Synthesis of 2-Amino-4-methyl-5-cyanothiazole from Acetonitrile

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For the purpose of obtaining 2-amino-4-methyl-5-aminometylthiazole (VII) which is presumed as the substance to be produced by reduction of 2-(*p*-acetylphenylazo)-4-methyl-5-(*p*-acetylphenylazomethyl)-thiazole (VI) believed(1),(2),(3) to be an azo-color from thiamine as shown in Schema 2, a new thiazole, 2-amino-4-methyl-5-cyanothiazole (V) was synthesized from acetonitrile (I) according to the processes shown in Schema 1,

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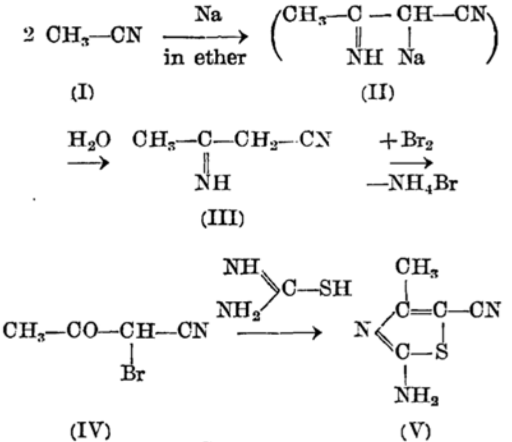
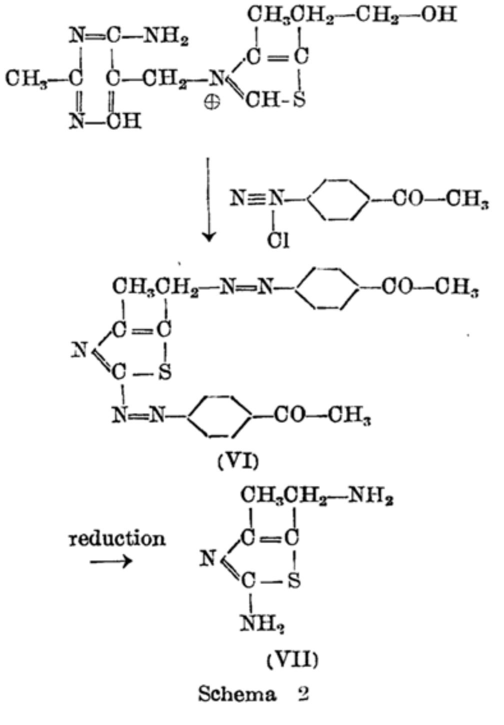
(1) K. Murata, *J. Chem. Soc. Japan*, **64**, 1379 (1943).
(2) K. Murata, *J. Chem. Soc. Japan*, **66**, 57 (1945).
(3) K. Murata, *J. Chem. Soc. Japan*, **66**, 59 (1945).



Schema 1



Schema 2

Catalytic reduction of 2-amino-4-methyl-5-cyanothiazole (V) is being carried on now under several conditions, but it is not yet completed, so the synthesis of this thiazole (V) is reported here.

Experimental

(1) β-Iminobutyronitrile (III).—The preparation of this substance was carried out according to Hortzwart⁽⁴⁾. A three-necked flask of 500 cc. content, equipped with a sealed stirrer, dropping funnel and reflux condenser under the protection of the moisture was used. Metallic sodium (8 g.) in small pieces were put in 300 cc. of absolute ether in the flask, and 25 g. of pure acetonitrile were gradually added with thorough stirring. After all of the metal had dissolved, the flask was warmed for 1 hour at 40° on a water-bath. The precipitates were separated from ether. The crude precipitates (30 g.) presumed as sodio-β-iminobutyronitrile (II) were dissolved in a little water (*ca.* 10 cc.), to which 50 cc. of ether were added and boiled on the water-bath or shaken with ether and water. Then the ether solution was evaporated to one third of its original volume. β-Iminobutyronitrile crystallized from ether after standing for 2 or 3 days in the ice chest. The crude crystals (m. p. 47—65°) (1 g.) were receystallized from benzene at room temperature. The stable form⁽⁴⁾,⁽⁵⁾. (m. p. 47—48°) was obtained as crystals soluble in benzene and the labile form⁽⁶⁾ (m. p. 74—78°) was obtained from the insoluble part, in yields of 0.3 g. and 0.1 g. respectively. When 4 g. of crystals, m. p. 47—80°, were boiled with benzene for 30 min. on the water-bath, the crystals, m. p. 46—60°, was obtained. When this crystal was boiled again in benzene, the crystals, m. p. 47—48°, separated out in a yield of 0.3 g.

Both specimens, m. p. 47—48° and 46—60°, gave the oxime, m. p. 98—100° (Found: C, 49.26; H, 6.45%) and the semicarbazone, m. p. 159—160° (Found: C, 42.97; H, 6.05%) of β-iminobutyronitrile as described in the literature⁽⁷⁾.

(2) α-Bromo-β-ketobutyronitrile (IV).—Nineteen g. of bromine, *i. e.* theoretical amount, were dissolved in 200 cc. of ether and the solution was dropped into 400 cc. of ether solution containing 10 g. of β-iminobutyronitrile (m. p. 47—65° or 50—70°) cooled in an ice bath. The excess of bromine in the ether solution was removed by the treatment with aqueous solution of sodium bisulfite, and the solution was dried with sodium sulfate and evaporated. The resulting oil was separated from ammonium bromide and destilled in vacuum. α-Bromo-β-ketobutyronitrile, b. p. 70—73°/4 mm., was obtained in a yield of about 60% (Found; C, 29.94; H, 2.93%. Calcd. for $C_4H_4ON\,Br$: C, 29.64; H 2.47%.) The ammonium bromide recovered amounted to 70% of the theory.

(3) 2-Amino-4-methyl-5-cyanothiazole (V).—When the theoretical amount of powdered thiourea was mixed with α-bromo-β-ketobutyronitrile in water solution and warmed on the water-bath at 80°, the reaction went on gradually. The whole was allowed to stand overnight, and then dissolved in 10 cc. of water. After removing the unreacted substances by ether, the aqueous solution was fitlered and 2 *N* alkali solution (about 15 cc.) was added to the filtrate until *p*H 6.8. The precipitated substance was collected. The

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(4) A. Holtzwart, *J. prakt. Chem.*, (2) **39**, 230 (1889).

(5) E. Meyer, *J. prakt. Chem.*, (2) **52**, 84 (1895).

(6) E. Meyer, *J. prakt. Chem.*, (2) **52**, 83 (1895).

(7) E. Meyer, *J. prakt. Chem.*, (2) **78**, 504 (1908).

crystallization from water gave 2-amino-4-methyl-5-cyanothiazole, colorless needles, m. p. 164—166°, easily soluble in benzene, alcohol and hot water, 50% yield. (Found: C, 43.40; H 3.95%. Calcd. for $C_5H_5N_3S$: C, 43.17; H 3.53%.)

Summary

A new thiazole, 2-amino-4-methyl-5-cyanothiazole (V) m. p. 164—166° was synthesized from thiourea and α-bromo-β-ketobutyronitrile (IV), b. p. 70—73°/4 mm., prepared by the action of bromine on β-iminobutyronitrile obtained from acetonitrile.

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