[Contribution from the Chemical Laboratory of Smith College.]

THE SYNTHESIS OF IMINOURACIL-6-ACETIC ACID.

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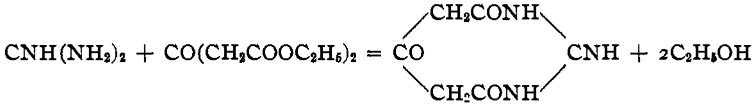
Introduction.

Acetoacetic ester[1] has been shown to react with urea to form β-uramidocrotonic ester, which may be made to undergo further condensation to a uracil derivative. This substance is important as it is the source of a well-known synthesis of uric acid. Guanidine[2] condenses more readily with acetoacetic ester, forming directly iminomethyluracil. It seemed desirable to investigate the behavior of these bases toward acetonedicarboxylic ester which contains 2 active methylene groups, but as this research has been temporarily abandoned because of a change of duties, only an account of preliminary experiments with guanidine are available.

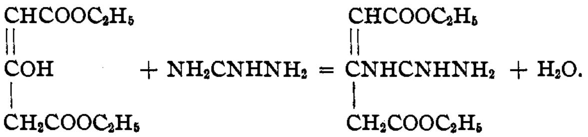
There appear to be a number of ways in which this ester may react with guanidine. One is the formation of an 8-membered ring compound as a result of the following reaction:



$$CNH(NH_2)_2 + CO(CH_2COOC_2H_5)_2 = CO\begin{array}{l}\diagup CH_2CONH \diagdown \\ \\ \diagdown CH_2CONH \diagup\end{array}CNH + 2C_2H_5OH$$

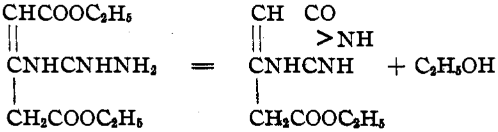
The compound actually isolated, however, had a much higher nitrogen content and was either a bis-cyclic derivative resulting from the interaction of 2 molecules of guanidine with the ester, or the guanidine salt of iminouracil acetic acid. The latter interpretation of the reaction proved to be correct.

The first step in the reaction as the researches of Behrend[3] would indicate is the elimination of a molecule of water with the formation of a guanidine derivative.



$$\begin{array}{l}CHCOOC_2H_5\\ \| \\ COH\\ | \\ CH_2COOC_2H_5\end{array} + NH_2CNHNH_2 = \begin{array}{l}CHCOOC_2H_5\\ \| \\ CNHCNHNH_2\\ | \\ CH_2COOC_2H_5\end{array} + H_2O.$$

This compound immediately loses a molecule of alcohol to form a pyrimidine.



$$\begin{array}{l}CHCOOC_2H_5\\ \| \\ CNHCNHNH_2\\ | \\ CH_2COOC_2H_5\end{array} = \begin{array}{l}CH\ \ CO\\ \| \qquad >NH\\ CNHCNH\\ | \\ CH_2COOC_2H_5\end{array} + C_2H_5OH$$

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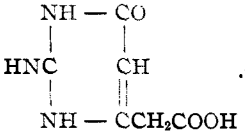
[1] Behrend, *Ann.*, **229**, 5 (1885).

[2] Kohler, *Ibid.*, **233**, 15 (1886); Jaeger, *Ibid.*, **262**, 365 (1891).

[3] *Loc. cit.*

Apparently the ester then hydrolyzes and the resulting acid decomposes the guanidine carbonate which was used in excess, to form a salt.

Experimental.

2-Iminouracil-6-acetic Acid, 

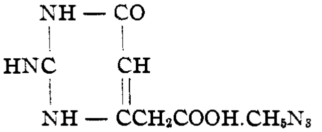
$$\begin{array}{rll} & \mathrm{NH} & -\ \mathrm{CO} \\ & | & \quad | \\ \mathrm{HN} & \mathrm{C} & \quad \mathrm{CH} \\ & | & \quad \| \\ & \mathrm{NH} & -\ \mathrm{CCH_2COOH} \end{array}$$

.—Ten g. of acetone-dicarboxylic ester and 8.9 g. of guanidine carbonate were mixed with 50 cc. of alcohol and refluxed for 5–6 hours. The mixture slowly changed to a yellow solution from which a white crystalline mass gradually separated. This was filtered off, washed well with alcohol and air dried at 110°, yielding 8 g. of quite pure guanidine salt. Further heating of the combined filtrates resulted in the deposition of considerably more of the salt, but it was found best to keep this separate as it contained colored impurities which were difficult to remove. Total yield about 90% theory.

The new compound was dissolved in the least amount of warm water and a slight excess of hydrochloric acid carefully added. A voluminous white precipitate immediately formed which after cooling was filtered, recrystallized from water and finally dried in a vacuum desiccator.

Calc. for $C_6H_7O_3N_3$: N, 24.9. Found: N, 25.0.

Properties of Iminouracil Acetic Acid.—It is nearly insoluble in alcohol and glacial acetic acid, but readily soluble in ammonium hydroxide, sodium hydroxide and conc. hydrochloric acid. It crystallizes from water in colorless square plates, which melt with decomposition at 289–290°. The new substance is acidic toward litmus paper and decomposes soluble carbonates. It reacts readily with bromine in glacial acetic acid solution forming a compound which crystallizes from a large volume of hot water in slender, silky needles and which melt with decomposition and foaming at 210–211°. The sodium salt of the acid, prepared by careful neutralization with sodium hydroxide forms a flocculent light green precipitate with copper sulfate which consist of microscopic pointed twinned plates, intersecting at right angles. Crystalline precipitates are also formed with nickel and cobalt nitrate solutions. Potassium permanganate is not decolorized by a cold solution of the acid.

Guanidine Salt of Iminouracil Acetic Acid, 

$$\begin{array}{rll} & \mathrm{NH} & -\ \mathrm{CO} \\ & | & \quad | \\ \mathrm{HN} & \mathrm{C} & \quad \mathrm{CH} \\ & | & \quad \| \\ & \mathrm{NH} & -\ \mathrm{CCH_2COOH.CH_5N_3} \end{array}$$

—The uracil derivative was first obtained in the form of the guanidine salt which was recrystallized from a mixture of alcohol and water and air dried at 110°.

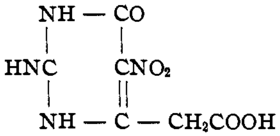
Calc. for $C_7H_{12}O_3N_6$: N, 36.8. Found: N, 37.2.

Properties of the Guanidine Salt.—It crystallizes from dilute alcohol in microscopic needles which decompose with foaming (due to evolution of ammonia, carbon dioxide and water vapor) at 213–214°, changing to an amorphous solid which softens gradually and is entirely melted at 230°. A solution of the salt on warming with copper sulfate solution quickly forms a compact deep green precipitate of beautiful diamond-shaped crystals. Pale green crystals are formed with nickel, and rose-colored plates with cobalt nitrate solutions.

Action of Nitric Acid on Iminouracil Acetic Acid.—Five g. of the uracil acetic acid (guanidine salt) was added in small amounts to 25 cc. conc. nitric acid, warmed to 70°. The substance dissolved with considerable foaming and evolution of heat. A white precipitate of 6-sided plates separated out during the addition. The mixture was allowed to stand for a few minutes and then poured into 5 volumes of water. The precipitate was apparently the nitric acid salt of the expected nitro compound, as on washing with water it changed to an amorphous yellow mass which was air dried at 110°. Yield, 3 g. A similar product was obtained by the nitration of the free acid.

Calc. for $C_6H_6O_5N_4$: N, 30.8. Found: N, 31.0.

The new substance is 2-imino-5-nitrouracil-6-acetic acid,



Properties of Iminonitrouracil Acetic Acid.—It is insoluble in water and the usual organic solvents, but readily soluble in sodium hydroxide and carbonate solutions. It decomposes at 309–310° with preliminary softening. The sodium salt separates on evaporation of the water solution in small, colorless rods. The barium salt is insoluble in water.

Summary.

It has been shown that guanidine carbonate and acetonedicarboxylic acid condense smoothly in alcohol solution to form the guanidine salt of iminouracil acetic acid. The free acid is obtained by the action of hydrochloric acid on the guanidine salt. Both the acid and salt form characteristic crystalline copper derivatives. Nitric acid and bromine react readily with iminouracil acetic acid.

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