

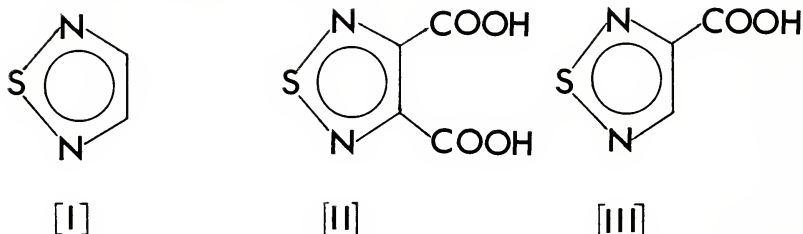
The Chemistry of 1,2,5-Thiadiazoles. I. The Parent Compound¹

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Abstract

1,2,5-Thiadiazole was synthesized for the first time in our laboratory by the stepwise thermal decarboxylation of 1,2,5-thiadiazole-3,4-dicarboxylic acid. At 160-180° Centigrade the first carboxyl is lost as carbon dioxide, and at temperatures above 200° Centigrade the second carboxyl is lost. Mono- and di-deuterio derivatives have also been prepared. Several convenient procedures for the preparation of the two key intermediates, 1,2,5-thiadiazole-3,4-dicarboxylic acid and 1,2,5-thiadiazole-3-carboxylic acid, are described. The mechanism of the oxidation of 2,1,3-benzothiadiazole has been investigated, and the structures of several minor oxidation products have been elucidated. A comparison of the physical properties of 1,2,5-thiadiazole is made with the three other known isomers: 1,2,3-, 1,2,4-, and 1,3,4-thiadiazole.

1,2,5-Thiadiazole [I] is a colorless, stable liquid boiling at 94.1°C, first prepared in our laboratory (14), by the stepwise thermal decarboxylation of 1,2,5-thiadiazole-3,4-dicarboxylic acid [II] through the monocarboxylic acid [III]. It is the purpose of this paper to describe two alternative synthetic routes to the key derivatives [II] and [III] which were developed in our laboratory (5, 10, 14, 15) and to compare several of the physical and chemical properties of 1,2,5-thiadiazole with those of the other three possible, known thiadiazoles, *viz.*: 1,2,3- [IV], 1,2,4- [V], and 1,3,4- [VI] (12).



The most direct entry into the chemistry of mono-cyclic 1,2,5-thiadiazoles was achieved by reaction of α,α' -diaminomaleonitrile ([VII], also known as "hydrogen cyanide tetramer") with thionyl chloride, a

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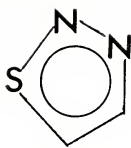
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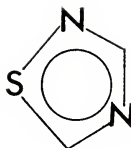
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[IV]



[V]



[VI]

reaction which directly yields 1,2,5-thiadiazole-3,4-dicarbonitrile [VIII] in good yield. Alkaline hydrolysis of the dinitrile yields the carboxylic acid [II], which loses one carboxyl group smoothly at 160-180°C to produce the monocarboxylic acid, [III]. The decarboxylation reaction was conveniently carried out in a high-boiling ether such as phenetole. The two acids, [II] and [III], proved to be very convenient intermediates and were converted by us into numerous other mono- and difunctional derivatives of 1,2,5-thiadiazole.

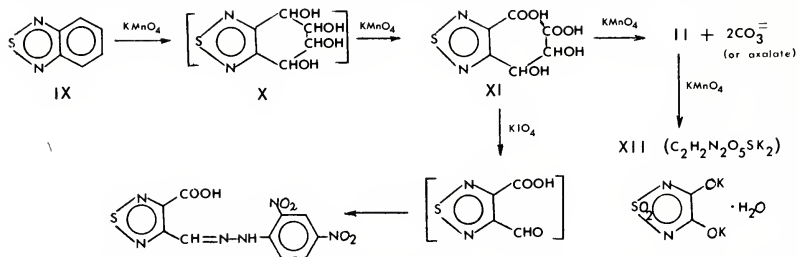
The decarboxylation of [III] occurs at temperatures above 200°C, and was carried out alternatively in a sealed tube without solvent or in a high-boiling solvent from which the 1,2,5-thiadiazole could be distilled at atmospheric pressure.

If the dicarboxylic acid [II] is equilibrated with deuterium oxide several times, the acidic hydrogens are both replaced with deuterium, and the subsequent decarboxylation of this deuterium-substituted acid yields the 2,4-dideuterio-1,2,5-thiadiazole. Similarly, replacement of the one acidic hydrogen of [III] with deuterium in D₂O yields the mono-deuterio-[III], which decarboxylates to give [I] containing principally 3-deuterio-1,2,5-thiadiazole, with small amounts of dideuterio- and unsubstituted [I]. The deuterium-labeled compounds proved useful in the identification of the fragments observed in mass spectra (12), and were also made available for studies of infrared vibrational analysis (11).

The oxidation of the long-known 2,1,3-benzothiadiazole (3, 6) with aqueous potassium permanganate was very thoroughly investigated and eventually developed into a procedure which produced good yields of dicarboxylic acid, [II]. At first, we assumed that such an oxidation would proceed most smoothly if the benzenoid ring were substituted with electron-donating groups such as hydroxy or alkoxy which would be expected to make attack on the carbocyclic ring much easier than on the heterocyclic portion. Not only were such substituted benzothiadiazoles difficult to synthesize, but the fundamental underlying assumption was called into question when we found that we could achieve a rather clean oxidation of 4-nitro-2,1,3-benzothiadiazole by means of aqueous potassium permanganate at 65-70°C. The isolation and purification of the principal product [II] was first accomplished by means of its mono-silver salt. The experience with the nitro derivative was transferred to the oxidation of 2,1,3-benzothiadiazole, which yielded two important minor products in addition to the major

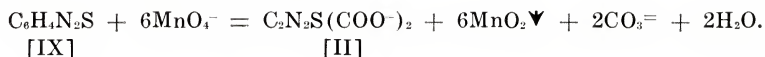
acid, [II]. Careful fractionation of the silver salts of acidic products yielded not only the nitric acid insoluble silver salt of [II] but also a more soluble silver salt of a dicarboxylic acid containing *all* of the carbon atoms of the starting compound.

Our interpretation of the oxidation procedure is shown in the sequence of compounds, [IX] $\rightarrow$ [X] $\rightarrow$ [XI] $\rightarrow$ [II], below. Our extensive studies of the 1,2,1-thiadiazole ring system later revealed that



it is a very powerful electron-attracting nucleus, which is capable of strongly modifying the π -electron system of the benzene half of benzothiadiazole and making it more susceptible to oxidizing attack. If the carboxylic portion tends to behave more like an alicyclic diene than a benzene ring, then the postulation of a hydroxylated intermediate of permanganate oxidation [X] seems reasonable. It would be expected to cleave to a dihydroxydicarboxylic acid; the Acid [XI] was in fact isolated in small yield and characterized. It would be expected to cleave further with loss of two carbon atoms as either oxalate or carbonate (both were identified in the oxidation reaction mixtures) to yield the principal acidic product [II].

The overall stoichiometry of the main desired reaction is represented by the following equation:



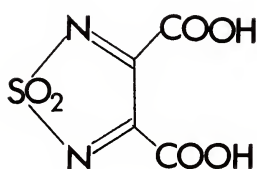
It appeared to be advantageous to use no more than the indicated six formula weights of permanganate for each mole of benzothiadiazole and to avoid both extremes of excess base and temperature. Typically, the oxidation was carried out at 40°C and oxidant was added by portions.

In addition to the products [II] and [XI], small and variable yields of another oxidation product [XII] were isolated as a dipotassium salt of low water-solubility. It was shown that this product could be produced as the major oxidation product when the oxidation of either [IX] or [II] was carried out at 80-100°C.

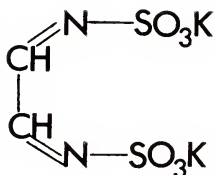
The structure of the oxidation product [XII] was determined from its elemental analysis, C₂N₂O₅SK₂·H₂O (water of crystallization was shown), the infrared spectra, the conversion into several heterocyclic sulfone derivatives (which will be the subject of separate publica-

tions), and finally by direct synthesis from sulfamide and dimethyl or diethyl oxalate by means of basic catalysts (13, 15). The oxidation of 1,2,5-thiadiazole derivatives to the well-defined crystalline dipotassium salt [XII] has proved to be a good general structure proof for the presence of the 1,2,5-thiadiazole nucleus in reactions where the product was not predictable with certainty (7, 8).

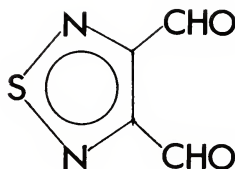
Russian workers have also examined the oxidation of benzo-thiadiazole and reported results somewhat different from ours. Khaletskii, Pesin, and Tsin Chou (4) reported that permanganate oxidation yielded [XIII] and [XIV]:



[XIII]



[XIV]



[XV]

Ozonolysis of [IX] yielded 1,2,5-thiadiazole-3,4-dicarbal [XV] and a small yield of [II]. We have never observed a product resembling [XIII] in any oxidation with permanganate. It seems very likely that their compound represented by Formula [XIV] was in reality the same as our by-product salt which we proved to have the structure [XII]. Sekikawa (9) has reported the oxidation of 5-methyl-1,2,5-thiadiazole to the acid [II] and the conversion of [II] into [III].

In Table I, some of the physical properties of the four isomeric thiadiazoles are compared (12). It will be noted that, while all of the four isomers appear to show aromatic character, they differ sharply in many respects, and should provide an excellent family of compounds for the correlation of physical and chemical properties with calculations based upon orbital theory (16, 17).

TABLE 1. *Some properties of the four isometric thiadiazoles (12 and references cited).*

Compound	Mp	Bp	Odor	Dipole Moment	Ultraviolet (water) nm	max log
1,2,5-Thiadiazole (I)	—50°	94.1°	pyridine-acetone	1.56D	254	3.90
1,2,3-Thiadiazole (IV)	—19°	157°	unpleasant		246 209	3.19 3.27
1,2,4-Thiadiazole (V)	—35° to —33°	121°	pyrimidine		227	3.73
1,3,4-Thiadiazole (VI)	+42—3°	204—5°	odorless	3.28	210	3.26

In subsequent papers we shall describe synthesis and properties of a considerable number of different derivatives of the 1,2,5-thiadiazole family and make comparisons with their isoelectronic analogues.

Experimental

Synthesis of 1,2,5-Thiadiazole-3,4-dicarboxylic Acid [II](1)

4-Nitro-2,1,3-benzothiadiazole (25.0 g; 0.138 mole) was warmed with 500 ml of water to 60°C, and 131 g of potassium permanganate (0.828 mole) was added in 2600 ml of water during 45 minutes, the temperature being maintained at 65-70°C. Excess permanganate was destroyed with a little ethanol, the manganese dioxide was filtered and washed with 400 ml of water. The filtrate was adjusted to pH 1 with nitric acid, and a solution of 23.5 g of silver nitrate in 50 ml of water was added. The colorless, crystalline mono-silver salt was removed by filtration, washed with 200 ml of water in portions, and dried; yield of product was 30 g, and it darkened without melting at 235-55°C. The free acid was isolated by passing hydrogen sulfide into a suspension of the silver salt in 300 ml of water. The mixture was treated with activated charcoal, filtered, washed with warm water, and the clarified filtrate concentrated to a moist residue, then dried over phosphorus pentoxide. The product (14.3 g) was a *monohydrate*, mp 174-8°C. Recrystallization from glacial acetic acid gave the *anhydrous acid*, mp 184°C.

Analysis. Calculated for $C_6H_2N_2SO_4$: C, 27.59; H, 1.15; N, 16.09; S, 18.49. Found: C, 28.09; H, 1.26; N, 16.19; S, 18.16.

Exposure of the anhydrous acid to ordinary atmospheric moisture caused it to regain one molecule of water of crystallization $[II \cdot H_2O]$:

Analysis. Calculated for $C_6H_4N_2SO_5$: C, 25.00; H, 2.10. Found: C, 25.04; H, 2.08.

The Mono-Silver Salt of 1,2,5-Thiadiazole-3,4-dicarboxylic Acid

The silver salt formed during the isolation in the preceding section could be recrystallized from 1000 parts of hot water as a colorless, crystalline mono-silver salt, which blackened without melting at 235-55°C.

Analysis. Calculated for $C_6HN_2SO_4Ag$: C, 17.11; H, 0.36. Found: C, 17.23; H, 0.53.

The Mono-Potassium Salt of 1,2,5-Thiadiazole-3,4-dicarboxylic Acid

Potassium hydroxide solution was added to an aqueous solution of the dicarboxylic acid [II] until the pH was 3, then an equal portion of acetone was added. The salt which separated was purified by recrystallization from water-acetone, mp 293°C (dec.).

Analysis. Calculated for $C_6HN_2SO_4K$: C, 22.64; H, 0.48; N, 13.20. Found: C, 22.47; H, 0.31; N, 13.21.

The Mono-Ammonium Salt of 1,2,5-Thiadiazole-3,4-dicarboxylic Acid

To an aqueous solution of the dicarboxylic acid, II, was added ammonium hydroxide to pH 3. Some mono-ammonium salt precipitated upon cooling and was collected by filtration; the remainder was precipitated by addition of acetone to the filtrate. Recrystallization from water-acetone yielded the mono-ammonium salt, mp 253-4°C.

Analysis. Calculated for $C_4H_5N_3O_4S$: C, 25.13; H, 2.64; N, 21.99; S, 16.77. Found: C, 25.65; H, 2.67; N, 21.89; S, 16.53.

Methyl 1,2,5-Thiadiazole-3,4-dicarboxylate

A mixture of 40 g of the dicarboxylic acid, II, 40 g of methanol, 8 ml of concentrated sulfuric acid and 126 ml of ethylene dichloride was warmed on the steam bath for 18 hours (Method of Clinton and Laskowski (2)). The organic layer was separated, washed once with 50 ml of 5% sodium bicarbonate, then water, and dried over anhydrous magnesium sulfate. The *dimethyl ester* was recovered as a yellow oil (36 g, 82% yield). It could be purified by distillation, bp 84-5° (0.1 mm).

Analysis. Calculated for $C_6H_8N_2O_4S$: C, 35.64; H, 2.99; S, 15.85. Found: C, 36.01; H, 3.03; S, 15.77.

1,2,5-Thiadiazole-3,4-dicarboxamide

Anhydrous ammonia gas was passed through a solution of the dimethyl ester in methanol and the solution was allowed to stand for several hours. The diamide which separated was filtered and recrystallized from hot water to yield colorless crystals, mp 240°C.

Analysis. Calculated for $C_4H_4N_4O_2S$: C, 27.90; H, 2.34; N, 32.54. Found: C, 27.95; H, 2.34; N, 32.40.

1,2,5-Thiadiazole-3,4-dicarbonitrile [VIII] from the Diamide

1,2,5-Thiadiazole-3,4-dicarboxamide (0.96 g) was heated at reflux temperature with 6 ml of phosphorous oxychloride for approximately 40 minutes, then the mixture was agitated with 250 ml of crushed ice and extracted 3 times with ether. Removal of the ether from the carefully washed and dried extracts yielded crystalline 1,2,5-thiadiazole-3,4-dicarbonitrile [VIII], mp 47-9°C. It was identical in mp, mixture mp, and spectral properties with the product prepared in the following procedure.

1,2,5-Thiadiazole-3,4-dicarbonitrile [VIII] from "HCN Tetramer" [VII]

α,α' -Diaminomaleonitrile [VII], also known as "hydrogen cyanide tetramer" (0.100 g), was heated in a glass reflux apparatus with 10 ml of purified thionyl chloride for 2.5 hours, after which the excess unreacted thionyl chloride was removed under gentle vacuum and the residual product was purified by sublimation at 67°C (0.7 mm). The crystalline sublimate of colorless crystals melted at 48-9°C. It showed no depression of mp when admixed with the product of the preceding synthesis. The compound showed a strong band at 2240 cm^{-1} characteristic of -CN.

Analysis. Calculated for $C_8H_6N_2S$: C, 35.28; N, 41.15; S, 23.57. Found: C, 35.92; N, 41.34; S, 23.16.

The dinitrile was hydrolyzed by heating in alcoholic sodium hydroxide, acidification with nitric acid, conversion of the acid to the silver salt as described in preceding sections, and finally to the mono-ammonium salt of II, identical with that described in the foregoing sections.

Oxidation of 2,1,3-Benzothiadiazole to the Acids, [II] and [XI]

To 10 g of 2,1,3-benzothiadiazole (0.735 mole) dissolved in 300 ml of water containing 4.1 g (0.735 mole) of potassium hydroxide was added, in 5-gram portions, 70 g (0.41 mole) of potassium permanganate. The temperature was kept below 40°C. When permanganate no longer appeared to be reduced, the excess was destroyed with a little alcohol, the manganese dioxide was filtered and washed with 200 ml of hot water. The pH of the filtrate was brought to 1 with 20 ml of concentrated nitric acid in 50 ml of water, and a solution of 14 g of silver nitrate in 50 ml of water was added. The precipitated mono-silver salt (mostly of dicarboxylic acid II) was filtered, washed with water until neutral, and reconverted into free dicarboxylic acid II with hydrogen sulfide in 75 ml of water as described in a foregoing section describing the oxidation of 4-nitro-2,1,3-benzothiadiazole. The yield of dried 1,2,5-thiadiazole-3,4-dicarboxylic acid was 9.0 g (70%).

The filtrate from the mono-silver salt which had been precipitated at pH 1 was adjusted to pH 3 by addition of concentrated ammonium hydroxide, whereupon precipitation of another silver salt began and continued while further ammonium hydroxide was being added. Throughout the precipitation the pH remained at 3 but rose to pH 5 after solid stopped separating. The precipitate was filtered, washed with water, then suspended in 30 ml of water and treated with hydrogen sulfide and Darco. The suspension was filtered by gravity, and the filtrate gently desiccated, yielding a new oxidation product as Acid [XI] crystals, mp 194-5°C (ir in Nujol mull: 3240, 3280, 1720, 1695 cm^{-1}). It titrated as a dibasic acid with pK_a values of 3.04 and 4.44 (neutral equivalent for overall titration, 123). It gave a negative test with 2,4-dinitrophenylhydrazine reagent, but formed a precipitate with ferric chloride solution. The ultraviolet spectrum in water showed λ max 265 nm; $\log \epsilon$ 3.86.

Analysis. Calculated for $C_8H_8N_2O_7S$ (monohydrate): C, 28.57; H, 3.19; N, 11.07; S, 12.71; N.E. 252/2. Found: C, 28.46; H, 3.24; N, 11.26; S, 12.40; N.E., 123.

Oxidation of the Dicarboxylic Acid [XI] with an excess of potassium periodate in water, followed by treatment of the filtered solution with 2,4-dinitrophenylhydrazine in phosphoric acid, yielded orange crystals of a *mono-2,4-nitrophenylhydrazone*, mp 201.5-203°.

Analysis. Calculated for $C_{10}H_8N_4O_8S \cdot H_2O$: C, 33.70; H, 2.26; N, 23.60. Found: C, 33.88; H, 2.27; N, 24.22.

Oxidation of 2,1,3-Benzothiadiazole at 90-100°C

Five grams of [IX] was oxidized with 38 g of potassium permanganate in 150 ml of water during 2 hours on a steam bath, with vigorous stirring throughout. The mixture was filtered and the manganese dioxide cake washed with water. The total filtrate was concentrated to dryness on a steambath, leaving a pinkish residue which was treated with 6 N hydrochloric acid to pH 4, then the pink crystalline solid was filtered, recrystallized from water to yield colorless needles which evolved gas at 185°C and decomposed at 265-75°C. The ir of a potassium bromide mull showed bands at 3510, 3333, 1667, 1642, 1353, 1249, 1228, 1129, 962 and 756 cm⁻¹. The ultraviolet spectrum showed only strong end absorption at short wavelengths, hence no thiadiazole nucleus was present.

Analysis. Calculated for C₂H₂N₂O₅SK₂: C, 9.84; H, 0.83; N, 11.50; K, 31.8. Found: C, 9.96; H, 1.08; N, 13.08; K, 29.2.

The filtrate from the rather insoluble dipotassium salt was adjusted to pH 6 with ammonium hydroxide and from it, after a period of standing in the cold, separate crystals of ammonium oxalate.

A very similar oxidation was carried out except for the utilization of 1,2,5-thiadiazole-3,4-dicarboxylic acid [II] as the substrate and a temperature of 80°C during a 50-minute period of reaction. Some of the starting acid [II] was recovered, and the same dipotassium salt [XII] was formed and isolated as in the preceding section.

Synthesis of the Dipotassium Salt [XII]

A mixture of 1.86 g of sulfamide (duPont), 1.11 g of potassium hydroxide, 40 ml of methanol containing 5 ml of water was heated and a solution of 2.3 g of dimethyl oxalate in 20 ml of methanol was added with stirring, heated for 2 hours, and treated with another 1.11 g of potassium hydroxide in 15 ml of methanol. After 4 hours' heating, the mixture was filtered hot, the precipitate was washed with hot methanol and recrystallized from 5 ml of boiling water. The colorless prisms, C₂H₂N₂O₅SK₂, were identical with the oxidation by-product [XII] isolated from the vigorous permanganate oxidation of [IX] and [II].

Preparation of 1,2,5-Thiadiazole-3-carboxylic Acid [III]

1,2,5-Thiadiazole-3,4-dicarboxylic acid ([II]; 100 mg) was heated in a test-tube suspended in an oil bath at 185°C. Decarboxylation occurred vigorously, and the product sublimed to the upper portions of the tube; the yield was 58 mg (78%), mp 163-4°C. Recrystallization from water did not raise the mp. For larger quantities, better control of decarboxylation was achieved by heating 34 g of the dicarboxylic acid [II] in 200 ml of freshly distilled phenetole at 144-5°C for 24 hours, then cooling in the refrigerator over night. The monocarboxylic acid [III] crystallized and was filtered. Recrystallization from acetone-benzene yielded a product melting at 166-7°C; the yield was 22.8 g (91%).

Analysis. Calculated for $C_3H_2N_2SO_2$: C, 27.68; H, 1.55; N, 21.53; S, 24.64; N.E., 129. Found: C, 27.78; H, 1.58; N, 22.11; S, 24.35; N.E., 132.

1,2,5-Thiadiazole [I]

Three combustion tubes, each containing 3.0 g of 1,2,5-thiadiazole-3,4-dicarboxylic acid [II], were heated at 200°C for 16 hours. The product was taken up in ether, dried over anhydrous magnesium sulfate, and distilled in a good fractionating column. The yield was 2.82 g (63%), bp 94.1°C. A better control of the decarboxylation was maintained by heating the dicarboxylic acid (or, alternatively, the monocarboxylic acid [III]) in diphenyl ether contained in a distillation apparatus. The temperature was raised cautiously first to 150-70°C when [II] was decarboxylated, and a vigorous evolution of carbon dioxide took place from the dicarboxylic acid. After the initial evolution of gas had subsided, the temperature was raised to 245°C, and the second carboxyl was lost as carbon dioxide. 1,2,5-Thiadiazole was distilled from the solution in approximately 70% yield. Traces of incompletely decarboxylated thiadiazolecarboxylic acids were removed from the product by treating it with freshly crushed barium oxide and distilling the volatile product from the oxide in a vacuum line system.

Acknowledgments

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