Synthesis of 2-Amino-4-methyl-5-aminomethylthiazole

By Kiku MURATA and Hideo IKEHATA

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For the purpose of obtaining 2-amino-4-methyl-5-aminomethylthiazole presumed as the reduction product of azo-color from thiamin, reduction of 2-amino-4-methyl-5-cyanothiazole, the synthesis of which was reported in a previous report⁽¹⁾, was carried out by several different methods. Among them the reduction by Raney-nickel was successful, although the other methods were not good. The results obtained will be reported here.

Experimental

(1) Catalytic Reduction with Palladium Charcoal.—In 30 cc. of acetic and 20 cc. of 20% distilled hydrochloric acid, 1 g. of 2-amino-4-methyl-5-cyanothiazole was dissolved and air in the vessel was replaced by hydrogen gas three times, then 2 g. of palladium charcoal* in acetic acid was added and the mixture was shaken for about 16 hours at room temperature. After absorption of the calculated amount of hydrogen, the solution was separated from the charcoal and condensed in vacuo, and then aqueous sodium carbonate was added to the residue. Orange colored crystal crystallized out from the solution. The crystal was separated from the solvent and recrystallized from hot water. In spite of repeated crystallization, the content of nitrogen in this substance was very low indicating that a loss of ammonia set free from the aminomethyl group produced by the reduction of the cyano group could have taken place. Therefore pure crystal of 2-amino-4-methyl-5-aminomethylthiazole was not obtained.

(2) Attempted Reduction by Electrolysis.—One gram of 2-amino-4-methyl-5-cyanothiazole was dissolved in 150 cc. of 20% distilled hydrochloric acid and placed in the cathode chamber of a large cell. In the anode chamber was placed 50 cc of 20% distilled hydrochloric acid. Electrolysis was carried out at the initial current of one ampere and potential of six volts. The electrolyte was evaporated in vacuo. From the residue unreacted 2-amino-4-methyl-5-cyanothiazole was collected again.

(3) Reduction with Lithium Aluminium Hydride.—To 50 cc. of absolute ether added with 0.9 g. of lithium aluminium hydride, 130 cc. of absolute ether containing 1 g. of 2-amino-4-methyl-5-cyanothiazole were added drop by drop under stirring in an ice bath, and thereafter the stirring was continued for 30 min. more at room temperature. The destruction of the excess of lithium aluminium hydride was accomplished by 30% solution of sodium hydroxide, and the reaction product was extracted with ether three times. The etherial solution was washed with aqueous sodium bicarbonate, dried with sodium sulfate, and was evaporated. From the residue 0.2 g. of orange colored crystal, m. p. 145—162°C. was obtained, and 0.6 g. of oil containing a mineral substance was obtained from the filtrate. By recrystallization of the crystals from methanol and water needles-shaped crystals, m. p. 165—166°C. were obtained. Mixed melting point with the crystals, m. p. 165—166°C. obtained by the reduction with Raney nickel, did not show depression. However the yield was not satisfactory.

(4) Catalytic Reduction with Raney Nickel.—By the method of W. Huber⁽²⁾, 5 g. of 2-amino-4-methyl-5-cyanothiazole was dissolved in 120 cc. of absolute methanol containing 11 g. of ammonia. This solution was poured into an autoclave with a capacity of 500 cc. and 10 g. of Raney nickel was added.

After filling the autoclave with hydrogen gas until it reached 25 atmosphere, it was shaken at 10—15°C. for two hours. Then the methanol solution was separated from Raney nickel and condensed in vacuo at 35—40°C., and thereby 0.8 g. of crystals containing mineral substance as impurity was obtained. Gaseous hydrochloric acid was passed into the filtrate and allowed to stand overnight in an ice chest. The next day, 4.5 g. of colorless crystals, m. p. 120—225°C. (decomp.) was obtained in 60% yield. The crystals were dissolved in methanol, filtered and recrystallized three times from methanol by adding one third its volume of butanol. Colorless crystals of 2-amino-4-methyl-5-aminomethyl-thiazole hydrochloride m. p. 215—225°C. (decomp.) were obtained (Found: C, 27.56, H. 5.46, Calcd. for $C_5H_9N_3S \cdot 2HCl$; C, 27.68, H. 5.13). On addition of aqueous sodium carbonate to an aqueous solution of the hydrochloride, the free thiazole crystallized out, which after recrystallization from methanol and water, gave orange-colored needles, m. p. 165—167°C.

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(1) K. Murata, This Bulletin, **25**, 16 (1952).

* This charcoal contains 5% of palladium chloride.

(2) W. Huber, *J. Am. Chem. Soc.* **66**, 876 (1944).

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Osaka Municipal Institute for Hygiene, Osaka