SYNTHESIS OF DERIVATIVES OF 1, 2, 4-TRIAZOLE-3, 5-DICARBOXYLIC ACID

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 5, pp. 913–915, 1969

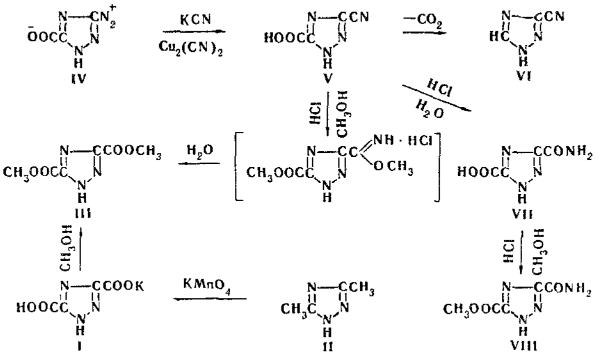
UDC 547:792.6.07:592.938

By oxidation of 3,5-dimethyl-1,2,4-triazole the monopotassium salt of 1,2,4-triazole-3,5-dicarboxylic acid was obtained. The mononitryl of 1,2,4-triazole-3,5-dicarboxylic acid was isolated during the reaction between 3-diazo-1,2,4-triazole-5-carboxylic acid and potassium cyanide in the presence of copper cyanide. Acid hydrolysis of 3-cyano-1,2,4-triazole-5-carboxylic acid leads to the formation of 3-carbamido-5-carboxy-1,2,4-triazole, which on esterification with methanol gives rise to 3-carbamido-5-carbomethoxy-1,2,4-triazole.

The derivatives of 1, 2, 4-triazole-3, 5-dicarboxylic acid may be of interest as physiologically active preparations. Thus a study was made of the formation of certain compounds of this series and their transformations were investigated.

From patented data [1] it is well known that it is possible to obtain 1, 2, 4-triazole-3, 5-dicarboxylic acid in the form of salts from 1, 2, 4-triazole and carbon dioxide. However, in this patent there are no analytical data for salts of 1, 2, 4-triazole-3, 5-dicarboxylic acid.

We obtained 1, 2, 4-triazole-3, 5-dicarboxylic acid in the form of the monopotassium salt on oxidation of 3, 5-dimethyl-1, 2, 4-triazole (II). Esterification of this compound by methyl alcohol led to the formation of 3, 5-dicarbomethoxy-1, 2, 4-triazole (III). However, the ease with which 1, 2, 4-triazole-3, 5-dicarboxylic acid undergoes decarboxylation hinders this reaction. In certain experiments we isolated the methyl ester of triazolomonocarboxylic acid, probably formed as a result of partial decarboxylation.



Derivatives of 1, 2, 4-triazole-3, 5-dicarboxylic acid are obtained from diazotriazolecarboxylic acid (IV) by a different pathway. Exchange of the diazo group for the nitrile group takes place by Zandmeyer's reaction in the presence of cuprous cyanide. The mononitrile of triazoledicarboxylic acid (V) readily underwent decarboxylation with the formation of 3-cyano-1, 2, 4-triazole (VI), which has been described previously [2]. Alkaline hydrolysis of compound V proceeded extremely slowly and led to the formation of a mixture of products the identity of which was impossible to determine. During acid hydrolysis of compound V, 3-carbamido-5-carboxy-1, 2, 4-triazole (VII) was isolated, which did not undergo subsequent hydrolysis even when heated for many hours with hydrochloric acid. By esterification of compound VII with methyl alcohol in the presence of hydrogen chloride, 3-carbamido-5-carbomethoxy-1, 2, 4-triazole (VIII) was obtained. Compound V was converted into the dimethyl ester of 1, 2, 4-triazole-3, 5-dicarboxylic acid (III) through the iminoester [3].

EXPERIMENTAL

3,5-Dimethyl-1,2,4-triazole (II). A solution of 20.7 g (0.3 mole) sodium nitrite in 100 ml water was added at 20–30° C with stirring over the course of 2.5 hr to a solution of 22.4 g (0.2 mole) 3,5-dimethyl-4-amino-1,2,4-triazole in 65 ml of 6 N HCl. The reaction mass was neutralized with sodium carbonate to pH 8 and evaporated to dryness in a water bath. 3,5-Dimethyl-1,2,4-triazole was extracted with ether in a Soxhelt apparatus. The yield was quantitative mp 140–141° C (from benzene) [4].

Monopotassium salt of 1,2,4-triazole-3,5-dicarboxylic acid (I). A 63.2 g (0.4 mole) quantity of potassium permanganate and 250 g of a 1% KOH solution were added to a solution of 9.8 g (0.1 mole) of compound II in 50 ml water. The mixture was stirred at 70° C for 24 hr. The precipitate of manganese dioxide was filtered and washed with warm water. The filtrate and washings were concentrated to 100 ml. The cooled solution was neutralized to pH 6–7 with 25% H_2SO_4 and the resulting precipitate of the salt of compound I was collected. Yield, 16.8 g (85.2%). The compound does not melt up to 350° C. Found, %: C 24.59, 24.20; H 1.38, 1.23; N 21.81, 21.57. Calculated for $C_4H_2N_3O_4K$, %: C 24.61; H 1.04; N 21.53.

3-Cyano-1,2,4-triazole-5-carboxylic acid (V). A 52 g (0.79 mole) quantity of potassium cyanide was added on cooling with water to a suspension of 20 g cuprous chloride in 120 ml water. Onto the resulting solution was sprinkled 3-diazo-1,2,4-triazole-5-carboxylic acid (IV), obtained from 15 g (0.12 mole) of aminotriazolecarboxylic acid [2]. After maintaining the mixture for one hour at 20–25° C a solution of 71 g (30% excess) of ferrous sulfate (heptahydrate) in 200 ml water was added. The precipitate was removed by filtration, washed with water, and added in portions to 300 ml of 30% sulfuric acid. After one hour the solution was filtered and the filtrate was extacted with ether. After evaporation of the ether colourless crystals of the acid of compound V were obtained which were purified by dissolving in ethyl acetate and precipitation with petroleum ether. Yield: 4 g, mp 98–100° C (with decomposition), when the substance solidifies and remelts at 182–183° C. Found, %: C 28.50; H 3.05; N 33.59, 33.80. M 164 (by potentiometric titration). Calculated for $C_4H_2N_4O_2 \cdot 5H_2O$, %: C 29.10; H 3.04; N 33.90. M 165.

3-Cyano-1,2,4-triazole (VI). On melting the acid of compound V and maintaining the fusion at 105–110° C for 5 min the compound undergoes decarboxylation. The cyanotriazole formed crystallized from benzene, mp 187° C [2]. Found, %: C 38.45; H 2.40; N 59.80. M 94 (by potentiometric titration). Calculated for $C_3H_2N_4$, %: C 38.30. H 2.13; N 59.56. M 94.

3-Carbamido-5-carboxy-1,2,4-triazole (VII). A 7 g quantity of the acid of compound V was heated with 70 ml conc HCl for 8 hr at 50–55°

C. The precipitate was washed with water and dried. Yield, 6.5 g (96.5%). The compound does not dissolve in organic solvents, and is extremely sparingly soluble in water. Purification is conducted by dissolving in 10% alkali and precipitating in 10% H_2SO_4, mp 302° C. Found, %: C 31.00; H 2.70; N 35.91. Calculated for $C_4H_4N_4O_2$, %: C 30.80; H 2.56; N 35.90.

3-Carbamido-5-carbomethoxy-1, 2, 4-triazole (VIII). A 2.5 g quantity of compound VII was suspended in 130 ml absolute methanol and dry hydrogen chloride was passed through the suspension for 3 hr at 25–30° C. The mixture was maintained for 4 hr at room temperature, and then filtered and the filtrate was evaporated under vacuum at room temperature, and then filtered and the filtrate was evaporated under vacuum at room temperature. After evaporation of the filtrate the precipitate was washed with water and crystallized from water. Yield, 0.5 g (18.5%), mp 224° C. Found, %: C 35.20; H 3.60; N 33.05. Calculated for $C_5H_6N_4O_3$, %: C 35.30; H 3.53; N 32.95.

Dimethyl ester of 1, 2, 4-triazole-3, 5-dicarboxylic acid (III). A) A 2 g quantity of the acid of compound V was dissolved in 45 ml absolute methanol and at 0° C hydrogen chloride gas was passed for 2 hr. The mixture was then maintained for 48 hr at this temperature. The mixture was poured into water and extracted with ethyl acetate. After evaporation of the ethyl acetate the precipitate was equivalent to 1.5 g (60%), mp 149–150° C (from water). Found, %: C 39.00; H 3.79; N 22.61. Calculated for $C_6H_7N_3O_4$, %: C 38.92; H 3.81; N 22.70.

B) A 6 ml volume of conc H_2SO_4 was added dropwise with cooling to a solution of 6 g of compound I in 150 ml absolute methanol. The mixture was stirred for 2 hr and maintained for 12 hr. A small quantity of colorless precipitate was formed from which by multifold extraction with ethyl acetate and subsequent evaporation 2.5 g (45%) of the ester of compound III was isolated, mp 150–152° C (from water). Found, %: C 39.00; H 3.79; N 22.61. M 186 (by potentiometric titration). Calculated for $C_6H_7N_3O_4$, %: C 38.92; H 3.81; N 22.70. M 185.

A sample of a mixture of the compounds obtained by methods (A) and (B) did not give rise to depression of the melting point.

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18 April 1967

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