[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Thiazolopyrimidines

BY SCOTT J. CHILDRESS AND R. L. MCKEE

An extension of the synthesis of thiazolo[5,4-d]pyrimidines of Weidel and of Fischer has been carried out. 2-Methylthiazolo[5,4-d]pyrimidine-5,7-diol has been converted into the 5,7-dichloro analog and hence into the 5,7-diamine. The previously reported synthesis of thiazolo[4,5-d]pyrimidines has been shown to be unreliable and an alternate synthesis has been developed.

The recent publication concerning thiazolo[5,4-d]pyrimidines[1] prompts us at this time to submit a report of our findings with these compounds as well as with certain thiazolo[4,5-d]pyrimidines.

Thiazolo[5,4-d]pyrimidine-5,7-diol and its 2-methyl- and 2-phenyl-[1] analogs were prepared from thiouramil by the action of formic acid, acetic anhydride and benzoic anhydride, respectively, in accord with and in extension of previous work.[2,3] From 2-methylthiazolo[5,4-d]pyrimidine-5,7-diol and phosphorus oxychloride, 5,7-dichloro-2-methylthiazolo[5,4-d]pyrimidine was obtained which with aqueous ammonia was converted into 5,7-diamino-2-methylthiazolo[5,4-d]pyrimidine.[1] The latter compound has been submitted to the National Cancer Institute for pharmacological evaluation.

Our attempts to prepare thiazolo[4,5-d]pyrimidines from bromobarbituric acid and thioamides[4] have been unsuccessful. Both mono- and dibromobarbituric acid formed with thioformamide a sulfur-free product which we have been unable to purify, while with thioacetamide a smooth conversion to barbituric acid and sulfur was observed. These results have now been confirmed.[5]

The action of sodium hypobromite upon thiazole-4,5-dicarboxamide and its 2-methyl- and 2-phenyl analogs has given rise to compounds which we now regard as thiazolo[4,5-d]pyrimidine-5,7-diol and its 2-methyl- and 2-phenyl analogs (further examples of pyrimidine formation from 1,2-diamides[6]), although they differ widely in properties from those reported.[4] To eliminate the possibility that a somewhat unusual oxidation had occurred, 2-methylthiazolo[4,5-d]pyridazine-4,7-diol was prepared from diethyl 2-methylthiazole-4,5-dicarboxylate[7] and hydrazine and shown to differ from the above 2-methylthiazolo[4,5-d]pyrimidine-5,7-diol (Fig. 1).

Surprisingly, and in contrast to the behavior of 2-methylthiazolo[5,4-d]pyrimidine-5,7-diol, neither thiazolo[4,5-d]pyrimidine-5,7-diol nor its 2-methyl analog react with phosphorus oxychloride or phosphorus pentachloride under usual conditions. (A conceivable parallel has been observed in the inert behavior of 2,4-dihydroxy-6-aminopyrimidine toward phosphorus oxychloride in contrast to the ready reaction of 4,6-dihydroxy-2-aminopyrimidine.) However, action of excess phosphorus pentachloride at 200° unexpectedly converted thiazolo[4,5-d]pyrimidine-5,7-diol into 6-amino-2,4,5-trichloropyrimidine whose structure was confirmed by conversion into 5-chloro-2,4,6-triaminopyrimidine[8] by ammonia, a reaction indicating the presence and point of attachment of the pyrimidine ring. Ultraviolet absorption spectra of these compounds is shown in Figs. 1, 2 and 3.

(1) E. A. Falco and G. H. Hitchings, THIS JOURNAL, **72**, 3203 (1950).

(2) E. Fischer and L. Ach, *Ann.*, **288**, 157 (1895).

(3) H. Weidel and L. Niemilowicz, *Monatsh.*, **16**, 721 (1895).

(4) H. Erlenmeyer and H. P. Furger, *Helv. Chim. Acta*, **26**, 366 (1943); **30**, 585 (1947).

(5) H. P. Furger, *ibid.*, **33**, 1689 (1950).

(6) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 229 (1945).

(7) T. Roubleff, *Ann.*, **259**, 253 (1890).

Experimental

Thiazolo[5,4-d]pyrimidine-5,7-diol.—A suspension of 1 g. of thiouramil[2,3] in 20 ml. of 85% formic acid was refluxed four hours, cooled and filtered. The product was dissolved in 35 ml. of hot ammonium hydroxide, treated with Norite, and reprecipitated with hot dilute hydrochloric acid to yield 0.9 g. of a faintly yellow powder which did not melt below 360°.

Anal. Calcd. for $C_5H_3N_3O_2S$: N, 24.8; S, 18.9. Found: N, 24.8; S, 19.0.

2-Phenylthiazolo[5,4-d]pyrimidine-5,7-diol.[1]—A mixture of 1.5 g. of thiouramil and 15 g. of benzoic anhydride was heated on a steam-bath for three hours and at 170° for one-half hour. After cooling ether was added and the product filtered and washed thoroughly with ether leaving 2.0 g. of material melting well above 360° with decomposition. For analysis a portion was crystallized from 50% acetic acid.

Anal. Calcd. for $C_{11}H_7N_3O_2S$: N, 17.1; S, 13.1. Found: N, 17.2; S, 13.2.

5,7-Dichlorothiazolo[5,4-d]pyrimidine.—A mixture of 0.5 g. of thiazolo[5,4-d]pyrimidine-5,7-diol and 5 g. of phosphorus oxychloride was heated for 12 hours at 200°, cooled and poured onto 30 g. of crushed ice. The product was filtered, dried, crystallized from methanol and sublimed *in vacuo* to give 0.1 g. of white crystals melting at 148.5–149.5°. An additional 0.05 g. of purified material was obtained from the original acidic filtrate by neutralization.

Anal. Calcd. for $C_5HN_3SCl_2$: N, 20.4; S, 15.5. Found: N, 20.4; S, 15.5.

5,7-Dichloro-2-methylthiazolo[5,4-d]pyrimidine was prepared analogously from 3 g. of 2-methylthiazolo[5,4-d]pyrimidine-5,7-diol[3] and 50 g. of phosphorus oxychloride at 170°. The yield of white crystals melting at 109–110° was 2.7 g.

Anal. Calcd. for $C_6H_3N_3SCl_2$: N, 19.1; S, 14.6. Found: N, 19.0; S, 14.7.

5,7-Diamino-2-methylthiazolo[5,4-d]pyrimidine.—A mixture of 1 g. of 5,7-dichloro-2-methylthiazolo[5,4-d]pyrimidine and 15 ml. of concentrated ammonium hydroxide was heated for four hours at 155°, chilled and filtered. The combined crude product from five such reactions weighed 2 g. and was crystallized twice from methanol to give 1.2 g. of white crystals melting at 255–257°, in reasonable agreement with the value previously reported.[1]

Anal. Calcd. for $C_6H_7N_5S$: N, 38.7; S, 17.7. Found: N, 38.7; S, 17.7.

Thiazole-4,5-dicarboxamide.—Fifteen grams of diethyl thiazole-4,5-dicarboxylate[9] and 40 ml. of concentrated ammonium hydroxide gave 9 g. of crude product melting from 280–295°. A portion was crystallized from water, washed with dilute ammonia and dried at 100° *in vacuo* to form white crystals, m.p. 298–300° (dec.).

Anal. Calcd. for $C_5H_5N_3O_2S$: N, 24.6; S, 18.7. Found: N, 24.6; S, 18.8.

(8) S. J. Childress and R. L. McKee, THIS JOURNAL, **72**, 4271 (1950).

(9) H. Erlenmeyer and H. von Meyerburg, *Helv. Chim. Acta*, **20**, 204 (1937).

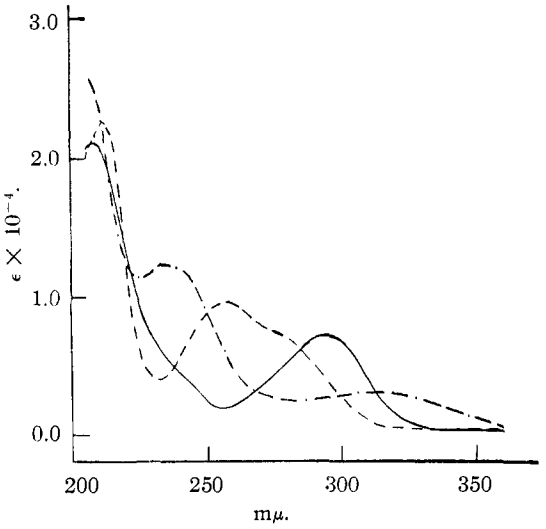

Fig. 1.—Absorption spectra in water solution: ——, 2-methylthiazolo[4,5-d]pyrimidine-5,7-diol; - - - - - -, 2-methylthiazolo[5,4-d]pyrimidine-5,7-diol; - - · - - ·, 2-methylthiazolo[4,5-d]pyridazine-4,7-diol.

2-Methylthiazole-4,5-dicarboxamide was likewise prepared from 8 g. of crude diethyl 2-methylthiazole-4,5-dicarboxylate[7] and 20 ml. of concentrated ammonium hydroxide. The crude product weighed 4 g. and melted from 290–294°. For analysis a portion was crystallized from 50% alcohol giving white crystals melting at 296° with decomposition.

Anal. Calcd. for $C_6H_7N_3O_2S$: N, 22.7; S, 17.3. Found: N, 22.8; S, 17.2.

2-Phenylthiazole-4,5-dicarboxamide was similarly prepared in a crude yield of 2.5 g. from 3 g. of diethyl 2-phenylthiazole-4,5-dicarboxylate.[10] A portion was crystallized from glacial acetic acid to form white crystals, m.p. 319–321°.

Anal. Calcd. for $C_{11}H_9N_3O_2S$: N, 17.0; S, 13.0. Found: N, 17.2; S, 13.0.

Thiazolo[4,5-d]pyrimidine-5,7-diol.—A solution of 1.8 g. of bromine in 28 ml. of water containing 3.6 g. of potassium hydroxide was prepared at 0° and added to 2 g. of thiazole-4,5-dicarboxamide. The mixture was stirred for three hours at 0°, additional hypobromite solution being added at intervals until the diamide dissolved. The solution was allowed to stand overnight in the refrigerator, filtered from a small amount of unreacted diamide and heated 20 minutes at 80°. The compound after precipitation with acetic acid, filtration and washing with water weighed 1.3 g. and did not melt below 360°.[4] The compound was redissolved in dilute ammonia, treated with Norite, and reprecipitated with dilute hydrochloric acid; a slight yellow color persisted.

Anal. Calcd. for $C_5H_3N_3O_2S$: N, 24.8; S, 18.9. Found: N, 24.9; S, 19.0.

One and one-half grams of this substance was heated with 30 g. of phosphorus pentachloride for 12 hours at 200°, added to 200 g. of crushed ice, and the solid filtered. After sublimation *in vacuo*, the product weighed 0.2 g. (m.p. 155–165°). The acidic filtrate was made slightly alkaline (ammonia) giving 0.8 g. of light yellow needles melting from 165–168°. Sublimation *in vacuo* gave 0.7 g. of white crystals melting at 170–171.5° and having a nitrogen content consistent with formulation as **6-amino-2,4,5-trichloropyrimidine**.

Anal. Calcd. for $C_4H_2N_3Cl_3$: N, 21.2. Found: N, 21.1.

A mixture of 0.7 g. of this pyrimidine and 10 ml. of concentrated ammonium hydroxide was heated overnight at 100°, chilled and filtered. The solid was leached with a small amount of hot 95% alcohol and the residue crystallized from 95% alcohol to give a small amount of a white crystalline product whose melting point, 299–300°, was not depressed when mixed with **4,6-diamino-2,5-dichloropyrimidine**.[8] The alcohol-soluble portion was recovered by evaporation and crystallized from water to give 0.3 g. of material melting at 197–199° and showing no depression when mixed with **2,4,6-triamino-5-chloropyrimidine**.[8]

(10) E. H. Huntress and K. Pfister, THIS JOURNAL, **65**, 2167 (1943).

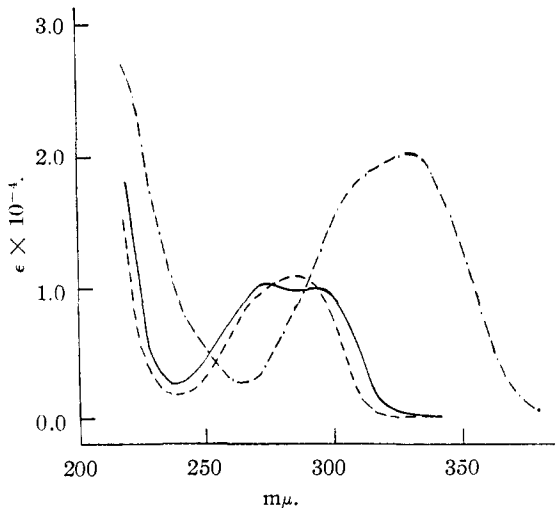

Fig. 2.—Absorption spectra in 0.001 molar sodium sodium hydroxide: - - - - - -, thiazolo[5,4-d]pyrimidine-5,7-diol; ——, 2-methylthiazolo[5,4-d]pyrimidine-5,7-diol; - - · - - ·, 2-phenylthiazolo[5,4-d]pyrimidine-5,7-diol.

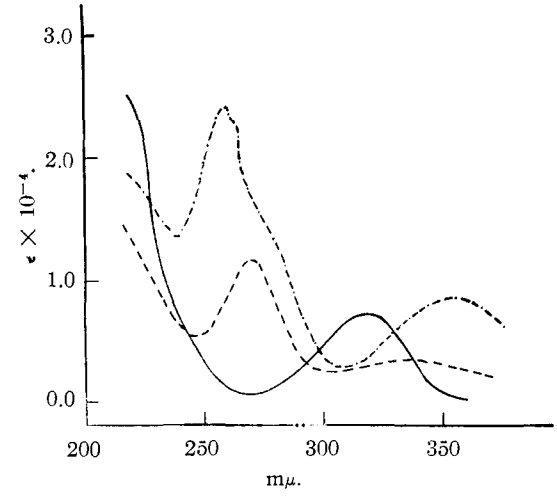

Fig. 3.—Ultraviolet absorption spectra in 0.001 molar sodium hydroxide: - - - - -, thiazolo[4,5-d]pyrimidine-5,7-diol; ——, 2-methylthiazolo[4,5-d]pyrimidine-5,7-diol; - - · - - ·, 2-phenylthiazolo[4,5-d]pyrimidine-5,7-diol.

2-Methylthiazolo[4,5-d]pyrimidine-5,7-diol.—Two grams of 2-methylthiazole-4,5-dicarboxamide when similarly treated with hypobromite gave rise to 1.7 g. of product retaining a very pale yellow color and which did not melt below 360°.[4]

Anal. Calcd. for $C_6H_5N_3O_2S$: N, 23.0; S, 17.5. Found: N, 23.0; S, 17.4.

2-Phenylthiazolo[4,5-d]pyrimidine-5,7-diol.—When 1.8 g. of 2-phenylthiazole-4,5-dicarboxamide was treated with as much as 56 ml. of potassium hypobromite, it did not completely dissolve and the yield of crude product was only 0.5 g. of material melting at about 325°. A portion crystallized from 50% acetic acid appeared as light cream crystals melting at 331–332°.[4]

Anal. Calcd. for $C_{11}H_7N_3O_2S$: N, 17.1; S, 13.1. Found: N, 17.1; S, 13.1.

2-Methylthiazolo[4,5-d]pyridazine-4,7-diol.—When 1 g. of crude diethyl 2-methylthiazole-4,5-dicarboxylate[7] and 5 ml. of 85% hydrazine hydrate were allowed to react for one hour in 10 ml. of alcohol at room temperature, a product was

obtained which melted at 187° after crystallization from alcohol. The analysis indicated that this was the **di-hydrazide.**

Anal. Calcd. for $C_5H_9N_5O_2S$: N, 32.6; S, 14.9. Found: N, 32.4; S, 14.8.

Seven grams of the above thiazole diester was dissolved in 50 ml. of ethanol, 5.3 g. of 85% hydrazine hydrate added and the mixture heated for 48 hours at 100° and, inadvertently, one-half hour at 140°. The solid product was filtered and washed with 50% acetic acid and with water leaving 2 g. of material melting from 352–355° (dec.). A portion was crystallized from glacial acetic acid and from water to give a pale yellow powder which darkened slightly above 300° and melted at 355° with decomposition.

Anal. Calcd. for $C_6H_5N_3O_2S$: N, 23.0; S, 17.5. Found: N, 23.1; S, 17.4.

2-(β-Styryl)-thiazolo[5,4-d]pyrimidine-5,7-diol was prepared by refluxing 0.7 g. of 2-methylthiazolo[5,4-d]pyrimidine-5,7-diol in 10 g. of benzaldehyde containing 1 g. of zinc chloride. After crystallization twice from 90% acetic acid, the product weighed 0.3 g., was cream colored, and did not melt below 360°.

Anal. Calcd. for $C_{13}H_9N_3O_2S$: N, 15.5; S, 11.8. Found: N, 15.4; S, 11.8.

2-(β-Styryl)-thiazolo[4,5-d]pyrimidine-5,7-diol was prepared similarly, 0.7 g. of 2-methylthiazolo[4,5-d]pyrimidine-5,7-diol yielding 0.3 g. of the recrystallized product, a yellow powder which melted at 329–331° with decomposition.

Anal. Calcd. for $C_{13}H_9N_3O_2S$: N, 15.5; S, 11.8. Found: N, 15.5; S, 11.9.

Acknowledgment.—We wish to thank Merck and Company, Elkton, Virginia, for a generous gift of thioformamide. We also wish to express our sincere appreciation to Dr. H. Erlenmeyer who most graciously undertook a reinvestigation of the reactions between bromobarbituric acid and certain thioamides.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Derivatives of Sulfenic Acids. VI. The Synthesis of α-Nitro Sulfides

BY NORMAN KHARASCH AND JAMES LORNE CAMERON[1]

The reaction of sulfenyl halides with the sodium salts of nitroalkanes leads to the heretofore unreported α-nitro sulfides. A series of the new products has been prepared and evidence is given to substantiate their structures.

This paper reports the preparation of a series of α-nitro sulfides by the interaction of sulfenyl chlorides, bromides or thiocyanates with the sodium salts of nitroalkanes. The new products obtained are listed in Table I.

Whereas the sulfenyl halides fail to react with nitroalkanes, the sodium salts react smoothly. The reaction presumably involves a nucleophilic attack on sulfur by the nitroalkane anion.

$$ArSX + [RR'CNO_2]^- + Na^+ \longrightarrow ArSC(R)(R')-NO_2 + Na^+ + X^-$$

I

Absolute ether or benzene serve as suitable solvent for the preparations.

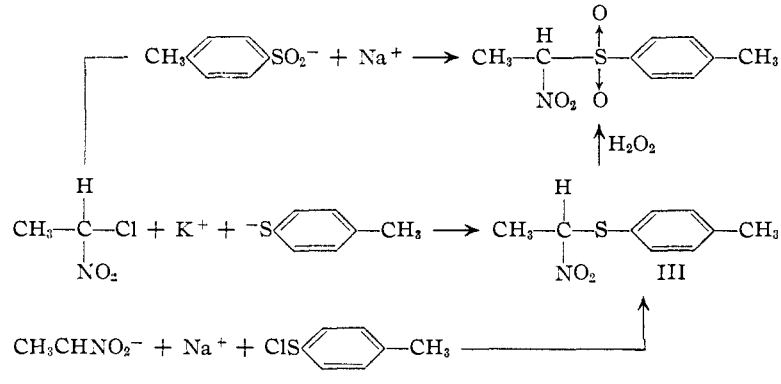
Consideration of the mode of synthesis, elementary analyses, and—in one instance—the molecular weight suggests that the products listed in Table I have either structure I or II.

$$ArS-O-N=CR'$$

II

The following observations, however, strongly favor the α-nitro sulfide structures. (1) Those products which we have designated as having the formula $ArSCHR(NO_2)$ are acidic. They dissolve in 10% aqueous alkali, and acidification of the solutions with aqueous acetic acid regenerates the original compounds. Isomeric substances corresponding to structure II would not be expected to behave in this manner.

(2) As shown below, α-nitroethyl *p*-tolyl sulfone (IV) was obtained in three alternative ways: In 70% yield by oxidation of the product resulting from the reaction of *p*-toluenesulfenyl chloride and the sodium salt of nitroethane. (2) In 71% yield



via sodium *p*-toluenesulfinate and 1-chloro-1-nitroethane and (3) in 15% over-all yield by oxidation of the mixture obtained by reaction of 1-chloro-1-nitroethane and the potassium salt of *p*-thiocresol.[2] Similarly, the product obtained from *o*-nitrobenzenesulfenyl halides and the sodium salt of 1-nitropropane was also oxidized to a new compound whose analysis corresponds to that of *o*-nitrophenyl 1-nitropropyl sulfone. Such sulfones would not be expected by oxidation of compounds of type II.

(3) On the basis of the well-known properties of

(1) Commercial Solvents Predoctoral Fellow, 1950–1951.

(2) N. Melnikov [*J. Gen. Chem.* (*U. S. S. R.*), **7**, 1546 (1937); *C. A.*, **31**, 8504 (1937)] reported reactions of 1-halo-1-nitroalkanes with certain thiophenols, including "thiocresol," but did not isolate α-nitro sulfides under the conditions he employed. Mention is made in his work of the α-nitro sulfides as unstable intermediates.