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The Preparation of 5-Aminouracil and of Some of its Derivatives

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Requiring considerable quantities of 5-aminouracil in our studies of colored derivatives of uracil, we were led to attempt improvements in the existing methods of its preparation. 5-Aminouracil has generally been prepared by the reduction of 5-nitrouracil,[2] ferrous sulfate and ammonia being recommended for this purpose.

We have found technical sodium hydrosulfite to be a convenient reagent for effecting this reduction not only with 5-nitrouracil but also with its derivatives. 5-Nitrouracil itself may be obtained without previously isolating uracil by nitrating the reaction mixture obtained in the preparation of uracil according to Davidson and Baudisch.[3] In this way a considerable saving of time and of nitric acid is effected.

Sodium hydrosulfite is also useful in reducing the nitroso derivative of 6-aminouracil to 5,6-diaminouracil. In the experimental part is given a rapid modification of Traube's synthesis of this diamine.[4] Hepner and Frenkenberg[5] have also reported the use of sodium hydrosulfite in the reduction of a 5-nitroso-6-aminouracil derivative.

Experimental

Preparation of 5-Nitrouracil.—The hot reaction mixture obtained after heating the uracil reaction mixture for one hour according to Davidson and Baudisch[3] is stirred mechanically while 100 cc. of nitric acid (1.5) is slowly run in from a dropping funnel. The addition of the nitric acid causes a rise in temperature of the reaction mixture, which is allowed to proceed until the temperature reaches 105-110°. The flask may now be surrounded with water while the addition of nitric acid is continued, maintaining the inner temperature between 105-110°. It is important to maintain this temperature; otherwise nitric acid will accumulate in the reaction mixture and the reaction finally proceed with violence. When all the nitric acid has been added, the flask is heated on the steam-bath for one hour. It is then cooled and the contents poured into 1500 g. of ice. 5-Nitrouracil separates and is filtered off, washed with water and air dried; yield, 55-60 g. (47-51%). This product may be used without purification for the preparation of 5-aminouracil.

Preparation of 5-Aminouracil.—To a suspension of 15.7 g. of 5-nitrouracil in a solution of 10 cc. of concentrated ammonia in 250 cc. of water is added while stirring 75 g. of technical sodium hydrosulfite. The solution warms up, reaching 55° in ten to fifteen minutes. The mixture is finally heated to boiling, then cooled and filtered. The crude

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(2) Johnson and Matsuo, THIS JOURNAL, **41**, 782 (1919).

(3) Davidson and Baudisch, *ibid.*, **48**, 2379 (1926); Johnson and Flint, *ibid.*, **53**, 1079 (1931).

(4) Traube, *Ber.*, **33**, 1371 (1900); *Ann.*, **432**, 266 (1923); Conrad, *ibid.*, **340**, 310 (1905); Biltz and Schmidt, *ibid.*, **431**, 94 (1923).

(5) Hepner and Frenkenberg, *Helv. Chim. Acta*, **15**, 350 (1932).

product (10.0 g.) is dissolved in a mixture of 10 cc. of concentrated hydrochloric acid and 100 cc. of water. The solution is clarified with a bit of norite, diluted to 300 cc., heated to boiling, treated with 10 cc. of concentrated ammonia and cooled. 5-Aminouracil is obtained as colorless, silky needles; yield, 9.2 g. (73%).

Anal. Calcd. for $C_4H_5O_2N_3$: C, 37.8; H, 3.9. Found: C, 37.7; H, 3.9.

Preparation of Derivatives of 5-Aminouracil.—When the procedure given above is applied to 5-nitro-6-methyluracil[6] and to 5-nitrouracil-6-potassium carboxylate[7] similar results are obtained.

Preparation of 5,6-Diaminouracil.—To a solution of 4.6 g. of sodium in 75 cc. of absolute alcohol is added 6 g. of powdered urea and 11.3 g. (10.6 cc.) of ethyl cyanoacetate. The mixture is heated under reflux for two hours and then filtered hot. The sodium salt of 6-aminouracil thus obtained is washed with alcohol and air dried. It is then dissolved in 100 cc. of water, to which is added 50 g. of ice and 8 g. of sodium nitrite. This mixture is dropped into a mixture of 24 g. of acetic acid, 25 g. of water and 75 g. of ice. Concentrated ammonia is then added until the solution becomes ammoniacal, when the rose-colored salt of 5-nitroso-6-aminouracil is filtered off. This salt is then suspended in 250 cc. of hot water, 40 g. of technical sodium hydrosulfite added, and the mixture heated to boiling while being stirred mechanically. The rose-colored salt is thus transformed into a buff-colored precipitate of 5,6-diaminouracil sulfate. The mixture is chilled and filtered. To purify the product, it is dissolved in 100 cc. of 6% sodium hydroxide containing a little sulfite, and the clarified solution poured into a boiling solution of 10 cc. of concentrated sulfuric acid in 100 cc. of water. After chilling, the 5,6-diaminouracil sulfate is filtered off, washed with water and air dried; yield, 13.0 g. (62%).

Anal. Calcd. for $(C_4H_6O_2N_4)_2H_2{\cdot}SO_4$: C, 25.4; H, 3.6. Found: C, 25.3; H, 4.2.

For analysis the product was dried at 120°.

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Summary

Sodium hydrosulfite has been found to be a convenient reagent for the reduction of 5-nitro or nitroso derivatives of uracil to 5-amino derivatives.

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[6] Behrend and Osten, *Ann.*, **343**, 133 (1905).

[7] Behrend, *ibid.*, **240**, 1 (1887); Biltz and Heyn, *ibid.*, **413**, 110 (1916).