STUDIES IN THE FIELD OF 2,1,3-THIA- AND -SELENADIAZOLES

LVII. 2,1,3-Thiadiazole-4-carboxylic and -4,5-dicarboxylic Acids*

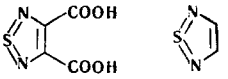
V. G. Pesin, V. A. Sergeev, B. S. Mirkin, and L. P. Mikheeva

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 2, pp. 243–246, 1969

UDC 547.794.3

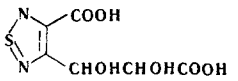
Benzo-2,1,3-thiadiazole and its 4- and 5-methyl and 5,6-dimethyl derivatives are oxidized by chromic anhydride in sulfuric acid to 2,1,3-thiadiazole-4,5-dicarboxylic acid (I) in maximum yield at 80° C. Below or above 80° C, the yield of I falls. At the same temperature, the methyl derivatives are converted into acid I in lower yield than benzo-2,1,3-thiadiazole. When I is heated in nitrobenzene at 160° C, an 80% yield of 2,1,3-thiadiazole-4-carboxylic acid is formed.

2,1,3-Thiadiazole-4,5-dicarboxylic acid (I) is a readily accessible starting material for the synthesis of 2,1,3-thiadiazole (II) and its derivatives [2–10].



I II

The latter includes substances possessing valuable properties, some being biologically active [11–15]. The acid I is a hardener for epoxide resins [11]. It can be obtained by oxidizing benzo-2,1,3-thiadiazole (III) and some of its derivatives with ozone [2], aqueous potassium permanganate [3,5–7], or chromic anhydride in sulfuric acid [4]. Oxidation with potassium permanganate gives a mixture of oxidation products from which compounds IV, V, and VI have been isolated, in addition to the acid I [3,7,8].



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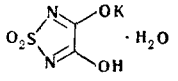
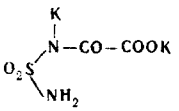


V**



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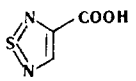

VII

*For part LVI, see [1].

**The structures of compounds V and VI require confirmation.

The composition of the mixture depends on the reaction conditions, the yield of acid I not exceeding 40–50%. Its isolation from the reaction products presents considerable difficulties [3]. It has been shown previously [4] that the acid I can be obtained in 45% yield by the oxidation of III with chromic anhydride in sulfuric acid.

In this work we studied the influence of the temperature of the reaction and of substituents and their positions in compound III on the yield of acid I. Compound III and its 4-methyl, 5-methyl, and 5,6-dimethyl derivatives were subjected to oxidation. It was found that the acid I is formed in highest yield (~77%) at 80° C. When the reaction is carried out above or below 80° C, the yield of I falls. Under similar conditions, the acid I is formed in greatest yield by the oxidation of compound III; the methyl derivatives are converted into I in lower yields. The reaction of compound I with organic bases has given the corresponding salts. 2,1,3-Thiazole-4-carboxylic acid (VII) can be obtained by the decarboxylation of I by heating it in phenetole at 160° C [6,7,15]. We carried out this reaction in nitrobenzene. The acid VII was obtained in 80% yield. The corresponding salts were obtained by the reaction of this acid with a number of organic bases. Thionyl chloride yielded the chloride of acid VII, and this formed with β-phenylisopropylamine an amide which is an analog of phenatine (the β-phenylisopropylamide of nicotinic acid).

EXPERIMENTAL

Oxidation of benzo-2,1,3-thiadiazole and its methyl derivatives (Table 1). A solution of 0.01 mole of a benzothiadiazole in 30 g of sulfuric acid (d 1.84) was added dropwise with stirring to a solution of 8 g of chromic anhydride in 20 ml of water. Then a solution of 8 g of chromic anhydride in 10 ml of water was added to the mixture, and it was stirred for 20 min and poured into an equal volume of water; the mixture was cooled to 20° C and filtered. The filtrate was extracted with ether, the extracts were dried with sodium sulfate and filtered, and the solvent was driven off. The residue formed colorless

Table 1

Yield (in %) of 2,1,3-Thiadiazole-4,5-dicarboxylic Acid in the Oxidation of Benzothiadiazoles

Reaction temperature, °C	From benzo-2,1,3-thiadiazole	From 5-methylbenzo-2,1,3-thiadiazole	From 4-methylbenzo-2,1,3-thiadiazole	From 5,6-dimethylbenzo-2,1,3-thiadiazole
0	35	11.5	10	7.5
20	43	22	22	19
40	47	26	25	24
60	68.5	29	29	28
80	77.5	34.5	33	31
100	74	30	28	20
120	49	18	17	15.5

Table 2

Salts of 2, 1, 3-Thiadiazole-4, 5-dicarboxylic Acid and Organic Bases

Base	Mp, °C	Empirical formula	Found, %		Calculated, %		Yield of salt, %
			N	S	N	S	
N-Methylaniline	124—126	$C_4H_2N_2O_4S \cdot C_7H_9N$	15.68; 15.71	11.26; 11.67	14.95	11.39	90
N,N-Dimethylaniline	185 (decomp.)	$C_2H_2N_2O_4S \cdot C_8H_{11}N$	14.23; 14.77	10.31; 10.64	14.23	10.84	88
Quinoline	210 (decomp.)	$C_4H_2N_2O_4S \cdot C_9H_7N$	14.23; 14.37	10.21; 10.27	13.86	10.56	71
Morpholine	172 (decomp.)	$C_4H_2N_2O_4S \cdot 2CH_4H_9NO$	16.16; 16.52	8.69; 8.89	16.09	9.19	85
α-Picoline	174—175	$C_4H_2N_2O_4S \cdot C_6H_7N$	15.91; 15.91	11.63; 12.01	15.73	11.96	72
β-Picoline	165—167	$C_4H_2N_2O_4S \cdot C_6H_7N$	16.70; 16.82	11.72; 11.88	15.73	11.96	88
γ-Picoline	200 (decomp.)	$C_4H_2N_2O_4S \cdot C_6H_7N$	15.71; 15.95	11.73; 11.84	15.73	11.96	91
o-Anisidine	167 (decomp.)	$C_4H_2N_2O_4S \cdot C_7H_9NO$	14.70; 14.95	10.37; 10.54	14.14	10.77	90
β-Bromopyridine	163 (decomp.)	$C_4H_2N_2O_4S \cdot C_5H_4BrN$	—	10.29	—	9.63	90

or pale green crystals with mp 182° C (decomp.), readily soluble in water and ethanol [4].

Salts of 2, 1, 3-thiadiazole-4, 5-dicarboxylic acid (Table 2). 2, 1, 3-Thiadiazole-4, 5-dicarboxylic acid (I) was dissolved in the minimum volume of ethanol and an equimolar amount of an alcoholic solution of a base was added. The colorless crystals that separated out (sometimes after the addition of ether) were filtered off and washed with ether; an additional small amount of salt could be obtained from the filtrate (after evaporation). All the salts were readily soluble in water and hot ethanol.

2, 1, 3-Thiadiazole-4-carboxylic acid (VII). A mixture of 6 g of I and 20 ml of nitrobenzene was heated at 160° C until dissolution was complete (2 hr). The brown precipitate that deposited after cooling was filtered off, washed with benzene until the smell of nitrobenzene had disappeared, and dried. Yield 3.7 g (80%). Ash-colored crystals, mp 166° C (decomp.). The substance was characterized in the form of salts with various bases (Table 3).

2, 1, 3-Thiadiazole-4-carboxylic acid chloride (VIII). A mixture of 1.95 g (0.015 mole) of VII and 9.9 ml of thionyl chloride was boiled for 3 hr, and the excess of thionyl chloride was driven off to give a substance with mp 44–45° C, after sublimation, mp 49° C. Found, %: S 20.99. Calculated for C_3HClN_2OS, %: S 21.58.

2, 1, 3-Thiadiazole-4-carboxylic acid β-phenylisopropylamide. A solution of 0.6 g of β-phenylisopropylamine in 1.8 ml of benzene was added to a solution of 0.65 g of VIII in 3.3 ml of benzene. After the elimination of the benzene, an oily residue was obtained which solidified on being cooled in an ice bath. Yield 0.52 g (48%). Colorless crystals, mp 73–75° C (from 30% ethanol). Found, %: S 12.85; 13.30; N 17.02; 17.23. Calculated for $C_{12}H_{13}N_3OS$, %: S 12.95; N 17.00.

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9 November 1966

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Table 3

Salts of 2, 1, 3-Thiadiazole-4-carboxylic Acid (VII) and Organic Bases

Base (amount, ml)	VII, g	Mp, °C	Empirical formula	Found, %		Calculated, %		Yield of salt, %
				N	S	N	S	
Aniline (1.85)	1.3	178—179	$C_3H_2N_2O_2S \cdot C_6H_7N$	18.85; 18.87	14.43; 14.50	18.67	14.23	50
N-Methylaniline (0.25)	0.3	79—80	$C_3H_2N_2O_2S \cdot C_7H_9N$	18.01; 18.10	13.10; 13.46	17.72	13.50	98
o-Toluidine (1.0)	0.9	177—179	$C_3H_2N_2O_2S \cdot C_7H_9N$	17.30; 17.53	13.08; 13.50	17.72	13.50	90
m-Toluidine (0.75)	0.7	174—175	$C_3H_2N_2O_2S \cdot C_7H_9N$	17.72; 17.93	13.67; 13.70	17.72	13.50	57
p-Toluidine (0.7 g)	0.7	181—183	$C_3H_2N_2O_2S \cdot C_7H_9N$	17.63; 17.69	13.34; 13.48	17.72	13.50	100
p-Phenetidine (0.3)	0.33	170—172	$C_3H_2N_2O_2S \cdot C_8H_{11}NO$	16.53; 16.74	11.60; 11.92	15.73	11.98	80
p-Anisidine (0.25 g)	0.5	180—182	$C_3H_2N_2O_2S \cdot C_7H_9NO$	16.39; 16.49	12.66; 12.69	16.60	12.65	70
o-Anisidine (0.3)	0.33	120—121	$C_3H_2N_2O_2S \cdot C_7H_9NO$	16.95; 16.97	12.36; 12.42	16.60	12.65	85
β-Phenylisopropylamine (0.7)	0.65	190—191	$C_3H_2N_2O_2S \cdot C_9H_{13}N$	16.02; 16.10	11.64; 11.94	15.73	11.98	83