[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

A Novel Sulfidation Reaction and its Application to Some 4-Substituted-2-aminothiazoles

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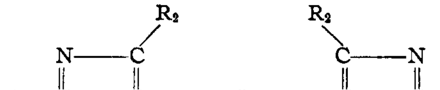
While preparing 2-amino-4-methylthiazole from acetone, iodine and thiourea, by the procedure developed by Dodson and King,[1] we noticed that a small amount of crystalline sludge was thrown out with the thiazole at the point when the reaction mixture was made alkaline with aqueous sodium hydroxide.

Investigation proved this crystalline product to be the bis-[2-amino-4-methyl-5-thiazolyl] sulfide prepared by Gibbs and Robinson.[2] A mixed melting point of our material and some bis-[2-amino-4-methyl-5-thiazolyl] sulfide prepared by the "second method" of Gibbs and Robinson from 2-amino-4-methyl-5-bromothiazole and alcoholic potassium hydrosulfide showed no depression.

We also found that on reducing the normal twelve to eighteen hours reaction time of the Dodson and King aminothiazole preparation to one hour, the yield of the bis-sulfide compound was greatly increased. This led us to the discovery of a novel, very rapid procedure for the preparation of certain organic sulfides.

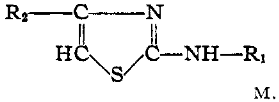
TABLE I



2-R_1	-4-R_2-	bis-[-5-Thiazolyl] sulfides	M. p. (cor.), °C.	Empirical formula	Sulfur, % Calcd.	Sulfur, % Found	Yield, %
H-	CH_3-	2-Amino-4-methyl	190.8-191.2	$C_8H_{10}N_4S_3$	37.25	37.35	70.9
CH_3CO-	C_6H_5-	2-Acetamido-4-phenyl	243-244 dec.	$C_{22}H_{18}O_2N_4S_3$	20.63	20.85	[a]
H-	$CH_3CHCOOC_2H_5$-	2-Amino-4-(α-carbethoxyethyl)	221-222	$C_{16}H_{22}O_4N_4S_3$	22.37	22.22	30.0
H-	C_2H_5-	2-Amino-4-ethyl	178.3-179.8	$C_{10}H_{14}N_4S_3$	33.55	33.35	32.3
H-	$C_2H_5CHCOOC_2H_5$-	2-Amino-4-(α-carbethoxypropyl)	226.5-228	$C_{18}H_{26}O_4N_4S_3$	21.00	21.10	[a]
CH_3CO-	C_3H_7-	2-Acetamido-4-propyl	271.5-272.5 dec.	$C_{16}H_{22}O_2N_4S_3$	24.13	24.25	57.1

[a] See experimental section.

TABLE II



2-R_1	4-R_2	Thiazole	M. p., (cor.), °C.	Empirical formula	Sulfur, % Calcd.	Sulfur, % Found	Yield, %
H-	$CH_3CHCOOC_2H_5$	2-Amino-4-(α-carbethoxyethyl)	108.5-110.6	$C_8H_{12}O_2N_2S$	16.02	15.89	30.3
H-	$C_2H_5CHCOOC_2H_5$	2-Amino-4-(α-carbethoxypropyl)	103.4-104.4	$C_9H_{14}O_2N_2S$	14.95	14.92	19.6
CH_3CO-	C_3H_7	2-Acetamido-4-propyl	101.2-101.3	$C_8H_{12}ON_2S$	17.41	17.43	

The procedure essentially consists of dissolving in a water or water–alcohol solution of the organic compound first thiourea and an elemental halogen and then making the mixture alkaline with sodium hydroxide. The entire reaction is practically instantaneous.

During our investigation of the mechanism and applicability of this sulfidation reaction to organic compounds in general, we had occasion to prepare a short series of sulfides by means of iodine from some 4-substituted-2-aminothiazoles. As there has been some recent interest shown in the possibility of these thiazolyl sulfides possessing biological activity,[2] we thought it advisable to report on this phase of our studies at the present time.

The bis-[4-substituted-2-amino-5-thiazolyl] sulfides prepared (Table I) were in general very lustrous, highly crystalline materials. When this was not the case, it was found that the diacetyl derivatives were very crystalline and well characterized.

Three new 4-substituted-2-aminothiazoles prepared during this investigation, which have not heretofore been reported in the literature, are summarized in Table II.

Experimental

bis-[2-Amino-4-methyl-5-thiazolyl] Sulfide.—Five grams of 2-amino-4-methylthiazole[1] and 5.1 g. of thiourea were dissolved in 50 cc. of warm distilled water. Eleven and one-tenth grams of iodine or its equivalent in bromine or chlorine were added in small portions to the warm solution which was gently stirred. A small amount of tar was

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(1) Dodson and King, THIS JOURNAL, **67**, 2242 (1945).

(2) Gibbs and Robinson, *J. Chem. Soc.*, 925-927 (1945).

filtered off. To the clear, reddish, filtrate was added solid sodium hydroxide until the solution was just neutral to litmus. The bis-[2-amino-4-methyl-5-thiazolyl] sulfide immediately separated in voluminous, pale yellow curds. After three recrystallizations from aqueous alcohol the product was snow white.

bis-[2-Acetamido-4-phenyl-5-thiazolyl] Sulfide.—Three and six-tenths grams of 2-amino-4-phenylthiazole,[1] 7.6 g. of iodine and 1.52 g. of thiourea were dissolved in 50 cc. of warm distilled water. The solution was then made alkaline with solid sodium hydroxide. A brownish-black granular tar separated out and settled to the bottom. The supernatant liquor was poured off and the tar was quickly washed with water. As various attempts, on small portions of this material, to separate the crystalline and amorphous portions were unsuccessful, the tar was brought to a boil in acetic anhydride, from which, after standing overnight, the bis-[2-acetamido-4-phenyl-5-thiazolyl] sulfide was obtained as a voluminous deposit of golden-yellow, fibrous crystals. The product was recrystallized from acetic anhydride.

2-Amino-4-(α-carbethoxyethyl)-thiazole.—Forty-seven and four-tenths grams of thiourea were dissolved in 500 cc. of distilled water, to this was added 139 g. of ethyl γ-bromomethylacetoacetate.[3] The mixture was vigorously shaken for about fifteen minutes when the organic layer suddenly solidified. The reaction mixture was then allowed to stand forty-five minutes, after which the solid matter was filtered off. The cake was dissolved in 125 cc. of hot alcohol and allowed to crystallize overnight. After three recrystallizations from alcohol, the product was snow white.

bis-[2-Amino-4-(α-carbethoxyethyl)-5-thiazolyl] Sulfide.—Five grams of 2-amino-4-(α-carbethoxyethyl)-thiazole, 1.15 g. of thiourea and 3.82 g. of iodine were gently warmed with 25 cc. of distilled water. A black liquid collected on the bottom of the flask. The mixture was made alkaline with sodium hydroxide, whereupon the black liquid solidified and was filtered off. On standing three days, more solid material was thrown out of the filtrate. All solid fractions were combined and recrystallized three times from hot alcohol. The product was obtained in the form of pale yellow needles.

2-Acetamido-4-ethylthiazole.—The 2-amino-4-(α-carbethoxyethyl)-thiazole was hydrolyzed to the corresponding carboxylic acid and then decarboxylated[4] in one step by evaporating to dryness a solution of the thiazole in a large excess of hydrochloric acid and then heating the crystalline residue to 150–160° until it had a melting point approximating that of the hydrochloride of 2-amino-4-ethylthiazole (*i. e.*, 185.5–187.5°[5]). The brownish crystalline residue was then dissolved in water and ammonia added to the neutral point. This threw the 2-amino-4-ethylthiazole out of solution as a dark oil which was taken up in ether. The dark, oily product remaining after evaporation of the ether was used without further purification in the preparation of the corresponding bis-[5-thiazolyl] sulfide.

A small portion was converted to its monoacetyl derivative by boiling with acetic anhydride. The crystalline residue remaining, after removal of excess acetic anhydride by evaporation under vacuum, was recrystallized from hot dilute ammonium hydroxide solution. The 2-acetamido-4-ethylthiazole was obtained as a mush of fine, white needles, m. p. 116.9–118.9° (cor.). Bergeim, Coy and Lott[5] have recorded a melting point of 117.5° for this compound.

Anal. Calcd. $C_7H_{10}ON_2S$: S, 18.83. Found: S, 18.90.

bis-[2-Amino-4-ethyl-5-thiazolyl] Sulfide.—This was prepared from 2-amino-4-ethylthiazole in the same manner as the methyl compound. It was recrystallized from a mixture of 1 part alcohol to 3 parts water and was a light tan crystalline powder.

2-Amino-4-(α-carbethoxypropyl)-thiazole.—This was prepared from ethyl ethylacetoacetate *via* the γ-bromo compound in the same manner as the -ethyl compound. It was easily purified by recrystallization from a large amount of hot alcohol.

bis-[2-Amino-4-(α-carbethoxypropyl)-5-thiazolyl] Sulfide.—This was prepared in a manner similar to that employed in preparing the corresponding ethyl compound. The product was contaminated with a large amount of an orange-red amorphous material from which a small portion was obtained as a light tan, micro-crystalline powder.

2-Acetamido-4-propylthiazole.—It was prepared like the corresponding ethyl compound. After recrystallization from ammoniacal hot water the product was in the form of fluffy, pure white crystals, which, when dry, were highly electrified.

bis-[2-Acetamido-4-propyl-5-thiazolyl] Sulfide.—bis-[2-Amino-4-propyl-5-thiazolyl] sulfide was prepared in the same manner as the ethyl compound, with the exception that the reaction medium was alcohol–water (1:1, by vol.). As the amino compound was obtained as a viscous, intractable oil, it was converted to the diacetyl derivative by boiling with acetic anhydride from which it crystallized in very lustrous, light tan needles.

Summary

1. bis-[2-Amino-4-methyl-5-thiazolyl] sulfide is shown to be a product of the Dodson and King procedure for the preparation of 4-substituted-2-aminothiazoles.

2. A novel reaction for the preparation of certain organic sulfides is reported, which consists essentially of making alkaline a solution containing the organic compound, an elemental halogen and thiourea.

3. The sulfides of some 4-substituted-2-aminothiazoles have been prepared by this reaction.

4. Three new 4-substituted-2-aminothiazoles were prepared and have been characterized.

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[3] Conrad and Kreichgauer, *Ber.*, **29**, 1046 (1896).

[4] Steude, Ann. **261**, 30 (1891); *cf.* also, Ziegler, THIS JOURNAL, **63**, 2946 (1941).

[5] Bergeim, Coy and Lott, *ibid.*, **62**, 1873-1874 (1940).