugation of the lone pair on the inverting center with the attached arene π system, an effect which is more pronounced for first- than for second-row elements, and which finds its maximum expression in the transition state for the inversion process.

It is generally accepted that conjugation of a nitrogen lone pair with a π system decreases the barrier to inversion of the pyramidal nitrogen site, which at the same time is flattened more or less depending on the amount of conjugation. A wide variety of compounds (*e.g.*, amides, cyanamides, aromatic amines) present such characteristics. However, a homogeneous series of substrates is needed in order to study the electronic effects more quantitatively and eventually to allow a separation of the empirically defined concepts of substituent electronegativity and conjugative ability.

Such studies have previously been carried out in related systems. Recent investigations into the factors influencing the pyramidal stability of sulfoxides have shown that the inversion barrier for these compounds is remarkably insensitive to attached substituent groups.[3] Thus acyclic dialkyl, alkyl aryl, and diaryl sulfoxides racemize at 210° with free energies of activation[4a] covering the relatively narrow range[4b] of 38–41 kcal/mol. Parallel investigations into the pyramidal stability of phosphines have shown that the inversion barrier in these compounds is only slightly more sensitive to attached substituent groups.[5] Thus, acy-

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(3) (a) D. R. Rayner, A. J. Gordon, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4854 (1968); (b) D. R. Rayner, E. G. Miller, P. Bickart, A. J. Gordon, and K. Mislow, *ibid.*, **88**, 3138 (1966).

(4) (a) Calculated from one-point rate constants reported in ref 3a using the Eyring equation and assuming a transmission coefficient equal to unity. (b) Excluded from this range are two compounds (1 and 2 of ref 3a) for which a steric effect on the rate is indicated.