Structural Reassignment of the Alleged 6-Hydroxy-1,2,4-triazine-3,5-(*2H*,*4H*)dione

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The reaction of 6-amino-1,2,4-triazine-3,5-(*2H*,*4H*)dione with sodium hydroxide or nitrous acid has been shown to give 5-hydroxy-1,2,4-triazole-3-carboxylic acid instead of 6-hydroxy-1,2,4-triazine-3,5-(*2H*,*4H*)dione as reported in the literature. The triazolecarboxylic acid was also obtained from the aminotriazine and hydrochloric acid.

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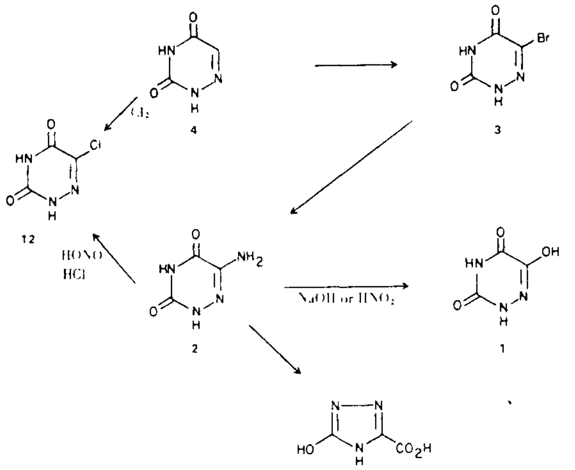
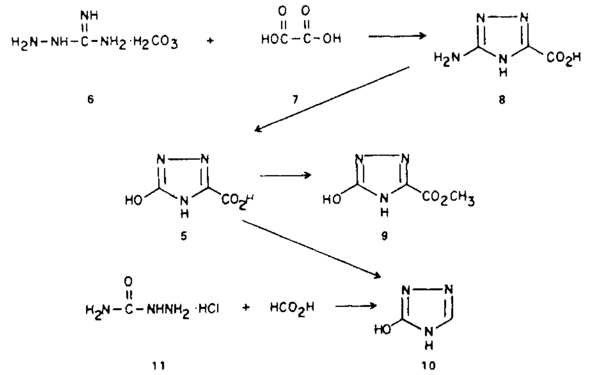
Chang reported the preparation of 6-hydroxy-1,2,4-triazine-3,5-(*2H*,*4H*)dione (**1**, 5-hydroxy-6-azauracil) by the reaction of 6-amino-1,2,4-triazine-3,5-(*2H*,*4H*)dione (**2**) with either sodium hydroxide or nitrous acid (2). The amine **2** was prepared by amination of **3** which was derived from **4** (2).

This work was repeated in our laboratories and it was found that the product of the reaction of **2** and sodium hydroxide was 5-hydroxy-1,2,4-triazole-3-carboxylic acid (**5**) rather than **1**. Acid **5** was previously synthesized in a two-step sequence originating with aminoguanidine bicarbonate (**6**) and oxalic acid (**7**). Reaction of **6** and **7** gave 5-amino-1,2,4-triazole-3-carboxylic acid **8** which upon treatment with nitrous acid afforded **5** (3,4).



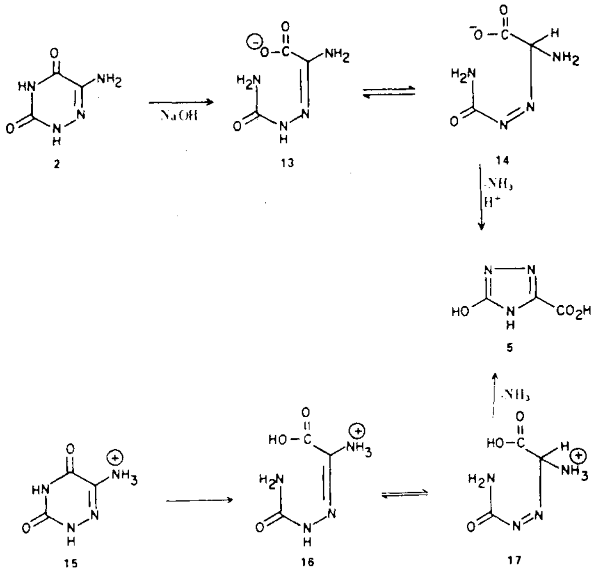


The structure proof of **5** rests upon the following two considerations, both of which prove that the compound contains the carboxyl function: a) esterification of **5** with methanol in sulfuric acid was shown previously to give the methyl ester **9** (5); b) decarboxylation of **5** afforded 3-hydroxy-1,2,4-triazole (**10**) which was prepared unequivocally from semicarbazide hydrochloride (**11**) and formic acid (4).

Although the infrared spectra of authentic **5** (3,4) and the product derived from triazine **2** were identical, the latter product was decarboxylated to **10** to completely validate the triazole carboxylic acid structural assignment.

The possibility that triazine → triazole rearrangement could have occurred during the amination of **3** to **2** is ruled out by the fact that Chang effected the conversion of amine **2** to the chlorotriazine **12** (2). Since compound **12** prepared by this method was identical to that obtained by chlorination of 1,2,4-triazine-3,5-(*2H*,*4H*)dione, the integrity of the triazine ring was maintained in the amination of **3**.

Reaction of **2** with nitrous acid using the procedure of Chang (2) also gave the triazole carboxylic acid **5** instead of **1** as reported. Another non-identifiable product was



also isolated. None of the reported 6-hydroxy-1,2,4-triazine-3,5-(2*H*,4*H*)dione was found.

Finally, to demonstrate the facile conversion of **2** to **5**, this transformation was effected in dilute hydrochloric acid.

The conversion of **2** to **5** in sodium hydroxide is rationalized as follows: reaction of **2** with base results in cleavage at the 4,5-position to give **13** which tautomerizes to **14**. Cyclization of **14** occurs with loss of ammonia.

Likewise, the conversion of **2** to **5** in nitrous acid and dilute hydrochloric acid or in acid alone is envisioned as cleavage of the protonated species **15** at the 4,5-position to the acid **16** which tautomerizes to **17** and ring closes to **5**.

EXPERIMENTAL

Melting points were taken in a Mel-Temp apparatus in open capillary tubes and are uncorrected. Infrared spectra were determined as Nujol mulls on a Perkin-Elmer 137B spectrophotometer.

Reaction of 6-Amino-1,2,4-triazine-3,5-(2*H*,4*H*)dione (**2**) with Sodium Hydroxide.

The amine **2** was prepared by Chang's method (2) and treated with sodium hydroxide as described previously (2).

The product, m.p. 235-237° [literature m.p. 228-230° (2)], was obtained in 32% yield after recrystallization from water: ir: μ 3.05, 3.20 (N-H), 5.80-6.02 (C=O).

Anal. Calcd. for $C_3H_3N_3O_3$: C, 27.91; H, 2.34; N, 32.55. Found: C, 27.99; H, 2.43; N, 32.55.

The infrared spectrum of the product was identical to that of an authentic sample of 5-hydroxy-1,2,4-triazole-3-carboxylic acid (**5**) prepared by the literature method (3,4).

No other isolable products were formed in this reaction.

5-Hydroxy-1,2,4-triazole-3-carboxylic Acid (**5**).

Diazotization of 5-amino-1,2,4-triazole-3-carboxylic acid (**8**) and treatment of the resulting filtered diazonium salt with 25% sulfuric acid by the literature method gave a 42% yield of **5** (3,4): m.p. softens at *ca.* 200°, melt at 235-237°, literature m.p. 205° dec. (4). The melting point of **5** varied with rate of heating. Presumably, the decarboxylation to **10**, m.p. 235-237°, is occurring thus causing these discrepancies.

Methyl 5-Hydroxy-1,2,4-triazole-3-carboxylate (**9**).

This material was prepared by esterification of acid **5** as described previously (5).

Decarboxylation of **5** to 3-Hydroxy-1,2,4-triazole (**10**).

The procedure of Chipen, *et al.* (4), was followed and product **10** was obtained in 29% yield, m.p. 236-237° [literature m.p. 233-234° (4)]; ir: 3.20-3.30 (N-H and O-H), 5.85-6.00 (C=O).

Anal. Calcd. for $C_2H_3N_3O$: C, 28.24; H, 3.55; N, 49.40. Found: C, 28.07; H, 3.56; N, 49.27.

The infrared spectrum of the product **10** was identical to that of an authentic sample of the compound prepared from semicarbazide hydrochloride and formic acid (4).

Decarboxylation of the Product Derived from **2** and Sodium Hydroxide.

A 0.30 g. (0.0023 mole) sample of the product was heated at 235-245° for 25 minutes. The solid was recrystallized from methanol-water (1:1) to give 0.08 g. (40%) of **10**, m.p. 235-237°.

Anal. Calcd. for $C_2H_3N_3O$: C, 28.24; H, 3.55; N, 49.40. Found: C, 28.49; H, 3.66; N, 49.57.

The infrared spectrum of the product was identical to that of an authentic sample of **10** prepared above.

Reaction of 6-Amino-1,2,4-triazine-3,5-(2*H*,4*H*)dione (**2**) with Nitrous Acid by Chang's Method (2).

A mixture of 1.28 g. (0.010 mole) of **2** in 50 ml. of 28% hydrochloric acid was cooled to -10°. A solution of sodium nitrite (0.33 g./ml.) was added until a positive potassium iodide starch test was observed. Only 1.0 ml. of solution was required while on this scale the literature procedure would have used 2.50 ml. The mixture was stirred for 30 minutes and an additional 1.50 ml. of the nitrite solution was added.

The mixture was diluted with 15 ml. of water and heated on a steam bath for 30 minutes. Contrary to the literature report, not all solids dissolved. The mixture was boiled for 5 minutes and refrigerated for 24 hours to give 0.30 g. of a tan unidentified solid.

The filtrate was refrigerated for an additional week and 0.05 g. (4%) of acid **5** was isolated.

Further cooling of the filtrate gave an additional 0.30 g. of the unidentified solid. the infrared spectrum of which was identical to that of the first product. Recrystallization from water gave a sample which melted at 237-240°.

No 6-hydroxy-1,2,4-triazine-3,5-(2*H*,4*H*)dione (**1**) was isolated from the reaction mixture.

Conversion of **2** to **5** in Acid.

A mixture of 0.25 g. (2.0 mmoles) of **2** and 12 ml. of 28% hydrochloric acid was stirred and refluxed for 1.5 hours. The solution was refrigerated for 18 hours and 0.045 g. (17%) of the triazole carboxylic acid **5** separated.

REFERENCES AND NOTES

(1) Taken in part from the thesis presented by T. J. Sanford in partial fulfillment of requirements for the Bachelor of Arts Degree at Hartwick College, Oneonta, New York in May, 1977.

(2) P. K. Chang, *J. Org. Chem.*, 26, 1118 (1960).

(3a) G. Cipens, *Metody Poluch. Khim. Reakt. Prep.*, 14, 9 (1966); *Chem. Abstr.*, 67, 64306v (1967); (b) J. Thiele and W. Manchot, *Ann. Chem.*, 303, 36 (1898).

(4) G. E. Chipen, R. P. Bokalder, and V. Ya. Grinshtein, *Khim. Geterosikl. Soedin.*, 2, 110 (1966).

(5) T. J. Schwan and R. L. White, Jr., *J. Heterocyclic Chem.*, 12, 771 (1975).