*Oxidation of 5-Methyl-2, 1, 3-benzothiadiazole with Potassium Permanganate**

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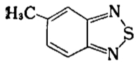
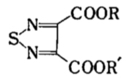
As one of the series of studies on the relation between the antitubercular activity and the molecular structure, 2, 1, 3-benzothiadiazole-5-carboxylic acid was synthesized from 5-methyl-2, 1, 3-benzothiadiazole (I) by conversion via the corresponding 5-bromomethyl- into a formyl-derivative, followed by oxidation with silver oxide.[1]

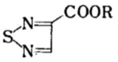
For the purpose of preparing this acid, I was oxidized with potassium permanganate at 60°C but in vain; an acid of different structure (II) was formed.[2] This new acid was finally found to be in its structure a potassium 3-carboxy-1,-2, 5-thiadiazole-4-carboxylate.



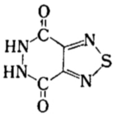
I



II R = H, R′ = K
III R = R′ = C_2H_5
V R = R′ = H



VI R = H
VII R = C_2H_5



X

Product II was an acidic potassium salt, m. p. 278°C decomp., extremely insoluble in organic solvent, with an empirical formula of $C_4HO_4 \cdot N_2SK$ or $C_4H_3O_4N_2SK$ as measured by microanalysis. This salt was recrystallized unchanged from dilute hydrochloric acid and was not hydrogenated over palladium-charcoal at room temperature.

Esterification of product II yielded a colorless diethylester (III), b. p. 140~142°C (10 mmHg). The molecular formula of product III was $C_8H_{10}O_4N_2S$, as measured by microanalysis and molecular weight determination. The diethylester was converted into a diamide (IV), $C_4H_4O_2N_4S$, m. p. 234~235°C decomp., with aqueous ammonia at room temperature. Hydrolysis of the diethylester together with the diamide in boiling aqueous potassium hydroxide, followed by acidification with acetic acid, regenerated product II. From these observations the molecular formula of product II was assumed to be $C_4HO_4N_2SK$. When the diethylester was hydrolyzed with diluted hydrochloric acid, a free diacid (V) was obtained, m. p. 154~155°C, $C_4H_2O_4N_2S \cdot 2H_2O$.

On decarboxylation of diacid V in the presence of quinoline and copper powder, no definite product was obtained, but when heated at 180~190°C in vacuo, the diacid evolved carbon dioxide and was converted into a white mono acid (VI), m. p. 167°C. Acid VI was purified by sublimation, and its molecular formula was formed to be $C_3H_2O_2N_2S$, as measured by microanalysis and molecular weight determination. Mono acid VI formed an ester (VII), b. p. 72°C (6 mmHg) and an acidhydrazide (VIII), m. p. 150~151°C, $C_3H_4 \cdot ON_4S$. This indicates that the partial structure of mono acid VI may be $C_2HN_2S \cdot COOH$. Mono acid VI was not hydrogenated over palladium-charcoal at room temperature, being stable in boiling concentrated hydrochloric acid.

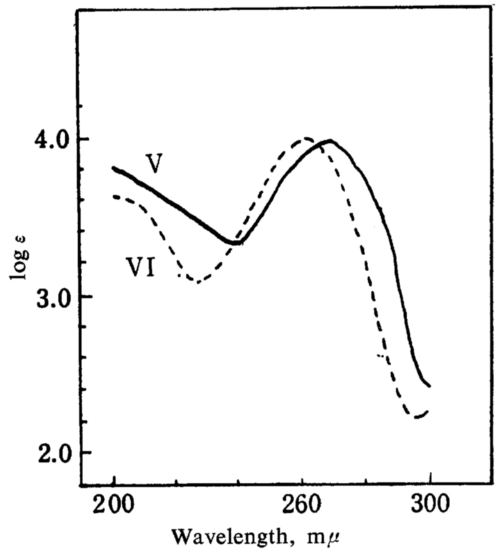


Fig. 1. Ultraviolet spectra of V and VI in water.

The ultraviolet spectrum (Fig. 1) of diacid V showed a pattern identical to that of acid VI. The diethylester of diacid V assigned the structure of product III, since the infrared spectra (Fig. 2) of both products VII and III showed a S–N band at 890 cm^{-1} [3].

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* A part of this study was presented at the Annual Meeting of the Chemical Society of Japan, Kyoto, April 2, 1959.

[1] I. Sekikawa, This Bulletin, 32, 551 (1959).

[2] I. Sekikawa, This Bulletin, 31, 252 (1958).

[3] The seven kinds of 1, 2, 5-thiadiazole compounds, showed a weak absorption band in the region of 900~880 cm^{-1}. D. H. Hadzi, *J. Chem. Soc.*, 1957, 847; T. Momose et al., *Chem. Parm. Bull.*, 7, 734 (1959).

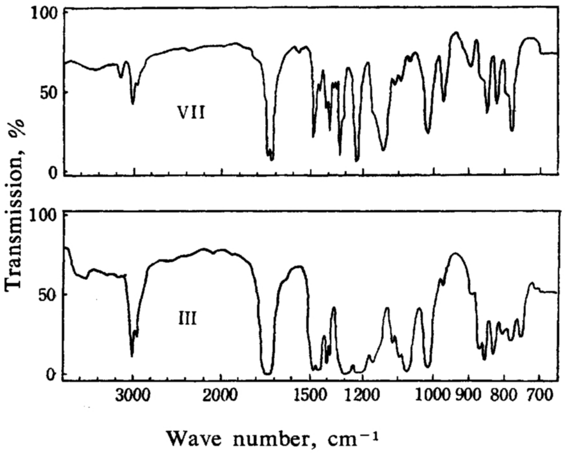

Fig. 2. Infrared spectra of VII and III.

Since the C_2N_2S-skeleton exists in sample I, it is almost certain that the white mono acid VI is 1, 2, 5,-thiadiazole-3-carboxylic acid. The presence of the 1, 2, 5-thiadiazole nucleus has been hitherto unknown.

Treatment of diethylester III with excess hydrazine hydrate in alcohol yielded almost quantitatively an orange-yellow dihydrazide (IX), m. p. 245°C decomp. with sintering from 170°C on, $C_4H_6O_2N_4S$. By hydrolysis with boiling dilute hydrochloric acid for 8 hr., one mole hydrazine was split off, from product IX and facile ring closure occurred, giving yellow 4, 5, 6, 7-tetrahydro-4, 7-dioxopyridazino-(4, 5-d)-2, 1, 3-thiadiazole (X), m. p. 333°C decomp., $C_4H_2O_2N_2S \cdot H_2O$. On the contrary, although one mole hydrazine was likewise split off, alkaline hydrolysis of product IX did not lead to product X, but to another product, which contained no sulfur atom and showed an empirical formula of $C_4H_6O_2N_4$, m. p. 331°C decomp. The determination of the structure of this compound is now in progress.

Recently, A. M. Khalexskiĭ et al. reported that acid V was obtained by ozonolysis of 2, 1, 3-benzothiadiazole and that on the contrary alkaline permanganate oxidation gave a 2, 1, 3-thiadiazole-4, 5-dicarboxylic acid *S*, *S*-dioxide.[4] The oxidation of sample I to product II with potassium permanganate was a reaction similar to the oxidation of quinoline to quinolinic acid.[5]

Experimental[6]

Oxidation of I with Potassium Permanganate.—To a suspension of 10 g. of 5-methyl-2, 1, 3-benzothiadiazole in 200 ml. of water, 53 g. of potassium permanganate dissolved in 1300 ml. of water was added during 8 hr. at 60°C with vigorous stirring. After the last addition, the mixture was heated for 30 min. to complete the oxidation and then unchanged 5-methyl-2, 1, 3-benzothiadiazole was removed by steam distillation. The separated manganese dioxide was removed by filtration and washed with 500 ml. of water. The filtrates were combined, acidified with glacial acetic acid and evaporated to dryness. The residue was recrystallized from water to give 8.0 g. of white needles (II), m. p. 276~277°C (decomp.)[7]. The ultraviolet absorption bands at 270 mμ (log ε=3.94).

Found: C, 22.34; H, 0.94; N, 13.05; K, 18.58.
C, 22.29; H, 0.99; N, 12.76; K, 18.34.
C, 22.32; H, 0.71; N, 13.27.
Calcd. for $C_4HO_4N_2SK$: C, 22.64; H, 0.47; N, 13.20; K, 18.42. $C_4H_3O_4N_2SK$: C, 22.42; H, 1.41; N, 13.08; K, 18.25%.

III.—A mixture of 1.3 g. of II, 100 ml. of absolute ethanol and 1 ml. of concentrated sulfuric acid was refluxed for 24 hr. The separated potassium sulfate was filtered off and the filtrate was concentrated in vacuo. The residue was treated with 100 ml. of water and neutralized with sodium hydrogen carbonate. The mixture was extracted with 50 ml. of ether (twice), and the ether extract was dried and evaporated. The pale yellow oil was then distilled in vacuo, and a fraction boiling at 140~142°C (10 mmHg) was collected. The analytical sample distilled at 133°C (8 mmHg).

Found: C, 41.91; H, 4.61; N, 11.55; mol. wt. 235 (Rast mol. wt. determination).
Calcd. for $C_8H_{10}O_4N_2S$ (230.3): C, 41.74; H, 4.38; N, 12.17%.

IV.—To a solution of 5 g. of III in 50 ml. of ethanol, 10 ml. of aqueous ammonium hydroxide (*d* =0.8) was added. After about 1 hr. a white precipitate separated. After the solution was kept overnight at room temperature, the white crystalline solid was collected by filtration and washed with cold ethanol; yield; 3 g. Recrystallization from ethanol yielded white needles, m. p. 234~235°C (decomp.).

Found: C, 28.21; H, 2.60; N, 32.38.
Calcd. for $C_4H_4O_2N_4S$: C, 27.90; H, 2.34; N, 32.54%.

Hydrolysis of III.—A mixture of 1 g. of III and 25 ml. of 15% hydrochloric acid was heated under reflux for 5 hr. The reaction mixture was filtered to remove a small amount of suspended solid and evaporated under reduced pressure. The residual solid was recrystallized from water to give 0.5 g. of white sandy crystals (V).

It softened at 97°C, melted at 154~155°C with effervescence and was decomposed at 160°C. The ultraviolet absorption bands at 270 mμ (log ε=3.97).

Found: C, 22.71; H, 3.05; H_2O, 16.91.
Calcd. for $C_4H_2O_4N_2S \cdot 2H_2O$; C, 22.86; H, 2.88; H_2O, 17.14%.

Pyrolysis of V.—One gram of V was placed in a sublimation tube and heated for 5 min. at 180~190°C. Under this condition the material rapidly

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[4] A. M. Khalexskiĭ, V. G. Pesin and Tsin Chou, *Doklady Akad. Nauk. S. S. S. R.*, **114**, 811 (1957); *Chem. Abstr.*, **52**, 4605 (1958).

[5] S. Hoogewerff und W. A. van Dorp, *Ber.*, **12**, 747 (1879).

[6] All the melting points are uncorrected.

[7] The m. p. of 281°C (decomp.) was recorded in the previous paper[2].

melted with evolution of carbon dioxide. The tube was then connected to a vacuum-pump and the decarboxylated product was sublimed at 190°C to give 0.5 g. of white crystals (VI), m. p. 164~165°C. The ultraviolet absorption bands at 260 mμ (log ε= 3.98).

Found: C, 27.51; H, 1.42; N, 21.50.

Calcd. for $C_3H_2O_2N_2S$: C, 27.69; H, 1.55; N, 21.53%.

Rast mol. wt. detn. gave value of 135.8, $C_3H_2O_2N_2S$ requires 130.1.

VII and VIII.—The esterification was carried out by gently refluxing for 10 hr. a mixtur of 0.9 g. of VI, 10 ml. of absolute ethanol and 0.5 ml. of concentrated sulfuric acid. After removal of the excess of ethanol, the residue was treated with water and neutralized with sodium hydrogen carbonate. The mixture was extracted with ether (twice), and the ether extract was dried, evaporated, and the residual oil was distilled to give 0.6 g. of ester (VII), b. p. 72°C (6 mmHg).

A mixture of 6.2 g. of VII, 0.2 ml. of hydrazine hydrate (80%), and 2 ml. of ethanol was heated on a water bath for 5 hr. After removing the ethanol, the solidified residue was recrystallized from ethanol, affording 0.1 g. of acid hydrazide (VIII) in the form of white needles. It softened at 140°C and melted at 150~151°C.

Found: C, 25.13; H, 3.00; N, 38.53.

Calcd. for $C_3H_4ON_4S$: C, 24.99; H, 2.80; N, 38.87%.

IX.—To a solution of 4.2 g. of diethylester III in 20 ml. of ethanol, 3.7 ml. of 80% hydrazine hydrate was added. An orange-red solid immediately separated from the reaction mixture, which was set aside overnight at room temperature and then filtered to give 3.6 g. of product. Recrystallization from water yielded yellow needles.

It softened at 150°C, reddened at 180°C and was decomposed at 248°C.

Found: C, 23.57; H, 3.20; N, 41.33.

Calcd. for $C_4H_6O_2N_6S$: C, 23.76; H, 2.99; N, 41.57%.

Hydrolysis of IX with Diluted Hydrochloric Acid.—A mixture of 2 g. of dihydrazide IX, 3 ml. of concentrated hydrochloric acid and 100 ml. of water was heated under reflux for 8 hr. Cooling and filtering yielded 1.3 g. of white crystals, which were recrystallized from water to give light yellow plates. m. p. 333°C (decomp.) (monohydrate). The ultraviolet absorption bands at 265 mμ (log ε=4.20).

Found: C, 25.63; H, 2.35; N, 29.94; H_2O, 9.35.

Calcd. for $C_4H_2O_2N_4S \cdot H_2O$: C, 25.53; H, 2.14; N, 29.78; H_2O, 9.57%.

The filtrate from the above reaction mixture was evaporated to dryness. The residue was recrystallized from water to give white needles, m. p. 198°C (decomp.).

This material was identical with a hydrazine hydrochloride..

Hydrolysis of IV and III with Potassium Hydroxide.—A mixture of 0.5 g. of diamide IV, 0.3 g. of potassium hydroxide and 20 ml. of water was heated for 2 hr., after which time ammonia evolution had ceased. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water, acidified with acetic acid and the precipitated solid was collected by filtration. The product was recrystallized from water to give white needles. m. p. 274°C (decomp.).

Hydrolysis of diethylester III with dilute potassium hydroxide for 1 hr., followed by isolation of the product as described above, afforded I in 60% yield.

The products from diamide and diethylester were shown to be identical with I by a microanalysis and by comparison of infrared spectra.

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